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MENTAL HEALTH RESEARCH WITH INCLUSIVITY IN MIND

Welcome to the Conference Supplement of Psychiatria Danubina for the

7th Biennial Cambridge International Conference on Mental Health held at Clare College, University of Cambridge

The 7th Biennial Cambridge International Conference on Mental Health remains popular as ever amongst presenters who not only include world class researchers, opinion leaders, young rising researchers, but also medical students who are having their first stab at research and publishing. This makes this scientific journal truly inclusive and unique in its nature.

The authors origins though dominated by Europe, also includes those who hail from US and middle east. The variety of topics covered includes, aspects of physical health issues impacting mental health and vice versa, as described for example in the paper exploring level of Vitamin D and magnesium and mental health by Woodward et al. and effects of eating disorder in pregnancy on mother and baby by Mahon and Agius. Inclusivity is clearly evident since both papers are led by medical students with senior researchers as co-authors. The link between physical health, mental health and lifestyle (diet and exercise) is also explored by Zaman et al. in paper titled, Lifestyle factors and mental health, whilst the role of gut microbiome is reviewed by Dubois et al. in their paper titled, Role of gut microbiota in the interaction between immunity and psychiatry: a literature review.

Why do we value inclusivity? Well it is well known that psychiatry is not the most popular medical specialty for newly qualified doctors. It suffers from widespread stigma and is considered by many medics of different specialities as somewhat woolly and unscientific. Many studies as well as our own experience suggests that involving young medical students in psychiatry research and its academic aspects not only helps to dispels many negative myths about psychiatry, but it also fosters interest in psychiatry as future specialty. This of course has been our experience here in Cambridge given that we have been involving medical students in research for number of years. A number of our past students have gone on to follow academic careers in psychiatry and feel fulfilled in their career choice. Other ways to raise interest of medical students in psychiatry has been described by Hankir et al., Kings College London Global health society event discussing global mental health to increase interest in psychiatry as a career: A pilot study.

This supplement includes papers covering a wide variety of research from UK, US, UAE and many European countries, including, Belgium, Croatia, Ireland, Italy, Poland, Russia, Slovenia and Switzerland. We will continue to encourage and facilitate publication from not only the senior researchers and those in early stage of their research career, but importantly, the young and ambitious medical students not only from Cambridge, or rest of UK, but also from other European countries and beyond as we have done so in past.

I would like to thank my guest editorial colleagues for helping me to put together this supplement which would not have been possible without the hard work of Rajko Horvat. Additionally, I would like to thank Miro Jakovljevic, Marija Eljuga and other staff from Medicinska Naklada involved in producing this supplement journal.

I hope you will enjoy reading the wide range of interesting papers.

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THE SERAFICO INSTITUTE IN ASSISI (PERUGIA)

The Serafico Institute in Assisi (Perugia) is a Rehabilitation Center accredited with the Italian National Health Service. Its mission is the provision of clinical and social services, rehabilitation, psychoeducational intervention and bring individuals with complex multiple disabilities into mainstream.

The Serafico Institute was founded on September 17, 1871 by St. Ludovico da Casoria, a Franciscan friar who made it his life goal to establish a charitable organization in the city of St. Francis. The founder provided basic services to those individuals who at the time were considered outcasts and marginalized from society: the deaf and the blind. In fact, at this time, the prevalent need of these individuals was educational in nature, since deaf and blind people had limited or no access to schools.

The name "Serafico" recalls how St. Francis' fellow friars referred to him during the final years of his life, almost completely blind, in addition to being deeply wounded in the flesh by the stigmata received from Christ.

Throughout its existence, Serafico's mission has evolved based on emerging needs in health care. Currently the Serafico Institute is an internationally renowned center providing comprehensive rehabilitation services to children, adolescents and young adults with severe and complex disabilities. Among the many specialty areas addressed are blindness, intellectual disabilities, communication disorders, movement disorders, epilepsy, rare diseases, infantile cerebral palsy, genetic syndromes, neurodegenerative diseases, and neurodevelopmental disorders.

The Serafico Institute provides services of a multidisciplinary nature at various levels of care, including an accredited 86-bed residential area, and a semi-residential or "day hospital" area accredited for 30 patients.

In addition, the institute provides outpatient /ambulatory care services offering specialized rehabilitation treatments, diagnostic services, educational laboratories providing habilitative interventions (ceramics, craft and graphic arts laboratories, art therapy), pet therapy, theater, music, horticulture as well as adapted physical education programs.

Two of the residential beds in the institute are part of the special humanitarian project "The beds of St. Francis". This project is made available to needy pediatric clients in situations of distress: from refugees arriving from poor or war-torn countries, to persons with disadvantaged conditions who for various reasons find themselves not covered under the National Health Service.

The beds of St. Francis are completely funded by individual and corporate donor efforts.

Each day, the Serafico Institute welcomes and cares for over 150 children, adolescents and young adults. In 2018 the institute provided approximately 16,000 specialized rehabilitation interventions and 17,000 educational interventions. Over 7,000 volunteer hours were donated to its patient population. Approximately 60,000 meals were distributed.

The Serafico Institute's model of care is based upon the intrinsic value and dignity of life: we do not adopt a fragmented or reductionist view of the individual in context of impaired functions or compromised organs, but we consider the person in his totality and are attentive to every dimension of his/her existential being.

The care relationship at Serafico combines the specific skills and knowledge base possessed by each and every staff member within the context of a harmonious and empathic relationship formed with the patients treated: reciprocity, sensitivity and warmth are fundamental elements which comprise the "essential qualifications " of everyone employed at the institute.

We believe that limits and fragility are considered a resource for the whole community and are fundamental to the development of a more compassionate and humane society.

Serafico is a home that embraces life, where the meaning of "caring for" the individual derives directly from the call to be custodians of human life.

In 2018 the Serafico Institute inaugurated the "InVita" Research Center specialized in research and development and innovation in the rehabilitation of children and young adults with multiple disabilities and psychiatric and neurodevelopment disorders, activating a joint effort with the University of Perugia. Current research areas are focused on multidisciplinary sectors: neurophysiopathology, genetics, neurodevelopmental disorders, and technological innovation.

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LIFESTYLE FACTORS AND MENTAL HEALTH

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SUMMARY

A number of lifestyle factors have been recognised to play an important role in positively modifying medical and psychiatric diseases and their associated morbidity and mortality. These include, eating healthy food, greater physical activity, cessation of smoking, avoidance of alcohol and illicit substances. Additional lifestyle factors for healthy living include, safe and peaceful environment, optimal sleep, de-stressing and enjoyable activities, social connections/support and healthy mental activities. Physicians from the ancient times, through the middle ages to the early 20th century have recommended adoption of healthy lifestyle factors such as diet and exercise to manage medical and psychiatric disorders without really understanding their scientific basis.

In this short paper, we discuss the important role lifestyle factors play in morbidity and mortality related to many important and common medical and psychiatric diseases. We explore how and if positively modifying lifestyle factors can help to improve and or prevent medical and psychiatric disorders with particular emphasis on food, diet and exercise.

Key words: lifestyle factors - food - diet - exercise - medical and psychiatric diseases

* * * * *

*Brain is there to be used
Body is there to be moved*

Rashid Zaman

INTRODUCTION

A wide ranging and increasing number of medical and psychiatric diseases are recognised to be caused and modified by the way individuals live with associated lifestyle factors playing major part.

A number of lifestyle factors have been recognised to play an important role in positively modifying medical and psychiatric diseases and associated morbidity and mortality. These include, eating healthy food, greater physical activity, cessation of smoking, avoidance of alcohol and illicit substances. Additional lifestyle factors for healthy living include, healthier environment, optimal sleep, de-stressing and enjoyable activities, social connections/support and healthy mental activities.

Whilst slogan such as “no mental health without physical health” and “no physical health without mental health” are being widely used by health providers, most of the public and many professionals in healthcare are not aware of the important growing research evidence explaining how and why adopting of healthier lifestyle factors leads to positive benefits for both physical and mental health.

In this short paper, we discuss the important role lifestyle factors play in morbidity and mortality related to many important and common medical and psychiatric diseases. We explore how and if positively modifying lifestyle factors can help to improve and or prevent medical and psychiatric disorders with particular emphasis on food, diet and exercise.

LIFESTYLE FACTORS AND DISEASES

Using a broader definition, lifestyle factors generally include, level of physical activity, use of tobacco smoking, amount of food consumed, level of obesity, consumption of healthy/unhealthy food, level of alcohol consumption, use of illicit substances, sexual health and access to 'healthy' environment.

The term lifestyle diseases refer to the diseases which are associated with the way individuals live their lives. These diseases are commonly caused by a number lifestyle factors, such as smoking, alcohol, drug misuse, unhealthy eating, lack of physical activity and exposure to unhealthy environment.

Numerous diseases have been recognised as lifestyle diseases, including, Alzheimer's disease, atherosclerosis, asthma, cancer, liver diseases, type 2 diabetes, metabolic syndrome, renal diseases, osteoporosis, stroke and depression.

The number and types of lifestyle diseases are rising with increasing contribution of psychiatric diseases. Whilst depression and type 2 diabetes may appear to be widely apart in their nature and presentations, they are not only linked, but are likely to have same underlying pathology. Indeed, there is growing evidence that the common underlying pathology for both type 2 diabetes and depression is chronic inflammation as is the case in many chronic diseases (Stuart 2012, Baumeister et al. 2014), with varying amount of genetic contribution.

Genetics and other common modifiable lifestyle risk factors are often the underlying cause for the development of most chronic medical and psychiatric diseases. These risky/unhealthy lifestyle factors include, unhealthy diet (Munoz et al. 2008), obesity (Whitlock et al. 2009),

physical inactivity (Paganini-Hill et al. 2011), tobacco smoking (World Health Organization 2011), excessive alcohol consumption (Murray & Lopez 2013), misuse of drugs, risky sexual behaviour (Penner et al. 2019), high blood pressure (Gabin et al. 2017) and metabolic syndrome (Brenda et al. 2018).

Whilst, identification and addressing of specific unhealthy lifestyle factor is helpful, it is important to recognise that more often individuals have multiple unhealthy lifestyle factors. For example four common risky lifestyle factors, smoking tobacco, excessive alcohol consumption, limited physical activity and poor diet often go hand in hand. Excessive food consumption with limited physical activity can lead to obesity, however, presence of additional risk factors such as smoking and excessive alcohol consumption can further exacerbate the negative impact of obesity and lack of exercise alone, since smoking can worsen fitness level, leading to further inactivity, whilst excessive alcohol consumption can cause sleep deprivation thus further worsening obesity. Therefore, co-existing unhealthy lifestyle factors not only work synergistically to exacerbate worsening of physical and mental health, they are also difficult to address when compared to managing just single unhealthy lifestyle factor acting in isolation.

Much of epidemiological research has shown that lifestyle factors, such as diet, exercise, mental activity and stress, are significant influences on health extension (Li et al. 2018).

LIFESTYLE FACTORS, HISTORICAL ASPECTS

Despite, lacking modern scientific understanding of mental disorders and with no real understanding of how lifestyle factors influence morbidity and mortality related to psychiatric (and medical) disorders, physicians throughout the history have recommended use of lifestyle modifications such as diet and exercise to treat psychiatric disorders such as depression. For example, Hippocrates (400 BCE) suggested treating melancholia (historical name for depression) by bloodletting, bathing, exercise and dieting. In the middle ages muslim physicians also emphasised the beneficial role of diet, exercise and emotional support through counselling and behaviour therapy. As Europe emerged from the dark ages, enlightened physicians such as Robert Burton in 1621 (who published the *Anatomy of Melancholy*), suggested various treatments which included, dietary measures, exercise along with distraction, travel, cleanses, bloodletting, herbal remedies, marriage and music therapy (Zaman 2018).

However, despite expanding scientific knowledge, little attention appeared to have been paid to the important role lifestyle factors were playing with regards to health until well into mid 20th century when smoking began to be recognised as a crucial lifestyle factor causing lung cancer (Doll & Hill 1950) and later other cancers, as well as, multitude of other diseases. Tobacco is said be the leading risk factor for at least 5 of the 10

leading causes of death worldwide which include, ischemic heart disease, cerebrovascular disease, tracheal, bronchial and lung cancers, lower respiratory infections, and chronic obstructive pulmonary disease (Murray & Lopez 2013).

CAN POSITIVELY MODIFYING LIFESTYLE FACTORS HELP IMPROVE OR PREVENT MENTAL HEALTH DISORDERS?

Much of epidemiological research has shown that lifestyle factors, such as diet, exercise, mental activity and stress have significant influences on health extension (Li et al. 2018). The research evidence for improving and preventing psychiatric disorders by positively modifying the lifestyle factors continues to grow (Cotman et al. 2007, Rohrer et al. 2005, Tanka & Shirakawa 2004, Scheewe et al. 2013). As described above smoking has clearly been shown to cause significant morbidity and mortality through the development of various cancers and number of other diseases, which in turn have negative impact on mental health (Kadan-Lottick et al. 2005, Ganz et al. 2003, Ormel et al. 2007, Aras et al. 2017).

Apart from smoking, diet and exercise (discussed below), other important lifestyle factor that can modify mental health is social connections/interactions. Whilst, the value of social connections is generally argued to be positive for mental health, the relationship is not straight forward as argued by some. Kawachi and Berkman (Kawachi & Berkman 2001) point out that whilst social ties generally have beneficial role, their protective effects on mental health vary amongst different groups and sexes. The type of social support derived from social networks appear to differ amongst men and women. It is noted that social connections may paradoxically increase levels of psychiatric symptoms amongst women with low resources, particularly if these women are obliged to provide social support in return. They argue that “despite some successes reported in social support interventions to enhance mental health, further work is needed to deepen our understanding of the design, timing, and dose of interventions that work, as well as the characteristics of individuals who benefit the most.”

The idea that everyone, regardless of age, gender, educational level, social and cultural background will benefit from increased social network, particularly online is somewhat simplistic, given the changing complexities of human connections (Pantic 2014) and effects of pre-existing mental illness (Leff & Vaughn 1981).

FOOD, DIET AND EXERCISE

In ancient times, human survival dependent upon their ability to obtain enough food (availability was somewhat haphazard) and survive other predators (humans were the food!). Hence, both required humans to be physically active. Therefore, obesity (unless due to particular medical condition) would not have been much

of an issue. As human began to grow food and were able to store it, food supply generally became less of an issue, whilst the need to survive predators persisted and therefore, physical activity persisted. As human moved into the modern times, they were no longer the food for the predators, food supply became plentiful and stable (with some exceptions) and with presence of transport system and ever increasing automation, the need to move (physical activity) decreased substantially, leading to obesity and its related physical and mental health problems.

Obesity is described as chronic relapsing disease where abundance of food (particularly those high in energy density, such as sugar rich, fat-laden, low fibre and processed food) is a primary cause that interacts with low level of physical activity and other environmental factors along with genetic susceptibility to lead to positive energy balance. The body stores this positive energy as fat (mostly visceral fat) which results in metabolic, hormonal and inflammatory changes, which cause damage to various body organs such as the arteries, brain, heart, liver, muscle and pancreas (Bray et al. 2107). This results in emergence of several chronic diseases (lifestyle diseases), such as Alzheimer's disease, atherosclerosis, asthma, cancer, liver diseases, type 2 diabetes, metabolic syndrome, renal diseases, osteoporosis, osteoarthritis, stroke and depression. Without doubt obesity has become a global health issue which is likely to get worst (Kelly et al. 2005), unless urgent worldwide public health measures are taken to address it.

Obesity has been rising exponentially for last 70 years (Caballero 2007). It is suggested that dietary changes have been major contributory factor. These changes include, rise in proportion of sugar and carbohydrate (particularly food with high glycaemic index) rich food (processed food). This has contributed to exponential rise in metabolic diseases such as type 2 diabetes which has been associated with psychiatric disorders such as depression possibly due to same underlying inflammatory pathology (Stuart & Baune 2012).

The role of dietary modification to lose weight and exercise is well recognised for healthy living. However, more specific advice is needed as to what type of dietary modification should be adopted to lose weight. For example those who are overweight with possible family history of type 2 diabetes and therefore likely to be vulnerable to development of insulin resistance and hence eventual progression to type 2 diabetes, would best be advised not just to lose weight but also to lose weight by reducing the proportions carbohydrate rich food (particularly with high glycaemic index) and carryout appropriate exercises.

Arguments between proponents of various diets to reduce obesity, type 2 diabetes and other physical and mental health disorders are rife. These diets include, low to no-carbohydrate/ketogenic diets, Mediterranean diet, paleo diet and vegetarian diet. It is beyond the scope to this paper to discuss these various diets. However, overall, large body of evidence suggests that consumption of

well-balanced meals, rich in fruits and fibre, with optimal amount of protein and healthy fats and relatively low level of sugar and carbohydrates (particularly those with high glycaemic index) along with overall lower amount of food (hence calories) promotes good physical and mental health.

In addition to dietary measures, the importance of exercises leading to positive benefits for physical and mental health cannot be overemphasised.

Scheewe and colleagues (Scheewe et al. 2013), reported that exercise therapy, when performed once to twice a week, improved mental health and cardiovascular fitness and reduced need of care in patients with schizophrenia.

Exercise has numerous beneficial effects. It has social benefits (being with others in gym, by taking part in group sports) and medical benefits since it reduces peripheral risk factors such as diabetes, hypertension and cardiovascular disease and hence provide protection for psychiatric (depression) and neurological diseases (Alzheimer's disease).

The improvement in blood circulation has positive benefits for brain function through various ways. It increases neuroplasticity (hence memory function), improves synaptic structure and strength through its positive action on neurogenesis, metabolic pathways and vascularity.

Exercise also leads to increase in levels of brain-derived neurotrophic factor (BDNF) and other growth factors which increase resistance to brain insult and improve learning and mental performance (Cotman et al. 2007).

BDNF has been shown to promote survival and differentiation of 5-HT neurons. It is also reported that administration of selective serotonin reuptake inhibitors (SSRIs) antidepressants enhance BDNF gene expression (Martinowich & Lu 2008).

CONCLUSION

Clearly large body of research evidence points to importance of lifestyle factors in medical and psychiatric diseases. Research also suggest that positive modification of lifestyle factors is essential for both improvement and maintaining of physical and mental health.

Each individual is unique and hence requires their own unique set of programmes of lifestyle modification. Indeed, it is helpful to recognise that each lifestyle factor is linked to and influences other lifestyle factors through various underlying mechanisms such as improvement in inflammatory processes which can result from inactivity, over consumption of unhealthy/inflammatory foods, obesity and smoking. Whilst it may be easier to take a step by step approach by modifying of one lifestyle factor at one time, efforts should be made to modify all lifestyle factors in conjunctions, since they tend to work synergistically and are likely to have greater effect on positively modify morbidity and mortality related to physical and mental health.

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Contribution of individual authors:

Rashid Zaman conceived the idea of the paper, carried out literature search and wrote the paper.

Ahmed Hankir & Monem Jemni reviewed the literature and contributed to the final draft.

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SERUM VITAMIN D AND MAGNESIUM LEVELS IN A PSYCHIATRIC COHORT

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SUMMARY

Background: Both Vitamin D deficiency and magnesium deficiency have an increased prevalence and have been associated with an increased risk of and increased severity of symptoms in both depression and schizophrenia (Boerman 2016, Tarleton & Littenberg 2015). This effect appears more pronounced in younger populations and is often apparent from the time of initial diagnosis and is present with adjustment for confounding factors. Thus, the evidence suggests that Vitamin D and magnesium deficiency reflects not only dietary or somatic aspects of health but also may have a role in the pathophysiology of depression and schizophrenia.

Subjects and methods: A single site audit of serum Vitamin D and magnesium levels in patients at an Acute Day Treatment Unit was carried out. Blood tests were performed on admission and analysed in house. Data were collected between April - June 2019 and was analysed subsequently, as described below (n=73).

Results: Our data show that our psychiatric day treatment unit cohort (n=73) had a higher proportion of vitamin D deficiency (52%) than the general population (40%), although due to the limited sample size this was not significant (p=0.22, Chi-squared test). The percentage of patients who were magnesium deficient was 78.6% (n=22/28). However, the F60 subgroup of patients with personality disorders showed a high prevalence of vit D deficiency (p=0.07), highlighting a trend towards significance despite the limited size of this subgroup.

Conclusions: We carried out a single-site audit of serum vitamin D and magnesium levels in a psychiatric day unit population in order to assess the extent of vitamin deficiency in such patients. These data indicate that the proportion of patients with vitamin D deficiency is higher than in the general population. Further larger analysis is needed to establish the statistical significance of these data and whether treatment with vitamin D supplementation improves outcomes.

Key words: psychiatry - vitamin deficiency – audit - vitamin D - magnesium

* * * * *

INTRODUCTION

Vitamin D deficiency is widely accepted as a marker for poor somatic health status (van den Berg et al. 2016). Vitamin D plays a crucial role in neuroprotection and neurodevelopment and low levels are associated with psychiatric conditions such as depression and schizophrenia (Cieslak et al. 2014).

However, in addition to this, vitamin D level and magnesium deficiency have been explored as correlates in psychiatric subpopulations in levels above that of the average population. This is even despite a relatively high prevalence in northern European countries' general populations. Several studies show an association between schizophrenia and vitamin D deficiency (Boerman 2016, Lally et al. 2016). A Dutch single centre study (n=118) found vitamin D deficiency was 4.7 times more common among psychiatric outpatients with bipolar disorder, schizophrenia, or schizoaffective disorder than among the Dutch general population (Boerman 2016).

Both Vitamin D deficiency and magnesium deficiency have been associated with an increased risk of and increased severity of symptoms in both depression and schizophrenia (Black et al. 2014, Graham et al. 2015,

Doğan Bulut et al. 2016). This effect appears more pronounced in younger populations and is often apparent from the time of initial diagnosis and is present with adjustment for confounding factors. This supports the hypothesis that Vitamin D and magnesium deficiency does not merely reflect poor somatic health status but may also has a role in the pathophysiology of depression and schizophrenia. The mechanism of which is hypothesised to be due to its beneficial effects on neurotransmitters, metabolic profiles, biomarkers of inflammation, and oxidative stress, possibly exerting an overall anti-inflammatory effect (Sepehrmanesh et al. 2016).

There is growing evidence that Vitamin D plays a key role in reducing inflammation (Zhu et al. 2015). This is potentially important as low-grade inflammation has been shown to have a contributory role in the development of depression (Yary et al. 2016). A Chinese study (n=93) found depression was inversely related to raised C-reactive protein (CRP) in a matched case-control study (Zhu et al. 2015). Also, Vitamin D deficiency may be associated with pro-inflammatory cytokines which could explain the higher incidence of comorbidities such as heart failure, hypertension and stroke seen in patients with depression or schizophrenia (Lally et al. 2016).

Magnesium also plays a key role in many pathways involved in the pathophysiology of depression and is found in several key enzymes, hormones and neurotransmitters (Tarleton & Littenberg 2015). Higher magnesium intake is also associated with lower levels of inflammation markers such as CRP.

We postulated the rates of Vitamin D and magnesium deficiency would be higher in an outpatient acute day treatment psychiatric setting in Hertfordshire. To explore this, we carried out an audit of serum Vitamin D levels and serum magnesium in patients who had a blood test as part of their admission to an Acute Day Treatment Unit, Stevenage between April - June 2019 (n=28/73).

SUBJECTS AND METHODS

A literature search was initially undertaken to identify any association of vitamin D or magnesium with mental health conditions such as depression, psychosis, anxiety and ADHD in the literature in the last 10 years. A systematic literature review was performed using PUBMED to source evidence using the following search title terms in MEDLINE summarised in Table 1.

Abstracts were screened for the following key words: vitamin D or magnesium to depression, psychosis, anxiety or schizophrenia. Examinations of vitamin D or serum magnesium in a specific subsection of the population (i.e. pregnant women) were excluded. Literature that was not a literature review or original research were also excluded comprising of 25 articles. There were 37 publications identified. The results are presented in Table 2. Most evidence that reported or studied the association of vitamin D deficiency was linked to unipolar depression followed by schizophrenia.

The audit was undertaken by reviewing the serum Vitamin D levels and serum magnesium on the patients who had a blood test as part of their admission to an Acute Day Treatment Unit,

Stevenage between April - June 2019 (n=73). This was collated with the patient's age, gender, psychiatric diagnosis and ethnic origin.

Population characteristics were characterised and analysis of variance (ANOVA) was used to assess differences was used to for all patients and each subgroup, in both serum vitamin D and magnesium level with a Type I error rate of 0.05. The vitamin D level of this population was assessed against the literature for the primary outcome. Vitamin D deficiency was defined as the threshold for treatment are based on total 25-OH Vit D i.e. 25-OH Vitamin D2 and 25-OH Vitamin D3 combined. Total 25-OH Vitamin D >50 nmol/L (≥ 20 ng/mL) is sufficient for almost the whole population (Cieslak et al. 2014). Secondary outcomes were assessed by categorising patients based on the following variables: World Health Organisation (WHO) International Classification of Diseases 10th edition (ICD-10) diagnosis, sex, ethnicity, age (by decade). Additionally, the Pearson correlation between serum vitamin D and magnesium was assessed.

Table 1. Summary of Search Terms used in Systematic Literature Review

Search terms	Search results
((Vitamin D[Title] OR Magnesium[Title]))	
AND	
(schizophrenia[Title] OR depression[Title] OR psychosis[Title] OR anxiety[Title])	243
AND	
"last 5 years"[PDat]	120
AND	
Humans	82
AND	
Aged 19 years old and above	
<i>Total</i>	<i>62</i>

Table 2. Literature search results by type of psychiatric condition

Articles	Number
Articles linked to unipolar depression	22
Articles linked to bipolar depression	2
Articles linked to schizophrenia	10
Articles linked to psychosis	6
Articles linked to Attention Deficit Hyperactivity Disorder only	0
Articles linked to anxiety only	0
Total Articles	37

RESULTS

Vitamin D levels and magnesium levels were collected for 28 patients out of the 73 who presented the acute day treatment unit (38%) of the cohort studied. The gender split of the cohort was relatively equal between males (n=35, 48%) and females (n=38, 52%) and is detailed in Figure 1. The median age of each sex was 31 (females) and 38 (males). The median age of the cohort was 34 (IQR 25-49, range 19-72). 64 participants (91.4%) were Caucasian. The most frequent diagnosis as defined by the WHO ICD-10 was personality disorders (F60, n=13), followed by schizophrenia (F32, n=9), major depressive disorder (F41, n=7), generalised anxiety disorder (F33, n=6), major depressive disorder (F32, n=9).

We show that the prevalence of vitamin D deficiency in this cohort was 52%, in comparison with the general population (40%, (Parva et al. 2018)), which are shown in Figure 2a. Although the prevalence in this cohort was higher than the population level, it was not significant (p=0.22; Chi-squared test). When considered by ICD-10 diagnosis, we identify heterogeneity in levels of vitamin D3 between disease subtypes (Figure 2b). For example, 80% of patients with specific personality disorders are vitamin D deficient, using a threshold of 50 nmol/L (F60, specific personality disorders), which shows a trend towards significance (p=0.07, Chi-squared test) despite data being available for only 5 patients.

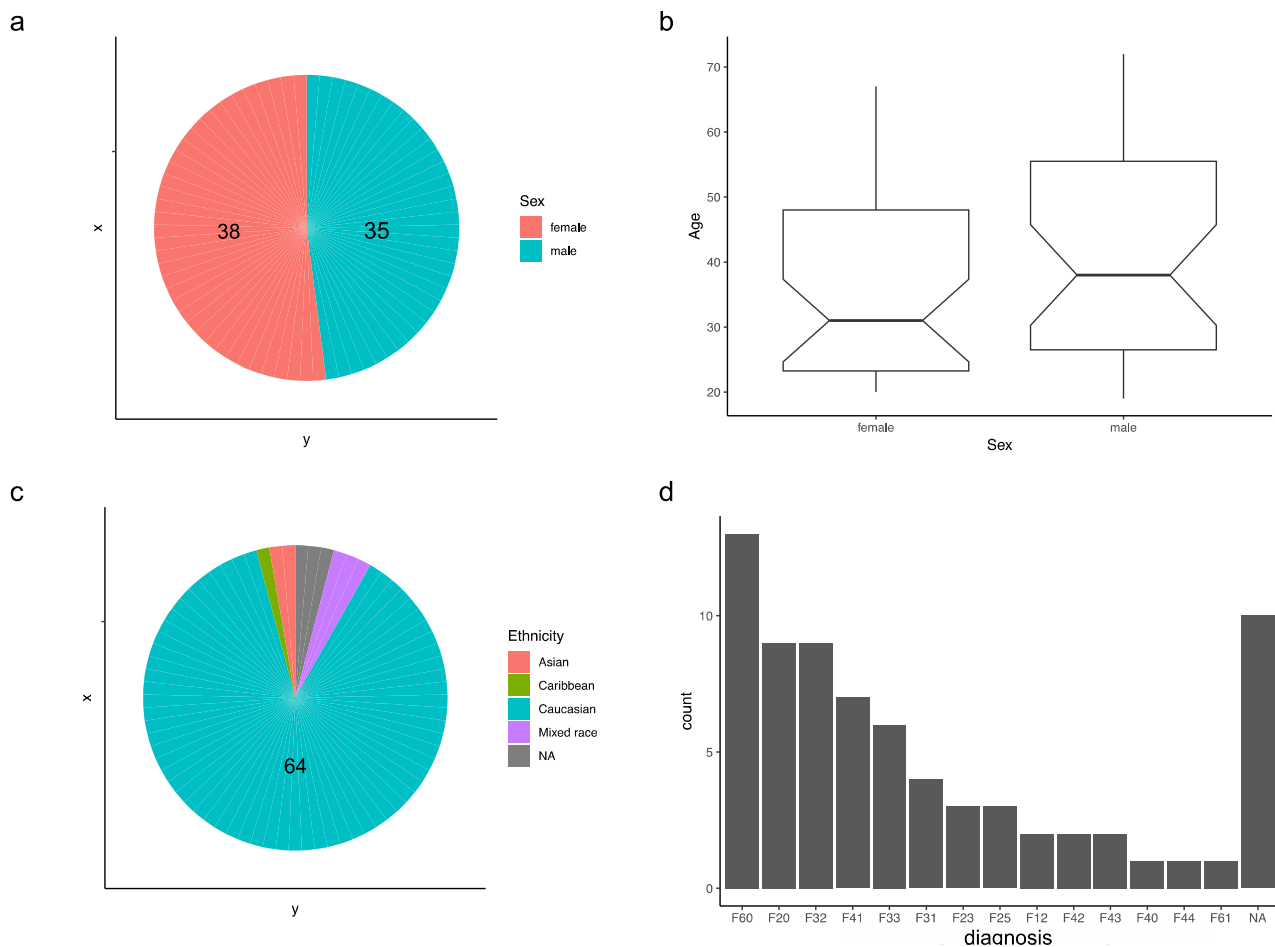


Figure 1.

- a.** Pie chart of sex of participants in the study. In this study, there were 35 male (48%) and 38 female (52%) participants;
- b.** Age distributions of each sex. The median age of each sex was 31 (females) and 38 (males). The median age of the cohort was 34 (IQR 25-49, range 19-72);
- c.** Pie chart of ethnicity of participants in the study. 64 participants (91.4%) were Caucasian;
- d.** Diagnosis breakdown by World Health Organisation International Classification of Disease, 2016. F60, personality disorders; F20, schizophrenia; F32, major depressive disorder; F41, generalised anxiety disorder; F33, major depressive disorder; F31, bipolar disorder. NA, data not collected

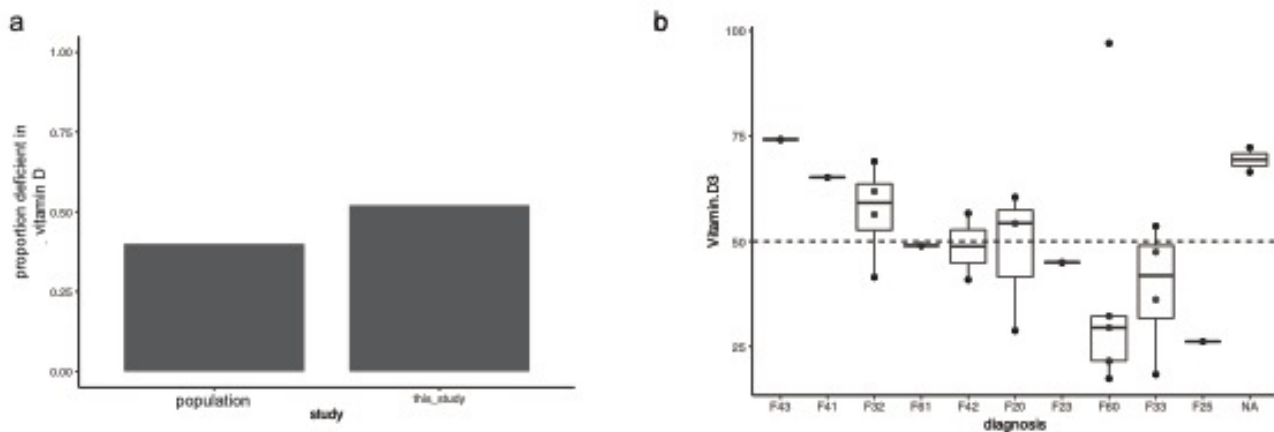


Figure 1. Prevalence of vitamin D deficiency identified in this cohort (52%) in comparison to the general population (40%). Although the prevalence in this cohort was higher than the population level, it was not significant ($p=0.22$; Chi-squared test);

Box plots of vitamin D level across the cohort, stratified by diagnosis. The threshold for vitamin D deficiency is shown as a horizontal line at 50 nmol/L. The vitamin D3 level for individuals with an F60 diagnosis (personality disorder) had a trend towards being lower ($p=0.07$, Chi-square test, $n=5$)

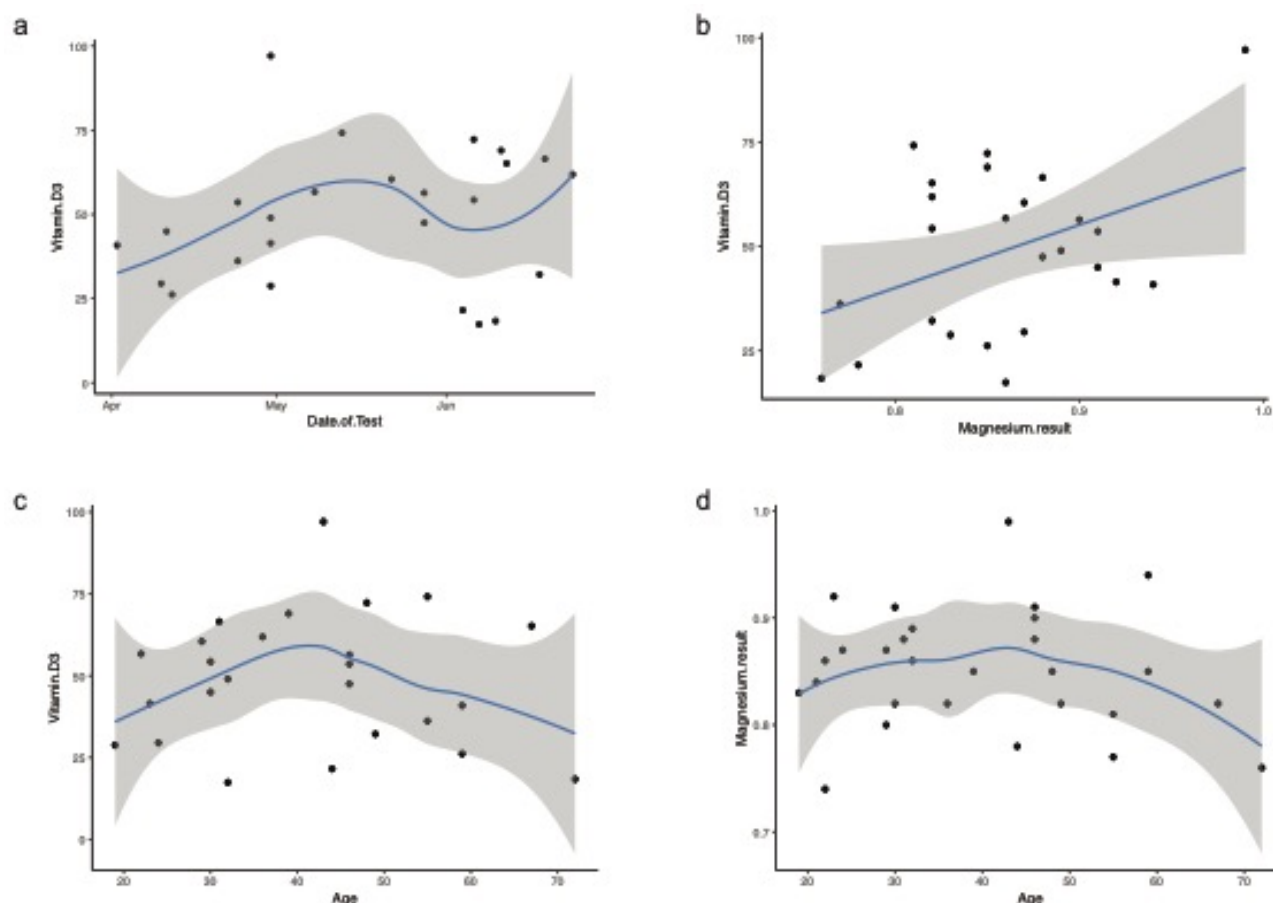


Figure 3.

- a. Vitamin D3 levels over time between April and June. There was no significant correlation between the date of sampling and the vitamin D3 level ($p=0.16$, Pearson correlation). The blue line indicates a smoothed line of best fit, and the grey area indicates the standard error of the fit;
- b. Comparison of magnesium and vitamin D3 levels. There was a significant correlation between magnesium and vitamin D3 levels ($p=0.04$, Pearson correlation);
- c. Vitamin D3 levels of patients of varying age. We observe highest levels of serum vitamin D3 in patients aged 40 years old, with lower levels in both younger and older patients;
- d. Magnesium levels of patients of varying age. We observe a similar trend as in vitamin D3, i.e. levels peak at 40 years of age

We observe a seasonal variation in vitamin D levels which was identified when visualising levels by month (Figure 3). We observe median vitamin D3 levels rising from 41.2 nmol/L in April, to 56.7 nmol/L in May then 58.1 nmol/L in June, suggesting a seasonal effect on vitamin D. We show a significant positive correlation between Vitamin D deficiency and serum magnesium levels ($p=0.04$, Pearson correlation), consistent with food sources of vitamin D also containing magnesium or indicating shared metabolic pathways between these nutrients. We studied the distributions of vitamin D and magnesium by age, which showed peak levels of both nutrients at the age of 40, with lower levels in both young and older patients. Overall, 78.6% ($n=22/28$) of patients were magnesium deficient (<0.9 mmol/L) as defined by serum magnesium. The median serum magnesium level was 0.85 mmol/L.

DISCUSSION

Our audit has identified a higher prevalence of vitamin D deficiency than the general population consistent with previous research (Boerman 2016). Both lifestyle and physical health factors associated with low vitamin D such as smoking, high body mass index and social withdrawal precipitating or exacerbating lack of sun exposure are all found more frequently in people with psychosis (Lally et al. 2016). It is also known that individuals who suffer from heart failure, hypertension, stroke and other cardiovascular diseases tend to have lower vitamin D levels (Lally et al. 2016). Discerning whether vitamin D deficiency is a causative or contributory factor or merely an association is challenging however it is clear from the literature vitamin D deficiency identified in this cohort has associated negative outcomes so treatment and patient care should be optimised to account for this.

Reduced levels are strongly associated with increased symptoms of depression in young adult males (Black et al. 2014). Our audit indeed identifies that younger patients (those below 40) have lower serum vitamin D levels. This consistent with a previous study in England in community psychiatric patients (n=324) (Lally et al. 2016). Potential vitamin D supplementation, particularly in this young cohort, could reduce the severity of their symptoms of depression as well as potentially have an anti-inflammatory effect and reduce the likelihood of complications from other comorbidities.

Our study identifies a clear increased risk of vitamin D deficiency in our psychiatric population which could potentially be treated with vitamin supplementation. Vitamin D treatment has been identified to be beneficial in a large Australian study of young adults with depression (n=1565) with 78% (n=1220) completing a Depression Anxiety Stress Scales (DASS-21). After adjustment for confounding factors, an increase in serum 25(OH)D concentrations of 10 nmol/L decreased total DASS-21 scores in males by 9% (rate ratio (RR) 0.91; 95% CI 0.87, 0.95; $p < 0.001$) but no association was seen with anxiety or stress levels. Supplementation may, therefore, be a pertinent approach in the younger patient to potentially reduce the severity of depression symptoms.

Our study also identified a clear drop off in vitamin D levels in patients over 50 indicating deficiency. This may be for dietary or social reasons; elderly patients are less likely to be as active outdoors and more likely to spend time indoors. However, the association of severity of depression and reduced serum vitamin D levels is less strong in elderly cohorts in which most research on vitamin D levels has been performed making it more uncertain there is a benefit in treatment in the elderly (Black et al. 2014).

Research shows that lower vitamin D levels in schizophrenia are also associated with more severe symptoms. Lower vitamin D levels are associated with increased negative symptoms and overall cognitive deficits (Graham et al. 2015, Doğan Bulut et al. 2016). Unlike in depression and schizophrenia, no evidence of Vitamin D supplementation improving mood or anxiety in bipolar however was seen in studies identified (Boerman 2016), suggesting that vitamin D is unlikely to be involved in the pathogenesis of bipolar disorder.

Seasonal variation in vitamin D levels was identified in our UK study which is relevant to other Northern European countries. This is consistent with previous studies (Lally et al. 2016). Our study identified a higher incidence of vitamin D deficiency despite taking place during spring-summer. Despite only studying a 3-month, seasonal effects were observed with vitamin D levels lower in those tested during April compared to June (Figure 2). This may be due to levels of sunlight or diet during the transition from winter to summer. Repeating our analysis to look at patients presenting during the winter months may show an increased incidence of vitamin D deficiency compared to the current study.

The association of magnesium levels and vitamin D deficiency in our study may be linked to poor dietary or physical status. However further research concerning patient's magnesium intake is likely to be a more reliable indicator of magnesium status (Tarleton & Littenberg 2015). Poor magnesium intake has also been linked to worsening depressive symptoms in a Finnish cohort study of patients with depression (n=2320) (Yary et al. 2016). Patients who were in the middle tertile of dietary magnesium intake had a statistically significant decreased risk of getting a hospital discharge diagnosis of depression compared to participants in the lowest tertile of magnesium intake (HR 0.49, CI 0.25-0.95, $p = 0.035$) in the prospective setting after multivariable adjustments. In addition, an inverse association between magnesium intake and the risk of depression was found when the combined middle and highest tertiles of magnesium intake were compared with the lowest tertile (HR 0.53, CI 0.29-0.95, $p = 0.033$) (Yary et al. 2016).

Younger patients identified in the cohort had lower levels of serum magnesium than those of middle age which is consistent with the literature identified. Magnesium deficiency is associated with depression particularly in younger adults; these form a significant proportion of an acute day treatment units demographic (Tarleton & Littenberg 2015).

This may offer treatment benefit in an ADTU setting as an adjunct for patients for which supplementation could be continued within primary care to reduce the risk of relapse. Vitamin D and magnesium supplementation could be an additional intervention to recommend in order to optimise care. Deficiency could potentially be identified in this setting and supplementation could be continued in primary care to form a targeted intervention to help patients ensure they are getting both pharmacological and psychological support. There is good evidence to suggest patients respond well to vitamin supplementation. Magnesium supplementation is well accepted and adherence is high in psychiatric populations where it is identified and is also effective (Tarleton et al. 2017, Tarleton & Littenberg 2015, Rajizadeh et al. 2017, Mehdi et al. 2017).

CONCLUSIONS

Our audit population shows higher prevalence of vitamin D deficiency compared to the general population, however, given the limited sample, it does not reach the level of statistical significance. When comparing various diagnostic groups, we found strong association between Vitamin D deficiency in patients with personality disorders.

Additionally, we have shown a significant positive correlation between Vitamin D deficiency and serum magnesium levels.

We recommend larger studies to gain better understanding of numerous factors that interact (from the molecular to clinical level) to show somewhat consistent link between low Vitamin D and magnesium levels

and various psychiatric disorders. Our own study points to further exploration of relationship between Vitamin D and magnesium and personality disorder.

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Contribution of individual authors:

Rashid Zaman conceived and designed the study and revised the manuscript.

Kiran Viswanath collected samples and data.

George Woodward & Jonathan C. M. Wan wrote the manuscript and analysed the data.

George Woodward performed the literature review.

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BEYOND THE DISEASE: "...AM I MY BROTHER'S KEEPER?"

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SUMMARY

Today, the concepts of health and illness require a global vision of man; the suffering of the person places the entire environment in great difficulty: health professionals, family, society. It is important not to simplify the response to a purely health-focused view of the disorder, because fragile people possess a deep need to feel welcomed, listened to, understood and accepted.

Service provision that is respectful of the dignity of the person is an important challenge both for those who are responsible for providing services to individuals and their families as well as for the entire community. Therefore in providing care the human qualities of the health professional and not only his technical skills come into play: blending together science and humanitarian ethos. The provision of care therefore "forces" us to broaden our horizons and requires us to face the challenge of responsibility towards the Other, the human condition of being-for. However, ethical capacity cannot be born solely out of sharing standards or adhering to regulations and respecting prohibitions: it stems from high and unconditional moral values and meanings. The ME-YOU relationship represents the primary ethical factor of the human being: my responsibility towards the Other is unconditional.

In the book of Genesis when the Lord asks Cain: "... where is Abel, your brother?" He responds with another question: "Am I my brother's keeper?" In this biblical passage Cain kills Abel: the rejection of brotherhood and the care of the other only leads to the death of the Other.

"Where is your brother?" This question is crucial in today's day and age and must be taken seriously: it is the decisive question that forces us to decide how to place ourselves in relationship with the other and with the world: do we choose proximity or distance, connection or indifference?

Key words: care relationship - vulnerability - responsibility - ethical attitude - mirror neurons

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INTRODUCTION

A recent World Health Organization survey shows that 75% of patients have no obvious organic disorder.

This survey highlights how the traditional medical model is in difficulty: it is clear that the organicistic approach adopted mainly by health workers is no longer sufficient to meet the demands and needs of caring for people.

Today, the concepts of health and illness require a comprehensive view of man; the suffering of the person, made even more complex by the presence of one or more deficits, puts the whole environment in great difficulty: health workers, family, society.

Complexity and multiplicity are concepts that are now part of the construction of any model of support and care.

First of all, it is necessary not to reduce the type of responses to a purely health-focused view on the disorder or deficit, because people with vulnerabilities need to feel welcomed, listened to, understood and accepted.

Providing care responses that respect the dignity of the person is an important challenge nowadays, not only for those who have the task and mission of providing services to people and their families, but for the entire community.

In the assistance and care processes, the human qualities of the health workers thus come into play, not only their technical knowledge; it is not a matter of questioning scientific knowledge, but of avoiding the

domain of technicalism: science and humanitarian ethos to be fertilised together (Jaspers 1991)

It is urgent to provide health professionals with knowledge and tools that, combined with specialised skills, can enable the vulnerable person to feel welcomed and understood in his/her entirety as a human being.

THE CARE RELATIONSHIP

In care relationships, the human dimension of professional action begins, first of all, from the type of "look" through which the operator "sees" the person with a disability.

A look that labels with a diagnosis, risks turning the person into a "classified object", prevents us from recognizing them through their experiences and makes us forget even that that person has a life story.

This gaze conveys stigma and prejudices, hurts and distances the person (Goussot 2011). The purely technical view of the expert (as well as the pietistic gaze) risks making us see the person with vulnerabilities only as a symptom, a problem, an unhappy being.

Alexandre Jollien, French philosopher and writer who had been diagnosed with cerebral motor and intellectual insufficiency as a child, states that what makes a person with vulnerability sick is not the complexity of the deficit, but the condition of permanent humiliation in which they find themselves living: "... a look that has caged me in a category, a gaze that paralyzes and makes you powerless" (Jollien 2003).

The type of gaze through which each of us sees, interprets or considers the other and the facts of the world, however, does not depend only on the perception of external stimuli, but also derives from "internal perceptions", which originate and develop in relation to our past.

Our inner world in fact, continually projects on others, more or less unconsciously, images, problems or possibilities that also refer to us, to our experiences, to our passions, desires, sufferings, to our limits.

Establishing a relationship of care, first of all means seeing the other as a person, it means taking pleasure or sorrow by looking at them realistically, turning to him with interest in a continuous exchange of emotions, feelings and thoughts.

It means going to meet the person in a creative way, exploring their potential, fantasising about them: the most varied images will emerge in us, sometimes far from reality, as in fairy-tale or mythological characters.

These creative fantasies, in a symbolic form, can also express and represent the potential of the person with vulnerability: each person has limits, but the resources of life are nevertheless varied and manifold.

If we look at the other as in a photo, we will behave in an impersonal and un-creative way; the person, on the other hand, is never something static: a person is life, past, present, future and is continuous development (Guggenbuhl & Craig 1987).

In the care relationship, it is common for the operators to often find themselves facing extreme and very serious situations where it seems impossible to establish any communicative relationship with the other; in these moments specific personal efforts are required: "... *put yourself in their shoes!*" is perhaps the most used expression to indicate empathy, a way to enter the impenetrable world of the other.

Empathy is certainly a "tool of the trade" of the health worker which is very useful in care relationships, but often it is not enough to understand a need or a desire when they are expressed in an "encrypted" way through body language, a self-injurious or bizarre behaviour or with a prolonged silence.

When any form of mutual communication seems impossible and we are faced with an obstacle that seems insuperable, what Husserl expresses with the word *enteropathy* can help us; this word expresses the characteristic attitude through which the person "lives" within themselves the experiences of others: it is possible to understand the experiences of the other, when we assume them as analogous to ours (Husserl 2016).

It is not a matter of identifying with the patient, it would be pure sentimentality: it means, instead, having an acute and painful awareness of illness, vulnerability and limits as expressions of human life, which concern everyone and unite us with one another.

This experience is also expressed effectively by Manicardi, a brother of Bose, commenting on the

parable of the Samaritan: "... *it is painful to be struck by situations that afflict man ... the Samaritan becomes neighbour not because he is a philanthropist, not because he is motivated by the intention to do good, but because seeing a wounded wayfarer breaks his heart*" (Manicardi 2016).

Here is the experience of taking care of the other and of fraternity founded on the common vulnerability.

In the care relationship, therefore, when all the doors of access to understanding seem to be closed, a key to opening them is certainly to ask oneself to listen to the suffering of the other and, in reciprocal mirroring, to listen to oneself.

On the other hand, it is a common experience that, in every relationship, we communicate much more than what is expressed in words or gestures.

However, this type of listening requires a further effort: to create a benevolent "inner place" that is conducive to mutual exchange; in this place "... *we must be cautious and humble*".

The health worker's caution and humility can bring people who are injured in the body and in the psyche closer than the batteries of tests and observation grids (Goussot 2011)

This human approach has always been taken into very little consideration by official medicine, because it is considered scarcely scientific; today, instead, it finds its own legitimacy in the latest scientific acquisitions of neuroscience.

THE CARE RELATIONSHIP AND NEUROSCIENCE

The scientific answers to the fascinating questions concerning the human and therapeutic aspects of the treatment relationships come from the discovery of "mirror neurons", a particular population of neurons identified with neuroimaging techniques by a group of researchers from the University of Parma led by Giacomo Rizzolatti.

This discovery is considered as one of the most important in recent years in the field of neuroscience; the scientist Ramachandran states that: "... *mirror neurons will be for psychology what DNA has been for biology*".

The peculiarity of mirror neurons consists in the fact these neurons are activated not only when a person performs actions, but also when the person observes the same actions performed by others.

The latest acquisitions of the mirror system are even more surprising: even when the person does not see the conclusion of an action performed by another, specific mirror neurons are immediately activated in a distinct area of the cortex. This suggests the presence in man of a natural ability to recognise in advance also the aims of a given act, differentiate it from others and respond in the most appropriate way.

Today neuroscience demonstrates the presence in man of an innate ability to understand the intentions of the Other (Rizzolatti 2018).

The neuronal mirroring of human behaviour, active from birth, reveals that in the brain structure the image of the US is present even before the psychological development of the EGO.

The fundamental importance of these data for clinical activity has led to the development of new heterogeneous lines of research united by a single objective: the study of reciprocal "*affective attunements*" in human relations, starting from the analysis of the very first phases of the mother-child relationship (Schore 2004, Tronick 2008, Imbasciati 2009, Feldman 2010, Terranova 2013).

Actually, neurosciences demonstrate much more: they provide the evidence that we are human because we succeed in identifying ourselves in the other, we are human because we can experience and feel what the other experiences and feels.

We are human because life means being in relation to the Other.

Today we can say that the visions of life, man and human existence proposed by an anthropology that, over the centuries, has been nourished by Greek philosophy, the Bible, the thoughts of St. Augustine, Kierkegaard, Kant, Husserl, Heidegger, Freud and Jung, to name a few of the best known sources, also had a demonstrable scientific basis.

BEYOND THE DISEASE AND THE PATIENT

The relationship with the Other is certainly an *interpersonal* affair, which also has *intrapersonal* effects as it changes the mental state and the biology of the individual.

Being next to the person with vulnerability in fact, as Jollien says, not only "*educates everyone to know each other better*" but also reveals "*the degree of humanity, solidarity and respect for the others in a community*" (Jollien 2003).

The care relationship "*forces*" us to broaden our horizons and requires us to face the challenge of *responsibility towards the Other*, the human condition of *being-for* (Bauman 2018).

The growth of the ethical component of man, however, cannot be separated from the recognition and integration in the EGO of the *shadow* elements, which prevent the person from interacting with the Other through ethically significant behaviours.

In this context, Jung believes that the shadow represents that portion of the Ego designated as "bad and unwanted", thus hidden and relegated to the unconscious part of the psyche.

Therefore, the function of the shadow is to channel all our negative aspects into the unconscious.

Suffering, shame and humiliation deriving from the recognition of these "renegade" aspects of the Self, are faced through the projection to the outside: one's negative sides are attributed to someone else, e.g. to a friend, relative, colleague, lover or even one's child.

Having an ethical behaviour implies, first of all, recognising that the reprehensible aspects of the other actually belong to us too; the key element to really recognise the Other and to deal ethically with them is the withdrawal of our shadow projections (Jung 1982, 1986, Christopher 2003).

But, is our ethical attitude innate or learned? Over the centuries, human thought has produced copious theoretical orientations, distinguished on the basis of the importance attributed to the influence of nature or education.

Today, in the light of scientific contributions too, an integrated model that sees a combination of environmental influences and innate components, seems the most likely hypothesis.

Neurosciences reveal in fact the presence in humans, since birth, of a device unifying neurobiology and the external environment, an integrated circuit that plays a key role in relational processes with the other.

Nature did not make us monads, but people who continually react with others and are able to participate in others' lives (Christopher 2003, Rizzolatti 2006, 2018).

The first ethical experience of the child, obviously lived on an unconscious level, consists in the struggle between dependence on another person (who guarantees nourishment and care) and their aggressive impulses (Jung 1986, Winnicott 2004)

The individual faces the choice between good and evil since the first moment of the encounter with the Other, long before we are told what is "good" and what is "evil" (Bauman 2018).

But in everyday life, how can we establish a relationship with the other that is the expression of an authentically ethical attitude?

Bauman considering that "*... US is not the plural of EGO*", believes that being an ethical person means being the guardian of the other, whether they have the awareness of having duties to the other. "*... My responsibility to the other is unconditional*" regardless of whether the other behaves in a moral way or not.

The ethical capacity therefore does not arise from sharing and adhering to rules, prescriptions or prohibitions, but derives from high and unconditional human values and meanings (Bauman 2018) to conform to universal ethical criteria (Jung 1986).

The ME-YOU relationship is therefore also the primary ethical factor of the human being: we are not born to be selfish, but we have an archetypal basis that makes us altruists.

On a personal and professional level, our authentic ethical attitude in the relationship develops, however, only starting from the overcoming of narcissism, both

individual and collective, a veritable epidemic of current times (Cesareo 2016).

The current narcissistic epidemic manifests itself through a collective attitude of exploiting the Other and the environment for the exclusive fulfilment and immediate gratification of one's desires.

It is an *ideal ego* built on a model of childhood narcissistic omnipotence that prevents the development of an authentic *ideal of the Ego* that integrates the personal physiological narcissistic needs with collective ideals (Chasseguet & Smirgel 1991).

Ethical behaviour also means taking responsibility for the world we live in and for future generations.

In the book of Genesis (4,9) when the Lord asks Cain: "...Where is your brother Abel?", he answers with another question: "Am I my brother's keeper?"

Levinas observes that every immorality began with this angry question asked by Cain, because "... it is certain that I am responsible for my brother; I am a moral being until I ask for a special reason to be so ... my brother's well-being depends on what I do or refrain from doing "(Levinas 2008).

In the Genesis, Cain kills Abel: the rejection of brotherhood and care of the other leads only to the death of the Other.

Where is your brother?

This question is crucial today and must be taken seriously: it is the decisive question that asks us how to place ourselves in relation to the other and the world: do we choose proximity or distance, involvement or indifference?

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Contribution of individual authors:

Sandro Elisei: conception and preparation of the manuscript.

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Chiara Bedetti: revision of the manuscript.

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ANXIETY AND DEPRESSION IN PATIENTS WITH ACUTE LEUKAEMIA TREATED WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION

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SUMMARY

Background: Acute leukemia and hospitalization for hematopoietic stem cell transplantation (HCT) are the great psychological stressors. The aim of this study was to assess anxiety and depression associated with such conditions and their psychophysical predictors before and after HCT.

Subjects and methods: We conducted a longitudinal study using self-descriptive tools. The questionnaires: LOT-R, AIS, Mini-Mac, CECS, RSCL and HADS were filled by 60 patients with acute leukaemia before and after HCT.

Results: Anxiety and depressive symptoms correlated positively with psychological symptom distress. The correlation with depressive symptoms was weak, however, with anxious symptoms was moderate. In both cases, the higher was a level of psychological symptom distress, the higher level of anxiety and depression was observed in patients. The results indicated the weak, positive correlation between onerousness of physical symptoms and a level of anxiety. The greater was the severity of physical symptoms, the higher was the level of anxiety. The negative predictor of anxious symptoms was control of anxiety but it was weakly associated with a lower level of the explained variable. The negative predictor of anxious symptoms was also dispositional optimism whose high level accompanied the lower severity of the explained variable. However, the positive predictor of anxious symptoms was the variable of onerousness of symptoms whose high level accompanied the higher severity of anxious symptoms in the examined group

Conclusion: Patients with acute leukemia who are hospitalized for HCT require detailed monitoring of their psychological distress to introduce the proper psychological and pharmacological interventions that reduce anxiety as well as boost "dispositional optimism" and mechanisms of control.

Key words: hematopoietic stem cell transplantation - anxiety - depression - dispositional optimism

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INTRODUCTION

Hematopoietic stem cell transplantation (HCT) is acknowledged as an invasive but nowadays a front-line conventional therapeutic method in many hematological malignancies. It is associated with distressing physical symptoms resulting from toxicity of the treatment as well as emotional and psychological problems during the transplant (e.g. Pidala et al. 2009, Prieto et al. 2005). Its efficacy in acute leukemia is limited by higher mortality associated with treatment in a case of allogenic hematopoietic transplants or higher risk of relapse in a case of autogenic hematopoietic transplants (e.g. Fife et al. 2010, Gooley et al. 2010). The uncertainty of the therapy outcomes requires new strategies for adaptation and draws attention of clinicians and medical staff members to its psychosocial consequences, mainly assessed in terms of life quality understood as a functional result of illness and its treatment perceived by a patient (e.g. Braamse et al. 2012). According to the American Society for Blood and Marrow Transplantation, one of the most important issues affecting patients treated with HCT is psychological distress (e.g. Majhail et al. 2012). Despite many limitations in conclusions of research studies, transplant clinicians agree with the general opinion

that the highest degree of distress is experienced by patients during hospitalization for HCT (e.g. Pidala et al. 2009, Jacobsen et al. 2002).

Anxiety and depressive disturbances are diagnosed in 5 to more than 40% patients with hematological malignancies (e.g. Mosher et al. 2009). It has been proved in prospective studies of depression in patients treated with HCT that the highest risk of depression occurred just before or shortly after transplantation procedures (e.g. Goetzmann et al. 2006, Prieto et al. 2005, Illescas-Rico et al. 2002). Some studies have indicated that depression and anxiety can become chronic years after the transplantation (e.g. Syrjala et al. 2004, Andrykowski et al. 2005). The deterioration of mental state during and after transplant hospitalization may be a consequence of the fact that patients experience it as „the traumatic event“ leading to the development of psychological distress.

Past research has identified factors such as personal resources, social support and disease-related or transplantation-related complication as the potential predictors of further mental state and life quality (e.g. Braamse et al. 2012).

In this study, we sought to describe whether anxiety and depression affects the course of hematopoietic stem cell transplantation. Second, we investigated whether

mental state may be influenced by the symptoms associated with treatment and the personality predispositions. Third, we tried to assess the personal resources as predictors of anxiety and depression.

SUBJECTS AND METHODS

Study Population

This longitudinal study was performed with approval of the Committee of Bioethics at the Medical School of Silesia in Katowice in Poland. All study participants had acute myeloblastic or lymphoblastic leukemia and underwent bone marrow transplantation. They had to satisfy the following recruitment criteria: consent to participation in the study, age from 18 to 70, absence of hallucinations and delusions, absence of cognitive disturbances, ability to fill self-report questionnaires.

The patients completed the following questionnaires during hospitalization by admission and discharge.

The following self-report questionnaires were used in the study:

- The Acceptance of Illness Scale (AIS) developed by Felton et al. (1984), adapted to the Polish language by Juczyński (2001) is applied to measure the degree of acceptance of illness. It consists of 8 items, that describe negative consequences of undesirable health. A participant assumes his/her attitude to particular 5-degree items, where 1 means “strongly agree” and 5 means “strongly disagree”. The higher a scale results is, the better the patient accepts his/her illness and adapts more suitably to the illness with lower feeling of psychological discomfort. The AIS has satisfactory psychometric properties. The Cronbach’s *alpha* for the Polish version is 0.82.
- The Courtald Emotional Control Scale (CECS) developed by Watson and Greer (1983), adapted to the Polish language by Juczyński (2001) consists of three 7-item subscales, which refer to various ways of anger, depression and anxiety expression. A participant assumes his/her attitude to particular items describing a frequency of use of emotional expression ways, where 1 means “almost never” and 4 means “almost always”. The tool allows to measure rates for the particular subscales as well as the general rate of emotional control, which is a sum of all subscales and reflects the participant’s own opinion about own capacity to control own reactions in a situation, when negative emotions are experienced. The higher result is achieved by the participant, the greater tendency to suppress negative emotions is shown. The Cronbach’s *alpha* coefficients are estimated as: 0.80 for the control of anger, 0.77 for the control of depression, 0.78 for the control of anxiety and 0.87 for the common coefficient of emotional control.
- The Life Orientation Test (LOT-R) developed by Scheier et al. (1994), adapted to the Polish language by Juczyński (2001) assesses generalized optimism.

The questionnaire consists of 10 items and 6 of them refers to generalized optimism. A participant assumes his/her attitude to a particular 5-degree statement. The higher result, the higher level of generalized optimism. The Cronbach’s *alpha* coefficient is estimated as 0.76.

- The Mental Adjustment to Cancer (MAC) developed by Watson et al. (1994), adapted to the Polish language by Juczyński (2001) as (Mini-Mac) is a tool, which allows to measure coping reactions in patients with cancer. The questionnaire consists of 29 items referring to various strategies of coping with cancer. A participant assumes his/her attitude to particular 4-degree statements about currently used coping strategies, where 1 means “definitely no” and 4 means “definitely yes”. The Polish version of the tool allows to measure rates for four coping reactions: “anxious preoccupation”, “fighting spirit”, “helplessness-hopelessness” and “positive redefinition”. The scale “positive redefinition” in the Polish version is an equivalent of the scale “fatalism” in the original version, and the strategy originally called “cognitive avoidance” corresponds the strategy called “fighting spirit” in the Polish version. The higher result is in each scale, the more dominating the particular strategy is. The Cronbach’s *alpha* coefficients are estimated as: 0.92 for the helplessness-hopelessness, 0.90 for the fighting spirit, 0.89 for the anxious preoccupation and 0.87 for the positive redefinition.
- The Rotterdam Symptom Checklist (RSCL) developed by de Haes et al. (2012), adapted by Majkowicz (2000) is a self-report tool to assess the quality of life in patients with cancer. The tool consists of 39 items forming 4 subscales: physical symptom distress (23 items), psychological symptom distress (7 items), activity level (8 items) and overall valuation of life (1 item). A participant assumes his/her attitude to particular 4-degree statements about severity of a particular symptom. The only exclusion is the scale called “overall valuation of life”, which is the 7-degree Likert’s scale. The higher result of physical and psychological symptoms, the worse the patient’s state. However, the high result in the scales called “activity level” and “overall valuation of life” reflects better functioning of a particular patient. The coefficients of inner consistency based on the Polish studies conducted on a group of terminal patients were estimated as: *alpha*=0.86 for physical symptoms, *alpha*=0.83 for psychological symptoms and *alpha*=0.87 for activity.
- The Hospital Anxiety and Depression Scale (HADS) developed by Zigmond and Snaith (1983), adapted by Majkowicz (2000) detects states of anxiety and depression. The questionnaire consists of 7 items for anxiety and 7 items for depression. A participant assumes his/her attitude to particular 4-degree statements about a frequency of negative emotions. The higher result, the greater severity of anxiety or

depression. The questionnaire is a commonly used tool and the result more than 8 points in each subscale means, that the particular patient is in a risk group of the clinical anxiety or depressive disturbances. The inner consistency (Cronbach's *alpha*) measured at the stage of the first treatment is estimated as 0.79 for the scale of anxiety and 0.83 for the scale of depression.

Statistical Analysis

Statistical analyses were performed using STATISTICA version 12.5. Descriptive statistics were summarized for quantitative variables as mean ± standard deviation or for qualitative variables as frequency and percentage.

The questionnaires' results achieved before and after HCT were compared using Wilcoxon test. Correlation between examined variables was accessed using a cofactors' analysis of tau-b Kendall correlation.

A likelihood of depressive decompensation was estimated using an analysis of logistic regression. The fact of depressive symptom intensification in reference to a result achieved in HADS scale before HCT was established as a dependent variable. The coping strategies with illness, acceptance of illness, control of emotions and severity of symptoms after HCT (high results with a lower limit calculated through addition a half of standard deviation to mean value or results below 7th sten) and the presence of objective complications after HCT and the sex (male) were introduced as the predictors.

RESULTS

A total of 63 patients with acute myeloblastic and lymphoblastic leukemia were included. Of those, 60 completed all questionnaires. Average age of this cohort was 39.62±12.80. There were observed complications associated with HCT in 60% patients; mainly inflammatory complications 40% more rarely toxic 11.7%, thrombotic 8.3% or hemorrhagic 6.7% complications. Table 1 illustrates the sociodemographic and medical characteristics of the examined patients.

Table 1. Characteristics of participants in reference to sociodemographic and medical data

Characteristics	N	%
Gender		
Female	34	56.7
Male	26	43.3
Level of education		
Primary	2	3.3
Vocational	17	28.4
Secondary	20	33.3
University	21	35.0
Employment status		
Unemployed	5	8.3
Retired	22	36.7
Student	3	5.0
Physical work	12	20.0
White-collar work	18	30.0
Marital status		
Married	41	68.4
Widowed	2	3.3
Divorced	2	3.3
Single	15	25.0
Having children (yes)	39	65.0
Type of leukemia		
Acute lymphoblastic leukemia	19	31.7
Acute myeloblastic leukemia	41	68.3
Type of transplantation		
Allogeneic	47	78.3
Allogeneic sibling	13	21.7
Risk level		
Intermediate	11	18.3
High	49	81.7
Complications (yes)	36	60.0

The average severity of anxiety at admission to hospital was 6.53 (*SD* 4.08) and at discharge 6.35 (*SD* 4.19). The average severity of depression at admission to hospital was 3.93 (*SD* 3.42) and at discharge 4.07 (*SD* 3.91).

The analysis of line regression was conducted to check whether there were the significant predictors of anxious symptoms among the psychological variables. The predictors were introduced simultaneously to the model. Table 2 shows the results of the analysis.

Table 2. Psychological predictors of anxiety symptoms in patients after hematopoietic stem cell transplantation

Model	Non-standardized coefficients		Standardized coefficients	t	Significance
	B	SE B	Beta		
Constant of regression	4.712	7.532		0.626	0.534
Acceptance of illness	-0.017	0.093	-0.022	-0.179	0.859
Control of anger	0.182	0.115	0.221	1.582	0.120
Control of depression	0.103	0.138	0.114	0.746	0.459
Control of anxiety	-0.242	0.123	-0.319	-1.967	0.040
Dispositional optimism	-0.230	0.125	-0.222	-1.830	0.048
Anxious preoccupation	0.085	0.112	0.092	0.757	0.453
Fighting spirit	-0.257	0.162	-0.185	-1.587	0.119
Helplessness/hopelessness	0.090	0.138	0.072	0.651	0.518
Positive redefinition	0.058	0.176	0.035	0.329	0.743
Onerousness of symptoms	0.182	0.061	0.375	2.987	0.004

Table 3. Onerousness of symptoms experienced by patients after HCT and its association with the severity of depressive symptoms

Onerousness of symptoms (RSCL)	Severity of symptom		Association with severity of depressive symptoms		Association with severity of anxiety symptoms	
	M	SD	tau-b	p	tau-b	p
The physical symptom distress	32.92	6.490	0.180	0.058	0.199	0.033
lack of appetite	1.70	0.830	0.189	0.077	0.107	0.308
tiredness	1.95	0.723	0.225	0.035	0.202	0.054
sore muscle	1.55	0.746	-0.004	0.971	0.064	0.549
lack of energy	1.78	0.715	0.200	0.062	0.110	0.295
low back pain	1.58	0.809	-0.084	0.437	-0.002	0.988
nausea	1.50	0.813	0.167	0.125	0.149	0.163
difficulty sleeping	1.52	0.701	0.232	0.033	0.255	0.017
headaches	1.30	0.530	-0.068	0.540	-0.048	0.658
vomiting	1.22	0.585	-0.036	0.747	0.037	0.732
dizziness	1.15	0.481	0.166	0.137	0.213	0.052
decreased sexual interest	1.65	0.971	0.055	0.603	0.057	0.585
abdominal (stomach) pain	1.35	0.709	0.175	0.112	0.187	0.083
constipation	1.30	0.671	0.036	0.746	0.095	0.380
diarrhea	1.12	0.372	0.127	0.258	-0.004	0.970
acid indigestion	1.23	0.427	0.042	0.711	0.095	0.390
shivering	1.35	0.633	0.086	0.432	0.065	0.544
tingling hands or feet	1.32	0.596	-0.002	0.987	0.061	0.576
difficulty concentrating	1.28	0.585	0.158	0.152	0.181	0.094
sore mouth/pain when swallowing	1.23	0.465	0.163	0.146	0.083	0.450
loss of hair	1.53	0.965	0.126	0.244	0.103	0.331
burning/sore eyes	1.37	0.551	-0.044	0.694	-0.085	0.435
shortness of breath	1.23	0.465	0.147	0.190	0.114	0.301
dry mouth	1.70	0.788	-0.068	0.529	-0.030	0.778
The psychological distress scale	11.53	3.780	0.261	0.007	0.454	<0.001
irritability	1.72	0.715	0.155	0.151	0.291	0.006
worrying	2.03	0.823	0.205	0.055	0.414	<0.001
depressed mood	1.57	0.767	0.309	0.000	0.459	<0.001
nervousness	1.68	0.725	0.137	0.206	0.323	0.002
despairing about the future	1.37	0.610	0.386	0.001	0.477	<0.001
tension	1.58	0.696	0.248	0.023	0.399	<0.001
anxiety	1.58	0.645	0.146	0.184	0.355	0.001

The obtained model of regression seemed to match the data well. It explained 43% variability with regard to anxious symptoms, but the real results with regard to the explained variable differed from the expected one averagely on 3.16 point. There was no autocorrelation of the regressive rests ($d=1,900$) in the model. The regressive rests had the arrangement congruent with the normal one. There was no collinearity of the predictors.

The negative predictor of anxious symptoms was control of anxiety but it was weakly associated with a lower level of the explained variable. The negative predictor of anxious symptoms was also the dispositional optimism whose high level accompanied the lower intensity of the explained variable. However, the positive predictor of anxious symptoms was the variable of the onerousness of symptoms whose high level accompanied the higher intensity of anxious symptoms in the examined group (Table 3).

The results indicated the weak, positive correlation between onerousness of physical symptoms and a level of anxiety. The greater was the intensity of physical symptoms, the higher was the level of anxiety. The analogous tendency of correlation was observed with regard to depressive symptoms, but it was insignificant statistically, although on a border of importance.

Tiredness correlated positively with a level of depression in patients with regard to the physical symptoms. Difficulty sleeping correlated positively with the severity of depression as well as anxiety.

Both groups of the symptoms (depressive and anxious), correlated positively with psychological symptom distress. The correlation with depressive symptoms was weak, however, with anxious symptoms was moderate. In both cases, the higher was a level of psychological symptom distress, the higher level of anxiety and depression was observed in patients.

The specific symptoms (irritation, worrying, nervousness and anxiety) were positively correlated with anxious symptoms. The other symptoms (depressed mood, despairing about the future, tension) were correlated with anxious as well as depressive symptoms, but the association with anxiety was stronger.

DISCUSSION

The statistical analysis used in the study allowed to prove the significant association between anxiety and onerousness of symptoms, especially linked to psychological distress. It was also proven that onerousness of symptoms was a moderate predictor of anxiety. The correlation between depressive symptoms and psychological distress was less significant statistically and associated with a smaller number of symptoms. The results did not allow to estimate a significant association between physical distress and occurrence of anxious and depressive symptoms, what is probably a result of the use of the HADS. The use of the HADS, which does not intentionally assess physical symptoms of depression, allows to avoid physical burdens accompanying such medical treatment as HCT (e.g. Zigmond and Snaith, 1983).

Our results referring to anxiety and depression before and after HCT confirm the similar with other studies prevalence of their symptoms in the group of patients who underwent HCT (e.g. Goetzmann et al. 2006, Prieto et al. 2005, Hjermsstadt et al. 2004, Trask et al. 2002). In contrast to other studies, a decrease of anxiety after HCT was not observed (e.g. Fife et al. 2000, Shirinbakhsh Masule et al. 2014). It may be explained by the severity of physical symptoms merely to a small extent because such an association was only in a case of sleep disturbances. The current prospective longitudinal studies have indicated that the transplant hospitalization is experienced by patients as the traumatic event that can lead to the development of posttraumatic stress disorder (e.g. El-Jawahri et al. 2016). However, such a conclusion requires better identification of the factors that boost psychological distress, e.g. coping strategies and social support (e.g. El-Jawahri et al. 2015).

The negative predictors of anxiety were dispositional optimism and control of anxiety what means that their high results were associated with a later smaller intensification of anxious symptoms (e.g. Coyne et al. 2010, Goetzmann et al. 2008). It might be understood that optimistic attitude and control as an adaptive capacity to rationalize own anxiety were these mechanisms protecting against overwhelming fears, especially before HCT (e.g. Herzberg et al. 2013, Rasmussen et al. 2009, Schou et al. 2004). In practice, it would mean that all therapeutic interventions boosting the protective mechanisms would allow to reduce general psychological distress after HCT.

Several limitations of the study should be taken into account in the analysis. The first one is associated with

the fact that the study was limited only to a period of the transplant hospitalization and there is a lack of further observation of the patients with regard to psychological and physical symptoms and their association with factors occurring in their natural environment. The second limitation is a small number of the patients what decreases representativeness of the population examined in the study.

CONCLUSION

The association of anxiety and to a smaller degree depression with onerousness of symptoms, especially psychological distress, should induce teams of clinicians and medical workers to some interventions. Such interventions should be focused on detailed monitoring of the distress symptoms. In their consequence, all suitable psychological and pharmacological approaches would be introduced to protect the patients against their post-transplantation complications and to improve their post-transplantation adjustment and recovery.

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Contribution of individual authors:

Anna Warchala: design of the study, literature researches and analyses, statistical analyses, interpretation of data, manuscript writing.

Irena Krupka-Matuszczyk: literature researches and analyses, manuscript writing.

Krzysztof Krysta: manuscript writing.

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FAMILY RELATIONSHIPS AND HEALTH LOCUS OF CONTROL AS COVARIABLES IN THE EVOLUTION OF MAJOR DEPRESSIVE DISORDER

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SUMMARY

Background: In a two-year study, we compared the efficacy of noradrenergic and serotonergic antidepressants with and without the addition of 100 mg acetylsalicylic acid (ASA) in subjects suffering from major depressive disorder (MDD). In this article we examine the influence of the health locus of control, family relationships and personality traits on the progress of MDD.

Subjects and methods: 40 people with MDD (MDD group) were randomly assigned to the different treatment groups. They were followed in parallel with a group of 20 'healthy' subjects (HG). At the beginning of the study, sociodemographic data were collected, and patients were asked to complete the Multidimensional Health Locus of Control (MHLC) scale, the NEO Five-Factor Inventory (NEO-FFI), and the Family Adaptation and Cohesion Scale (FACES III). During the study subjects were regularly assessed using the Hamilton Depression Scale (HDS), the Short Form Health Survey (SF-12) and the Clinical Global Impression scale (CGI).

Results: Regardless of the type of treatment, physical health is the best predictor of variation at two years in the MDD group; 45% of variance is explained by a linear regression model that includes three variables from the MHLC, FACES III and NEO-FFI scales. Similarly, 40% of CGI and 24% of HDS variance is predicted. These explanatory variables are statistically less powerful in the MDD group than the HG group.

Conclusion: While drug treatment is a determinant in changes on the HDS, CGI and SF12 scales, factors such as family relationships, MHLC or personality are important covariates of these changes. The question remains whether we can influence these covariates to improve the response to antidepressants.

Key words: depression - MHLC - FACES III - NEO-FFI

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INTRODUCTION

The efficacy of antidepressant medication remains a major research challenge. Despite new generations of antidepressants that have revolutionized treatment administration compared to older tricyclics, it appears that they have not, ultimately, improved responses or remission rates (Zdanowicz et al. 2008). Amitriptyline and clomipramine thus continue to appear as the most effective treatments in meta-analyses, while new drugs such as agomelatine, escitalopram or vortioxetine are emerging (Parikh et al. 2018; Cipriani et al. 2018). At the same time, randomized studies find that, regardless of the antidepressant, 60–70% of patients respond, whereas in 'real life' this rate is only $\pm 30\%$ (Keller et al. 2000). How can we increase the number of responders? It is possible that there are different MDD profiles that are more or less sensitive to a given treatment (Drysdale et al. 2017)? While another strategy consists in adding an NSAID to the antidepressant, results have proven to be very inconsistent. Finally, with respect to long-term effectiveness, knowledge remains very fragmented. At present, we only know that psychotherapy prevents the risk of relapse (Teasdale et al. 2000).

In the past, noradrenergics have sometimes shown to perform better than serotonergics. Therefore, in this context, in 2012 we launched a two-year study to compare a selective serotonin reuptake inhibitor (escitalopram) with a serotonin and norepinephrine reuptake

inhibitor (duloxetine); both with and without 100 mg acetylsalicylic acid (ASA). We published the first results in 2017 (Zdanowicz et al. 2017). These findings showed that when ASA was combined with duloxetine, there was a more rapid improvement in the Hamilton Depression Scale (HDS) score as early as two months ($t=-3.114$, $p=0.01$), in the Clinical Global Impression scale (CGI) score at five months ($t=-2.119$, $p=0.05$), and a better remission rate ($\chi^2=6.296$, $p=0.012$) than the escitalopram + placebo subgroup. Our results also showed that the brain-derived neurotrophic factor can be a response indicator. Furthermore, our study investigated other areas that could explain the evolution of MDD, such as the therapeutic alliance, and physical and mental health. While throughout the study physical health was found to be correlated with HDS ($r=-0.519^{**}$) and CGI ($r=-0.536^{**}$) scores, the link was only indirect, (Zdanowicz et al. 2018) ($r=0.530^{**}$).

In this article we look in more detail at the influence of three psychological dimensions: 1) health locus of control; 2) family relationships; and 3) personality.

- 1) Health locus of control was defined by Walston at the end of the 1970s (Walston et al. 1978) and has not only proved to be a determining factor in the response to antidepressants in randomized studies (Reynaert et al. 1995), but also an indicator of the risk of depression (Zdanowicz et al. 2016).
- 2) In the same vein, the links between family dynamics and depression have been the subject of numerous

studies. We know that disagreements within couples (Whisman et al. 1999, 2012) and family conflicts (Campbell & Thomas 1986, Stark et al. 2012, Widmer & Reuben 1991) also directly impact the development, course, and severity of MDD. In earlier work (Zdanowicz et al. 2016) we showed that there was a correlation between intensity of depression and the functioning of the family of origin.

- 3) Finally, during a prospective, two-year study of a healthy sample, certain personality traits, such as conscientiousness (see below), were found to be predictive of mental health status (Zdanowicz et al. 2012).

SUBJECTS AND METHODS

Subjects

We carried out a randomized, open-label study from June 1st 2012 on the first 40 inpatients meeting inclusion criteria. Patients were followed up for two years. Inclusion criteria for the MDD group were as follows:

The patient must meet DSM-IV-R criteria for a major depressive episode:

- It must be the patient's first or second depressive episode;
- No symptoms of depression during the preceding two years;
- No history of other psychiatric disorders on Axis I of the DSM-IV-R;
- No history of gastritis, or gastric or esophageal ulcers;
- Aged between 18 and 63 years;
- At the beginning of the study the patient must be free of any other medical condition.

Patients taking depressogenic drugs (e.g. beta blockers, morphine derivatives) were excluded, and no formal psychotherapy took place during the study.

Volunteer screening was conducted, and written consent was validated by the local ethics committee (under agreement number B03920072846). Patients were then randomized into one of the four study groups. In total, 40 patients completed the study. The antidepressant + placebo group (n=20) comprised a duloxetine (D) + placebo (DP) subgroup (n=11), and an escitalopram (E) + placebo (EP) subgroup (n=9); the antidepressant + ASA group (n = 20) comprised a duloxetine + ASA (DASA) subgroup (n=8) and an escitalopram + ASA (EASA) subgroup (n=12).

In parallel, we formed a second group of 20 'healthy' subjects. Twenty Caucasians were selected at random from the telephone directory and enlisted following written agreement and signed consent. Subjects who had been diagnosed with any psychiatric disorder on Axis I of the DSM IV or who suffered from any physical pathology (unless it was chronic and stable) were excluded. Results regarding changes in this healthy group have already been published (Zdanowicz et al. 2011, 2012).

Methods

No further medication was administered to patients in the MDD group who were in remission (disappearance of all of diagnostic criteria for a major depressive episode) at six months, but follow-up continued until the end of the study. For patients who left, the last score obtained was recorded for the remaining assessments (the Last Observation Carried Forward method).

The protocol outlined below was applied to all members of both groups:

At time 0, the following assessments were carried out:

- The Mini-International Neuropsychiatric Interview: to exclude any past or present psychiatric pathology.
- Sociodemographic data: age; gender; number of people in the household; and socioeconomic status, evaluated by approximate net income per month (€; <1000, 1000–2000, 2000–3000, 3000–4000, >4000).
- Olson's questionnaire (Family Adaptation and Cohesion Scale FACES III (Olson 1986)): to investigate family dynamics. This model evaluates two dimensions of the functioning of a relational system: cohesion and adaptability. Cohesion is defined as "the emotional ties that every member develops with regard to the others". Adaptability is "the ability of the system to change its power structure, its roles and rules in response to stressful situations".
- Wallston's MHLC scale (Multidimensional Health Locus of Control) (Wallston et al.1978). This model explores how people relate to their own health. While certain individuals think they can act to avoid or fight disease (an internal 'health locus of control'), others attribute the causes of their health to destiny, or the influence of 'others' (members of the family or health professionals). The MHLC distinguishes three sub-scales: Internality (IHLC, Internal Health Locus of Control), Powerful Others (PHLC, Powerful others Health Locus of Control), and Chance (CHLC, Chance Health Locus of Control).
- Personality was measured according to the NEO-FFI typology (Costa 1992). This instrument explores five dimensions of personality: neuroticism, extraversion, openness, agreeableness, and conscientiousness. Neuroticism refers to emotional stability and adaptability. The more present this dimension, the more the subject feels negative affect such as fear, sadness, anger, guilt, disgust, and embarrassment. Extroverts are sociable, although gregariousness is only one facet of extraversion. Extrovert people prefer large groups, are active, energetic, verbose, and optimistic. Open participants are curious about everything that originates in their internal and external universe, and their life is rich in experiences. They typically conceive new ideas, adopt unconventional values, and experience intense positive and negative emotions. Participants who have low scores on the openness dimension tend to be conservative and conventional in their opinions and behaviors. People

who score high on agreeableness are altruistic, likable, helpful, and think they are likely to get help in return. Conversely, people who score low are ego-centric, suspicious of others' intentions, and are more likely to compete than cooperate. Conscientiousness refers to the capacity to manage one's desires. This capacity for self-control supports active planning, organizing, and carrying out tasks. A positive score is associated with academic and professional success. A negative score is correlated with exaggerated and painful requirements, a compulsive need for order and cleanliness, and work overload.

Patients were assessed with the 17-item Hamilton depression scale (HDS) at 0, 0.5, 1, 1.5, 2, 3, 6, 12, 18, and 24 months. The clinical global impression (CGI) scale was completed at each visit. Physical health (physical functioning, physical daily life functioning, physical pain, and general health), and mental health (vitality, social functioning, daily mental life functioning, and mental health) were evaluated with the Short Form Healthy Survey (SF-12) (Ware et al. 1996) were recorded at 0, 6, 12, 18, and 24 months.

Parametric statistical analysis was carried out using SPSS 25, taking Type 1 and 2 errors into account. No post hoc tests were carried out. A Pearson correlation analysis was carried out to identify potential covariates. Where necessary, linear regressions were run. Qualitative variables were compared with the Chi-squared test, and means were compared using Student's t-test. Significance levels were set at $p > 0.95$ and $p < 0.05$. Data are presented as mean \pm standard deviation.

RESULTS

Patient demographics

The MDD group contained significantly more women than the HG (33♀/7♂ versus 9♀/12♂ $\chi^2=10.091$ $p=0.001$). The age difference between the two groups was not significant. Subjects in the MDD group had

significantly fewer relatives living at home (2.73 versus 4.05; $t=3.209$; $p=0.003$). Per-head income was almost double in the MDD group compared to the HG, and around the national average of 1400 euro/ person.

Predictability of HDS in the MDD group

Table 1 shows that the CHLC and I/E ratio of the MHLC are correlated at almost all times with the change in depression intensity measured by the HDS.

Table 1. HDS – MHLC correlations

	CHLC	IE Ratio
HDS 0	0.429**	0.432**
HDS 0.5	0.592**	0.583**
HDS 1	0.638**	0.642**
HDS 1.5	0.437**	0.434**
HDS 2	0.572**	0.563**
HDS 3	0.498**	0.483**
HDS 6	0.535**	0.527**
HDS12	0.543**	0.537**
HDS18	0.533**	0.526**
HDS 24	0.529**	0.521**

*** (Bilateral) correlation is significant at the 0.001 level;

** (Bilateral) correlation is significant at the 0.01 level;

* (Bilateral) correlation is significant at the 0.05 level

There is also a link between HDS and extroversion at one month ($r=-0.421^*$) and with adaptability of the family of origin at one year ($r=0.407^{**}$).

If we introduce these three explanatory variables into a linear regression (Table 2), 27.7% of the change in HDS at two years can be predicted.

Predictability of the CGI in the MDD group

As with the HDS, the I/E ratio and the CHLC dimension of the MHLC are correlated at virtually all times with change in the CGI (Table 3).

Table 2. Linear Regressions

	Variable	Std Error	F or t	Adjusted R ² or standardized β
HDS	Total Model	6.714	7.283	0.239***
	IE ratio	0.177	2.658	0.311**
	Externality	0.137	-2.691	-0.330**
	FoAda	0.155	-0.428	-0.052
CGI	Total Model	1.185	6.963	0.408**
	IE ratio	0.046	3.958	0.628**
	FnCo	0.020	2.844	0.479*
	Open	0.062	0.739	0.468
PH24	Total Model	9.386	6.331	0.451**
	FnCo	0.173	-1.302	-0.230
	FoCo	0.206	-1.234	-0.208
	Cons	0.212	-1.114	-0.173
	IHLC	0.542	3.180	0.489**

*** (Bilateral) correlation is significant at the 0.001 level; ** (Bilateral) correlation is significant at the 0.01 level;

* (Bilateral) correlation is significant at the 0.05 level

Table 3. CGI – MHLC correlations

	CHLC	IE Ratio
CGI 0	0.100	0.120
CGI 0.5	0.327*	0.330*
CGI 1	0.517**	0.500**
CGI1.5	0.407**	0.421**
CGI 2	0.522**	0.539**
CGI 3	0.557**	0.593**
CGI 6	0.409**	0.417**
CGI 12	0.385*	0.398*
CGI 18	0.385*	0.398*
CGI 24	0.386*	0.399*

*** (Bilateral) correlation is significant at the 0.001 level;

** (Bilateral) correlation is significant at the 0.01 level;

* (Bilateral) correlation is significant at the 0.05 level

The CGI can also be predicted from the openness of the patient at five months ($r=0.330^*$), six months ($r=0.345^*$) and 24 months ($r=0.315^*$), and from the cohesion of the nuclear family, which is correlated at 12 months ($r=0.386^*$) and 18 months ($r=0.386^*$). If we run a linear regression on these three explanatory variables, 40% of the change in CGI at two years can be predicted (see Table 2).

Predictability of the SF12 in the MDD group

While mental health at two years can be predicted based on the cohesion of the ideal couple ($r(6\text{ months})=-5.23^{**}$; $r(12\text{ months})=-0.421^{**}$; $r(18\text{ months})=-0.412^{**}$; $r(24\text{ months})=-0.410^*$), we are mainly interested in the predictability of physical health (PH) – for two reasons. On the one hand, we know that there is a correlation with HDS and CGI scores (see introduction) and, on the other hand, our earlier work looked at the change in PH over two years in the healthy group (Zdanowicz et al. 2011). If we compare HG and MDD groups at time 0, the PH of MDD subjects is, unsurprisingly, poorer than the HG (PH: 36.74/51.14, $t=6.353$, $p\ 0.000$). What is interesting, however, is that after two years of remission, although members of the MDD group describe themselves as improved (36.74→39.09, $t=-2.032$, $p=0.049$), their PH scores remain lower than those of the healthy group (39.09→52.39, $t=4.659$, $p\ 0.000$) (Table 4).

Comparison of explanatory variables between HG and MDD groups

A comparison of means for the two groups suggests that IHLC levels ($\Delta=3.91$; $IC=1.624$; $t=3.419$; $p\ 0.000$), cohesion in the family of origin ($\Delta=6.78$; $IC=2.889$; $t=3.419$; $p=0.005$), cohesion in the nuclear family ($\Delta=7.1$; $CI=1.654$; $t=2.651$; $p<0.012$), adaptability in the family of origin ($\Delta=4.54$; $IC=1.526$; $t=3.238$; $p<0.002$), and extroversion ($\Delta=6.75$; $IC=3.747$; $t=4.504$; $p\ 0.000$) are lower in patients with MDD.

Table 4. Physical Health (PH) correlations

	foCo	fnCo	Consc	IHLC
PH0	-0.367*	-0.330	-0.197	0.182
PH6	-0.381*	-0.565**	-0.197	0.502**
PH12	-0.399*	-0.601**	-0.322*	0.329*
PH18	-0.380*	-0.602**	-0.327*	0.250
PH24	-0.390*	-0.520**	-0.362*	0.296

*** (Bilateral) correlation is significant at the 0.001 level;

** (Bilateral) correlation is significant at the 0.01 level;

* (Bilateral) correlation is significant at the 0.05 level

foCo: cohesion of the family of origin; fnCo: cohesion

of the nuclear family; Cons: conscientiousness;

IHLC: Internal Health Locus of Control

DISCUSSION

The first point to note is the small sample size, which greatly limits the generalizability of our conclusions. Nevertheless, three points seem important to highlight.

First, we are impressed by the percentage of variance explained in linear regressions. Two groups of variables can be distinguished: on the one hand, HDS scores (20%) and, on the other hand, CGI and PH scores (40%). The HDS is a more specific scale than the CGI (which is inherently more global), and the SF12, especially if only the physical health dimension is considered. It seems to us that the more specific the scale is, the more we should be able to explain a significant part of the variance and, conversely, the less specific the scale is, the more the explanatory effect becomes diluted. It appears that MDD is much more of a global and physical ‘disease’ than the simple mood dimension (investigated via the HDS) would suggest.

Second, among the explanatory factors, we believe that the ‘personality’ dimension should not be retained because correlations with traits vary according to the variable studied (HDS, CGI or PH). On the other hand, the Internality dimension of the MHLC is constant, whether measured directly in the IHLC or indirectly in the Internality/ Externality ratio. Similarly, the family, whether nuclear or of origin and especially the cohesion dimension – which is a measure of emotional distance – is also constant.

Third, while we already knew from previous studies, that low Internality or weakly cohesive families are additional risks factors for MDD, we see here that these factors are also dynamic prognostic factors. These factors could therefore not only be used to predict the response of patients, but could also become part of the therapeutic arsenal. Increased cohesiveness and internality could be additional therapeutic weapons.

CONCLUSION

While drug treatment is determinant in changes in HDS, CGI and SF12 scores, factors such as family relationships, MHLC or personality are important covariates. The question that remains is whether we can influence these covariates to improve the antidepressant response.

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Nicolas Zdanowicz, Christine Reynaert, Denis Jaques, Brice Lepiece & Thomas Dubois all made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data.

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USING EXPERTS BY PERSONAL AND PROFESSIONAL EXPERIENCE (EPPE) TO INCREASE INTEREST IN PSYCHIATRY AS A CAREER AT SIXTH-FORM LEVEL

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SUMMARY

Background: Psychiatrists play a multifaceted and critical role in improving the lives of people with mental illness. However, despite how rewarding, important and thrilling a career in mental health is, there continues to remain a shortage of psychiatrists in Low-, Middle- and High-Income Countries. There has been resurgence in interest in improving the image of psychiatry over recent years and several initiatives have been launched to increase recruitment into the specialty at Sixth Form level in the UK.

Design: We conducted a single-arm, pre-post, comparison study with Sixth Form students at an inner-city school in London. Students were invited to complete a survey before and after exposure to an assembly on mental health that was delivered by an Expert by Personal and Professional Experience (EPPE). Our aims were to detect and measure if there were any changes in perceptions of psychiatry and if there was an increase in interest in pursuing this profession as a career in this group.

Results: 63 out of 123 participants completed the before and after survey (51% response rate). Following exposure to the assembly, there were statistically significant improvements between the pre- and post- intervention means for, "Psychiatry has a positive impact on peoples' lives" (p value <0.0001), "People with mental illness can achieve success and be the best at what they do" (p value <0.0001) and, "I would consider psychiatry as a career" (p value <0.0001).

Conclusion: Notwithstanding the limitations of this pilot study, our findings suggest that an assembly on mental health delivered by an EPPE (i.e. 'Wounded Healer') might be effective at increasing interest in psychiatry as a career at Sixth Form level. We suggest that assemblies on mental health and psychiatry be delivered by 'Wounded Healers' in schools and colleges nationwide to help drive recruitment into psychiatry.

Key words: psychiatry – recruitment – experts by personal and professional experience – Sixth Form students

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The Scale of Global Mental Illness

The World Health Organisation (WHO) defines health as, "A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO 2014, P.1). With an ageing population through a period of great epidemiological transition, the emphasis is now on non-communicable diseases (Vigo et al. 2016). It is estimated that mental health disorders account for 14% of the global burden of disease (WHO 2011) (both DALYS and YLD combined), with depression predicted to be the leading cause of disease globally by 2030 (Scheffler et al. 2011). As a consequence, this leads to direct adverse economic losses through consumption of mental health services, but also indirect losses through social inefficiency (WHO 2011).

Whilst policy makers and international organisations have attempted to recognise the scale of the issue, as demonstrated by the addition of mental health in the sustainable development goals (target 3.4 and 3.5) (WHO 2019), there still continues to be significant numbers of untreated mental health disorders globally. Over the years this can be attributed to: the disparate focus between physical and mental health, in part due to the persistent stigma and marginalisation of those suffering with mental disorders (Vigo et al. 2016); governmental budgets; lack of education; accessibility; affordability and scarcity of resources (Scheffler et al. 2011, Luitel et al. 2017). One fundamental element hindering the failure to progress is the severe global shortages of the human workforce.

A Recurring Issue: The Global Shortage of Psychiatrists

The human workforce provides the backbone for an effective mental healthcare service able to treat the global population (Vigo et al. 2016). Psychiatrists in particular have a multifaceted and critical role in improving health outcomes. They act on the front line as clinicians directly treating patients, but also participate in education, research, public health and policy and advocacy (WHO 2017).

Despite the growing burden of mental disorders and the need for a fully trained, well-equipped workforce, there remains a pervasive gap between need and supply (Vigo et al. 2016). The 2017 report as part of WHO's Mental Health Atlas project demonstrates this gap to be greatest in low-income countries, with the median number of mental health workers per 100,000 of the population to be below 2; compared to above 70 in high-income countries. Of the workforce the numbers of trained psychiatrists suffer further shortages with less than 0.1 in low-income countries, compared to 11.9 per 100,000 in high-income countries. For subspecialties like child psychiatry, the numbers are inadequate with approximately 0.1 psychiatrists per 100,000 across all regions, except for high-income countries with 1.19 per 100,000. By observing trends using Project Atlas's datasets from 2011 to 2017 it is clear that the number of psychiatrists globally is at a critical shortage with approximately one physician per 100,000 (WHO 2017).

The Challenges of Recruiting into Psychiatry

Recruitment into psychiatry represents a global concern acknowledged by the World Psychiatric Association (WPA) that further drives shortages (Brown & Ryland 2019, Shields et al. 2017). An important element prominent in the literature that affects the numbers entering into the field is medical students' perceptions of psychiatry and the factors that influence this (Brown & Ryland 2019, Shields et al. 2017, Nortje et al. 2013, Goldacre et al. 2013).

A prospective cohort study conducted by Goldacre et al. examined responses on psychiatry as a future career from all UK medical schools, using questionnaires across 12 sets of new doctors between 1974 and 2009. They found that between the first- and fifth-year post qualification, only 4-5% of doctors expressed a desire to pursue psychiatry. This value remained constant between 1974 and 2009. These figures were similar to other developed nations such as the USA and Australia (Goldacre et al. 2013, Davies 2013).

However, since 2009 Health Education England reported its highest number of new core trainees in 2018 (386 doctors). Such an increase could be attributed to campaigns such as "Choose Psychiatry" in 2017 which gathered much media coverage (Rimmer 2018). This illustrates Sartorius et al. point that the negative repre-

sentation of psychiatrists in the media plays an important role in numbers (Sartorius et al. 2010).

Malhi et al. conducted a study among 580 second year medical students at the University of New South Wales in Australia, to investigate the desirable and least desirable traits of psychiatry as a potential career. The results showed only a 15% strong likelihood of choosing psychiatry. Factors that informed their decision were lack of prestige, psychiatry being classed as "unscientific," and low therapeutic success rates (Malhi et al. 2011). Other studies have echoed similar perceptions in addition to stigma, poor remuneration and public image (Gadit 2008, Shields et al. 2017), suggesting the deeply ingrained poor image of psychiatry impedes attempts to bolster numbers.

A study by Nortje et al. highlighted that recruitment in low and lower-middle income countries (LLMIC) is even more of a concern. An understaffed workforce has less time to dedicate to educating and instilling enthusiasm in their young counterparts. Without appropriate supervision, students are more likely to apply their own cultural beliefs and stigmatised views on mental health (Nortje et al. 2013). In low-income countries, the focus still remains on large inpatient hospitals so students are exposed to poorer working conditions, chronic refractory disease, overcrowding, uncivilised ways of detainment, and medicines shortage (Brown & Ryland 2019).

The Migration of Psychiatrists

The shortage of psychiatrists in low-middle income countries (LMIC) is further exacerbated by the migration of physicians to more developed nations, from urban to rural areas and from public to private sectors (Patel 2009). Undoubtedly, this "brain drain" curbs recruitment shortages in recipient countries like the USA, UK, Canada and Australia, but precludes efforts to scale up mental health services in developing countries (Mullan 2005).

Factors that incentivize this transition include better financial rewards, more educational opportunities and an established structure to recognize higher specialty qualifications and professional development. In addition, political volatility, lack of funding and poor working environment in donor countries further drives this movement (Gadit 2008).

In the UK the international fellowship scheme of 2003 aimed to recruit international medical graduates (IMGs) to improve service provision. Of 202 posts, 124 were filled by psychiatrists (Goldberg 2004). In Pakistan and India, whose doctors constitute a large proportion of IMGs in places like the UK, their already strained resources cannot be expected to progress with this kind of migratory movement (Khan 2004). On the contrary it can be argued, that to stop free movement of workers is unethical and against human rights (Gadit 2008). Gadit (2008) proposes that in recruiting inter-

national medical graduates, developed nations could offer financial rewards to recompense low income countries for the loss of their physicians. Such financial gains could contribute to further education and services in donor countries. This would be in line with the Commonwealth code of practice (Gadit 2008).

Stimulating Student Interest in Psychiatry

The significant shortage of psychiatrists (Choudry & Farooq 2017) relative to other specialties has catapulted a movement to propagate academic interest in psychiatry through focused initiatives aimed at relevant target populations. A plethora of initiatives have been launched in recent years to stimulate interest in psychiatry at two important target population levels: students and graduates, all with the unified aim to improve attitudes, increase interest and recruitment into the field of psychiatry, and to help address the ever-increasing shortage of trainees.

Schemes targeted at increasing medical students' interest in psychiatry have been in the form of clinical placements, teaching styles and unique enrichment activities outside the traditional scope of academic and clinical medicine. Many of the initiatives undertaken to increase medical students' interest in psychiatry have centered around the hypothesis that with more exposure to psychiatry in an experiential learning context, interest in psychiatry will undoubtedly increase. The theory of experiential learning, developed by Kolb (1984), stipulates that with active participation and post-experience reflection, learning becomes most effective. Exposure to psychiatry through clinical placements in the specialty forms the experiential learning which drives medical students' engagement in the field of psychiatry.

Importantly, the literature demonstrates that with more clinical experiences and placement in psychiatry during medical school training, a pronounced positive attitudinal shift is observed in medical students' attitudes towards the specialty. Lyons and Janca (2015) found that an 8-week psychiatry clerkship undertaken by Year 4 medical students significantly increased students 'definitely considering' psychiatry (10.5% at follow up vs 4.6% baseline). This correlates with findings from Lampe et al. (2010) who demonstrated an attitudinal and career interest improvement following an 8-week clinical attachment in psychiatry in medical students at Sydney Medical School. Similar findings were demonstrated by Khajeddin et al. (2012) who showed a significant improvement in students' attitudes towards the specialty, albeit no significant change in intentions to career pursuit, at Ahwaz Jondishapour University who undertook a month-long psychiatric attachment. Further to this, Malloy et al. (2008) showed that interest in psychiatry increased following inpatient Child and Adolescent Psychiatry experience in third-year clerkship, emphasizing the significance of the link between hospital experience and interest. Adekunte et al. (2016)

showed that a 4-week psychiatry placement positively impacted students' attitudes towards psychiatry with an increase in psychiatry interest as one of their preferred career choices increasing from 7% to 20%, with corresponding results reported by Xavier et al. (2010).

Innovating and Enriching Experiences

Unique enrichment activities encompassing psychiatry student selected modules, academic research, and psychiatry clubs undertaken in medical schools, have allowed medical students to experience the specialty in environments unconfined by traditional teaching methods. Such schemes depict the specialty in a unique light and engage students in a more creative way to propel their interest in the field. The launch of the Psychiatry Summer School in 2009 by the Institute of Psychiatry, Psychology and Neuroscience and the Royal College of Psychiatrists at King's College London depicts a hallmark example of a scheme aimed at propelling existing seeds of interest in psychiatry in medical students. The efficacy of summer schools in influencing a significant positive change in attitudes towards the specialty ($p < 0.001$) in medical students has also been demonstrated by Beattie et al. (2013).

Weintraub et al. (1999) showed that medical students who participated in an enriched psychiatry program at the University of Maryland were significantly more likely to choose it as a career compared with their 'regular' psychiatry curriculum counterparts. Interestingly, more abstract clinical experiences can change medical students' outlook on psychiatry. Mortlock et al. (2017) demonstrated how a one-day visit to a high secure forensic psychiatric unit can positively influence medical students' attitudes towards Psychiatry (207/277, 74.7%).

The use of alternative, more innovative teaching approaches has also been trialed as a method of delivering psychiatry teaching in a format that students can enjoy. One such teaching method of using role play based learning (RBL) was trialed at the University of Melbourne with qualitative data responses from students being overwhelmingly positive showing improvements in their engagement and confidence in their learning (King et al. 2014). Similarly, Pullen et al. (2013) have shown that a video-teleconferencing lecture series created for medical students with the aim of improving their exposure to child and adolescent psychiatry had a positive influence on 48% students in their views towards psychiatry. One-off bespoke events targeted at increasing medical students' interest in psychiatry have demonstrated a positive shift in attitude towards psychiatry. Robertson et al. (2009) recorded 123 medical students' perceptions towards psychiatry before and after viewing a 15-minute DVD on psychiatry showing significant increases in students considering this medical specialty. Vasudevan et al. (2015) trialed a similar promotional film intervention among Malaysian medical students

with results showing a positive, albeit modest improvement in perceptions. Similar findings were reported by Ahmed et al. (2015) on Medfest, the national medical film festival which also demonstrated positive attitude shifts towards Psychiatry. Agyapong and McLoughlin (2014) discuss the use of a public-speaking competition to increase interest in psychiatry of Ghanaian medical students showing that 78 % of the 37 medical students were more engaged in psychiatry after participating in the competition.

Engaging Junior Doctors

The significant workforce shortage in Psychiatry has been recognized at a nationwide level in the UK and has prompted the launch of the 'Choose Psychiatry' campaign by the Royal College of Psychiatrists in 2017, which has demonstrated the use of social media in dispelling stigma and increasing awareness around the tangible impact psychiatrists have on patients suffering with mental health. The focus of the six-week media campaign centered around creating motivation for trainees and students alike in psychiatry. Further to this, the Expansion of the Foundation Programme report (Perry et al. 2016) has broadened the post- graduation psychiatry foundation placements with the forecast of engaging more junior doctors in psychiatry. As shown by Kelley et al. (2013), a foundation programme psychiatry placement has a positive effect on recruitment with 14.9% of trainees pursuing a career in the specialty post-placement, compared with 1.8% who did not have any psychiatry exposure.

Experts by Personal and Professional Experience (EPPE)

The Canadian Psychiatric Association reported that conventional education alone will not reduce stigmatizing attitudes (towards those with mental illness and psychiatry) in medical students (Stuart et al. 2014). AH pioneered, 'The Wounded Healer', an innovative method of pedagogy that blends the performing arts with psychiatry. The main aims of the Wounded Healer are to engage, entertain and to educate to challenge mental health related stigma, debunk myths about mental illness and encourage care seeking (Hankir et al. 2014). The Wounded Healer harnesses the power of story telling and traces AH's remarkable recovery journey from when he was a hopeless and impoverished 'service user' to receiving the 2013 Royal College of Psychiatrists Foundation Doctor of the Year Award and the 2018 Royal College of Psychiatrists Core Psychiatric Trainee of the Year Award (the RCPsych awards mark the highest level of achievement in psychiatry in the UK (Hankir et al. 2013). Hitherto, the Wounded Healer has been delivered to over 75,000 people in 15 countries in five continents worldwide. The Wounded Healer has also been inte-

grated into the medical school curriculum of 4 UK universities and it has featured in the 2014, 2017 and 2018 Royal College of Psychiatrists National Medical Student Conference in Liverpool, Leeds and Cardiff Universities respectively. Audiences report that the Wounded Healer is 'inspirational' and 'the best lecture they have ever attended'. The written feedback below from a delegate who attended the 2014 RCPsych National Medical Student Conference in Liverpool illustrates that the Wounded Healer positively influences students' perceptions of psychiatry:

'Unbelievable. This guy had charisma in spades. It was so reassuring to know that a doctor with mental health issues can overcome them and be so successful. Quite possibly the poster boy for my future career choice' (Zaman et al. 2018)

STUDY DESIGN

We conducted a single-arm, pre- post- comparison study on Sixth Formers who attended an assembly on mental health delivered by an EPPE at an inner-city school in London. The aims were to improve the image of psychiatry and increase interest in pursuing this specialty as a career. We designed a survey (see below) and administered it on participants before and after exposure to the assembly on mental health event. Informed consent was obtained from all participants, parents and the school.

Measures

The survey aimed to detect and measure any changes in the views towards psychiatry in the participants before and after exposure to the event and if there was an increase in interest in pursuing this medical specialty as a career. Responses to statements 1 to 5 were on a five-point Likert scale:

- Strongly Agree (5)
- Agree (4)
- Neutral (3)
- Disagree (2)
- Strongly Disagree (1)

The responses for question 6 were inversely scored. The statements were as follows:

1. "Psychiatry is interesting".
2. "Psychiatry has a positive impact on peoples' lives."
3. "People with mental illness can achieve success and be the best at what they do."
4. "I would talk positively about psychiatry to other people."
5. "I would consider psychiatry as a career."
6. "Seeking help for Mental Health problems is a sign of weakness."

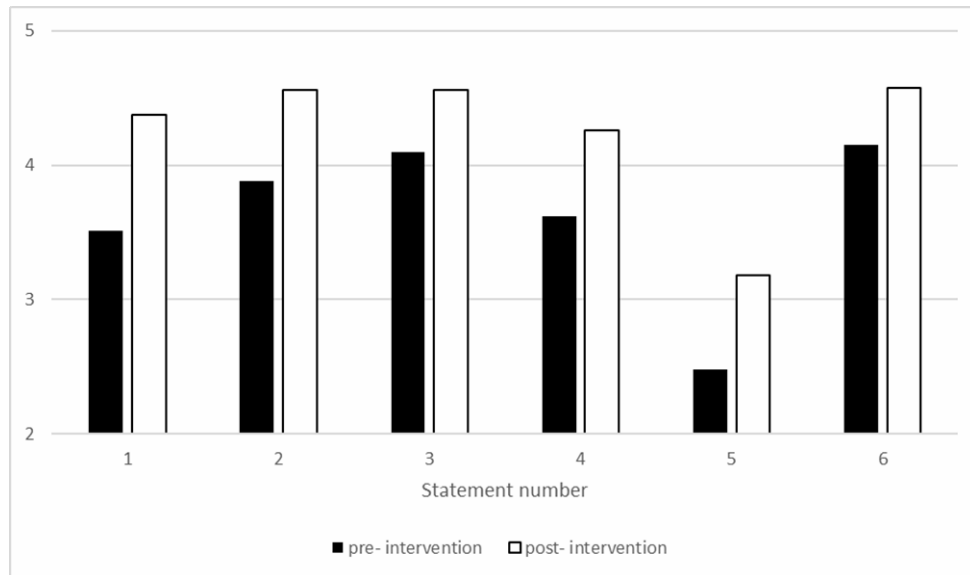


Figure 1. Pre- and post-intervention means for statements before and after exposure to an assembly on mental health delivered by an Expert by Personal and Professional Experience (n=63)

Statistical Analysis

Descriptive and inferential statistics were carried out on the data obtained. Paired, t-tests were computed to compare the participants' responses to statements before and after exposure to the event. Results were considered statistically significant at $p < 0.05$ with a confidence interval of 95%.

RESULTS

For statement 1, "*Psychiatry is interesting*" there was a statistically significant improvement between the pre- (3.5) and post-intervention (4.4) means (P value < 0.0001) (see figure 1).

For statement 2, "*Psychiatry has a positive impact on peoples' lives*" there was a statistically significant improvement between the pre- (3.9) and post-intervention (4.6) means (P value < 0.0001) (see figure 1).

For statement 3, "*People with mental illness can achieve success and be the best at what they do*" there was a statistically significant improvement between the pre- (4.1) and post-intervention (4.6) means (P value < 0.0001) (see figure 1).

For statement 4, "*I would talk positively about psychiatry to other people*" there was a statistically significant improvement between the pre- (3.6) and post-intervention (4.3) means (P value < 0.0001) (see figure 1).

For statement 5, "*I would consider psychiatry as a career*" there was a statistically significant improvement between the pre- (2.5) and post-intervention (3.2) means (P value < 0.0001) (see figure 1).

For statement 6, "*Seeking help for mental health problems is a sign of weakness*" there was a statistically significant improvement between the pre- (4.1) and post-intervention means (P value = 0.0111) (see figure 1).

DISCUSSION

To the best of our knowledge, this is the first study published in the literature to date that reports on the effectiveness of an Expert by Personal and Professional Experience increasing interest in psychiatry as a career in Sixth Form Students. Our findings show that the brief intervention was highly impactful; there were statistically significant improvements in the means in all six statements following exposure to an assembly on mental health delivered by an EPPE. Perhaps the most encouraging finding was the statistically significant improvement in statement 5, "I would consider psychiatry as a career" since this was the main aim of the study.

There were several limitations to our study. There was a small sample size, lack of follow up and the absence of a control group. Moreover, the survey that was administered on participants was not validated. Due to these limitations, our results are not representative, nor are they generalizable. Nonetheless, our findings are promising and provide provisional support that talks on psychiatry and mental health delivered by an EPPE are associated with increased interest in psychiatry as a career in Sixth-Form students.

CONCLUSION

As discussed above, despite the launching of numerous initiatives, psychiatry continues to remain under-subscribed. The 'recruitment crisis' in psychiatry contributes to the global burden that mental illness places on those who live with these conditions, their families and broader society. Notwithstanding this fact, we believe that there are innovative and exciting ways in which we can stimulate interest in psychiatry in students (at Sixth Form and medical school levels) and junior doctors so that we can increase recruitment into the

profession and ultimately attempt to narrow the pervasive treatment gap for those living with mental, neurological and substance use disorders in Low-, Middle- and High-Income Countries. We believe that the design, development and delivery of talks and assemblies by EPPEs will help stimulate interest in psychiatry at all levels and increase recruitment into the profession. More research in this area is urgently needed.

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Contribution of individual authors:

Ahmed Hankir, Frederick R. Carrick & Rashid Zaman conceived the idea for the study and contributed to the literature review and revised the manuscript.

Jahangir Mahmood & Sabah Ali contributed to the literature review and revised the manuscript.

Nour Houbby collected and analysed the data and contributed to the literature review and revised the manuscript.

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PERSONALITY DISORDERS IN BLACK PEOPLE: LESS PREVALENT OR THE RESULT OF HEALTHCARE INEQUALITIES?

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SUMMARY

The prevalence of personality disorders (PDs) in black people has consistently been reported as significantly lower than in their white equivalents. If this result is accurate, then it may reveal important clues as to the aetiology of personality disorders, which could provide invaluable insights as to how we should support these patients. However, if this result does not reflect the truth, then important questions must be answered as to why black people with personality disorders are under-represented. There has been limited investigations into what may cause a discrepancy in the PD prevalence between ethnicities. This review aims to determine whether the lower prevalence of PDs in black people is likely to be accurate, and if it isn't, explore some of the potential causes for the difference. This is an important issue to address as may reveal pertinent inequalities in healthcare.

Key words: personality disorder – ethnicity –black people

* * * * *

INTRODUCTION

A personality disorder (PD) is a way of thinking, feeling and behaving that deviates from the expectations of the culture, causes distress or problems functioning, and lasts over time (DSM-5 definition, American Psychiatric Association 2013). The DSM-5 currently identifies ten PDs, which share core features of rigid, distorted thoughts, problematic emotional responses, impulsivity and significant interpersonal problems (DSM-5, APA 2013).

In the UK, the prevalence of PDs has been estimated to be 4.4% (Coid et al. 2006), with a greater prevalence reported in white people (4.5%) compared to other ethnicities (2.6%), including those of black ethnicity. This has also been reported elsewhere (Hossain et al. 2018), but the reason for this discrepancy is unclear: are PDs less prevalent in black populations or is there an under-representation of black people with PDs? If it is the case that PDs are truly less prevalent in black people, then this could provide important insights into the aetiology of PDs. But, if it is rather that black people are underrepresented in services, then it highlights a need to understand why this is and to promote awareness of the mental health services that are available to people. This is especially true for people with PDs, as they are at increased risk of mortality and suicide (Tyrer et al. 2015).

The prevalence of personality disorders in black people

The prevalence of PDs between ethnic groups has been investigated in different settings (communities, prisons, inpatient and outpatient settings) and locations (USA and UK). Whilst this makes synthesis of the data more difficult, a meta-analysis (McGilloway et al. 2010)

of 7 studies was possible that found that PDs were significantly less prevalent in black populations compared to white (OR 0.476). This result was based on studies from hospital (Compton et al. 2000, Coid et al. 1999, Coid et al. 2000, Castaneda & Franco 1985, Maden et al. 1999), prison (Trestman et al. 2007) and community populations (Huang et al. 2006). It is important to note that in the only study conducted in the community, results from 43093 participants showed a significantly greater prevalence of PDs in black people (16.6%) compared to white (14.6%) ($p < 0.05$) (Huang et al. 2006). The prevalence of PDs increases at each level of care, that is that PDs are more prevalent in psychiatric hospitals than in the general population. However, whilst this pattern is observed overall, it is unclear whether it occurs across all ethnicities, especially considering the recognised barriers that can exist between black communities and mental health services (Memon et al. 2016). The settings within which studies were completed could therefore significantly affect the results. In support of this, data from subgroup analysis (McGilloway et al. 2010) showed that black people were less likely than white people to have a PD in a hospital (OR 0.357), but most likely to have a PD in the community (OR 1.164). A recent study (Hossain et al. 2018) has found a similarly low prevalence of PDs in black patients admitted into East London hospitals compared to white British patients (OR 0.19 for Black African, 0.22 for Black Caribbean and 0.38 for Other Black). These results must be investigated further.

Personality disorders are less prevalent in black people: true or an artefact?

The finding that PDs are less prevalent in black people is controversial, and whether this is accurate is unclear. There are many explanations that could account for

under-representation of black people with PDs, with an important consideration being the avoidance of services. Many people, but particularly those in black communities, have dangerous preconceptions about mental health services (Keating et al. 2002). These become part of a 'circle of fear', in which black people are mistrusting and fearful of services, and service staff are weary of the black community in return. This leads to black people avoiding accessing services where possible, and as a result becoming underrepresented within them. It is important to acknowledge however that black people are not underrepresented in all of psychiatry. Notably, black people are more likely to be sectioned under the Mental Health Act (Davies et al. 1996, Lloyd & Moodley 1992) over-diagnosed with schizophrenia and subject to the use of depot-type psychotropic medication (Lloyd & Moodley 1992). These contribute to the distrust towards services, reinforcing fear and increasing disengagement. Measuring the prevalence of PDs in black people in a hospital or other care setting is therefore unlikely to be representative of a true result. A more accurate estimate would likely be based on studies conducted in the community, including the Huang et al. US study (Huang et al. 2006) that found an increased prevalence of PDs in black people compared to white (16.6% vs. 14.6%). Similar results were reported in a community-based British study (Crawford et al. 2012), that found the risk of PD was again higher in black people (OR 1.44). If the results of these studies are accurate, then important changes must be made to improve engagement of black people with mental health services.

More than just disengagement: cross-cultural bias

Disengagement from services is likely to be a significant factor in the apparent reduced prevalence of PDs in black people, but there are also likely to be additional factors involved. In the McGilloway meta-analysis (McGilloway et al. 2010), subgroup analysis revealed that when studies used both case notes and interviews to identify people with PDs, black people were more likely to have a PD (OR 1.140), but when only case notes were used, black people were less likely (0.281). Methodological differences between studies may account for these findings, but this could also suggest that the routine care of black people is likely to overlook PD diagnoses. Interestingly, there is also evidence that when forensic psychiatrists are presented with identical cases except for the ethnicity of the patient, they are more likely to diagnose PDs in white people compared to black (OR 2.7) (Mikton & Grounds 2007). This cross-cultural bias is likely the result of many factors, but notably that the intrinsic diagnosis of a PD assumes an understanding of the patient's culture (the DSM-5 definition describes a deviation from the expectations within a culture). In the previous study (Mikton & Grounds 2007), psychiatrists were given identical cases except for the ethnicity: Caucasian or African Caribbean. Of the 220 psychiatrists that precipitated in the study, none were African

Caribbean, which limits their ability to identify what is a deviation within this culture. This bias is likely to be representative of real clinical practice, where it has previously been found that just 4% of doctors in the UK are black, compared to 63% white (Bowler 2004).

Ethnic variations: why we may not always spot a personality disorder

It must also be considered that black people may truly be less likely to have PDs, or rather PDs that are "easier" to recognise in clinical practice. There have been few studies into the ethnic variation of PDs, however it may cause significant differences in which PDs are more likely between ethnicities. Previously, black people have been found as significantly more likely to have schizotypal personality disorder (STPD) (Chavira et al. 2003) compared to both Caucasians and Hispanics ($p < 0.05$). A more recent study has similarly found a significantly increased risk of STPD in black women (Pulay et al. 2009). STPD is an understudied PD and is often not recognised, which leads to no diagnosis or misdiagnosis (Rosell et al. 2014). Additionally, core features of STPD include social isolation and social anxiety (DSM-5), which may hinder the ability of people with STPD to access mental health services. If STPD represents a large proportion of PDs in the black population, it could explain in part why we see a smaller prevalence of PDs than we expect.

Misdiagnosis: when we think personality disorders are something different

Ethnic variation may have additional effects on the prevalence of PDs between ethnicities. Features of STPD, which may be more common in black people (Chavira et al. 2003, Pulay et al. 2009), include odd or unusual thought processes (including magical thinking), circumstantial or metaphorical speech, unusual beliefs and experiences and feelings of persecution (DSM-5). These features are very similar to those reported in schizophrenia, which could lead to misdiagnosis. This could explain both the lower prevalence of PDs seen in black people and may account somewhat for the significantly higher prevalence of schizophrenia in this population. Additional factors that contribute to the increased prevalence of schizophrenia in black people have previously been explored (Ngaage & Agius 2016), including the use of social withdrawal as a primary diagnostic symptom for schizophrenia when it is a key stress suffered by immigrants. Social withdrawal is also a common feature of many PDs, which likewise will increase the risk of misdiagnosis.

CONCLUSION

The prevalence of PDs in black people is controversial. Studies have reported conflicting data that seems to be associated with the setting within which the study was completed, where inpatient settings were more likely

to report a reduced prevalence of PDs in black people. There are many factors that could potentially contribute to this result, but notably one should consider disengagement from services, cross-cultural bias within the healthcare system and ethnic variations of PDs, which could lead to misdiagnosis. The effect of each of these must be quantified to determine whether PDs are truly less prevalent in the black population, or if black people are under-represented. This distinction is key as it could provide insight into the aetiology of PDs or highlight an inequality within mental health services.

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Contribution of individual authors:

Lucille Mclean devised the literature search and drafted the paper.

Mark Agius supervised the project

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THE IMMUNOMODULATORY EFFECT OF KETAMINE IN DEPRESSION

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SUMMARY

Major depression is one of the most frequent psychiatric conditions. Despite many available treatment methods, more than 30% of patients do not achieve remission, even after trying several antidepressants and augmentation strategies. *S*-enantiomer of ketamine, well-known anesthetic and analgesic, has been recently approved by Food and Drug Administration in the intranasal form as a new generation antidepressant. However, the mechanism in which ketamine reduces depressive symptoms in treatment-resistant depression patients is still not completely understood. There are several theories explaining how ketamine might reduce depressive symptoms, which have been described in detail; one of them is immunomodulatory effect of ketamine, according to the inflammatory theory of depression. In the review authors present and summarize studies showing ketamine effect on human immune system *ex vivo* and *in vitro*, including changes in cytokine levels, number, ratio and activity of various immune cell population and the correlation with clinical improvement in depressive symptoms. Most of the results confirm the anti-inflammatory effect of ketamine. There are only a few studies in the population of patients suffering from depression receiving ketamine, focused on correlation between immunological changes and clinical outcome of the therapy; further studies of that area are necessary for understanding the immunomodulatory effect of ketamine in depression.

Key words: ketamine - depression - inflammation - cytokines - lymphocytes

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INTRODUCTION

Major depression is one of the most occurring psychiatric condition. Despite many available treatment methods, more than 30% of patients do not achieve remission, even after trying several antidepressants and augmentation strategies. Therefore, seeking for other antidepressive agents with different mechanism of actions is necessary to help patients suffering from treatment-resistant depression.

Ketamine is a well-known, widely used anesthetic and analgesic drug. Its *S*(+) enantiomer esketamine in the intranasal form has been recently approved by Food and Drug Administration (FDA) as a new generation antidepressant (Walsch 2019). Its rapid antidepressive activity has been proven in numbers of studies (Berman et al. 2000, Zarate et al. 2006, Daly et al. 2019). Newport's meta-analysis shows that a single intravenous infusion of ketamine at a dose of 0.5 mg/kg produces robust and rapid antidepressant response within 24 hours after administration that declined steadily, but remained statistically significant up to 2 weeks (Newport et al. 2015). However, the mechanism in which ketamine reduces depressive symptoms in treatment-resistant depression (TRD) patients is still not completely understood.

KETAMINE MECHANISM OF ACTION IN DEPRESSION

There are several theories explaining how ketamine might reduce depressive symptoms (Figure 1). The most

known mechanism of ketamine is its effect on glutamatergic system. Ketamine directly blocks N-methyl-D-aspartate (NMDA) receptors in the brain, which reduces neuronal excitotoxicity caused by glutamate. On the other hand, blockade of NMDAR on γ -aminobutyric acid (GABA) neurons leads to disinhibition of pyramidal cells in prefrontal cortex causing locally increased glutamate release (Abdallah et al. 2016). It results in activation of the α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, glycogen synthase kinase 3 (GSK-3) phosphorylation, mammalian target of rapamycin (mTOR) signaling activation, inhibition of eukaryotic elongation factor 2 (eEF2) kinase and increased production of brain-derived neurotrophic factor (BDNF), which overall increase synaptogenesis, dendrite spine density and neuroplasticity, resulting in antidepressive effect (Pescic et al. 2016, Miller et al. 2014, Li et al. 2010).

Ketamine binds to both $\sigma(1)$ and $\sigma(2)$ receptors and thus reduces the depressive symptoms in rats (Robson et al. 2012). Even though function of this receptors is still poorly understood, it seems that ketamine's antidepressive effect might be associated with stimulation of BDNF release caused by increased activity of cAMP response element-binding protein (CREB) (Zhang et al. 2017). Antidepressive properties of ketamine may result from modulation of other neurotransmitter systems. It has been shown that ketamine increases dopamine levels (Kokkinou et al. 2018), reverses deficit in dopamine-dependent synaptic plasticity (Belujon & Grace 2014),

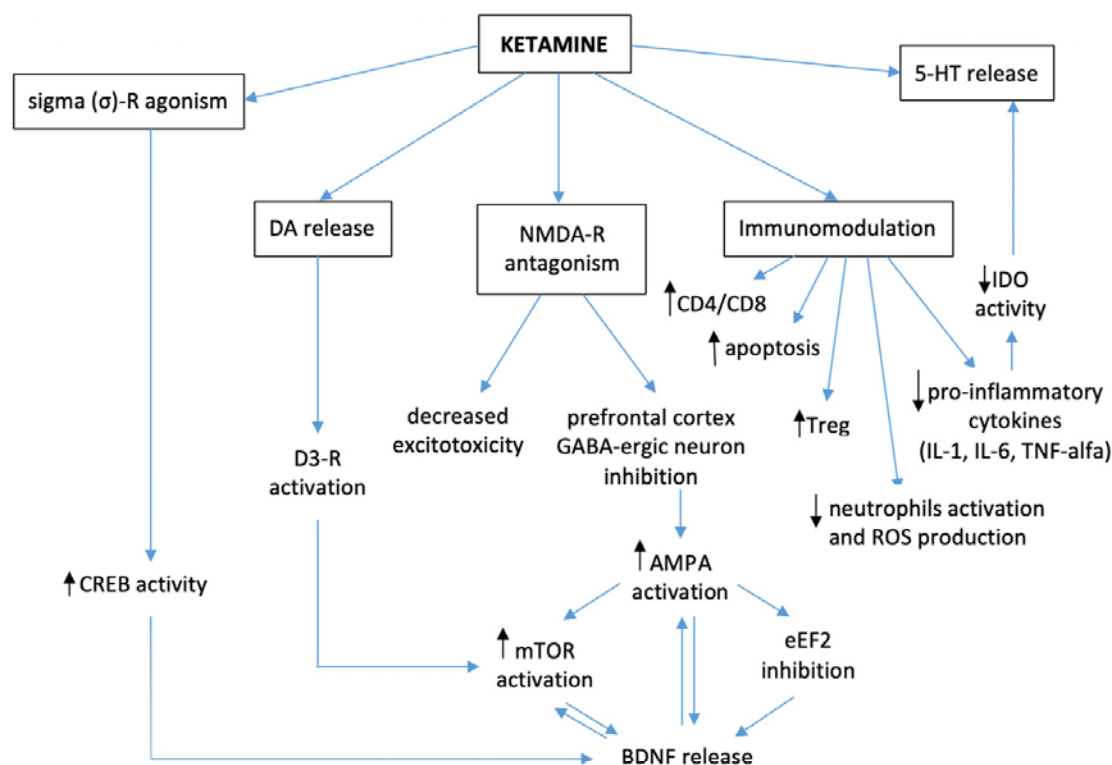


Figure 1. Ketamine's mechanisms of action in depression

and modulates mTOR signaling in rodent limbic system due to activation of dopamine D3 receptors (Chiamulera et al. 2018). Serotonin activity in the brain is also modulated by ketamine. Studies have shown that ketamine enhances serotonin release in medial prefrontal cortex by cholinergic neurons projecting from pedunculo-pontine tegmental nucleus to dorsal raphe nucleus (Kinoshita et al. 2018).

Modulation of serotonergic system is connected to the kynurenine pathway. Studies show that in patients suffering from depression there is a shift in tryptophan metabolism towards neurotoxic metabolite of kynurenine pathway – quinolinic acid, a NMDA-R agonist, instead of serotonin or neuroprotective kynurenic acid (KYNA) (Zou et al. 2015). Intravenous administration of ketamine seems to be reversing these changes causing significant increase in KYNA serum level after 24 hours, which is associated with clinical antidepressive effect (Zhou et al. 2018).

The changes in kynurenine pathway described above are strongly connected to the hypothesis that ketamine might have antidepressant properties due to its anti-inflammatory effect. Pro-inflammatory cytokines, such as IFN- γ , IL-1 or IL-6 produced excessively by activated immune cells in depressed patients are responsible for triggering pro-depressive effects through the induction of indolamine 2,3-dioxygenase (IDO), an enzyme involved in the shift of tryptophan to kynurenine and consequently to quinolinic acid (Dantzer et al. 2016). There are several other mechanism in which ketamine modulates immune system, and thus contribute to the antidepressive effect.

IMMUNOMODULATORY EFFECT OF KETAMINE

Regulation of immune system activity and chronic inflammation seems to play an important role in the pathogenesis of depression, as we reported recently (Szalach et al. 2019). The inflammatory hypothesis of depression has been described in a number of studies. It has been demonstrated that concentrations of pro-inflammatory cytokines, mainly IL-1, IL-6, IFN- γ and TNF- α , are elevated in the serum of patients suffering from depressive disorders, which has been confirmed in several meta-analyses (Dowlati et al. 2010, Haapakoski et al. 2015, Schmidt et al. 2014). Also, the increase in the level of pro-inflammatory cytokines is accompanied by an increased plasma concentrations of granulocyte-macrophage colony-stimulating factor (GM-CSF) (Schmidt et al. 2014) and monocyte chemoattractant protein 1 (MCP-1) (Király et al. 2017).

Ketamine effect ex vivo

So far, only two articles have been published describing the immunomodulatory effect of ketamine in human participants suffering from depression. Király et al. (2017) performed a study in which 33 medication-free patients suffering from treatment-resistant depression received a single dose of intravenous ketamine (0.5 mg/kg). Next, 4 and 24 hours after drug administration blood samples were taken and Montgomery-Åsberg Depression Rating Scale (MADRS) assessment was performed. Before receiving ketamine, pro-inflammatory cytokines

IL-6 and G-CSF, GM-CSF, MCP-1 as well as one of isoforms of platelet-derived growth factor (PDGF-BB) were significantly elevated in comparison to healthy volunteers. After 4 hours, levels of IL-6 and G-CSF along with IL-1 α and interferon gamma-induced protein 10 (IP-10, a chemoattractant for many different immune cells) decreased. Authors haven't found any changes in BDNF levels at any point of time. Changes in cytokine levels were not correlated with MADRS score. However, it was shown that patients responding to treatment with ketamine are characterized by lower level of basic fibroblast growth factor (FGF-2) and alpha subunit of interleukin 10 receptor (IL-10RA) after 24 hours (Kiraly et al. 2017).

Another randomized, double-blind control study was performed by Chen et al. (2018). 71 patients with TRD were assigned into one of the three groups according to received treatment: 0.5 mg/kg ketamine, 0.2 mg/kg ketamine or saline infusion. Proinflammatory markers including C reactive protein (CRP), IL-6 and TNF- α were examined at baseline and at 40 min., 240 min., day 3, and day 7 after drug infusion. MADRS was used for assessment of depressive symptoms across time. Results showed that decrease in IL-6 and TNF- α levels was visible after just 40 minutes. Specifically, levels of TNF- α were significantly lower in patients who received 0.5 mg/kg of ketamine. The decrease in TNF- α between baseline and 40 min. post-infusion was positively correlated with a decrease in MADRS scores across time in these patients (Chen et al. 2018). This is the first clinical study to support a positive correlation between changes in cytokine levels after ketamine infusion and improvements in depressive symptoms in patients suffering from TRD.

The anti-inflammatory effect of ketamine also was examined in different groups of patients receiving ketamine as an anesthetic or analgesic drug. Dale et al. (2012) performed meta-analysis in which the effect of perioperative ketamine administration on postoperative inflammation was assessed. Postoperative IL-6 concentrations (up to 6 hours after surgery) was set as an outcome. The meta-analysis showed a mean preoperative-postoperative IL-6 concentration difference which supported the hypothesis that ketamine has an anti-inflammatory effect (Dale et al. 2012). Another study was conducted in group of patients undergoing orthotopic liver transplantation (Yang et al. 2006). Ten patients were given intravenous bolus injection of ketamine in a low dose of 0.25 mg/kg followed by ketamine infusion at 0.5 mg/kg/h until the end of operation except in the anhepatic phase. Arterial blood samples were obtained at the start of surgery, 5 min. before the anhepatic phase, 5 min. before recirculation, 15 and 60 min. after recirculation and 0, 4 and 24 hours after operation, and serum levels of TNF- α , IL-6 and IL-10 were measured. The cytokines levels, especially of IL-6 and IL-10, increased significantly during

anhepatic phase as compared with the baseline levels. The levels of TNF- α and IL-6 in patients who received ketamine before anhepatic phase and early post-operative period were significantly lower than in the control group. Serum level of IL-10, which is an anti-inflammatory cytokine, did not show any significant difference between the two groups (Yang et al. 2006).

Ketamine effect in vitro

Immunomodulatory effect of ketamine on human immune system was widely examined *in vitro* after stimulation of human blood cells with bacterial antigens in the presence of various ketamine concentrations in the cell culture. It has been demonstrated that ketamine at concentrations exceeding 50 μ M significantly suppresses staphylococcal enterotoxin B (SEB)-induced TNF- α production (Kawasaki et al. 2001). Ketamine isomers at higher concentrations (more than 100 μ M) significantly suppressed IL-6 and IL-8 production as well. No significant differences between the suppressive effects of S(+)-ketamine and R(-)-ketamine on pro-inflammatory cytokine production was seen (Kawasaki et al. 2001). Similar results were observed when human blood cells were activated with lipopolysaccharide (LPS) (Kawasaki et al. 1999). Meanwhile, Larsen et al. (1998) demonstrated that ketamine inhibits LPS-induced production IL-1 β .

Immune changes caused by ketamine are not only prominent in the pro-inflammatory cytokine levels, but also in the number, ratio and activity of various immune cell populations – alterations in that area are seen and described in patients suffering from depression (Szalach et al. 2019). An increase in the number of cells involved in the innate immune responses, i.e. monocytes, macrophages and neutrocytes (Demir et al. 2015), as well as increased production of reactive oxygen species (ROS) has been reported (Wei et al. 2015). An increase in the ratio of CD4⁺ T (Th) cells to CD8⁺ cytotoxic (Tc) T lymphocytes, which are responsible by adaptive immune responses, has also been described (Zorrilla et al. 2001, Di Rosso et al. 2016). Additionally, an increase in the percentage of CD4⁺CD25⁺ T cells (activated cells) (Patas et al. 2018, Müller et al. 1993) with the accompanying decrease in the total number of regulatory T lymphocytes (Treg) (Toben and Baune 2015), which are responsible for suppression of immune responses, have also been observed.

Studies show that ketamine inhibits *in vitro* induced up-regulation of (integrin beta chain-2) (CD18) and L-selectine (CD62L) on the human neutrophils surface, both of which play a significant role in cellular adhesion (Weigand et al. 2000). Ketamine also caused a significant suppression of oxygen radical generation of isolated human neutrophils regardless of whether the racemic mixture or isomers were tested (Weigand et al. 2000).

Randomized, double-blinded clinical study performed by Zilberstein et al. (2002) examined the function of neutrophils *in vitro* in patients, who received ketamine as an additional anesthetic during cardiopulmonary bypass grafting. The addition of small-dose (0.25 mg/kg) ketamine reduced increased production of the superoxide anion (O_2^-) by neutrophils compare to patients who were not given ketamine. In addition, ketamine increased the percentage of neutrophils on postoperative days 2 to 6 (Zilberstein et al. 2002).

In another study, whole blood from healthy men as well as monocyte and promyelocyte line cells were incubated in the presence of ketamine in order to examine its influence on transcription factors, such as activator protein 1 (AP-1) or nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) (Welters et al. 2010), which not only regulate the immune response but also take part in processes responsible for synaptic plasticity (Albensi & Mattson 2000, Tuvikene et al. 2016). Ketamine inhibited both transcription factors in a concentration-dependent manner; these effects did not depend on opiate or NMDA receptors. Moreover, ketamine also reduced IL-8 production in whole blood and decreased surface expression of CD11b (adhesion molecule) and CD16 (molecule that takes part of antibody-dependent cell-mediated cytotoxicity) on neutrophils (Welters et al. 2010). Another study performed on human glioma cells confirmed that endotoxin-induced NF- κ B activation can be suppressed by ketamine (Sakai et al. 2000).

It seems that ketamine also can influence T cells. In a study of Hou et al. (2016), peripheral blood mononuclear cells (PBMCs) isolated from whole blood samples of patients suffering from gastric cancer were incubated for 24 hours with different concentrations of ketamine (25, 50 and 100 μ M). The ratio of CD4⁺/CD8⁺ T cells as well as the percentage of Tregs were significantly increased in the presence of rising concentrations of ketamine (Hou et al. 2016). Studies in healthy people show that ketamine may inhibit the phorbolmyristate-acetate (PMA) and ionomycin induced differentiation of Th0 lymphocytes, especially towards Th2 cells, which are responsible for regulating humoral responses (Gao et al. 2011). In addition, Braun and colleagues have shown that ketamine acts pro-apoptotic on lymphocytic and neuroblastoma cell lines in a concentration-dependent manner (Braun et al. 2010). Authors observed that S(+)-ketamine was less toxic to neuroblastoma cells but this difference was minor and therefore unlikely to be mediated via the NMDA receptor. These results showed that ketamine could induce programmed cell death of lymphocytes thus reducing T cell-dependent immune responses. At the same time, it points to its potential neurotoxic properties.

CONCLUSIONS

The mechanisms of antidepressant action of ketamine are still not fully understood. It seems that this

phenomenon may be partly related to its immunomodulatory effect, especially its anti-inflammatory properties. Currently, there are only a few studies in the population of patients suffering from depression, especially taking into account the effect of ketamine on immune cells, which means that there is a further need for such studies.

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Contribution of individual authors:

Lukasz P. Szalach, Katarzyna A. Lisowska & Wiesław J. Cudała: design of the study, manuscript writing, literature research and analysis, data interpretation
Jakub Słupski, Natalia Górską & Joanna Szarmach: literature research and data interpretation
Adam Włodarczyk, Katarzyna Jakuszkowiak-Wojten, Maria Gałuszko-Węgielnik, Mariusz Stanisław Wigłusz, Alina Wilkowska: manuscript redaction

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SUICIDALITY IN TREATMENT RESISTANT DEPRESSION: PERSPECTIVE FOR KETAMINE USE

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SUMMARY

Suicidal ideations or attempts in patients with major depressive disorder (MDD) are emergent conditions that require immediate treatment. Numerous therapeutic interventions to reduce suicide risk in psychiatric disorders are effective in long-term suicide prevention, but there is necessity of sufficient, rapid pharmacological treatment of suicidal risk in MDD.

Ketamine, an N-methyl-D-aspartate (NMDA) antagonist, has been reported to have rapid antidepressant effect. Depressive symptoms, anxiety, hopelessness, suicidal ideation had decreased within hours after ketamine infusion. Ketamine's rapid symptoms relief and reduction of suicide thoughts has aroused growing interests in psychiatric association.

Key words: ketamine – NMDA – glutamate - suicidal ideation - depression

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INTRODUCTION

Every year some 800 000 people die due to suicide according to WHO (World Health Organization). The neurobiology of suicidal behavior still remains to a large degree unclear. The link between suicide and mental disorders is well established. Depression affects more than 350 million people worldwide (WHO). About 50-60% of patients with MDD fail to achieve remission despite treatment with multiple antidepressants and are considered to suffer from TRD (treatment resistant de) (Fava 2003). Limitations of currently available antidepressant therapies include late -onset response (typically 4-6 weeks), adverse effects and treatment resistance. Difficulties are also associated with treating patients quickly enough to significantly reduce suicidal ideation (Diaz Granados 2010). Rapid antidepressant and anti-suicidal effects of low ketamine doses have been reported since 2000 (Chen 2019). There is a relationship between suicidal ideations and serotonergic, noradrenergic and dopaminergic dysfunctions, however the role of glutamatergic system in suicide has received more attention recent years (Nowak 1995, Zarate 2006, Machado-Vieira 2009, Kalkman 2011, Furczyk 2013, DeLorenzo 2015, Tomassetti 2019).

KETAMINE MECHANISM OF ACTION IN DEPRESSION

The target of majority of conventional antidepressants is monoaminergic system resulting in monoamine amplification. The major biological mechanism of rapid antidepressant ketamine action is different. The process initiated by an N-methyl-D-aspartate (NMDA) antagonist -ketamine in gamma- aminobutric acid interneurons leads to increase synaptogenesis and BDNF (brain-

derived neurotrophic factor) relief (Zarate 2012, Grunebaum 2017, Zanos 2018, Chen 2019). Evidence suggest that low-dose ketamine significantly increases BDNF levels what has been negatively correlated with depression symptoms (Kavalali & Monteggia 2012). However, there are mix findings exploring BDNF levels in anti-suicidal ketamine's effect. Ballard found no correlation between BDNF levels and antisuicidal effects (Ballard 2018). BDNF polymorphism may predict the treatment response of ketamine infusion (Niciu 2017, Chen 2019) Bay-Richter indicated that NMDA receptor antagonists may be effective in suicide and depression due to dys-regulated kynurenine pathway (Bay-Richter 2015).

Ketamine has been widely used in pain management and for induction and maintenance of anesthesia via intravenous or intramuscular administration in many countries since 1970 (Morgan 2012). Ketamine's optimal antidepressant dose in intravenous administration remains unknown. Numerous placebo-controlled studies have demonstrated the ability of ketamine, to induce rapid (within hours), transient antidepressant effects at subanesthetic doses (0.5 mg/kg-1.0 mg/kg over 40 min) (Fava 2019). The infusions of ketamine were relatively well tolerated, except for dissociative symptoms and transient blood pressure elevations with the higher doses, the most common ketamine's adverse effects were headaches and nausea (Singh 2015; Fava 2019). Adverse effects after low doses of ketamine were transient-usually lasted within 30 minutes to 4 hours after administration (Berman 2000, Diazgranados 2010, Zarate 2012, Murrough 2013, Lapidus 2014, Singh 2015, Singh 2016, Daly 2018). It is worth mention, due to its hallucinogenic effect ketamine is used as recreational drug and in larger doses may have addictive properties with its harmful physical and psychological consequences (Curran 2000).

CLINICAL STUDIES REVIEW

Ketamine has shown rapid antidepressant effects in many trials in both single and multiple administration (Berman 2000, Zarate 2006, Diazgranados 2010, Zarate 2012, Sos 2013, Murrugh 2013, McGirr 2014, Shiroma 2014, Lapidus 2014, Singh 2015, Loo 2016, Singh 2016, Daly 2018, Mu-Hong Hen 2019). However, repeated ketamine infusions seem to be more beneficial (Zhan Yanni 2019). Ketamine resulted in a rapid anti-suicidal effect in a group of depressed patients with suicidal ideations (Price 2009, Diazgranados 2010, Larkin 2011, Price 2014, Ballard 2015, Ionescu 2016, Bartoli 2017, Grunebaum 2017, Canuso 2018). Some studies (Larkin & Beautrais 2011, Bartoli 2017) showed significant decrease in suicidal ideations score after single ketamine infusion. Study by Grunebaum (2017) reported that ketamine had larger effect on suicidal ideations compared to midazolam. Wilkinson meta-analysis (Wilkinson 2018) of 10 placebo- control randomized trials involving 167 patients with major depressive disorder, bipolar depression and posttraumatic stress disorder revealed that ketamine significantly reduced suicidal ideations in clinician-administrated and self-reported outcomes. In contrast to earlier trials, other studies (Ballard 2018; Ionescu 2019) revealed that patients with long-standing history of chronic SI were less likely to respond to ketamine. The possible explanation is that dose 0.5 mg/kg over 40 minutes was not sufficient in treatment resistant patients and the level of chronicity in these samples were higher than in prior studies (Ballard 2018, Ionescu 2019). Some authors suggested that suicidal ideations response to ketamine occurs partially independently of antidepressant response and can be treated as distinct target what aligns with previous studies (Wilkinson 2018, Grunebaum 2018, Ballard 2018, Zhan 2019). The anti-suicidal response is not entirely driven by the antidepressant effect of ketamine but there are possible other explanations (Zhan 2019) e.g. reduction of anhedonia (Ballard 2017) or decreased nighttime wakefulness in MDD and Bipolar disorder (Vande 2017). Mechanism of anti-suicide ketamine efficacy still remains unclear.

CONCLUSION

Patient with TRD are at risk of suicide. Therefore, there is a significant need to develop novel treatments for the rapid relief of depressive symptoms. The glutaminergic system has recently obtained a particular concern as a potential therapeutic target. There is growing interest in NMDA antagonist- ketamine due to rapid antidepressant and antisuicidal effect of this agent compared to delayed onset of routine methods (Diaz Granados 2010, Bartoli 2015). The bioavailability of ketamine depends on the route of administration (Mathew 2012). The limitation of ketamine for treating depression is due to it requires intravenous administration and hospital setting with appropriate safety monitoring. Esketamine, the S-enantiomer of ketamine was developed

as an intranasal formulation for therapy in treatment-resistant depression (TRD) (Dally 2018; Popova 2018). Intranasal esketamine has regulatory FDA approval for treatment resistant depression since March 2019 and is available in certified clinics.

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Mariusz S. Wiglusz & Krzysztof Krysta literature research, manuscript revision.

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IDENTIFICATION AND EVALUATION OF COGNITIVE DEFICITS IN SCHIZOPHRENIA USING "MACHINE LEARNING"

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SUMMARY

Background: Schizophrenia can be interpreted as a pathology involving the neocortex whose cognitive dysfunctions represent a central and persistent characteristic of the disease, as well as one of the more important symptoms in relation to the impairment of psychosocial functioning and the resulting disabilities. Given the implication of cognitive functions in everyday life, they can better predict the degree of schizophrenia. The study proposes to use Machine Learning techniques to identify the specific cognitive deficits of schizophrenia that mostly characterize the disorder, as well as to develop a predictive system that can diagnose the presence of schizophrenia based on neurocognitive tests.

Subjects and methods: The study employs a dataset of neurocognitive assessments carried out on 201 people (86 schizophrenic patients and 115 healthy patients) recruited by the Neuroscience Group of the University of Bari "A. Moro". A data analysis process has been carried out, with the aim of selecting the most relevant features as well as to prepare data for training a number of "off-the-shelf" machine learning methods (Decision Tree, Random Forest, Logistic Regression, k-Nearest Neighbor, Neural Network, Support Vector Machine), which have been evaluated in terms of classification accuracy according to stratified 20-fold cross-validation.

Results: Among all variables, 14 were selected as the most influential for the classification problem. The variables with greater influence are related to working memory, executive functions, attention, verbal fluency, memory. The best algorithms turned out to be Support Vector Machine (SVM) and Neural Network, showing an accuracy of 87.8% and 84.8% on a test set.

Conclusions: Machine Learning provides "cheap" and non-invasive methods that potentially enable early intervention with specific rehabilitation interventions. The results suggest the need to integrate a thorough neuropsychological evaluation into the more general diagnostic evaluation of patients with schizophrenia disorder.

Key words: cognitive disorders - neuropsychological evaluation - schizophrenia - machine learning

* * * * *

INTRODUCTION

Among psychiatric disorders, schizophrenia is one of the main causes of disability today, as delusions, hallucinations and negative symptoms lead to a cognitive impairment that represents the most significant deficit of this mental disorder (Marder & Fenton 2004). All these symptoms contribute to the deterioration of the personal and social functioning of the subject, causing the person to lose touch with reality.

Today the research interprets schizophrenia as a neocortex pathology whose main, purely cognitive, role is represented by information processing: cognitive dysfunctions therefore represent, in this perspective, a central and persistent characteristic of the disease, as well as one of the more important symptoms in relation to the impairment of psychosocial functioning and the resulting disabilities (Gold et al. 2002). These dysfunctions can be already detected in the premorbid period, are present at the onset of the disease and persist, even in the periods of clinical stability, after the resolution of the acute phases (Reichenberg & Harvey 2007). Due to these characteristics, cognitive disorders are currently among the most studied as possible endophenotypes in the psychiatric field (Bertolino et al. 2001, 2006, Weinberger 2001, Zhang et al. 2007). From published data it has been demonstrated that, on average, the cognitive performance is from 1 to 2 standard deviations below

the healthy controls in several domains (Dickinson et al. 2007, Keefe et al. 2011).

Memory, learning, attention and processing speed, executive functions and abstraction ability have been highlighted as the most deficient areas (Green 2006, Heinrichs et al. 1998, Reichenberg et al. 2009). There is a wealth of evidence that shows how cognitive deficits are closely related to low levels of psychosocial functionality in the context of interpersonal relationships, in the field of work and in the dimension of the perception of Quality of Life (Marder & Fenton 2004, McGurk et al. 2004). Given the implication of cognitive functions in everyday life, they can better predict the degree of disability, especially in schizophrenia (Shamsi et al. 2011).

The aim of the study is to succeed in developing an accurate prediction model for the diagnosis of schizophrenia, through the identification of possible characteristic cognitive deficits already present in the initial phase or even before the onset of the disease.

SUBJECTS AND METHODS

Purpose of the study

Given the growing evidence in favor of neurocognitive impairment in schizophrenic disorders, the present study proposes to use machine learning techniques as a tool to:

- Identify the specific cognitive deficits of schizophrenia that characterize the disorder more markedly only through neurocognitive tests;
- Develop a predictive system that is based on the detection of the values of neurocognitive variables that can diagnose the presence of schizophrenia.

The study was conducted on two samples: 1) a sample of people diagnosed with schizophrenia who underwent a series of neuropsychological tests to measure cognitive functions; 2) a sample of healthy people evaluated with the same neuropsychological tests.

The hypothesis is that, through the comparison of the same variables in healthy subjects and those with schizophrenia, carried out through the application of machine learning techniques, it is possible to perform, on an empirical and predictive basis, a more accurate diagnosis of schizophrenia based on specific cognitive deficits.

The tool chosen for the "data understanding" phase and the subsequent machine learning phase is Orange (<https://orange.biolab.si/>).

Subjects

The dataset consists of neurocognitive assessments carried out on people recruited from the research conducted, from 2006 to 2015, by the Neuroscience Group directed by Prof. Alessandro Bertolino of the University of Bari "A. Moro". A total of 201 subjects were randomly selected from all the participating subjects: n. 86 schizophrenic patients (SCZ) diagnosed with SCIID and 115 healthy controls (NC), 83 women and 118 men. The sample is aged between 18 and 63 and is homogeneous for the age and sex variables.

Methods

A battery of tests, taken from the Protocol created in the framework of research by the Neuroscience Group, was used for the neuropsychological evaluation, with the aim of detecting the socio-cultural level, the laterality and the different aspects related to attention, memory, praxic, visuospatial and executive functions. In Table 1 the domains and the relative variables are displayed.

In the data understanding phase, the domains associated with the 28 variables measured by neuropsychological tests were described. The data were prepared, taking decisions on the missing data, the feature selection was made, also taking into consideration the analysis of the correlation of the variables, and the features ranking was made with ReliefF algorithm (Kononenko 1994). The results are shown in Figure 1, where the rankings of 14 main variables are displayed.

The dataset was divided (holdout) into a training set (80%) and a test set (20%). Machine learning techniques were applied to the training set and various predictive models (Tree, Random Forest, Logistic Regression,

k-Nearest Neighbor, Neural Network, Support Vector Machine) were analyzed (Berthold et al. 2010). Since all the records of the dataset already had a classification, this was supervised learning. The sample was validated with 20-fold Cross Validation and many tests were made, repeatedly changing the parameter settings of each prediction algorithm. Finally, based on the simulations, the best performing algorithm was chosen by evaluating the Classification Accuracy (CA). The best algorithms turned out to be Support Vector Machine (SVM) and Neural Network (Figure 2).

Table 1. Measured Domains and Related Tests

Measured domain	Test
Socio-economic condition	Hollingshead
Lateralization (right-left)	Edinburgh Handedness Inventory
Pre morbid intelligence	Brief Intelligence Test (TIB)
Executive functions	Wisconsin Card Sorting Test (WCST)
Working memory	N-Back 0, N-Back 1, N-Back 2
Verbal and non-verbal memory	Wechsler Memory Scale
Verbal fluency	Phonological Fluence Test Semantic Fluence Test
Executive functions	Trail Making Test A e B
Attention	Continuous Performance Test (CPT)

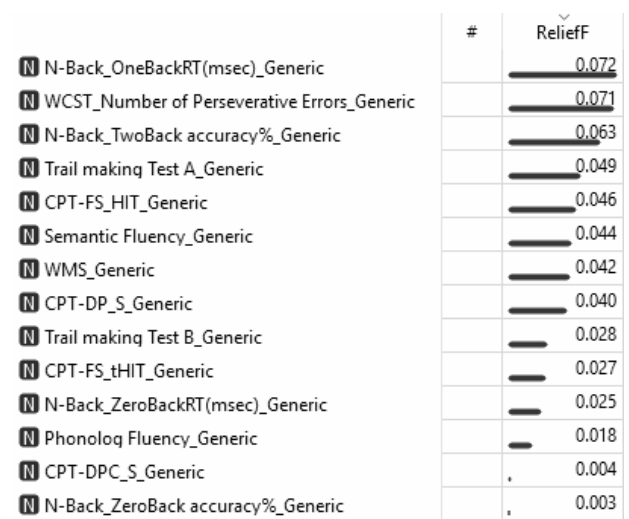


Figure 2. Feature ranking

Evaluation Results						
Model	AUC	CA	F1	Precision	Recall	
SVM	0.933	0.910	0.860	0.949	0.787	
Neural Network	0.950	0.910	0.860	0.949	0.787	
Logistic Regression	0.940	0.895	0.844	0.884	0.809	
Random Forest	0.947	0.880	0.818	0.878	0.766	
Tree	0.861	0.850	0.778	0.814	0.745	
kNN	0.894	0.812	0.658	0.923	0.511	

Figure 3. Best performing training algorithms

RESULTS

For each of the two algorithms we set up the settings that maximized performance and we applied them to the test set. Comparing the results of the predictions made by the algorithms with the diagnosis made by the Neuroscience Group, it was found that:

- SVM misses the prediction of 4 records out of 33;
- Neural Network fails to predict 5 records out of 33.

Compared to the first objective of the study, the data set revealed that some cognitive variables, which can be evaluated rapidly through neurocognitive tests, can indicate the onset of schizophrenia early. As shown in Figure 1, the variables with greater weight identify the following cognitive domains: working memory, executive functions (flexibility of thought and visual-motor coordination), attention, verbal fluency, memory. The analysis through statistical methods and a machine learning tool (Orange) has shown that the distribution of the values of these variables separate the NC and SCZ classes in a defined manner.

With respect to the second objective of the study, two machine learning algorithms effective in predicting membership to one class or another have been identified, Support Vector Machine with an accuracy of 87.8% and Neural Network with an accuracy of 84.8%.

DISCUSSION

The machine learning analysis of cognitive variables can be a valid support for operators for the early diagnosis of schizophrenia. It is a "cheap" and non-invasive method that shortens the time because it allows early intervention with specific rehabilitation interventions, such as cognitive rehabilitation (Vita 2013).

As future developments, it would be useful to validate the experiment with a larger dataset. It would also be useful to study the impact on the outcome of the study of the other variables that were excluded from the experiment, namely Age, Gender, Hollingshead, TIB QI and Edinburgh Scale. Future studies may investigate the existence of relationships between schizophrenia and other factors such as socio-economic status, level of education and the familiarity of the disorder. Having available neuroimaging data, it will be possible to relate cognitive aspects and biological and functional aspects.

CONCLUSION

This study demonstrates how Data Analysis and Machine Learning can be useful tools that have great potential in the study and rehabilitative treatment of mental disorders. The reproducibility and strength of these results suggest the need to integrate a thorough neuropsychological evaluation into the more general diagnostic evaluation of patients with this disorder.

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Contribution of individual authors:

All three authors conceived and designed the study.

Antonella Vacca made the clinical and psychological writing.

Roberto Longo made data analysis and applied machine learning algorithms.

Corrado Mencar supervised the final draft.

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NEUROSTIMULATION IN TREATING ADHD

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SUMMARY

Background: Neurostimulation techniques are potential methods of treating ADHD, involving stimulation of brain areas showing abnormal activity in ADHD. They are associated with benefits that last longer with fewer side effects. This literature review will evaluate the effectiveness of these methods.

Subjects and methods: A literature search using scientific databases including PubMed and the Cochrane Library, using "ADHD" and "Attention Deficit Hyperactivity Disorder" combined with "Transcranial Magnetic Stimulation", "TMS", "Transcranial Direct Current Stimulation", "tDCS", "Vagus Nerve Stimulation", "VNS", "Trigeminal Nerve Stimulation", "TNS", "Deep Brain Stimulation", "DBS", "Electroconvulsive Therapy", "ECT", "Ultrasound stimulation" as keywords was conducted, yielding 417 references, 30 of which are used in this paper.

Results: Mixed results have been found in the effectiveness of neurostimulatory methods in treating ADHD.

Conclusions: Neurostimulation techniques have potential in treating ADHD, with some studies having positive results. More research using greater sample sizes and standardised outcome measures could be done to verify the results of previous studies.

Key words: Attention Deficit Hyperactivity Disorder (ADHD) - Transcranial Magnetic Stimulation (TMS) - Transcranial Direct Current Stimulation (tDCS) - Trigeminal Nerve Stimulation (TNS)

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterised by persistent patterns of inattentive, hyperactive and impulsive behaviour in an individual, inappropriate for their developmental stage and causing functional problems in the academic, social and occupational domains of their life, present before 12 years of life and not being explained by other psychiatric or personality disorder (1). Individuals with the condition could present with predominantly inattentive symptoms, predominantly hyperactive/impulsive symptoms or both.

ADHD has a prevalence of 7.2% (Thomas et al. 2015) and is associated with significant economic costs (Matza et al. 2005), academic underachievement (Barbatesi et al. 2007), comorbid psychiatric conditions like oppositional defiant disorder (Barkley et al. 2002) and epilepsy (Tan et al. 2005) and social rejection (Hoza 2007), making it an important problem to be addressed in psychiatry.

The exact pathophysiology of ADHD is unknown, though past studies have pointed to a neurochemical and neuropsychological basis for the disease. Association studies of candidate genes have found significant associations in the DRD4, DRD5, DAT, DBH, 5HTT, HTR1B, SNAP25, MAOA, TPH2 and ADR2A, genes associated with the dopaminergic, noradrenergic and serotonergic systems (Faraone et al. 2005, Gizer et al. 2009). Stimulants like amphetamine and methylphenidate, drugs that increase levels of noradrenaline and dopamine via inhibition of reuptake, seem to work,

again pointing to the involvement of these neurotransmitters in the pathophysiology of ADHD. Neuropsychological theories of ADHD suggest a primary deficit in executive function (Willcutt et al. 2005), supported by imaging studies showing impairments in several networks associated with cognitive control, attention, timing and working memory, as well as poor deactivation of the default mode network (Rubia 2018).

Current Treatments for ADHD

Current treatments for ADHD have focused on rectifying the neurochemical abnormalities present in ADHD pharmacologically through the use of methylphenidate, amphetamine, atomoxetine and clonidine, with help via psychosocial methods including cognitive behavioural therapy, behaviour parent training, classroom modifications and psychoeducation.

Current treatments seem to be effective, as suggested by reviews on the topic. Randomised control trials have found amphetamines and methylphenidate improved clinicians' and teachers' ratings of symptom severity (Cortese et al. 2018), while psychosocial treatments were considered efficacious once all studies were considered, as reviewed by (Fabiano et al. 2016), and are associated with sustained long-term gains (Lopez-Pinar et al. 2018).

Problems, however, have been associated with the use of pharmacotherapy in treating ADHD. Various side effects including decreased appetite, stomach pain, sleep disturbances, headaches, labile mood, growth suppression and possible sudden cardiac death have been asso-

ciated with pharmacotherapy (Cortese et al. 2013, Dalsgaard et al. 2014), with no reduction in symptom severity following extended use (Swanson et al. 2017). Misperceptions of ADHD medication have resulted in the formation of stigmatising beliefs and the association of it with costs rather than benefits in children with ADHD (Harpur et al. 2008) and possibly lowered self-esteem in children who take the medication (Davis-Berman and Pestello 2010). Pharmacotherapy is also known not to work in a significant minority cases of ADHD, leading to the need for new methods of treating ADHD to be found.

Neurostimulation in Treating ADHD

Given the problems of current methods of treating ADHD, new methods of treating the condition have been explored, with neurostimulation being one of them. Neurostimulation involves the electrical or magnetic stimulation of the brain to cause long term changes in excitability or neurochemical activity, allowing for the rectification of key problems seen in neuropsychiatric conditions. This stimulation could be used to affect focal areas of the brain (eg. Using transcranial magnetic stimulation, transcranial direct current stimulation, ultrasound stimulation and deep brain stimulation), the whole brain (eg. Using electroconvulsive therapy) or neurochemical pathways via ascending connections of the areas stimulated (eg. Using vagus nerve stimulation and trigeminal nerve stimulation). Given the pathophysiology of ADHD, this represents a new method of treating the condition while bypassing the problems of current treatment methods.

This review will describe each of these methods, describe the trials investigating the effectiveness of these methods, and evaluate these trials.

SUBJECTS AND METHODS

Literature Search

A literature search for this paper was conducted on 16 March 2019 using scientific databases including PubMed and the Cochrane Library, using “ADHD” and “Attention Deficit Hyperactivity Disorder” combined with “Transcranial Magnetic Stimulation”, “TMS”, “Transcranial Direct Current Stimulation”, “tDCS”, “Vagus Nerve Stimulation”, “VNS”, “Trigeminal Nerve Stimulation”, “TNS”, “Deep Brain Stimulation”, “DBS”, “Electroconvulsive Therapy”, “ECT”, “Ultrasound stimulation” as keywords. This produced 417 references, 30 of which are included in this paper.

RESULTS

Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation is a non-invasive method of neurostimulation that is able to depolarise or hyperpolarise cortical neurons (George et al. 2003). It

involves the placement of an electromagnetic coil against the scalp of the subject, which delivers brief, powerful magnetic pulses which induce electrical activity in neuronal membranes, stimulating them. Different coil types are able to produce different magnetic field patterns, changing the area of the cortex stimulated. Figure-eight coils, for instance, produce a more focal pattern of stimulation, while H-coils activate deeper areas of the brain.

Repetitive TMS (rTMS), the application of successive trains of such pulses, has been found to cause long-term effects on the excitability of cortical areas, depending on the frequency used – Low frequency rTMS (of 5 Hz or less) reduces neuronal excitability and cerebral blood flow of the area stimulated, while high frequency rTMS (of above 5 Hz) increases neuronal excitability and cerebral blood flow of these areas. The intensity of rTMS stimulation is measured in terms of motor threshold (MT), the intensity of stimulation of the motor cortex producing the smallest reproducible activation of a muscle (normally the abductor pollicis brevis muscle). Due to the possibility of inducing epileptic activity as a result of continuous stimulation, trains of pulses are interspersed with intervals of varying times, with the total dose of an rTMS session ultimately being dependent on the number of pulses (a function of the frequency and the time stimulated) and the intensity of rTMS stimulation.

The side effects of rTMS tend to be mild, ranging from transient headaches to scalp discomfort (Janicak et al. 2008), with a very low incidence of seizures and hypomania (Loo et al. 2008), making it a promising new method of treating neuropsychiatric conditions. Its therapeutic use has been investigated in a wide range of neuropsychiatric disorders, including, depression (George et al. 2007), OCD (Zaman and Robbins 2017) and schizophrenia (Aleman et al. 2007) as well as ADHD.

12 studies analysing the effects of rTMS on ADHD symptoms were found, mostly focusing on the stimulation of the dorsolateral prefrontal cortex (DLPFC), an area associated with executive control.

Niederhofer described a case of a 42-year-old female with ADHD with mainly hyperactive symptoms, who was treatment resistant to methylphenidate, which was stopped 2 months prior to the trial. A 5-day course of rTMS of the motor additional area, given at a frequency of 1 Hz, totalling to 1200 pulses per day given over an hour was administered. ADHD symptoms on the Connor’s rating scale (CSRS) for adults before the treatment and after the treatment, as well as after a course of sham stimulation (with the application of the coil without any pulses delivered) four months after the course of active rTMS. Some improvement in her hyperactive symptoms was found after active stimulation, lasting for at least 4 weeks, with no such improvement seen after the sham stimulation. However, no improvement of in her inattentive symptoms were seen

(Niederhofer 2008). A further study by Niederhofer examined the effectiveness of rTMS in a similar patient, stimulating at the same frequency and pulse rate, but over the right motor area for 21 days, while the patient was on methylphenidate. Again, the CSRS for adults was used to assess symptomatology before and after treatment. Clinical improvement of symptoms was seen after the first 5 days of the experiment, prompting Niederhofer to lower the patient's dose of methylphenidate to 10 mg daily (from an original dose of 20 mg daily). Again, improvement was seen in the patient's hyperactive symptoms, with no difference in inattention, with the effect lasting at least 3 weeks (Niederhofer 2011).

Bloch and colleagues described a double-blind crossover trial involving 13 patients with ADHD. Participants were exposed to 1 session of active Fig8 rTMS (involving 42 cycles of 20 Hz stimuli for 2 s, followed by 30 s intertrain intervals over the right DLPFC at 100% MT, found via measuring 5 cm anterior to the motor threshold) and 1 session of sham rTMS (whereby patients were subjected to rTMS with 1 wing of the Fig8 being in contact with the scalp at 45 degrees, causing no active stimulation), scheduled a week apart, with half the participants having the active rTMS session first while the other half having the sham rTMS session first.

Scores on the Positive and Negative Affect Scale (PANAS), Visual Analogue Scales (VASs) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) were assessed before and after each trial. Significantly higher attention scores on the PANAS and VAS were found post-active rTMS, with no such difference being seen post-sham rTMS, though no difference in ADHD symptoms was seen, as assessed by the Adult ADHD Self Report Scale (ASRS), Wender-Utah adult ADHD scale (WUAAS) and clinical evaluation (Bloch et al. 2010).

Weaver and colleagues described a randomised sham-controlled crossover study involving 9 adolescents with ADHD, aged 14 to 21. Participants were made to stop all stimulant medications 2 weeks before randomisation, before having 2 weeks each of active Fig8 rTMS (involving 50 cycles of 10 Hz stimuli for 4 s, followed by 26 s intertrain intervals, for 5 sessions per week of the right DLPFC at 100% MT, found via measuring 5 cm anterior to the motor threshold) and sham rTMS (involving the coil being tilted at 90 degrees, with a week of no stimulation between the phases of the experiment). Significant changes were seen in the Clinical Global Impression of Improvement scale (CGI-I) and the ADHD-IV scale, though significant differences in scores between the active and sham conditions were only seen in the CGI-I scale, and not the ADHD-IV scale (Weaver et al. 2012).

Ustohal and colleagues described a case report of a 36-year-old man diagnosed with ADHD in childhood, unresponsive to atomoxetine, with comorbid depressive

disorder. After five sessions of 10 Hz stimulation of the left DLPFC at 120% MT, with 10 s of stimulation followed by 30 s intertrain interval, for a total of 1500 stimuli per session, the patient showed improvement in attention, assessed via the d2 Test of Attention. Of note, though, was that the patient also showed an improvement after sham stimulation, and showed adverse effects of dysphoria, inability of respond emotionally, hypobulia, tension and impaired attention after a single session of stimulation of the right DLPFC (done after the 5 sessions of left DLPFC stimulation), and showed improvements in attention after sham stimulation (done before the 5 sessions of left DLPFC stimulation) (Ustohal et al. 2012).

Gomez and colleagues described a trial of 1 daily session of 1 Hz rTMS over the left DLPFC, with 1500 stimuli given per session at 90% MT over 5 consecutive days, administered to 10 boys aged 7 to 12 with ADHD, resistant to conventional therapy. ADHD symptoms were assessed via a symptoms check list filled in by parents and teachers before and 1 week after the rTMS sessions, and found that the inattentiveness symptoms at school and hyperactivity/impulsivity symptoms at home improved after treatment (Gomez et al. 2014).

Shahar and colleagues conducted a double-blind randomised control study of 15 sessions of high frequency rTMS using either deep, Fig8 or sham coils over the right prefrontal cortex on 20 adults with ADHD, and found improvements in the attention measures using the Conner's Adult ADHD Rating Scales (CAARS) and response inhibition using the Stop Signal Reaction Time (SSRT) test (Shahar et al. 2014).

Paz and colleagues conducted a double-blind placebo-controlled trial of H-coil rTMS on 22 adults with ADHD. Participants were subject to either 4 consecutive weeks of rTMS sessions, of 5 days per week, with 55 cycles of pulses at 18 Hz, lasting 2 s per train, followed by 20 s intertrain interval at 120% MT of both prefrontal cortices, or sham rTMS. While improvements were seen in both the CAARS and the Tests of Variables of Attention (TOVA) scores, no differences were seen between the active and sham groups (Paz et al. 2017).

Harmelech and colleagues conducted a blinded sham-controlled trial of H-coil rTMS on 34 adults with ADHD, with participants randomised to receive either right, left or sham DLPFC rTMS after cognitive training, for 15 sessions spread over 3 weeks. Improvements were seen in the CAARS inattention subscale and the attention and executive function scores of the Mindstreams cognitive assessment battery for the group with right DLPFC stimulation, with increased activation of that area during a working memory task, as measured via fMRI (Harmelech et al. 2018).

Finally, Cao and colleagues conducted 2 trials examining the effects of rTMS on ADHD symptoms. 64 children with ADHD, aged 6 to 13, were assigned randomly to 3 groups, receiving 6 weeks of either

atomoxetine, rTMS (using a Fig8 coil, 5 sessions per week, of 25 minute sessions of 50 cycles of 4 s of 10 Hz stimulation followed by 26 s intertrain interval at 100% MT, totalling to 2000 pulses per session, of the right DLPFC, measured via moving 5 cm forward from the motor threshold), or both. Significant improvements were seen in the attention deficit, hyperactive/impulsive and oppositional defiance subscales of the SNAP-IV questionnaire, with a non-significant difference between the group treated with atomoxetine and the group treated with rTMS in the attention deficit and hyperactive/impulsive subscales, and non-significant differences between all 3 groups in the oppositional defiance subscale. Improvements were also seen in hot and cold executive functions, measured using the subscales of arithmetic, digit span and coding of the continuous performance test (CPT) and Weschler Intelligence Scale for Children (WISC), and the Iowa Gambling Task (Cao et al. 2018). A further study by Cao and colleagues had 66 patients with ADHD randomly divided to receive 6 weeks of either rTMS (using a Fig8 coil, 5 sessions per week, of 30 minute sessions of 60 cycles of 4 s of 10 Hz stimulation followed by 26 s intertrain interval at 100% MT, totalling to 2400 pulses per session of the right DLPFC, found via moving 5 cm forward from the motor threshold), sham rTMS (with the coil placed perpendicular to the scalp), atomoxetine (0.5 mg/kg/d, increased to 1.2 mg/kg/d after 3 days) or a placebo. Again, significant improvements were seen in the attention deficit, hyperactive/impulsive and oppositional defiance subscales of the SNAP-IV scale, with rTMS being almost as effective as atomoxetine, with no improvements seen in the sham rTMS and placebo groups (Cao et al. 2019).

Transcranial Direct Current Stimulation (tDCS)

Transcranial Direct Current Stimulation (tDCS) is another method of neurostimulation, using direct current passed through the scalp to stimulate brain areas. Current is passed through electrodes placed on the scalp, flowing from the anodal electrode to the cathodal electrode, with anodal stimulation depolarising neuronal membranes while cathodal stimulation hyperpolarising neuronal membranes. This causes long term changes in cortical excitability, with effects persisting post-stimulation, making it another method to treat neuropsychiatric conditions such as ADHD.

tDCS treatments normally involve a ramping up period, whereby current is slowly raised to the desired level, before being maintained at that level for the period of stimulation. Sham conditions normally involve having this ramping up period, but have the current turned off directly after the peak level has been reached. The dose of tDCS given during each course of treatment is dependent on the energy supplied per unit surface area, which is turn is affected by the intensity of stimulation, duration of stimulation and the surface area of electrodes used.

Much like with rTMS, the side effects of tDCS tend to be mild, mainly being skin lesions similar to light burns on areas where electrodes were placed, with a low incidence of mania or hypomania in depressed patients (Matsumoto and Ugawa 2017). Its therapeutic use has been investigated in different conditions including depression (Bennabi and Haffen 2018), schizophrenia (Agarwal et al. 2013) and ADHD 13 studies examining the effects of tDCS on ADHD symptoms were found, again mostly focusing on the DLPFC.

Cosmo and colleagues described a randomised control trial of 60 patients with ADHD aged 18 to 65. Participants were split into groups of 30, receiving a single session of either active tDCS (with anodal stimulation of the right DLPFC and cathodal stimulation of the left DLPFC, using electrodes of 5 x 7 cm, with 30 s ramping up time followed by 20 minutes of 1 mA stimulation, and 30 s ramping down time) or sham tDCS (with no stimulation apart from the initial 30 s ramping up time). No differences were found between the groups in changes in performance in the Go/NoGo task, with the effect size of group differences in changes in scores being small (Cosmo et al. 2015).

Soltaninejad and colleagues conducted a single-blinded crossover sham-controlled study of 20 high school students with ADHD symptoms, aged 15 to 17. Participants were rotated through 3 phases of the experiment, receiving a single session of either anodal stimulation (with the anode over the left DLPFC and cathode over the right supraorbital, electrodes of 7 x 5 cm, 15 s ramping up time followed by 15 minutes of 1.5 mA stimulation and 15 s ramping down time), cathodal stimulation (with the same conditions as the anodal stimulation, but with the cathode over the left DLPFC and anode over the right supraorbital instead) or sham stimulation (with no stimulation apart from the 15 s ramping up time). Participants were also made to perform the Go/NoGo task followed by the Stroop test after 8 minutes of stimulation in each condition, for the remaining period of stimulation. An interval of 72 h was given between phases. Anodal stimulation showed no effect on interference inhibition (as measured by the Stroop test), though an increased proportion of correct responses was seen in the Go portion of the Go/NoGo test. Cathodal stimulation, on the other hand, increased inhibition accuracy of the inhibition stage of the Go/NoGo task compared to sham stimulation (Soltaninejad et al. 2015).

Breitling and colleagues described a trial of 21 male patients with ADHD, matched with 21 healthy controls, aged 13 to 17. Participants were rotated through 3 phases of the experiment, receiving single sessions of either anodal stimulation (with the anode over the right inferior frontal gyrus and cathode posterior to the left mastoid, electrodes of 7 x 5 cm, with 30 s ramping up time followed by 20 minutes of stimulation at 1 mA and 30 s ramping down time), cathodal stimulation (with the same conditions as the anodal stimulation, but with the

anode posterior to the left mastoid and the cathode over the right inferior frontal gyrus) and sham stimulation (with 30 s of ramping up time followed by 30 s stimulation at 1 mA and

30 s ramping down time, electrode positions as per anodal stimulation). Participants were also made to perform the Flanker task after 5 minutes of stimulation, for the remaining period of stimulation. An interval of 1 week was given between phases. Due to a significant learning effect being observed between sessions, only the first session was taken into account. Improved interference control was observed in ADHD patients receiving anodal stimulation to almost comparable levels to controls, with impaired performance observed in ADHD patients receiving either cathodal or sham stimulation (Breitling et al. 2016).

Bandeira and colleagues described a trial of tDCS on 9 patients with ADHD, aged 6 to 16. 7 x 5 cm electrodes were used for both cathodal and anodal stimulation, with the cathode being placed over the right supraorbital area and the anode being placed over the left DLPFC. Stimulation was held at 1 mA for the 1st minute, before being increased to 2 mA for the 2nd to 29th minute, before being reduced to 1 mA for the final minute of stimulation before the end of the trial. Participants were made to play the game "Super Lynx", a game stimulating the DLPFC, during stimulation. 5 sessions were conducted over consecutive days for the trial. Participants showed an improvement in the selective attention part of the visual attention test (TAVIS-3), along with improvements in some stages of the Neuropsychological Development Assessment (NEPSY-II), namely the time to check information and the frequency of errors in the alternating attention task after stimulation. No improvements were seen in digit span (measured using the WISC-III) and visual working memory (using the Corsi cubes test), though (Bandeira et al. 2016).

Cachoeira and colleagues described a randomised, double blind, placebo-controlled trial of tDCS on 17 adults with ADHD aged 18 to 45 were randomised to receive either active or sham tDCS treatment, with anodal stimulation of the right DLPFC and cathodal stimulation of the left DLPFC, using electrodes of 7 x 5 cm. 2 mA of current was applied for 20 minutes per day for 5 consecutive days for the active tDCS condition, with the device being turned off 1 minute after the start of stimulation in the sham tDCS condition. Participants were instructed to relax, read, listen to music or sleep while being stimulated. Improvements were seen in the self-report ASRS scale in both the sham and active tDCS condition, with the improvement being greater in the active condition, though not significantly different from that of the sham condition. Closer examination of ASRS scores, however, revealed significant differences in the inattention subscale between active and sham conditions. Sheehan Disability Scales were also seen to be significantly lower in the active compared to the sham condition. These effects did seem to decrease with time, though (Cachoeira et al. 2017)

Soff and colleagues described a double-blinded randomised sham-controlled crossover study of 15 adolescents with ADHD, aged 12 to 16 years. Participants received either 5 sessions of active tDCS with anodal stimulation of the left DLPFC (involving a round anode of surface area 314 mm² and a cathode surface area of 1250 mm² over the vertex, with a ramping up period of 8 s before 20 minutes of stimulation at 1 mA, followed by 8 s ramping down period) or 5 sessions of sham tDCS (involving the same electrodes and placement, but with a ramping up time of 8 s followed by only 5 s of 1 mA stimulation before another 8 s ramping down), before 2 weeks of washout before receiving the other stimulation. Each stimulation session occurred while participants were in an MRI scanner, to record fMRI activity, as well as having a resting state fMRI scan directly after stimulation. Additionally, participants were made to do the n-back working memory paradigm before and during each session of stimulation. Active tDCS showed a significant reduction in clinical symptoms of inattention and impulsivity (assessed by the FBB-ADHD, filled in by parents) compared to the sham tDCS condition, and also showed a significant reduction in inattention and hyperactivity, measured by the QbTest. These effects were more pronounced 7 days after the end of stimulation (Soff et al. 2017).

Sotnikova and colleagues described a similar experiment using the same paradigm as (Soff et al. 2017), except using cathodes of 35 cm² and anodes of 13 cm². fMRI scans done found increased activation in the left DLPFC, left premotor cortex, left supplementary motor cortex and precuneus after active tDCS stimulation, with strengthened DLPFC connectivity outlining the working memory network 20 minutes after stimulation. Improvements in reaction time variability was also seen in active tDCS stimulation but not in sham stimulation (Sotnikova et al. 2017).

Nejati and colleagues conducted a randomised double-blind sham-controlled trial involving 25 children with ADHD, having moderate to severe SNAP-IV scores. 15 participants received either active stimulation (with anodal stimulation of the left DLPFC and cathodal stimulation of the right DLPFC, using 25 cm² electrodes, with a ramping up period of 30 s followed by 15 minutes of stimulation at 1 mA and 30 s ramping down period) or sham stimulation (with no stimulation apart from the 30 s ramping up period, with electrodes placed in the same position), followed by a 72 h washout period and reception of the other condition. Participants were made to perform the Go/NoGo task, n-back task, Wisconsin Card Sorting Task (WCST) and Stroop task after stimulation in each condition. No differences were observed in performance in the Go/NoGo and WCST tasks, with no improvements in working memory (measured by the n-back task), though reaction time was reduced and performance on the Stroop task improved in the active condition compared to the sham condition.

10 participants were instead rotated through 3 phases, consisting of anodal stimulation (with the anode over the left DLPFC and cathode over the right orbitofrontal cortex, using the same electrode size and stimulation protocol as the other group), cathodal stimulation (with the same protocol, but with the cathode over the left DLPFC and anode over the right orbitofrontal cortex) or sham stimulation (with electrode placement as per anodal stimulation, but with only 30 s ramping up time followed by no stimulation). Significant increases in NoGo accuracy was observed after cathodal stimulation compared to sham stimulation. Both anodal and cathodal stimulation reduced perseverative errors and total errors while increasing completed categories in the WCST, with anodal stimulation being more effective in doing so than cathodal stimulation. Accuracy and reaction time in the n-back task was seen to improve following anodal stimulation (Nejati et al. 2017).

Aycicegi-Dinn and colleagues described a study involving 53 university students with or without elevated scores on a measure of ADHD. Participants received a single tDCS session with anodal stimulation of the left DLPFC and cathodal stimulation of the frontopolar region, at an intensity of 2 mA for 20 minutes or sham tDCS. Participants receiving active tDCS did not obtain higher scores on measures of executive control and working memory, with no differences seen in performance in the California Verbal Learning Test (CVLT) and Rey Complex Figure Test (RCFT). That said, male participants receiving active tDCS were found to have higher scores on the CVLT compared to males in the sham group, a difference not seen in female participants (Aycicegi-Dinn et al. 2018).

Jacoby and Lavidor described a double-blind sham-controlled crossover study involving 20 adults with ADHD and 15 healthy controls, aged 19 to 29. Participants were rotated between single sessions of either double anodal bilateral tDCS (with anodes placed over the right and left DLPFC and cathode over the cerebellar cortex 1 cm below theinion, anode surface area 3 x 3 cm, cathode surface area 5 cm x 7 cm, 30 s ramping up period followed by 20 minutes stimulation at 1.8 mA and 30 s ramping down period) or sham stimulation (with the same electrodes and placement but no stimulation other than the initial ramping up period), with a 1 week period between each session. Participants were made to perform the MOXO-CPT test 20 minutes after each session, as well as the PANAS. Hyperactivity, as assessed by the MOXO-CPT, improved following active stimulation compared to sham stimulation in ADHD patients but not in controls, with all other measures assessed by the MOXO-CPT (impulsivity, reaction time and attention) showing only a learning effect (Jacoby and Lavidor 2018).

Allenby and colleagues conducted a double-blind sham-controlled crossover study involving 37 adults

with ADHD, aged 18 – 65. Participants were rotated through 2 phases of the experiment, each consisting 3 sessions (conducted on alternating days) of either active tDCS (with the anode placed over the left DLPFC, cathode over the right supraorbital area, 5 x 5 cm electrodes, 30 s ramping up period followed by 19 minutes of stimulation at 2 mA and 30 s ramping down time) or sham tDCS (with the same electrodes and placement but with a 30 s ramping up period immediately followed by a 30 s ramping down period at the beginning and end of the session instead), with a 2 week washout period between each phase of the experiment. Participants were made to perform a fractal n-back training task during each session. Participants were also made to do the Conners Continuous Performance Task and stop signal reaction time task 3 days after the final stimulation sessions of each phase of the experiment. Participants receiving active tDCS made fewer false positive errors compared to baseline, though no improvement was seen in true positive errors, response time or SSRT scores, and the effect on false positive errors did not persist at follow-up (Allenby et al. 2018).

2 studies were found analysing the effects of transient oscillating DCS (toDCS) on sleep in patients with ADHD, another function affected in the condition. Prehn-Kristensen and colleagues conducted a trial of toDCS on 12 boys with ADHD and 12 healthy boys aged 10 – 14. Electrodes were placed over the DLPFC and mastoids of participants, with current intensities ranging from 0 to 250 uA at a frequency of 0.75 Hz, initiated 4 minutes after participants fell into stage 2 non-REM sleep, for 5 cycles of 5 minutes of stimulation followed by 1-minute intervals free from stimulation. Participants were made to play the card game “Concentration”, involving an encoding session just before sleep and a retrieval session upon waking up. Memory loss in children with ADHD was worse than healthy controls, but this difference vanished after the toDCS session, with slow oscillation power in stage 4 non-REM being enhanced after toDCS (Prehn-Kristensen et al. 2014). Munz and colleagues performed a similar experiment involving 14 boys aged 10 to 14 with ADHD. The same protocol as (Prehn-Kristensen et al. 2014) was used, with cognitive performance assessed using the Go/NoGo task, the alertness subtest of the KiTAP and a finger sequence tapping task. Reaction times and variability, as assessed by the Go/NoGo task, were found to be shorter after the night of stimulation. No differences were found in alertness, though, and participants showed a gain in speed in the finger tapping task regardless of stimulation (Munz et al. 2015).

Vagus Nerve Stimulation (VNS)/ Trigeminal Nerve Stimulation (TNS)

Other methods of neurostimulation have focused on remedying the neurochemical deficits present in

patients with ADHD. Vagus nerve stimulation (VNS) is one such method, involving the electrical stimulation of the vagus nerve via a surgically-implanted electrode, delivering pulses at a programmable frequency, charge, duration and active period. It is currently used to treat treatment-resistant epilepsy. The exact mechanism of VNS is unknown, though it has been found that chronic VNS increases locus coeruleus (LC) activity in rats, as measured through direct recordings of neural activity (Groves et al. 2005) and via measurements of c-fos levels in the LC post-VNS (Naritoku et al. 1995). This seems to increase noradrenaline levels in the hippocampus and prefrontal cortex, measured via microdialysis (Roosevelt et al. 2006, Follesa et al. 2007).

Trigeminal Nerve Stimulation (TNS) works similar to VNS, using a small stimulator worn during sleep, emitting mild electrical signals which are conducted via adhesive electrode pads worn on the forehead over the trigeminal nerve. Again, through its connections with the LC (De Cicco et al. 2018), it could increase noradrenaline levels much like VNS, but without the potential side effects of vocal cord palsy and postoperative haematoma (Revesz et al. 2016).

Given the possible involvement of the noradrenergic system in ADHD (Pliszka 2005), VNS and TNS could represent a new method of treating ADHD. No studies have been done to assess the effects of VNS on patients with ADHD directly, though trials on healthy controls have yielded some positive results – VNS has been seen to enhance post-error slowing (Sellaro et al. 2015), which is deficient in patients with ADHD (Balogh et al. 2016); VNS is also seen to have a positive effect on response inhibition as measured by a stop-signal task (Schevernels et al. 2016), another deficit in patients with ADHD.

2 studies examining the effects of TNS on patients with ADHD were found. McGough and colleagues described an 8-week trial of TNS on 21 children with ADHD, aged 7 to 14. TNS was administered to children, at a frequency of 120 Hz, 250 us pulse width, and a duty cycle of 30 s on and 30 s off, with bilateral stimulation of the V1 branches of the trigeminal nerve for 7-9 h per night. Symptoms of inattention and hyperactivity / impulsivity, measured by the ADHD-RS were found to improve after the treatment, with reductions in CGI-I scores as well. Parental reports using the Behaviour Rating Inventory of Executive Functioning (BRIEF), showed improvements as well. Improvements were also seen in the Attention Network Task (ANT) incongruent reaction times, alongside improvements in sleep anxiety and sleep problems, as measured by the Children's Sleep Habits Questionnaire (CSHQ) (McGough et al. 2015). A further sham-controlled double-blind study by McGough and colleagues involving 62 children with ADHD aged 8 to 12 was done. Participants were randomised, receiving either active or sham TNS, with bilateral

stimulation of the V1 branch of the trigeminal nerve for 8 h per night for 4 weeks, with the active TNS group receiving stimulation of 2–4 mA, with the same protocol as the earlier study by the same group. ADHD-RS scores of both groups showed improvements during the first week, with improvements in subsequent weeks seen only in the group having active stimulation. The group receiving active stimulation also showed significantly improved CGI-I scores compared to the group receiving sham stimulation. No differences were seen between groups in CSHQ scores, though (McGough et al. 2018).

Other methods

Other methods of treating neuropsychiatric conditions using neurostimulation include deep brain stimulation (DBS), ultrasound stimulation and electroconvulsive therapy (ECT).

Deep Brain Stimulation (DBS) is the surgical implantation of an electrode in an area of the brain, allowing for the delivery of electrical stimuli which disrupt abnormal patterns of neural signalling or stimulate the area of the brain which the electrode is implanted. DBS is currently used to treat Parkinson's disease (PD), essential tremor, dystonia, epilepsy, Tourette syndrome, chronic pain, depression and obsessive-compulsive disorder (Delaloye & Holtzheimer 2014, Martinez-Ramirez et al. 2018, Laxatives et al. 2014). Similar to tDCS and rTMS, it could be used to directly stimulate areas of the brain that show abnormal activity in patients with ADHD, albeit being an invasive procedure. No trials have been conducted to treat ADHD with DBS. Much like with VNS, the invasive nature of the procedure would make it unlikely to be approved for treatment of ADHD.

Ultrasound stimulation another possible method of noninvasively stimulating focal areas of the brain, making it a possible treatment for ADHD, given the specificity of brain regions affected in the condition. Low intensity focused ultrasound is used to stimulate areas of the brain with greater resolution and depth (Bystritsky et al. 2011). Current research in its use in medicine has focused on mental states (Hameroff et al. 2013) and diagnosis of psychiatric conditions (Drepper et al. 2017), with no research conducted on its therapeutic use in ADHD.

Electroconvulsive Therapy (ECT) is a method of neurostimulation involving the passage of electrical current to induce a seizure in patients (when under general anaesthesia), causing relief of neuropsychiatric symptoms. It has been used in the treatment of depression, catatonia and schizophrenia (Weiner and Reti 2017), with high remission rates (Kellner et al. 2010) though it has been associated with memory loss and cognitive deficits (Sackheim et al. 2007). Again, as yet no studies analysing the effects of ECT on ADHD symptoms have been done.

DISCUSSION

As seen above, some studies have been done analysing the effect of rTMS on ADHD symptoms, mostly focusing on stimulation of the DLPFC, with some investigating the stimulation of other areas, including the PFC (Paz et al. 2017, Shahar et al. 2014) and the motor areas (Niederhofer 2008, Niederhofer 2011). The studies investigating the effects of rTMS on DLPFC stimulation mostly agreed with each other – increasing the excitability of the right DLPFC through high frequency rTMS and decreasing the excitability of the left DLPFC through low frequency rTMS improve ADHD symptoms (Weaver et al. 2012, Bloch et al. 2010, Gomez et al. 2014, Harmelech et al. 2018 and Cao et al. 2018), albeit with (Ustohal et al. 2012) reporting the worsening of depression in a patient with right DLPFC stimulation, with improvements in ADHD symptoms in left DLPFC and sham stimulation. The studies on PFC stimulation have had mixed results, with (Shahar et al. 2014) reporting improvements in ADHD symptoms while (Paz et al. 2017) reporting no differences in results between active rTMS and sham rTMS.

That said, there are problems with these studies – most of them have small sample sizes, all of them except (Cao et al. 2018, Cao et al. 2019) having less than 30 participants, decreasing the power of the studies. Study populations have been heterogenous, with some recruiting children while others recruiting adults. This could be a problem if rTMS works differently at different ages. Further, the determination of the area of stimulation in the studies have generally been via usage of approximations, via moving the stimulator 5 cm anterior from the area where the motor threshold is determined, which could raise questions on the precision of stimulation target. Perhaps more accurate ways of determining the location of the DLPFC could be made (eg. Through the use of infrared neuronavigation or correlational fMRI). Finally, outcome measures have been rather heterogenous, with different scales being used, ranging from the CGI-I, CSRS, ADHD-IV and SNAP-IV to task performance in the IGT, CPT TOVA and SSRT. Standardisation of outcome measures and sample populations could be done perhaps using a single agreed ADHD symptom scale and the use of multiple tasks to judge the efficacy of treatment on different groups of patients, even following their symptoms through time via having follow-up studies on the same population.

Studies analysing the effect of tDCS and toDCS on ADHD symptoms have mostly focused on stimulation of the right DLPFC and inhibition of the left DLPFC or the reverse, with a study focusing on the inferior frontal gyrus (Breitling et al. 2016) and 2 studies investigating the effect of toDCS.

Studies investigating the effect of right DLPFC stimulation and left DLPFC inhibition have yielded mixed results, with (Cosmo et al. 2015) finding no

differences in test performance, while (Cachoeira et al. 2017) finding improvements in the ASRS and (Soltaninejad et al. 2015) noting improvements in inhibition accuracy in the Go/NoGo task. Studies investigating the effect of left DLPFC stimulation have yielded more positive results, patients having left DLPFC stimulation had an increased proportion of correct responses in the Go portion of the Go/NoGo task (Soltaninejad et al. 2015), improvements in selective attention in the TAVIS, improvements in time to check information and reduced errors in the alternating attention task in the NEPSY (Bandeira et al. 2016), reduced clinical symptoms of inattention and impulsivity, as reported by parents as well as through the QbTest (Soff et al. 2017), reduced reaction time in the Stroop test, reduced perseverative errors and total errors in the WCST, improved accuracy and reaction time in the n-back test (Nejati et al. 2017), improvements in the CVLT (Aycicegi-Dinn et al. 2018) and fewer false positive errors in the CPT test (Allenby et al. 2018). One study focused on IFG stimulation, reporting increased interference control in the flanker task (Breitling et al. 2016). toDCS also seems to show results, with improvements in memory (Prehn-Kristensen et al. 2014) and reaction times and variability in the Go/NoGo test (Munz et al. 2015) being reported.

However, the same problems can be seen in these studies as with the studies on rTMS – all of the studies have small sample sizes of less than 60, with some having as few as 9. Study populations are again heterogenous, with participants coming from different age groups and having different inclusion criteria. Outcome measures are again heterogenous, with multiple different tasks being used, making it difficult to compare results. All in all, a trial of tDCS with more participants, standardised outcome measures and inclusion criteria could be done, perhaps through multi-centre trials.

The invasive nature of VNS implantation and its potential associated side effects could make VNS unlikely to be approved for the treatment of ADHD, given the other less invasive methods of stimulation, including TNS. That said, a study analysing the effects of VNS on ADHD symptoms could be done, given the increased incidence of ADHD in epileptics (Williams et al. 2016) and its use to treat symptoms of epilepsy. This could allow the indirect observation of the effects of VNS on ADHD symptoms, albeit in a select group of patients with the condition.

As seen through the 2 studies analysing the effects of TNS on ADHD symptoms, TNS seems to be a promising new method of treating ADHD, with both studies showing improvements in ADHD symptoms, as measured through different tasks, including the ANT, ADHD-RS and CGI-I. That said, more studies could be done with larger sample sizes to confirm these findings, as well to assess the safety and compliance of patients for this method of treatment.

No studies have been done analysing the effects of DBS on ADHD symptoms, with the procedure being unlikely to be approved for the treatment of ADHD, given its invasive nature. Ultrasound, on the other hand, could represent a potentially new method of treating ADHD, given its specificity in targeting brain areas while being non-invasive in nature. Studies could be done focusing on stimulation of the DLPFC or the IFG, areas known to be affected in ADHD, to study its effects on ADHD symptoms.

No studies have been done analysing the effects of ECT on ADHD symptoms, though much like with VNS, studies could be done to indirectly observe the effects of ECT on ADHD symptoms in patients with comorbid depression or schizophrenia being treated using ECT.

CONCLUSION

In conclusion, research suggests that in ADHD, there is underlying disturbance in neurotransmitter pathways and select regions of the brain, ultimately manifesting as significant problems with inattention, hyperactivity and impulsivity. Current methods of treating the condition mainly with pharmacotherapy has been associated with side effects and indeed fail to work in a significant minority of patients. Given this situation, Neurostimulation could be a promising new method of treating ADHD, with fewer side effects. Many studies analysing effects of Neurostimulation such as rTMS and tDCS on ADHD symptoms has yielded generally positive results. However, more studies with greater sample sizes, standardisation of treatment parameters and outcome measures are needed to confirm these findings. Other methods of neurostimulation, including, ultrasound stimulation and electroconvulsive therapy could represent new ways of treating ADHD, though their effects have not been studied directly.

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Contribution of individual authors:

Heng Chun Wong carried out the literature search and analysis and wrote the first draft of the manuscript.

Rashid Zaman conceived and supervised the project, carried out literature search and revised the manuscript.

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AN AUDIT OF THE REPORTING OF DEPRESSION & ANXIETY IN COPD PATIENTS

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SUMMARY

Anxiety and depression contribute to a substantial burden of Chronic Obstructive Pulmonary Disease-related morbidity by impairing quality of life and by reducing adherence to treatment. The identification of COPD patients with comorbid depression or anxiety symptoms is vital, as it is estimated that only a third of patients with these co-morbidities are receiving appropriate treatment. The aim of this audit was therefore to identify whether current methods of anxiety and depression screening in elderly patients (over the age of 65) with severe COPD (FEV1 <50% at most recent spirometry reading) are adequate by assessing how frequently anxiety and depression is reported as "discussed with patient" in COPD review appointments across two practices. SystemOne was used to identify a total of 83 patients, and the recording of depression and anxiety discussions in this cohort's review appointments was analysed and compared with the incidence of QOF-coded depression and anxiety in the patient notes. The results show that both the rate and the quality of depression and anxiety reporting in these review appointments is highly heterogeneous, and has led to 'missed' patients suffering from comorbid mental health issues. Additionally, this audit identified a number of patients with depression or anxiety directly related to their COPD, and it highlighted a trend among this cohort towards more frequent appointments with their General Practitioner, and towards related presentations at the Emergency Department. The results of this audit suggest there is room for amelioration of the current practice, such as the implementation of a structured screening tool into System One's COPD review appointment template.

Key words: audit - depression - anxiety - COPD

* * * * *

INTRODUCTION

Anxiety and depression contribute to a substantial burden of COPD-related morbidity by impairing quality of life and reducing adherence to treatment (Yohannes et al. 2010). In a recent longitudinal study by Schneider et al. (2010) looking at 35 000 patients with COPD over a 10 year period, the incidence of depression was 16.2 cases per 1000 person-years in the COPD group compared with 9.4 cases per 1000-person years in the non-COPD control group. This study also found that those with severe COPD were twice as likely to develop depression compared with patients with mild COPD. This is generally corroborated by the literature, with studies suggesting that the prevalence of anxiety and depression in COPD are "generally higher than those reported in other advanced chronic diseases" (Maurer et al. 2008). In addition to supporting the idea that patients with COPD have a higher risk of anxiety and depression than controls without the condition, studies such as that by Eisner et al. (2009) found that the higher the severity of COPD, and consequently the higher the degree of dyspnoea, the greater the risk of anxiety among patients.

Untreated depression and anxiety in patients with COPD have negative effects on their physical functioning and their social interaction, including increased fatigue and healthcare utilisation (Dalal et al. 2011). Depressed patients with chronic physical illnesses have

been found to be more severely affected than their non-depressed counterparts across a range of medical illnesses including diabetes (Ciechanowski et al. 2000). This is no different for COPD: both anxiety and depression have been found to be significantly associated with decreased functional status and worse health status in patients with psychological symptoms comorbid with COPD, compared to those without psychological symptoms. While there is evidence that depression and anxiety in COPD may be treated with pharmacological therapy (Argyropoulou et al. 1993) or as little as a single cognitive behaviour therapy session (Kunik et al. 2001), fewer than one third of COPD patients with comorbid depression or anxiety symptoms are receiving appropriate treatment (Yohannes & Alexopoulos 2014). Maurer et al. (2008) attribute this to barriers on a patient, physician, and system level. These barriers include, on a patient level, a lack of patient knowledge and a real or perceived stigma regarding mental illness. However, one of the major factors that is consistently identified throughout the literature as being a barrier to detecting mood disorders in the COPD population is the lack of a consensus on the most appropriate screening tool for identification of anxiety and depression in patients with COPD. Many of the screening tools for depression and anxiety contain somatic symptoms, and thus overlap with the physical symptoms of COPD. This makes the interpretation of these scales more challenging.

CURRENT GUIDELINES

NICE Guideline *Chronic obstructive pulmonary disease in over 16s: diagnosis and management* (2018) recommendation 1.2.95 is as follows: “Be alert for anxiety and depression in people with COPD. Consider whether people have anxiety or depression, particularly if they have severe breathlessness, are hypoxic, or have been seen at or admitted to a hospital with an exacerbation of COPD”.

NICE *Clinical Guideline 19*, recommendation 1.3.1 is as follows:

Ask patients with a chronic physical health problem two questions:

- During the last month, have you often been bothered by feeling down, depressed or hopeless?
- During the last month, have you often been bothered by having little interest or pleasure in doing things?

If a patient answers yes to either of the depression identification questions, they should be referred to an appropriate professional who is competent to perform a mental health assessment.

AIMS, OBJECTIVES AND STANDARDS

The aim of the audit was to identify whether current methods of depression screening in elderly patients

(over the age of 65) with severe COPD (FEV1 <50%) are adequate. Therefore the objectives were to assess how often anxiety/depression is reported as “discussed with patient” in COPD review appointments and to assess how effective this is as a method of screening for depression or anxiety in the selected cohort. The standards used were NICE guideline CG19 and NICE guideline CG101 (2018 update) described above.

COPD REVIEW TEMPLATE

This is the page of the template currently used in the COPD review appointment in the GP Computer System, SystemOne. The area of interest is whether "Anxiety/Depression discussed with patient" (highlighted in red, answer "discussed with patient") is an adequate method to screen for depression in this high risk, complex group of patients (Figure 1).

METHODOLOGY

The populations of two general practices were searched on the practice computers for patients aged 65 years or older (“elderly”) AND patients with a FEV1 < 50% at their latest spirometry reading.

Patients were identified from QOF indicators list of achieved COPD patients.

The screenshot shows a form titled "COPD Diagnostic Codes" with fields for Chronic bronchitis, Emphysema, and Chronic obstructive lung disease, each with a red 'R' and an 'X' icon. Below this is a "Spirometry codes" section with fields for FEV1 and FEV1/FVC codes. A "Show Medication/History" button is present. The "Anxiety/Depression discussed with patient" field is highlighted with a red border. Below this is a "Sputum appearance" field with a red 'R' and an 'X' icon. The "Review Codes" section includes fields for MRC breathlessness score and COPD review codes. The "Inhaler technique" section has radio buttons for various techniques. The "Pulse Oximetry" section has fields for pulse oximetry and a checkbox for "Record Oxygen Saturation level for all patients with MRC score 3 or above".

Figure 1. COPD review appointment in the GP Computer System, SystemOne

Data was collected by searching of tabbed journal using key words:

- FEV1
- COPD
- Depression / depress / low / mood / low mood
- Anx / anxiety / worried / worri /worry.

The GP computer system ‘SystmOne’ was used to identify a total of 83 patients across the two GP practices audited, and the recording of depression and anxiety discussions in this cohort’s review appointments was analysed and compared with the incidence of QOF-coded depression and anxiety in the patient notes.

In the first practice, this search identified 47 patients aged 65 and over who were recorded as having an FEV1 of <50% at their most recent spirometry reading (severe COPD). In the second practice, 36 patients meeting the inclusion criteria were identified. Once the cohort had been identified, Information was collected on when their COPD diagnosis was coded in their record, when their last COPD review appointment was, the most recent date that “Anxiety/Depression discussed with patient” was recorded, whether they had previously had a depression screen from another review appointment, whether (and how) depression/anxiety/low mood previously was recorded in the patient notes, and whether the patient was or had previously been treated for mental health issues.

RESULTS

Practice 1

81% of patients had had "Anxiety/Depression discussed with patient" recorded as part of their most recent COPD check. 9% of patients had had this in a COPD check from the previous year. For 6% of patients, it had been more than 1 year since "Anxiety/Depression discussed with patient" had been recorded in their COPD check, despite several more recent COPD review appointments. For 4% of the sample, this had never appeared in their COPD review (Figure 2).

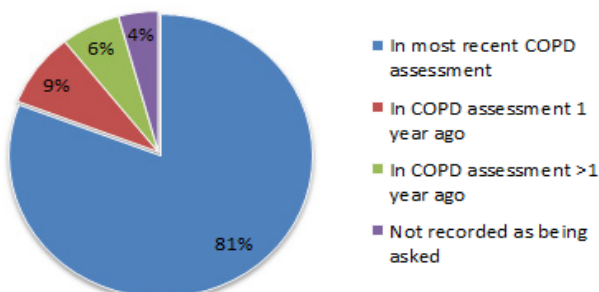


Figure 2. Most recent recorded data of “Anxiety/Depression discussed with patient”

Of the 47 patients in the cohort, 66% had only had formal depression screening in the form of the "Anxiety/Depression Discussed with patient" from COPD review appointments. 15% had been assessed using a

questionnaire as part of their diabetes review, 9% had been assessed in a similar, more formal way, as part of their CHD review. 6% had been screened as part of a different review appointment (examples included a Mental Health Physical Check). 4% had no depression screening recorded in any format on their notes (Figure 3).

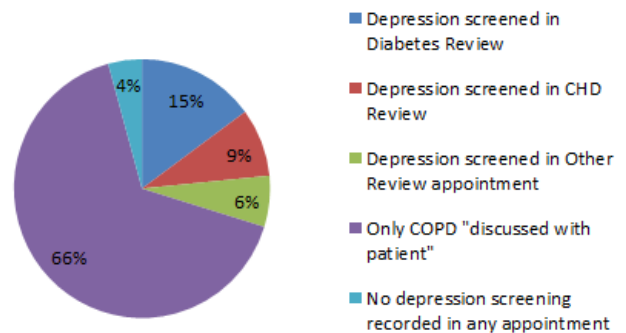


Figure 3. Screening for depression in other appointments

Of the 34% of patients with depression recorded in their notes, 87.5% were receiving active treatment or had been previously medically treated for either depression or anxiety. 31.2% of patients' depression was documented after their diagnosis of COPD. 31.2% of patients had depression or anxiety recorded as related to their COPD. Only 2 patients had low mood/depression/mental health symptoms documented in their COPD review appointments. 34% of the cohort (16 patients) had depression/low mood/anxiety recorded in their notes in some way. Of these patients, 14 were being or had previously been receiving medication for this. 5 patients had depression documented after their diagnosis with COPD. 5 patients had recorded links between COPD and their depression/anxiety. Only 2 patients had low mood/depression/mental health symptoms actively documented on their COPD review appointment notes (Figure 4).

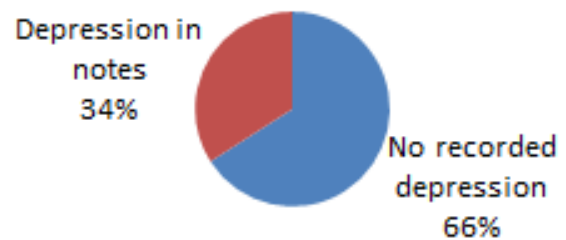


Figure 4. Recording of depression in patient notes

Practice 2

In practice 2, 39% patients had ‘Anxiety/depression discussed with patients’ recorded in their most recent COPD review assessment, while the majority (42%) had had this in their assessment 1 year ago. It had been more than 1 year since this had been recorded in the COPD review assessment for 11% of patients, and 8% of the identified cohort had not been had this coded in their review assessment at all (Figure 5).

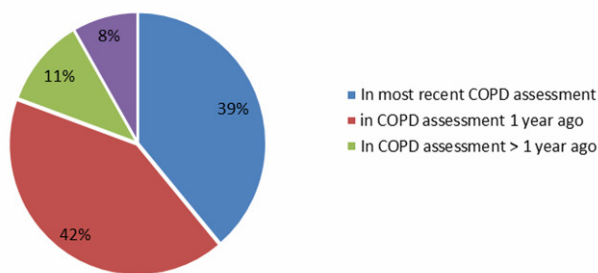


Figure 5. Most recent recorded data of “Anxiety/Depression discussed with patient”

In practice 2, as in practice 1, the majority of patients had not had depression recorded anywhere in their patient notes. However, of the 22% of patients who did have recorded depression elsewhere in their notes, 75% were currently receiving or had previously received medical treatment for this depression. As many as 8 patients at practice 2 had recorded symptoms of mental health issues related in part to their COPD, including “lack of confidence going out alone” and feeling “low due to reduced mobility”. 6 patients had had ‘low mood’ or symptoms of anxiety recorded in their notes after depression screening in their COPD review, but there was no follow-up or treatment for this recorded in their notes (Figure 6).

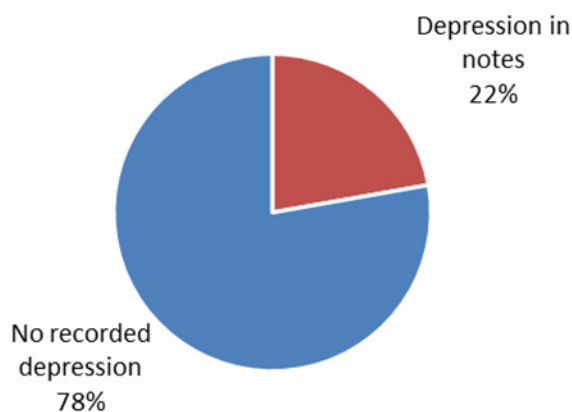


Figure 6. Recording of depression in patient notes

CASES TO CONSIDER

We here discuss the issues raised by two patient records which raise issues common to all the records examined:

Case 1

The patient had a COPD review in 2017, in which it was recorded that depression/anxiety was discussed with patient. No other reference to depression, anxiety or mood was noted. However, soon after the COPD review, the patient had an appointment with their GP in which he presented with a low mood which he described as feeling “linked to his chronic diseases, esp (ecially) breathing which stops him from doing what he

would like to be able to do”. The GP recorded this encounter as a severe depressive episode, and the patient was subsequently started on mirtazepine.

Points raised by this case are that although the notes for the COPD review appointment recorded having discussed anxiety/depression with patient, there was no further documentation of low mood, depression or other mental health symptoms at this appointment. Hence the following questions arise; Is the current method not adequate at identifying depression in patients? Or are the patient’s answers not being documented thoroughly enough? Furthermore, would identification of depression during the COPD review appointment have had an impact on the patient’s care?

Case 2

Patient 2 had not had ‘anxiety/depression discussed with patient’ documented in his COPD review appointment notes since 2016, although he had attended a more recent COPD review in 2017. However, “low mood” was found to be documented in COPD review appointments in July 2016, January 2016, July 2015, and May 2015. The patient had a history of severe recurrent depression documented since 1985, and COPD was coded in the notes from 2014. In 2015, the patient had several GP consultations where he was noted to be “very anxious about COPD”, “worried re COPD”, “very anxious, stopped going out around people in case he gets an infection”.

Points raised by this case are that, in contrast to case 1, the COPD review appointments for patient 2 had documented some discussion of low mood beyond “anxiety/depression discussed with patient”. So what arises are questions as to what accounts for the variation in reporting, both between cases and between individual appointments for patients? Should there be a unified objective system that would allow for more reliable identification of people suffering from COPD-related depression and/or anxiety? Despite recurrent episodes of depression throughout his life, patient 2 began experiencing clear issues linking his physical health condition to his mental health following his diagnosis of COPD. So does this reinforce the idea of improved depression screening in patients with COPD even if they are known to suffer or previously had suffered from depression? Finally, would this have an effect on the number of GP appointments made by these patients?

CONCLUSIONS

In practice 1, 81% of patients have had “Anxiety/Depression discussed with patient” recorded at their most recent COPD review appointment. This is a good rate of recording, but could be improved upon, in light of the fact that 4% of the cohort had never had this recorded in their notes in any form. In practice 2, the rate of recording at the most recent COPD review

appointment was much lower, with only 39% of patients having had "Anxiety/Depression discussed with patient" marked. There is scope for improvement in the rate of recording at this practice. In practice 1, 16 patients had depression or anxiety recorded in their notes, but only 2 patients had any mention of low mood, depression, or other mental health issues in their COPD review appointments. In practice 2, 6 patients had low mood, depression, and other mental health issues recorded in their COPD review appointments using the free text option in the online form. This, in combination with the cases discussed previously, highlights the fact that depression and anxiety documenting in the COPD review appointments is widely heterogeneous, with an overarching tendency to have no additional information documented. This may suggest that the free text option in the COPD template is being underused, or used inconsistently, and these issues are being under-documented if they are being discussed in the appointments. The results may also indicate that simply discussing anxiety/depression with the patient is not an adequate method of screening for and identifying these mental health conditions in this cohort, and may be leading to potential missed cases.

In practice 1, 5 patients were found to have depression or anxiety related to their COPD, and had frequent GP appointments and/or ED attendances as a result of these issues. A comparable number of patients in practice 2 were recorded as having low mood or anxiety linked to the physical symptoms of COPD. This may suggest that support for, education about, and management of COPD-related depression is not currently at a high enough level for patients in this cohort. Changes made in this area may therefore lead to a reduction in such appointments or emergency presentations.

5 patients in practice 1 and 6 patients in practice 2 were documented as having depression/anxiety/other mental health problems which were recorded after the date of their COPD diagnosis. These results may corroborate the findings from other studies and meta-analyses which have identified a link between COPD and depression and anxiety. However, 70% of patients in the total cohort of the two practices combined had no recorded depression, anxiety or other mental health issues in their notes. Furthermore, the sample size of this audit was relatively small, which limits the interpretation of these results. Further investigation on a larger scale would be required to further confirm this conclusion.

Suggestions for future practice

Suggestions for future practice include: encourage healthcare professionals to use the blank fill boxes in the template and record mood assessments more thoroughly; integrate the use of the two questions recommended by NICE CG19 for use in screening for depression in patients with chronic physical health

conditions into the COPD review appointment. These are as follows:

- During the last month, have you often been bothered by feeling down, depressed or hopeless?
- During the last month, have you often been bothered by having little interest or pleasure in doing things?

These questions are the PHQ 2, and are validated questions for screening for depression. Positive answers should lead to a full assessment for depression.

Integration of a more structured depression/anxiety screening tool into the COPD review appointment template could mitigate the subjective nature of the current system, which is subject to variation depending on the professional carrying out the review appointment.

Alternatively, Self-assessment questionnaires regarding depression or anxiety could be filled out by the patient before the appointment to help improve time constraint issues. Suggestions from the nurses who undertake the COPD review appointments included self-assessment questionnaires that patients would be able to fill out in the waiting rooms prior to their appointment. Such self-assessment questionnaires could be the PhQ 9 and the GHQ 7, which are currently used in the QOF for screening for depression and anxiety respectively.

Action plan

We recommend the following action plan; to implement one or more changes detailed in these recommendations above, and to re-audit in 6/12 in order to demonstrate changes in practice. Furthermore, comparison with a younger age group could provide insight into confounding factors including age. One study (Cleland et al. 2007) found that anxiety and depression did indeed differ by age group of patients with a diagnosis of COPD, but found that clinically significant levels of depression and anxiety were in fact more prevalent in patients aged less than 60 years old, thus suggesting that psychological comorbidities are more common in younger patients. An audit of the two practices' younger patients with COPD could therefore help to illuminate this issue further.

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Juliette Murphy & Gloria Lau developed the Audit Standards and carried out the audit.

Mark Agius supervised the analysis and writing up of the project.

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EMOTIONALLY UNSTABLE PERSONALITY DISORDER IN PRIMARY CARE: A THEMATIC REVIEW AND NOVEL TOOLKIT

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SUMMARY

Emotionally Unstable Personality Disorder (EUPD) causes significantly impaired personality functioning to include feeling of emptiness, lack of identity, unstable mood and relationships, intense fear of abandonment and dangerous impulsive behaviour including severe episodes of self-harm. The vast majority of EUPD patients are managed in the community, and have less contact with specialist psychiatric services when compared to patients with other mental illnesses. Despite the burden of this condition on primary care, the academic literature focuses on EUPD in psychiatric inpatients. This paper therefore aims to redress this balance through, first, establishing the key themes present in the available body of work on EUPD in the community, and second, highlighting areas for future research. Further, in the spirit of reducing stigma surrounding mental illness, the authors present a novel and non-pejorative toolkit for the recognition of EUPD in primary care.

Key words: Emotionally Unstable Personality Disorder - psychiatric services - community - stigma

* * * * *

INTRODUCTION

Emotionally Unstable Personality Disorder, also known as Borderline Personality Disorder, is defined as causing 'significant impairments in personality functioning with one or more pathological personality traits' (APA 2013). Those with EUPD demonstrate – most notably – intense and unstable interpersonal relationships, dysregulation of emotions and impulses and an inconsistent sense of self (Beatson & Rao 2013). Such personality traits persist across time and place, causing affected individuals marked functional impairment such as high rates of unemployment and social exclusion (Javaras et al. 2017).

Despite this, it is well documented that fewer personality disorder patients make contact with psychiatric services when compared to those with other conditions such as depression or schizophrenia (Andrews et al. 2001). This can be at least partially explained by the absence of evidence based and effective pharmacotherapy for EUPD, as well as the prevalence of stigma associated with the diagnosis felt by patients and practitioners alike (Beatson & Rao 2013, Wehbe-Alamah & Wolgamott 2014). The net result is that the vast majority of personality disorder patients reside in the community with only occasional contact with secondary psychiatric care, usually in the form of psychotherapy (Beatson & Rao 2013). Thus personality disorders represent a significant burden on primary care (Moran et al. 2000).

The high prevalence of personality disorders in patients attending primary care has been quantified as up to 4.4% of the general household population (Moran et al. 2000, Coid et al. 2006). Yet the academic literature on emotionally unstable personality disorder is lar-

gely focused on the condition in psychiatric inpatients and thus confers limited value to the vast majority of patients contending with the challenges of 'real world functioning' in the community (Javaras et al. 2017).

This paper therefore aims to redress this balance through, first, establishing the key themes present in the available body of work on EUPD in the community, and second, highlighting areas for future research. Further, in the spirit of reducing stigma surrounding mental illness, the authors present a novel and non-pejorative tool for the recognition and diagnosis of EUPD in primary care.

METHODS

Design

This paper employed a systematic, thematic analysis of the academic literature accessible via the online repository PubMed, relating to emotionally unstable personality disorder in the community. The authors agreed upon the following search terms and combinations to locate a total of 30 related works (Table 1).

Data Selection and Analysis

Once the 30 papers had been retrieved, the authors independently reviewed the abstracts, excluding works that had no clear link to primary care in the UK, including papers based on findings from non-comparable healthcare systems. The authors discussed excluded papers and underlying rationale to produce the final set of 17 papers of clear relevance to emotionally unstable personality disorder as encountered in the UK primary care setting.

Table 1. Search Terms

Key Words	Combined Search Terms	No. Papers Retrieved
EUPD, Emotionally Unstable Personality Disorder	-	-
BPD, Borderline Personality Disorder	-	-
Community	EUPD + Community BPD + Community	24
General Practice	BPD + General Practice EUPD + General Practice	1
Primary Care	BPD + Primary Care EUPD + Primary Care	5

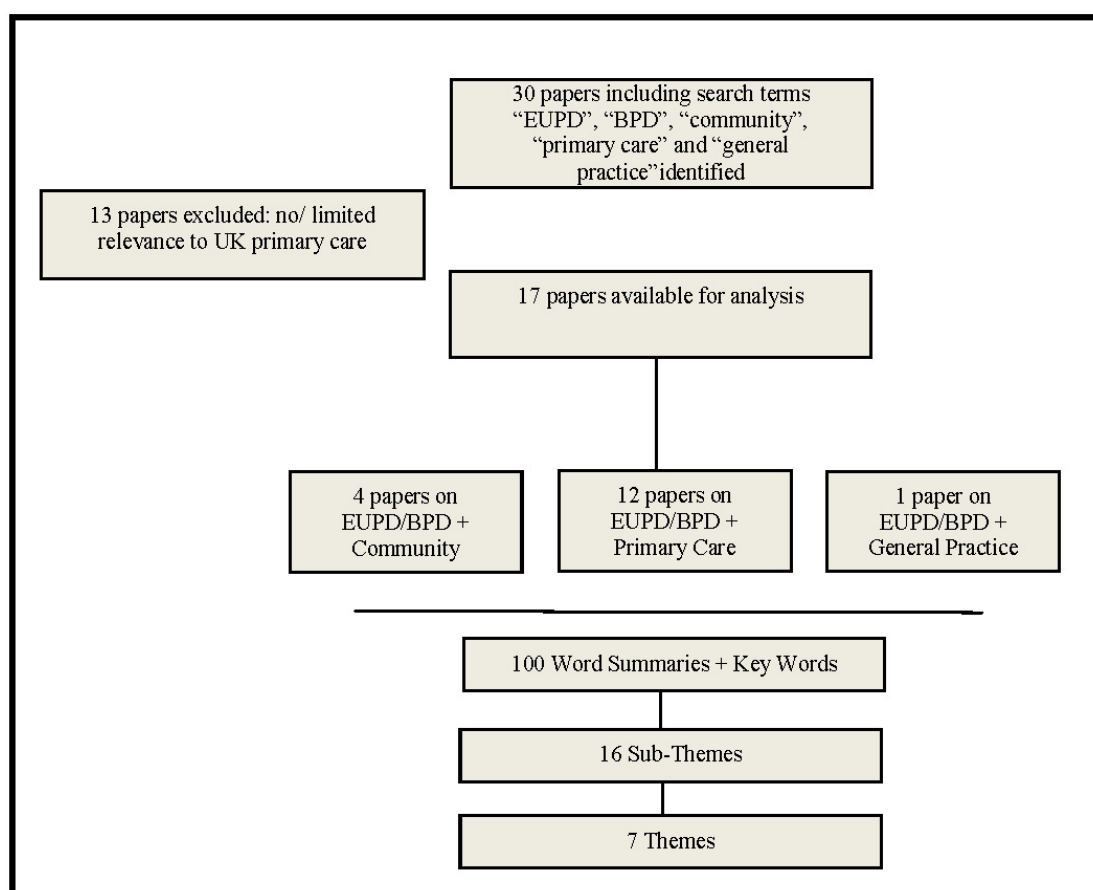


Figure 1. Flow chart of process for data selection and analysis

The authors carried out inductive thematic analysis to generate and refine emerging trends upon reading the papers making up the final data set, using methods described by Braun and Clarke (2006). For each paper, the authors independently produced a summary of up to 100 words, and then from the summary selected key words. The next level of analysis involved a collaborative effort to produce 16 sub-themes from the key words, before the sub-themes were subsumed into the final set of seven themes. The process for data selection and analysis is summarised in Figure. 1.

RESULTS

Inductive thematic analysis revealed 16 subthemes, which were subsumed into a total of seven broader themes characterizing the patient and practitioner

experiences of emotionally unstable personality disorder in the community setting. The themes include therapeutic relationships, psychiatric and medical comorbidities, patient functioning and EUPD prevalence, recognition, and management in primary care. The seven themes are displayed along with exemplar quotes from the existing literature in Table 2.

DISCUSSION

EUPD Prevalence in Primary Care

EUPD is not an uncommon psychiatric diagnosis in patients looked after by their GP. The proportion of patients cared for in the community with EUPD has been variably reported as between 4-6% (Sievewright et al. 1991, Gross et al. 2002, Coid et al. 2006). Personality disorder is particularly common in urban areas,

Table 2. Themes, Subthemes and Exemplar Literature

Theme	Subthemes	Exemplar Literature
The Thera- peutic Relation- ship	Stigma	<p>“ There may be no psychiatric diagnosis laden with more stereotypes and stigma than borderline personality disorder” (Nehls 2000)</p> <p>" Clinicians perceive patients with BPD as being manipulative and difficult" (Nehls 1998)</p> <p>" Recent ethnographic work has demonstrated that nurses show less sympathy for them than patients with other mental illnesses" (Rogers & Dunne 2011)</p> <p>"This paper identifies that patients with an overt diagnosis of personality disorder are believed to be harder to manage by clinicians than those with a covert diagnosis of personality disorder." (Tyrer et al. 2008)</p>
	Communication & Boundaries	"Doctors who exhibit judgmental attitudes when dealing with demanding complex patients may validate the sense of abandonment experienced by BPD patients" (Holm et al. 2009, Raven 2009)
Psychiatric Comorbidity	Depression	<p>"Major depressive disorder (MDD) commonly co-occurs with BPD. The lifetime prevalence of major depression in the course of BPD was 83% in one large study"</p> <p>"The consensus of informed opinion over many years has been that depression co-occurring with BPD does not respond as well to antidepressant medication as depression in the absence of BPD" (Beatson & Rao 2013)</p>
	Substance Misuse	<p>"Chronic pain is also particularly important in patients with BPD because of the risk of prescribing opioids in this population. Patients with BPD have a high degree of substance use disorder comorbidity, although the rates of comorbidity decrease significantly over time" (Trull et al. 2000, Choi-Kainet al. 2010)</p> <p>"In psychiatric, primary care and internal medicine clinics, there are high rates of prescription medication abuse among patients with BPD" (Sansone et al. 2010)</p> <p>"GPs have a potentially key role to play in intervening with patients diagnosed with PD, particularly in the presence of comorbid alcohol misuse, which may help reduce suicide risk." (Webb et al. 2016)</p>
Medical Comorbidity	Pain	<p>"A German clinical sample of patients with chronic pain found that 58% of patients had a diagnosis of BPD" (Sansone et al. 2010).</p> <p>"Patients with BPD are more likely to experience pain and rate their pain as more severe than patients with other personality disorders" (Fischer-Kern et al. 2011)</p> <p>"Patients with BPD experience significantly more pain disorders, such as chronic fatigue syndrome, fibromyalgia and temporomandibular disorders, than patients with other personality disorders." (Frankenburg & Zanarini 2004)</p>
	Vomiting	"Patients with borderline personality disorder often are found and treated in psychiatric settings following episodes of self-mutilation, such as wrist-slashing (...) but in primary care settings wrist-slashing or other physical mutilation is a less common presenting problem. Frequently these patients complain of such symptoms as nausea and vomiting" (Johnson 1993)
Prevalence in Primary Care	Demography	<p>"EUPD patients account for 6% of the patients seen in routine clinical practice" (Gross et al. 2002) "personality disorder was diagnosed in 5.3% by the GP" (Sievwright et al. 1991)</p> <p>"Cluster B disorders were more prevalent in urban environments, in younger age groups, in men, separated or divorced people, those of lower social class and those renting their accommodation" (Coid et al. 2006)</p>
	Healthcare Utilization	<p>"Patients with BPD who have not remitted use significantly more health-care services than patients with other personality disorders" (Frankenburg & Zanarini 2004)</p> <p>"patients with personality disorders were only more expensive if they had psychiatric comorbidity" (Rendu et al. 2002).</p>
Functioning in the Community	Motherhood	"Some women with BPD may begin to dysregulate in pregnancy if, for example, their body feels invaded, physical discomfort unsettles, memories of past sexual abuse are triggered, or partner problems are highlighted" (Sved Williams & Apter 2017)
	Socio-economic status	"...less than one-half of community-based participants with BPD experienced good overall functioning (steady, consistent employment and at least one good relationship), in contrast to over three-quarters of community-based participants without BPD." (Javaras et al. 2017)

Table 2. Continues

Theme	Subthemes	Exemplar Literature
Diagnosing EUPD in Primary Care	Recognition	"Some red flags that may alert a primary care provider to possible diagnosis of BPD comprise (...) an excessive interest in the PCP's personal life as well as attempts to test or invade professional boundaries" (Carlat 1998, Gross et al. 2002, Sansone & Sansone 2010)
	Discussion	"...every clinician in my sample acknowledged the particular stigma of this label and worried that the diagnosis would do more harm than good." (Sulzer et al. 2016) "The vast majority of patients in the sample expressed relief and feeling a sense of belonging as well as understanding. "It finally makes sense why I've been the way I've been for so many years". As one patient shared, "I've had it for at least 20 years; it's a relief to finally be diagnosed". Many viewed the diagnosis as a crucial step toward getting effective treatment and information" (Sulzer et al. 2016)
Management in the Community	Treatments	"The principal treatment for BPD is psychosocial - that is, some form of psychotherapy, which may be combined with psychotropic medication aimed at specific symptoms" (Beatson & Rao 2013).
	Patient Coping Strategies	"Online support communities provide an additional venue for BPD sufferers, friends, families, and significant others, to learn about the disorder and identify resources for treatment." (Wehbe et al. 2012)

with Cluster B disorders (including EUPD) are more prevalent in younger age groups, in men, separated or divorced people, those of lower social class and those renting their accommodation (Coid et al. 2006). Additionally, EUPD is associated with functional psychosis and affective or anxiety disorders, and these individuals are more likely to be unemployed, have criminal convictions (including time in prison) and to have been in local authority care as children (Coid et al. 2006).

Analysis of the literature revealed a commonly held belief that EUPD patients utilize healthcare services, and primary care in particular, at higher rates than other patients (Hueston et al. 1999, Bender et al. 2001, Jackson & Burgess 2004). However, further research suggests that after adjusting for comorbidity and demographic variables, including socio-economic status, the evidence that those with personality disorders consult services much more frequently than other patients 'disappeared' (Coid et al. 2006). Further, the suggestion that personality disorders are associated with higher mean total healthcare costs failed to remain statistically significant following multivariate analysis – instead, patients with personality disorders were only more expensive if they had psychiatric comorbidity (Rendu et al. 2002).

The Therapeutic Relationship

The idea that there 'may be no psychiatric diagnosis laden with more stereotypes and stigma than borderline personality disorder' immediately suggests potentially difficult relationships between those with EUPD and those making and managing their diagnosis (Nehls 2000). Indeed, Nehls (1998) explained that 'clinicians perceive patients with BPD as being manipulative and difficult' which is mirrored in the inpatient setting where 'recent ethnographic work has demonstrated that nurses show less sympathy for them than patients with other mental illnesses' (Rogers & Dunne 2011). It

would follow, then, that the quality of the therapeutic relationships between EUPD patients and their healthcare providers is inversely proportional to the level of felt or enacted stigma around the condition. It is also commonly suggested in the literature that 'doctors who exhibit judgmental attitudes when dealing with demanding complex patients may validate the sense of abandonment experienced by BPD patients' (Holm et al. 2009, Raven 2009). These findings indicate that the attitudes of healthcare professionals towards the EUPD diagnosis and the patients affected by the condition are a potential source of iatrogenic harm.

Diagnosing EUPD in Primary Care

The oft-quoted 'red flags' that may alert a clinician to a possible EUPD diagnosis include a history of doctor shopping, legal action against healthcare professionals, suicide attempts, several brief marriages or unsuccessful intimate relationships, an immediate idealization of the latest doctor as the most "wonderful doctor" in comparison to any previous practitioners, and most importantly, an excessive interest in the PCP's personal life as well as attempts to test or invade professional boundaries (Carlat 1998, Gross et al. 2002, Sansone & Sansone 2010). Analysing the therapeutic relationship for a potential EUPD diagnosis is an approach to be employed with caution. It is well documented that doctors who lack compassion and tolerance, or exhibit judgmental attitudes when dealing with 'demanding, complex patients may validate the sense of abandonment and lack of trust experienced by BPD patients (Holm et al. 2009, Raven 2009).

That is not to suggest, however, that making an EUPD diagnosis ought to be avoided altogether. The stigma associated with the condition can cause clinicians to be 'worried that the diagnosis would do more harm than good', yet the 'vast majority' of patients given the EUPD diagnosis 'expressed relief and feeling

a sense of belonging as well as understanding'; one interviewed patient said "it finally makes sense why I've been the way I've been for so many years" and the diagnosis was seen as a 'crucial step' towards accessing effective treatment (Sulzer et al. 2016).

EUPD Management in the Community

The mainstay of EUPD management in hospital and community settings alike is psychosocial intervention; most commonly a referral for psychotherapy (Beatson & Rao 2013). Psychotropic medication is generally restricted; there is no evidence that such medications provide long-term benefit (Chanen & Thompson 2016). However, psychotherapy may be combined with psychotropic medication if aimed at specific symptoms of comorbid affective disorders, for instance (Beatson & Rao 2013). However, clinicians may need to 'exercise caution' in prescribing lithium for patients with BPD and MDD, in light of the 'significant risk (about 25%) of self-harm through overdose of prescription medication in patients with BPD' – and in any event, 'treatment of BPD with specific psychotherapies tends to result in remission of co-occurring MDD' (Beatson & Rao 2013).

It is increasingly common for individuals with EUPD to develop coping strategies outside of the medical domain, too. Indeed, 'internet blogging may have important implications in care'; online communities provide an additional 'venue' for learning about the disorder and resources for treatment, and can be places of significant support 'in the form of hopeful messages, resources, educational material, and sharing of personal stories and experiences with BPD', as well as a 'coping mechanism or form of therapy'. While largely positive, the dangers of unregulated online communities cannot be ignored: in particular, blogging may normalise dangerous behaviours and 'coping mechanisms shared by BPD bloggers may delay treatment' (Wehbe-Alamah & Wolgamott 2014). An awareness of the existence of such online communities serves as a reminder of the crucial importance of effective therapeutic relationships between healthcare providers and EUPD patients in order to develop appropriate and successful management strategies for patients in the community.

Psychiatric Comorbidity

The lifetime prevalence of major depressive disorder in patients with a diagnosis of EUPD has been reported as high as 83% (Beatson & Rao 2013). As such, it is absolutely crucial that primary care practitioners are aware of the condition and the subtleties in managing co-morbid depression in patients with EUPD. The consensus of the academic literature is that 'depression co-occurring with BPD does not respond as well to antidepressant medication as depression in the absence of BPD' (Beatson & Rao 2013, Gunderson et al. 2004). Further to this, the quality of depression in patients with EUPD differs from the general population (Silk 2010).

Most notably, these patients are rarely melancholic but rather display instability of negative affect with feelings of loneliness, emptiness, clinging dependency on significant others and a sense of 'inner badness' accompanied with merciless attack on the self, expressed also via increased suicidal ideation and behaviours (Beatson & Rao 2013). The idea that 'combined depression and personality disorder is associated with a poorer outcome than depression alone' is widely accepted, and highlights the need for effective treatment (Newton-Howes et al. 2006). The recommendation is therefore that 'psychotherapy should take priority' in patients with comorbid EUPD and major depressive disorder, since 'once the BPD abates, so will the depression' (Gunderson et al. 2004).

A second psychiatric comorbidity is widely reported in the literature on EUPD: substance misuse. Put simply, 'in primary care...there are high rates of prescription medication abuse among patients with BPD' (Choi-Kainet al. 2010). While conceding that the rates of substance misuse comorbid in the EUPD community 'decrease significantly over time' following diagnosis and support, Trull et al. (2000) suggest that it is particularly risky to prescribe opioid medication to this patient population. This bears particular relevance to EUPD since pain is often a chief medical complaint of this cohort.

Medical Comorbidity

It is well documented in the literature that patients with EUPD are 'more likely to experience pain and rate their pain as more severe than patients with other personality disorders' (Fischer-Kern et al. 2011). In addition, when compared to patients with other personality disorders, those with EUPD 'experience significantly more pain disorders, such as chronic fatigue syndrome, fibromyalgia and temporomandibular disorders' (Frankenburg & Zanarini 2004). An additional study by Sansone et al. (2010) demonstrated that 58% of patients with chronic pain 'had a diagnosis of BPD'. While the exact aetiology remains unknown, it has been suggested that chronic pain 'may be a manifestation of a self-regulatory disturbance among some patients with BPD' (Sansone et al. 2001). Further, there are three reported predictors of the severity of pain in those with BPD: older age, major depressive disorder, and the severity of childhood abuse (Biskin et al. 2014). Taking a thorough social and psychiatric history from EUPD patients presenting with chronic pain in general practice is therefore crucial, since 'a focus on the management of medical and psychiatric comorbidities may improve their long term functioning' (Biskin et al. 2014).

Similarly, persistent and unexplained nausea and vomiting may not be an obvious presentation of psychopathology, yet vomiting has been described as 'a primary care analogue of self mutilation in some patients with borderline personality disorder' (Johnson 1993). As such, the importance of taking a careful history in

the primary care setting cannot be overstated. Indeed, obtaining a history of, for instance, childhood abuse in patients presenting with unexplained vomiting 'should not only mitigate extensive, costly and invasive gastrointestinal system evaluations but also suggest more effective treatment strategies' in those with emotionally unstable personality disorder (Johnson 1993).

Patient Functioning in the Community

A careful history in the primary care setting can also be used to elicit the degree of functional impairment a community-dwelling patient with EUPD might experience. Javaras et al. (2017) report that 'less than one-half of community-based participants with BPD experienced good overall functioning (steady, consistent employment, at least one good relationship), and in contrast to over three-quarters of community-based participants without BPD.' Further, the study warned that even for the 38% of those with EUPD in the community who 'appear to be functioning well' in educational, occupational, social and recreational domains, EUPD still has a detrimental effect on quality of life.

It is possible that the impact of EUPD on functioning in women may be exacerbated by new motherhood. Pregnancy might be a trigger – due to unsettling physical discomfort, feelings of bodily invasion, memories of past sexual abuse – for some women with EUPD to 'dysregulate'. This typically involves 'feelings of inadequacy as a parent, self-hate and sometimes self-harming behaviours to relieve her inner tensions' and the patient may describe her infant as demanding, or indeed hateful, and disclose fears of harming her child' (Sved Williams & Apter 2017). Eliciting such concerns is paramount: not only would primary care be a key source of support and gateway to treatment for the mother, GPs play a 'crucial role in identifying burdened children and ensuring their follow-up', in particular with access to mental health support (Hafting et al. 2019).

Areas for Future Research:

The etiology of EUPD remains unclear, though the current view implicates deficient co-regulation and social communication in infancy, as leading to emotional dysregulation and social cognition deficits in later development (Winsper 2018). Indeed, there is a high incidence of personality disorder, particularly EUPD, in those who have been in local authority or institutional care, suggesting that 'preventative and treatment strategies in this population could have a major influence on public health' (Coid et al. 2006). Adolescence is considered a 'crucial' developmental phase in those at risk of EUPD, and nonsuicidal self-injury is a 'promising target' for intervention (Hessels et al. 2018). However, more work is required to systematically characterize the risk factors and full range of early presentations signaling EUPD development in order to facilitate early detection and intervention in at-risk adolescents.

EUPD: A NOVEL TOOLKIT

Often, the literature discussing EUPD contains the sentiment that it is 'one of the most challenging mental health disorders to treat' (Wehbe-Alamah & Wolgamott 2014). This paper has highlighted the importance of the therapeutic relationship for successfully managing EUPD in the community, as well as the risks that negative perceptions of the condition held by healthcare professionals might reinforce 'fears of stigmatization and prejudice' (Markham 2003, Trull et al. 2010). To assist with the diagnosis of EUPD, a simple tool in the form of the I DESPAIRR mnemonic was developed to highlight the 'hallmarks and red flags that identify a person as potentially having BPD' (Carlat 1998). While this tool is certainly of value in the primary care setting, the language used directly references the sense that 'BPD has historically been difficult to diagnose and laden with stigma' (Sulzer et al. 2016). Stigma may be a particular problem for patients with EUPD since a central tenet of the condition is an intense fear of abandonment or rejection, and therefore stigmatisation from healthcare professionals 'can present obstacles to effective caregiving' (Knaak et al. 2015). Indeed, Beatson & Rao (2013) hold that the key to successful management of EUPD is a respectful, cooperative, collaborative, active, open and non-judgmental relationship with the patient.

In light of the clear barrier to such therapeutic relationships with the I DESPAIRR mnemonic, we would like to put forward a novel mnemonic designed for use as a diagnostic tool for EUPD in the primary care setting. It is designed to be simple and non-pejorative, employing the EUPD acronym to cover the major presenting complaints associated with the disorder. The 'core dimensions of psychopathology' underlying EUPD are characterised as disturbance in self-image, pervasive affective instability, unstable interpersonal relationships, fear of abandonment and impulsivity (Kulacaoglu & Kose 2018, Palihawadana et al. 2018). These defining features are incorporated in our novel EUPD diagnostic tool, displayed in Figure 2.

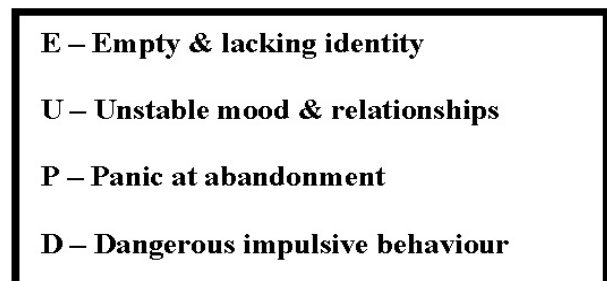


Figure 2. Novel EUPD Diagnostic Tool

CONCLUSIONS

The quality of the therapeutic relationship is key to the successful management of EUPD in the community. General practitioners must have an awareness of the

demographics of the EUPD population and an understanding of their social circumstances – including degree of functional impairment and support structures, include online communities – in order to best support those affected. A key challenge for primary care is accurate and timely recognition of EUPD. A thorough history is essential to elicit potential personality disorder triggers, as is an awareness of the subtle presentations of EUPD, including unexplained vomiting and chronic pain. Perceived or enacted stigma from healthcare professionals can deter patients from accessing services, and so this paper has contributed a novel diagnostic tool in the form of the EUPD mnemonic (Figure 2), as a small step toward cultivating a more positive and collaborative approach to EUPD diagnosis and management in primary care. Further research is required to elicit the precise etiology of EUPD, and to evaluate the options for early detection and thus intervention in at-risk individuals.

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HAJJ AND THE MENTAL HEALTH OF MUSLIM PILGRIMS: A REVIEW

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SUMMARY

Mass gatherings occur in different situations and settings around the world. A mass gathering can range in size from thousands to millions and in nature from recreation (i.e. concerts) to religious festivals (i.e. the Hajj pilgrimage). Such mass gatherings can result in high rates of morbidity and mortality from communicable and non-communicable diseases, 'accidents' and, over recent years, terror attacks. Disproportionately lower consideration has been given to the mental health and wellbeing of people during mass gatherings compared to that given to physical health during such events. Hajj is a religious pilgrimage to Mecca in Saudi Arabia that all Muslims are Islamically obliged to fulfil at least once in their lifetime. With up to 3 million pilgrims attending Hajj annually, it has been described as, 'The largest and longest-standing mass gathering event on Earth'. Although Hajj is a spiritual experience that is considered enlightening by many pilgrims, it can also be highly stressful which can have adverse effects on both physical and mental health. Few studies have been published hitherto on the impact that Hajj has on the mental health of pilgrims. This review article provides a narrative summary of studies conducted on Hajj and the relationship that this mass gathering has with the mental health of pilgrims.

Key words: Hajj – mass gatherings – Muslim mental health – pilgrimage – mental illness

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INTRODUCTION

Approximately 1.8 billion or 24.1% of the world population are Muslims of which 62% live in Asian-Pacific countries (e.g., Indonesia, Pakistan, India, Bangladesh, Iran and Turkey), 20% in the Middle East or North Africa (e.g., Egypt, Yemen, Sudan, Saudi Arabia, Algeria, Syria), 15% in Sub-Saharan Africa (e.g., Nigeria, Rwanda, Kenya), 3% in Europe (e.g., France, Belgium, Austria, United Kingdom) and less than 1% in North America (e.g., United States, Canada) (Lipka et al. 2017).

Hajj is an annual Islamic pilgrimage to the holy city of Mecca in Saudi Arabia involving approximately 3 million Muslim pilgrims for over 30 days including a 5-day core period of intensive rituals and prayers. Hajj has been described as, 'The largest and longest-standing mass gathering event on Earth'. Hajj is one of the Five Pillars of Islam; it is a mandatory religious duty for adherents of the Islamic faith that must be carried out at least once in their lifetime. Pilgrims can also go to Mecca to perform the rituals at other times of the year. This is sometimes called the "lesser pilgrimage", or Umrah. However, even if pilgrims choose to perform

the Umrah, they are still obliged to perform the Hajj at some other point in their lifetime.

HISTORY OF THE HAJJ PILGRIMAGE

The present custom of Hajj was established by the prophet Muhammed (PBUH). However, according to the Quran, aspects of the present custom of Hajj trace back to the time of the prophet Abraham (RA). According to Islamic tradition, Abraham (RA) was commanded by God to leave his wife Hagar and his son Ishmael (RA) alone in the barren desert of ancient Mecca. It is narrated that Hagar succumbed to despair and ran seven times between the two hills of Safa and Marwah in search of water to quench her own thirst and that of her son but to no avail. Returning in a state of resignation to her baby son Ishmael, she saw that her child started rubbing the ground with his leg and a fountain of water gushed forth beneath his foot. Later, Abraham (RA) was commanded to build the Kaaba and to invite people to perform pilgrimage there. The Quran refers to these events in chapter 2 ('The Cow') verses 124–127 and chapter 22 ('The Pilgrimage') verses 27–30.

The pilgrimage occurs from the 8th to 12th (or in some cases 13th) of Dhu al-Hijjah, the last month of the Islamic calendar. Because the Islamic calendar is lunar and the Islamic year is about eleven days shorter than the Gregorian year, the Gregorian date of Hajj changes from year to year.

HAJJ AND HEALTH

Most pilgrims take the necessary precautions when it comes to their physical health before they travel to Mecca. For example, they would make sure they take all the injections and immunizations that their doctor recommends (Visser et al. 2011). It would be equally important for pilgrims to look after their mental health in the same way they do their physical health. This may seem counterintuitive to many Muslims since Hajj is considered a spiritual journey that is beneficial for a Muslim's mental health and 'soul'.

Muslims consider Hajj and the performing of it to be a blessing and pilgrims describe it as 'enlightening' and a 'life-changing experience'. However, there are factors that contribute to Hajj being a highly stressful experience such as: unfamiliar environment, overcrowding, heat, physical exertion, limited dietary intake, exhaustion, sleep deprivation and being on a foreign land that is far away from home (Masood et al. 2011). These stressors can adversely affect the mental health and wellbeing of pilgrims (Masood et al. 2011) as will be discussed and described in the review below.

COMMON MISCONCEPTIONS ABOUT MENTAL ILLNESS IN MUSLIMS

Muslims often attribute mental health difficulties to supernatural causes like Jinn possession and/or the evil eye (Hankir et al. 2017). Muslims with mental health difficulties may think that Allah is punishing them for a sin they committed or that they have weak faith (Hankir et al. 2015). Of course, this isn't true; although Islam can be a protective factor against mental illness there are many Muslims who experience mental health difficulties despite having strong faith (Hankir et al. 2015). Prayer can provide relief and comfort and is very important, but since mental health problems are often caused by a psychiatric disease, it is important to seek help from a doctor for medical treatment in addition to prayer. The Prophet (PBUH) said:

"Make use of medical treatment, for Allah has not made a disease without appointing a remedy for it ..." (Kitah Al-Tibb of Sunan Abu-Dawud).

THE EFFECTS OF HAJJ ON MENTAL HEALTH

Previous studies have shown that most pilgrims who developed mental health problems were not told about the "actual" difficulties involved or the details of rituals

during Hajj. Muslims may have pre-existing mental illness or may experience mental illness for the first time during Hajj. Pilgrims going to Hajj for the first time and older people seem to be at increased risk of experiencing a mental illness. Pilgrims who are from rural backgrounds and who have low exposure to urban life also seem to be at increased risk of certain mental illnesses (Masood et al. 2011).

The first few weeks of arrival in Mecca and the core Hajj period can be the most stressful and this is when Muslims can feel most anxious. Fear of getting lost, being on a foreign land and language barriers are all factors that can cause stress. Anticipation of a mishap such as a stampede or a terror attack are other factors that can contribute to stress and confusion. Heat and dehydration are some of the preventable causes of sudden confusion, especially in older people (Masood et al. 2011).

Common mental illnesses seen in Hajj are:

- Stress related;
- Psychosis (experiencing unusual and frightening beliefs and often hearing voices);
- Insomnia (difficulty sleeping);
- Mood disorders.

Cases of psychosis were often due to the discontinuation of anti-psychotic medication without medical advice. It is therefore crucial that Muslims with pre-existing mental illness such as psychosis continue adhering with their psychotropic medication. Simple measures such as going to an isolated place, physical comforting, nearness to family members, repeated reassurance, fluids and repeated verbalization of sequence of events as well as reorientation and deep breathing all help (Masood et al. 2011).

Narrative Review of Published Research on Hajj and the mental health of Muslim Pilgrims

Below is a narrative summary of studies conducted on Hajj and the relationship that this religious mass gathering has with the mental health of pilgrims.

Bakhtiari and colleagues at the Sharif University of Technology investigated the relationship between the Hajj pilgrimage and mental health among university students in Iran (n=350). The General Health Questionnaire (GHQ) and the Meaning in Life Questionnaire were administered on participants before and after the Hajj pilgrimage. The authors of the study report that pilgrimage to Mecca lowered anxiety, depression, and stress levels in their sample and that there were improvements in social functioning and meaning in life (Bakhtiari et al. 2017).

However, Fateh and colleagues conducted a longitudinal study on the psychological effects of Hajj using the same instrument as Bakhtiari and colleagues did (the General Health Questionnaire (GHQ)). The findings of Fateh's study revealed that there was no statistically significant difference in the GHQ scores of pilgrims before and after the Hajj (Fateh et al. 2019).

Clingingsmith and colleagues estimated the impact of Hajj on 1,605 pilgrims from Pakistan. They reveal that female pilgrims were more likely to report negative feelings that suggest distress, and are less likely to report positive feelings of well-being (higher levels of distress were detected in female pilgrims, as measured by a version of the K6 screening scale). This could potentially be due to the impact of the Hajj on physical health. Indeed, the negative physical health effects were stronger for women than they were for men suggesting that part of the negative effect of the Hajj on women's feelings of well-being could be explained by poorer physical health. The findings could also potentially be due to the changes in pilgrim's beliefs and frame of reference discussed below (which the psychology literature suggests can lead to stress). Increased distress in female pilgrims might be due to the stark contrast between the typical Pakistani woman's daily life and the relatively greater equality and integration experienced during the Hajj. The impact of the Hajj on gender attitudes suggests an increased realization that the constraints and restrictions women are accustomed to in Pakistan may not be part of global Islam. It is important to note that this study revealed that while the Hajj has a negative impact on a female pilgrim's emotional state, it does not affect overall life satisfaction (Clingingsmith et al. 2009).

Khan and colleagues conducted a study on 136,000 Indian Hajj pilgrims in 2016 (Indian Medical Mission). They revealed that 182 patients developed psychological problems (1.3%) of which 45.7% were stress related issues, 9.8% psychosis, 7.3% insomnia and 5.6% mood disorders. The most common symptoms recorded in this sample were apprehension (45%), poor sleep (55%), anxiety (41%), and fear of being lost (27%). All cases of psychological problems were on their first Hajj, 60% were male and a majority were from rural areas. 22 patients (12%) required admission to hospital and only 12 pilgrims (6.8%) reported a past history of a mental illness (Khan et al. 2016).

Ozen and colleagues carried out a study on 130,000 Turkish Hajj pilgrims in 2008 (Turkish Mecca Hospital). 294 participants (0.2%) in their sample presented to psychiatric services, of which 38.4% reported anxiety, 22.1% mood disorders and 11.2% sleep disorders. The most common symptoms recorded were discomfort (70%), poor sleep (55%), anorexia (35%), 'whining' (30%) and fatigue (28%). 60% of those who presented to psychiatric services had a previous psychiatric history, 40% were male, 77% had low education and 71% had not been abroad before (Ozen et al. 2009).

Psychological impact of mass gatherings

The traditional view (which has now largely been discredited) is that people in crowds tend to:

- Lose their sense of self;
- Lose their sense of judgement;
- Become capable of the most extreme actions.

However, in social identity theory, people perceive a common group membership and assume a shared social identity in a 'psychological crowd'. This leads to:

- *A cognitive transformation* - People stop behaving in terms of their idiosyncratic beliefs and start behaving on the basis of shared norms, values, and understandings.
- *A relational transformation* - The crowd is part of an extended group rather than "others". This leads to a shift towards greater intimacy and trust, respect, cooperation, mutual influence, helping, and also expectations of help from others.
- *An emotional transformation* - The crowd can display intense positive effect, termed 'effervescence'. Close and supportive relationships can contribute positively to feelings of wellbeing.

A study of 1,194 pilgrims attending Mecca in 2012 found that people felt safer and perceived the crowds to be less dangerous when they strongly identified with others in the crowd. Social identity theory helps to explain the perception that others in the crowd were supportive. The survey of pilgrims attending the 2012 Hajj showed that, although increasing levels of crowd density reduced feelings of safety, this effect was moderated by identification with the crowd and perceptions that others identified as Muslim. Specifically, those who were high in identification with the crowd actually felt safer as density increased. Mediation analysis was consistent with the idea that this moderation effect was because of the perception that others in the crowd were supportive, which was higher the more that people identified with the crowd. This same relationship was found for those pilgrims from Arab countries and Iran compared with those from other countries, whose greater reported safety was explicable in terms of their crowd identification and perceptions of support (Alnabulsi et al. 2014).

CONCLUSION

Although Hajj is a spiritual experience that has been described as enlightening, it can also be highly stressful which can have adverse effects on both physical and mental health. Few studies have been published hitherto on the impact that Hajj has on the mental health of pilgrims. Currently the literature in relation to the mental health of Muslims during Hajj is conflicting and the conclusions from these studies must be interpreted with caution.

Protective factors against developing mental health difficulties during the Hajj pilgrimage include:

- Preparation for Hajj (i.e. being aware of the challenge and exertion of performing the Hajj (a detailed understanding of what is involved)) and physical fitness and healthy diet in months before Hajj.
- Support while on Hajj (i.e. family/close friends competent tour staff, realistic itinerary for visit, professional health services during Hajj, asking for help during Hajj from fellow pilgrims, consideration for less crowded times and areas).

Future research investigating the impact of Hajj on the mental health and wellbeing of pilgrims is urgently needed.

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Contribution of individual authors:

Ahmed Hankir & Zavid Chariwala conceived the idea for the paper and contributed to the literature review and revised the manuscript.

Usman Siddique, Frederick R. Carrick, Ian Walker & Rashid Zaman contributed to the literature review and revised the manuscript.

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A KING'S COLLEGE LONDON GLOBAL HEALTH SOCIETY EVENT DISCUSSING GLOBAL MENTAL HEALTH TO INCREASE INTEREST IN PSYCHIATRY AS A CAREER: A PILOT STUDY

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SUMMARY

Introduction: Despite the launching of multiple initiatives to increase recruitment into psychiatry, the profession continues to remain undersubscribed. Studies have shown that teaching on global mental health can improve attitudes toward psychiatry in medical students. To the best of our knowledge, no studies have been published hitherto that evaluate if a brief teaching session (i.e. 60 minutes in duration) on global mental health improves perceptions of psychiatry and increases interest in this specialty as a career.

Subjects and methods: We conducted a single-arm, pre- post- comparison study on participants who attended a King's College London Global Health Society event on Global Mental Health. Participants completed a survey before and after exposure to the event. Our aims were to detect and measure if there were any changes in perceptions of psychiatry and if a brief teaching session on global mental health would increase interest in pursuing psychiatry as a career.

Results: 71 out of 90 participants responded (77.8% response rate). Following exposure to the event, there were statistically significant improvements in the scores for, "Psychiatry is interesting" (pre-event score 4.41, post-event score 4.66 p value <0.001), "I would talk positively about psychiatry to other people" (pre-event score 4.02, post-event score 4.48 p value <0.00001), and, "I would consider psychiatry as a career" (pre-event score 3.24, post-event score 3.72 p value <0.001).

Conclusion: The results of our pilot study suggest that a brief lecture on global mental health may improve perceptions of psychiatry and increase interest in this specialty as a career. We recommend that global mental health be introduced into the medical school curriculum since this may help to increase recruitment into psychiatry.

Key words: psychiatry – recruitment – global mental health

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INTRODUCTION

The World Health Organization (WHO) has identified a chronic shortage of psychiatrists on a global scale (Hankir et al. 2015). In order to address the, 'Recruitment crisis' in psychiatry several initiatives have been launched i.e. the Royal College of Psychiatrist's Choose Psychiatry campaign in the United Kingdom (<https://www.rcpsych.ac.uk/become-a-psychiatrist/choose-psychiatry/choose-psychiatry-a-career-that-makes-a-difference>). However, although there has been an increase in the number of psychiatry posts filled in the UK, the profession continues to remain undersubscribed (<https://www.rcpsych.ac.uk/news-and-features/latest-news/detail/2019/07/11/number-of-junior-doctors-choosing-psychiatry-at-all-time-high>).

There are multiple factors that contribute to the 'recruitment crisis' in psychiatry (Zaman et al. 2018). For example, Weisenfeld and colleagues revealed that

negative comments from friends and family can deter Canadian medical students from choosing psychiatry as a career (Weisenfeld et al. 2014). Unfortunately, derogatory remarks about psychiatry are not limited to the general public; indeed, the medical community itself is also complicit. Recent research has revealed that psychiatry was the specialty that was 'badmouthed and bashed' the most and in the medical community and that the stigmatisation of psychiatry was negatively influencing recruitment into the profession (Ajaz et al. 2016). Finally, "self-stigma" amongst some psychiatry practitioners does not help either (Zaman et al. 2018)

With all of these forces seemingly colluding and conspiring to deter medical students from choosing psychiatry as a career, we must consider and embrace all options to improve the image of this profession.

Global mental health is a field in psychiatry that has generated much interest among medical students and will be discussed further.

SUBJECTS AND METHODS

Global Mental Health Review

Global mental health (GMH) is grounded on four basic principles:

- Mental health is global public good: “All countries can be thought of as developing countries in the context of mental health”.
- Health problems exist on a continuum.
- Health is individual and a unique product of social and environmental influences.
- Mental health is a fundamental human right that requires a rights-based approach (Chavan & Aneja 2016, Koplan et al. 2009).

GMH has significantly contributed to the inclusion of mental health into the United Nations Sustainable Development Goals (SDGs) (Patel et al. 2018).

Although progress has been made in reducing the treatment gap, the global burden of mental illness continues to increase (Collins et al. 2013). Moreover, abuse and human rights violations of people with mental illnesses occur globally (Patel et al. 2018) and the available mental health treatments are usually of a lower quality than treatments for physical illnesses (Patel et al. 2018).

The Lancet Commission on global mental health and sustainable development highlighted that despite recent research discoveries on actions that could be taken to prevent and treat mental illness and to strengthen and support mental health systems, real-world applications of these recommendations have been lacking (Patel et al. 2018). This has had a profoundly negative impact on population well-being and productivity (Vigo et al. 2016).

There is a sizeable mental health treatment gap between low-income and middle-income countries (LMICs) and high-income countries (HICs). Approximately 80% of people experiencing severe mental illnesses in LMICs receive no treatment (Murphy et al. 2017, Vigo et al. 2016).

LMICs are challenged by a significantly lower numbers of psychiatrists and mental health care professionals compared to HICs (Kakuma et al. 2011, Nortje & Seedat 2013, Rathod et al. 2017). For example, the global average of psychiatrists per 100 000 people is 3.96, however, there are 1.55 psychiatrists per 100,000 people in China (Jacob et al. 2007).

In comparison, HICs are challenged by a lack of interest in psychiatry by medical students (Murphy et al. 2017). For example, in 2017, only 69% of psychiatry vacancies were filled in the United Kingdom (NHS Health Education England 2017).

As enumerated above, misperceptions of psychiatry and negative stereotypes of psychiatrists may deter medical students from choosing psychiatry as a career. However, teaching methods, quality and length of clinical exposure and electives in mental health are some of the factors that can improve the ‘image’ of psychiatry (Farooq et al. 2013).

Although there are teaching programmes dedicated to global health education (GHE) in HICs (Mitchell et al. 2013, Peluso et al. 2017), high quality GHE remains limited (Liu et al. 2015). Furthermore, in LMICs there have also been an increased number of students partaking in GHE in their home country, other HICs or other LMICs (Abedini et al. 2014, Liu et al. 2015). This presents a unique opportunity to expand GHE and the potential to increase the number of trained mental health care professionals and ultimately narrow the global mental health treatment gap. Thus, there is a pressing need to develop a cost-effective, long-term and mutually beneficial education programmes that partners HICs and LMICs to reduce the treatment gap (Murphy et al. 2017).

A recent study evaluated the effectiveness of utilizing digital problem-based learning (PBL) between paired United Kingdom and Somaliland medical students in facilitating cross-cultural understanding and increasing factual knowledge of mental health (Murphy et al. 2017). The qualitative results showed that a peer-to-peer digital PBL education programme between medical students in a high-income country and a low- and middle-income country positively improved attitudes towards psychiatry. Students were motivated towards GHE and they also enjoyed connecting with peers and learning about cultural and psychosocial variances in global mental health. This suggests that peer-to-peer digital platforms and PBL could be a valuable and cost-effective tool to reduce barriers in resource limitations in LMICs and motivate students in HICs to understand cultural and psychosocial differences in global mental health (Murphy et al. 2017). It also suggests that global mental health can increase interest in psychiatry as a career in medical students.

Anecdotally, global mental health has been highly popular among medical students. We wanted to ascertain if a global mental health event would improve the perception of psychiatry and encourage students to consider pursuing this specialty as a career.

Study design

King’s College London (KCL) Global Health Society (GHS) organized an event on Global Mental Health to improve the image of psychiatry and increase interest in pursuing this specialty as a career. We designed a survey (see below) and administered it on participants before and after exposure to the KCL GHS global mental health event. Informed written consent was obtained from all participants.

Measures

The survey aimed to detect and measure any changes in the views towards psychiatry in the participants before and after exposure to the event and if there was an increase in interest in pursuing this medical specialty as a career. Responses to statements were on a five-point Likert scale:

- Strongly Agree (5)
- Agree (4)
- Neutral (3)
- Disagree (2)
- Strongly Disagree (1)

The statements were as follows:

- “Psychiatry is interesting.”
- “Psychiatry has a positive impact on peoples’ lives.”
- “I would talk positively about psychiatry to other people.”
- “I would consider psychiatry as a career.”
- “Psychiatry is a respectable profession.”

Statistical Analysis

Descriptive and inferential statistics were carried out on the data obtained. Paired, two-tailed t-tests were computed to compare the participants’ responses to statements before and after exposure to the event. Results were considered statistically significant at $p < 0.05$ with a confidence interval of 95%.

RESULTS

Out of 90 attendees, 71 completed the surveys pre- and post- event (77.8% response rate). The majority of respondents were female and were in the 18-30 age group (84.48%). The ethnic make-up of the respondents was diverse as illustrated in Figure 1. Most of the respondents were in the healthcare sector (medical and dental students and professionals).

The mean score for the first question, “Psychiatry is interesting” prior to the talk was 4.41 (Standard Deviation (SD)=0.68), and after the talk 4.66 (SD=0.53) with a statistically significant p-value ($p < 0.001$) (see Figure 2).

The scores for the second question, “Psychiatry has a positive impact on peoples’ lives” also showed statistically significant changes ($p < 0.01$) when the means of the pre- and post- event were compared (pre-event mean 4.15 (SD=0.82), post-event mean 4.56 (SD=0.73) (see Figure 2)).

The third question, “I would talk positively about psychiatry to other people” showed statistically significant improvement when the pre-event and post-event scores were compared and analysed (pre-event mean score 4.02 (Standard Deviation = 0.934) and the post-event mean was 4.48 (SD=0.71), $p < 0.00001$ (see Figure 2)).

The fourth question, “I would consider psychiatry as a career” also showed statistically significant changes ($p < 0.001$) (pre-event average 3.24 (SD=1.18), post-event average 3.72 (SD=1.16) (see Figure 2)).

Finally, the fifth question, “Psychiatry is a respectable profession” also showed statistically significant changes ($p < 0.05$) (pre-event average 4.45 (SD=0.67), post-event average was 4.61 (SD=0.54) (see Figure 2)).

Free-text comments

Below are some free-text comments that participants provided that also reveal how positively received the event on global mental health was:

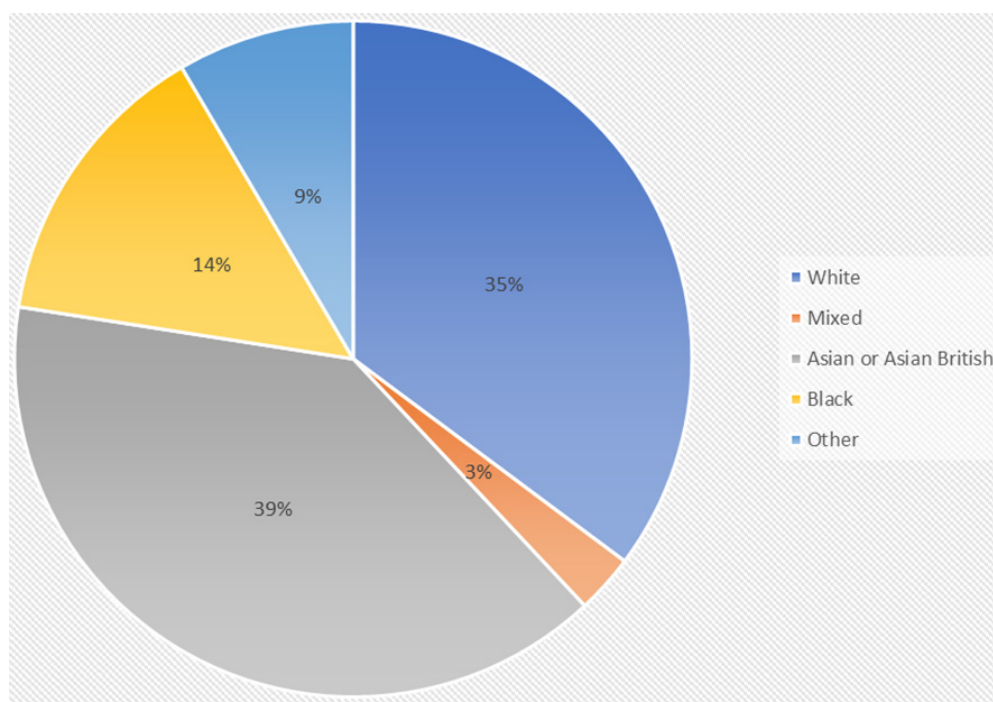


Figure 4. Ethnicity of respondents

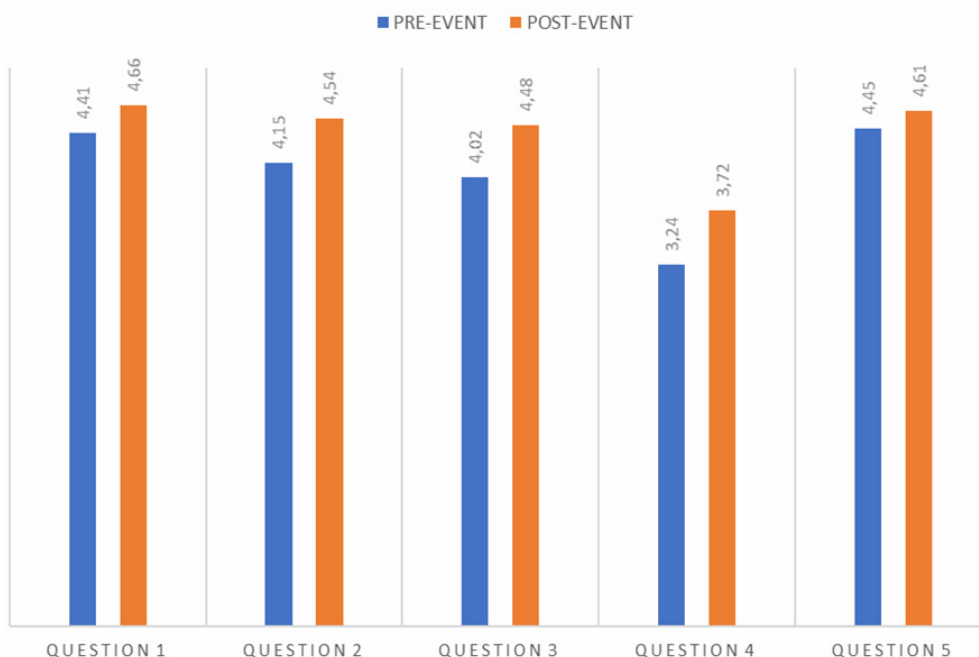


Figure 5. Bar chart representing the comparison between the pre and post-intervention responses

“My experience of psychiatry in the UK has been underwhelming but this event has renewed interest!”

“This topic should be incorporated into the medical school curriculum.”

“An interesting topic that urgently needs to be addressed.”

“Super!”

“It definitely needs to be discussed about in more depth and breadth. Different countries have different issues yet they share similar characteristics such as people with mental health being stigmatized. It’s important to raise awareness within the community and to embrace and treat the people with mental health needs.”

“Very powerful presentation.”

“Wonderful lecture, extremely informative.”

DISCUSSION

This study aimed to ascertain if a brief event on Global Mental Health may improve the overall perception of psychiatry by healthcare students and increase interest in pursuing this medical specialty as a career. The findings of this study are promising, with statistically significant improvements in scores being obtained for all 5 statements after exposure to the event. The results for question 4, “I would consider psychiatry as a career” were perhaps the most encouraging since the aim of this event was to increase interest in psychiatry as a career. Moreover, as enumerated above, psychiatry is the medical specialty that is ‘bashed and badmouthed’ the most. The fact that there were statistically significant improvements in the scores for the statements, “I would talk positively about psychiatry to other people”

and “Psychiatry is a respectable profession” may indicate that a brief event on global mental health may help to make conversations about psychiatry more positive.

There are several limitations to this study. The survey that we administered on participants in this study was not validated. There was a small sample size and no longitudinal data (i.e. participants were not followed up). There was no control group and there was also a selection bias since participants were ‘self-selecting’ i.e. they decided to attend the event on their own volition. Therefore, the results of this pilot study may not be generalizable or representative.

CONCLUSION

In summary, an event on global mental health had a positive impact on the respondents’ perception of psychiatry and increased interest in psychiatry as a career. Pre- and post-questionnaire comparisons yielded statistically significant improvements in scores. Although there are several limitations to the study, the results are nonetheless promising. Further research in this area is needed.

Contribution of individual authors:

Ahmed Hankir, Frederick R. Carrick & Rashid Zaman conceived the idea for the study and contributed to the literature review and revised the manuscript.

Deyl Djama & Ho Yi Lo collected the data and analysed it.

Deyl Djama wrote the manuscript and contributed to the design of the study.

Ho Yi Lo contributed to the manuscript and review of the paper.

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THE PREVALENCE OF LYME DISEASE AND ASSOCIATED CO-INFECTIONS IN PEOPLE WITH A CHRONIC POST-CONCUSSIVE SYNDROME

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SUMMARY

Introduction: There is increasing awareness that Lyme borreliosis (LB) and traumatic brain injury (TBI) may cause mental health symptoms. TBI and Lyme disease compromise the health and activities of millions of patients per year. The chronic symptoms and disability of TBI and Lyme disease share a similar clinical presentation. We have identified an alarming number of individuals suffering from post-concussion syndrome (PCS) that are refractory to care and that have serologically tested positive for Lyme disease.

Subject and methods: A single-center retrospective review of patient charts that were symptomatic a minimum of one year after a TBI that were tested for Lyme disease to ascertain if there was a relationship.

Results: 217 PCS patient records (93 females with a mean age of 34 years, 120 males with a mean age of 40 years and 4 individuals with unknown gender) were included in the review. 38% had a positive Western Blot Igenex IgM. There was a statistically significant relationship of a positive Western Blot Igenex IGM predicting chronic PCS Pearson $\chi^2(1)=6.8866$, $P=0.009$, Fisher's exact score $p=0.015$ and $\phi=0.2813$ representing a moderate effect size.

Conclusions: Long term PCS over one year's duration is associated with undiagnosed Lyme disease. There was statistical and substantive significance between individuals with chronic PCS having a positive Western Blot Igenex IgM. Males were more likely to have a positive Western Blot Igenex IgM than females.

Key words: Lyme disease - traumatic brain injury - post-concussion syndrome - mental illness

* * * * *

INTRODUCTION

Traumatic brain injuries (TBI) and Lyme disease compromise the health and activities of millions of patients per year. The chronic symptoms and disability of TBI and Lyme disease share a similar clinical presentation. Lyme disease causes immune and metabolic effects that result in a gradually developing spectrum of neuropsychiatric symptoms, usually presenting with significant comorbidity which may include developmental disorders, autism spectrum disorders, schizoaffective disorders, bipolar disorder, depression, anxiety disorders (panic disorder, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, intrusive symptoms), eating disorders, decreased libido, sleep disorders, addiction, opioid addiction, cognitive impairments, dementia, seizure disorders, suicide, violence, depersonalization, dissociative episodes, derealization and other impairments (Bransfield 2018).

Moreover, current evidence suggests a link between sports-related concussion and depression symptoms in elite athletes (Rice et al. 2018) and students who expe-

rience a concussion may be at increased risk for poor mental health outcomes, including suicide attempts (Yang et al. 2019). Our specialist TBI clinic has appreciated an alarming incidence of Lyme disease in patients suffering from a post-concussion syndrome (PCS) secondary to TBI. Furthermore, we have witnessed a dramatic improvement in function and reduction in disability following treatment of these patients. TBI, according to the World Health Organization, will surpass many diseases as the major cause of death and disability by the year 2020. With an estimated 10 million people affected annually by TBI, the burden of mortality and morbidity that this condition imposes on society makes TBI a pressing public health and medical problem (Hyder et al. 2007). TBIs are categorized into mild, moderate and severe based on clinical factors such as the severity of the injury, and loss of consciousness. Eighty to ninety percent of TBIs are classified as mild and labeled concussions. Despite many concussions healing relatively quickly, a number of these patients are refractory to treatment and have persistent disabling symptoms referred to as PCS. Furthermore, according to

the Centers for Disease Control and Prevention (CDC), Lyme disease is the most commonly reported vector-borne illness and the fifth most common disease in the National Notifiable Diseases Surveillance System, making it a significant public health concern (Younger et al. 2016). The Neurological manifestations of Lyme disease, called Neuroborreliosis, are reported in up to 15% of patients with Lyme disease (Rice et al. 2018, Yang et al. 2019) with symptoms similar to those of PCS. Despite numerous studies and increased awareness of concussions, there continues to be a paucity of understanding regarding why some patients recover and others remain symptomatic. Our clinical team attends TBI, PCS and Lyme patients that are referred to us from around the globe. We have identified an alarming number of individuals suffering from PCS that are refractory to care and that have serologically tested positive for Lyme disease. As a consequence, we were interested in testing PCS patients for Lyme disease that had no history of or testing for Lyme disease.

Research Question

We desired to investigate the prevalence of Lyme disease and co-infections in our PCS patients that remained symptomatic over one year after a TBI. We searched a variety of databases for randomized controlled trials of PCS and Lyme Disease up until January 2018 without success. Our search included Cochrane Injuries Group's specialized register, Cochrane Depression, Anxiety and Neurosis Group's specialized register, Cochrane Central Register of Controlled Trials, MEDLINE, PsycINFO, EMBASE, CINAHL, AMED, ERIC, and PsycBITE. Because of the lack of research in this area, we decided to perform a retrospective chart review of our patients that were symptomatic a minimum of one year after a TBI that we also had tested for Lyme disease to ascertain if there was a relationship.

Hypothesis

Based on our experience and clinical observations, we hypothesized that a significant percentage of patients with PCS symptomatology that are symptomatic after 1 year from the date of injury might continue to be symptomatic due to ongoing undiagnosed and untreated Lyme disease or associated co-infection.

SUBJECTS AND METHODS

The study was a single-center retrospective review of patient charts performed at our clinical facility in San Francisco, California. All charts were anonymized ensuring patient confidentiality appropriate to the Declaration of Helsinki and approved by the Carrick Institute for Graduate Studies Institutional Review Board. We reviewed the complete history of current complaints, past history, social history, surgical and medication history, social history, review of symptoms and family

history to identify all inclusionary and exclusionary factors. Each record that was accepted in our review met the study criteria for inclusion and was not disqualified by any of the exclusionary criteria.

Inclusion criteria

- All participants had at least one PCS symptom (e.g., headache, irritability, dizziness, vertigo, difficulty concentrating) for more than 12 months in combination with a negative brain computed tomography (CT) or magnetic resonance imaging (MRI) scan.
- All participants had undergone testing for Lyme disease at our facility that included IgG Western Blot and IgM Western Blot.

Exclusion criteria

- Patients that previously tested serologically positive for Lyme and /or co-infection.
- Patients that have had ≥ 2 weeks of antibiotics since the date of injury.
- Patients with other diagnosed primary neurological illness such as seizure disorder, or multiple sclerosis.
- Post-stroke syndrome.

Statistical Analysis

The statistical analysis was performed using STATA 14 (College Station, Texas). Linear and Logistic regression models and correlations were fitted to identify any laboratory predictors of TBI and effect size was identified by Eta Squared and Cohen d calculations.

RESULTS

Our review identified 217 PCS patient records that met our criterion (93 females with a mean age of 34 years, 120 males with a mean age of 40 years and 4 individuals with unknown gender). The normality of the distributions of data was verified using Kolmogorov-Smirnov with Lilliefors Significance Correction and Shapiro-Wilk tests of normality. A linear regression model including all laboratory tests and including males and females revealed a high statistically significant predictor of PCS if the patient had a positive Western Blot Igenex IgM test ($P < 0.0001$). We removed the subjects that had unknown values for TBI and Western Blot Igenex IgM from the analysis to consider only those subjects with data for both of these variables. This reduced the sample from 217 to 87 subjects (18 without a history of TBI and 69 with a history of TBI). Of the remaining subjects with a history of TBI, 37.68% had a positive Western Blot Igenex IgM while 62.32% did not. For those remaining patients without a history of TBI, 72.22% had a positive Western Blot Igenex IgM, and 27.78% had a negative Western Blot Igenex IgM. An examination of the relationship between a history of

TBI and Western Blot Igenex IgM revealed a Pearson $\chi^2(1)=6.8866$, $P=0.009$ and a Fisher's exact score $p=0.015$. ϕ was calculated as 0.2813 representing a moderate effect size. A ϕ with an absolute value from 0.0 to 0.19 is considered weak, from 0.20 to 0.49 is considered moderate, and from 0.50 and above is considered strong (Table 1).

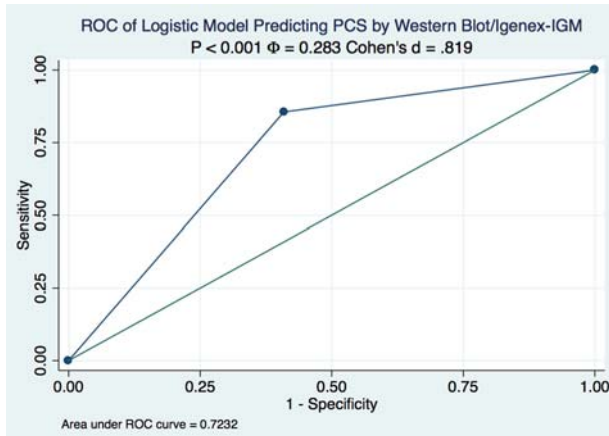


Figure 1. ROC of Logistic Model Predicting PCS by Western Blot/Igenex-IgM

We desired to assess the discrimination of a fitted logistic model, via the receiver operating characteristic (ROC) curve in patients with chronic PCS and Western

Blot Igenex-IgM. We plotted the values of sensitivity against one minus specificity, as the value of the cut-point was increased from 0 through to 1. A model with high discrimination ability will have high sensitivity and specificity simultaneously, leading to a ROC curve which goes close to the top left corner of the plot. A model with no discrimination ability will have a ROC curve that is the 45-degree diagonal line. The area under the ROC curve (AUC) can range from 1 (perfect discrimination) to 0.5 (no discrimination). A fitted logistic model of PCS subjects predicted by Western Blot Igenex-IgM had good discrimination values (AUC=0.7232). The Cohen's $d=0.819$ representing a strong effect size (Figure 1).

We analyzed male and female subjects removing those that had unknown values for TBI and Western Blot Igenex IgM from the analysis (50 females and 36 males). Of the female subjects with a history of TBI, 36.59% had a positive Western Blot Igenex IgM while 63.41% did not. For those remaining female subjects without a history of TBI but with PCS like symptoms, 77.78% had a positive Western Blot Igenex IgM, and 22.22% had a negative Western Blot Igenex IgM. An examination of the relationship between a history of TBI and Western Blot Igenex IgM in female subjects revealed a Pearson $\chi^2(1)=5.0822$, $P=0.024$ and a Fisher's exact score $p=0.032$. ϕ was calculated as 0.3188 representing a moderate effect size (Table 2).

Table 1. TBI and Western Blot Igenex-IgM History in Subjects with chronic PCS Symptoms

	Western Blot/Igenex-IgM for All Subjects				χ^2	ϕ	P
	TBI	Negative	Positive	Total			
Frequency	No	5	13	18			
χ^2 contribution		2.40	3.00	5.50			
Row percentage		27.78	72.22	100.00			
Frequency	Yes	43	26	69			
χ^2 contribution		0.60	0.80	1.40	6.866	0.2813	0.009
Row percentage		62.32	37.68	100.00			
Frequency	Total	48	39	87			
χ^2 contribution		3.10	3.80	6.90			
Row percentage		55.17	44.83	100.00			

Table 2. TBI and Western Blot Igenex-IgM History in Females with chronic PCS Symptoms

	Western Blot/Igenex-IgM for Female Subjects				χ^2	ϕ	P
	TBI	Negative	Positive	Total			
Frequency	No	2	7	9			
χ^2 contribution		1.80	2.30	4.20			
Row percentage		22.22	77.78	100.00			
Frequency	Yes	26	15	41			
χ^2 contribution		0.40	0.50	0.90	5.0822	0.3188	0.024
Row percentage		63.41	36.59	100.00			
Frequency	Total	28	22	50			
χ^2 contribution		2.20	2.80	5.10			
Row percentage		56.00	44.00	100.00			

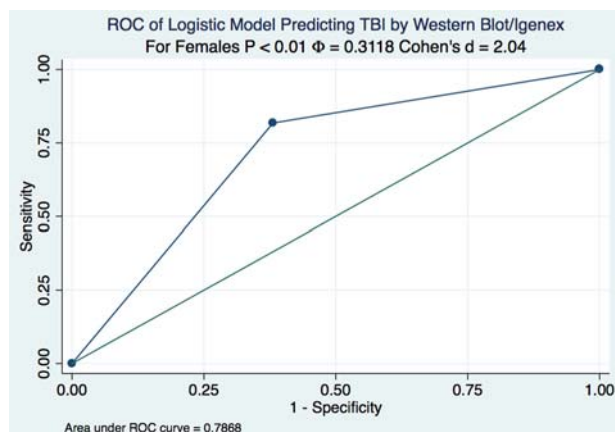


Figure 2. ROC of Logistic Model Predicting TBI by Western Blot/Igenex for Females

We desired to assess the discrimination of a fitted logistic model, via the receiver operating characteristic (ROC) curve in female patients with chronic PCS and Western Blot Igenex-IgM. We plotted the values of sensitivity against one minus specificity, as the value of the cut-off point was increased from 0 through to 1. A fitted logistic model of PCS subjects predicted by Western Blot Igenex-IgM had good discrimination values (AUC=0.7470). The Cohen's $d=0.819$ represents a strong effect size (Figure 2).

Of the male subjects with a history of TBI, 39.29% had a positive Western Blot Igenex IgM while 60.71% did not. For those remaining male subjects without a history of TBI but with chronic PCS like symptoms, 75.00% had a positive Western Blot Igenex IgM, and 25.00% had a negative Western Blot Igenex IgM. An examination of the relationship between a history of TBI and a positive Western Blot Igenex IgM in male subjects revealed a Pearson $\chi^2(1)=3.1844$, $P=0.074$ and a Fisher's exact score of 0.114. ϕ was calculated as 0.2974 representing a moderate effect size (Table 3).

We desired to assess the discrimination of a fitted logistic model, via the receiver operating characteristic (ROC) curve in male patients with chronic PCS and Western Blot Igenex-IgM. We plotted the values of sensitivity against one minus specificity, as the value of the cut-off point was increased from 0 through to 1.

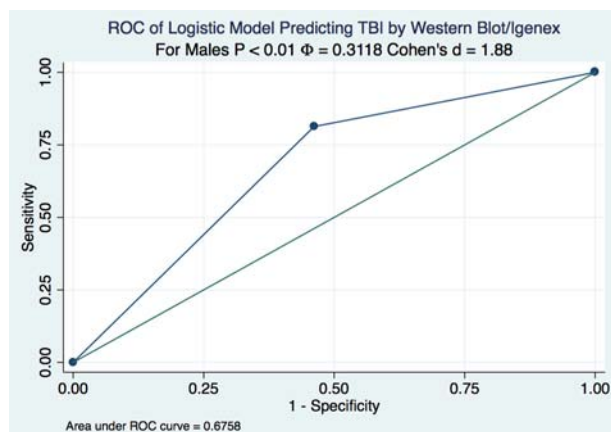


Figure 3. ROC of Logistic Model Predicting TBI by Western Blot/Igenex for Males

A fitted logistic model of PCS subjects predicted by Western Blot Igenex-IgM had fair discrimination values (AUC=0.6758) that were less than those calculated for females, however, the Cohen's $d=1.18$ represented a strong effect size but less than that calculated for females (Figure 3).

37.68% of the sample of subjects that had suffered a TBI and had longstanding PCS symptoms had a positive Western Blot Igenex IgM. Males were more likely to have a positive Western Blot Igenex IgM (39.29%) than females (36.59%).

We removed the subjects that had unknown values for TBI and Western Blot Igenex IgG from the analysis to consider only those subjects with data for both of these variables. This reduced the sample from 217 to 87 subjects (18 without a history of TBI and 70 with a history of TBI). Of the remaining subjects with a history of TBI, 25.71% had a positive Western Blot Igenex IgG while 74.29% did not. For those remaining patients without a history of TBI, 33.33% had a positive Western Blot Igenex IgG, and 66.67% had a negative Western Blot Igenex IgG. An examination of the relationship between a history of TBI and Western Blot Igenex IgG revealed a Pearson $\chi^2(1)=0.4190$, $P=0.517$ that was not statistically significant with a Fisher's exact score $p=0.559$. ϕ was calculated as 0.0690 representing a weak effect size (Table 4).

Table 3. TBI and Western Blot Igenex-IgM History in Males with chronic PCS Symptoms

	Western Blot/Igenex-IgM for Male Subjects				χ^2	ϕ	P
	TBI	Negative	Positive	Total			
Frequency	No	2	6	8			
χ^2 contribution		1.20	1.30	2.50			
Row percentage		25.00	75.00	100.00			
Frequency	Yes	17	11	28			
χ^2 contribution		0.30	0.40	0.70	3.1844	0.3188	0.074
Row percentage		60.71	39.29	100.00			
Frequency	Total	19	17	36			
χ^2 contribution		1.50	1.70	3.20			
Row percentage		52.78	47.22	100.00			

Table 4. TBI and Western Blot Igenex-IgG History in Subjects with chronic PCS Symptoms

	TBI	Western Blot/Igenex-IgG for all Subjects			χ^2	ϕ	P
		Negative	Positive	Total			
Frequency	No	12	6	18			
χ^2 contribution		0.10	0.20	0.30			
Row percentage		66.67	33.33	100.00			
Frequency	Yes	52	18	70			
χ^2 contribution		0.00	0.10	0.10	0.4190	0.0690	0.517
Row percentage		74.29	25.71	100.00			
Frequency	Total	64	24	88			
χ^2 contribution		0.10	0.30	0.40			
Row percentage		72.73	44.00	100.00			

Table 5. TBI and Western Blot Igenex-IgG History in Females with chronic PCS Symptoms

	TBI	Western Blot/Igenex-IgG for Female Subjects			χ^2	ϕ	P
		Negative	Positive	Total			
Frequency	No	9	0	9			
χ^2 contribution		0.60	2.00	2.50			
Row percentage		100.00	0.00	100.00			
Frequency	Yes	30	11	41			
χ^2 contribution		0.10	0.40	0.60	3.0957	0.2488	0.079
Row percentage		73.17	26.83	100.00			
Frequency	Total	39	11	50			
χ^2 contribution		0.70	2.40	3.10			
Row percentage		78.00	22.00	100.00			

Table 6. TBI and Western Blot Igenex-IgG History in Males with chronic PCS Symptoms

	TBI	Western Blot/Igenex-IgG for Male Subjects			χ^2	ϕ	P
		Negative	Positive	Total			
Frequency	No	3	5	8			
χ^2 contribution		1.10	2.20	3.30			
Row percentage		37.50	62.50	100.00			
Frequency	Yes	22	7	29			
χ^2 contribution		0.30	0.60	0.90	4.2109	0.2488	0.040
Row percentage		75.86	24.14	100.00			
Frequency	Total	25	12	37			
χ^2 contribution		1.40	2.80	4.20			
Row percentage		67.57	32.43	100.00			

We analyzed male and female subjects removing those that had unknown values for TBI and Western Blot Igenex IgG from the analysis (50 females and 36 males). Of the female subjects with a history of TBI, 26.83% had a positive Western Blot Igenex IgG while 73.17% did not. For those remaining female subjects without a history of TBI but with PCS like symptoms, none had a positive Western Blot Igenex IgG, and 100% had a negative Western Blot Igenex IgG. An examination of the relationship between a history of TBI and Western Blot Igenex IgG in female subjects revealed a Pearson $\chi^2(1)=3.0957$, $P=0.079$ that was not statistically significant with a Fisher's exact score

$p=0.177$. ϕ was calculated as 0.2488 representing a moderate effect size (Table 5).

Of the male subjects with a history of TBI, 24.14% had a positive Western Blot Igenex IgG while 75.86% did not. For those remaining male subjects without a history of TBI but with PCS like symptoms, 62.50% had a positive Western Blot Igenex IgG, and 37.50% had a negative Western Blot Igenex IgG. An examination of the relationship between a history of TBI and Western Blot Igenex IgG in female subjects revealed a Pearson $\chi^2(1)=4.2109$, $P=0.040$ that was statistically significant with a Fisher's exact score $p=0.083$. ϕ was calculated as 0.3374 representing a moderate effect size (Table 6).

TBI and Western Blot Igenex-IgG history in Males with chronic PCS symptoms are statistically significant with a moderate effect size, whereas there is no significant relationship that was found in female subjects. TBI and Western Blot Igenex-IgM have both statistical and substantively significant relationships.

DISCUSSION

Traumatic brain injuries are a significant cause of death and disability among people of all ages affecting approximately 10 million people worldwide (Yang et al. 2019). According to the US Center for Disease Control and Prevention (CDC), in 2010 about 2.5 million emergency department (ED) visits, hospitalizations, or deaths were associated with TBI (<https://www.cdc.gov/>). Over the past decade, concussions have been widely discussed concerning contact sports, motor vehicle accidents, and as the signature injury of soldiers. They also occur in falls among the elderly and victims of domestic abuse. Most patients with mild traumatic brain injury (mTBI) recover rather quickly, but other report persistent symptoms of PCS, the underlying pathophysiology of which is mostly unknown (Blennow et al. 2016). The CDC estimates the annual rate of concussion to be approximately 1.4–3.8 million. However, these numbers are likely to be an under-estimate, because a large number of concussions go unnoticed and unreported. PCS is a complex disorder characterized by multiple pathophysiological processes or “poly-pathology” whose main features are white matter degradation, neuronal loss, protein misfolding, and persistent neuroinflammation. Alterations in the neurotransmitter and neuroendocrine systems are also widespread (Newcombe et al. 2011, Stocchetti et al. 2016). The symptoms of PCS include headache, dizziness, neck pain, exercise intolerance, irritability, anxiety, insomnia or other sleep problems, cognitive problems and memory loss, poor concentration, difficulty with problem-solving, noise and light sensitivity and affective symptoms. In clinical practice, the symptoms are often subjective, vague, and non-specific, making the diagnosis of PCS difficult (Radhakrishnan et al. 2016). Despite emerging new understandings of the pathophysiology of these injuries, there is relatively little sound epidemiological data to predict risk factors for PCS accurately. Numerous studies have documented risk factors such as age (children and elderly being more susceptible than adults), female sex, injury-related litigation, pre-existing stress and premorbid psychiatric or cognitive conditions (such as learning disabilities) (Radhakrishnan et al. 2016, Bernard et al. 2016). Additionally, several genetic polymorphisms involving brain-derived neurotrophic factor (BDNF) and the interleukins (IL) have been shown to have a potential effect on the severity of an axonal injury, inflammation, blood-brain barrier disruption, neuronal survival, regeneration, and plasticity. One of the most documented

allelic variations present in individuals who experience poor recovery post-TBI is the E4 allele. The apolipoprotein E4 allele is the most neurotoxic isoform due to an induction of neuropathology via proteolytic cleavage and reduced growth and branching of neurites (Davidson et al. 2015). It has long been known that the production of cytokines is increased in the brain following contusions, with an expression of IL-6, IL-1b, and TNF-a by mononuclear cells and IL-1b by astrocytes (Rathbone et al. 2015). However, there has been little reported on the role of systemic infections such as Lyme disease that present with a similar profile of symptoms. A relatively inexpensive and widely used blood test to assess the prevalence of Lyme disease in PCS would dictate the need for appropriate antimicrobial treatment to cure the infection. It is likely that this intervention, could also alleviate symptoms such as cognitive disturbances, dizziness, and fatigue. Given the cost of interventions for PCS, the diagnosis and treatment of co-morbid infections could prove to have a significant impact on the standard of care of PCS. We have identified that specific Lyme blood markers are statistically significant predictors of PCS in our patient population. We do not know if this correlation is specific to our clinical population of PCS patients or if there is a general or global association. Numerous plausible mechanisms may account for our findings correlating PCS and LNB that warrant further investigation. Furthermore, we believe that many of these individuals suffering from PCS are compromised due to secondary LNB. Despite numerous theories and much speculation, our extensive review of the literature reveals that several questions remain to be answered.

Is there a large subset of the population infected with the *B. burgdorferi* spirochetes that are mostly asymptomatic or is their infection being misdiagnosed given we know LD to be the “great imitator”? It has been well understood that despite inducing both innate and adaptive immune responses, *B. burgdorferi* *sensu lato* species is one of the few extracellular pathogens that can cause persistent asymptomatic infection in various species, especially rodents (Tracy et al. 2017, Bernard et al. 2018). This mechanism of pathogens surviving with minimal effects on its host is referred to a reservoir host, and its persistence can be in part due to a multitude of factors that requires further study as to its relevance in humans. Tracy and Bumgarth, (Tracy et al. 2017) present a detailed overview of eight factors contributing to persistence of *Borrelia burgdorferi* in rodent hosts, some mechanisms of which have already been studied in humans: Spirochete shape (Charon et al. 2002, Moriarty et al. 2008) antigenic variation and changes in gene expression (Rogovskyy et al. 2015, Grimm et al. 2004, Norris et al. 2014) plasminogen binding and destruction of the extracellular matrix (Coleman et al. 1999) interference with the adaptive immune response, (Elsner et al. 2015a, Hastey et al. 2012, Elsner et al. 2015b) host-pathogen co-evolution, tick salivary

protein-mediated immunosuppression (Kotal et al. 2015) adhesions allowing entrance into the vasculature and tissue (Coburn et al. 2013, Brissette et al. 2014), and interference with complement via CRASPs, and BBK32 (Garcia et al. 2016, de Taeye et al. 2013, Kraiczky et al. 2016, Pietikainen et al. 2010). Bernard, Pal, et al. Recently reported a discovery of BBA57, a spirochete surface protein of unknown function that “orchestrates unique host immune evasion strategies crucial for early spirochete infection in mammals, suppresses host complement-mediated killing and neutrophil-derived microbicidal responses, including induction of antimicrobial peptides, and promotes pathogen dissemination by regulating type 1 interferon.” (Bernard et al. 2018). Furthermore, earlier studies reported positive serology in a population at risk, but clinical disease occurred infrequently (Fahrer et al. 1991, Zhioua et al. 1998).

Some theorize that the majority of Lyme disease patients are cured relatively quickly; however, approximately 10% have prolonged somatic and neurocognitive symptoms, such as fatigue, difficulty in sleeping, arthralgia, myalgia, memory impairment, and headache (Cairns 2005) termed Post Lyme disease syndrome (PLDS) or post-treatment Lyme disease syndrome (PTLDS). A recent study conducted at Tulane University revealed that spirochetes, that can evade the immune response, were able to infect vital organs such as the brain and heart, despite a traditional 28-day course of Doxycycline (Embers et al. 2017). It was also found that all subjects treated with antibiotics were found to have some level of infection 7 -12 months post-treatment, and despite testing negative by antibody tests for Lyme disease, two of 10 subjects were still infected with Lyme bacteria in heart and bladder (Embers et al. 2017). Fallon et al. observed significantly reduced blood flow in certain white matter areas of the brain, particularly in the posterior temporal and parietal lobes bilaterally, in patients with post-LB syndrome compared with healthy subjects, flow reductions in white matter areas were significantly associated with deficits in memory and visuospatial organization. These studies do not explore whether the patients that have such sequela have had a history of TBI or PCS (Fallon et al. 2003, Fallon et al. 2009).

The anatomic and physiologic changes witnessed following a TBI, such as hypoxia, alteration in glucose metabolism, a significant increase in proinflammatory cytokines IL-6, IL-1b, and TNF-a by mononuclear cells and IL-1b by astrocytes to the blood-brain barrier, maybe allow pre-existing autoreactive T-cells to transmigrate into the central nervous system (Pachter et al. 2003). We anticipate that future epidemiological investigation can determine the likelihood of patients developing PLDS/PTLDS or PCS secondary to previous exposure of LD or TBI. Understan-

ding such might provide significant impact in understanding the pathophysiology of PCS and neurodegenerative conditions such as Chronic Traumatic Encephalopathy (CTE). Hazeldine et al. provide a comprehensive overview of the underlying mechanisms of systemic immune suppression involving neutrophils, monocytes, natural killer cells, and T cells, following TBI (Hazeldine et al. 2015). These mechanisms substantially increase the risk of infections. We opine that if a high number of subclinical infections, asymptomatic, and/or misdiagnosed cases exist, then compromise of the blood-brain barrier and immunological suppression as a result of TBI might explain our observations.

CONCLUSIONS

Our retrospective review of records of patients seen in our facility suffering from mental health issues and PCS over one year’s duration is significantly associated with undiagnosed Lyme disease. We found that there was statistical and substantive significance between individuals with chronic PCS who had suffered a TBI and having a positive Western Blot Igenex-IgM test. We also found that males who had suffered a TBI and had chronic PCS also had statistical and substantively significant relationships with a positive Western Blot Igenex-IgG. 37.68% of the sample of subjects that had suffered a TBI and had longstanding PCS symptoms had a positive Western Blot Igenex IgM. Males were more likely to have a positive Western Blot Igenex IgM (39.29%) than females (36.59%). This relationship demands an adequately designed multi-site randomized controlled study that might provide insights into the relationship of undiagnosed Lyme disease complicating recovery in PCS patients. We suggest that it may be worthwhile to test for Lyme Disease in PCS patients, with and without mental health issues even if they have no history of a known Tick bite.

Limitations

This is a single site review of records that does not allow generalization to the global population of PCS patients. Furthermore, due to the lack of standardization of Lyme disease laboratory testing, it is possible that differing labs will yield varying results. As a records review, the report does not have the benefit of a robustly designed randomized controlled trial.

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Contribution of individual authors:

Sergio Azzolino conceived the idea for the study and contributed to the literature review, statistical analysis and revised the manuscript.

Rashid Zaman & Ahmed Hankir contributed to the literature review and revised the manuscript.

Frederick Carrick collected and analysed the data and contributed to the literature review and revised the manuscript.

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LEVERAGING DIGITAL TECHNOLOGY TO CHALLENGE MENTAL HEALTH STIGMA IN WEST BENGAL: A PROTOCOL

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SUMMARY

Mental health related stigma is a pernicious phenomenon that permeates and pervades our world. As stigma continues to evolve so too must our approach to reduce it. This paper outlines a protocol that leverages the power of virtual contact and digital technology to challenge mental health related stigma in West Bengal, India.

Key words: mental health stigma - digital technology - explanatory models - mental illness - global mental health

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Sharmistha Ghosh composed a first-person narrative about her personal and professional experiences working in front-line psychiatry in the District of Purulia and the metropolis area of Kolkata, West Bengal, India. Below she discusses and describes the mental health related stigma that she witnessed and encountered whilst working as a psychiatrist in West Bengal.

INTRODUCTION

I am a medical graduate (MBChB) from Kolkata Medical College, West Bengal, India. I have also completed a Diploma in Psychiatric Medicine (DPM) from the Institute for Post Graduate Medical Education and Research in Kolkata. Upon qualifying from medical school, I worked as a Specialty Doctor in Psychiatry at the Institute for Mental Health Care, Purulia, West Bengal. I am currently a Core Trainee in the UK and I am a Member of the Royal College of Psychiatrists.

Working in front-line psychiatry in the metropolis area of Kolkata and the District of Purulia provided me with opportunities to assess and treat people with mental illness across the socioeconomic strata of society. During my training in psychiatry in West Bengal, mental health services were predominantly 'ageless'. I assessed and treated younger people with mental health difficulties brought by their parents. Conversely, I provided care to older people who presented with memory loss and who were brought in by their children. A common denominator in the aforementioned vignettes

was the unwillingness of patients and their families to accept a mental health diagnosis and the insistence that a physical illness be identified as the chief cause of their symptoms.

I initially thought that the resistance to accept a psychiatric diagnosis was mainly because people in West Bengal were unaware of mental health issues. However, as I progressed with my training it became more apparent to me that the refusal to accept a psychiatric diagnosis was strongly influenced by the societal shame attached to mental illness. Below are a few anecdotes from my own personal and professional experiences.

A patient was brought to a psychiatric clinic by his relative. Whenever I saw this patient in my clinic, his relative almost always appeared stressed and anxious. When I shared my observations with the patient's relative, he immediately reacted in a defensive manner as if I was suggesting that he, too, might be experiencing some type of mental illness.

Patients were often referred to my outpatient psychiatry clinic by my medical colleagues. Patients with mental illness would commonly visit general medicine clinics complaining of somatic symptoms like chest pain or shortness of breath. These patients were often bewildered to receive a psychiatry referral after extensive tests and investigations effectively ruled out an organic cause of their symptoms. Many patients would simply refuse to accept that they have might a mental illness which, if and when confirmed, often resulted in non-adherence with their psychotropic medication.

Once a lady I met spoke about how her husband would behave in a bizarre manner and how he would express his delusional beliefs. I suggested to her that she bring him to the psychiatric clinic and that I would personally arrange for him to be reviewed however she politely declined the offer. She then unambiguously stated that if her neighbours discovered that they went to a mental health clinic, it would irrevocably damage their social standing and blemish their reputation.

I discussed the above examples with my colleagues and the consensus was that mental health stigma was a factor that might explain why patients with mental illness in West Bengal are often in denial. I find it deeply saddening that stigma is a major barrier to mental health care. I want to seize this opportunity to issue a clarion call that we must do everything in our power to reduce mental health related stigma in West Bengal and elsewhere in the world.

Global Mental Health

On the 9th and 10th of October 2018, London hosted the inaugural Global Ministerial Mental Health summit. The Summit was comprised of six work-streams to showcase innovations from across the globe. Work-stream four was entitled, '*A Just Society: supporting societal shifts, tackling stigma and discrimination, creating inclusive societies...*' (<https://mhfaengland.org/mhfa-centre/news/global-mental-health-summit/>).

The importance of challenging mental health related stigma cannot be over-emphasized. British Health Minister Matthew Hancock's Tweet below about the Summit supports this assertion:

"Tell us what you think the world needs to break the stigma surrounding mental health using #TheWorldNeeds". (<https://www.trendsmap.com/twitter/tweet/1041675690372939777>).

Mental health stigma is a formidable barrier to mental health care on a global scale and despite the availability of effective treatment many people with mental illness throughout the world continue to suffer in silence (Mehta et al. 2015). As SG clearly illustrated in her poignant first-person narrative, West Bengal is certainly no exception.

Mental Health Related Stigma in West Bengal

Arabinda Chowdhury and colleagues conducted a study to identify the indicators of stigma for a variety of mental health problems among laypersons and health care providers (HCP) in a rural community in West Bengal, India. The Explanatory Model Interview Catalogue (EMIC) was adapted and translated into the Bengali language and administered on a random sample of 21 laypersons and 17 healthcare providers (HCP). The interviews comprised of case vignettes depicting typical presentations of depression, somatoform disorders, deliberate self-harm, psychosis, hysteria and spirit possession. The study revealed that indicators of

mental illness-related stigma were more prominent among Health Care Providers compared with laypersons. The authors conclude that anti-stigma programmes targeting Health Care Providers in West Bengal must be designed, developed and delivered (Chowdhury et al. 2000).

Stigma, Shame and, 'Idioms of Distress'

Many Bengali patients who present to healthcare services with depressive illness do not report feeling sad, but rather express somatic symptoms such as generalized aches and pains, dizziness and difficulty in breathing and fatigue. This is partly due to the stigma attached to mental illness in West Bengal. Training on the 'idioms of distress' of depression (for example) can enable health care professionals to identify this disorder and to develop an appropriate treatment plan. Healthcare providers in West Bengal must also be trained about the stigma and shame attached to mental illness and how this can influence 'the idioms of distress' that people in their communities use for depression (Desai et al. 2017).

Explanatory Models of Mental Illness in the Muslim Population in West Bengal

According to the 2011 Census of India, the West Bengal state has over 24.6 million Muslims, who form 27.01% of the state's population. Muslims form the majority of the population in three districts: Murshidabad, Malda and Uttar Dinajpur (<https://www.livemint.com/Politics/XkVYBX2IaBk5Sqf8yr2XMM/Hindu-population-declined-Muslims-increased-2011-census.html>).

Any programme designed to challenge mental health related stigma targeting a given population must take into account the explanatory models of mental illness that that population formulates (Hankir et al. 2017, Hankir et al. 2017). We will now focus on the explanatory models that Muslims who experience psychological and/or behavioural disturbances formulate.

Mental Illness in the Muslim population

The global Muslim population is estimated to be around 1.7 billion people (www.pewforum.org), which makes up about 24% of the world's population. According to the Pew Research Centre, this number is expected to rise by 73% by 2050, making it the fastest growing major religion in the world (www.pewforum.org).

As the global burden of mental illness grows at a staggering rate, Muslim populations continue to be an understudied demographic despite evidence of higher susceptibility. Besides from widely implicated reasons for psychological distress such as familial and inter-generational conflicts, economic challenges and crisis of identity (which all hold true), additional causes may include perceived discrimination, racism, bullying and the growing phenomenon of Islamophobia.

Studies have shown that although Muslim beliefs and ethnic sub-cultures are heterogeneous, there exists a proclivity to perceive them as a monolithic group which may be negatively stereotyped and subjected to significant interpersonal and structural discrimination (Jasinskaja-Lahti et al. 2006)

The core tenet of the Muslim faith, Islam, is that there is one God (the Arabic word for God, Allah, is used universally by Muslims, regardless of ethnic group or language of origin) and Allah causes everything including illness.

Historically speaking, the Muslim conception of illness, be it mental or physical, can be broadly divided into three categories, (a) theologically derived positions based upon the Quran and Prophetic traditions (b) theoretical concepts developed by Islamic philosophers and scholars and (c) beliefs of individuals and groups in traditional Muslim societies. These beliefs include definitions of illness, aetiology as well as treatments which may significantly differ from western philosophy of psychopathology as known today.

In Muslim cultures, mental illness may be perceived as a test or punishment from God (Abu-Ras et al. 2008). Belief in Qadr - or destiny (God's Will) as well as Tawakul – resilience derived from absolute reliance on God, play an integral role.

Asides from the theological conceptions mentioned above, cultural influences on presentation of symptoms and mental health problems also need to be considered. Due to the lesser stigma of physical symptoms as well as cultural idioms revolving around the physical body, mental health problems are often expressed as physical symptoms (Douki et al. 2007). In parallel, explicit mood symptoms such as hopelessness, self-deprecatory thoughts, and worthlessness, are uncommon; in particular, women ultimately diagnosed with depression frequently first present with “conversion” disorders and no self-recognition of psychological distress or sadness (Al-Krenawi et al. 2000). Additionally, normative cultural beliefs in the existence of jinn (evil spirits) may be confused with delusions of possession and control, and may prevent patients and family members from recognizing medical or psychiatric problems (El-Islam 2008). Significant cultural differences with respect to gender may also put women at risk of diagnosis and treatment of mental health problems in Muslim communities (Al-Krenawi 2005).

Interpretations of the causes of mental illness as a combination of both supernatural and social factors has been found in previous studies in Muslim majority countries in Southeast Asia as well as Pakistan (Azhar et al. 2000). Similar studies have noted attribution of mental illness to be a direct result of God's Will, divine punishment or Jinn possession in Muslim countries as well as Muslim immigrant and refugee populations (El-Islam 1982).

The Power of Lived Experience

According to the results of a systematic review and meta-analysis on challenging the stigma of mental illness, social contact with someone who has recovered from mental illness is the most effective way of reducing stigma (Corrigan et al. 2012). Sara Evans Lacko and colleagues revealed that virtual contact (i.e. a film that contains a testimony from someone who has recovered from mental illness) is almost as effective as ‘live’ social contact at reducing mental health stigma. Evans-Lacko argues that film-based, anti-stigma interventions are more accessible and easier to scale-up than live social contact and are also cheaper and more cost-effective (Winkler et al. 2017).

Anjali is a mental health rights organization that works in three mental health hospitals in West Bengal. Anjali works with people who have suffered from mental health stigma.

The key objectives of Anjali are to:

- Create partnerships with local, state and national government to humanize mental health hospitals and systems.
- To end the stigma of mental illnesses within society and mainstream mental health services (<http://www.anjalimentalhealth.org/>).

Protocol to Leverage Digital Technology to Challenge Mental Health Related Stigma in West Bengal

We propose to commission a short film targeting healthcare providers in West Bengal comprised of:

- An expert by lived experience.
- An expert by professional experience (i.e. a psychiatrist in West Bengal).

The clip would be educational and it would harness the power of virtual contact with someone who has lived experience of mental illness. It would contain information about mental health stigma and how this might influence the ‘idioms of distress’ that people with mental illness in West Bengal use. The clip would also be sensitive and respectful towards the explanatory models that Muslims formulate for psychological and/or behavioral disturbances.

The digital clip would be 5-17 minutes in duration. We will administer validated psychometric scales on healthcare professionals before and after exposure to the intervention to measure for any changes in stigma (i.e. Bengali Depression Stigma Assessment Questionnaire) (Wei et al. 2018).

We are pleased to share that we are in the final stages of securing funding to deliver an innovative programme that leverages the power of digital technology and virtual contact to challenge mental health related stigma in West Bengal using the protocol that we have outlined in this manuscript.

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Contribution of individual authors:

Ahmed Hankir conceived the idea for the protocol, contributed to the literature review and revised the manuscript.

Sharmistha Ghosh provided the first-person narrative about working in front-line psychiatry and mental health stigma in West Bengal.

Syed Mustafa Ali contributed to the literature review and revised the manuscript.

Frederick R. Carrick & Rashid Zaman conceived the idea for the protocol and revised the manuscript.

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THE FEDERATION OF STUDENT ISLAMIC SOCIETIES PROGRAMME TO CHALLENGE MENTAL HEALTH STIGMA IN MUSLIM COMMUNITIES IN SCOTLAND: THE FOSIS GLASGOW STUDY

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SUMMARY

Introduction: A recent study commissioned by the Scottish Government on the prevalence of mental disorders in Muslims in Scotland revealed that over 50% of the sample met the diagnostic criteria for a mental illness. Stigma is a major barrier to mental health services and despite the availability of effective treatment, many Muslims in Scotland with mental health difficulties continue to suffer in silence. The Federation of Student Islamic Societies (FOSIS) Scotland branch organized a mental health conference in Glasgow to improve Mental Health Literacy and challenge mental health related stigma in the Scottish Muslim community. The conference was comprised of: A counsellor with a background of Islamic psychology, a psychiatrist and an Imam (a Muslim religious leader).

Design: We conducted a single-arm, pre- post- comparison study on Muslims who attended the FOSIS mental health conference in Glasgow, Scotland. Validated psychometric stigma scales measuring knowledge (Mental Health Knowledge Schedule (MAKS)), attitudes (Community Attitudes towards the Mentally Ill (CAMI)) and behaviours (Reported and Intended Behaviour Scale (RIBS)) were administered on participants before and immediately after exposure to the programme.

Results: 34 out of the 55 participants who attended the conference responded (response rate 62%). 34/34 (100%) of the respondents were Muslim and the mean age was 22.7 years (Std. Dev. 6.04, min. 18, max. 49). There were no statistically significant changes in stigma across the domains of knowledge, attitude and behaviour in respondents following exposure to the event.

Conclusion: Previous FOSIS anti-stigma conferences in England and Ireland featuring an Expert by Lived Experience were associated with statistically significant reductions in mental health related stigma. The results of the FOSIS Glasgow study supports the, 'Power of contact' with an Expert by Lived Experience at reducing mental health related stigma in the Muslim community. More robust research in this area is urgently required.

Key words: mental health stigma – mental illness – Muslim community – Islamophobia – Expert by Lived Experience

* * * * *

INTRODUCTION

According to the National Records of Scotland, as of June 2018 the estimated population of Scotland is 5,438,100 (Scottish Government 2018). More than one in three people in Scotland are estimated to be affected by a mental health problem (Scottish Government 2018). The Scottish Government has recently launched a ten-year mental health strategy in order to tackle the rising numbers of individuals affected by mental health disorders. The approach mainly focuses on prevention and early intervention, access to treatment and services and the physical well-being of individuals with mental health problems. The overall aim is to create a stigma-free environment and focus on patient-centred mental healthcare. As a result, several actions have been taken

by the Scottish Government which include increasing the mental health workforce by 800 within primary care, secondary care, police stations, schools and prisons; reviewing counselling services in educational establishments and creating an emphasis on prevention within the Child and Adolescent Mental Health Services (Scottish Government 2018).

Muslim population in Scotland

The Second World War marked the point at which the Muslim population grew not only in Scotland but around the whole of the UK (Scottish Government 2018). There are 75,300 Muslims in Scotland which constitutes approximately 1% of the total population (Scottish Government 2018). The prevalence of mental

health issues amongst Muslims in Scotland was examined in a study commissioned by the Scottish Government. The study showed that 35.6% (n=79) met the criteria for a mild mental illness whilst 13.6% (n=30) were found to suffer from a more serious form of mental illness (Hussain 2009).

Mental health related stigma in Scotland

The most well-known and accepted definition of stigma was produced by Goffman in his acclaimed work, “Stigma: Notes on the Management of Spoiled Identity”. In his work Goffman defines stigma as, “A deeply discrediting attribute that reduces the bearer from a whole a usual person to a tainted and discounted one. The individual is thus disqualified from full social acceptance” (Goffman 1963).

Generally, there are two types of stigma related to mental health: social/public stigma and self-stigma (Haddad et al. 2015, Zaman et al. 2018). Social stigma refers to negative perceptions and stereotypes of people suffering from poor mental health. Self-stigma results from the internalisation of social stigma. Self-stigma cultivates feelings of inadequacy, hopelessness and low self-esteem which can inevitably result in further deterioration of mental illness. Stigma presents persistent and serious challenges that have negative implications on numerous domains of a person’s life ranging from health to income (Yang et al. 2017). Stigma is a formidable barrier to mental health services and consequently many people with mental illness continue to suffer in silence despite the availability of effective treatment (Sartorius 2007).

Mental health related stigma is rampant in Scottish society. Over one third of people in Scotland who suffer from mental health problems report experiencing stigma and discrimination and being impacted by it (SAMH 2017).

“See Me” is Scotland's National Programme to tackle mental health related stigma and discrimination. “See Me” are funded by the Scottish Government and Comic Relief and are managed by SAMH and The Mental Health Foundation (<https://www.seemescotland.org/about-see-me/>).

“See Me’s” mission is:

- To mobilise people to work together and lead a movement to end mental health related stigma and discrimination.
- To work with people to change negative behaviour towards those with mental health problems.
- To ensure that the human rights of people with mental health problems are respected and upheld (<https://www.seemescotland.org/about-see-me/>).

Mehta et al. analysed trends in public attitudes towards people with mental illness in England and Scotland using Department of Health Attitudes to Mental Illness Surveys, 1994-2003. Comparing 2000 and

2003, they revealed that there was significant deterioration for 17 out of 25 (68%) of the items on the surveys in England and for 4 out of 25 (16%) of the items in Scotland. Neither country showed significant improvements in items between 2000 and 2003. Mehta et al. conclude that public attitudes towards people with mental illness in England and Scotland became less positive during 1994-2003, especially in 2000-2003, and to a greater extent in England. They posit that the results were consistent with early positive effects for the 'see me' anti-stigma campaign in Scotland (Mehta et al. 2009).

Islamophobia and Psychological Distress amongst Muslims

The 9/11 terror attacks in the United States of America heralded the beginning of a dramatic change in the quality of life for most Muslims living in the West (Hankir et al. 2017a). Following the attack, Islamophobia, a form of discrimination rooted in racism, became more prevalent, seeping into everyday conversation as well as the media (Sheridan, 2006). Research indicates that there has been increased hostility towards Muslims by non-Muslims in the United States. This parallels the increasing anti-Muslim discourse by politicians and media outlets. Compilation of Islamophobic hate crimes by the Council on American-Islamic Relations (CAIR) explicitly shows that between 2014 and 2016, anti-Muslim bias incidents rose by 65% (CAIR 2017).

Islamophobic hate crimes are by no means limited to the United States and occur throughout the West (Hankir et al. 2017a). Recent studies have clearly illustrated the stark positive correlation between incidences of Islamophobic attacks and the increase in anxiety and psychological distress experienced by Muslims (Kunst et al. 2013). Islamophobia can also exacerbate pre-existing mental illness (Hankir et al. 2015).

The media’s biased portrayal of Muslims has fuelled the feeling of ‘otherness’ between Muslim communities and the rest of society (Shaver et al. 2017). Additionally, some of the stringent measures integrated into society in an attempt to prevent a reoccurrence of 9/11, such as counter-terrorism laws and Schedule 7, has only served to heighten the sense of alienation Muslims feel within their community. A recent study showed that Pakistanis and Bengalis believe that they are treated in a harsher manner by police compared to their Caucasian counterparts. This has led to Muslim youth viewing law enforcement with increased tension, anxiety and hostility (Choudhury et al. 2011).

In a society already plagued by stigma pertaining to mental health, the feeling of “otherness” only serves to further marginalise those within the Muslim community who are suffering from mental illness. This intersectionality (i.e. the stigma attached to being a Muslim and the stigma attached to mental illness) is known as, ‘Double-stigma’ in the literature (Ciftci et al. 2013).

Mental health literacy

Anthony Jorm coined the term Mental Health Literacy (MHL) in 1997 and defined it as, "Knowledge and beliefs about mental disorders which aid their recognition, management or prevention". Components of MHL include: the ability to recognise different types of psychological distress; knowledge and beliefs about risk factors and causes; self-help interventions; professional help interventions; how to seek mental health information and attitudes which facilitate recognition and appropriate help-seeking (Ahmedani 2011). Mental health literacy is a concept many anti-stigma campaigns use to promote mental health awareness (Rüsch et al. 2005).

Although there has been a rise in research on MHL, the existing literature predominantly assesses the MHL of healthcare professional. However, the MHL of the public remains neglected. A recent study on MHL of the public indicated that among 273 patients with anxiety and mood disorders, an average of 7 years was required to identify the problem (Ahmedani 2011). A longitudinal study in Germany conducted in 1993 to 2001 concluded that the recognition of mental disorders by the general public had improved within this time period. In 1993, 17.1% and 26.9% could identify schizophrenia and depression, respectively, which increased to 22.4% and 37.5% in 2001 showing an improvement in MHL (Ahmedani 2011). However, despite an increase in MHL, the desire for social distance from people suffering with depression or schizophrenia remained unchanged (Angermeyer et al. 2009). This supports that notion education alone to improve MHL is not effective at reducing mental health related stigma.

At a governmental level, public interventions and strategies are necessary in order to increase help-seeking behaviours and reduce mental health stigma. This would allow early intervention reducing overall morbidity and mortality associated with poor mental health (Sartorius 2007). Mental health campaigns should be sensitive, specific to the target audience with clear aims and objectives, otherwise they may risk being inadequate.

Generally speaking, there are low-levels of mental health literacy in the Muslim community. American Muslim Health Professionals launched several mental health programs and initiatives to enhance community level capacity to identify mental health issues early on, increase awareness about available resources and support, de-stigmatize mental health illness and improve mental health literacy in families and communities (<https://amhp.us/mental-health/>).

Federation of Student Islamic Societies (FOSIS)

The Federation of Student Islamic Societies (FOSIS) is an umbrella organisation aimed at representing, uniting and supporting student Islamic Societies across the UK and Ireland. FOSIS has been serving Muslim

students since 1963 making it one of the oldest Muslim student organisations in the UK.

On the 3rd of March 2019, FOSIS Scotland organized a conference entitled, 'Let's talk about mental health' in Glasgow, Scotland at the University of Strathclyde. Through a series of lectures and interactive workshops, the one-day conference aimed to increase awareness of mental health, improve MHL and reduce the stigma and misconceptions associated with mental health issues amongst the student Muslim population in Scotland. The conference was targeted at students but was also open to the general public.

With regards to the speakers, the conference invited a counsellor with a background in Islamic psychology, a psychiatrist and an Imam (a Muslim religious leader). These speakers were selected to educate our audience on mental health by addressing three of its elements: the psychological, physical and spiritual respectively.

STUDY DESIGN

We conducted a single-arm, pre- post- comparison study on participants who attended the FOSIS Scotland, 'Let's talk about mental health' conference. Validated psychometric stigma scales on knowledge, attitudes and behaviour were administered on participants before and immediately after exposure to the intervention. Muslims who attended the conference were recruited to participate in the study. The study was explained during the introductory lecture and verbal consent was obtained. The questionnaires were printed in paper format for attendees to complete due to previous studies indicating that this improves response rate (Hankir 2014) (Figure 1).

Measures

Three measures were used in this study to assess stigma and discrimination:

- Mental Health Knowledge Schedule (MAKS)
- Reported and Intended Behaviour Scales (RIBS)
- Community Attitudes to the Mentally Ill (CAMI)

These are self-administered psychometric scales of mental health knowledge, attitudes and behaviour in the form of a questionnaire scored on a five-point Likert scale. Each takes 1-2 minutes to complete.

Mental Health Knowledge Scale (MAKS)

MAKS has been designed to measure mental health-related knowledge among the general public and evaluate anti-stigma interventions (Evans-Lacko 2010). It comprised six items (1-6) on stigma-related mental health knowledge areas and six items (7-12) on the classification of various conditions as mental illness. Participants were asked to indicate whether they agreed or disagreed with the items on a five-point Likert scale.



Figure 1. Promotional material used to recruit participants for the FOSIS Glasgow Study

Reported and Intended Behaviour Scales (RIBS)

RIBS has been designed to measure mental health-related behavioural discrimination among the general public and document behavioural trends (Evans-Lacko 2011). It comprised four items (1-4) which assess the prevalence of behaviour and four items (5-8) which on intended behaviour in the same contexts. Participants were asked to indicate whether they agreed or disagreed with items 5-8 on a five-point Likert scale.

Community Attitudes to the Mentally Ill (CAMI)

CAMI has been designed to measure mental health-related attitudes among the general public. Participants were asked to indicate whether they agreed or disagreed with the three statements below on a five-point Likert scale.

One of the main causes of mental illness is a lack of self-discipline and will-power

- There is something about people with mental illness that makes it easy to tell them from normal people;
- It is frightening to think of people with mental problems living in residential neighbourhoods.
- In addition to this, participants were also asked to complete a short form requesting demographic data.

Statistical analysis

The total scores for MAKS, RIBS and CAMI were calculated with higher scores indicating lower levels of stigma. A paired sample t-test for means was conducted to compare pre- intervention and post-intervention scores. Results were considered significant at $p \leq 0.05$.

RESULTS

Although 55 participants attended the conference, 62% (n=34) completed both the pre- and post- stigma scales. 34/34 (100%) Of participants were Muslim.

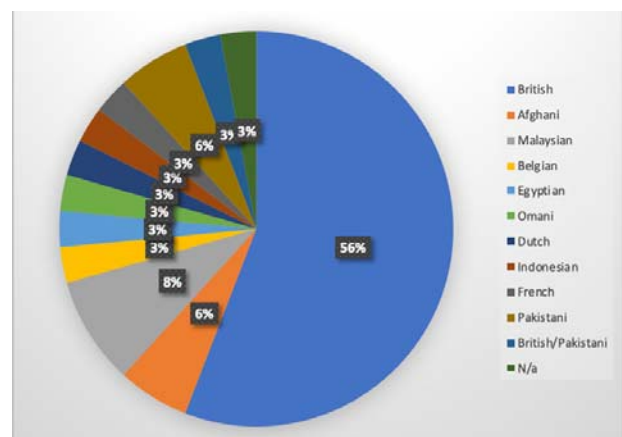


Figure 2. Nationalities of respondents

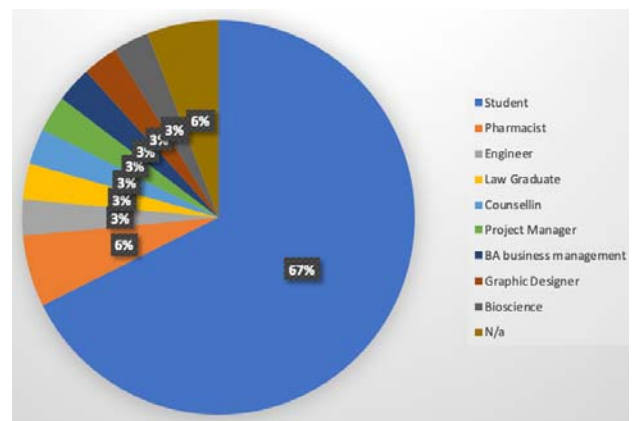


Figure 3. Educational/ occupational background of respondents

The occupational/educational backgrounds and nationality of attendees are represented in figures 2 and 3 respectively. The mean age of participants was 22.7 (Std. Dev. 6.04, min 18, max 49)

The mean pre-RIBS score was 16.91 (Std. Dev. 2.47, 95% Conf. Interval 17.76–16.05) and the mean post-RIBS score was 16.75 (Std. Dev. 3.25, 95% Conf. Interval 17.88–15.62). There was no statistically significant difference in the pre-RIBS score compared to the post-RIBS score ($p=0.7446$) (see figure 4).



Figure 4. Pre-post scores for CAMI, MAKS and CAMI. (CAMI- Community Attitudes to the Mental Ill, MAKS- Mental Health Knowledge Schedule, RIBS- Reported and Intended Behaviour Scales)

The mean pre-MAKS score was 22.84 (Std. Dev. 2.78, 95% Conf. Interval 23.81–21.88) and the mean post-MAKS score was 23.44 (Std. Dev. 2.27, 95% Conf. Interval 24.22–22.65). There was no statistically significant difference in the pre-MAKS score compared to the post-MAKS score ($p=0.1976$) (see figure 4).

The mean pre-CAMI score was 10.00 (Std. Dev. 1.92, 95% Conf. Interval 10.66–9.34) and the mean post-CAMI score was 9.75 (Std. Dev. 1.83, 95% Conf. Interval 10.66–9.34). There was no statistically significant difference in the pre-CAMI score compared to the post-CAMI score ($p=0.4982$) (see figure 4).

DISCUSSION

As far as the authors are aware, this is the first ever intervention study on challenging mental health related stigma in Muslim communities in Scotland published in the literature. The FOSIS Glasgow study did not show any statistically significant reduction in mental health related stigma in the domains of reported and intended behaviour, attitudes towards the mentally ill and mental health knowledge. This could be due to several factors:

Participants were self-selecting and may have had a previous interest in the topic of mental health. They may already have had a good understanding of mental health issues and low levels of stigma relative to the general Muslim Scottish population. It can therefore be hypothesised that this was a factor that contributed to the results (i.e. that there were no statistically significant changes in scores in respondents following exposure to the conference).

The short duration of the conference could have been a factor affecting the impact of the conference. The one-day event limited the contact time of our audience with the specialists and thus may have hindered the attainment of the full educational impact that this conference could have had.

The statistically insignificant results could also be partly attributable to the intervention itself. Previous FOSIS conferences in Birmingham (Hankir et al. 2017b) and Dublin (Hankir et al. 2017c) included a contact-based, anti-stigma programme, known as, ‘The

Wounded Healer’, delivered by an expert by lived experience, whereas this was not present in the FOSIS Glasgow Study.

The main limitations of our study were the small sample size and the lack of follow up and no control group. A larger sample size, a comparison group and a longitudinal design might help to control for confounding factors. Due to the limitations of our study, our results are not representative, nor generalizable.

CONCLUSION

To the best of our knowledge, the FOSIS Glasgow study is the first intervention study challenging mental health related stigma in the Muslim community in Scotland to be published in the literature. There were no statistically significant reductions in knowledge, attitude and behaviour in participants who attended the event. Previous FOSIS studies held in Birmingham and Dublin (Hankir et al. 2017b, 2017c) supported the, ‘Power of contact’ to reduce mental health related stigma (Corrigan et al. 2012). The results of the FOSIS Glasgow Study suggest that a conference that excludes an expert by lived experience may not be effective at reducing mental health related stigma in the Muslim community. More research in this area is urgently needed.

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Contribution of individual authors:

Ahmed Hankir, Frederick R. Carrick & Rashid Zaman conceived the idea of the study, contributed to the literature review and revised the manuscript.

Rafa Abushaala organised the study, collected the data, and contributed to the literature review.

Loubna Kraria & Aleema Sardar collected the data and contributed to the literature review.

Deemah Al-Obaidly collected the data, contributed to the literature review and revised the manuscript.

Sanah Ghafoor revised the manuscript.

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IMPROVEMENT OF SACCADIC EYE MOVEMENTS AFTER HEAD-EYE VESTIBULAR MOTION (HEVM) THERAPY AND NEURO-PSYCHIATRIC CONSIDERATIONS

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SUMMARY

Introduction: Eye movement pathology can assist in the identification, diagnosis and treatment of mental health disorders. Eye-tracking paradigms have been utilized to provide greater ecological validity, and directly capture the detailed sequence of processes in perception and attention, while quantifying classifiers in mood, anxiety, and psychotic disorders. Saccadic eye movements serve as an endophenotype for various mental health disorders.

Subjects and methods: Patients suffering from post-concussive syndrome and mental health concerns performed saccadic eye movements that were quantified for amplitude, velocity, latency and accuracy before and after Head-Eye Vestibular Motion therapy (HEVM).

Results: HEVM therapy is associated with statistical and substantive significant improvements in mental health and in saccadic metrics.

Conclusions: Oculomotor dysfunction is related to the symptom dimensions of mental health disorders that may be treated with physical rehabilitation modalities. We feel it reasonable to suggest that psychiatrists and others involved in the treatment of mental health disorders quantify eye movements and use them as biomarkers in the evaluation of the outcomes of varied therapies.

Key words: mental disorders - behavior outcomes - concussion - mild traumatic brain injury - psychiatry - saccades

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INTRODUCTION

Eye movement pathology can assist in the identification, diagnosis and treatment of mental health disorders. Eye-tracking paradigms have been utilized to provide greater ecological validity, and directly capture the detailed sequence of processes in perception and attention, while quantifying classifiers in mood, anxiety, and psychotic disorders (Kerr-Gaffney et al. 2018). The complexities of mental health demand an understanding of the principles of operation of neural systems. The integration of brain models to neuro-muscular biomechanical models providing relevant visual and proprioceptive feedback signals facilitate the understanding of complex brain function as a controller for movement and behavior (James et al. 2018). Cortical and sub-cortical structures involved in controlling behavior also act as the neural controllers of saccadic eye movements and visual fixation. The analysis of eye movements (EM) by eye-tracking has been carried out for several decades to investigate mood regulation, emotional

information processing, and psychomotor disturbances in depressive disorders and can be used to discriminate patients with depressive disorders from controls, as well as patients with bipolar disorder from patients with unipolar depression (Carvalho et al. 2015).

Oculomotor dysfunction is one of the most replicated findings in schizophrenia with relations between the symptom dimensions of schizophrenia and saccadic task performances in both clinical (schizophrenia) and pre-clinical (clinical high risk) populations (Obyedkov et al. 2019). As well as the functional observations of eye movement characteristic of schizophrenia, there are also structural changes in cortical thickness (Morita et al. 2019). Antisaccade error rate is an endophenotype for schizophrenia patients because they engage different cognitive processes in the antisaccade task when compared to healthy individuals (Thomas et al. 2018). These patients make significantly more errors associated with increased severity of hallucinations, and smaller amplitudes, less accurate final eye positions and slower latencies of their correct responses in comparison to

healthy controls (Subramaniam et al. 2018). While impaired eye movements are one of the cognitive hallmarks of schizophrenia patients, they are also found to be pathological in their relatives with a phenotype of error rates between patients and healthy controls (Myles et al. 2017).

Suicide is a major public health problem, and it remains unclear which processes link suicidal ideation and plans to the act of suicide. Affective temperaments, especially depressive and irritable, are strongly associated with suicidal risk (Vazquez et al. 2018) and the majority of suicidal patients diagnosed with major depression or bipolar disorder report repetitive suicide-related images and thoughts that may be reduced in frequency and intensity by Eye Movement Dual Task (EMDT) (van Bentum et al. 2019).

Current evidence suggests a link between mood disturbance and sports-related concussion with noted depression symptoms in elite athletes (Rice et al. 2018). There is a consistent positive association between a history of concussion and depression among former athletes with public concern catalyzing research investigations addressing the potential long-term negative health consequences associated with sport-related concussion and sub-concussive impacts (Hutchison et al. 2018). Although one concussion may be associated with mental health impairment, multiple concussions appear to be a significant risk factor for cognitive impairment and mental health problems (Manley et al. 2017).

Our group reported that head-eye vestibular motion (HEVM) therapy is associated with improvement of the mental and physical health of post-concussive syndrome (PCS) patients that had been severely impaired for greater than 6 months after a mild traumatic brain injury (Carrick et al. 2017). Saccadic eye movements are an endophenotype for mental health disorders. HEVM therapy does not include strategies specific to saccadic eye movement retraining but is associated with amelioration of mental health conditions. We were therefore interested in measuring saccadic eye movements before and after HEVM therapy to see if a non-saccadic rehabilitation regime would change the endophenotype of saccades associated with mental health syndromes.

SUBJECTS AND METHODS:

This study was a single-center, retrospective review of records performed at our Institutional Brain Injury Clinic conducted in accordance with the Declaration of Helsinki with equipoise. The Carrick Institute Institutional Review Board approved the records review and written informed consent was obtained from each patient prior to his or her examination and treatment. We identified patients that were disabled from work or school for a period of time exceeding 6 months after suffering a sports concussion and depression. These subjects all were enrolled in a 5-day HEVM rehabilitation program at our Institutional Brain Center with pre- and post- saccadic eye movement outcomes. Blinded

investigators that were not involved in the treatment of subjects nor had any interaction with them or the treating physicians did the review.

Saccadic eye movements were measured by the Ober Saccadometer (Consulting 2017) a FDA registered Class II Medical Device that perform strict quantitative evaluations of saccadic dynamic performance (latency and velocity), using micro-miniature equipment. The Ober Saccadometer utilizes the method of Direct Infra-Red Oculography, which is embedded in the Cyclop ODS type sensor (ODS- Oculus Dexter Sinister) and measures the resultant rotations of the left and the right eye taken together. Due to the conjugacy and synchronicity of the saccadic eye movements, the rotation of left and right eyes, can be added and averaged. The inner canthi of the left and right eyes are illuminated with the low intensity IR light (irradiance below 1 mW/cm² (operating condition)) and the difference between the amounts of IR reflected back from the eye surfaces carries the information about the eye position changes. The measuring rate is ± 35 degrees with a band width of 9.200 HZ and a noise level of 0.5 arc min (peak to peak) with a signal to noise ratio (SNR) of 41.6 dB (referenced to a 10 degree saccade). The average linearity error is in the range ± 15 deg; 1.4 deg; maximal error: 2.9 deg.

The protocol used to acquire saccadic data in this investigation required the subject to be comfortably seated 1 m from a wall (with uniform texture and neutral gray color to reduce scatter of the laser beams hitting the wall). After calibration, 100 saccades (alternated 50 to the right and 50 to the left) were performed by the subjects between two peripheral targets (at 10° amplitude each from the midline, for a total saccade amplitude of 20°). The pace was random between 1.3 s and 2.3 s. The software (LatencyMeter v 6.6 - Ober Consulting – Poznań, Poland) recorded for each eye movement the position of the eyes (relative to the beginning of the saccade) and calculated, for each movement, the latency, duration, amplitude, peak velocity, mean velocity (calculated as amplitude over duration) and Q factor. As output, the latency versus time (showing each eye movement position using as origin of the time scale the presentation of the target), and the velocity versus time were also provided. Graphs and numerical results could be also subdivided based on the direction of the saccade (left or right).

The primary treatment was gaze stabilization exercises administered with coordinated HEVM at positions and speeds associated with a decomposition of head and eye tracking movements. Subjects would attend to a visual target that would move in a plane at a velocity approximating the speed of head-eye decomposition while moving their head in combinations of pitch, yaw, and roll. The visual target underwent a gradual increase of its velocity and amplitude until head-eye movements further degraded or became synchronous at which time the session would stop. These sessions had durations of 3 min at a time followed by a 3-min rest and then repea-

ted three times. The sessions would be scheduled five times per day with a rest period of a minimum of 1.5 h between sessions over 5 days.

A secondary treatment of vestibular and somatic stimulation was administered by placing the patient in an accelerated rotation in a multi-axis rotational chair (MARC) (Centers 2017) from 0 to 60°/s over 15 s about a plane opposite to the plane of head movements that were slower than coordinated eye movements in combined slow visual pursuits. Subjects underwent 3–30 s acceleration–deceleration rotations with the accelerated rotations beginning at 0 and terminating at 60°/s over 15 s followed by a 15-s deceleration from 60 to 0°/s. The acceleration–deceleration was linear and followed by a 2-min break between each rotation and repeated two times per day over 5 days. Subjects were also rotated in a unique Roll plane combination with the same acceleration/deceleration paradigm as in Pitch and Roll and at the same time resulting in a novel 3-axis rotation of the subject.

A tertiary treatment of somatic sensory motor movements involved subject complex movements of the upper and lower extremity, both passively with a therapist and actively (right arm, left arm, right leg, and left leg) and in combination (right arm-left leg, left arm-right leg, right arm-right leg, and left arm-left leg). Subjects participated in somatic sensory motor movements for three sessions per day. The eye should not move if the head moves at the same speed of a slow-moving target while fovealizing on the target. Neck musculature that exhibits increased tone or resistance to stretch and movement results in a sensory mismatch between head and eye movement. Manipulation of the cervical spine was administered to all patients on the side opposite the greatest eye movement observed with coordinated head eye targeting of slow pursuit targets in the horizontal plane.

Statistical Analysis

Statistical analysis was performed with STATA 14, Statacorp LP, College Station, TX, USA. Two sample paired *t* tests with equal variances were calculated for each variable (pre and post treatment intervention) independent of other variables. The effect size was calculated by Cohen's *d* to indicate the standardized difference between two means. A Cohen's *d* of 0.2 is considered to be a small effect size, 0.05 a medium effect size, and 0.08 a large effect size.

RESULTS

The review of records of patients was limited to those that had suffered from post-concussion syndrome for a duration greater than 6 months with documented mental health issues including depression, traumatic stress, increased or decreased emotionality, irritability, sadness and anxiety. The normality of the distributions

of data was verified using Kolmogorov-Smirnov with Lilliefors Significance Correction and Shapiro-Wilk tests of normality. We identified 154 subjects, 91 males and 63 females with a mean age of 36.73 years (Std. Dev 21.58 minimum age of 5 years and maximum age of 91 years). There was no difference between male and female performance, therefore they were combined in the analysis. We analyzed saccadic performance including amplitude, velocity and latency.

The amplitude of the total saccade was 20°. We defined hypometria as an amplitude that was $\leq 19^\circ$ and hypermetria as an amplitude that was $\geq 21^\circ$. We found statistical and substantive significance in the performance of saccades before and after HEVM treatment. Table 1 summarizes the differences between saccadic performance before and after treatment.

Figures 1 & 2 are scatterplots of the Pre and Post HEVM treatment for all saccadic metrics.

DISCUSSION

The endophenotype of saccadic performance and mental health issues is becoming an interesting biomarker that might demonstrate the consequence of a variety of treatment modalities. We have quantified the standard characteristics of saccades including the amplitude, velocity, direction, latency and accuracy and measured them before and after HEVM treatment that has been associated with the amelioration of some mental health syndromes.

Disorders of midbrain, cerebellum, or basal ganglia can lead to prolonged transition time during gaze shift with an associated decreased saccade velocity (Puri and Shaikh 2017). We have observed these phenomena and the resultant changes in metrics that suggest HEVM treatment affects neurological integration in these areas. The mental health concerns of structural and physiological changes in these areas of the brain are well established.

The cerebellum guarantees the precision of ocular movements to optimize visual performance and occupies a central role in all classes of eye movements both in real-time control and in long-term calibration and learning (i.e., adaptation) (Beh et al. 2017). It is logical to assume that the consequences of HEVM therapy have a significant cerebellar component. The caudal fastigial nucleus (cFN) of the cerebellum is the output nucleus that influences the brainstem saccade generator. An imbalance in the intrasaccadic activity between the two caudal fastigial nuclei impairs the amplitude of saccades resulting in dysmetria (Goffart et al. 2003). Our observations suggest that HEVM therapy results in decreasing a mismatch between cFN resulting in improvements in saccadic accuracy and decreased dysmetria. We found changes in saccadic accuracy after HEVM therapy that must influence the control signal sent to the motor neurons to bring the fovea to the target requiring changes in cerebellar circuitry located in the posterior vermis and fastigial nucleus.

Table 1. Paired T tests of difference in saccadic eye movements and their statistical and substantive significance after a 5-day program of HEVM before and after HEVM Treatment. P values <0.05 are in *italics*. A Cohen's d is considered to be small (0.2), medium (0.5) and large (0.8)

Saccade Metrics	N	Mean	Std Dev	95% CI	T	P	Cohen's d
Pre Amplitude Left $\leq 19^\circ$	99	14.61	3.98	13.81607 15.40413	0.02	<i>0.0183</i>	-0.2239
Post Amplitude Left		15.58	4.67	14.64996 16.5157			
Pre Amplitude Right $\leq 19^\circ$	113	14.91	3.73	14.21678 15.608	-4.14	<i>0.0001</i>	-0.3942
Post Amplitude Right		16.48	4.20	15.69617 17.26489			
Pre Amplitude Left $\geq 21^\circ$	12	23.94	1.45	22.82782 25.06107	2.17	0.0609	1.2660
Post Amplitude Left		21.47	2.35	19.6558 23.27753			
Pre Amplitude Right $\geq 21^\circ$	12	25.62	3.11	23.23076 28.01369	4.77	<i>0.0040</i>	2.080
Post Amplitude Right		18.08	4.08	14.9425 21.21305			
Pre Velocity Left $\leq 350^\circ/s$	27	266.89	71.58	238.5706 295.1998	-2.98	<i>0.0061</i>	3.057
Post Velocity Left		363.67	149.69	304.4514 422.8819			
Pre Velocity Right $\leq 350^\circ/s$	30	274.49	72.46	247.4283 301.545	-4.90	<i>0.0000</i>	2.908
Post Velocity Right		0.17	1.38	-0.1582953 0.5011524			
Pre Latency Left ms	154	210.18	90.97	195.7069 224.6698	2.38	<i>0.0188</i>	0.1325
Post Velocity Left ms		197.81	95.80	182.5544 213.056			
Pre Latency Right ms	154	217.75	110.24	200.2033 235.3032	1.91	<i>0.0288</i>	0.1193
Post Velocity Right ms		205.18	100.15	189.2389 221.1247			
Pre Latency Left ≥ 200 ms	64	280.75	102.97	255.0297 306.4703	2.47	<i>0.0164</i>	0.1936
Post Latency Left ms		0.58	1.70	0.1787652 0.9926633			
Pre Latency Right ≥ 200 ms	56	309.05	139.69	271.6435 346.4636	2.61	<i>0.0117</i>	0.3045
Post Latency Right ms		266.91	137.06	230.2045 303.6169			

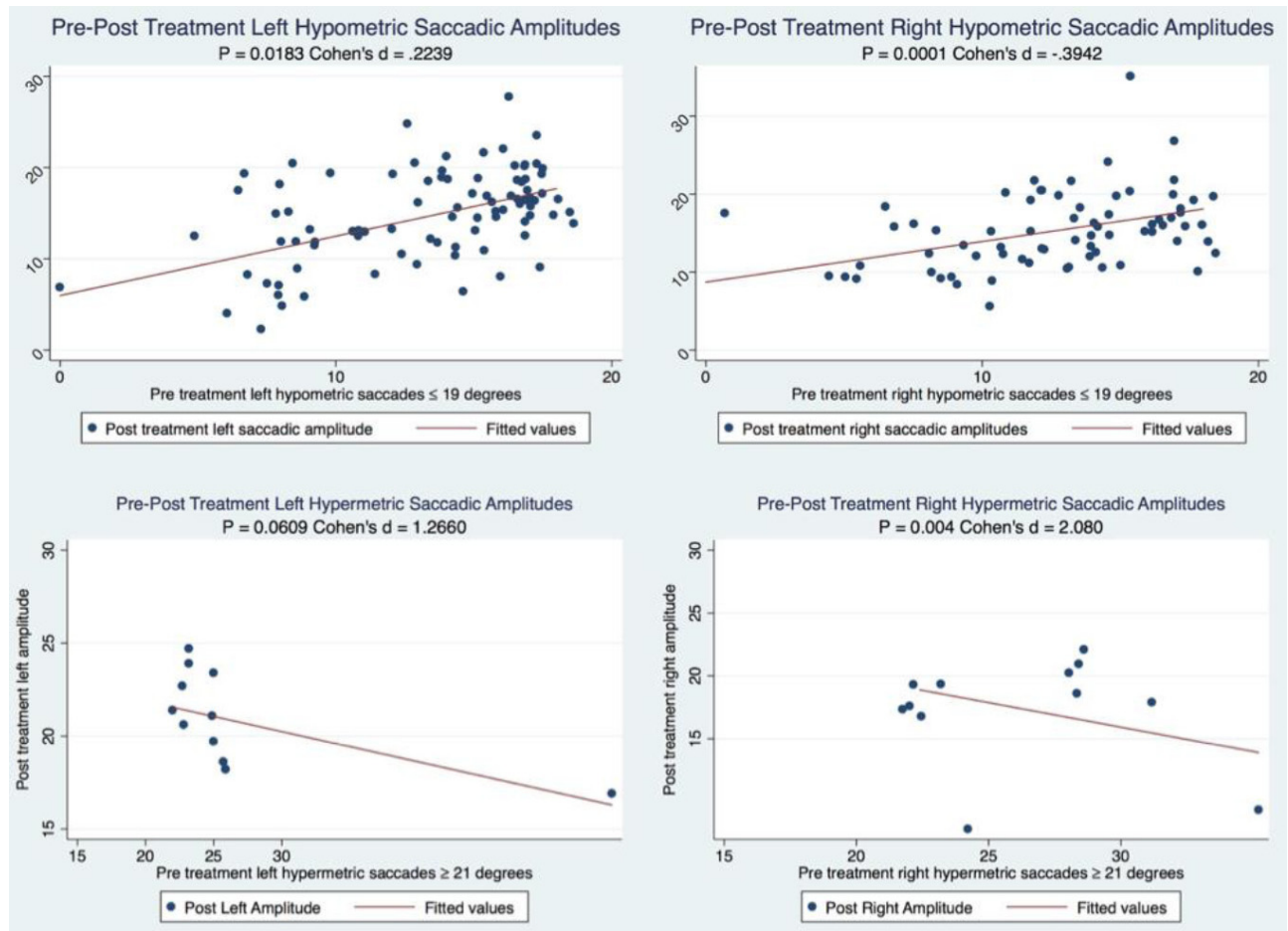


Figure 1. Scatter plots of hypo and hypermetric saccadic eye movements before and after HEVM Treatment

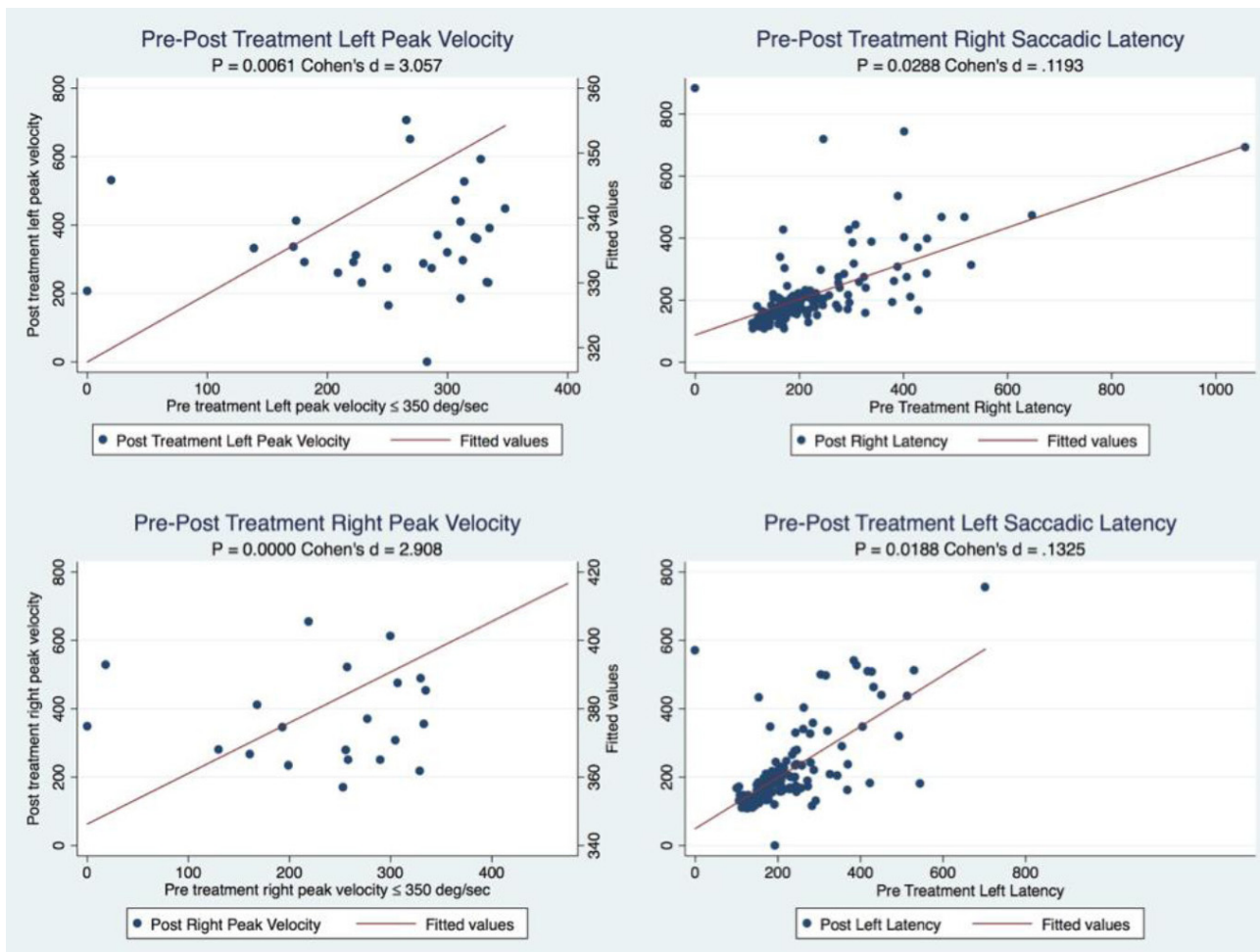


Figure 2. Scatter plots of peak velocity and latency of saccadic eye movements before and after HEVM Treatment

The neural control of saccades is initiated by the deep layers of the superior colliculus and terminated by the cerebellar fastigial nucleus involving circuitry in the paramedian pontine reticular formation, vestibular nucleus, abducens nucleus, oculomotor nucleus, cerebellum, substantia nigra, nucleus reticularis tegmenti pontis, thalamus, deep layers of the superior colliculus and the oculomotor plant for each eye (Enderle & Engelken 1996). Clearly these structures are involved in the integration of higher cognitive function associated with psychiatric applications and affected by HEVM therapy. The seminal paper by Paul Dean and colleagues gives a robust overview of a model of brainstem-cerebellar interactions affecting learning and saccadic accuracy of how the cerebellum adaptively controls it (Dean et al. 1994). It is reasonable to suggest that HEVM therapy involves this interaction.

Gaze is oriented to a target by combined displacements of the eye and head using a feedback system that is internally created and fed back to the superior colliculus controlling gaze (Guitton 1992). The changes in accuracy of gaze after saccadic eye shifts to targets were quantified in this review. We feel it reasonable to suggest that psychiatrists and others involved in the treatment of mental health disorders quantify

eye movements and use them as biomarkers in the evaluation of the outcomes of varied therapies. As patients with depressive disorders demonstrate significantly abnormal eye movement indices compared to healthy controls (Li et al. 2016) we find that therapy addressing eye movement not customarily associated with psychiatry may have great applications in the treatment of a variety of neuropsychiatric syndromes.

CONCLUSIONS

This study has confirmed that rehabilitation strategies that involve subjects in procedures involving HEVM therapy can affect saccadic metrics with statistical and substantive significance. These metrics are associated with a variety of mental health conditions and suggest that impairments in the cognitive-behavioral flexibility associated with saccade generation may be used to guide further research and therapeutic applications.

Limitations

This is a single clinical location study that may not be generalized to a general population.

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Conflict of interest: None to declare.

Contribution of individual authors:

Frederick R. Carrick, Rashid Zaman, Matthew M. Antonucci, Guido Pagnacco, Sergio Azzolino & Elena Oggero conceived the idea of the study, contributed to the literature review and revised the manuscript.

Ahmed Hankir organised the study, collected the data, and contributed to the literature review and revised the manuscript.

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METROLOGICAL PERFORMANCE OF INSTRUMENTS USED IN CLINICAL EVALUATION OF BALANCE

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SUMMARY

Clinical assessment of a patient, monitoring the progress of a condition, and/or titration of a therapy is dependent on the metrological characteristics of diagnostic equipment. While metrological performance of instruments is commonly assessed in research, it is not so often done in clinical practice. Physical rehabilitation applications may benefit individuals with mental health concerns and are associated with an accurate analysis of balance and gait. There is a paucity of published data regarding the metrological characteristics of commonly used clinical instruments used in posturographic measurements. We desired to assess the accuracy, trueness, precision and resolution of four posturography systems that we use clinically in practice: a Bertec BP-5050, a Vestibular Technologies CAPS® Professional and a Vestibular Technologies CAPS® Lite three-component balance platforms, and a NeuroCom® Balance Manager SMART EquiTest®. Metrological performance by posturography instruments was recommended in 2013 by the International Standardization Committee for Clinical Stabilometry of the International Society for Posture and Gait Research (ISPGR). Clinical and research findings may be erroneous, or at the least misleading, if the instruments used to make clinical decisions are associated with significant error. We suggest that there is a strong need for posturographic instrumentation with appropriate metrological characteristics used in clinical applications. The ISPRG recommendations appear to be reasonable and appropriate, and our results show they are obtainable. Physical measurements and functional testing used to correlate and design mental health and physical based rehabilitation strategies are often dependent upon the accuracy and metrological integrity of diagnostic instruments used in posturography.

Key words: postural balance – instrumentation - data accuracy – standardization - metrological characteristics

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INTRODUCTION

The development of safe diagnostic instruments that have acceptable levels of metrological performance (e.g., accuracy, trueness, precision, resolution, repeatability, reproducibility) is critical if clinical decisions will be made based on the results obtained using such instruments (Webster 2010). Inconsistency and differences in metrological characteristics between diagnostic instruments are problematic for clinicians whose applications are based upon a presumed “accuracy” of the instrumentation. If instruments properly measure what they purport to measure they might be considered sufficiently reliable to document outcomes of the treatment of a condition or progression of disease. Repetitive subject functional testing is useful only if changes of the measured results are not due to inherent variability of the instrument (Pagnacco et al. 2015). If an instrument’s metrological characteristics are not appropriate for a specific clinical application, then comparing these results with those obtained with different instruments may lead to error in diagnosis and treatment affecting patient outcomes.

This seems to be an issue of particular interest in posturography, where there appears to be some conflicting results based on the utilization of varied instrumentation. For example, Johnson and colleagues used static and dynamic posturography during a whole-body leaning task to measure sway, spatial accuracy and directional control of tasks in Parkinson’s patients with bilateral deep brain stimulation of the globus pallidus pars interna (Johnson et al. 2015). They found differences in sway that were dependent upon medication and deep brain stimulation. Prosperini and colleagues determined that the Center of Pressure (CoP) path measurement in the static position is an accurate tool for detecting potential falls in subjects affected by Multiple Sclerosis, if the posturographic measurements are sufficiently sensitive (Prosperini et al. 2013). Cappa and colleagues demonstrated clinical applicability of accurate movement measurements of a novel parallel spherical robot (SR) for dynamic posturography (Cappa et al. 2010). The Sensory Organization Test (SOT) has been applied with dynamic posturography by Fu and colleagues to assess postural sway angle to provide clinical

guidance associated with the treatment of multiple ankle sprains when there is a deficiency of ankle proprioception and standing balance (Fu & Hui-Chan 2005).

On the other hand, Yeh and colleagues found that the Sensory Organization Test (SOT) was not “sensitive” enough to “accurately” quantify postural control in elderly patients with vestibular disorders (Yeh et al. 2014). They enhanced the performance of the SOT by using a nonlinear algorithm of empirical mode decomposition (EMD), and verified the differences of effects caused by aging and/or illnesses as benefits to clinical diagnosis. They found that EMD successfully improved the “accuracy” of SOT measurements by increasing the “sensitivity” of the analysis. Their outcomes suggest that when an instrument’s “sensitivity” is increased, clinical applications might be developed with greater “accuracy”. Alahmari and colleagues found significant correlations between the Balance Rehabilitation Unit (BRU) and the SOT using the SMART EquiTest® device, ranging from 0.64 to 0.81 for Center of Pressure (CoP) area and from 0.44 to 0.76 for CoP velocity (Alahmari et al. 2014). The reliability and validity of CoP measurements obtained during testing of the sensory integration processes were demonstrated using the BRU, but these conclusions are dependent upon the reliability and validity of the SMART EquiTest®. Clearly, the BRU is as reliable and valid for CoP measurements as is the SMART EquiTest®, or perhaps equally as inaccurate. Rossi-Izquierdo and colleagues attempted to validate two different posturographic techniques as part of their research looking for clinically useful risk factors for predicting falls (Rossi-Izquierdo et al. 2014). They found that assessment with a free-field body sway analysis (using the VertiGuard® device) is more efficient in identifying fallers than the parameters of the SOT. Similarly, Bhatt and colleagues demonstrated that the Timed Up & Go test predicts fall outcomes better than static posturography (Bhatt et al. 2011). Pawlak-Osińska and colleagues found that posturography results did not provide specific difference in finding between children with vertigo and healthy controls (Pawlak-Osińska et al. 2006). The apparently conflicting results of these studies would seem to be counterintuitive when considering the measurements possible with posturography, unless the “accuracy” and “sensitivity” of the instruments used were not appropriate to the task.

In 2013, to help address the issues arising from insufficient metrological performance of the posturographic instruments, the International Standardization Committee for Clinical Stabilometry of the International Society for Posture and Gait Research (ISPGR) recommended for CoP measurements an “accuracy” of 0.1 mm and a “precision” and “resolution” of 0.05 mm (Scoppa et al. 2013). These are much more restrictive than the accuracy of 1 mm previously suggested (Bizzo et al. 1985, Browne & O'Hare 2000).

Accuracy, precision and resolution are measures of the error expected when using an instrument and are part of the metrological performance characteristics of

all instruments. Over time the meaning of these terms in the technical and scientific literature has evolved and changed, unfortunately leading to some possible confusion. In this paper, we use the definitions set forth by the ISO 5725:1994 standard (ISO 1994):

§ 3.6 – **accuracy**: *The closeness of agreement between a test result and the accepted reference value.*

§ 3.7 – **trueness**: *The closeness of agreement between the average value obtained from a large series of test results and an accepted reference value.*

§ 3.12 – **precision**: *The closeness of agreement between independent test results obtained under stipulated conditions.*

According to ISO 5725:1994, accuracy is a combination of trueness and precision. Resolution, although not defined in ISO 5725:1994, is traditionally defined as the smallest change an instrument can detect in the quantity that it is measuring. It should be noted that there is no mention of trueness in the ISPGR recommendations, which instead refer to accuracy, precision and resolution; we suspect that they were using the old definition of accuracy, replaced in the ISO 5725:1994 with trueness.

In our clinical work, we use a variety of instruments based on force platform technology to assess sway and balance. Our review of the scientific literature found a paucity of information on the metrological performance characteristics of posturographic instruments even though they are commonly used in many of the investigations we previously mentioned. Therefore, we decided to investigate the metrological performance of the posturographic instruments that our team uses to assess if they satisfy the ISPGR recommendations. To further evaluate how the instruments’ performance affects the measures, we also quantified maximum sway and mean CoP velocity measured when a static weight is used as a subject.

MATERIALS AND METHODS

We tested the following instruments that we utilize in our clinical testing:

- a NeuroCom® Balance Manager SMART EquiTest® using the NeuroCom® SMART EquiTest®/InVision/HT-SOT Version 9.1 software (NeuroCom®, a division of Natus®, Clackamas, OR, USA);
- a Bertec BP-5050 three-component balance platform using the Bertec Digital Acquire Version 4.0.11.407 software (Bertec Corporation, Columbus, OH, USA);
- a Vestibular Technologies CAPS® Professional and a Vestibular Technologies CAPS® Lite three-component balance platforms using the Vestibular Technologies Force Platform Control Panel Software Version 3.0 (Vestibular Technologies, LLC, Cheyenne WY, USA).

At the time we performed these tests, the instruments had been in use in our clinics for several years and had been maintained according to the manufacturer’s

Table 1. Trueness, precision and resolution for the different instruments at various loading levels

Load		NeuroCom® SMART EquiTest®	Bertec BP 5050	Vestibular Technologies CAPS® Lite CAPS® Professional		
15 kg	ML	Trueness (mm)	1.26 ± 0.10	0.72 ± 0.02	0.15 ± 0.03	<i>0.09 ± 0.01</i>
		Precision (mm)	1.69 ± 0.29	0.89 ± 0.04	0.12 ± 0.03	0.09 ± 0.00
		Resolution (µm)	<i>6.18 ± 9.83</i>	<i>0.10 ± 0.00</i>	<i>0.03 ± 0.03</i>	<i>0.17 ± 0.19</i>
	AP	Trueness (mm)	2.26 ± 0.18	0.74 ± 0.01	0.14 ± 0.03	<i>0.10 ± 0.01</i>
		Precision (mm)	2.86 ± 0.19	1.05 ± 0.03	0.12 ± 0.04	0.09 ± 0.01
		Resolution (µm)	106.84 ± 83.71	<i>0.10 ± 0.00</i>	<i>0.04 ± 0.06</i>	<i>0.17 ± 0.21</i>
	2D	Trueness (mm)	2.83 ± 0.12	1.16 ± 0.03	0.23 ± 0.05	0.15 ± 0.01
		Precision (mm)	3.14 ± 0.05	1.27 ± 0.04	0.15 ± 0.04	0.11 ± 0.01
		Resolution (µm)	109.40 ± 53.77	<i>0.07 ± 0.07</i>	<i>0.01 ± 0.01</i>	<i>0.03 ± 0.02</i>
35 kg	ML	Trueness (mm)	0.35 ± 0.04	0.09 ± 0.01	<i>0.06 ± 0.01</i>	<i>0.03 ± 0.00</i>
		Precision (mm)	0.32 ± 0.04	0.08 ± 0.01	<i>0.05 ± 0.01</i>	<i>0.02 ± 0.00</i>
		Resolution (µm)	<i>14.81 ± 0.08</i>	<i>0.11 ± 0.05</i>	<i>0.01 ± 0.01</i>	<i>0.07 ± 0.13</i>
	AP	Trueness (mm)	1.03 ± 0.05	0.12 ± 0.01	<i>0.06 ± 0.01</i>	<i>0.04 ± 0.01</i>
		Precision (mm)	1.28 ± 0.03	0.11 ± 0.00	<i>0.04 ± 0.00</i>	<i>0.04 ± 0.01</i>
		Resolution (µm)	118.09 ± 4.93	<i>0.09 ± 0.04</i>	<i>0.01 ± 0.01</i>	<i>0.06 ± 0.06</i>
	2D	Trueness (mm)	1.17 ± 0.06	0.17 ± 0.01	<i>0.10 ± 0.01</i>	<i>0.05 ± 0.01</i>
		Precision (mm)	1.25 ± 0.03	0.11 ± 0.01	<i>0.05 ± 0.01</i>	<i>0.04 ± 0.01</i>
		Resolution (µm)	<i>49.80 ± 8.52</i>	<i>0.05 ± 0.05</i>	<i>0.00 ± 0.00</i>	<i>0.01 ± 0.01</i>
53 kg	ML	Trueness (mm)	0.36 ± 0.02	0.18 ± 0.01	<i>0.04 ± 0.01</i>	<i>0.02 ± 0.00</i>
		Precision (mm)	0.44 ± 0.03	0.19 ± 0.01	<i>0.04 ± 0.01</i>	<i>0.02 ± 0.01</i>
		Resolution (µm)	<i>14.82 ± 0.61</i>	<i>0.07 ± 0.04</i>	<i>0.01 ± 0.01</i>	<i>0.04 ± 0.05</i>
	AP	Trueness (mm)	0.74 ± 0.03	0.12 ± 0.02	<i>0.04 ± 0.01</i>	<i>0.03 ± 0.00</i>
		Precision (mm)	1.02 ± 0.02	0.12 ± 0.02	<i>0.03 ± 0.00</i>	<i>0.02 ± 0.00</i>
		Resolution (µm)	86.50 ± 0.77	<i>0.11 ± 0.10</i>	<i>0.03 ± 0.05</i>	<i>0.05 ± 0.06</i>
	2D	Trueness (mm)	0.91 ± 0.03	0.23 ± 0.02	<i>0.06 ± 0.01</i>	<i>0.04 ± 0.00</i>
		Precision (mm)	1.05 ± 0.03	0.21 ± 0.01	<i>0.04 ± 0.00</i>	<i>0.03 ± 0.01</i>
		Resolution (µm)	88.23 ± 24.91	<i>0.03 ± 0.02</i>	<i>0.00 ± 0.00</i>	<i>0.01 ± 0.00</i>
75 kg	ML	Trueness (mm)	0.27 ± 0.03	0.10 ± 0.00	<i>0.02 ± 0.00</i>	<i>0.02 ± 0.00</i>
		Precision (mm)	0.38 ± 0.05	0.10 ± 0.00	<i>0.02 ± 0.00</i>	<i>0.01 ± 0.00</i>
		Resolution (µm)	<i>14.66 ± 0.27</i>	<i>0.03 ± 0.02</i>	<i>0.01 ± 0.01</i>	<i>0.02 ± 0.02</i>
	AP	Trueness (mm)	0.72 ± 0.06	0.18 ± 0.01	<i>0.03 ± 0.00</i>	<i>0.02 ± 0.00</i>
		Precision (mm)	0.95 ± 0.06	0.16 ± 0.01	<i>0.03 ± 0.01</i>	<i>0.02 ± 0.00</i>
		Resolution (µm)	67.59 ± 11.00	<i>0.04 ± 0.02</i>	<i>0.01 ± 0.01</i>	<i>0.01 ± 0.01</i>
	2D	Trueness (mm)	0.83 ± 0.06	0.22 ± 0.01	<i>0.04 ± 0.00</i>	<i>0.03 ± 0.00</i>
		Precision (mm)	0.98 ± 0.06	0.16 ± 0.01	<i>0.03 ± 0.00</i>	<i>0.02 ± 0.00</i>
		Resolution (µm)	59.41 ± 9.89	<i>0.03 ± 0.02</i>	<i>0.00 ± 0.00</i>	<i>0.00 ± 0.00</i>

ML: medio-lateral; AP: antero-posterior; 2D: two-dimensional; the results are reported as Mean ± Standard Deviation of the 10 repetitions; values satisfying the ISPGR standards are in italic; Trueness, and precision are in millimeters, the resolution is in micrometers, i.e. 10-3 mm.

instructions. As described in detail by Pagnacco and colleagues (Pagnacco et al. 2014), trueness, precision and resolution characteristics of force platforms can be assessed either by applying known forces in known discrete locations on the surface of the instrument, or by applying dynamic forces using a system similar to what was proposed by Morasso and colleagues (Morasso et al. 2002) such that the resultant CoP is continuously varying during the test. Comparing these two methods, Pagnacco and colleagues concluded that using a continuously varying CoP produces loading conditions that include shear forces and are more representative of what happens when a subject is standing on the instrument, allows one to easily test a larger number of CoP loca-

tions, and is a superior method to determine “in situ” the metrological characteristics of force platforms that satisfy the stringent recommendations adopted by the ISPGR (Pagnacco et al. 2014). Therefore, to assess the trueness, precision, and resolution of the instruments, we used a custom device similar to the one suggested in (Pagnacco et al. 2014). The rotating mass of 0.200 kg was positioned at a radius of 0.173 m and a height of 0.480 m. The fixed ballast masses used were 15.01 kg, 34.86 kg, 53.37 kg, and 74.62 kg. As in (Pagnacco et al. 2014), the maximum rotational speed considered was 4 Hz for the two smaller ballast masses and 4.5 Hz for the others; the minimum was 0.5 Hz. The resultant span of the CoP for each ballast mass value was approximately 3.3-72.7 mm,

1.5-31.5 mm, 1.0-26.0 mm, and 0.7-18.6 mm respectively. For each ballast mass, 10 repetitions were performed and the trueness and precision were averaged across the repetitions. The maximum sway and the mean CoP velocity the instruments measure when a static weight is used as a test subject were quantified by stacking up to four 25 kg steel weights in the approximate center of each instrument. A total of 10 repetitions of 5 s each were performed for each load. Data were acquired from all instruments at 100 Hz and exported as a text file using the software's export function. The NeuroCom® system available for this investigation did not have the capability to acquire custom tests, therefore the SOT protocol tests with static support surface were used to collect the data. Subsequent data analysis was performed in MATLAB® (The MathWorks Inc., Natick, MA, U.S.A.). The trueness and precision were computed considering the absolute distance of each CoP location sampled by the instrument and the corresponding theoretical CoP location obtained by the equations describing the theoretical CoP trajectory. The resolution was determined considering the average across the repetitions of the smallest non-zero distance between CoP locations collected during each test. The maximum sway was determined considering two times the maximum radial CoP excursion from the average CoP location during the

test. The mean CoP velocity was computed by dividing the length of the CoP path by the test duration.

All tests were performed at our clinical facility and the local value of the gravity acceleration was determined to be 9.7953 m/s² by using the online NGS Surface Gravity Prediction tool of the US National Oceanic and Atmospheric Administration.

RESULTS

Table 1 reports, as mean ± standard deviation, for each value of the testing device mass and the four instruments, the trueness, precision and resolution in the antero-posterior (AP) and medio-lateral (ML) directions as well as in terms of two-dimensional distance (2D).

The corresponding 95th percentile of the absolute CoP error is reported in Table 2.

Figure 1 shows an example of the CoP trace obtained during the experiments. The case considered is the one that had, on the NeuroCom® device, the overall smallest 95th percentile error for that device.

Table 3 reports, as mean ± standard deviation, for each of the four static loads considered, the maximum CoP sway and the mean CoP velocity obtained for the four instruments.

Table 2. 95th percentile absolute CoP error for the different instruments at various loading levels

	Load	NeuroCom®	Bertec	Vestibular Technologies	
		SMART EquiTest®	BP 5050	CAPS® Lite	CAPS® Professional
ML	15 kg	4.54 ± 0.69	2.75 ± 0.10	0.36 ± 0.08	0.25 ± 0.01
	35 kg	1.00 ± 0.14	0.26 ± 0.03	0.15 ± 0.03	0.06 ± 0.00
	53 kg	1.21 ± 0.04	0.62 ± 0.02	0.12 ± 0.02	0.07 ± 0.01
	75 kg	1.08 ± 0.16	0.33 ± 0.01	0.07 ± 0.01	0.05 ± 0.00
AP	15 kg	8.28 ± 0.87	2.54 ± 0.05	0.38 ± 0.10	0.29 ± 0.03
	35 kg	3.67 ± 0.20	0.35 ± 0.02	0.15 ± 0.02	0.11 ± 0.03
	53 kg	2.95 ± 0.07	0.38 ± 0.05	0.10 ± 0.01	0.07 ± 0.01
	75 kg	2.88 ± 0.25	0.51 ± 0.02	0.08 ± 0.02	0.04 ± 0.00
2D	15 kg	9.24 ± 0.49	3.67 ± 0.13	0.49 ± 0.15	0.36 ± 0.02
	35 kg	3.72 ± 0.20	0.39 ± 0.01	0.18 ± 0.02	0.12 ± 0.03
	53 kg	3.12 ± 0.10	0.70 ± 0.03	0.15 ± 0.02	0.10 ± 0.02
	75 kg	3.04 ± 0.27	0.55 ± 0.02	0.11 ± 0.01	0.06 ± 0.00

ML: medio-lateral; AP: antero-posterior; 2D: two-dimensional; the results are reported as Mean ± Standard Deviation of the 10 repetitions

Table 3. Mean CoP Velocity in mm/s and Maximum CoP Sway in millimeters reported by the instruments at different static loading levels

Load		NeuroCom®	Bertec	Vestibular Technologies	
		SMART EquiTest®	BP 5050	CAPS® Lite	CAPS® Professional
25 kg	Mean Vel (mm/s)	34.55 ± 5.62	5.88 ± 0.23	0.43 ± 0.02	1.60 ± 0.05
	Max Sway (mm)	2.06 ± 0.40	0.29 ± 0.03	0.04 ± 0.00	0.15 ± 0.02
50 kg	Mean Vel (mm/s)	17.90 ± 6.45	3.28 ± 0.36	0.26 ± 0.03	0.80 ± 0.07
	Max Sway (mm)	1.01 ± 0.09	0.15 ± 0.02	0.02 ± 0.00	0.07 ± 0.00
75 kg	Mean Vel (mm/s)	12.34 ± 4.41	7.68 ± 1.83	0.38 ± 0.08	0.53 ± 0.02
	Max Sway (mm)	0.69 ± 0.09	0.31 ± 0.09	0.02 ± 0.00	0.05 ± 0.00
100 kg	Mean Vel (mm/s)	9.79 ± 3.90	5.20 ± 0.70	0.40 ± 0.10	0.44 ± 0.05
	Max Sway (mm)	0.68 ± 0.43	0.25 ± 0.04	0.03 ± 0.01	0.04 ± 0.01

The results are reported as Mean ± Standard Deviation of the 10 repetitions

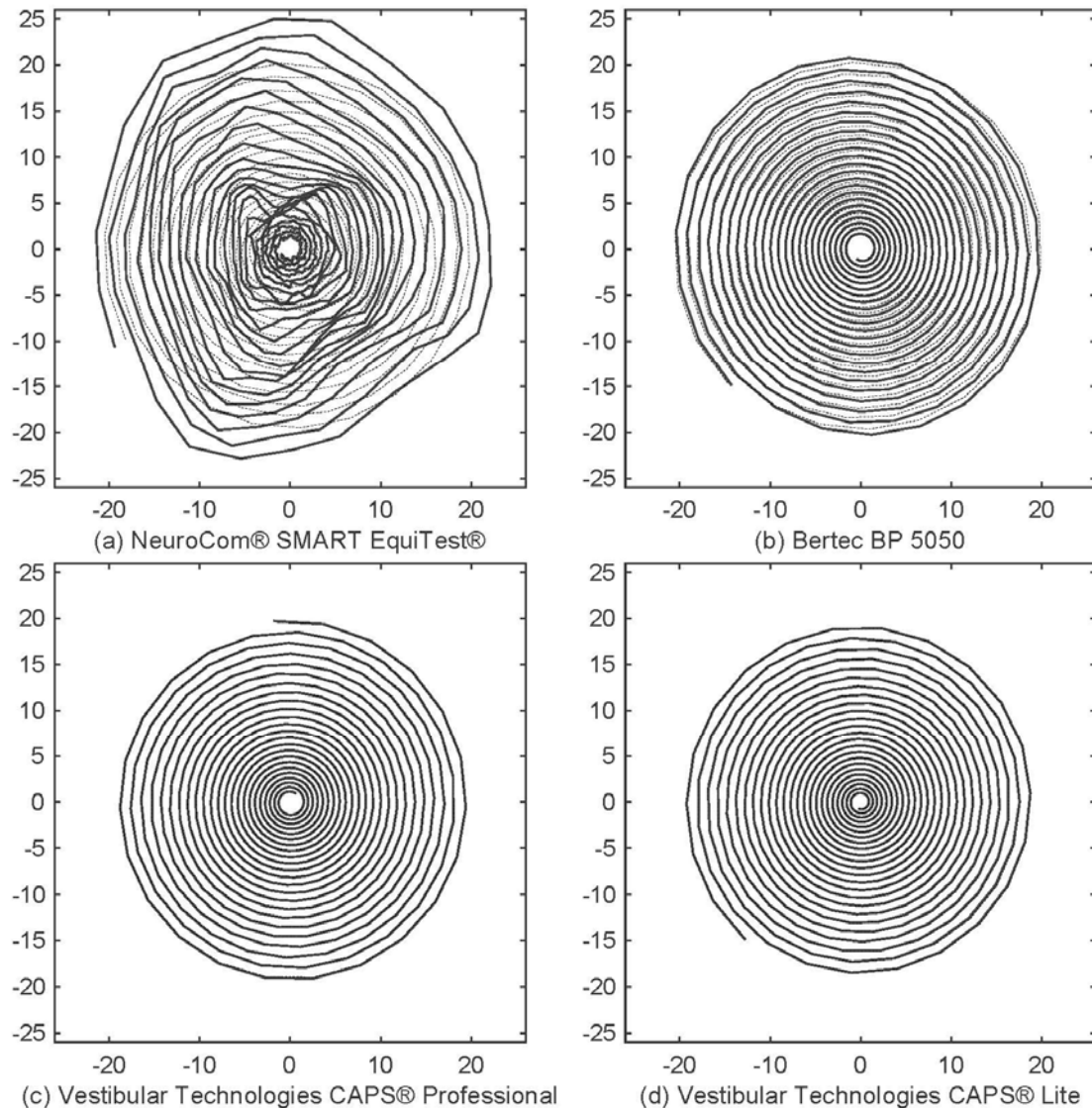


Figure 1. Example of experimental (continuous line) and theoretical (dashed line) spiral CoP traces for the different instruments at the 75 kg load; dimensions are in millimeters

DISCUSSION

The results in Table 1, together with what was previously reported by other investigators (Cappello et al. 2011, Bartlett et al. 2014) show that many instruments commonly used in clinical practice (as well as research) to measure human sway do not satisfy the recent recommendations adopted by the ISPRG. Cappello and colleagues found that force platforms designed for gait studies (AMTI OR6, Bertec 4060-08, Bertec 4080-10, and Kistler 9286A) have at best, after a very sophisticated non-linear in situ recalibration possible only in research environments, a 2D trueness of 0.5 mm and a 2D precision of 0.2 mm (Cappello et al. 2011). Analyzing an AMTI OR6-6-1000 and a Nintendo Wii™ Balance Board, Bartlett and colleagues reported at best a trueness of 1.6 mm with a precision of 1.7 mm for the Wii device and a trueness of 1.2 mm with a precision of 1.1 mm for the AMTI instrument (Bartlett et al. 2014).

In our tests, the NeuroCom® system, one of the devices most cited in the literature, also has a trueness and precision both in the order of a millimeter. Our results for the Bertec BP-5050 show that force platforms designed for balance studies (i.e., balance platforms) can have better trueness and precision than what has been previously reported for models from the same manufacturer designed for gait analysis (Cappello et al. 2011), but they do not necessarily meet the ISPRG recommendations.

The results of this investigation confirm the results for the two Vestibular Technologies CAPS® systems previously reported by Pagnacco and colleagues (Pagnacco et al. 2014), and meeting the ISPRG recommendations: the CAPS® instruments, both 8 years old at the time of the experiments, did so, at least at loads of 35 kg and greater, a weight that according to the Centers for Disease Control is reached by most before the 11th birthday (CDC 2000). At a load of 15 kg, a weight reached by most before the 4th birthday (CDC 2000), no

device meets the new recommendations. However, while the other devices show, at that load, a 2D trueness and precision worse than a millimeter, the CAPS® devices are still on the order of 0.1 mm, which is similar to what was found for the other instruments at the higher loads.

Perhaps the most interesting results for both clinicians and researchers are the absolute CoP errors reported in Table 2. As described in the Introduction, the ISPGR recommendations appear to aim for a CoP error (“accuracy” according to ISO 5725:1994) of less than 0.2 mm. This is again much smaller, often by an order of magnitude, than what studies have reported for force platforms designed for gait studies: from the results presented by Cappello and colleagues (Cappello et al. 2011), it is easy to estimate that, even with advanced non-linear in situ recalibration, the errors are in the order of 1 mm; with a more conventional in situ recalibration, they are in the order of 2-5 mm. Similar results were found by Bartlett and colleagues (Bartlett et al. 2014). Our investigation found the NeuroCom® device to have 2D CoP errors of over 3 mm, which are similar to the aforementioned level of error. The Bertec balance plate, although still not satisfying the recommendations, had smaller errors than a gait platform from the same manufacturer (as reported in (Cappello et al. 2011)). The difference between the errors of the previously mentioned non-ISPGR-compliant devices, and those of the two ISPGR-compliant Vestibular Technologies CAPS® Systems can easily be appreciated. To put these results in perspective, CoP errors of millimeters are of the same order of magnitude of the amount of sway of a person (Browne & O’Hare 2000, Moghadam et al. 2011), and those above 0.5 mm can be greater than the Minimum Detectable Change (MDC) for some subjects (Pagnacco et al. 2015).

The results reported in Table 3 provide an indication as to how the trueness and precision affect the maximum CoP sway and mean CoP velocity the instruments measure for a dead weight: because of noise, instruments not satisfying the ISPGR recommendations can measure values comparable to those reported in the literature for human subjects. For instance, Moghadam and colleagues reported, for subjects standing with eyes open on a rigid surface, a mean CoP velocity of 13.7 mm/s with a MDC of 3.9 mm/s (Moghadam et al. 2011).

In most clinical measurements, errors having the relative magnitude as those reported in the literature and in our results for non-ISPGR-compliant devices would be considered unacceptable because they are larger than the clinical MDC of some subjects. The error of a device satisfying the ISPGR recommendations appear to be much more acceptable. In light of these results, it is possible that the values reported by investigations using instruments not meeting the ISPGR recommended trueness and precision could be incorrectly estimating the amount of sway, its velocity and related measures. While this is of great consequence in research, we

suggest that it is also important in clinical applications where ameliorating poor metrological characteristics of the instruments via statistical methods is typically not possible.

CONCLUSIONS

Clinicians need and depend upon accuracy in their diagnostic instruments. Mental health practitioners are increasing the use of physical rehabilitation procedures in their therapies. Posturographic measurements must be better than bedside testing, or there is no rationale for them when simple standard physical examination criteria will suffice. As more clinical applications in the treatment of neuro-psychiatric disorders are being derived from posturographic measurements, clinicians need to be assured that the measurements are more accurate than their own observational skills. Research investigations rely on the accuracy of the instruments used. Poor metrological performance of some instruments is a possible logical explanation for the often-conflicting findings of some prior investigations.

The scientific and clinical consequences associated with accuracy of measurement should be self-evident. Measures obtained and data collected are only as good as the instrument used to collect them. Clinical and research findings could be erroneous, or at the least misleading, if measurement errors are too large.

We suggest that there is a strong need for a greater accuracy (as the combination of trueness and precision) of posturographic instrumentation, especially if the data obtained are to be used in a clinical application or in correlation studies with other quantitative outcomes. The 2013 ISPRG recommendations appear to be reasonable and appropriate, and our results show they are obtainable yet our clinical team and others often use instruments that do not meet them. Incorrect measurements may contribute to a widespread perception of posturography being “experimental”. We believe this will change only when the accuracy of posturographic measurements meets higher standards, such as the minimal standards recommended by the ISPRG.

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Contribution of individual authors:

Frederick R, Carrick, Rashid Zaman & Cameron H. G. Wright conceived the idea of the study, contributed to the literature review and revised the manuscript. Ahmed Hankir organised the study, collected the data, and contributed to the literature review and revised the manuscript.

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PERCEIVED ACADEMIC AND PSYCHOLOGICAL STRESS AMONG ADOLESCENTS IN UNITED ARAB EMIRATES: ROLE OF GENDER, AGE, DEPRESSION, AND HIGH EXPECTATION OF PARENTS

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SUMMARY

Introduction: Academic learning is the most important source of stress among young students worldwide and appears to be quite severe in eastern countries. We aimed to examine the relationship between academic stress and depression among adolescents.

Methods: A cross-sectional study was conducted among adolescents in United Arab Emirates using the Perceived Stress Scale – 14 (PSS-14) and Educational Stress Scale (ESS) for Adolescents (English and Arabic versions).

Results: The overall PSS was high in 186 (20%) of the respondents, and moderate in 695 (76%). A multiple regression model of predictors of the PSS showed statistically significant correlations between the total PSS-14 scores and age ($p < 0.0004$), gender ($p < 0.0001$), and grade ($p < 0.001$). A multiple regression model of the PSS-14 questionnaire as predictors of the ESSA revealed that Four variables on PSS-14 were statistically significant predictors of the ESSA: history of depression ($p < 0.0001$), content with academic achievement ($p < 0.0001$), high academic expectation of parents ($p < 0.003$), and a believe capable of meeting parental expectations ($p < 0.0001$).

Conclusions: Adolescents with severe academic stress need to be identified early. We suggest that an interdisciplinary team in the schools including student advisors and counselors be developed to further address stressors. In addition, students should be taught different stress management techniques such as cognitive behavioral skills to improve their ability to cope with school demands. The identification of stressors may lead to strategies that might address the quality of teaching and mental health evaluation among adolescents.

Key words: academic stress - psychological stress - adolescence - United Arab Emirates

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INTRODUCTION

Recent reports demonstrate that academic learning is the most important source of stress among young students worldwide and this appears to be quite severe in eastern countries (Brown et al. 2006, Park 2018). Eastern students usually have a high academic burden, low satisfaction regarding their academic performance, high expectations and may suffer more academic stress than their counterparts in English speaking countries (Ang et al. 2016). Academic stress is a significant contributor to a variety of mental and behavioral disorders, such as depression, anxiety, and suicidal behavior (Fawzy 2017, Latiff et al. 2016).

Therefore, the impact of stress on adolescent students and possible stress management interventions are of growing interest to educators throughout the world. Students' stress has been shown not only to adversely influence their academic performance but also to contribute towards psychiatric morbidity and substance abuse and may lead to the tragic consequence of suicide

(Dyrbye et al. 2008). Suicide is considered to be the second most common cause of death in adolescents in industrialized countries (Aaron et al. 2004, Rey et al. 1997). Some of the coping strategies used by students to deal with stress include using alcohol, tobacco, and other drugs (Ashton & Kamali 1995) or over sleeping and going into isolation (Shaikh et al. 2004). In recent years, studies have revealed a strong relationship between academic stress and depression, anxiety, low self-esteem, and suicidal ideation among students in secondary and high schools (Crystal et al. 1994, Page et al. 2011). Similar to psychological stress in general, academic or educational stress is a subjective state associated with an individual's perception of possible future outcomes or consequences related to academic performance and in reaction to external stressors, including the burden imposed by people and school systems.

United Arab Emirates (UAE) is a young country with multicultural and multinational environment. The schools in UAE are divided to governmental (exclusively for UAE nationals) and private, that is for both

UAE nationals and expatriates. However, the majority of UAE nationals prefer to have their children study in private schools. This contributes to more psychological stress on the students because most of the private schools are in English and the students who are native Arabic speakers have to be bilingual to participate. Over the past four decades, the UAE has gone through a profound and rapid socioeconomic transition leading to fundamental changes in the population's lifestyle, dietary habits and patterns of physical activity (Trainer 2010), similar to the modernization processes that occurred in the western world, but in a much shorter time. Currently, adolescents in UAE are under high pressure due to their academic settings. They spend almost the entire day studying at school and they have to deal with excessive homework and study in order to achieve a higher GPA. Only those who attain high scores can enter one of UAE's prestigious universities that traditionally are believed to guarantee jobs with higher salaries at prominent companies. Thus, Parents have high academic expectations for their children that might affect the psychological wellbeing of the child. Yet, no study has analyzed this important topic in this part of the world (e.g. Arab countries and Middle East). The present study was planned to determine levels of stress in adolescent school children, the psychological health, prevalence of educational stress among adolescents, and any correlation between these variables. We aimed to contribute to the scientific and sociological understanding of these dynamics at the regional and national level.

METHODS

Study Design

This descriptive cross-sectional survey was conducted among adolescents (aged 10-19) of all nationalities; attending the common schools in the emirate of Dubai; from September 2018 until February 2019.

Study participants and Procedure

The study was conducted in the form of an electronic survey available in both English and Arabic languages. Participants for the study were recruited by a simple random sampling method. The participants were between 10-19 years, UAE citizens (nationals) and expatriates, living in UAE. Students were accepted into the study that were able to read and understand English or Arabic, and consented to participate in the study. The participants were assured of the confidentiality of the information provided and protection of their rights to privacy. The sample size was calculated using epidemiological information for a population of 820,387 (population of total adolescents living in UAE), with an alpha of 5% and a 95% confidence level. We needed a minimum required sample size of 384 (Bagiella & Chang 2019).

Survey Design (Evaluation tools)

A structured questionnaire was designed and developed by a multidisciplinary team after a thorough review of the literature from relevant studies (Moksnes et al. 2010, Latiff et al. 2016, Anderman 2002, Ang & Huan 2006, Ang et al. 2016). The evaluation tool was then pre-tested among 20 adolescents to assess the ease of understanding and time required for completion. The survey instrument consisted of 47 items and was designed to incorporate the sociodemographic variables and potential academic stressors of the participants. The sociodemographic data included age, nationality, parental marital status, educational level of both parents, type of school attended, the grade attended, and whether they are a single child or if they have siblings. The second part of the questionnaire contained five questions on the adolescents' perception on his/her academic achievements, parent's expectations, if he/she is meeting the parent's expectation, any history of depression, and whether the family is emotionally supportive. For each potential stressor, the frequency of occurrence was classified as never, rarely, sometimes, often, and always. The severity of each stressor was rated using a Likert scale (1-5) ranging from not severe to very severe.

The remaining sections of the questionnaire focused on the Perceived Stress Scale – 14 (PSS-14) and the Educational Stress Scale for Adolescents (ESSA). The students with a perceived stress score ≥ 38 were labeled as highly stressed, those with a perceived stress score 19-37 were labeled as moderately stressed, and scores < 18 were labelled as low stress.

Data analysis and statistics

All collected data were entered into STATA 14.2 (StataCorp, College Station) for statistical analysis. Descriptive statistics were computed for all socio-demographic variables and the overall responses to each item of the survey were recorded as a percentage of the total. The percentage differences in the total responses were determined using the Chi-square test and ANOVA and statistical significance recorded for non-parametric data. For all analyses, alpha (α) was set at 0.05.

Ethics statement

The study was approved by the institutional review boards of Dubai Health Authority, Dubai (Approval # DSREC-SR-09/2018-01) and conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). All subjects gave informed consent and assured that patient anonymity would be preserved. Aggregate reporting of data assured to enhance confidentiality and accurate reporting by the respondents. A code linking respondents to their surveys was kept isolated from the investigators.

RESULTS

Out of 980 individuals approached, 914 agreed to participate in the study (response rate of 93%). The majority of our respondents were 14-16 years of age, female, Non-UAE national, attending secondary school (grades 7-9), attending private schools, residing in the capital of Abu Dhabi, with parents married and living together, and their parents had at least a bachelor's degree. The majority (407, 45%) of the adolescents described their academic level as being very good and their family to be emotionally supportive (724, 79%). Yet, most of the respondents mentioned that their parents have high expectations from them (770, 84) and they thought that they were capable of meeting these expectations (668, 73%). Two out of five of our respondents (382, 42%) reported experiencing depression at least once (Table 1).

Findings of Perceived Stress Scale – 14

The overall perceived stress scale was high in 186 (20%) of the respondents, moderate in 695 (76%), and low in 32 (4%). A multiple regression model of predictors of the Perceived Stress Scale (PSS) – 14 was calculated with predictors. Statistically significant correlations were found between the Total PSS-14 scores and age ($p < 0.0004$), gender ($p < 0.0001$), and grade ($p < 0.001$) (Figure 1).

Educational Stress Scale for Adolescents

Bivariate correlations were calculated between the Educational Stress Scales for adolescents (ESSA) and sociodemographic variables of the adolescents. To evaluate the correlations ($|r| = 0.1$ is weak, $|r| = 0.3$ is moderate

Table 1. Descriptive demographic characteristics of participants (n =914)

Variable, n (%)				
Gender	Male	Female		
	170 (19)	744 (81)		
Age (Years)	10-13	14-16	17-19	
	10 (1)	468 (51)	436 (48)	
Nationality	UAE	Non-UAE		
	201 (22)	713 (78)		
Which grade do you attend	Secondary school (grades 7-9)	Secondary school (grades 7-9)		
	111 (12)	803 (88)		
Type of your school	Private	Governmental		
	701 (77)	213 (23)		
Emirate you are residing in	Dubai	Abu Dhabi	Sharjah	Northern Emirates
	229 (25)	334 (36.5)	218 (24)	133 (14.5)
Your parent's marital status	Married and living together	Married not living together	Divorced/widowed	
	842 (92)	22 (2)	50 (6)	
Father level of education	high school or less	bachelor	postgraduate	
	283 (31)	350 (38)	281 (31)	
Mother level of education	high school or less	bachelor	postgraduate	
	359 (39)	363 (40)	192 (21)	
Are you a single child	Yes	No		
	33 (4)	881 (96)		
If you're not a single child, specify your rank?	Eldest	Middle	Youngest	
	364 (40)	333 (36)	217 (24)	
What is your academic level	Excellent	Very good	Good	Fair
	209 (23)	407 (45)	251 (27)	47 (5)
Would you describe your family as being supportive emotionally?	Yes	No		
	724 (79)	190 (21)		
Have you ever suffered from depression	Once	More than once	Never	
	382 (42)	256 (28)	276 (30)	
Are you content with your academic achievements/ level?	Yes	No		
	402 (44)	512 (56)		
Do your parents have high expectations from you?	Yes	No	Not sure	
	770 (84)	57 (6)	87 (10)	
Do you believe you're capable of meeting their expectations?	Yes I do	No I don't		
	668 (73)	246 (27)		

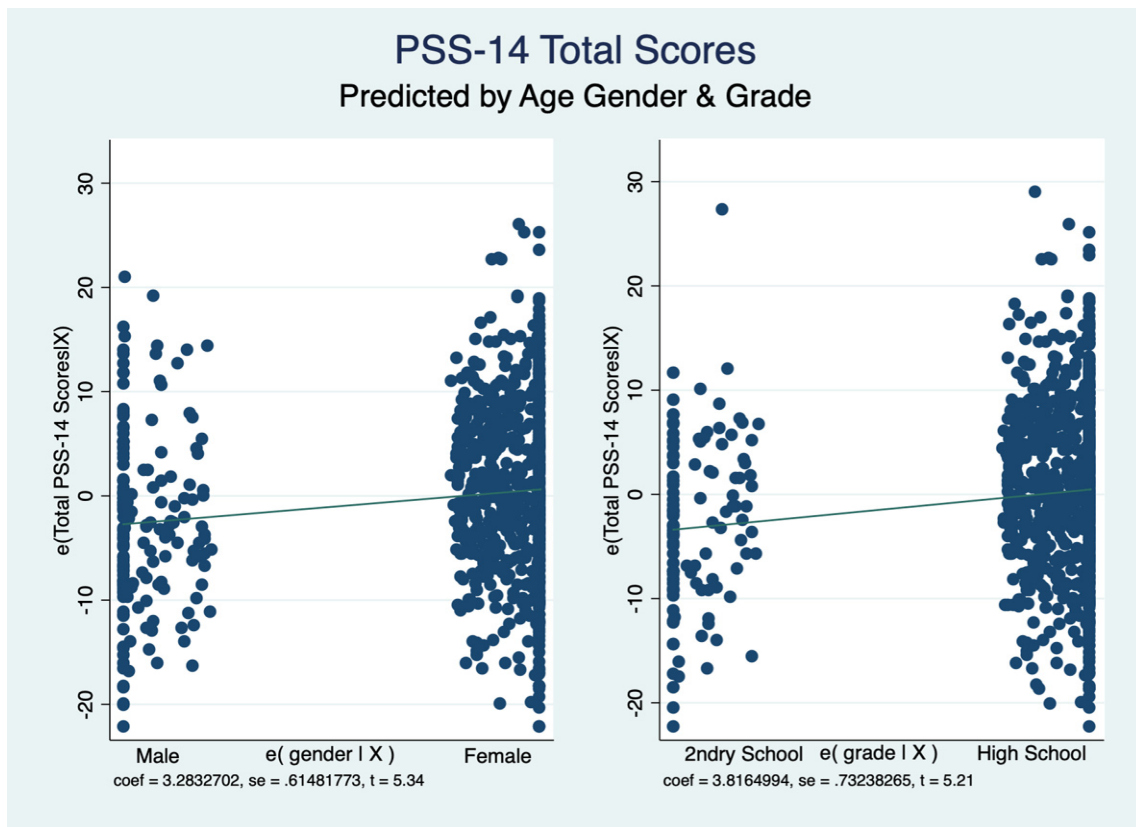


Figure 1. PSS-14 Total Scores Predicted by Age, Gender and Age

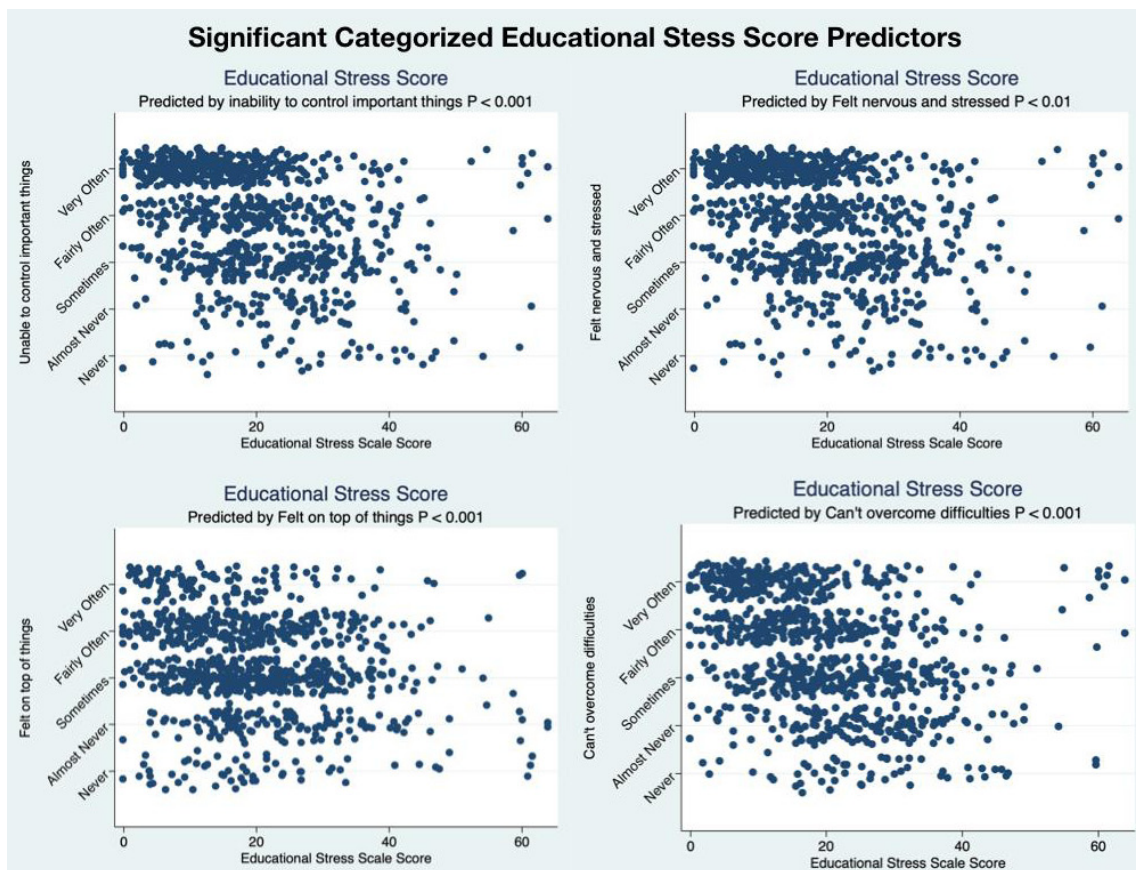


Figure 2. Educational Stress Score Predictors

and $|r|= 0.5$ is a strong relationship) the relationships between ESSA and adolescent responses were obtained. The grade of the adolescent was negatively correlated with the ESSA ($|r|=-0.0876$) ($p<0.008$) revealing that when the grade of the adolescent went up, the ESSA went down. The same trend was found for the adolescent's academic level which also correlated with the ESSA ($|r|=-0.0955$) ($p<0.003$) revealing that when the academic level of the adolescent went up, the ESSA went down. Similar correlations were observed between the ESSA and the adolescent having an emotionally supportive family ($|r|=-0.1291$, $p<0.0001$), content with academic achievement ($|r|=-0.2832$, $p<0.0001$) and a belief capable of meeting parental expectations ($|r|=-0.2829$, $p<0.0001$) demonstrating that as the ESSA went up these variable numbers went down. However a history of depression ($|r|=0.2692$, $p<0.0001$) was positively correlated with the ESSA, demonstrating that as the ESSA went up so did the number of individuals that reported a history of depression. The same phenomenon was found for adolescents whose parents had a high academic expectation of them ($|r|=0.0915$, $p<0.005$) such that the higher the expectations the higher was the ESSA. The Educational Stress Score was statistically significantly predicted by 4 categorized questions on a scale from Never to Very often.

PSS-14 questionnaire as predictors of the ESS

A multiple regression model of the PSS-14 questionnaire as predictors of the ESSA revealed that the model was statistically significant $F(14, 898)=20.53$, $p<0.0001$ demonstrating that we can explain 24% ($R^2=0.2424$) of the variance in the ESSA using all predictors. However only Four variables on PSS-14 were statistically significant predictors of the ESSA: being unable to control the important things life ($p<0.001$), feeling nervous and "stressed" ($p<0.01$), feeling on top of things ($p<0.001$) and can't overcome difficulties ($p<0.001$) (Figure 2).

DISCUSSION

Adolescence represents a time of change for all people and is associated with unique individuality and experiences. The physical, emotional, cognitive, and social changes central to a transition from childhood to adulthood are inimitable from person to person. We realize that fluctuations of the internal environment begins at puberty and is associated with biological changes at a time of external change in both social and academic realization. We realize that adolescents are individuals and that their development is unique. This distinctive development represents a transformation from child to adult that is considered to be a unique vulnerability period associated with personal stress based upon an infinite probability of personal and environmental challenges (Moksnes et al. 2010). Stress is commonly defined as the feeling experienced when a

person perceives the demands of the environment to exceed the personal resources available for coping with them. We wanted to formulate an understanding of the relationship of a variety of stressors as predictors of mental health concerns in adolescents. Other investigations have identified that a students' perceived stress over school demands and worries over school achievement is correlated with self-reported psychosomatic, psychological and emotional symptoms (Gustafsson et al. 2009, Aanesen et al. 2017). Further, greater self-reported stress may be associated with demands of high performance in school resulting in a student embracing a greater commitment to schoolwork over other activities (Kouzma & Kennedy 2004).

Our investigation demonstrates that one out of four of our respondent adolescents (256/914, 28%) reported an experience of depression at least once while the overall perceived stress scale was moderate in 76% (695/914) and high in 20% (186/914) of our respondents. It appears that the most dramatic mental health problems during adolescence are symptoms of being sad, feelings of worthlessness and withdrawal from friends or social activities (Thapar 2012). These findings are found throughout the world and are not unique to any individual environment. For instance, the frequency of self-reported mental ill health among young people in Sweden, has increased since the 1980s. The increase in depressive illness in Swedish adolescents is particularly pronounced in grade 9, but also in grade 7, especially among girls (Giota & Gustafsson 2017). We examined the relationship of depressive illness in UAE adolescents in our investigation using a global understanding of adolescent mental health. We used the PSS-14 and found several statistically significant correlations between the total PSS-14 scores and age ($p<0.0004$), gender ($p<0.0001$), and grade ($p<0.001$). Unfortunately, we were not able to identify anything else that might specifically be associated with the predictability of depression in our respondents. We understand that there is a gender difference in depressive illness reported by several studies with females found to be more prone to stress in response to school demands, coping resources, and increased likelihood of recurrent pain (Östberg et al. 2018).

We did note that there are three variables that were significantly correlated with ESSA among adolescents in this study. Similarly to the PSS-14 we identified the grade of the adolescent as a significant predictor and their academic level, but also noted the significance of a history of depression ($p<0.008$, $p<0.003$, $p<0.0001$). We found that when the grade/adolescent's academic level went up that there was a negative correlation with the ESSA and the ESSA score went down. Interestingly, a history of depression was positively correlated with the ESS, demonstrating that as the ESSA went up so did the number of individuals that reported a history of depression. The same phenomenon was found in adolescents

whose parents had high academic expectations of them ($p < 0.005$) such that the higher the expectations of the parent the higher was the ESS. These findings are similar to that of other reports that show a positive link between depression and ESSA (Jayanthi et al. 2015, Sun et al. 2011).

We also confirmed statistically significant correlations between the ESSA and the adolescent having an emotionally supportive family ($p < 0.0001$). Those students that were content with their academic achievement were significantly correlated with the ESSA ($p < 0.0001$), and a belief that students that were capable of meeting parental expectations ($p < 0.0001$) also demonstrated a negative correlation such that when these variable numbers went up, the ESSA went down.

Although the PSS-14 and ESSA are objective assessment tools that can quantify the degree to which situations in one's life are appraised as stressful (Cohen et al. 1983) they also might determine the stressors that can assist educators in obtaining a baseline for comparing educational interventions in future.

The results of our investigation strongly suggests a need to revisit the demands placed upon students in UAE schools that might contribute to student stress. Other investigators have identified that an overloaded curriculum and teaching quality have been reported to be positively correlated with increased academic stress, depression, and personal stress among adolescents (Liu & Lu 2012, Moksnes et al. 2010).

CONCLUSIONS

The mental health concerns of adolescents that experience severe academic stress should be identified as early as possible so that prompt interventions to treat depression might be developed. We suggest that students might benefit from counselling for stress factors that might be identified by school counsellors or school health nurses. The predictors we have identified that might be associated with depressive illness should be understood by teachers who should in turn identify them as part of a team approach to defeat depression. We suggest that an interdisciplinary team to address stressors should also include student advisors, peer education, and counselors. In addition, students should be taught different stress management techniques such as cognitive behavioral skills, particularly cognitive restructuring adapted from a treatment program for child anxiety to improve their ability to cope with school demands. The identification of stressors must lead to strategies that might address the quality of teaching and mental health evaluation. These strategies should include the family unit as it is essential for adolescents to maintain a stable attachment to their parents in addition to acquiring independence and autonomy (Kim et al. 2007). We suggest that training of all parents addressing the mental health

concerns of their adolescent children should also have a major impact on adolescents' development and social adaptation (Kang et al. 2008).

Limitation of study

The study has several limitations. Generalization about the total population is not warranted due to the random sampling approach and the heterogeneity of our sample. Since the information was collected on self-administered questionnaires, there remains the possibility of information bias. The cross-sectional design of the study precludes evaluation of temporal associations. Prospective studies are necessary to study the associations between the occurrence of stressors and incidence of stress. Finally, there might be other potential academic stressor factors, which were not included in the questionnaire. Yet, the sample was quite large, with a high response rate. Furthermore, the study investigated the factor of adolescents' psychological wellbeing for the first time in the region applying two of the most common used tools (PSS and ESSA). Moreover, this study was the first to evaluate these two tools in an Arabic country.

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Contribution of individual authors:

All authors (Noor Mahir Ali, Nowfala Arakkal Nowshad, Khadeeja Mohammed Mansoor, Rayan Ahmed Ibnouf, Rofida Moustafa Albehiery, Frederick Robert Carrick & Mahera Abdulrahman) were equally involved in the conception of the idea of the study, contributed to the literature review, statistical analysis and revision of the manuscript.

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MENTAL DISORDERS/DIFFICULTIES IN THE POSTPARTUM PERIOD

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SUMMARY

Introduction: Mental difficulties are common in the postpartum period. They can manifest in a mild form, but also as serious disorders which need to be treated in a timely manner. The most common psychological problem is "Baby blues" characterized by relatively short duration without consequences and treatment is largely unnecessary. Postpartum depression is characterized by a sense of sadness, loss of interest, insomnia, discomfort, loss of energy, reduced concentration. Postpartum psychosis is the most serious disorder but is also rare and may have serious consequences for the mother and child. Important factors in the postpartum mental problems/difficulties are genetic factors, situation of unwanted pregnancy, a feeling of discomfort with the role of motherhood and sudden hormonal changes.

Aim: to investigate the frequency and type of mental problems in postpartum period, as well as possible type of help needed by the women in postpartum period.

Subjects and methods: One hundred (112) respondents participated in the survey. The survey was conducted from November to December 2017 through a "google docs" application. The survey was placed on different social networks, and the participation in the survey was voluntary and anonymous. A series of 14 questions with the offered answers was used in the survey.

Results: The results of the survey have shown that psychological difficulties and disturbances in the postpartum period to be common problems encountered by almost 50% of women (44.46%). The most common difficulty is Baby blues, followed by postpartum depression and anxiety disorders. Age and the mode of birth did not affect the emergence of changes, while social factors such as family support had a great impact.

Conclusion: The provision of information to the mothers can help, but inaccurate information can do the opposite. Thus, the role of health care professionals is important for helping mothers in that period to prevent certain difficulties as well as in identifying and referring mothers to seek help in a timely fashion.

Key words: mental disorders /difficulties - health care professionals - education - prevention

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INTRODUCTION

The postnatal period, especially the first six weeks is very stressful for mothers in developing an emotional connection with a child, establishing the balance of the child's needs as well as at achieving their own good emotional and mental state (Misri & Burgman 1992). In the 1990s, the analysis of previous research has shown possible psychological changes during and after pregnancy such as postnatal sadness, depression or psychosis. Postnatal sadness or "Baby blues" is the slightest psychological discomfort mostly beginning on the third day after childbirth in about 45-80% of women with symptoms of sadness, crying, and unstable emotions (Misri & Burgman 1992). According to related researches, postpartum depression (PPD) occurs in about 10 to 43% of women and depends on age, relationship (Misri & Burgman 1992, Upadhyay et al. 2017), unwanted pregnancy, education, previous workplace, genetic and family history of depression (Veisani et al. 2013, El-Ibiary et al. 2013). Certain risk factors for PPD are also connected with young mothers (19-25) who experience parenthood for the first time (Upadhyay et al. 2017, Vismara et al. 2016), level of maternal stress during pregnancy, the

availability of postpartum support, previous diagnosis of depression (Laneset et al. 2011), low education and low socioeconomic status (Goyal et al. 2010, Gupta et al. 2013, Horowitz et al. 2011). Older mothers, mothers of younger children, those who are less willing to seek help and mothers who are more pleased with help have a lower prevalence for developing symptoms of PPD (Saligheh et al. 2014). Specific micronutrient deficiencies contribute to PPD development, probably through psychoneuroimmunology mechanisms (Ellsworth-Bowers & Corwin 2012). Mothers with depressive symptoms establish a weaker social interaction with their child (Mantisa et al. 2019, Ohashi et al. 20016). It is important to identify significant PPD predictors that can be easily detected by systematic testing in clinical practice for the identification of potentially risky mothers (Fiala et al. 2017). When talking about postpartum psychosis (PPP), a fast and accurate diagnosis is important for timely and appropriate treatment and providing rapid, complete recovery, prevention of future episodes, and risk reduction for the mother, child, and family (Sit et al. 2006). Mothers have four categories of their needs: the need for information, psychological support, the need for experience exchange, and needs for practical and material support

(Slomian et al. 2017). There is a direct correlation between depressive symptoms, anxiety and mothers' age, rural residence, and low income (Olaoluwa et al. 2019). Neuroscientists have shown that monitoring of some neural correlates of emotional anticipation in the postpartum period could identify changes occurring in neuronal folders responsible for certain emotions which affect the occurrence of depressive symptoms (Malin et al. 2017). This is also shown by research in Japan that established the validity of certain scales for measuring and screening of risk persons (Ikeda & Kamibeppu 2013). It is assumed that changes in mothers' behaviour in relation to a child can prevent PPD through several possible pathways of mediation: (1) increasing the effectiveness of parenting and consequently reducing negative self-deprivation; (2) a better sense of social support by the physician; (3) a better maternal dream; (4) more effective parental skills; (5) increased attachment to the child (Werner et al. 2015). Some studies have shown that interpersonal psychotherapy (IPT) intervention (Chien Wen et al. 2015) breastfeeding (Mezzacappa & Katkin 2002, Thome et al. 2006), mental training (Sheydaei et al. 2017, Potharst et al. 2017), light therapy (Crowley & Youngstedt 2012), and aromatherapy (Asazawa et al. 2017) can be successful treatment for PPD. Providing support to healthy women without any complications at home as well in the community, to prevent the occurrence of PPD is important (Takahashi & Tamakoshi 2014). The present study aimed to collect information about psychological disorder/disturbances in the postpartum period, to demonstrate which factors positively or negatively affect psychological difficulties after childbirth, how social support influences the prevention of psychological changes, and how community care affects the reduction of these difficulties in Croatia.

SUBJECTS AND METHODS

The survey was conducted from September to October 2017 and was conducted through a "google" application. The survey was placed on different social networks (www.roda.hr & www.forum.hr) in the Croatian language and the participation in the survey was voluntary and anonymous with the note that women with experience in childbirth were participating. A survey of 14 questions with the offered answers was used in the survey. One hundred and twelve (112) respondents participated in the survey. Before processing the data in order to evaluate the results of the survey, assessment was made as to how representative the sample was, and whether it was possible to obtain concrete results based on the obtained sample.

RESULTS

Most respondents (71.43%) were of the age of 26-35; 12.50% respondents were of the age between 18 and

25 and 16.07% were aged 36 and over. Most of the participants had had the first childbirth (57.14%), 32.14% of mothers had had the second childbirth, and 10.71% of them had had a third or more. Childbirth was mostly vaginal (83.04%), only 16.96% had had a Caesarean section. Most women (78.57%) did not fear a new childbirth. According to the occurrence of psychic changes after childbirth, even 29.46% of mothers answered that they did not hear about the possibility of psychological changes. The most common information source was the internet (59.82%), followed by information from a specialist (16.96%) and experience of a close person (12.50%). 10.71% of mothers did not receive information on psychological problems and disorders. In response to the presence of a partner during the delivery of the child, 61.61% of women responded that the partner was present. After delivery, most women (91.07%) had some form of support. The most frequent support came from family and friends (41.07%), then only the family (30.36%) and only the partner (19.64%). Most of the mothers (55.36%) did not have any difficulty, while the most common type of problems was Baby blues (25.00%). Other psychological changes were represented in a small percentage. Of the 50 participants experiencing some form of mental disturbance, most (23.21%) experienced changes immediately after delivery, 14.29% experienced change 2 weeks after, and 1-3 months after childbirth in 8.04% of women. Results have been shown in Figure 1.

The duration of mental difficulties/changes was variable; 16.07% of women answered that the duration was 1-3 months, for 15.8% participants the duration was less than a month, 3.57% of the participants had symptoms from 3 to 6 months, while in 10.71% of women changes lasted longer than 6 months; results are shown in Figure 2.

Most mothers (74.11%) had support during pregnancy, delivery and postpartum period, but 18.75% answered that they had no support. 7.14% of participants did not know if they had any support. The number of community nurse visits was satisfactory. There were one to three visits after childbirth (61.61%), four and more visits (36.61%), while a very small percentage of mothers (1.79%) answered they did not have a single visit. It is noted that more than 50% were satisfied (55.36%), while (34.82%) were partially satisfied, and 9.82% were not at all satisfied with the information they got. 44.64% of the families did not receive enough information.

Out of a total of 112 women responding to the survey, 50 of them have had some kind of mental difficulties/disorder. 35.71% of them at the age of 18-25 years had experienced some kind of psychological change. This percentage is 46.25% for women aged 26-35 and 44.44% for women older than 36 years. Figure 3 shows the distribution of psychological changes by age groups.

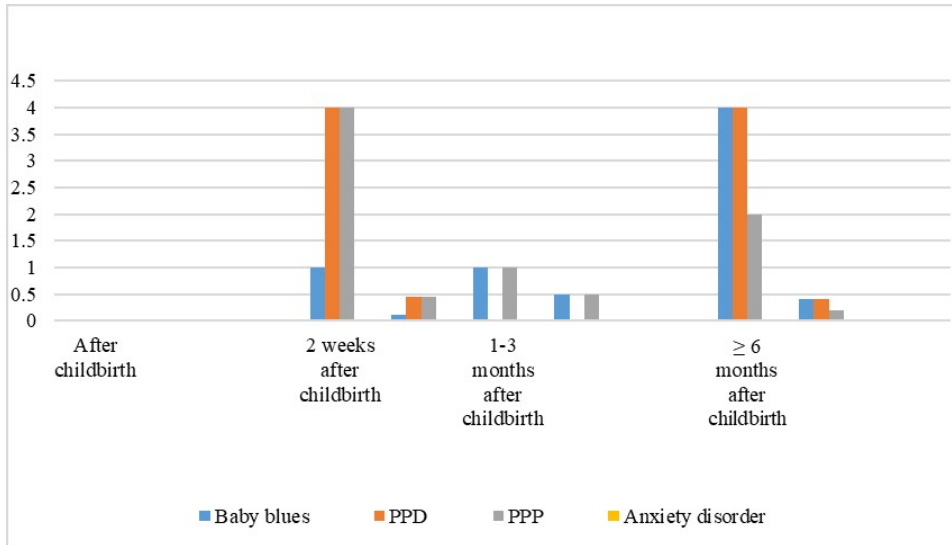


Figure 1. Percentage of psychological changes according to the beginning of the symptoms

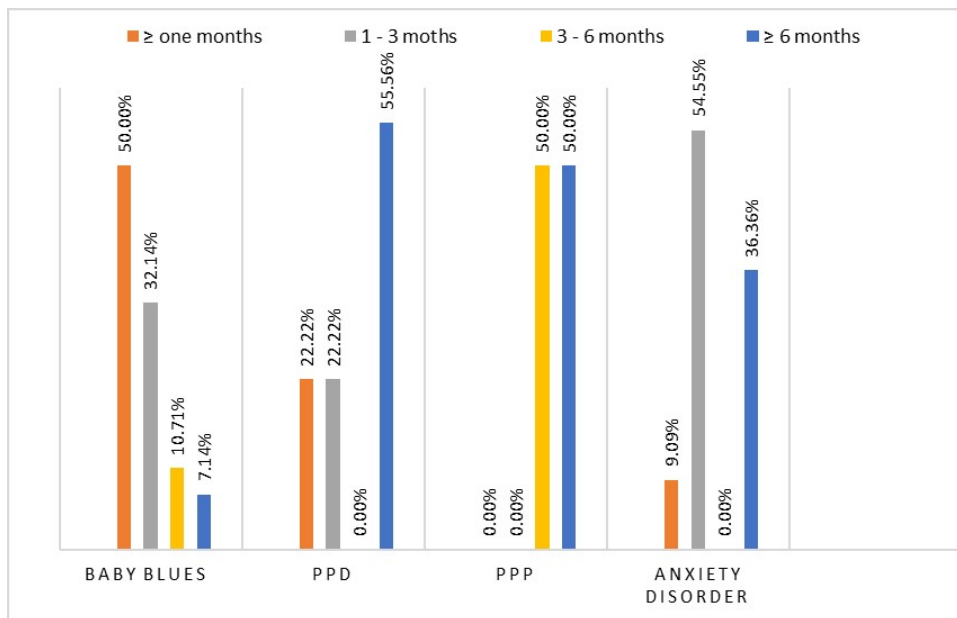


Figure 2. Percentage of psychological changes according to duration of the symptoms

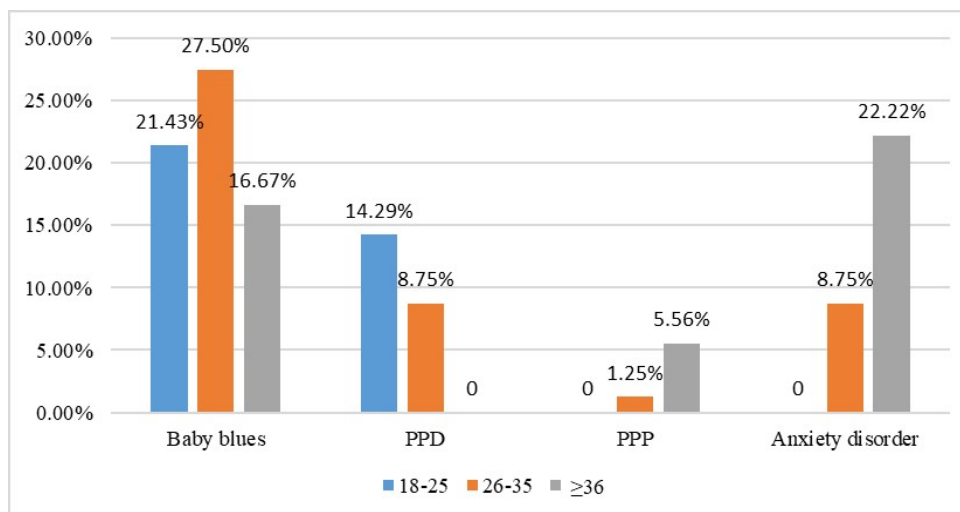


Figure 3. Percentage of psychological changes by age

The Baby blues is present in all age groups, but it is most common in women between the ages of 26-35 and 18-25. Women older than 36 have the smallest appearance of Baby blues. PPD is commonly reported in 18-25 age in 14.29% of patients, while at age 26-35 it is 8.75%. The results have shown that PPP appears at age 36 and older (5.56%), at 26-35 years of age the percentage is extremely small, only 1.25%, while at the age of 18-25 it did not at all appear. Results for PPP should be observed with reserve, since only two participants responded positively about this disorder, so the sample is not large enough.

Anxiety disorder occurs at the highest percentage at the age of 36 and older (22.22%), and this is the most common disorder occurring at that age, while in group 26-35 years its likelihood of appearing falls to 8.75%, and in the group aged 18 to 25 years it does not appear at all. According to the way of childbirth and psychological difficulties, the results have shown that 46.24% women who had vaginal childbirth have problems, and 36.84% of those who have had a Caesarean section - as we can see in Figure 4.

34.38% of mothers with first childbirth had Baby blues while in mothers who had second childbirth this

percentage was 16.67%. In participants who had three or more childbirths, Baby blues were not recorded. PPD also did not appear in mothers who have had three or more childbirths, while in mothers with second births the highest percentage of occurrence is 13.89% while in first births it is 6.25%. PPP was only reported in 3.13% in mothers with first childbirth, while in mothers with second or more childbirth it was not recorded. The results are shown in Figure 5.

Fear of new childbirth in mothers who have experienced psychiatric difficulties occurred in 26% of participants. Responding to the survey, 48.1% of women with difficulty/disorder responded that before childbirth they were informed about the potential psychological changes, while 27.91% of respondents did not know about this possibility. A large number of mothers with psychological changes had found information over the internet (50.75%). Information obtained from experienced persons was received by 42.86% of mothers, and the percentage of mothers who did not have information was 38.46%. The lowest incidence of changes was in mothers who received information through a specialist, that is 27.78%, which is certainly positive.

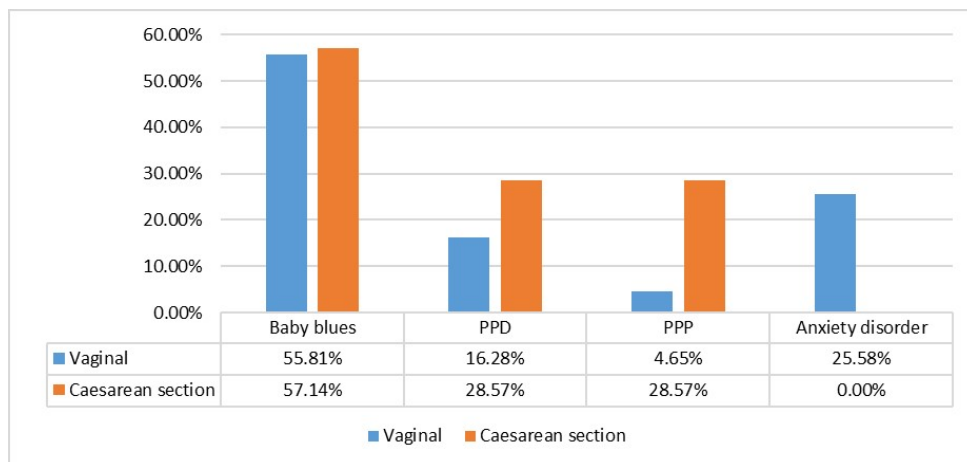


Figure 4. Percentage of psychological changes according to the way of childbirth

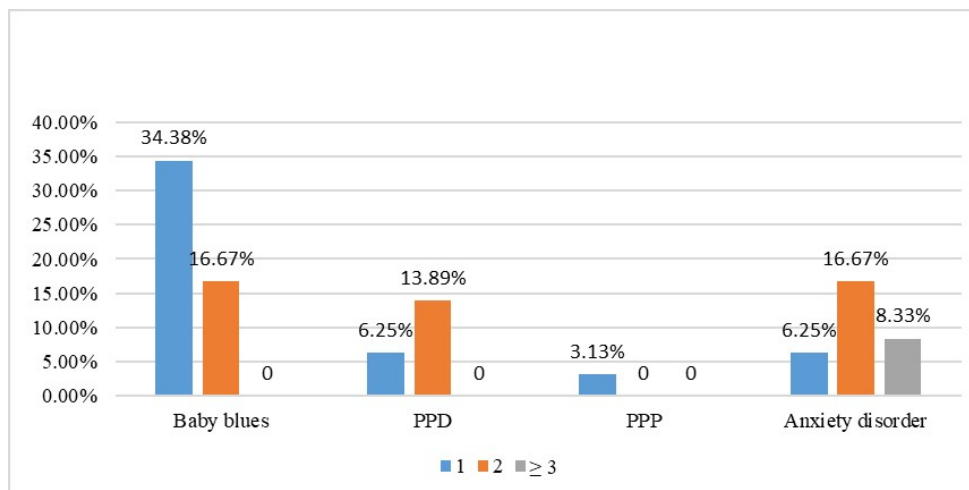


Figure 5. Percentage of psychological changes by the number of births

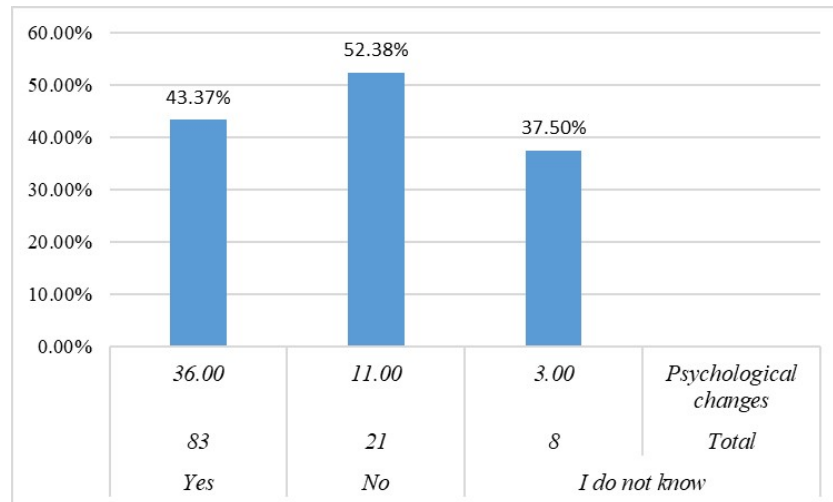


Figure 6. Percentage of psychological changes according to pregnancy support

Most mothers were under great stress when they arrived at the hospital, so the role of medical staff is very important. Figure 6 shows the assessment of the support of medical staff in the hospital before and after delivery. Mothers who did not have support before delivery had some form of mental problems (52.38%). Mothers with support had slightly less psychological problems, 43.37%, while mothers with undefined support had the lowest percentage of psychological changes (37.5%). Among women who were not satisfied with community nurse and information received, 63.64% developed psychological changes, this percentage reduced to 51.28% in women who were at least partially satisfied with the information they had received. Of those participants who were completely satisfied with the information, only 37.10% developed some form of mental problems.

DISCUSSION

Results of the research has shown that 54.46% of participants did not have any psychological changes in the postpartum period. Of the 45,54% of the participants reporting psychological difficulties, 25% of them have had the slightest changes or Baby blues which is, according to Misri & Burgman (1992) usually present in women after delivery and often start on the third day after childbirth. Although, according to numerous researches after the childbirth psychological changes tend to be at younger women, our results were recorded at an approximate percent in all three age groups, with the smallest percentage of change (35.71%) present in women of the youngest age. PPD is commonly reported in the 18-25 age group (14.29%) similarly to previous research (Misri & Burgman 1992, Upadhyay et al. 2017, Vismara et al. 2016). Results have shown that changes are more present after first childbirth than at next one which can be related to the previous experience of motherhood as shown by Vismara (2016) and Upadhyay (2017). Also, results have shown that women with sup-

port have less psychological changes that unsupported women as confirmed by others researches (Goyal et al. 2010, Veisani et al. 2013, Goyal et al. 2010, Veisani et al. 2013, Mezzacappa & Katkin 2002, Thome et al. 2006, Saligheh et al. 2017). The limitation of our research is the lack of information on socioeconomic status and education so we could not compare these segments with previous research. Also, PPD and PPP results should be taken with caution as there was no information on the existence of psychological changes in family history or information that would clarify the answers obtained. Our results only collected the responses of mothers who spoke the Croatian language, so this could present a small part of women at a certain point in life. The most common way of collecting information is the internet (59.82%), followed by information from experts (16.96%) and persons with experience (12.50%). The lowest incidence of changes was in mothers who received information through a specialist, in percentage 27.78%, which is certainly positive. The source of information can have an impact on timely and quality information that a mother should get in this period, so emphasis should be placed on professionals, doctors and nurses as well as psychologists who might be supportive in preventing/reducing psychological difficulties. The result of Croatian sample is not only because of the language barrier, but Croatian women who use the internet also do not get particular information because they are not familiar with the English language and there is not enough professional information available in the Croatian language on the internet. After the childbirth, most women in our research (91.07%) had some form of support that should impact the lower incidence of psychological changes. The most frequent support has come from family and friends (41.07%), then only from the family (30.36%) and finally only from the partner (19.64%), confirming the results that social support as well as performing various activities in the family could prevent psychological problems (Slomian et al. 2017, Thome et

al. 2006, Saligheh et al. 2017). Pregnant mothers had some type of mental problems (52.38%) indicating that prevention of these conditions should begin during pregnancy, especially in pregnancy courses. In women who developed these changes, the highest percentage (23.21%) occurred immediately after delivery and two weeks to one month after delivery as confirmed by the other results (Takahashi & Tamakoshi 2016, Gupta et al. 2013, Veisani et al. 2013). According to the duration of the symptoms, the highest percentage of responses was that duration was 1-3 months, and at 15.8% duration was less than one month. This is the time when a mother establishes an emotional relationship with a new-born baby, the time of adopting maternity and all the obligations that follow, so this may lead to a weaker adaptation, as shown by previous research (Mantisa et al. 2019, Fiala et al. 2017). Providing support to all mothers during this period to adapt to maternity and prevent unwanted situations is necessary. According to other studies adequate preparation of pregnant women for motherhood, breastfeeding, social support, mental training, light therapy, some dietary supplements and aromatherapy may influence the prevention of psychological changes or the reduction of difficulties (Thome et al. 2006, Sheydaei et al. 2017, Saligheh et al. 2017, Vismara et al. 2016, Asazawa et al. 2017, Potharst et al. 2017, Crowely et al. 2012, Olaoluwa et al. 2019).

CONCLUSION

Results of the research have shown that more than 50% of participants did not have any psychological changes in the postpartum period. Of the 45.54% participants reporting psychological difficulties, 25% of them have had the slightest changes or Baby blues. Most women (91.07%) had some form of support during and after pregnancy which should impact the lower incidence of psychological changes. Anxiety is more present after 36 age (22.22%) and could be connected with facing reality and problems of life, especially for those women who have more than two children. The lowest incidence of changes was in mothers who received information through a specialist, in percentage 27.78%, which is certainly positive. Preparation for maternity using a different technique, such as a pregnancy course, counselling, education is important for the future mother. According to assessment, it is necessary to use an adequate, valid scale for risk groups of women, especially for those with a positive family history (Mari et al. 2013, Horowitz et al. 2103, Werner et al. 2015). Mental difficulties/disorders in the postpartum period are one of the most common problems facing mothers. They can be relatively mild, such as Baby blues, or dangerous to the life of a mother and a child, such as psychosis. Each of them affects the quality of life of mother, child, and family, so it is important to have effective prevention and treatment.

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Contribution of individual authors:

Ivana Zivoder: design of the study, literature searches and analyses, interpretation of data, manuscript writing.

Sanja Martić-Biocina: design of the study, recruitment and collection of data, statistical analyses, manuscript writing.

Jurica Veronek: recruitment and collection of data, statistical analyses, writing of the report.

Natalija Ursulin-Trstenjak: literature searches and analyses, interpretation of data, writing of the report.

Melita Sajko & Marija Pauković: interpretation of data, statistical analyses, writing of the report.

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CONTRASTING VANTAGE POINTS BETWEEN CAREGIVERS AND RESIDENTS ON THE PERCEPTION OF ELDER ABUSE AND NEGLECT DURING LONG-TERM CARE

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SUMMARY

Background: Elder abuse and neglect can be defined as refusing or failing to fulfil a caregiver's obligation to meet the needs of elderly individuals in order to punish or hurt them. We aimed to explore perceptions of elder mistreatment of both caregivers and residents during long-term care, and highlight significant differences in the overall mistreatment perception regarding socio-demographic variables, as well as the type of care facility.

Subjects and methods: The study involved 171 caregivers and 245 elderly individuals in stationary facilities. Two structured questionnaires were used - one for caregivers and the other for institutionalized elderly residents, whose initial validation concerning question and factor selection has been based upon exploratory factor analysis and discriminant validity. Parametric and nonparametric tests were employed in the statistical analysis, and statistical significance was set at $p < 0.05$ (two-sided).

Results: We found significant differences in the perception of elder abuse and neglect between caregivers and elderly residents. More specifically, caregivers tend to recognize unnecessary or inappropriate medical/care procedures as indicators of elder mistreatment, while the elderly residents emphasize the removal of their personal belongings and inappropriate physical contact. According to the care facility, residents reported abuse/neglect more frequently in extended care units (21.4%), compared to the county-owned nursing home (11.4%) and private nursing home (12.1%) ($p=0.001$). Similarly, caregivers reported abuse/neglect more frequently in extended care units (75.4%), in comparison to county-owned nursing home (24.6%) and private nursing home (0%) ($p=0.039$). Shift work was also a significant predictor, as the morning nursing staff perceived abuse/neglect more frequently ($p=0.011$).

Conclusions: This study has shown that residents and caregivers have contrasting vantage points in relation to elder abuse/neglect perception, which underlines the need for evidence-based standardization of procedures to prevent any type of elder mistreatment.

Key words: elder abuse and neglect - elder mistreatment - nursing home - long-term care - nursing

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INTRODUCTION

Abuse is defined as a pattern of behaviour whereby an abuser seeks to gain power and control over the victim, and take advantage of the imbalance of power between them for personal gain; this is valid for elder abuse as well (Berg et al. 2001). Acts of psychological, sexual, physical, financial, and other forms of abuse carried out by the abuser, affect the personal integrity of the victim and limit his/her human potential, and are designed to make the victim subordinate, and gain, increase or maintain power over them (Samec 2010). Intentionally ignoring or treating someone in an unfriendly way, without any verbal or non-verbal communication by the caregiver, is also considered neglect (Viitasara 2001).

Elder abuse is a single, or repeated act, or lack of appropriate action, occurring within any relationship where there is an expectation of trust, which results in unnecessary suffering, injury or pain, the loss or violation of human rights, and a decreased quality of life for the older person (Krug et al. 2002). It rarely occurs as a single event, and various forms of elder abuse in an institutional setting may occur at the same time or over a longer period of time (Neuberg et al. 2018).

Abuse in the healthcare setting occurs in virtually all countries of the world, and it is perpetrated by medical staff, volunteers, visitors, and other employees. Abuse manifests itself as deficient nursing care, inadequate nutrition and disregard for dietary habits, infantilization of residents, restricted visits, rigid schedule of institutional care, and in particular, inappropriate behaviour of healthcare staff towards physically weaker residents, and restricting their access to information (World Health Organization 2005).

Nursing is considered as a profession that copes with high amounts of stress, pain, and suffering on a daily basis. Nursing interventions are often demanding, inconvenient, degrading, and sometimes outright scary (Neuberg et al. 2017). If the caregiver is not able to cope with the permanent stress in their working environment, conflicts with their elderly residents are inevitable (American Psychological Association 2015). Elder neglect and abuse in institutional settings are more frequently committed by medical technicians and inadequately educated/trained healthcare workers, while registered nurses in Ireland recognize neglect and abuse more often than healthcare assistants (Drennan et al. 2012). The situation is comparable to that in Croatia (Neuberg et al. 2018).

To obtain a good insight into the prevalence of neglect and abuse of older persons, it is necessary to consider their perceptions of this phenomenon. Elderly persons who are extremely frail, ill, and unable to protect themselves, depressed and demented individuals, as well as older people with other chronic illnesses are particularly vulnerable to neglect and abuse (Drennan et al. 2012). Furthermore, older persons in institutional settings are more vulnerable due to their dependency on professionals for care, and the care environment (Neuberg et al. 2018).

Older adults perceive elder mistreatment as any violation of human, legal, and medical rights; any deprivation of choices, decisions, status, finances, and respect; and any form of neglect, including social exclusion, isolation, and abandonment (World Health Organization 2005). Abuse in institutional settings is associated with the lack of social support, family support, and financial resources. The most common victims of abuse are care-dependent residents; residents who rarely receive visits; and dissatisfied residents (Ajduković et al. 2008).

Compared with research on other forms of interpersonal violence, elder abuse research, especially in institutions, is still in its infancy (Yon et al. 2019). However, research suggests that this phenomenon occurs in virtually all countries that have a considerable number of nursing homes and extended care facilities, and evidence suggests that it is a pervasive and growing problem (Pillemer et al. 2016, World Report on Violence and Health 2002). The World Health Organization (WHO) highlighted this problem in its Global strategy and action plan on ageing and health (World Health Organization 2016). However, a high-quality evidence-based approach to this issue requires a widely expanded research base.

The aims of this study were to establish the caregivers' and older persons' (residents') perceptions of

abuse and neglect in nursing homes and extended care facilities, as well as to highlight significant differences in the overall perception of abuse and neglect considering socio-demographic characteristics of both groups, as well as the type of institution.

SUBJECTS AND METHODS

Subjects

A survey was conducted of 245 older persons residing in care institutions in Varaždin and Međimurje counties and in the General Hospital Varaždin, specifically in extended care units in Novi Marof and Klenovnik. The survey included 171 caregivers; nurses and technicians holding secondary school leaving certificate, undergraduate degree, bachelor degree, or master's degree, who work with older people. The demographic profile of the participants in this study is presented in Table 1.

The instrument

The quantitative data were collected using two structured questionnaires – one for caregivers and nurses, and the other one for older persons residing in institutions. The items used in the questionnaire on abuse and neglect were taken from reports on abuse and neglect of elderly persons in Ireland by Drennan et al. (2012). All of the questions used in the preliminary research were tested for discriminant validity, and factor selection has been based upon exploratory factor analysis. The questions that did not increase or significantly reduce the overall Cronbach's alpha coefficient were excluded from further analysis. For each domain, the Cronbach's alpha factor was calculated and only the domains where Cronbach's alpha values were greater than 0.7 were used in the further interpretation.

Table 1. Demographic characteristics of the study sample

		N	%
Older persons (N=245)			
Gender	Male	72	29.40%
	Female	173	70.60%
Age group	≤75	51	20.80%
	75-84	109	44.50%
	≥85	85	34.70%
Highest level of education	Primary education	158	64.50%
	Secondary education	73	29.80%
	2-year post-secondary or university education	14	5.70%
Healthcare staff (N=171)			
Gender	Male	23	13.50%
	Female	148	86.50%
Age group	≤30	46	26.90%
	31-40	35	20.47%
	41-50	44	25.73%
	≥51	46	26.90%
Highest level of education	Secondary school leaving certificate	129	75.40%
	Undergraduate degree	39	22.80%
	Bachelor degree/ Master's degree	3	1.80%

Differences between the residents' and healthcare providers' perceptions of neglect and abuse have been estimated using 24 items (selected as described above), as can be seen in the results of this study. The health status of the respondents was determined based on questions inquiring whether they suffered from musculo-skeletal system diseases, cardio-vascular diseases, respiratory diseases, mental disorders, neurological disorders, sensory disorders, digestive system diseases, urinary tract diseases, skin diseases, malignant tumours, pathological obesity and/or diabetes. The aim was to determine whether there are differences between the perceived abuse and neglect depending on a particular health status.

Statistical data processing

Before presenting the data in tables, the Kolmogorov-Smirnov normality test was performed (depending on the results obtained). Adequate parametric and/or nonparametric statistical analyses and data visualization methods were applied. Quantitative data are presented as ranges, arithmetic means and standard deviations, i.e. medians and interquartile ranges in cases of nonparametric distribution. Categorical data are presented as absolute frequencies and respective shares. Differences in categorical variables were analysed using the Chi-square test. Relevant correlation coefficients were calculated to establish the relationship between individual scores obtained from questionnaires on stress

abuse and neglect. The data were analysed using Statistica 12.0 (StatSoft, v. 13.0, Dell Software, Austin, TX, USA). P-values less than 0.05 (two-tailed) were considered statistically significant.

Ethical approach

A written approval for this research was obtained from the Ethics Committee of the institutions (no. 02/1-91/77-2016) involved in the study in Varaždin. The study was performed in compliance with the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000), good clinical practice and relevant regulations. All participants gave their informed consent to participate in this study and patient anonymity has been preserved.

RESULTS

The study did not find any differences in the overall perception of abuse considering socio-demographic profile of residents, as measured by the chi-square test and presented in Table 2. Of the total number of respondents, 101 (72.1%) female and 39 (27.9%) male respondents observed abuse. Considering the age variable, neglect and abuse were most frequently observed by the respondents aged 75-84 (43.6%). Considering the respondents' level of education, the percentage of those who observed neglect and abuse is highest among

Table 2. Differences in the overall perception of abuse considering the socio-demographic characteristics of residents: chi-square test

Profile of residents		Observed abuse and neglect				p-value
		No		Yes		
		N	%	N	%	
Gender	Male	33	31.4%	39	27.9%	0.544
	Female	72	68.6%	101	72.1%	
Age group	<75	15	14.3%	36	25.7%	0.070
	75-84	48	45.7%	61	43.6%	
	≥85	42	40.0%	43	30.7%	
Highest level of education	Primary education	64	61.0%	94	67.1%	0.569
	Secondary education	35	33.3%	38	27.1%	
	2-year post-sec. or university education	6	5.7%	8	5.7%	
Family visits	No family	7	6.7%	3	2.1%	0.206
	Once a year	5	4.8%	9	6.4%	
	Several times a year	16	15.2%	21	15.0%	
	Once a month	24	22.9%	46	32.9%	
	Once a week	38	36.2%	49	35.0%	
Mobility level	Several times a week	15	14.3%	12	8.6%	0.229
	Immobile	18	17.1%	30	21.4%	
	Low mobility level	7	6.7%	16	11.4%	
	Moderate mobility level	48	45.7%	65	46.4%	
Type of home	Independent/Fully mobile	32	30.5%	29	20.7%	0.001
	Public	61	58.1%	93	66.4%	
	Private	32	30.5%	17	12.1%	
Diagnosed	Extended care unit	12	11.4%	30	21.4%	0.514
	No	6	5.7%	11	7.9%	
	Yes	99	94.3%	129	92.1%	

residents with primary education (67.1%). Older persons who had family visits once a week most frequently observed abuse and neglect (35.0%). Violence was most commonly observed by older persons with moderate level of mobility (46.4%). Considering the health status of the respondents, as many as 92.1% of residents diagnosed with a disease reported they had observed abuse. Significant differences in the perception of abuse and neglect by residents, as measured by the chi-square test, were associated with the type of residence: the perception of mistreatment was significantly more frequent among recipients of care in extended care units (21.4% compared to 11.4%; $p=0.001$). Given the fact that only one significant difference was found, it was not

possible to create a multivariate regression model (the predicted input of predictor variables was intended only for the variables that were univariately significant).

Table 3 shows differences in the overall perception of abuse with respect to socio-demographic characteristics of caregivers, as measured by the chi-square test. Of the total number of caregivers, serious mistreatment was observed by 52 (91.2%) female and 5 (8.8%) male respondents. Considering the age of the respondents, serious mistreatment was most commonly observed by the respondents under 31 years of age (29.8%). Considering the respondents' work experience, serious abuse/neglect was observed by 36.8% of respondents who have less than ten years of work experience. Of the total

Table 3. Differences in the overall perception of abuse considering socio-demographic characteristics of caregivers: chi-square test

		Serious abuse/neglect				p-value
		No		Yes		
		N	%	N	%	
Gender	Male	18	15.8%	5	8.8%	0.205
	Female	96	84.2%	52	91.2%	
Age group	≤30	29	25.4%	17	29.8%	0.617
	30-40	21	18.4%	14	24.6%	
	40-50	31	27.2%	13	22.8%	
	≥51	33	28.9%	13	22.8%	
Work experience	≤10	35	30.7%	21	36.8%	0.658
	11-20 years	22	19.3%	11	19.3%	
	21-30 years	30	26.3%	16	28.1%	
Living with a partner	≥31 years	27	23.7%	9	15.8%	0.559
	No	37	32.5%	16	28.1%	
	Yes	77	67.5%	41	71.9%	
Highest level of education	Secondary school leaving certificate	90	78.9%	39	68.4%	0.301
	Undergraduate degree	22	19.3%	17	29.8%	
	Bachelor degree/Master's degree	2	1.8%	1	1.8%	
Children	No	36	31.6%	16	28.1%	0.638
	Yes	78	68.4%	41	71.9%	
Workload	Optimal ratio of care recipients to nurses	15	13.2%	4	7.0%	0.172
	Occasionally, the number of care recipients is too high	27	23.7%	9	15.8%	
	The number of care recipients is constantly high	72	63.2%	44	77.2%	
Work schedule	Morning shift	19	16.7%	21	36.8%	0.011
	Morning and afternoon shift	16	14.0%	8	14.0%	
	Rotational shift work; night shift included	79	69.3%	28	49.1%	
Type of area	Urban	31	27.2%	12	21.1%	0.383
	Rural	83	72.8%	45	78.9%	
Type of facility	Public	24	21.1%	14	24.6%	0.039
	Private	12	10.5%	0	0.0%	
	Extended care unit	78	68.4%	43	75.4%	
Number of residents	<20	1	0.9%	3	5.3%	0.192
	21-50	18	15.8%	8	14.0%	
	51-100	10	8.8%	2	3.5%	
Assigned to work with the elderly without volunteering for it	>100	85	74.6%	44	77.2%	0.374
	No	94	82.5%	50	87.7%	
	Yes	20	17.5%	7	12.3%	

Table 4. Differences between the residents' and caregivers' (healthcare staff) perceptions of neglect and abuse: chi-square test

	Healthcare staff		Older persons		Chi-square value	Df	p-value
	N	%	N	%			
Not changing a resident each time they were wet or soiled after an episode of incontinence	50	29.2%	61	24.9%	0.970	1	0.325
Ignoring a resident when they call	67	39.2%	91	37.1%	0.178	1	0.673
Not bringing a resident a bedpan or not taking them to the toilet when they ask	44	25.7%	23	9.4%	19.908	1	<0.001
Administering laxatives once a week only	43	25.1%	19	7.8%	24.017	1	<0.001
Overmedicating a resident to keep them sedated/quiet.	47	27.5%	4	1.6%	62.576	1	<0.001
Refusing to help a resident with their hygiene needs	34	19.9%	24	9.8%	8.540	1	0.003
Placing a urinary catheter frequently and unnecessarily	39	22.8%	2	0.8%	54.817	1	<0.001
Refusing to help a resident with their feeding needs	26	15.2%	20	8.2%	5.077	1	0.024
Force-feeding a resident	71	41.5%	61	24.9%	12.846	1	<0.001
Putting a feeding tube in the resident's mouth unnecessarily and forcefully	18	10.5%	2	0.8%	20.748	1	<0.001
Neglecting to turn or move a resident to prevent pressure sores	65	38.0%	75	30.6%	2.470	1	0.116
Restraining a resident beyond what was needed at the time	30	17.5%	37	15.1%	0.444	1	0.505
Pushing, grabbing or pinching a resident	20	11.7%	42	17.1%	2.356	1	0.125
Throwing something at a resident	10	5.8%	3	1.2%	7.111	1	0.008
Slapping or hitting a resident	10	5.8%	2	0.8%	9.101	1	0.003
Kicking or hitting a resident	5	2.9%	1	0.4%	4.484	1	0.034
Hitting or trying to hit a resident with an object	3	1.80%	1	0.40%	1.917	1	0.166
Isolating a resident beyond what was needed to control them	22	12.90%	30	12.20%	0.035	1	0.851
Insulting or swearing at a resident	73	42.70%	78	31.80%	5.130	1	0.024
Shouting at a resident in anger	94	55.00%	115	46.90%	2.599	1	0.107
Denying a resident food or privileges as part of a punishment	18	10.50%	19	7.80%	0.954	1	0.329
Taking jewellery, money, clothing or something else from a resident or resident's room	13	7.60%	40	16.30%	6.895	1	0.009
Touching a resident in a sexually inappropriate way	4	2.30%	30	12.20%	13.167	1	<0.001
Encouraging a resident to participate in an inappropriate conversation	22	12.90%	32	13.10%	0.001	1	0.971

number of respondents who reported that they had observed mistreatment, 71.9% live with their partner, 68.4% have secondary education, while 77.2% find that the number of residents to take care of is constantly too high. Differences in the overall perception of abuse in relation to socio-demographic profile of caregivers, as measured by the chi-square test, were found to be significant in the variable 'type of work schedule'. More specifically, neglect and abuse were observed significantly less frequently by morning shift nurses (36.8%; $p=0.011$). Furthermore, differences in

the overall perception of abuse are significant depending on the type of institution. In other words, no acts of mistreatment were observed by caregivers in private nursing homes, in comparison to 75.4% in extended care units and 24.6% in state-owned nursing homes ($p=0.039$).

Table 4 shows differences between the residents' and caregivers' perceptions of neglect and abuse in relation to items used in the questionnaire. In a nutshell, caregivers/nurses observed neglectful and abusive behaviours in the form of unnecessary or inappropriate

health care, while residents highlighted appropriation of personal belongings and inappropriate physical contact.

Considering the type of facility and the reported forms of abuse, all forms of neglect and abuse were observed significantly less frequently in private nursing homes. Statistically significant differences ($p < 0.05$) were found in items "ignoring a resident when they call", "neglecting to turn or move a resident to prevent pressure sores", "restraining a resident beyond what was needed at the time", "pushing, grabbing or pinching a resident", "isolating a resident beyond what was needed to control them", "insulting or swearing at a resident", "shouting at a resident in anger", "taking jewellery, money, clothing or something else from a resident or resident's room", "touching a resident in a sexually inappropriate way", and "encouraging a resident to participate in an inappropriate conversation".

As for the frequency of abuse and/or neglect over the previous 12 months with regard to the health status factor/variable, as measured by the chi-square test, it was found that abuse and neglect of older persons with musculoskeletal system diseases is significantly more frequent ($p = 0.037$). An unexpected finding was that elderly people with skin diseases observed neglect less frequently ($p = 0.020$).

DISCUSSION

This is the first systematic approach to investigate the issue of elder mistreatment in institutional settings in Croatia. The results of this study (based on the comparison of the vantage points of both caregivers and residents on abuse/neglect) show that this phenomenon is widespread and multidimensional. Given that medical and sociological literature provides mainly anecdotal evidence, we find that this research makes a significant contribution to the discourse on this subject – not only from the scientific point of view, but also that of public health and regulatory framework.

Significant differences in the overall perception of abuse considered in relation to socio-demographic variables were found to be associated with the type of facility. More specifically, the perception of neglect and abuse in the extended care units and in the county-owned nursing home was much more pervasive than in the private nursing home. This can be explained by a more open attitude in private nursing homes, higher level of staff awareness, and more frequent visits by family and friends. The data obtained confirm that there is a relationship between family support to an elderly person in the institution and mistreatment of residents by institutional caregivers.

In contrast, the results of research conducted by Friedman et al. (2019) suggest that patients receiving care in for-profit institutions show more clinical signs of neglect than patients living in not-for-profit institutions

or in the community. These results are associated with the elderly care development strategy in the United States where, over the past ten years, the number of government and not-for-profit nursing homes has declined across the country, while the number of for-profit nursing homes has grown substantially.

The number of nurses in county-owned nursing homes and extended care units is low; residents are often seen as people who ended up there because they had no other choice, or who came there to die, rather than partners in care. Unless nurses' attitudes change, elder mistreatment will occur more frequently in the county-owned homes and in extended care units, as our research suggests. Obviously, instilling fear of sanctions is not a steadfast approach to preventing abuse; however, the system would benefit from standardization of procedures in cases of abuse and neglect. Education, training, and motivation of caregivers to work in partnership with care recipients towards developing standardised care procedures are all crucial factors in improving satisfaction and minimising conflicts.

One of the interesting findings of this research is that morning shift nurses and healthcare staff perceived elder mistreatment much more frequently. The extant literature does not provide data on the relationship between shift work in nursing care and the occurrence of abuse. Thus, future research should focus on this new insight. It is assumed that this happens because the number of nurses working the morning shift is larger, they see each other work, and hence notice abuse more often. Conversely, nurses working the afternoon, and in particular the night shift, often care for several residents by themselves and are for this reason unable to witness abuse by other caregivers.

When residents' health status is considered, the perception of elder abuse and/or neglect is more common among elderly residents with musculoskeletal system diseases. Moreover, older people with skin diseases observed neglect significantly less frequently. To our knowledge, such findings have hitherto not been described in the medical literature; nonetheless, the explanation may be that elderly people affected by skin diseases have been stigmatized for a longer part of their life, they feel rejected and unaccepted due to their appearance, and have thus become insensitive over the course of time (Neuberg et al. 2018). In addition, mistreatment was most commonly observed by women aged 74-85 (72.1%), which coincides with the findings of research conducted by Ho et al. (2017), where subgroup analyses showed that women were more likely to be abused. Ho et al. (2017) also found that emotional abuse is the most common form of abuse, which was the most common form of elder abuse in our study as well.

The following data suggest that there is a relationship between family support and the incidence of neglect and abuse in institutional settings: of the total number of older people who observed mistreatment,

23.5% receive family visits several times a year, once a year, or even less frequently. In contrast, as many as 76.5% of the total number of respondents who observed abused in the institution get family visits once a month, once a week, or several times a week. This suggests that family support plays a significant role in recognizing and perceiving abuse in institutional settings. Shame and discomfort felt by older persons in submitting themselves to the care of healthcare workers can be seen as disproportionate, i.e. as unfair. Instead of being recognized as internally generated, this unfair experience is attributed to others in the eliciting situation, which further creates discomfort in older persons (Erlingsson 2007). Therefore, the importance of communication skills should be highlighted as they can help nurses solve the many obstacles they face during care provision.

Even though the survey was anonymous, the fear and shame felt by respondents in reporting what they had witnessed must be taken into consideration, which means that the data obtained in the research may be even more discouraging than they appear. Disregard for residents' financial independence is one of the leading causes of financial abuse in institutional settings. The interventions for preventing this type of abuse include the education and training of staff and the sanctioning of perpetrators. The condoning of elder neglect and abuse in institutions is associated with high workload of nurses, staff conflicts, and lack of communication among team members (Drennan et al. 2012). In Ireland, sexual abuse was witnessed by 0.7% of respondents, while 0.2% of respondents reported that they had talked or touched the resident in a sexually inappropriate way in the previous twelve months. Twenty two respondents (12.9%) reported that they had observed a member of staff encourage a resident to participate in an inappropriate conversation. Four respondents (2.4%) reported that they had observed another member of staff touch a resident in a sexually inappropriate way, which is a significant percentage that should be cause for concern for both nurses and institutions. The World Health Organization (2002) reports that the sexual abuse of older persons is widespread; however, the problem is not recognized by caregivers as such, and the elderly individuals do not talk about it openly due to the omnipresent feelings of shame and fear.

In addition to the type of institution, the type of area in which the institution is located (rural or urban) also plays a significant role in preventing the mistreatment of older persons. The older population in rural areas may have easier access to nursing homes, and residents in nursing homes in rural areas may have less functional impairment than in urban areas (Malmedal 2013). Nursing homes across Croatia have similar occupancy. However, an investigation into the activities of the institutions involved in this research has revealed that nursing homes located in Varaždin, Ivanec and Čakovec had a significantly larger number of visits by volunteers,

various associations, children, as well as other activities. The smallest number of activities was recorded in extended care units where 90% of the residents were over 70 years old. They had been there between three months and several years and had not been offered any activities.

No significant differences were found in the frequency of observing elder mistreatment, considering the location of the institution, number of residents, and whether staff were assigned or volunteered to work with older persons, as was the case in other studies. According to Malmedal (2013), staff members working in nursing homes that have 30 residents or less are more likely to report committed acts of a physical character than staff working in nursing homes with more than 30 residents. Research conducted in Canada (Bravo et al. 1999) and Israel (Lowenstein 1999) indicates that in homes with fewer than 40 residents, up to 20% of the residents received inadequate care and experienced abuse. This could be explained by the fact that the institutions analysed were less open, and by the educational composition of the staff. Namely, nursing homes with a low number of residents have a large number of auxiliary staff and healthcare assistants, and a very small number of nurses.

In this context, one should mention the fact that over the last twenty years more and more people without any medical education, training, testing of empathy, or predilection for working with older people have been registering small residential care homes and foster homes for the elderly, which is a cause for concern. This research did not investigate such facilities; however, considering that the data collected through the survey of older people receiving care in nursing homes and extended care units suggest high incidence of mistreatment, it can only be assumed that the findings would be even more alarming in closed, isolated and private institutions such as foster homes for the elderly.

Madsen's study (2002) into everyday life of older people in old and new nursing homes in Norway concluded that the new and smaller nursing homes have a greater potential regarding social relations than the larger ones. In contrast, Allen et al. (2004), Jogerst et al. (2006) and Natan et al. (2010) found that the incidence of violence is greater in institutions with a large number of residents, which can be explained by highly demanding residents, the low number of staff, and the lack of necessary equipment.

When limitations of our study are concerned, the interpretation of the findings may be limited by the possibility of social desirability, as already mentioned. Recall bias may also be a problem, since the inaccurate or incomplete recollection of experiences/events from the past can potentially lead to differential misclassification. Another possible limitation is the sample size, but with the response rate as high as in our study and the general scarcity of nursing staff in nursing homes and extended care units, it can be considered appropriate.

CONCLUSIONS

This study has shown that residents and caregivers have contrasting vantage points in relation to elder abuse/neglect perception, which underlines the need for evidence-based standardization of procedures to prevent any type of elder mistreatment. Bearing in mind that the pace of population ageing around the world is increasing dramatically, the results of this study highlight the need for additional research aimed at identifying an optimal approach to abuse prevention, and helping victims of abuse and neglect in institutional settings, worldwide. Future research should focus on well-defined target populations, types of abuse, standardized instruments, as well as the relationship between healthcare workers and residents, which was a key part of our research. All of this will help develop various public health interventions with an overarching aim to address this growing global concern.

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Contribution of individual authors:

Marijana Neuberg outlined the methodological approach and was responsible for the study concept, paper composition, theoretical explanations, data interpretation and literature choice.

Tomislav Meštrović conducted the literature search, interpreted the obtained results, as well as critically drafted and revised the manuscript.

Rosana Ribić, Marin Šubarić & Irena Canjuga contributed to the data interpretation and manuscript write-up.

Goran Kozina participated in the study concept, and also contributed to the write-up and the final appearance of the paper. All authors gave their approval for the final version of the manuscript.

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INPATIENT MANAGEMENT OF GHB/GBL WITHDRAWAL

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SUMMARY

Background: Gamma-hydroxybutyrate (GHB) and its precursor gamma-butyrolactone (GBL) are popular drugs of abuse used for their euphoric, (potential) anabolic, sedative, and amnesic properties. Daily use of GHB/GBL can lead to addiction and the possibility of withdrawal syndrome on cessation which results in tremor, tachycardia, insomnia, anxiety, hypertension, delirium, coma.

Aim: To describe the baseline characteristics, treatment and retention in patients admitted for GHB/GBL withdrawal management.

Methods: A retrospective review of 4 consecutive cases of patients reporting GHB/GBL addiction who were admitted for inpatient management of withdrawal syndrome.

Results: All patients were using GHB/GBL daily, 1-1.5 ml per hour. One of them was using cannabis additionally, others were using alcohol, cocaine and amphetamine type stimulants. Psychiatric comorbidities as personality disorders, depression, anxiety and bigorexia were recognized. Patients were treated with benzodiazepines and/or clomethiazole, atypical and typical antipsychotics and beta-blockers. Delirium was developed in two patients. One patient completed detoxification and finished the treatment program. One patient completed detoxification but stopped his treatment earlier, two patients did not completed detoxification and left the program.

Conclusion: GHB/GBL withdrawal can be severe and retention in program is poor. Polysubstance use, psychiatric comorbidities and heavier GHB/GBL use as possible predictors of poor treatment outcome need consideration in treatment planning.

Key words: GHB/GBL - addiction - inpatient - treatment - withdrawal

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INTRODUCTION

Gamma-hydroxybutyrate (GHB) is a synthetic drug which was initially developed as an anaesthetic agent but later found to be a naturally occurring compound in mammalian brain and tissue, existing as a by-product of GABA metabolism and putative neurotransmitter. Major chemical and metabolic precursors include gamma-butyrolactone (GBL) and 1,4-butanediol which are both rapidly converted to GHB in the body (EMCDDA 2002). Acts primarily as a central nervous system depressant but at low doses can also produce euphoric effects and effects that appear to be like those of stimulants (Abdulrahim & Bowden-Jones 2015). GBL is absorbed more rapidly than GHB and potentially has a faster onset of action (EMCDDA 2002). GHB and GBL have a high affinity to GABA-B receptors and to a lesser extent to subtypes of GABA-A receptors. There are effects on glutamate, dopamine, serotonin, norepinephrine and cholinergic systems (Kamal et al. 2016). GHB is considered to have a high dependence potential, and abrupt discontinuation after long-term use can result in a severe withdrawal syndrome with the quick onset (Kamal et al. 2016). It can happen 30 minutes after the last dose, but more typically it is a few hours. GHB/GBL withdrawal symptoms have been reported to last from 3 to 21 days (mean 9 days) (Abdulrahim & Bowden-Jones 2015). Often seen withdrawal symptoms are tremor, tachycardia, insomnia, anxiety, hypertension, delirium, coma (Wojtowicz et al. 2008). The recreational use of GHB (including its precursor GBL) has been reported among subgroups of drug users in Europe for the last two decades. Although national estimates, where they exist, of the prevalence of GHB

use in adult and school populations remain low, there is a big clinical question what is the best treatment option for GHB/GBL addiction (EMCDDA 2019). The international evidence on the management of the acute and chronic harms related to the use of GHB and GBL mainly consists of case reports and series and a small number of prospective observational studies, retrospective cohort studies and analysis of patient records (Abdulrahim & Bowden-Jones 2015).

In the following sections, we discuss the clinical presentation of 4 patients hospitalized for GHB/GBL detoxification. All patients were admitted to the detoxification ward at the Center for Treatment of Drug Addiction Ljubljana at University Psychiatric Clinic Ljubljana and planned to complete the treatment program which lasts 16 weeks and provide a multidisciplinary approach.

Case 1

33-year-old male patient with a university degree, employed, began using cocaine and benzodiazepines when he was 28 years old. After 5 years he was admitted for the inpatient treatment of addiction to the detoxification ward but left the program earlier and abstained 14 days. He relapsed with cocaine and benzodiazepines and started to use GBL. Before his second admission to the detoxification ward (6 months after first admission) he used 30 ml of GBL a day, split into doses taken every 1.5 hours and 0.5 to 1 g of cocaine a day. Withdrawal symptoms appeared 2 hours after the last dose of GBL, and consisted of diaphoresis, tremor, tachycardia, hypertension and later delirium with disorientation to time, place and person, poor attention

and agitation. First-line treatment with diazepam (30 to 60 mg a day) and quetiapine (75 mg a day) was unsuccessful. Symptoms were successfully managed with clomethiazole (up to 1920 mg a day), propranolol (20 to 60 mg a day) and risperidone (up to 2 mg a day). After 3 days symptoms of delirium disappeared, other withdrawal symptoms gradually subsiding on day 10 allowing for the rapid reduction in clomethiazole dosage. No adverse effects were observed during treatment. His complete blood cell count and biochemistry profile were within normal limits. He continues his inpatient treatment, bigorexia was recognised as co-occurring disorders but he did not want to change his diet and workout regimen.

Case 2

30-year-old patient with a primary school education, unemployed and without permanent housing reported chronic use of different drugs (amphetamines, cannabis, cocaine...) from his adolescence. He was treated by psychiatrist after several suicide attempts and diagnosed with borderline personality disorder. Daily use of GHB/GBL started when he was 26 years old. After several unsuccessful detoxification attempts without any medical support he was admitted to the detoxification ward for the first time. At intake, he used 1.2 to 1.5 ml of GHB/GBL per hour in combination with different doses of methamphetamines. Withdrawal symptoms appeared 4 hours after the last dose of GHB/GBL and consisted of tremor, anxiety, hypertension, tachycardia, insomnia. To reduce withdrawal symptoms, we treated patient with clonazepam up to 6 mg, propranolol up to 80 mg and quetiapine up to 75 mg. Dosages were adjusted daily. Next day he began describing paranoid delusions that patients are against him and he was afraid. After introducing haloperidol up to 4 mg a day paranoid delusions subsided after 3 days, other symptoms gradually subsided on day 7 when he left the inpatient treatment program. No adverse effects were observed during treatment. His complete blood cell count and biochemistry profile were within normal limits.

Case 3

20-year-old female patient with a primary school education, unemployed, began using alcohol and drugs (cannabis, amphetamines, methamphetamines, psilocybin mushrooms...) when she was 15 years old after the death of both parents in less than 6 months. Patient began using GBL when she was 19 years old. Before admission at the ward she used up to 25 ml a day of GBL, split into doses taken every 1.5 to 2 hours, 3 to 4 cigarettes of cannabis a day, alprazolam up to 0.5 mg a day and irregularly 3-methylmethcathinone (3-MMC). She had one accidental GBL overdose and several withdrawal seizures in last months. Also, she had a car accident under the influence of GBL. Two hours after the last dose of GBL she became inattentive, unable to

maintain reasonable conversation. We started therapy with diazepam, but later in the same day she became agitated and responding to visual and auditory hallucinations. The patient had to be physically restrained. She was administered up to 60 mg of diazepam, up to 1152 mg of clomethiazole and up to 50 mg of quetiapine. No adverse effects were observed during treatment. A complete blood cell count showed leucocytosis $13,900/\text{mm}^3$, C-reactive protein 7, creatine kinase was $12.91 \mu\text{kat/L}$, no hydroelectrolytic disorders were found. Symptoms of delirium persisted for 5 days, after that we began gradually reducing dosage of prescribed therapy. On day 12 she left the inpatient treatment program prematurely.

Case 4

34-year-old patient with a university degree, unemployed, with a psychiatric history of anxiety disorder and depression began using GHB/GBL when he was 32 years old. The substance helped him to decrease his anxiety. He started during the weekends but gradually his use became daily (a total of 30 ml of GBL a day, split into doses every 1.5 to 3 hours). At admission, he unreliably reported lower dosage of GBL (10 to 30 ml a day) and use of alcohol in the evening (4 units of 40% spirit). Occasionally he used amphetamines and cocaine. He had 3 unintentionally amphetamine and GBL overdoses and was treated at the emergency unit. Two hours after the last dose of GBL he began reporting increased anxiety and craving. He was administered diazepam (a total of 60 mg, split into 6 doses), quetiapine 100 mg and pregabalin (a total of 200 mg, split into 2 doses, prescribed by his psychiatrist for anxiety), but the next day left the ward. He did not allow us to take a blood sample for laboratory tests.

DISCUSSION

These case reports describe inpatient GHB/GBL detoxification of patients who planned to complete the whole treatment program but most of them left the program earlier. According to studies uncompleted detoxification, the early relapse and the reduced time spent in treatment have been found to be associated with poorer outcomes at follow-up. A major challenge in addiction treatment is to identify which treatment modality or other factors motivate patients to stay in treatment (Brorson et al. 2013). We noticed the rapid onset of symptoms (2 to 4 hours from the last dose of GHB/GBL) similar to those of GABAergic withdrawal (diaphoresis, tremor, tachycardia, hypertension, anxiety, insomnia...) (Abdulrahim & Bowden-Jones 2015, Miotto et al. 2001). To reduce withdrawal symptoms patients were treated with long half-life benzodiazepines and/or clomethiazole (McDonough et al. 2004). Antipsychotics (typical and atypical) have been necessary for the treatment of psychotic symptoms. We also use atypical antipsychotics for their anxiolytic properties (McDonough

et al. 2004). Withdrawal symptoms can be self-limiting in some patients, but others can present with more severe withdrawal that can progress to delirium (Gonzalez & Nutt 2005). There are indications that heavy, frequent users are most likely to progress to severe delirium (Gonzalez & Nutt 2005). All our patients can be described as heavy, frequent users but just two of them progress to delirium. It has been proposed that withdrawal in cases of co-dependence on GHB/GBL and another CNS depressant (opiates or other sedatives) or a stimulant is likely to be more severe (McDonough et al. 2004). Patients were supervised with the daily therapy adjustments. All patients had more than one unsuccessful attempt of detoxification independently of any medical support what was already suggested to be a criterion for the indication of inpatient detoxification (von Theobald et al. 2017). All of them reported polysubstance use and had co-occurring psychiatric disorder what have been consider in treatment planning.

CONCLUSION

The symptomatic treatment is indicated for GHB/GBL withdrawal syndrome. Recommended therapy with benzodiazepines as a first line medication in combination with propranolol and antipsychotics was effective for reducing withdrawal symptoms. We also have a good experience with clomethiazole. We recognized patient's poor compliance as a main problem. Polysubstance use, psychiatric co-morbidities and heavier GHB/GBL use as a possible predictors of poor treatment outcome need consideration in treatment planning.

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MAST CELL AUTOCRINICITY NEAR CEREBRAL ARTERIAL WALL “REVERSE GLYMPHATIC FLOW” AS PRIME TARGET OF ELECTROMAGNETIC EFFECTS

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SUMMARY

Efforts to disclose the mechanisms of transcranial therapeutic electro-magnetic fields (EMF) acting on the brain's cells (Marino, Kibleur) and recently immune cells (Gülöksüz) meet unsolved physiological details of blood vessels, exclusively arterial vasomotion or the non-glial-related former g(lia)-lymphatic flow (Ilijf; Liu DX) - now replaced by an astrocytic AQP4-pipeline cooling the brain (Nakada 2014). Here within the convergent dyn4TAM-framework, which had suggested the first mast cell behavioral experiment (Fitzpatrick & Morrow 2017), three intertwined physiological concepts are contributed: A) “autocrinicity” – how flushed, thus absent, autocrine signals integrate external fluidics into cellular computations e.g. on motility: EMFs could increase such absences by targeting e.g. dipole-cytokines; B) a new concept of the arterial wall based on a tangible interpretation of the coronal histology of all arteries as a co-axial pulse-dampening engine (Treviranus 2012). In the brain this engine might provide the quickest cerebral outflow via the Cerebral IntraMural Reverse Arterial Flow (Treviranus 2018b), while transmitting further forces acting upstream to the paravascular spaces; C) some key roles for mast cells in neuro-psychiatry (Silver & Curley 2013) and their interactive lymphatic and non-luminal vascular routes to the brain dictated by peripheral imprinting as to destiny (Csaba 1987) and destination (Treviranus 2013). Within the skull they might advance against para-arterial upstream currents.

Some known causal mediators of the effects of transcranially applied EFMs and puzzling results are then put tentatively in perspective with the above “tangible” models, e.g. by aligning probable induced currents with arterial segments or the new direct meningeal-calvario-myeloid channels.

Results: The case for a role of mast cells and diverse flows in transcranial electromagnetic brain therapy seems promising.

Key words: transcranial electromagnetic stimulation - mast cells - arterial wall - vasomotion - autocrine signaling

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INTRODUCTION

Those attained by a unipolar major depression episode (MDD) as adolescents face a nearly 20% risk to fail treatments and remain in MDD for half their lifetime constituting 1% of the population (Zorumski 2015). As far as response and short-term effects are concerned, repetitive transcranial magnetic stimulation (rTMS) especially with H1-coils (Gellersen & Kedzior 2019) have become non inferior to tACS (Leggett 2015). Depressions respond twice as well to alternating-current electro-convulsion (tACS) as to conservative therapies. Electro-magnetic field (EMF)-effects on the brain achieved by chemical and meanwhile non-convulsive therapies (Zuo 2018, Akbarnejad 2018, Gazdag & Ungvari 2019) reveal their immune (Pozzi 2018) and occasionally harming mechanisms slowly (Marino 2016, Singh & Kar 2017, Kibleur & David 2018).

Here hypotheses add topics this speculative field: 1.) autocrinicity as integration of external fluidics through flushed and thus absent signals into cellular decisions e.g. in motility: EMFs could increase such absences by targeting e.g. dipole-cytokines; 2.) non-canonical migratory routes of mast cells MCs to the brain (Pavlov 2018); 3.) contradictory (Springer 2017) key roles for MCs in psychiatry. These are generated from the convergent dyn4TAM-framework, which already suggested the first behavioral MC experiment (see Treviranus

2018a, pp. S 621-2; Fitzpatrick & Morrow 2017) stopping rodent sign-tracking by interfering with thalamic MCs within the first cortico-thalamo-subcortico-cortical circuit (CSTC).

The decreased excitability after continuous trains at 5Hz (Huang 2017) maybe reflects MC exhaustion. A likely site of relevant encounters between transcranial EMFs and the above putative processes include the “para”- arterial Virchow-Robin Spaces (VRSs), where MCs possibly advance counter-current along the adventitia (as granulocytes do intraluminally; Lyck & Engelhardt 2012), while this arterial VRS could be modulated by the parallel but mostly disconnected and acellular arterial intramural flow (related to pulse dampening). Through markers this astonishing intramural route showed up as the (hence also electrically) quickest “lymphatic” exit from the brain (Bradbury & Cserr 1974-84, Carare 2008). Here (3.2) it is explained via its biomechanics as read from histology (CIMURAF; Treviranus 2018b), whereby its reverse vasomotion against pulses could also induce a reverse flow in VRSs.

Electrohydrodynamics, vectorial alignment, and “ecological autocrinicity”

Only matter, electrons, but also ions or molecules function as charge carriers. “Drift velocity” becomes the product of obstructed mobility and EMF (Grimnes &

Martinsen 2014). Electro-kinetics require supercomputing (Götz 2010), but the low velocity of solute simply adds to the carriers' drift velocity. The EMF-generated brain currents between two electrodes between alternative paths thus pass in proportion to their conductances: notably along arteries' and vein's VRSs and along the said reverse intramural flow.

Electromagnetic therapy and its puzzling effects of frequency and alignment

In early studies applying rTMS scores of major depression (MDD) and perfusion varied with personalized frequencies at 20 or 1 Hz (Speer 2000): With 20 Hz applied at the dorsolateral prefrontal cortex (dlPFC) key affective centers and cortical areas (compatible with the medial three CSTCs) received more blood and the subgenual anterior cingulate cortex (sgACC; where MDD concentrates neuronal loss, Meier 2016), received less. Applied close to cortex rTMS induced distant therapeutic changes involving the sgACC and the default mode network, while surprisingly the executive control network (ECN) remained spared (Philip et al 2018). Through an occipital to left fronto-parietal long-range effect tACS too changed the correlation between such networks (Cabral-Calderin 2016), while antagonistically resonating with local slow (possibly vasomotive) fluctuations. The incisive accelerated ITB-rTMS rapidly showed improved integration with remote modules and cognitive parsing by complexity (Caeyenbergs 2019): maybe through thalamic cortico-cortical facilitation (Collins 2018).

ELECTROMAGNETIC NEUROPSYCHIATRY WORKS - BUT HOW?

Convulsive tACS and alternatives interactively change neurogenesis, angiogenesis, the glia, the hypothalamic-pituitary-adrenal (HPA) axis, and neurotrophic factor levels (Rotheneichner 2014).

Between analogies and fluctuations

Through rTMS the dlPFC seems to rebalance lasting "homeostatic plasticity" (Turrigiano 2007, 2017). High activity potentiates positive (LTP), low activity negative synaptic learning (LTD) through unsupervised feedback via presynaptic and postsynaptic molecules like tumor necrosis factor α (TNF- α) Under rTMS "low-frequency leads to LTD, high-frequency elicits LTP (≥ 20 Hz)" while it also stimulates innumerable underlying 1st and 2nd order causes. Direct current stimulation (tDCS) instead paused for around 10 minutes, results in motor-effects opposing those of a previous priming in sense, while neurophysiological effects hardly survive one hour (Karabanov 2015). On the chemical side rTMS close to the dlPFC increased its γ -aminobutyric acid (Levitt 2019). Such processes could as well be compensatory for a subcortical (Zuo 2019) cortico-cortical (Collins 2018) disturbances. While the hippocampi (HC)

enlarge, favoring plasticity by tACS, it remains obscure despite modeling (Dokos 2013), how this comes about (Oltedal 2017, 2018) - even in peripheral nerves (Wang 2018).

Alternative tDCS (Dedoncker 2016) and rTMS (Serafini 2015) approach the efficacy of cumbersome convulsive tACS. The innovative "variable phase" tACS eliciting phased and traveling effects (Alekseichuk 2019) manipulates "resonances", reflecting statistically measured correlations which are actually blind to dimensionalities from e.g. CSTCs (Treviranus 2018a), in which tissue flows acquire weight, as reflected by signals of diffuse tensor imaging (MRT-DTI; Matsumae 2017, Sepehrband 2019, Dokos 2013) (Table 1).

Ecological autocrinicity

Only a few results (Silletti 1998, Doganer 2016) support a concept (beyond sensitivity to shear), that cells would be advantaged by autocrine signals flushed away by ecologically patterned and thus meaningful changes in external fluidics. Such an e.g. asymmetrical pattern of absences of signals (Lemmon 2016) would be integrated into cellular cybernetics and hereby e. g. modulate movement. A candidate molecule is adrenomedullin effecting motility (Zudaire 2006) and MC-degranulation (Lv 2018).

Induced EMFs conceivably could remove autocrine signals from the uniquely immature and long-lived MCs while these travel (putatively) along cerebral arteries to where they mature and settle. While they guard the blood-brain-barrier (BBB) as key drivers of immunology, the intrusion of deviant MCs into the brain (where they activate macrophages which only once migrate to the brain (Ginhoux 2010)) makes them an important therapeutic target (Silver & Curley 2013, Treviranus 2018a). Extracellular microvesicles (György 2011) may soon qualify as the most interesting of such autocrine signals (Chen 2017).

PERIARTERIAL AND CEREBRAL INTRAMURAL FLOW AND VASOMOTION

The glymphatic enthusiasm revised

Interest in the interstitial fluid (ISF), which takes a 20-100% larger part of brain's water than blood or CSF led to the "glymphatic" theory (Iliff 2012) which erroneously conceived a flush of the parenchyma by water drawn in by AQP4-channels from the «para»-vascular Virchow-Robin-Spaces (VRSs) expelling the parenchyma's ISF via venous VRSs back to CFS and as deep cervical lymph (Wang & Casley-Smith 1989). This "g(lia)-lymphatic" account was recently corrected by an inverse one, whereby astrocytes (ACs) provide a pipeline which circumvents the sealed BBB and no Starling-mechanism builds up (Hladky & Barand 2016). Few issues remain: a) the direction of flows (Bakker 2019) in the VRSs; b) the energetic origin of pressure gradients; c) the role of pressure pulsations; and d) the now contradicted (Nakada & Kwee 2019) contribution of the water-selective channels

Table 1. Putative Mechanisms of Transcranial Electro-Magnetic Therapies

Theory	Mechanism	R, G	Ref.
"BCM"	Post-/Pre-Synaptic learning		Cooper 2012
BCM in rTMS etc.	Analogy		Karabanov 2015
Fluid PNEI (tACS)	TRP-KYN, TDO/IDO	R	Gülöksüz 2015
PICs like TNF- α	↓ serum	R	Joshi 2016
P/AIC TNF- β , IL-5	↓ serum	R	Rotter 2013
Serotonin 5-HT	↓? binding to 5HT2AR		Yatham 2010
BDNF serum	↑ plasma	R	Polyakova 2015
VEGF serum	↑, mTOR Eifving 2012		Minelli 2014
HC cell proliferation:			
↗ → ↘ ↙ (rat)	-		Nakamura 2013
((↗)) adult human / primates	<i>Natural development</i>	-	Sorrells 2018
↗ → ↗ rat	<i>Antidepressant drug, 0 ECS</i>	+A	Malberg 2000
*Neural Stem Cell (SGZ)		(-)A	Segi-Nishida 2008
*Neural Progenitor Cell	+/- NSStC & ↑ NPG		Encinas 2006
Mossy fiber sprouting	↑ (<i>less, if ketamine</i>)		Chen 2001
DA to Mossy fiber	↑		Kobayashi 2017
Human HC volume	↑	R	Oltedal 2018, <i>Powell 2017</i>
Human DG volume	↑	R	Nuninga 2019 s
HC volume	<i>No ECT, Escitalopram</i>	R G	<i>Powell 2017</i>
HC, AMY volume	↑	R	Tendolkar 2013
HC, AMY volume	↑	R	Nordanskog 2103
Insula volume	↑	R	Van Eijndhoven 2016
Any neurogenesis ECS	↑	R	Alemu 2019
HC R ant. Perfusion	↑	R	Leaver 2019
dmTHAL	↑ ? <i>CSTC</i>	R	Leaver 2019
Glucose uptake	↓ PFC		Henry 2001
Spontan-fluctuation	<i>CIMURAF ?</i>		Cabral-Calderin 2016
Vasomotion	<i>CIMURAF ?</i>		<i>This project</i>
Autocrinicity			<i>This project</i>
Mast cells			<i>This project</i>
MC disorders			Georgin-Lavialle 2016

In Italics: Sources referring to Antidepressant drugs or Hypotheses followed by the author (e.g. Cerebral Intra MURal Flow). Abbreviations: CSTC: Cortico-subcortico-thalamo-cortical circuit; PIC pro-inflammatory cytokine; TRP-KYN, TDO/IDO: Tryptophan-Kynurenine metabolism through TDO-/IDO-enzymes; mTOR: mechanistic Target of Rapamycin; dmTHAL: dorsomedial thalamus; ECT: Electro-Convulsive Therapy; TNF- α : tumor necrosis factor α R: clinical response; G: genetical evidence; 0/(-) A: chemical Antidepressants for comparison (Italics): No or negative effect

(aquaporin-4; AQP4), since these are expressed inside the BBB and not dedicated to water exchanges with the outside. Astrocytes (ACs) use AQP-4 at the podocytes to acquire H₂O from just above the cortex (Suzuki 2017) for the AC's own hydration and again to expel H₂O into the VRS. During heat-alarm the latter shut down to hydrate ACs (Nakada 2014). There is no lymphatic "flush" like in other tissues.

Wondersome intra- and extramural "peri"-arterial flows

Following the clearance of Abeta (Carare 2008, Okamoto 2012, Ball 2010), from also cortical interstitial brain fluid (Bakker 2016), a wondersome rapid and reverse marginal "peri"-vascular intramural route had shown up in rodents (H.F. Cserr 1974-1984; Szentivanyi 1984). An application of peripheral arterial

reflected pulse waves to this process (Schley 2006, Diem 2016, 2017) lacked the required reflection surfaces (Coloma 2019) and valve-like macro-nano-links.

The Cerebral IntraMURal Reverse Arterial Flow-model (CIMURAF; Treviranus 2018b) was derived from a previous Co-axial Arterial Wall Engine (CAWE) interpretation of the aortic wall, proposed originally (Treviranus 2012) to explain its exceptional biomechanical resistive persistence.

The Co-axial Aortic-Wall-Engine: a smart macro-engine?

The CAWE-model is readily verified by coronal histology, but requires scientific testing. Since at least molluscs' arterial vascular smooth muscle cells (VSMCs) do not (usually) "hold hands", but in the tunica media attach obliquely to co-axial tubes made of elastic laminae

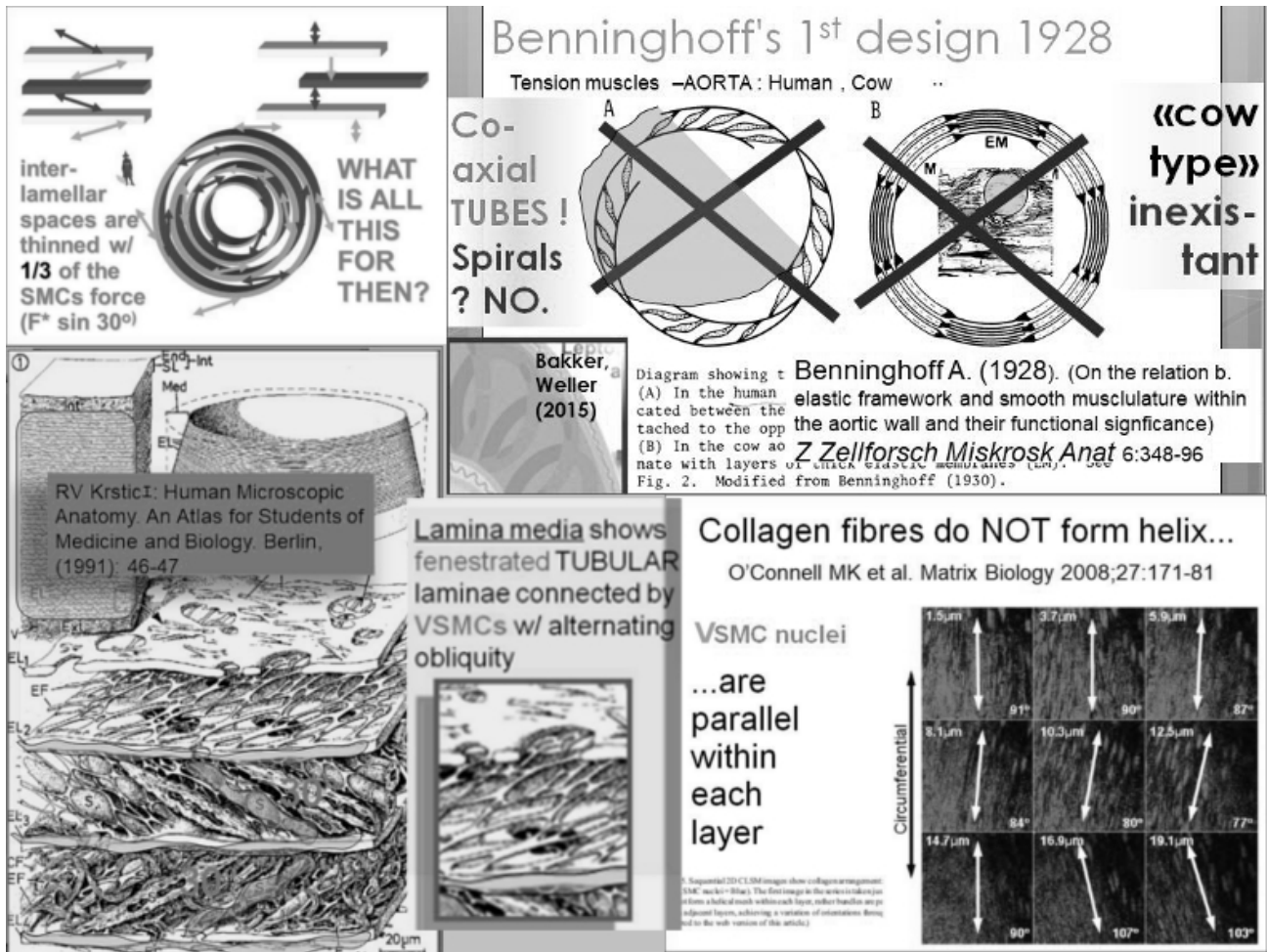


Figure 1. How arteries were seen: The two blueprints of the textbook author anatomist A. Benninghoff (1928) were both wrong. The helical version accepted by Bakker (2015) was refuted by O’Connell (2008). The correct blue-print by R.V. Krstic (1991) went unnoticed. The first insert shows the Co-Axial-Wall-Engine-model (Treviranus 2012)

starting with the lamina interna (López-Guimet 2017), which are separated by pressurized watery inter-lamellar compartments (ILCs; Carew 1968, Davis 1993). The human aorta is made out of more than 60 of such tubes stuck inside one another. Also, the sense of this obliquity alternates radially from tube to tube. Hereby most (~3/4) of the VSMCs more tangential action does not result in pressurizing by radial contraction (~1/4), but in small co-axial rotations (<10°) of the tubes, which in the aorta e.g. possibly follow the heart rate, but elsewhere might be related to the several-fold slower «vasomotion» (see below). These torsional movements, induced by VSMC contraction, extend anti-parallel elastin fibers, which after relaxation restore the system to baseline, whereby a simple harmonic oscillator is built. This neglected co-axial cylinder blueprint of arteries (Hayman 2016) is more hidden in other arteries (Hill 2016, Hinderer 2015, Eoh 2017) (Figure 1).

At the same time such neurally induced segment by its alternating axial momenta at each ILC - like a «christmas cracker» - causes two slight hyperboloid circular embayments (HCEs). When such a segment moves upstream to dampen the pulse (by appropriate nervous instigation-relaxation of the VSCMs) coupled

HCEs will resolve and renew themselves over a traveling distance. This will drive a “multilayered cushion” with a bow wave and a stern suctioning end. Within every ILC a) incoming contrary arterial pulses from heart-like pumps are dampened by working against the VSMCs’ torque (the primary evolutionary scope) and b) water is drawn into the ILCs of the segment – the fenestrations becoming radially aligned by torsion in order to refill them, and c) CIMURAF is accelerated in its reverse upstream direction behind the stern HCE, the radial outflow being shut again. This is peculiar to the brain where the radial lamellar fenestrations are twice as numerous, albeit obstructed by myo-endothelial-cell protrusions (Sandow 2009). CIMURAF is steered by four vasomotive nerve systems (Ainslie 2014, Taktakishvili 2010, Roloff 2016), and stronger during sleep (Xie 2013) (Figure 2).

Heat and not self-erasing impacts of electromagnetic fields on arteries

Although arteries, being larger and less complex per volume, can be expected to be «more aligned» to the curved and changing EMFs, the problem of complex and

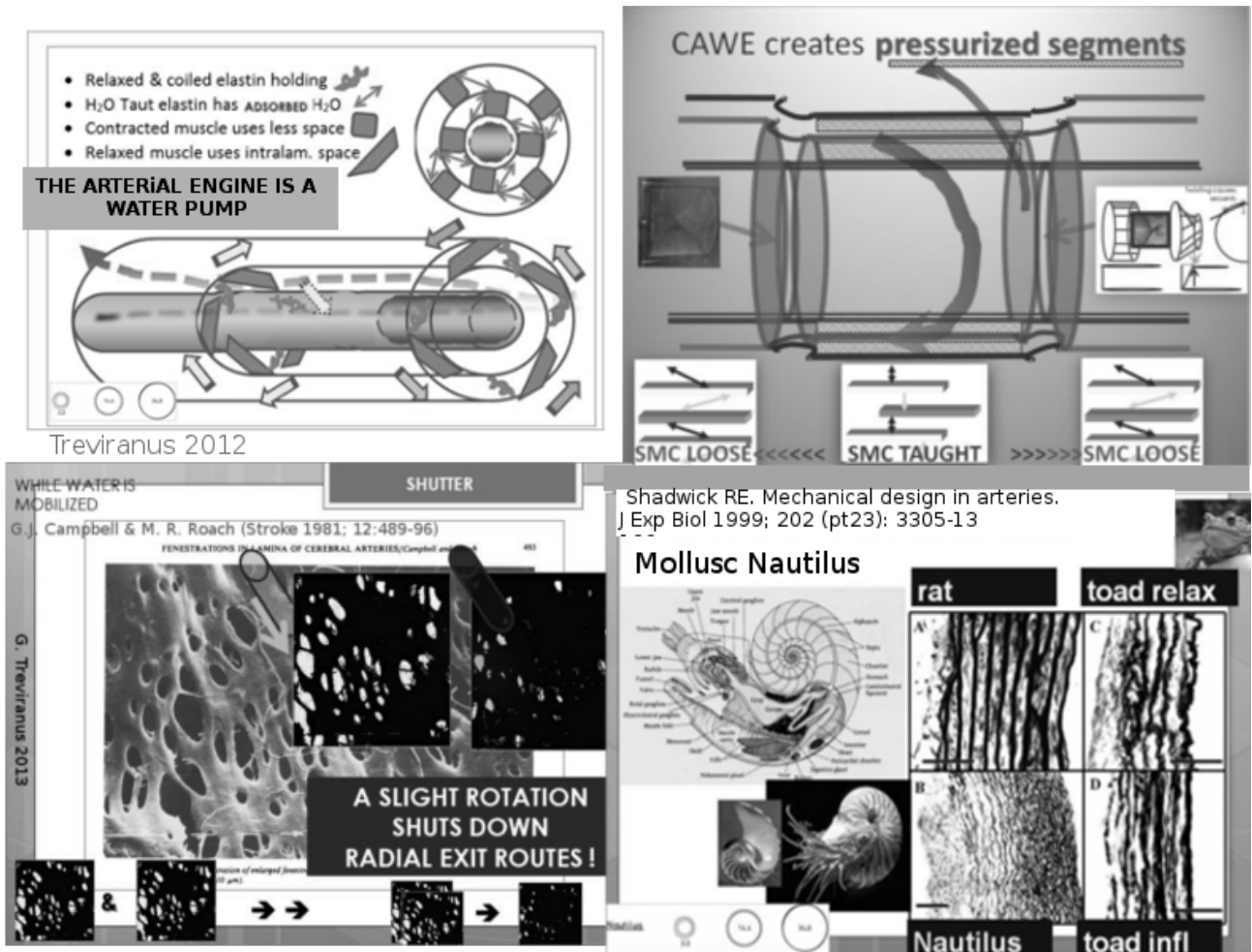


Figure 2. The Co-Axial-Wall-Engine-model with two interlaminal spaces with Vascular Smooth Muscle Cells axially twisting three laminar tubes against each other in a leftward vs. rightward sense creating a sliding pressured chamber between two zones between hyperbolic embayments. The shutter-mechanism effectively shuts down the radial tortuous exit towards the VRS as shown by sliding two overlaid copies of fenestrated laminae (image from Campbell & Roach 1981). Mollusc, reptile and mammals all show the exact same aortic blueprint (Gosline & Shadwick 1982)

opposite self-erasing effects of EMFs persists (see *Between analogies and fluctuations*). The effects of alignment followed during biphasic stimulation of cortical interneurons (Wang 2018, Sommer 2018) hardly reflect the tissue's neuronal, axonal or subcellular intricacies.

EFMs probably also pass through ionic gap junctions connecting same and different mural cells. But muscle contractions nevertheless require neuromuscular junctions (Kean 1974, La 2019, Kotecha & Neild 1988) - apart from vague nano-electro-sensitivity (Suzuki 2017, Oosawa 2018).

The VSMCs providing CIMURAF therefore are only allowed to perform the coronal obliquely tangential contractions following the CAWE-engine's architecture. How EFMs from diverse angles will affect VSMC-contractions remains understudied.

After the substitution of the "glymphatic" paradigm (see *The glymphatic enthusiasm revised*) the degree to which ACs might react towards heating (Nakada 2014) by the EMF-waves might move center-stage since 5/6 of

brain's perfusion remains unexplained. MCs have at least one highly temperature-sensitive proton channel (Kuno 1979), which is very present in microglia and stroke (Wu 2012). Both K⁺-channels KCC2 and NKCC, determining inhibitory transmission MDD or epilepsy via intracellular Cl⁻, decrease the latter in proportion to temperature (Hartmann & Nothwang 2011). About brains' temperature physiology despite clinical questions little exists (Wang 2014): The BBB becomes highly permeable upon heating up to fever and just beyond neurons perish. Axons instead concentrate the heat generation capacities with a role in neurotransmission.

Intramural muscles drive the para-vascular flow in Virchow-Robin spaces

The VRSs remained puzzling since their first description (His & Bastian 1867). Today their waste-flushing function (Di Marco 2015) stays crucial and pluri-segmental MRI 4D-velocimetry shows its deterioration along the Alzheimer spectrum (Rivera-Rivera 2016).

CIMURAF-engine and reverse acceleration in the Virchow-Robin-Spaces

Since the lamina interna is water-tight and the twisting dynamic of the wall opens the shutters in the segment right behind the bow wave, while the stern suction accelerates the CIMURAF within the normally radially closed ILCs, a compensatory similarly counter-current flow is predicted for the VRS. When the segment travels upstream the opportunities for radial influx first shortly increase by the initial segment up to compensation, but then subsides (while behind the stern HCE of the ILCs the radial exits are again obstructed). Thus there is always more radial influx into the wall upstream than downstream and this gradient is reinforced by the traveling speed of the segment, while the VSMCs keep working against the cardiac muscle in order to dampen the destabilizing effects of the pulse on the wall and the tissue homeostasis. This account is reversed if one assumes that the shutters would close in the segments, but that would destabilize the wall over the relaxed parts.

CSF-tracers are enriched up to 40-fold in the circle of Willis, (Bradbury 1981) which in fact cannot have sliding torsional segments and therefore could testify for the capacity of CIMURAF.

Vasomotion

The CAWE-blueprint concerning all arteries could be related to the slower vasomotion (VM) - for which only approximative molecular processes are put forward (Cole 2019). VM denotes rhythmic oscillations of about 10/min in the diameter of even isolated arteries and arterioles, which – in a way maybe related the origin of the BOLD-signal of MRT – seem to be neuronally entrained by energetic needs of cortical neuronal activities (Mateo 2017). VM, as CAWE/CIMURAF, seems to be unique for arteries. The wall of veins do not show this blueprint, and only games of nature like the original bat wing (Wharton 1852) show entirely different oscillations (Liu 2014, Scholbach 2016, Arpi 2018). Thus a "review" (Van Helden & Imtiaz 2019) focussed entirely on lymphatics.

VM can be influenced by many factors and correlates with cycling of force-generating myosin cross-bridges in VSMCs and their molecular and membrane potential context. The ensuing «flowmotion» reflects environmental physical and local influences from VSMC, paracrine ECs, perivascular fat (Nava & Llorens 2016), and from other cells. Where nitric oxide (NO) is low and availability and sensitivity to thromboxane (TBX) are high TBX elicits strong VM (Horváth et al. 2010). MCs again can be strong producers of TBX (Macchia et al. 1995).

IMPRINTABLE MAST CELLS: UNDERRATED AND MIGHTY

One-cell organisms can be induced by a single imprinting signal to respond lastingly in another way.

György Csaba extended this pioneering research with early glandular hormones to similarly imprintable MCs (Csaba 1987, 2012, 2014). MC are complex hubs (Niarakis 2014). They guard interfaces of tissues, varying their complexity. They respond to over 200 often combinatorial chemical, often psycho-social, neural, or physical, i.e. receptor- or surface-mechanical, hot-cold-, and electrical and/or fluidic inputs. These may doubly imprint them as to a) their migratory destination in the CNS through selective molecular pairing between cell and paths still immature cells, and b) as to their mature persistent destiny. Following signal integrations MCs respond through a dozen release modes. Rat peritoneal MCs e.g. one hour after injection were close to thalamic blood vessels, among 90% previous residents, and deep to the basal lamina, in nests of glial processes (Silverman 2000). MCs "orchestrate" fellow immunocytes early in response; but they can survive for years as guardians of barriers and homeostasis (Table 2).

The mast cell - "lymphatic cauldron" relations

Only recently meningeal lymphatics were discovered (Aspelund 2015, Louveau 2015, Absinta 2017) and channels draining from the calvarial bone-marrow (Cai 2019): a highly promising route for e. g. MCs to cause insomnia, hallucinations or hidden lesions in the cortex.

As, often subverted, first-line defendants and later "orchestrators" of innate and adaptive response and as likely intestinal lipid uptake monitors, MCs join the well-isolated inflammatory cauldron of the collecting and thoracic lymphatics to orchestrate immune responses in lymphatic tissue and to evaluate metabolic or toxic signals. The lymphatic ECs in fact decisively interact with MCs - else obesity occurs (Pal 2017, Gasheva 2019). Furthermore the lymphatics are regulated by autonomic peptidergic nerve signals (Ito 1989), which are often involved in permeability and MC communication.

Hypothetical events between lymphatics and mast cell

After distal challenges the, passive, lymphatic transport could be hastened by a plausible proximal neurally induced "sieving" of obstructing fluid (sigma-1-receptor; Trujillo 2017).

«IRF-4-dependent CD11b+ dendritic cells» (DCs) control the permeability of lymphatic collecting vessel (Ivanov 2016) through NF-κB signaling (Grumont & Gerondakis 2000) to their CCR7-receptors (already calling them into initial lymphatics; Pflücke & Sixt 2009), and later become "embraced" by the vascular ECs (Teijiera 2013). Now the NF-κB stems from a predominant MC/histamine/NF-κB axis (Nizamutdinova 2016), shielding the lymphatic's transport and barrier functions (Kang 2009), unless by failure the perivascular tissue becomes inflamed or infected (Zolla 2015).

Table 2. Incomplete synopsis of mast cell concepts. Mast cells are very versatile and their faculties seem to serve various “scopes” of which the “mechanisms” and “main proofs” are referred to leading sources

Theory of scope	Mechanism	Main proof	Source
Bioeconomical	Complexity deciding	0.5 bio years old	<i>This project</i>
Immunometabolism	(Fat sensing)	Masted by lymph	Paul Ehrlich 1877
Morphogenesis			Crivellato & Ribatti 2016
Early host defence	Etosis	Only armed cell	Möllerherm 2016
Adaptive Immunity	Lymph	Pellets with PICs	S. N. Abraham 2009
Guardians of BBB	PNEI		T. Theoharides 1996
Mind modulators	Ethology	Molecular biology	Silver & Silvermann 1996
Meningeal		Migraine	V. Dimitriadou 1997
Gut-Brain-Axis		AutismMoura	T. Theoharides 2015
Neuropsychiatry	BDNF (+)	Mastocytosis etc.	Moura 2011, Afrin 2015
Oligodendrocyte	<i>Tryptase</i>	<i>Complement 4 ?</i>	Medic 2010
CSTC modulator	Cognition	Sign-tracking (rats)	Fitzpatrick & Morrow 2017
	<i>MC degranulation</i>	<i>Uncertainty Orient</i>	<i>Treviranus 2018a</i>
Imprintability:		Destiny	G. Csaba 1987
Imprintability		<i>Destination</i>	<i>This project</i>
		<i>Author</i>	
		<i>GRS Treviranus</i>	
Transgranulation			M. Wilhelm 2005
Epigenetic changes	Histone	Tryptase	F. Levi-Schaffer 2014

In Italics: Sources referring to Hypotheses followed by the author

Exploring non-canonical migratory routes the following sequence can be imagined after “sieving” (Treviranus 2013): (A) Since MCs in order to activate lymph nodes (Kunder 2009) produce cytokine-protecting-pellets (CPPs, my term) which shield pro-inflammatory cytokines (PICs) from ultra-rapid disposal - such CPPs carrying TNF- α (which is also a chemokine) can be expected to be (B) spilled out of the lymphatics and (C) to attract MCs to where they happen to go. Then (D), occasionally a space would be created by the MC adjacent to a vessel and filled with CPPs, again through TNF- α , (E) tight-junctions (TJs) could be cracked (Marcos-Ramiro 2014), opening (F) a path into the main lumen or into a VV. Thereby (G) being rolled in and dragged on by laminar flow CPPs could advance. When (H) stuck inside a VV the CPPs – restarting the rope trick – would attract MCs or crack the TJs. At lympho-arterial crossings (I) MCs could switch vessels (J): a.) Towards the anterior cerebral circulation: lymphatic duct to aortic arch from below into the carotid “chimney” modulating the carotid, the jugular vein, and the vagal nerve; b.) Towards the posterior circulation: from the lymphatic retro-clavicular “end-curve” of the duct to the vertebral artery - MCs could thereby (J) cross-over from the lymphatics into the lumen or into a VV within arterial walls. Similar processes actually contribute to vascular pathologies e.g. in hepatic veins (Yamamoto 2000, Takahashi-Iwanaga 1990, Lukacs-Kornek 2016). Adventitial MCs have been described for long in relation to vasospasm, dissection (Wågsäter et al. 2016), and atherosclerosis (Lindstedt et al. 1999) as well as their relation to neurogenic inflammation (Laine et al. 2000) in blood vessels, and lymphatics (Pal 2017).

At the skull’s border, where the acellular intramural CIMURAF (Treviranus 2018b) leaves the arterial wall for the ethmoids, (K) MCs could surface on the adventitia and enter the VRS, advancing counter-current. The ensuing fluidic information together with chemokines and apt (imprintable) pairings of the EC surface molecules with their own, could (L) steer them into specific brain areas. Such hands-on details on migratory paths are being sought (Martinelli 2014).

Mast cells as related to electromagnetic therapies

MC regulate many cerebral sites, but, besides their strong presence in the stress systems, their main neuropsychiatric influences stem from their meningeal or thalamic residency. Currents applied to rodents have terminated thalamo-cortical spikes and waves, and provided on-demand anti-epileptic activity for weeks (Kozák & Berényi 2017). Also do MCs produce and store dopamine (Rönnberg 2012). Some dysfunctions in Parkinson’s diseases refer to the thalamus: e. g. tremor to insufficient self-inhibition of the ventral intermediate thalamus via external dopamine (Caligiore 2019, Dirx 2017). Motor performances improved through rTMS reduced the jointly pathogenic serum IFN γ and IL-17A, produced by striatal Th1- and Th17-cells (Idova 2012).

Grey matter cortical changes in MDD (Harrison et al. 2006) or schizophrenia (Xu 2017) instead are either due to isolated deficits in function (ACC, IPFC, putamen) or structure (frontal and temporal cortex) or in both (ACC, insula), whereby thalamic MCs could destabilize function (and neurotrophic activity) at the

CSTCs, and meningeal MCs could functionally disturb or attack neurons and oligodendrocytes directly after intruding e. g. from arterial walls of the anterior arterial supply, which densely crosses the insulas.

CONCLUSION

The challenge to explain the most effective treatment for several neuropsychiatric conditions should profit from incorporating not only "fluid" Psycho-neuro-endocrino-immunology, but also the highly versatile, long-lived, and mighty mast cells ascending to destinations and destinies within the brain from the lymphatics and via other non-canonical routes, possibly co-regulated by negative "autocrinicity". While the blueprint of arteries by itself calls for a comprehensive investigation it contributes to understand the regulation of intracerebral flows. All these are candidates as targets of electro-magnetic fields induced in the brain for therapeutic purposes.

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ADOLESCENTS IN TRANSITION TO YOUNG ADULTHOOD: EVOLUTION OF MENTAL HEALTH STATUS AND RISK FACTORS ASSOCIATED WITH DEPRESSIVE AND ANXIETY DISORDER

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SUMMARY

Background: In this paper we focus on adolescents in transition towards young adulthood (ATYA). We know from international studies that the transition process makes adolescents vulnerable to mental illness. However, little is known about Belgian ATYA mental-health status. Nor are risk factors associated with their mental illness understood, in particular with regard to depressive and anxiety disorder. The aim of this study is (1) to discuss evolution in time of prevalence of depressive disorder (DD) and anxiety disorder (AD) among Belgian ATYA and (2), to identify risk factors associated with these disorders among ATYA.

Subjects and methods: Data was extracted from the Belgian Health Interview Survey (BHIS), which is a cross-sectional population survey, carried out in 2001, 2004, 2008, and 2013. Information about the population's background characteristics, health services utilization, health behaviours and mental health status were extracted and statistically analyzed.

Results: ATYA prevalence of DD and AD was higher in 2013 in comparison with previous years. These changes were significant only for DD ($F=4.466$, $p=0.004$). In contrast with younger adolescents, among ATYA odds of DD were 28.2% higher (OR 1.282, 95% CI 0.967-1.698, $p=0.084$) and, odds of AD were 55.2% higher (OR 1.552, 95% CI 1.137-2.119, $p=0.006$). For ATYA, a poor quality of social support was the most predictive factor of DD (OR 11.187, 95% CI 5.530-22.629, $p<0.0001$) and AD (OR 6.238, 95% CI 2.845-13.676, $p<0.0001$); whereas, having a paid job was the most protective factor with regard to DD (OR 0.282, 95% CI 0.169-0.470, $p<0.0001$) and AD (OR 0.552, 95% CI 0.330-0.924, $p<0.024$).

Conclusion: Prevalence of mental illness among Belgian ATYA appears to worsen in time. In comparison with younger adolescents, ATYA are more vulnerable to anxiety disorders. Adverse and protective risk factors were identified and discussed in a way to improve access, continuity and mental healthcare pathways for Belgian ATYA.

Key words: adolescence - transition - mental-health status - risk factors

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INTRODUCTION

Recent conceptualization of adolescence argues for an expanded and more inclusive definition of adolescence, considering ages 10 to 24 years old (Sawyer et al. 2018). In this paper, we will particularly focus on the critical moment of transition towards young adulthood, which concerns the late adolescent developmental phase, around 19 to 24 years old, hereafter adolescents in transition to young adulthood (ATYA). This age is characterized by major transitions in adolescent life (e.g. school orientation, leaving family, autonomy, social expectations and integration, etc.).

There are several reasons to focus on ATYA. First, transition to the young adulthood period is identified both by mental health professionals and epidemiological studies as a moment of significant psychological vulnerability (Polanczyk et al. 2015, Costello et al. 2005). According to the WHO, the prevalence of any mental illness is higher among late adolescents in comparison with younger teenagers (WHO 2013). Secondly, access to appropriate care is not adequate for ATYA. Indeed, only one in four adolescents suffering from a significant mental disorder received specialized services. Interna-

tional literature shows that ATYA with a mental health disorder do not have sufficient access to appropriate care, while ad-hoc structures are lacking. Moreover, ATYA are often reluctant to seek help among mental health professionals and services (Malla et al. 2018). A rapid access to adequate care is fundamental. Indeed, it was estimated that around 50% of adult mental health conditions originate in adolescence (Kessler et al. 2007). Therefore, early intervention is recommended to avoid short and long-term negative consequences of early mental health problems. Indeed, in the short-term, adequate care decreases the length of mental health disorders and prevents negative social consequences (e.g. premature termination of schooling, social exclusion). In the long-term, relevant interventions help to reduce morbidity during adulthood and prevent socio-economic exclusion (De Girolamo et al. 2012, Beesdo-Baum 2015). Finally, an additional challenge for healthcare systems is that, historically, the division of services organized by "legal-administrative categories" (i.e. maximum age set at 18 years old) didn't match adolescent developmental phases and the continuum before and after 18 years old. Therefore, within healthcare systems and services from 18 years old onwards, individuals are considered as

adults and referred to different services compared to those younger than 18. This has considerable implications on care delivery: it jeopardizes continuity of care at a developmental turning point. This raises the question of how best to organize mental healthcare for ATYA. In Belgium, the 2015 reform of mental healthcare argues for inclusion of youth until the age of 23 in child-psychiatric services and the development of integrated care within enlarged network (primary care, social services, and mobile team) and community.

Adolescent mental health during transition to young adulthood is a critical issue for public health and has become a key challenge for health care systems and more specifically for mental health professionals. However, in Belgium one significant knowledge gap remains. Indeed, little is known about the mental health status among this specific group of ATYA and risk factors associated to their mental illness. By analysing the Belgian Health Interview Survey (BHIS) database, the aim of this paper is (1) to discuss evolution in time of prevalence of depressive disorder (DD) and anxiety disorder (AD) among ATYA, and (2), to identify risk factors associated with DD and AD among ATYA.

SUBJECTS AND METHODS

The Belgian Health Interview Survey (BHIS) is a repeated cross-sectional population survey where data are collected through face-to-face interviews. BHIS is based on a national representative sample of 10,000 participants, including adolescents aged 15 years and older. BHIS covers four domains: health status, medical consumption, lifestyle and prevention. It contains also socio-demographic and socio-economic background information. For the present study, data were extracted from surveys carried out in 2001, 2004, 2008, and 2013. Statistical analyses were performed with IBM SPSS 25®. Our study conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh in 2000).

RESULTS

Firstly, we present below evolution in time of the prevalence of depressive disorder (DD) and anxiety disorder (AD) for ATYA (19-24 y/o) in comparison with younger adolescents (15-18 y/o) and adults (25+ y/o). Secondly, we provide analysis of risk factors associated with depressive and anxiety disorders among ATYA.

Population distribution per age group and per year of data collection is described in table 1.

Table 1. Population distribution

Age groups	2001	2004	2008	2013
15-18	620	538	515	543
19-24	843	899	846	807
25+	8956	10262	8657	8117

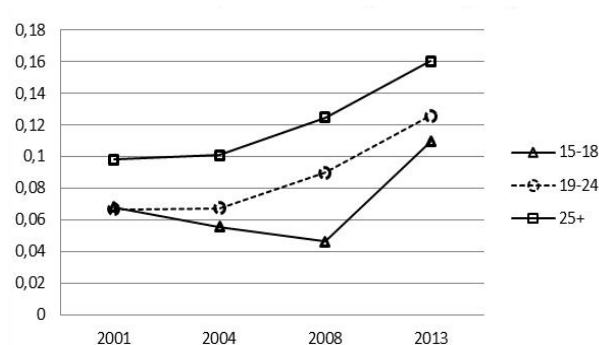


Figure 1. Evolution of depressive disorder prevalence per age

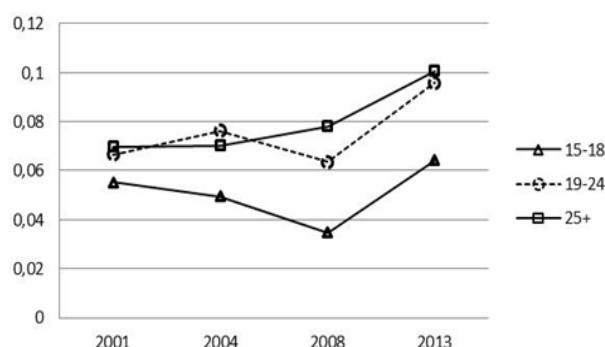


Figure 2. Evolution of anxiety disorder prevalence per age

Evolution in time of the prevalence of DD and AD within Belgian population per age groups is presented in figures 1 and 2.

Among the Belgian population, prevalence of DD was significantly higher in 2013 in comparison with previous years of data collection. This was observed for each age group, that is the 15-18 ($F=3.048$, $p=0.028$), the 19-24 ($F=4.466$, $p=0.004$) and the 25+ ($F=69.650$, $p<0.0001$). Regarding prevalence of AD, in comparison with previous years, all age groups showed a higher prevalence in 2013, but these differences were statistically significant only for the 25+ group ($F=26.216$, $p<0.0001$) and not for other age groups, that is 15-18 ($F=0.883$, $p=0.449$), and, 19-24 ($F=1.320$, $p=0.266$).

In contrast with the 15-18 group, we observed that odds of DD among ATYA were 28.2% higher (OR 1.282, 95% CI 0.967-1.698, $p=0.084$) and 91.4% higher for adults (OR 1.914, 95% CI 1.516-2.415, $p<0.0001$). Odds of AD among ATYA were 55.2% higher (OR 1.552, 95% CI 1.137-2.119, $p=0.006$) and 72.6% higher for adults (OR 1.726, 95% CI 1.325-2.248, $p<0.0001$) in comparison with the 15-18 group. Our logistic regression models were controlled for the following covariables: gender, year of survey, household income, region, urbanisation and country of birth.

The multivariate logistic regression analysis of risk factors associated with DD and AD is presented in table 2.

Table 2. Analysis of risk factors

	Sample	Depressive disorder			Anxiety disorder		
		Odds Ratio	p-value	95% CI	Odds Ratio	p-value	95% CI
Gender							
Male	1,101	1			1		
Female	1,183	1.993	<0.0001	1.368-2.904	2.408	<0.0001	1.663-3.487
Region							
Wallonia	906	1			1		
Flanders	851	1.447	0.078	0.959-2.182	1.169	0.469	0.766-1.783
Brussels	527	2.317	0.001	1.387-3.872	1.426	0.163	0.866-2.350
Urbanization							
Rural	646	1			1		
Urban	1,086	0.571	0.032	0.341-0.954	0.820	0.405	0.513-1.309
Country of birth							
Belgium	1,976	1			1		
EU member	125	0.716	0.341	0.361-1.422	0.626	0.226	0.293-1.336
Non-EU member	175	0.821	0.519	0.450-1.496	0.739	0.345	0.395-1.384
Household Income							
Q1	538	1			1		
Q2	320	0.552	0.043	0.310-0.982	0.631	0.110	0.359-1.110
Q3	328	0.689	0.197	0.391-1.214	0.677	0.184	0.381-1.204
Q4	395	0.992	0.975	0.592-1.661	0.722	0.248	0.415-1.254
Q5	369	0.614	0.118	0.333-1.133	0.590	0.094	0.318-1.093
Paid job							
No	363	1			1		
Yes	969	0.282	<0.0001	0.169-0.470	0.552	0.024	0.330-0.924
Student							
No	1,344	1			1		
Yes	936	1.040	0.802	0.767-1.409	0.873	0.417	0.629-1.212
GP contacts past year							
0 to 6	2,048	1			1		
7 to 12	140	2.628	0.001	1.519-4.544	2.189	0.007	1.236-3.876
13+	80	3.731	<0.0001	1.999-6.964	3.813	<0.0001	2.079-6.994
ED contact past year							
No	1,820	1			1		
Yes	362	1.544	0.034	1.034-2.304	1.524	0.042	1.015-2.288
Social support quality							
Strong	346	1			1		
Intermediate	487	1.871	0.053	0.992-3.528	1.990	0.051	0.997-3.972
Poor	126	11.187	<0.0001	5.530-22.629	6.238	<0.0001	2.845-13.676
Cannabis use past year							
No	1,333	1			1		
Yes	248	2.379	<0.0001	1.469-3.854	2.108	0.006	1.243-3.575
Problematic alcohol							
No	1,671	1			1		
Yes	140	2.869	<0.0001	1.646-5.000	2.919	<0.0001	1.645-5.180
$\chi^2=212.179$; $df=34$; $p<0.0001$				$\chi^2=143.030$; $df=34$; $p<0.0001$			
- 2LL=1077.877; Nagelkerke $R^2=20.50\%$				- 2LL=1031.669; Nagelkerke $R^2=15.10\%$			
H & L test ($\chi^2=8.153$, $p=0.419$)				H & L test ($\chi^2=15.570$, $p=0.049$)			
Classification accuracy 92.2%				Classification accuracy 93.2%			

Analyses were performed only on ATYA population, that is, a sample of 2284 individuals aged 19-24 y/o. Regarding population background, we found that females were more at risk than males of depressive and anxiety disorders. Living in Brussels was associated with higher odds of depressive disorder only. Perceiving

a poor quality of their own level of social support was the most predictive factor for depression (OR 11.187, 95% CI 5.530-22.629, $p<0.0001$) and anxiety (OR 6.238, 95% CI 2.845-13.676, $p<0.0001$). Being a student was not impacting risk of DD or AD whereas, having a paid job prevented risk of DD (OR 0.282, 95%

CI 0.169-0.470, $p < 0.0001$) and AD (OR 0.552, 95% CI 0.330-0.924, $p < 0.024$). Living in urban areas reduced risk of depression only. Univariate analysis reveals that higher quintiles of household income were significantly associated with lower odds of DD and AD, but these relations disappeared in multivariate models. Finally, country of birth was not impacting risk of both disorders.

Concerning health behaviours, we found that cannabis consumers in past year, were twice higher at risk of both DD and AD. ATYA who have had problematic alcohol consumption in their lives were close to three times higher at risk of depression and anxiety.

When considering health services utilization, we found higher odds of DD and AD among those who went at least one time to the emergency department in the past year. Proportion of ATYA with a DD frequenting at least one time in past year an emergency department was 12.98% and 11.87% for those suffering from an AD. Number of contacts with the general practitioner was predictive of higher odds of depressive and anxiety disorders.

DISCUSSION

The first aim of this study was to describe evolution in time of the prevalence of depressive disorder (DD) and anxiety disorder (AD) among ATYA (19-24 y/o). Moreover, we paid attention to ATYA as being, or not, a more vulnerable group in term of mental illness (prevalence of DD and AD), in comparison with younger adolescents (15-18 y/o) or adults (25+ y/o). We found that, between 2008 and 2013, prevalence of DD significantly increased for ATYA but also for the two other age groups of population. In comparison with previous years, we observed that in 2013, prevalence of AD was significantly higher only among adults. For ATYA, trends of AD showed an increase in 2013, but differences were not significant. These results confirm previous epidemiological studies showing an increase, these last years, of mental illness among adolescents and young adults (Twenge et al. 2019). It is a complex task to disentangle whether the burden of mental illness is resulting from social, economic or cultural global evolutions (e.g. socio-economic uncertainties; changes in the family environment; school pressures), or may reflect changes in how adolescents perceive and report mental health complaints. Various factors may converge.

Regarding the question of specific vulnerability to mental illness, during transition to young adulthood, we observed contrasted results. Indeed, ATYA prevalence of DD was not significantly different from the 15-18 group. But in comparison with these younger adolescents, ATYA were more vulnerable to AD. A study shows that anxiety is one of the most prevalent common mental health issues among ATYA; transition from adolescence to young adulthood supposes experiencing new roles, increases levels of autonomy, and seeking to fit in socially (Essau 2004). These issues are specific to ATYA and may generate anxiety.

The second aim of this study was to identify risk factors associated with DD and AD among ATYA population. Three categories of predictors were considered, population background characteristics, health behaviours, and services utilization. When controlling for covariables, significant relation between higher household incomes and lower risk of DD or AD disappears. ATYA belonging to a more privileged socio-economic stratum may be less prone to DD or AD, but this operates through intermediate pathways.

Regarding gender-related risk, our findings confirm what is known from literature, that women are more likely to experience DD or AD than men (Zahn-Waxler et al. 2008). It appears that these differences already occur during transition to young adulthood. Interaction between, neurodevelopmental, social, and cultural factors may be put forward to explain gender-related risk of mental illness.

Experiencing a poor quality of social support was the most predictive factor for both DD and AD. It is imprudent to confirm a direct causal relation between weak social support and mental illness, indeed this relation is more likely to be circular. We know that social ties and networks play a beneficial role in the maintenance of psychological well-being (Kawachi & Berkman 2001). Development of positive relations to peers is a crucial stake in the perspective of social integration of ATYA, those who fail may be at risk of distress, moving sometimes to mental illness. According to the "social sharing of emotion" theory (Rimé et al. 1998) the fundamental psychological need of giving meaning to life experiences is nourished through social sharing of emotions with significant peers. Objective or subjective weaknesses in ATYA social support may deteriorate the process of social sharing of emotions. This may be dramatic for adolescents in transition whom are fully dealing with worrying situations which precisely necessitate possibility to share concerns with peers. One alternative mean of social integration is work. Odds of mental illness among ATYA having a job were significantly reduced. Supporting a quick inclusion of ATYA in the labour market should be reinforced to prevent them from psychological distress.

Consumption of cannabis in the past year or long term alcohol misuse were both two significant predictors of DD and AD. Here again it is complicated to disentangle if this relation is linear or circular. Late-adolescence is known as a "sensation-seeking" stage for many young people (White et al. 2006). Alcohol and cannabis are highly available, and many ATYA have experienced these products without developing a misuse or any addiction. It is relevant to explore with ATYA their relation to alcohol or cannabis; these products may be particularly detrimental in case, in which they are used as an avoidance strategy with regard to questions raised by transition process.

One concern of this study was how best to organize mental healthcare for ATYA. General practice and emergency rooms may be relevant places to organize detection, orientation and, prevention of ATYA mental illness. Indeed, we observed that risks of both DD and AD were significantly multiplied among ATYA frequenting

more often their general practitioner (GP). Moreover, ATYA who have had a contact with an emergency department in the last year were also more at risk of DD or AD. As prevention needs time and continuity, it should take place in primary care. GPs should be sensitized to risk factors of mental illness among ATYA (i.e. gender-related effect, poor quality of social support, alcohol or cannabis misuse, job-seeking). Emergency departments should focus on detection of ATYA mental illness, and on orientation to the most relevant trajectory of care.

One limitation of the study is that data was extracted from a national health survey that lacks specificity regarding mental illness indicators. More accurate mental health outcomes and, theoretically grounded potential risk factors of mental illness during transition are necessary to build valid intervention aiming to reduce risk of mental illness during transition to young adulthood. Further researches should confirm trends observed in this study and, identify factors playing a role in mental illness trends evolutions among ATYA. Longitudinal designs may be considered. In international contexts, ATYA should become a specific sub-group of population for which mental illness is regularly monitored in relation with broader determinants of mental health. Also, specific mental health pathways should be developed for ATYA.

CONCLUSION

This study shows that prevalence of mental illness among Belgian ATYA appears to have worsened in time since 2008. In comparison with younger adolescents, ATYA are more vulnerable to AD; prevalence of DD is equivalent in both age groups. Some adverse and protective risk factors were identified and discussed in a way to improve access, continuity and mental healthcare pathways for Belgian ATYA. We advocate for a quick detection of mental illness among ATYA and a provision of suitable care. This is essential since psychological difficulties arising during transition to young adulthood may have cascading implications; it jeopardizes young adults' personal development and social integration.

Contribution of individual authors:

Lepièce Brice conceived the study, performed statistical analysis, and drafted the manuscript.

Lepièce Brice, Nicolas Zdanowicz, Emmanuel de Becker, Philippe de Timary & Vincent Lorant all made substantial contributions to interpretation of data and revision of the manuscript.

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MOBIUS SYNDROME AND OBSESSIVE COMPULSIVE DISORDER: A CASE REPORT

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SUMMARY

Background: Mobius syndrome is characterized by a bilateral congenital paralysis of the facial and abducens nerves which leaves the subject with an expressionless "mask-like" face.

Subjects and methods: Based on a literature review and a case discussion of an adult patient with Mobius syndrome and obsessive-compulsive disorder, initially undiagnosed and confused with a psychotic disorder, we will discuss the influence of Mobius syndrome in psychiatric evaluations.

Results: The lack of facial expressiveness and non-verbal emotional interactions may influence psychiatric evaluations and result in misdiagnosis and the inappropriate prescribing of antipsychotics. In the case analysis, we also observed other associated malformations such as renal atrophy, a bicuspid aortic valve and mitral valve prolapse.

Conclusion: We feel that educating the patient about the communicative consequences of impaired facial expressions and facial interactions is a necessary prerequisite for any psychiatric or psychological evaluation in subjects with Mobius syndrome. We also recommend using caution when prescribing antipsychotics in patients with Mobius syndrome given the motor side effects secondary to a potentially pre-existing hypotonia.

Key words: Mobius syndrome - OCD-renal atrophy-bicuspid aortic-mitral valve prolapse-BCT-delusions-drug induced dystonia

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INTRODUCTION

Mobius syndrome (described by the neuropsychiatrist Paul Julius Möbius 1853-1907), also called congenital facial diplegia or congenital oculofacial paralysis, is a rare non-progressive congenital neurological disorder that is characterized by a facial diplegia, partial or complete by damage of facial nerve (VII) frequently associated with others cranial nerves damages, particularly the abducens nerve (VI) who innervates the right lateral muscle which controls lateral eye movement.

The estimated prevalence of this syndrome is 1 out of 10,000 to 80,000 live births. It is caused by the defective development, in the hindbrain, of the cranial nerve nuclei (nerves VI and VII). The syndrome is multifactorial with genetics and environmental causes. The observed modalities of genetical transmission are autosomal dominant inheritance or recessive and also X-linked for a subgroup of affected patients (McKay et al. 2016).

Concerning environmental causes, it was observed: impairment of the blood supply to the cranial nuclei or infectious damages in the second month of pregnancy as well as taking certain medications or drugs (such as thalidomide, misoprostol, alcohol or cocaine).

The syndrome is also associated with muscle hypotonia and several orthopaedic malformations such as clubfoot, scoliosis, limb and upper extremity malformations (McClure et al. 2017).

In the eyes, we find a limitation of ocular abduction in all cases. In addition, we also often find esotropia, epicanthus and entropion, and sometimes exotropia and hypertropia (Borbolla et al. 2014).

Poland syndrome (unilateral aplasia of the pectoralis major muscle associated with mammary or nipple abnormalities) is also present in some cases (McClure et al. 2017).

In terms of orthodontics, reduced temporomandibular joint movement is observed as well as micrognathism or excessive maxillary growth, which is undoubtedly associated with lip muscle coaptation problems or tongue malformations (Magnifico et al. 2018).

Last, there are also reported cases of obesity and early puberty associated with Mobius syndrome (De Silva et al. 2018).

It can be difficult to diagnose Mobius syndrome. At birth, suckling, swallowing, feeding and breathing problems can be warning signs; however, it is not always easy to immediately associate these symptoms with the syndrome given that it is so rare. The lack of facial expressiveness and the various associated malformations leads to the diagnosis at an early age. Most authors recommend early screening and a multidisciplinary assessment (McKay et al. 2016), along with a paediatric examination, in the fields of plastic surgery, neurology, otorhinolaryngology, orthopaedics, ophthalmology and orthodontics (Magnifico et al. 2018). It is essential that

the child and family have medical support during the developmental course and the various surgeries, always using a multidisciplinary approach.

Although the syndrome is not progressive, it obviously has a major emotional impact on the patient and their family.

Using a case report of an adult with Mobius syndrome, we discuss the syndrome's psychological effects on the individual's development and also show how the characteristics of the syndrome can make it difficult to interpret and detect possible psychiatric symptoms.

SUBJECTS AND METHODS

Based on a literature review and a case discussion of an adult patient with Mobius syndrome and obsessive-compulsive disorder, initially undiagnosed and confused with a psychotic disorder, we will discuss the influence of Mobius syndrome in psychiatric evaluations.

Patient data was collected during 40 psychiatric visits between May 2011 and December 2018. The consultations were conducted at the Catholic University of Louvain, CHU UCL Namur, Psychosomatic Dpt, avenue Dr G. Therasse n°1, 5530 Yvoir, Belgium.

The literature review was conducted using the databases, PsycInfo, and Pubmed with the following keywords: mobius syndrome and psychiatry

A total of 39 articles were found in the search and 18 were selected for their clinical relevance.

RESULTS

The patient was 31 years old at the time of his first consultation. He has Mobius syndrome. We note the following in his medical history: hypothyroidism, hypercholesterolemia, bicuspid aortic valve, and mitral valve prolapse. With regards to the surgical history, the patient underwent a right nephrectomy for renal atrophy, two clubfoot surgeries, jaw surgery and an appendectomy.

Over the past five years, the patient has consulted 8 different psychiatrists without maintaining continuity of care. The following antipsychotic treatments were prescribed and discontinued due to intolerance with vomiting and especially drug induced dystonia: amisulpride, risperidone, haloperidol, pimozide, aripiprazole with the introduction each time of procyclidine in order to limit the drug induced dystonias. In the patient's last psychiatric follow-up file, we find the possibility of an unspecified psychotic disorder with episodes of hallucination and interpretative and paranoid symptoms.

The patient's current drug therapy consists of quetiapine 25 mg, paroxetine 20 mg and prazepam 30 mg.

The patient lives with his parents, is not employed, and is officially recognized as being disabled which allows him to receive disability benefits.

Clinically, the patient is calm. He is coherent when he speaks with a normal spatial-temporal orientation. His mood is described as sad with daily anxiety that comes in peaks (panic attacks) and which force the patient to lie down and stay in bed. His sleep is described as reduced to 4 hours with difficulty falling asleep and waking up with nightmares. He says he has a decreased appetite. The patient says that he has gained 20 kilos over a period of two years after taking the various antipsychotic drugs described above. The patient does not drink any alcohol, nor does he smoke cigarettes or cannabis. He also does not consume nicotine in any way, nor does he use heroin, cocaine or any other synthetic drugs.

The patient explains that he made an appointment following a cardiology consultation during which he was advised to try to start seeing a psychiatrist again for follow-up given the intensity of the panic attacks. Right at the outset, the patient says that he has been disappointed so far by the psychiatric follow-ups and emphasized that he feels misunderstood. He also mentions that the drugs he has been given have had more cons than pros.

The patient says that he sees horrible things throughout the day without at first specifying the content of his "hallucinations" that are causing the described panic attacks and that the medication does not allay this.

While collecting the patient's history, it is important to note that the patient's face is in fact expressionless, he does not smile, or show any emotions, he has a fixed gaze and does not blink his eyelids, the lip muscle coaptation is not perfect and his speech is sometimes unclear and at times the patient drools.

Therefore, the first two consultations are devoted to carrying out the "Mini International Neuropsychiatric Interview" as well as to negotiating the goals of the follow-up which are to re-evaluate the diagnosis of hallucinations and to see if a more effective treatment is possible.

The discussion also focuses on the observation that it seems difficult for the patient to maintain a regular follow-up with a psychiatrist.

The third consultation scheduled for July 2011 was cancelled by the patient. Following a telephone conversation, the patient gives a whole series of reasons for discontinuing the follow-up, which seem to be the result of confusion and misunderstandings that were not evident during the consultations. At the forefront of his explanation is the feeling that he is not understood.

While fully respecting his decision, the patient is nonetheless encouraged to make an appointment in order to clarify these misunderstandings. The patient eventually resumes contact in December 2011 only to discontinue the follow-up once again in March 2012. He resumes the follow-up in June 2012, this time with a regular follow-up possible until February 2013. The follow-up is once again discontinued by the patient who will come back in March 2014 when it was possible to engage in cognitive-behavioural therapy. Since then, the patient is followed-up regularly.

Prior to developing the diagnostic evaluation performed and the procedure for the cognitive-behavioural therapy goals, it seems to us that it is important to focus on the process that results in this patient initiating follow-ups only to discontinue them impulsively.

This behaviour was previously taken as a sign of paranoid and interpretative thoughts that may fall under a diagnosis of personality disorder or psychotic disorder with hallucinations and paranoid delusions. In trying to understand his experience of being misunderstood and persecuted and by analysing the misunderstandings, the influence of bilateral facial paralysis on communication was shown quite clearly.

The issue of the influence of facial paralysis on communication was introduced by taking another look at the lived experience of some patients met in liaison psychiatry who had developed unilateral facial paralysis ("Bell's palsy"). By merely changing their facial expression abilities, these patients described feeling as though they are no longer understood in the same way by their close friends and family.

Therefore, by using psychoeducation to teach the importance of non-verbal elements (particularly, emotion recognition using facial expressions) in communication, the patient was finally able to understand why he was feeling confused and misunderstood during the consultations. This is due in part to the fact that the therapist is looking at an inexpressive face and therefore is not able to perceive the emotional dimensions when the patient speaks. In addition, the therapist also has an expressionless face when looking at the patient, which may also result in a misunderstanding.

Thus, the increased awareness of this led to feedback being systematically given regarding the emotional experience at the end of each consultation.

This allowed for better compliance with the follow-up, and it was possible to continue the diagnostic work-up.

Based on the MINI and according to the DSM IV criteria, a moderate depressive disorder and a panic disorder were initially diagnosed.

The problem of hallucinations and feeling anxious raised the question of psychotic symptoms, which is also why the previous follow-ups mentioned the diagnosis of an unspecified psychotic disorder where several antipsychotic treatments were tried without obtaining satisfactory results.

Given the patient's better compliance with the follow-up and the therapeutic relationship that was developed, we were able to better analyse the content of his hallucinations. First observation, the patient describes that he is aware that it is not real but that he is still terrified when it happens. He describes them as images that intrude his mind. The content of these images is always the same: decapitation, mutilation of the face and the body. These intrusive images trigger certain behaviours in the patient such as having to touch his entire face to make sure it hasn't been disfigured as

well as repeatedly asking his relatives to reassure him that he has not disappeared and that no one is going to hurt him.

As we began to understand how these thoughts progress and the resulting behaviours, it was possible to diagnose the patient with obsessive-compulsive disorder and to subsequently formulate and negotiate cognitive-behavioural therapy goals with the patient.

The question of social phobia was investigated in the differential diagnosis. "The Appearance Anxiety Inventory: measure of body dysmorphic disorder" questionnaire (Veale et al. 2013), once completed, showed very low scores except for the question regarding excessive appearance concerns. Moreover, clinically, the patient describes feeling more comfortable if he is alone when he meets people because the people he meets talk directly to him; this is not the case when he is accompanied by his parents, the people he meets only see his "inexpressive" face and they interpret it as a sign of disability and do not directly speak to him, only to his relatives. This phenomenon of being considered as being "disabled", unable to express himself, seems to have rather reinforced the feeling of not existing and only being afraid of what the other person thinks. This facial reading could also explain the traumatic nature of the intrusive images that revolve around the theme of the fear of not being whole, being mutilated and feeling the need to be reassured. The patient has also established links between the intrusive images and the emotions associated with the experience of his various orthopaedic surgeries (foot and jaw) as well as future surgeries for multiple dental implants.

It was possible to carry out the cognitive behavioural therapy in a structured manner over 20 consecutive sessions. The work focused on psychoeducation about the mechanisms of obsessive compulsive disorder, by conceptualizing the principle of an obsession, experienced as a forced and intrusive thought or image even though it is virtual, that feels real and causes reactive anxiety. This compulsion, the act of thinking or actual motor behaviour, then leads the patient to try to lessen his anxiety but in fact reinforces the obsession.

The patient validated the indication for exposure therapy by preventing the behavioural response of checking his entire face and questioning his relatives.

Exposure to intrusive mental images with response prevention has been supported by systematic desensitization through the use of relaxation techniques.

Two family interviews also took place with psychoeducation about the treatment of obsessive-compulsive disorder and the supportive role the family should play in response prevention.

From the standpoint of the diagnosis of obsessive-compulsive disorder, the dose of paroxetine was increased to 30 mg (rather than the adding an antipsychotic drug).

In January 2015, based on a Visual Analogue Scale (VAS), the experience of intrusive images was assessed with a score of 9/10 in terms of discomfort on the quality of life scale and a score of 9/10 for the related anxieties. In January 2017, following the patient's continuing effort, the scores fell to 3/10 and 2/10, respectively.

Although there was a significant improvement in terms of decreasing his anxiety, the intrusive images did not completely disappear, however the patient was able to clearly change his emotional regulation. We were also able to note an increase in the frequency of the intrusive images, particularly around the time when several dental implant surgeries were performed; this would, once again, argue that these intrusive images are related to trauma.

The follow-up, more spaced out in terms of frequency, is still currently ongoing for reinforcement purposes.

DISCUSSION

Based on the discussion of the case report and with respect to the literature, we clearly observe the characteristics of Mobius syndrome, i.e. the "mask-like" face, the inexpressive face, a fixed gaze making it difficult for the caregiver to perceive what the patient is feeling. It is sometimes difficult to understand the patient when he speaks due to the "bilabial incompetence" (Vaca et al. 2018). In this work, we can already identify two major obstacles in the psychiatric evaluation of patients with Mobius syndrome.

The literature shows that in younger subjects with Mobius syndrome, psychological adjustment problems are more frequent and lead to early interventions (Briegel et al. 2019). Our case report could suggest that it is also important to continue to provide appropriate follow-up for adults with Mobius syndrome and to pay close attention, over the long term, to the traumatic effects of the disorder and any resulting surgeries.

The analysis of our case also shows how it is possible to confuse paranoid symptoms and the difficulties in emotion recognition of facial expressions, which could result in misunderstandings. Calder et al. (2000) uses a case study to suggest that patients with Mobius syndrome are able to recognize facial expressions shown on a computer even though they themselves are unable to produce these expressions on their face and that therefore it is not a prerequisite to be able to produce these expressions.

However, these results are obtained on static pictures of people expressing emotions. In a context of dynamic communication, what really happens when the lack of expression on the face of the person with Mobius syndrome means that the person to whom they are speaking does not return an emotional facial response and they do not understand what the patient's is experiencing emotionally?

Facial expressions of emotion allows a person to communicate their emotional states and act as adaptive functions that facilitate social interactions (De Stefani et al. 2019).

We believe that psychoeducation about the non-verbal elements of communication should be a prerequisite prior to any psychiatric evaluation in a person with Mobius syndrome. In another case report (Gianni et al. 1984), learning to recognize social codes and to correctly interpret social behaviours is described as important for patients with Mobius syndrome who have a smaller social network due to their "mask-like face".

For Briegel (2006), it is quite common to observe impaired psychomotor development and language in Mobius syndrome; mental retardation occurs in 10 to 15% of cases and there could be more cases of autistic spectrum disorders. Briegel et al. (2010) screened autism spectrum disorders in 19 patients and did not find increased prevalence of autistic disorders.

As with our case report, we could speculate that because emotional interaction deficits are not taken into account in facial expression exchanges, this leads to misdiagnoses in people with Mobius syndrome: pseudo-indifference, autistic traits, mistrust or paranoia as also suggested by Cole et al. (2009).

In our case, the patient is not mentally retarded. However, we were not able to perform an IQ test in order to precisely assess his level. But over the course of the interviews, it could clearly be assumed that the patient has a normal cognitive development. Paradoxically, normal intellectual functioning results in greater lucidity and understanding of the difficulties. Szajnberg and Nathan (1994) identified the existence of insecure and ambivalent attachment disorder in a case report. Briegel et al. (2012) also highlighted the fact that social problems are common between the ages of 4 and 17 years in affected patients and that these patients would need assistance and support from their family. Briegel (2010) also emphasized the importance of assessing the subject's self-perception regardless of their appearance (which could suggest a depressive state) for the diagnostic process. Based on our case analysis, we believe that these recommendations should be maintained in adulthood.

CONCLUSION

Mobius syndrome is associated with several malformations. In our case analysis, we note the presence of renal atrophy, bicuspid aortic valve and mitral valve prolapse in addition to clubfoot, and malformations of the jaw.

The lack of facial expression, characteristic of Moebius syndrome, could be misleadingly suggestive of autistic or depressive symptoms as described in the literature. Our case study shows that this can also result in diagnostic errors regarding paranoid or interpretive symptoms secondary to hallucinations whereas

the final diagnosis is actually an obsessive-compulsive disorder in reaction to trauma associated with the syndrome and the related surgeries.

Given that muscular hypotonia is related to the syndrome, we recommend exercising extreme caution when prescribing antipsychotics. In our case study, the various antipsychotics tested appear to have all caused disabling side effects at the usual recommended doses. The non-therapeutic response is also explained by the fact that these were not hallucinations related to a psychotic disorder but intrusive thoughts and images related to an obsessive-compulsive disorder that was best treated by cognitive and behavioural therapy.

If it is necessary to administer an antipsychotic drug to a patient with Mobius syndrome, we would recommend starting with very low doses.

We feel that educating the patient about the communicative consequences of impaired facial expressions and facial interactions is a necessary prerequisite for any psychiatric or psychological evaluation in subjects with Moebius syndrome.

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ROLE OF GUT MICROBIOTA IN THE INTERACTION BETWEEN IMMUNITY AND PSYCHIATRY: A LITERATURE REVIEW

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SUMMARY

Background: Psychiatric disorders may be correlated with a low-grade systemic inflammation but the origin of this inflammatory response remains unclear and both genetics and environmental factors seems to be concerned. Recent researches observed that gut microbiota seems to have an impact on the brain and immune processes.

Method: We review recent literature to a better understanding of how microbiota interacts with brain, immunity and psychiatric disorders. We search on Pubmed, PsycINFO, PsycARTICLES and Scencedirect articles with the keywords "gastrointestinal microbiota" and "mental disorders" or "psychological stress".

Results: We showed links between gut microbiota and brain-gut axis regulation, immune and endocrine system activity, neurophysiological changes, behavior variations and neuropsychiatric disorders. Communications between brain and gut are bidirectional via neural, endocrine and immune pathway. Microbiota dysbiosis and increase gut permeability with subsequent immune challenges seems to be the source of the chronic mild inflammation associated with neuropsychiatric disorders. Repeated immune or stress events early in life may lead to neurodevelopmental disorders or sickness behavior later in life.

Conclusions: psychological stress impact gut microbiota with subsequent immune activation leading to neurodevelopmental disorders or sickness behavior and altering neurophysiology and reactivity to stress or lifestyle.

Key words: microbiota - psychological stress - psychiatric disorder - immunity

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INTRODUCTION

We highlighted in a precedent review (Dubois et al. 2018) that psychiatric disorders may be correlated with a low grade systemic inflammation and mild immunosuppression. The origin of this inflammatory response remains unclear and both genetics and environmental factors seems to be concerned. Recent researches observed that gut microbiota seems to have an impact on the brain and immune processes. In this article we review recent literature to a better understanding of how microbiota interacts with brain, immunity and psychiatric disorders.

METHOD AND LIMITATIONS

We search on Pubmed, PsycINFO, PsycARTICLES and Scencedirect articles with the keywords «gastrointestinal microbiota» and «mental disorders» or «psychological stress». We have as much as possible promoted recent literature (2012 to early 2019) and human studies but they are limited and sometimes have a lower statistical significance than animals studies. We have been focused on the literature about immunity and endocrine system. Selection and interpretation bias are probably present for the subsequent conclusions.

RESULTS

Links between intestinal microbiota and brain-gut axis

We found several evidences emphasizing the fact that brain – gut axis is influenced by micro-organisms colonising the gut mucosa (gut microbiota). Enteric

nervous system (ENS) and central nervous system (CNS) are connected through the vagus nerve. Evidences showed that gut microbiota directly in contact with the ENS could modulate sensory neurons excitability and so information relayed to the brain (Parashar & Udayabanu 2016). Neurotransmitters such as catecholamines or gamma-aminobutyric acid (GABA) (Asano et al. 2012, Barret et al. 2012) are secreted by intestinal microbiota. Bacteria metabolism influences the serotonergic system by altering tryptophan availability to 5-HT synthesis (Rackers et al. 2018). There is evidences that host neurophysiology is modulated by changes in gut microbiota. Neufeld et al. (2011) observed changes in hippocampal brain derived neurotrophic factor (BDNF) mRNA in germ-free (GF) mice.

Links between intestinal microbiota and behavior

Significant evidences support correlations between behavior and gut microbiota composition. It was showed that intestinal microbiota influences sensitivity to stress. Huo et al. (2017) showed less anxiety-like behavior in GF mice while others studies showed opposite results (Crumevolle-Arias et al. 2014). Desbonnet et al. (2014) found a significant social behavior impairment in GF mice. These behavior shifts were normalized following colonization of the gut of GF mice. Short-chain fatty acids (SCFA) such as butyrate, acetate or propionate (PPA) are produced by microbial fermentation of dietary fiber and is a common preservative added to refined wheat and dairy products. SCFA are known to have neuroactive properties or induce neuroinflam-

mation and are associated with behavioral alterations. It was showed that PPA activate microglia of the hippocampus, white matter, cingulate, and neocortex (MacFabe et al. 2011) and can also alter the excitatory and inhibitory balance in neural circuitry via increased glutamatergic and decreased GABAergic transmission (MacFabe 2012). PPA seems to be linked with autism spectrum disorder symptomatology in human. Higher autistic symptoms are observed after eating food containing PPA and improvement is observed following the elimination of these product (Cenit et al. 2017).

Links between intestinal microbiota and immune system

Moreover, it seems that endocrine and immune system play an important role in the interaction between microbiota and brain. Microbiota composition may interact with hypothalamic-pituitary-adrenal (HPA) axis activity. Huo et al. showed a greater increase of HPA axis hormones levels with increased corticotrophin releasing factor (CRF) expression, elevated adrenocorticotropic hormone (ACTH) with corticosterone/cortisol levels and a reduce glucocorticoid receptor (GR) expression in GF stressed mice (Huo et al. 2017). Furthermore, stress may affect the composition of the gut microbiota and increase gut permeability (Kelly et al. 2015). Catecholamines are known to induce growth of gram negative bacteria (Lyte & Ernst 1992). CRF might play a role in the stress-induced gut permeability dysfunction (Rodríguez-Janeiro et al. 2015). Vanuystel et al. (2014) showed in humans that the mechanism might be the activation of mast cells receptors for corticotropin-releasing hormone. An increase gut permeability or a «leaky» gut facilitates translocation of bacteria into intestinal wall and contribute to the development of local inflammation but also the inflow of bacterial metabolites or harmful substance. Leading to a chronic systemic low-grade inflammation characterized by an increase level of pro-inflammatory cytokines and an activation of the HPA axis and secretion of cortisol (Brzozowski et al. 2016). Lipopolysaccharide (LPS) is a constituent of the outer membrane of Gram-negative bacteria. Toll-like receptor (TLR) are pattern recognition receptors (PRR) expressed by macrophages. LPS binds to TLR4 leading to nuclear factor- κ B (NF- κ B) activation and pro-inflammatory cytokines upregulation and so activation of immune system in the periphery and brain as well as stimulate the HPA axis (Mayerhofer et al. 2017). Moreover lipopolysaccharide (LPS) is known to produce systemic and psychiatric changes called sickness behavior such as fatigue, anorexia, depressed mood or apathy (DellaGioia & Hannestad 2010).

Links between intestinal microbiota and early life psychological stress

On Wah et al. (2018) showed in rats that early life immune challenges (induce by repeated LPS administration during adolescence or early adulthood) may induce

effects long after initial response has dissipated and are risk factor for neurodevelopmental disorders or sickness behavior later in life (such as anxiety or depressive-like behavior). Moreover, they demonstrated that administration of PPA later in life may potentiate symptoms and sickness behavior due to the priming effect of LPS. Perinatal period, early childhood and adolescence are reported to be vulnerable periods for both brain and gut microbiota development. Animals studies showed that stressful events and subsequent gut-brain axis dysregulation early in life lead to brain development perturbations and have consequences on behavior such as anxious-like or social behavior or cognitive function and even immune or metabolic disorders in adulthood (Stiemsma & Michels 2018, Desbonnet et al. 2015). Dysregulation of gut-brain axis early in life is correlated with dysbiosis, reduce BDNF, HPA axis activation, impaired GR-mediated negative feedback and increase stress reactivity in adulthood (Desbonnet et al. 2015, Malan-Muller et al. 2018, Farzi et al. 2018). Moya-Pérez et al. (2017) showed that *Bifidobacterium* (*B. pseudocatenulatum* CECT 7765) intake may modulate the consequences of chronic stress on the HPA axis in adulthood with positive consequences in brain biochemistry and behavior.

Links between intestinal microbiota and neuropsychiatric disorders

Evidences revealed that a disturbance of the intestinal ecosystem (dysbiotic microbiota) might be associated with gastro-intestinal disorders but also with neuropsychiatric disorders (Gulas et al. 2018). Functional gastro-intestinal disorders such as inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) are characterized by a stress-induced brain-gut-microbiota alterations and are often associate with psychological distress including anxiety or depression (O'Mahony et al. 2017). But also it was observed that gastrointestinal (GI) symptoms are common in individuals with autistic spectrum disorder (ASD) and studies suggested a microbiota imbalance and an increase gut permeability (or «leaky gut»). It is demonstrated that ASD is correlated with an increase inflammatory markers (such as IL-6 or TNF), immune cells infiltration in the GI tract and increased levels of IgA in stool sample. A recent study performed fecal transplantation in ASD and observed a significant improvement in both GI and behavioral ASD symptoms (Groen et al. 2018, Fowlie et al. 2018). Depressive disorder is correlated with shifts in the microbiome composition (Zhernakova et al. 2016). Variations in levels of Bacteroidetes, Proteobacteria, Actinobacteria and Firmicutes are observed in depressive patients stools compared to controls. But studies showed contradictory results concerning proportions of species represented in stools samples (Jiang et al. 2015, Zheng et al. Lin et al. 2017). Consumption of *Lactobacillus* and *Bifidobacterium* is related with a small but significant improvement of depression score in a double-blind

randomized placebo controlled study (Messaoudi et al. 2011). When transferring microbiota from patients with major depression to microbiota-depleted animals characteristics of depression are also transferred (Cenit et al. 2017). In recent findings it was showed that human gut microbiota is involved in host metabolism and weight regulation. Dysbiosis is also demonstrated in anorexia nervosa (AN). Studies found an increase concentration of *Methanobrevibacter Smithii* (*M. Smithii*) in patients with AN compared to individuals with normal weight or obese controls. Moreover, negative correlation are found between body mass index and increased concentration of *M. Smithii* (Seitz et al. 2019).

DISCUSSIONS

Microbiota dysbiosis is associated to behavior alterations and neuropsychiatric disorders

The human gut microbiota includes more than 1,000 species and over 7,000 subspecies. Bacteroidetes (composed by several bacteroides or prevotella species) and Firmicutes (such as *Clostridium*, *Ruminococcus*, *Lactobacillus*) are the most abundant phyla in the gut. Actinobacteria (such as *bifidobacterium*), Proteobacteria (*Enterobacteriaceae* such as *Escherichia coli*), Verrucomicrobia, Fusobacteria, Cyanobacteria and Spirochaetes are also found in intestinal flora. In adults, the intestinal microbiota consists of strictly anaerobic bacteria and relatively anaerobic bacteria are found but only in small amounts. Composition of microbiota is not constant during lifetime. The development occurs during early childhood and depends for example on maternal health or mode of delivery. After the age of three years the gut microbiota is relatively stable and tends to lose diversity in the elderly (Gulas et al. 2018). We showed that dysbiotic microbiota is connected with gastrointestinal disorders such as inflammatory bowel disease or irritable bowel disease but also with neuropsychiatric disorders such as depression, anxiety, autism or anorexia. Animals model is the most representative to understand the impact of intestinal dysbiosis on the brain and behavior. A total absence of microorganism is characterized by GF mice model correlated with behavior alterations such as impairment in social behavior, anxiety-like behavior and more reactivity to stress. There is also neuro-endocrine changes such as HPA axis hyperactivity and reduce GR expression but also neurophysiological perturbations such as a decrease of BDNF levels in hippocampal region. Dysbiosis is related to change in bacteria constituent or metabolites. Some species seems to have harmful and other protective effects but it is difficult actually to associate specific pattern of dysbiosis with a behavior or a psychiatric disorder. Administration of probiotics or improvement in lifestyle and diet in depressive patients or ASD are correlated with improvement of the symptomatology. Recently fecal microbiota transplant showed that the phenotype of the donor is transferred to the recipient.

There is bidirectional communications between gut and brain

Interactions between the gastrointestinal tract and the cerebral nervous system (CNS) are more commonly called «brain-gut axis». Within the digestive tract we found millions of neurons forming the ENS whose the role is to regulate autonomic function of the gut such as motricity or secretions. ENS is connected to the brain via vagus nerves. It is well known that emotions such as stress may be accompanied by transit perturbations. Furthermore, we showed that commensal microorganism living along the gut have also the possibility to interfere with autonomic nervous system. Bacteria may secrete several neurotransmitters implicated in communication within the ENS and also CNS. Besides microbiota dysbiosis it is especially through the disturbance of gut permeability that a gut-brain axis dysregulation may be observed. In fact an increase gut permeability (called «leaky» gut) is associated with more bacterial constituents (LPS) or metabolites passing by the blood inflow to the brain or infiltrating the gut mucosa. The mechanisms by which psychological stress result in a «leaky» gut seems to be multiple and probably involve vagus nerve and ENS but also neuroendocrine and immune system with a direct activation of mast cells receptors with corticotropin-releasing hormone (CRF). The subsequent effect of macrophages activation via LPS/TLR interaction is upregulation of pro-inflammatory cytokines and local and/or chronic systemic low-grade inflammation.

Gut microbiota as the source of inflammation leading to psychiatric disorders

Psychological and gastro-intestinal symptoms are often associated in inflammatory bowel disorders but also in psychiatric disorders. This is particularly demonstrated in ASD given both local inflammation and systemic low-grade inflammatory marked by pro-inflammatory cytokines. In a precedent review (Dubois et al. 2018) we showed that a similar chronic mild inflammatory response seems to be involved in most of psychiatric disorders. Cytokines may cross the brain blood barrier (BBB) and activate microglial cells to express more cytokines in the brain. Cytokines may activate indoleamine 2,3-dioxygenase (IDO) transforming tryptophan into kynurenine instead of serotonin. Some bacteria in the gut are also involved in tryptophan metabolism altering tryptophan availability to 5-HT synthesis. Subsequent kynurenine metabolites may interfere with glutamatergic pathway and induce oxidative damage to limbic structures or cognitive impairment. Oxidative stress leads to a reduction of brain derived neurotrophic factor (BDNF) and an activation of nuclear factor kB (NFkB) leading to an upregulation of pro-inflammatory cytokines. These brain alterations are similar to what is observed in some microbiota studies. Particularly studies concerning short-chain fatty acids (SCFA) such as propionate (PPA) having the capacity to activate microglia and alter glutamatergic/GABAergic balance in neural circuitry and induce neuroinflammation.

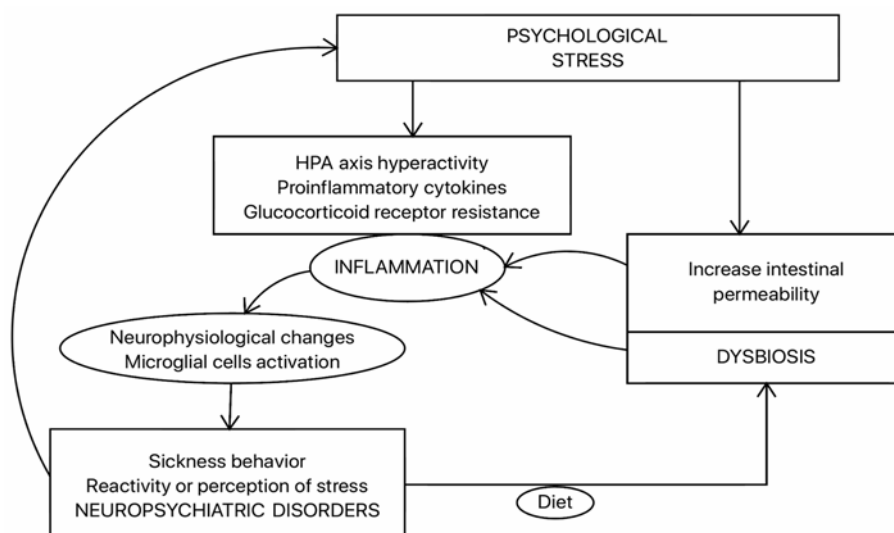


Figure 1. Hypothetical model of interactions between psychological stress, inflammation and gut microbiota

CONCLUSION

We showed that interactions between gut microbiota, psychological stress, psychiatric disorder and immunity are well documented but not fully understood. Acute stress activate HPA axis and pro-inflammatory cytokines and as hypothesized psychological stress have also an impact on gut microbiota and may lead to a deficiency of the intestinal barrier with subsequent immune system activation. Dysbiosis seems to play an important role in this immune challenge. Psychological distress may impact bacteria composition and ecosystem of gut microbiota. It seems that variations in composition is related to change in bacteria constituent or metabolites. Some species seems to have harmful and other protective effects (Figure 1).

Psychological stress and so repeated immune challenges during more vulnerable period for the brain such as perinatal period, early childhood or adolescence may lead to neurodevelopmental disorders or sickness behavior later in life. Early life inflammation may affect neurophysiology and microglial cells development and activity and psychological stress later in life lead to an exacerbated inflammatory response. Psychiatric disorders are often correlated to a chronic systemic low grade inflammation with concomitant mild immunosuppression. Sickness behavior and eventually psychiatric or neurodevelopmental disorders altering reactivity or perception of stress events and are also associated with poor lifestyle or unhealthy diet directly impacting gut microbiota.

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Thomas Dubois, Christine Reynaert, Denis Jacques, Lepiece Brice & Nicolas Zdanowicz all made substantial contributions to conception and design and or acquisition of data and/or analysis and/or interpretation of data.

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IQ OVER 130 AND PHOBIA: CORRELATION, CONSEQUENCES AND OTHER PSYCHOPATHOLOGIES

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SUMMARY

Background: Nowadays, anxiety disorders are becoming more and more important in our population. And if there is one category of people more vulnerable to this problem, it is the teenagers. In addition, more and more children and teenagers are diagnosed with an IQ greater than 130, causing all the stress and questions that it generates. In this project, we are comparing two groups of adolescents, one with an IQ over 130, the other with an IQ less than 130. We are wondering if there is any difference between these groups, in terms of phobia and other psychopathologies.

Subjects and methods: A sample of 35 teenagers, from 12 to 16 years old, separated in two groups (IQ over 130 and IQ below 130), fulfilled the following questionnaires: the School Rehabilitation Assessment Scale-Revised (SARS-R), the "Family Adaptability and Cohesiveness Evaluation Scale III" (FACES III), and the "Kiddie-SADS-lifetime" (K-SADS-PL), and a social data collection questionnaire.

Results: At the end of this study, we can retain the following relevant elements: adolescents with IQs greater than 130 are statistically more likely to be the eldest siblings (Cochran Test $F=9.159$, $p=0.010$). They do not develop more phobias, but are more shy ($t=4.375$, $p=0.036$) than the control population. These high-potential and shy teenagers have a whole list of commonalities, such as being easily irritable, being easily distracted, ect... They have fewer friends in real life ($t=2.255$, $p=0.033$), fewer virtual friends ($t=4.346$, $p=0.000$) and fewer virtual relationships ($t=2.431$, $p=0.021$). Their families are very cohesive (Test $t=0.004$). There is no significant role of the socio-professional class of parents playing in the value of the IQ of their children ($t=4.667$, $p=0.323$).

Conclusion: To conclude, being a teenager and having an IQ greater than 130 is not always a pleasure. Our results showed us that the majority of these young people consider themselves as shy, unsure of themselves and claim to have many fears. This is evidence of an increased anxiety component compared to the control sample. It seems important to insist on the need to be able and to know how to identify these young people as soon as possible, in order to propose appropriate therapeutic management.

Key words: IQ - phobia - adolescents - school - family

* * * * *

INTRODUCTION

Anxiety disorders (De Kerner 2015) are defined by the inappropriate or irrational reactions to a situation of daily life. Because of this great propensity for anxiety and phobias in the population, there are many books, articles and studies dealing with anxiety disorders in adults. But what about children and adolescents? In adolescents, we are aware of the high prevalence of anxiety disorders (Tassin et al. 2014). On the other hand, we know that about 2.3% of the school population between the ages of 6 and 16 is considered with high potential, which means, is diagnosed with an IQ over 130 (Leurquin 1996). In an increasingly stressful world, where everything goes faster and faster, it seems essential to look at anxiety disorders in these generations of future adults.

Is there a special connection between these young people with high potential, and these disorders? Is there a difference from a control group with no high potential detected?

To be more precise, we formulated these different questions:

- Are teens with IQ over 130 more likely to develop phobias compared to an adolescent control group with an IQ below 130?

- Are they more at risk of developing a school phobia, if so, are there any causal factors?
- Do they have fewer friendly relationships than the control group?
- Are there any elements of family dynamics associated with phobias in adolescents with IQ over 130?

SUBJECTS AND METHODS

This study comprises three main questionnaires: the School Rehabilitation Assessment Scale-Revised (SARS-R) (Brandibas et al. 2001), French version, the "Kiddie-SADS-lifetime" (K-SADS-PL) (Birmaher et al. 2009), and the "Family Adaptability and Cohesiveness Evaluation Scale III" (FACES III) (Joh et al. 2013), as well as a social data collection questionnaire (name, age, type of school attended, grade level, parent's job, place in siblings ...). SARS-R is a psychological assessment tool designed to assess the symptoms of school failure disorder in children and identify their reasons for avoiding school. This self-assessment questionnaire measures the frequency with which a child experiences emotions and behaviors related to school attendance. FACES III, also known as the Olson score, is a family assessment model designed to measure family cohesion (degree to which family members are separated from or connected to

their family) and family adaptability (extent to which the family system is flexible and able to change under stress). K-SADS-PL is a semi-structured diagnostic interview, providing information on current and past episodes of psychopathology in adolescents, according to the DSM-IV DSM-III-R criteria. The sample targeted by this study is a population of 15 adolescents between 12 and 16 years old, girls and boys, detected with an IQ greater than 130. We also passed these questionnaires to a control group consisting of 20 adolescents of the same age group, but these having been tested with an IQ less than 130.

The two cohorts were sought and contacted through specialized associations, as well as through social networks on the Internet, where people who have passed an IQ test and their parents meet to form discussion groups accessible to all. All are enrolled in general secondary schools and have passed a WISC IV type test (Wechsler Intelligence Scale for Children).

After exchanging emails with teenagers and their parents, the people agreeing to participate were then met individually to answer the different questionnaires. This study has been validated beforehand by an Ethics Committee from Mont-Godinne University Hospital (N°: 66/2016; NUB: B039201629159).

RESULTS

Socio-demographic data

Here are the results concerning our socio-demographic data questionnaire: there is no significant difference between the average ages of our two groups ($t=1.925$, $p=0.065$).

There is also no difference between the girls/boys distribution of our two groups ($\chi^2=1.020$, $p=0.313$). We were able to point out that adolescents with IQs greater than 130 are statistically more likely to be older siblings (Cochran test $F=9.159$, $p=0.010$), compared to adolescents with an IQ below 130. There is no significant role of the socio-professional class of parents playing in the value of the IQ of their children ($t=4.667$, $p=0.323$).

Hypothesis 1

To answer our first hypothesis, we will analyze and compare the results of the answers obtained for the questions concerning fear, from the Kiddie-SADS-lifetime questionnaire, and compare our two groups.

We observe that adolescents with IQs greater than 130 have fewer phobias and thus avoid them less (Phobias: $t=3.838$, $p=0.050$); (Avoidance of phobia: $t=4.644$, $p=0.031$).

Our hypothesis is thus invalidated, and we can answer it by affirming that adolescents with an IQ higher than 130 do not develop more phobias than those with an IQ lower than 130.

Nevertheless, arriving at the question "do you consider yourself as shy", we were able to highlight a statistically significant difference between our two groups: indeed, adolescents with IQ higher than 130 are more shy ($t=4.375$, $p=0.036$) than those with an IQ below 130. These high-potential and shy teenagers have a wide range of commonalities, such as being easily irritated, being easily distracted, being unable to relax completely, being more anxious (Table 1).

Table 1. Table regrouping Kiddie-SADS-lifetime items associated with IQ over 130 and shyness

Associated items	Value χ^2	Value p
Irritability/anger	15.00	0.000
Anhedonia	5.934	0.015
Think about death	12.381	0.000
Feeling of excitement/euphoria	6.667	0.010
Diminution of sleeping time	4.444	0.035
Ruminations/compulsive thoughts	15.00	0.000
Phobia	4.444	0.035
Impossible to totally relax	5.934	0.015
Obsessive thoughts	4.444	0.035
Attentionproblem	4.444	0.035
Easilydistracted	10.756	0.001
Have already lie	6.667	0.010
Have alreadyfought	0.000	1.000
Fear of being separated from their parents	4.444	0.035
Fear that something bad happen to their parents	5.934	0.015
Fear of social situation	6.667	0.010
Fear of strangers	8.148	0.004
Number of virtualrelationships	2.260	0.037

Hypothesis 2

For our second hypothesis, previously, we observed that our adolescents with an IQ greater than 130 were no more at risk of developing a phobia of any kind, compared to our adolescents with an IQ below 130. Since our hypothesis concerning school phobia is based on the hypothesis of phobia, and this being invalid, this hypothesis is therefore not plausible.

Hypothesis 3

For our third hypothesis, and after discovering that our teenagers with an IQ greater than 130 tended to be more shy, we will see what it is in reality. From our results, it is statistically significant that our participants with IQ greater than 130 have fewer friends in real life ($t=2.255$, $p=0.033$), fewer virtual friends ($t=4.346$, $p=0.000$) and fewer virtual relations ($t=2.431$, $p=0.021$) than those with an IQ less than 130. There is no difference between the two groups for the number of real relationships ($t=1.697$, $p=0.094$).

Hypothesis 4

For our fourth hypothesis, just as for our hypothesis on school phobia, the question we are trying to answer is closely related to our hypothesis "IQ adolescents over 130 are more at risk of developing phobias". As said before, we know this is not the case. But by analyzing our new population of shy teenagers with an IQ greater than 130, we come to question their family dynamics: is it particular? The FACES III questionnaire allows us to obtain the following results: our shy teenagers have a greater cohesion in their family of origin (Test $t=0.007$) than our non-shy teenagers. In addition, these teenagers would like this cohesion to be even stronger, as shown by our results concerning the cohesion of their future ideal family (Test $t=0.004$).

DISCUSSION

During this study, we note that these adolescents don't have a risk of developing more phobias, unless they also have the characteristic of being described as shy. Few studies exist on this subject today, so we cannot compare our results with the literature. It would be interesting in the future to dig deeper into this question, to look a little more closely at this category of people who consider themselves timid and socially inadequate, who in addition, have a tendency to develop more psychopathologies than others. Our sample is not statistically more at risk of developing a school phobia, although the literature seems to prove the opposite. Although in common thinking, high intellectual potential is associated with academic success, one third of children with IQ over 130 attending school from 6 to 16 years old are in great difficulty (Tordjman 2012). This difficulty can be explained by the boredom they experience during school hours, the rejection of other students, not accepting this different comrade. This can lead to isolation, leading to rejection of school, academic failure and sometimes even depression. In addition, the fact that a large part of those teenagers is shy, and that this shyness is associated with other symptomatic traits such as fear of a social situation, having few friends, ... All this may be in favor of a development of a school refusal, the school being a reflection of social learning, source of much of the anxiety of our teenagers with high potential. Although these observations are repeated in many articles of the literature, we could not prove this hypothesis with our study. This can be explained by a recruitment bias in our population or in the way we interview them. These teenagers generally have fewer friends than the control population, whether in the real world or in the virtual world, regardless of whether they say they are shy or not. High-potential children with psychopathological symptoms generally find it more difficult to adapt socially (Liratni & Pry 2011). They are often shy and think a lot before acting. This prevents them from operating as they would have liked for fear of the prejudice

or the gaze of others, which they have often experienced in a negative way. So that's a problem for integration with peers. The children or adolescents are blocked by their way of proceeding, untransmissible to their comrades for the moment: their way of reasoning, to see the world, to express themselves, often exposes them to the mockery of their classmates (Adda 2016). There is no real family dynamic conducive to phobias in our population. As for our shy adolescents, we see that there is a real family cohesion, which could turn into a vicious circle: the shy teenager takes refuge in his family, known and protective ground, which could ultimately prevent them from opening up and turning to the outside, increasing all the more their fears and shyness. Some studies show the importance of a good family arrangement: the greater the cohesion and the coherence between the parents and the entourage of the child or teenager, the greater the chances of integration and success of the child (Grubar et al. 1997). However, parents should be careful not to overdo it, at the risk that this cohesion will become a burden for the teenager. In extreme cases, some parents do too much and over-value their child who becomes either the restorative object of their personal failures or the object of their pride. Some parents tend to over-stimulate and overprotect the child at the expense of emotional development.

CONCLUSION

To conclude, being a teenager and having an IQ greater than 130 is not always a pleasure. Where some develop a certain advantage, others suffer. Our results showed us that the majority of these young people consider themselves as shy, unsure of themselves and claim to have many fears. This is evidence of an increased anxiety component compared to the control population. It seems important to insist on the need to be able and to know how to identify these young people as soon as possible, in order to propose appropriate therapeutic management.

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Contribution of individual authors:

Anne-Gaëlle Lacour & Nicolas Zdanowicz both made a substantial contribution to the design of the study, and/or data acquisition, and/or the data analysis and its interpretation.

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CANNABINOID HYPEREMESIS SYNDROME: A REVIEW OF THE LITERATURE

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SUMMARY

Background: Cannabinoid Hyperemesis Syndrome (CHS) is characterized by cyclic vomiting and compulsive need to take hot showers in the context of chronic cannabis use. Physicians' lack of knowledge of CHS often results in a diagnostic delay of several years. The purpose of this article is to describe CHS in order to enable physicians, and more particularly psychiatrists, to diagnose it as quickly as possible and thus avoid unnecessary additional invasive examinations.

Subjects and methods: Bibliographic search for scientific articles published between 2004 and 2019 in the Cochrane, Medline, PubMed, and Psycinfo databases. Key words used were "hyperemesis", "cannabis", "cannabinoid".

Results: CHS is associated with chronic cannabis use and typically manifests as incoercible cyclical vomiting, diffuse abdominal pain, and relief of symptoms by taking hot showers. Patients suffering from CHS generally visit emergency departments very regularly and undergo numerous additional examinations, both invasive and unnecessary. Since no organic cause can explain these symptoms, these patients are referred to the psychiatry department. The only curative treatment is the complete cessation of cannabis use.

Conclusion: CHS is an under-diagnosed pathology because it is little known to physicians. This syndrome has unique clinical characteristics. Early recognition of CHS avoids repeated visits to the emergency room and unnecessary follow-up examinations.

Key words: hyperemesis – cannabis - cannabinoid

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INTRODUCTION

Cannabis, extracted from the plant *Cannabis Sativa*, is the most widely used illicit drug in the world (Khattar & Routsolias 2018, Lu & Agito 2015). The main active substance in cannabis, responsible for psychotropic effects, is delta9-tetra-hydro-cannabinol (THC), which binds to the cannabinoid receptors CB1 and CB2 (Lu & Agito 2015). Numerous therapeutic properties of cannabis have been proven: analgesic, antiemetic, orexigenic, etc. This has led to its use in medicine in some indications, for example in nausea and vomiting induced by chemotherapy or in cachexia associated with AIDS (Khattar & Routsolias 2018, Lu & Agito 2015, Sun & Zimmerman 2013). However, many harmful effects are related to the chronic use of cannabis including increased risk of developing an anxiety and/or depression disorder, impaired cognitive performance, and amotivational syndrome. Chronic cannabis use was also correlated with the onset of a severe psychiatric disorder such as schizophrenia, particularly in people with pre-existing genetic susceptibility (Volkow et al. 2014). Another little-known adverse effect, often ignored by physicians, is the paradoxical proemetic effect that can occur in some chronic users. CHS was first described in Australia in 2004 by Allen et al. They reported a series of cases of 19 patients, chronic cannabis users, suffering from cyclic vomiting. These patients displayed a compulsive need to take hot showers to temporarily relieve their symptoms. It was also observed that the complete cessation of cannabis use led to the disappearance of symptoms, and on

resumption of consumption, these same symptoms reappeared. Since 2004, many cases of CHS worldwide have been described in the medical literature.

CHS typically occurs as recurrent episodes of nausea, vomiting, and abdominal pain. The cyclical and severe nature of these symptoms, as well as the lack of awareness of this syndrome by physicians, lead in these patients to repeated visits to emergency rooms, with numerous complementary invasive, costly, and unnecessary examinations. Without organic substrate, these patients may be referred to the psychiatry department for psychogenic vomiting, bulimia, or cyclic vomiting syndrome (Wallace et al. 2011). It is therefore important, in reference to a typical clinical picture, to evoke CHS and to make the link with cannabis use. In addition, with the increasing use of cannabis (recreational or medical) around the world, we may see an increase in cases of CHS in emergency rooms. The aim of this review is to inform physicians, and in particular psychiatrists, about this syndrome, which is little known and therefore under-diagnosed, in order to avoid further invasive examinations and to be able to properly care for patients as early as possible.

SUBJECTS AND METHODS

Literature review based on a bibliographic search of scientific articles published between 2004 and 2019 in the Cochrane, Medline, PubMed and Psycinfo databases. Key words used were "hyperemesis", "cannabis", "cannabinoid". All relevant publications (English and French) were selected.

RESULTS

Clinical description

CHS is a cyclical condition, occurring every week or month, characterised by asymptomatic intervals. Seventy percent of patients report more than seven episodes per year (Simonetto et al. 2012). This syndrome can be divided into three phases: prodromal, hyperemetic, and recovery (Allen et al. 2004, Lu & Agito 2015, Simonetto et al. 2012, Sun & Zimmerman 2013).

Prodromal phase

This phase precedes the acute phase of hyperemesis from several months to several years. It is characterized by morning sickness, abdominal discomfort, and fear of vomiting. Unlike eating disorders (anorexia, bulimia), eating habits remain normal with little or no weight loss. There is no compulsive need to take hot showers at this stage and patients tend to continue or even increase their cannabis use, hoping to alleviate their symptoms with the known antiemetic effect of the substance (Sun & Zimmerman 2013, Ukaigwe et al. 2014).

Hyperemetic phase

This phase usually lasts 24 to 48 hours. It is characterized by severe incoercible nausea and vomiting (up to five times per hour) (Galli et al. 2011). These symptoms are resistant to conventional antiemetic treatments. In the majority of cases, mild, diffuse abdominal pain is present. During this phase, the compulsive need to take hot showers to temporarily relieve the symptoms is observed. This relief is temperature-dependent: the hotter the water, the more effective it is and patients sometimes burn themselves (Cuppens et al. 2016, Khattar & Routsolias 2018, Lu & Agito 2015, Sun & Zimmerman 2013). Patients have decreased appetite and weight loss is seen in 83 percent of patients (Simonetto et al. 2012). During this hyperemesis phase, patients often visit the emergency department where they recorded as slightly dehydrated, but patients generally remain hemodynamically stable (Galli et al. 2011). They undergo numerous examinations (imageries, endoscopies, etc.) usually revealing negative cases. However, esogastroduodenoscopy reveals gastritis and esophagitis (Chen & McCarron 2013).

Recovery phase

This phase begins when cannabis use is stopped. The symptoms resolve within a few days. The patient regains normal eating habits and the compulsive need to take hot showers disappears. Symptoms recur when the patient resumes consumption.

Diagnosis

A patient presenting to the emergency department with severe nausea and vomiting should first be subjected to a thorough history and clinical examination to rule out any significant medical cause, such as pancreatitis, intestinal obstruction/perforation, or pregnancy

(Chen & McCarron 2013). Basic biology (ionogram, hemogram, liver function, amylase, lipase, beta HCG), urinary toxicology, and standard abdominal radiography are recommended as the initial examination (Chen & McCarron 2013).

In order to facilitate the diagnosis of CHS, Simonetto et al. developed a series of clinical criteria in 2012 after carrying out a study (the largest at present) on a series of cases of 98 patients, spanning a period of five years. First, the mandatory criterion for diagnosis of CHS is prolonged use of cannabis. The duration of cannabis use before the onset of symptoms varies widely, but most patients develop CHS within one to five years of initiating cannabis use (Simonetto et al. 2012). Next, Simonetto et al. proposed a series of major criteria:

- severe cyclical nausea and vomiting;
- resolution of symptoms upon stopping cannabis use;
- symptomatic relief by taking hot showers;
- abdominal, epigastric, or periumbilical pain;
- weekly cannabis use.

Finally, minor criteria:

- age less than 50 years;
- weight loss >5 kg;
- morning predominance of symptoms;
- normal intestinal transit;
- negative laboratory, radiological, and endoscopic tests.

Differential diagnoses

The main diagnoses for patients presenting with cyclic nausea and vomiting are CHS, migraine headaches, hyperemesis gravidarum, Addison's disease, bulimia, psychogenic vomiting, and cyclic vomiting syndrome (CVS) (Bajgoric et al. 2015, Lu & Agito 2015, Wallace et al. 2011). These last two diagnoses are the most confusing with CHS; only a precise anamnesis will distinguish them. CVS is typically characterized by psychological stressors and a family history of migraine, with no specific link to substance use (Bajgoric et al. 2015, Chen & McCarron 2013, Wallace et al. 2011). Psychogenic vomiting is generally associated with a psychiatric diagnosis, such as an anxiety disorder, a depressive episode, or a factitious disorder (Chen & McCarron 2013, Lu & Agito 2015). For CHS, pathogenic elements guiding the diagnosis are compulsive taking of hot showers and prolonged cannabis use (Bajgoric et al. 2015).

Pathophysiological elements

Cannabis contains more than 500 different chemical components, about 100 of which have a cannabinoid structure (Lafaye et al. 2017). The three main cannabinoids found in cannabis are delta9-tetra-hydro-cannabinol (THC), cannabidiol (CBD), and cannabigerol (CBG). THC is the main active substance responsible for the

psychotropic effects of cannabis. Cannabinoids are extremely lipophilic substances with a very long half-life. They easily cross the blood-brain barrier and accumulate in body fat (Lu & Agito 2015).

Cannabis is an ancestral plant that has been used for hundreds of years, so it is surprising that CHS has only been identified since 2004. Increasing THC concentrations in current cannabis plants may explain this paradox (Schreck et al. 2018).

Two cannabinoid receptors have been identified: CB1 and CB2 (Lu & Agito 2015). The CB1 receptor is found primarily in the central nervous system and the enteric nervous system (Simonetto et al. 2012). Our knowledge of the CB2 receptor is more limited. It is primarily present in immune cells and its activation plays a role in the inhibition of intestinal inflammation, visceral pain, and intestinal motility (Galli et al. 2011).

The exact pathophysiological mechanism of CHS remains unknown. Various hypotheses have been proposed to explain the development of this syndrome, the main ones of which are described here:

- Activation of central CB1 receptors is believed to be responsible for many of the known clinical effects of cannabis: altered cognitive function (memory, attention), euphoria, relaxation, appetite stimulation, analgesia, and an antiemetic effect (Lapoint et al. 2018, Lu & Agito 2015). In particular, the antiemetic action of cannabis could be explained by stimulation of CB1 receptors in the vomiting centre in the brain stem (Sun & Zimmerman 2013). However, over-stimulation of peripheral CB1 receptors (in the enteric nervous system) could create a potent proemetic effect, outweighing the antiemetic effect mediated by the central nervous system (Schreck et al. 2018).
- Prolonged use of cannabis leads to the down regulation of CB1 receptors, causing a proemetic effect (Lu & Agito 2015).
- Another hypothesis suggested is that genetic variation in some individuals in cannabinoid-metabolizing liver enzymes causes toxic accumulation of metabolites (Lu & Agito 2015, Schreck et al. 2018, Sun & Zimmerman 2013).
- Activation of central CB1 receptors could also disrupt the hypothalamic-pituitary axis and play a role in the development of CHS (Simonetto et al. 2012, Sun & Zimmerman 2013). Prolonged cannabis use could break the balance of the satiety, thirst, and digestion systems, and thermoregulation of the hypothalamus (Sun & Zimmerman 2013).

Two main hypotheses have been formulated to explain the relieve of symptoms by taking hot showers:

- Cannabinoids are believed to act on central CB1 receptors located in the preoptic area near the thermoregulatory centre located in the hypothalamus and cause hypothermia. Hot showers would temporarily restore this thermoregulatory dysfunction (Patterson et al. 2010, Simonetto et al. 2012).

- Symptoms of CHS could be explained by cannabinoid-induced vasodilation of blood vessels in the digestive tract. For example, hot showers, causing skin vasodilation, could divert blood flow from the digestive tract to the periphery, thereby relieving symptoms (Patterson et al. 2010).

Management of the acute phase of hyperemesis

Management of the acute phase of hyperemesis relies essentially on supportive measures: intravenous hydration, electrolyte disorders correction (Bajgoric et al. 2015, Khattar & Routsolias 2018). Administration of traditional antiemetics to relieve the symptoms of CHS is generally ineffective (Khattar & Routsolias 2018), unlike CVS (Desjardins & Stheneur 2016).

In the medical literature, various alternative treatments have been tried with some success. Several case reports describe the effectiveness of the following medications:

- Topical capsaicin (Dezieck et al. 2017, Graham et al. 2017);
- Haloperidol (Inayat et al. 2017, Jones & Abernathy 2016, Witsil & Mycyk 2017);
- Propranolol (Richards & Dutczak 2017);
- Lorazepam (Khattar & Routsolias 2018). Prescribing benzodiazepines, however, must be used on a reduced basis given the potential for abuse in a population already known to be substance-dependent (Bajgoric et al. 2015, Sun & Zimmerman 2013).

Opioids are sometimes prescribed to relieve CHS-associated abdominal pain, but are not effective and should be used with caution as they may increase symptoms (Bajgoric et al. 2015, Galli et al. 2011, Khattar & Routsolias 2018). Given the frequency of acute-phase CHS-associated esophagitis and gastritis, the use of proton pump inhibitors is recommended until vomiting is stopped (Galli et al. 2011, Rehman et al. 2019).

The most effective symptomatic treatment during the hyperemesis phase is taking hot showers (Desjardins & Stheneur 2016).

Recidivism prevention

Currently, the only effective treatment to prevent recidivism is the complete cessation of cannabis use. CHS symptoms usually resolve spontaneously in the days following cessation of the substance and these same symptoms reappear when consumption resumes. It seems essential to educate the patient about this risk and to reassure him / her about the complete disappearance of the symptoms after stopping cannabis (Galli et al. 2011, Lapoint et al. 2018). Various studies have shown the benefit of cognitive-behavioural therapies and motivational interviewing to help the patient with the cannabis withdrawal process (Cuppens et al. 2016, Galli et al. 2011).

DISCUSSION

CHS is an under-recognized and under-diagnosed medical condition, related to long-term cannabis use. The clinical diagnostic criteria proposed can be useful for diagnosing CHS. The treatment during the hyperemetic phase includes prevention of dehydration, vomiting cessation and relief of abdominal pain. It's also important to educate the patient about the link between CHS symptoms and cannabis. The only curative treatment is the complete cessation of cannabis use. The pathophysiologic mechanism underlying CHS appears to be very complex. It is also important to note that most chronic cannabis users will not develop this syndrome. Additional studies are needed to understand the full extent of this disorder, the exact pathophysiology and to identify risk factors, the prevalence, an optimal pharmacotherapy.

CONCLUSION

CHS, whose pathophysiology is uncertain, is a recently described medical condition and, therefore, little known to physicians. This syndrome has unique clinical characteristics. It should be considered in patients with severe cyclic vomiting associated with chronic cannabis use. The pathognomonic sign guiding the diagnosis is the compulsive need to take hot showers. With increasing cannabis use worldwide, we can expect an increase in cases of CHS in emergency rooms. Early diagnosis reduces the costs and morbidity associated with unnecessary follow-up examinations.

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Eleonore Deceuninck & Denis Jacques jointly conceived and designed the study, and completed data acquisition, analysis and interpretation.

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PROVIDING PSYCHIATRIC HEALTHCARE TO ASYLUM SEEKERS: REFLECTIONS AND CHALLENGES

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SUMMARY

Background: According to the United Nations High Commissioner for Refugees the number of people forced to leave their home as a result of conflict, persecution, violence or human rights violations remains high with 68.5 million forcibly displaced people worldwide. Asylum seekers are vulnerable in terms of mental health but they receive very little specific psychiatric care. The purpose of this literature review is to examine current situation regarding asylum seekers' psychiatric healthcare.

Subjects and methods: This research was conducted using a keyword search on Medline, PubMed and Google Scholar.

Results: The literature on the management of the mental health of asylum seekers focuses on the issue of post-traumatic stress disorder. There is little data on other forms of mental illness in this population. The prevalence of post-traumatic stress disorder among asylum seekers is higher than in the general population and its clinical expression is varied and often complex because it involves various vulnerability factors. Guidelines for post-traumatic stress disorder recommend cognitive behavioral therapy with, in some cases, the use of pharmacotherapy. Given the specificities of the asylum seekers' population, in many cases it is not possible to set up such therapy immediately. Asylum seekers face a number of challenges in accessing mental healthcare.

Conclusion: Management of the mental health of asylum seekers requires special attention and guidelines for the general population are not directly applicable to this specific population. The literature focuses on the issue of post-traumatic stress disorder. This review was not able to analyse the state of existing care offer in Belgium for managing the mental health of asylum seekers and the care pathways they take.

Key words: asylum seekers – mental health – treatment

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INTRODUCTION

According to the United Nations High Commissioner for Refugees, in its report for the first half of 2018, the number of people who have been forced to leave their home as a result of conflict, persecution, violence or human rights violations remains high with 68.5 million forcibly displaced people worldwide, including 40 million internally displaced people, 25.4 million refugees and 3.1 million asylum seekers. European countries are seeing an increase in the number of asylum applications (UNHCR 2018). In Belgium, the Federal Migration Centre reports that 15.373 people filed an initial application for international protection in 2017 (MYRIA 2018).

Migrants' access to health care is not equal to that of the host population (Silove et al. 2017). They receive very little specific psychiatric care (Laban et al. 2007). Asylum seekers are vulnerable in terms of their mental health (Tomasini 2016).

Several studies have addressed the issue of the prevalence of mental illness among migrants and asylum seekers. There is great variability in this prevalence among the various studies in relation to methodological and clinical factors (Turrini et al. 2017). However, it is possible to show a trend in the prevalence of certain mental disorders (Fazel et al. 2005). The prevalence of mood disorders and substance use disorders is similar to

that of the host population. There are no prevalence data available about psychotic disorders for asylum seekers group. The prevalence of post-traumatic stress disorder is higher for asylum seekers (Priebe et al. 2016).

Post-traumatic stress disorder experienced by asylum seekers has a different expression, severity and evolution from that observed in the general population, with the presence of more frequent psychiatric comorbidities (Nose et al. 2017). This difference is related to the specific circumstances that asylum seekers face (Beltran et al. 2008), including the traumatic events experienced in their country before migration but also the traumatic events experienced during the migratory journey. Asylum seekers also face post migratory factors and daily stressors after arriving in the host country (Crumlish & O'Rourke 2010, Silove et al. 2017, Turrini et al. 2017). The migration itself can also be experienced as traumatic or destabilizing (Tomasini 2016).

Studies have shown that there is a correlation between the number of traumatic events in the country of origin and during the migratory journey and the development of post-traumatic stress disorder (Tomasini 2016). It has also been shown that post-migration factors play a role in the development and maintenance of post-traumatic stress disorder (Kinzie 2006, Palic & Ask 2011). Post-migration factors also influence mental health with an increase in psychiatric morbidity (Momartin et al. 2006).

Given the increasing number of asylum seekers and their potential vulnerability with regards to mental health, the purpose of this review is to look at current data from the literature on taking care of the mental health of asylum seekers.

SUBJECTS AND METHODS

This research has been conducted by using a keyword search on Medline, PubMed and Google Scholar. The keywords used were essentially: asylum seekers, mental health, depression, post-traumatic stress disorder, prevalence, treatment, psychotherapy, social intervention. A second step was to compare the results collected.

RESULTS

The literature on the management of the mental health of asylum seekers focuses on the issue of the management of post-traumatic stress disorder. There is little data about other types of mental illness in this population. Given the specificities of the asylum seeker population, the management of post-traumatic stress disorder in the general population is not completely transferable to asylum seekers and needs some adaptation (Nose et al. 2017).

The guidelines for the management of post-traumatic stress disorder among asylum seekers suggest the use of trauma-focused cognitive behavioral therapy (Turrini et al. 2017). Cognitive behavioral therapy focused on specific symptoms can be used for people who are not suitable or who are reluctant to engage in trauma-focused cognitive behavioral therapy (NICE 2018). Antidepressant treatments as Sertraline or Venlafaxine may also be considered, but not as a first-line treatment (NICE 2018, Sandahl et al. 2017, Sonne et al. 2016). Antipsychotic treatments (Risperidone in first-line) may be considered if there are disabling symptoms and behaviors and if the symptoms have not responded to other drugs or psychological treatments. Guidelines emphasize the need to include the person itself and its family members or carers in the care process. It is also important to maintain safe environments to avoid continued exposure to trauma-inducing environments (NICE 2018).

Asylum seekers face a number of challenges in accessing mental health care. It is important to be able to develop solutions to prevent these difficulties leading to inequality in the management of the mental health of asylum seekers (Priebe et al. 2016).

One of the first difficulties encountered is the language barrier, which makes it difficult to seek care and to be understood by caregivers. Communication difficulties represent a major obstacle, including in the process of psychotherapy. The use of interpreters must be proposed (Priebe et al. 2011).

Another problem is the lack of records concerning medical and psychiatric history. A careful anamnesis must be constructed (Priebe et al. 2011).

Asylum seekers are also faced with a lack of knowledge regarding the health care network of the host country (Leduc & Proulx 2004). In particular, they do not know where to ask for medical support, resulting in more frequent use of emergency departments. Caregivers themselves have a lack of knowledge of the healthcare network and the specificities of caring for asylum seekers. Health professionals who are working with asylum seekers must be able to inform asylum seekers of the availability of care and the procedures for using it. This implies that professionals must themselves be trained in this subject (Priebe et al. 2016).

Cultural differences in understanding and beliefs about mental health and its treatment are also a challenge that needs to be addressed. Professionals should be aware of these differences and must be attentive to this reality. They must be trained specifically in caring for asylum seekers' health (Priebe et al. 2011).

It is also important to take into consideration that asylum seekers do not have stable administrative status (Momartin et al. 2006). In addition, they often face precarious living conditions that force them to prioritize their basic needs rather than mental health care (Silove et al. 2017). The instability of housing and frequent moves do not allow continuity of care in mental health. Finally, it must be remembered that asylum seekers face an asylum procedure. Mental healthcare services that treat asylum seekers need to have some flexibility in terms of organization (Tomasini 2016). Good coordination between and within services is encouraged, in order to ensure continuity of care and facilitate the transition from one service to another. It is important to work with family members and any carers that the patient identifies (NICE 2018). The literature also highlights the importance of supporting the social integration of asylum seekers given the complex interactions between mental health and social insecurity (Heeren et al. 2012). The vulnerability of some asylum seekers should be taken into account in the asylum procedure (Vanoeteren & Gehrels 2009).

Another difficulty in managing the mental health of asylum seekers is the identification of psychiatric pathologies. Indeed, it is difficult to distinguish between post-traumatic stress disorder and distress reactions in people who are continually exposed to post-migration stressors (Nose et al. 2017, Silove et al. 2017). In addition, the clinical presentation of post-traumatic stress disorder is variable, with sometimes atypical presentations or presentations that highlight somatizations pointing to a physical origin which may not be referred to psychiatric care. It is essential that professionals be informed of such possibilities in order to detect and treat mental pathologies. Similarly, it is important to ensure good coordination between physical and mental care because physical care can be a gateway to mental health care (Tomasini 2016).

Finally, it should be noted that asylum seekers can sometimes feel a certain mistrust of healthcare professionals or have certain expectations that healthcare professionals cannot take into account (Priebe et al. 2016). Caregivers can also experience psychological repercussions when taking care of people in traumatic situation (Roisin 2010). The literature recommends favouring stable therapeutic relationships and organizing care in a humane and respectful environment. Multidisciplinary teamwork with time for sharing and time for group supervision is also highlighted.

DISCUSSION

The management of the mental health of asylum seekers is complex and requires some adjustments to the methods of management of the mental health of the general population.

One of the first difficulties is the identification of mental disorders, as Silove et al. point out. It is necessary to be able to distinguish temporary distress linked to environmental factors from psychiatric disease. Psychiatric illnesses have varied and sometimes atypical clinical pictures: distinguishing the different conditions would allow better orientation towards the appropriate services (Silove et al. 2017). Identifying people with a psychiatric vulnerability would also allow them to be directed to the appropriate form of care before a psychiatric disorder becomes chronic, psychiatric comorbidities appear, or auto- or hetero-aggressive behavior causes a risk to life (Heeren et al. 2012). In some cases, the first request for care is during a moment of crisis (behavioral disorder, self-harm, suicidal ideation): professionals are asked to find solutions in an emergency. So it appears to be essential to promote prevention in mental health care for asylum seekers. It is therefore necessary that front-line actors who are working with asylum seekers (social and legal workers, volunteers) and care professionals be sufficiently trained on particular aspects of the mental health of asylum seekers as well as the existing arrangements for their care. They must be able to inform asylum seekers of the availability of care and the procedures for using it. It would seem to be important to pay more attention to the points of access to asylum seekers' mental healthcare and their care pathways in order to use the current offer of care correctly and to think about the creation of new services that take into account the specific needs of this population.

Management of mental healthcare requires some creativity and flexibility on the part of the therapist. Patients rarely have immediately sufficient capacity to start trauma-focused cognitive behavioral therapy and, in addition, it is difficult to address the issue of trauma in precarious and unsafe conditions. According to Tomasini and Silove et al, psychotherapy with asylum seekers must be conceived as a combination of work

that aims to recreate a supportive social environment that reduces daily stressors and individual trauma-focused psychotherapy (Silove et al. 2017, Tomasini 2016). In addition, the psychotherapeutic work should make a space for events in the news and be done with caution when the question of the trauma is approached. This psychotherapeutic work around the traumatic history needs a bond of trust to be created with the therapist in advance. There are few studies of alternatives to cognitive behavioral therapy and the studies are less methodologically rigorous (Palic & Ask 2011). More studies about psychotherapeutic work with asylum seekers are required. For the patient to be psychologically available for psychotherapy, his or her basic needs (including sleeping in safe conditions, having access to food, water, clothing and physical care) must be met.

Engaging in psychiatric follow-up with an asylum seeker often means that professionals are involved in the asylum procedure: including requests for reports to corroborate a health problem that the procedure should consider, reports to prove the requirement for continuation of health care in Belgium, reports for the granting of specific aid. Apart from these documents, there is all the support of the person in this path of asylum application. During the asylum application, asylum seekers must provide a precise chronological account of the reasons for which they are seeking asylum. This account is sometimes called into question by the authorities, which leads some people to feeling that the trauma they have experienced is not recognized. The phases of the asylum procedure and its stressful context as well as the resulting waiting period can adversely affect some asylum seekers. The temporality of the procedure that imposes a detailed life story where the psychotherapy will accompany the person to a process of reconstruction of this story is also an element that must be taken into consideration during psychotherapeutic work (Vanoeteren & Gehrels 2009).

Taking care of the mental health of asylum seekers requires particular attention to networking. Networking with providers of physical care is important to avoid unnecessary additional medical examinations but also not to label as "psychiatric" a physical pathology. Good coordination between the different services ensures continuity of care. This coordination should extend to the various health services that asylum seekers use, but some information can also be extended to the social services, legal services or migrant aid associations they are involved with. Obviously, they must have respect for medical confidentiality. Networking must be done with attention to specificities such as language barriers, cultural differences or belief systems. This kind of working coordination must allow a mesh to be knit around the patient, and this in a climate of welcome and kindness.

It is important to emphasize the importance of multidisciplinary teamwork for this type of care. Indeed, as caregivers we are confronted with the unbearable nature of some life stories, precarious social circumstances and the difficulty of being able to create a link in the therapeutic relationship, as the therapist may be considered to be a source of insecurity by the patient. All of this sometimes leads to feelings of discouragement and helplessness and time for supervision and sharing within the team is essential.

CONCLUSION

The literature on the management of the mental health of asylum seekers has mainly focused on the issue of the management of post-traumatic stress disorder. There is little data about other mental conditions. The prevalence of post-traumatic stress disorder among asylum seekers is higher than in the general population and clinical expression is varied and often complex because it involves multiple vulnerability factors. The management of the mental health of asylum seekers requires special attention and guidelines for the general population are not directly applicable to this specific population.

Post-traumatic stress disorder guidelines recommend cognitive behavioral therapy with, in some cases, the use of pharmacotherapy. Nevertheless, in many cases it is not possible to set up trauma-focused cognitive behavioral therapy immediately and mental health-care follow-up is often a combination of social support to reduce daily stressors and provide basic needs associated with therapeutic work, taking into account current events while putting in place progressive and careful work on the trauma.

This literature review has highlighted the importance of training those professionals working with asylum seekers on the mental health of this population and the specificities of its care. It is particularly important to distinguish people with a psychiatric pathology from those with psychosocial distress, in order to provide them with adequate care and to prevent possible complications related to mental disorders. If psychiatric care is required, it must be realized through networking and within a multidisciplinary team. The literature also stresses the importance of supporting the social integration of asylum seekers given the complex interactions between mental health and social insecurity.

The purpose of this literature review was not to analyse existing care offer in Belgium for managing the mental health of asylum seekers and the care pathways they take. However, such work would permit to have a better picture of the existing healthcare offer in Belgium, ensure better coordination between the available services, avoid saturating certain existing care services thanks to better targeting and consider the creation of new care options.

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Contribution of individual authors:

Derlet Ophélie & Deschietere Gérald both made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data.

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TEENAGE PREGNANCY IN BELGIUM: PROTECTIVE FACTORS IN A MIGRANT POPULATION

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SUMMARY

Background: Teenage pregnancies occur frequently in developing countries and are associated with social issues, including poverty, lower levels of health and educational attainment. Although frequent in European countries in the 20th century today, teenage pregnancies account for only 4% of first children. These pregnancies are usually unplanned and they are considered a vulnerability factor during the pregnancy and the postnatal period, both for the mother and the child. The purpose of our study was to evaluate the evolution of mothers and children of teenage pregnancies, several years after childbirth and to identify factors which may protect or increase the patient's vulnerability.

Subjects and methods: We conducted a retrospective search in our patient database in order to identify all teenage pregnancies between 2010-2014 at CHU Brugmann Hospital. Outcome data were obtained from the medical files. Mothers were contacted by phone and asked to complete our questionnaire which focused on maternal and paediatric care; and infant and child development after hospitalization.

Results: Out of the 342 patients identified, 84 patients were contactable and only 72 patients completed the full questionnaire. With only 4 patients originating from Belgium, our population was largely immigrant. Despite this, obstetrical, maternal and paediatric outcomes were remarkably favorable when compared to other published studies.

Conclusion: Our study suggests that some migrant teenage mothers may have a dual advantage in terms of the wealth of a developed country in which have settled and the low social stigma related to their country of origin. More research needs to be done to further investigate this hypothesis.

Key words: teenage pregnancy - adolescent pregnancy - vulnerability

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INTRODUCTION

Pregnancy can occur any time after puberty, usually at around the ages of 12 or 13. Teenage pregnancy, also known as adolescent pregnancy, is defined as any pregnancy under the age of 20.

Teenage pregnancies in developing countries are associated with social issues, including poverty, lower levels of health and educational attainment. 13 million births (10% of all births worldwide) each year are to women under the age of 20, and more than 90% of these births occur in developing countries. Overall, a third of women from developing countries gave birth before the age of 20 - ranging from 8% in East Asia to 55% in West Africa (Major 2004).

On average, women in the European Union (EU) are 29 years old when they became mothers for the first time. Teenage pregnancy was not uncommon in European countries in the 20th century. Among Norwegian women born in the early 1950s, nearly a quarter became teenage mothers by the early 1970s (Lappegård 2000). Today, teenage pregnancies in the EU are usually unintended and account for 4% or 93 000 births of first children. The highest proportion of births of first children to teenage mothers are recorded in Romania (with 12.3% of total births of first children in 2015) and Bulgaria (11.9%). 47% of women in the European Union (EU)

who gave birth to their first child in 2015 were in their 20s, while 45% of first-time mothers were in their 30s. Around 87 000 (4% of first-time births) were to women over the age of 40 (Eurostat 2017).

Adolescence is a vulnerability factor during pregnancy and the postnatal period, both for the mother and the child (Fernandes de Azevedo et al. 2015, Maravilla et al. 2017). For girls aged 15–19, risks are more associated with socioeconomic factors (McCarthy et al. 2014). There are additional concerns for those under the age of 15, as they are less likely to be physically mature enough to support a healthy pregnancy or to give birth (Makinson 1985).

The purpose of our study was to evaluate mother and child's evolution following teenage pregnancy, several years after childbirth. Our primary goal was to improve the screening for vulnerability factors patients during teenage pregnancy. While recognizing that a patient's young age is a factor of vulnerability itself, other factors may either be protective or in some cases, increase the patient's vulnerability.

SUBJECTS AND METHODS

A retrospective search in our database was conducted for patients who delivered between 2010-2014 at CHU Brugmann, a level 3 maternity hospital in Brussels. All patients during the period who gave birth under the

age of 20 were included and their contact details and pregnancy outcome data was collected. Stillbirths, termination of pregnancy and early neonatal mortality were all excluded as the objective was to evaluate the child's development in relation to maternal follow-up.

Data was obtained from the medical files and a questionnaire was created based on literature search. Patients were contacted by phone to conduct our questionnaire concerning the maternal and paediatric care received and also development following discharge home. The questionnaire was conducted over the telephone by two of the authors, in French, Dutch or English according to language preferences of the patient. The purpose of the questionnaire was explained and all patients had the option to refuse. Informed consent was obtained orally from each patient prior to conducting the questionnaire. For statistical reasons and in accordance with the available prospective research, only the first pregnancy for each patient was taken into account in the statistical analyses.

Statistical analyses were performed using SPSS. Linear regression analyses were carried out to determine relationships between the risk factors in a teenage pregnancy. Multivariate analyses were used to study confounders. The chi-squared test was used to determine whether significant differences could be found between expected and observed frequencies in one or more categories.

RESULTS

368 teenage pregnancies were registered from 2010-2014, comprising 351 patients. 9 patients (2.56%, N=351) were excluded because of perinatal mortality. Out of 342 patients, 84 patients (24.56%, N=342) were contactable. 12 patients (14.29%, N=84) refused to participate in the study. The main reason for refusal (8 patients, 75.00%) was a language barrier. 72 patients (21.05%, N=342) completed the full questionnaire.

Maternal demographics and outcomes

Teenage mothers were between 14 and 19 years old at time of delivery. With only 4 out of 72 Belgian patients, our population comprised mostly immigrants. 45.8% of them were Caucasian, 29.2% from North-Africa or West-Asia and 25.0% from Sub-Saharan Africa. 50% of the 72 patient who replied to the questionnaires were the highest proportions in those 3 categories, respectively from Romania (n=15), Morocco (n=12) and Guinea (n=8) (Table 1).

62 patients (86.1%) were primiparous. 52 pregnancies (72.2%) were planned, for 20 patients (27.8%), the pregnancy was unexpected. Unexpected/unplanned pregnancy was significantly associated to the absence of a father during and after pregnancy and suboptimal or no prenatal care. The father was present during the pregnancy in 83.3% of the cases. At the time of our study, 19 mothers were no longer in a couple with the father (26.4%). In 31.6% of the cases the pregnancy was one of the reasons for the break-up. We report 8 single mothers (15.3%).

Table 1. Country of origin

Albania	3
Belgium	4
Bulgaria	5
Cameroun	1
Congo	5
Croatia	1
France	1
Guinea	8
Ivory cost	1
Jordan	1
Lebanon	1
Macedonia	1
Morocco	13
Nigeria	1
Pakistan	1
Portugal	1
Rumania	15
Rwanda	1
Togo	1
Turkey	5
Ukraine	1
TOTAL	72

22.2% of the mothers had a postnatal follow-up at ONE (Office de la naissance et de l'enfance) and 13.9% consulted a social worker. Only 6.9% of the mothers consulted a psychotherapist in the post-natal period. 52 mothers (72.2%) reported any mother-oriented support in the post-natal period. An unexpected pregnancy was a risk factor for suboptimal antenatal care ($p=0.019$) but did not seem to influence post-delivery maternal or paediatric follow-up ($p=0.364$; $p=0.065$). Presence of the father had no influence on the quality of the antenatal care ($p=0.473$).

19 patients (26.4%) refused postpartum contraception. Reasons for refusal are summarized in table 2: pregnancy planning, non-compliance, intolerance or other non-specified reasons. Another 33 patients stopped contraception since; two thirds (66.7%) of them as part of pregnancy planning and another 8 patients (24.2%) for non-compliance (Table 2). The patient's decision to start contraception was only influenced by the nationality of the patient ($p=0.024$). 59 of the patients (81.9%) had at least one other pregnancy.

Since completion of their pregnancy, 18 mothers (25%) obtained a degree in secondary or higher education. However, another 11 (15.3%) could not successfully complete their educational program. At the time of our study, 26 mothers (36.1%) were employed and 6 (8.3%) were in higher education. Another 33 patients (45.8%) were neither actively employed nor in an educational program.

Obstetrical outcomes

Preterm delivery was reported for 7 pregnancies (9.7%). 5 neonates (6.9%) had a low birth weight (LBW) of whom 1 had an extremely low birth weight (ELBW). Four out of five patients (80.6%) delivered vaginally, 13 patients (18.1%) had a caesarean section.

Table 2. Reasons for contraception refusal or stop considering time after delivery

	Early postpartum refusal (N=19)		Stop in follow-up period (N=33)	
	N	%	N	%
Pregnancy wish	8	42.1	22	66.7
Non-compliance	2	10.5	8	24.2
Intolerance			2	6.1
Refusal	5	26.3	1	3.0
Unknown	4	21.1		

Table 3. Comparison of unplanned and planned pregnancies

	Planned pregnancies(N=52)		Unplanned pregnancies (N=20)		p-value
	N	%	N	%	
Age					0.471
Ethnicity*					0.065
Albania	1	1.9	1	5.0	
Belgium	3	5.8	1	5.0	
Bulgaria	4	7.7	1	5.0	
Congo	1	1.9	4	20.0	
Guinea	3	5.8	4	20.0	
Morocco	10	19.2	2	10.0	
Romania	11	21.2	1	5.0	
Turkey	1	1.9	1	5.0	
Optimal prenatal care	35	67.3	14	70.0	0.021
Paternal presence					
during pregnancy	35	67.3	12	60.0	< 0.001
after pregnancy	29	55.8	9	45.0	0.003
Maternal follow-up					
ONE	5	9.6	6	30.0	0.191
social assistant	3	5.8	5	25.0	0.330
psychotherapist	2	3.8	2	10.0	0.647
Maternal occupancy					
in education	3	5.8	3	15.0	0.459
education achieved	6	11.5	10	50.0	0.011
education drop-out	6	11.5	3	15.0	0.955
employed	18	34.6	9	45.0	0.931
employment stopped	1	1.9	3	15.0	0.081
Child's residence					
with mother	51	98.1	19	95.0	0.378
with family	1	1.9	1	5.0	0.478
Pediatric follow-up					
ONE	34	65.4	19	95.0	0.964
medical	23	44.2	13	65.0	0.594
SAJ/SPJ	1	1.9	3	15.0	0.060
Contraception	25	48.1	15	75.0	0.959
New pregnancy	33	63.5	15	75.0	0.071

* When the overall prevalence for a country is 1, the country of origin was excluded from the table

Paediatric outcomes

68 of the children (94.4%) lived with their mother and the remaining four others (5.6%) lived with other family members. However, all children were contact with their mothers on a regular basis. 66 children (91.7%) benefited from an ONE follow-up. 65.3% of the children visited a paediatrician or a family doctor on a regular basis. The correlation between the presence of the father after delivery and the medical follow-up of the child nearly reached significance ($p=0.065$) whereas the antenatal presence of the father was not significant

($p=0.786$). Furthermore, there was no relation between the presence of the father and the child's follow-up by ONE. All children were in school at the time of the study. Two children were not in regular education due to autistic spectrum disorders.

Unplanned pregnancies

We compared unplanned pregnancies with planned pregnancies (Table 3). As previously mentioned, planned pregnancies benefit more often from optimal prenatal care ($p=0.021$) and presence of the father during and

after the pregnancy ($p \leq 0.001$; $p = 0.003$). Significantly more mothers completed their education successfully ($p = 0.011$). However, we did not observe any difference in unsuccessfully terminated studies and employment ($p = 0.955$; $p = 0.931$).

When evaluating postpartum paediatric and maternal care, no difference were found between both groups for medical or psychosocial care. After an unintended pregnancy, more children have been in contact with SAJ (services for help for youngsters) and with SPJ (service for legal protection) but the difference was not significant ($p = 0.060$).

There were no differences in terms of contraception use ($p = 0.959$) after an unintended pregnancy. We found that ethnicity nearly reached significance ($p = 0.065$).

DISCUSSION

Teenage pregnancy is often mentioned in literature as a risk factor for obstetrical complications, namely prematurity, low birth weight (LBW) and extremely low birth weight (ELBW) (Fernandes de Azevedo et al. 2015). In our teenage sample these obstetric risks are similar to those reported for an average population (OECD 2018, World Health Organization 2018, Purisch & Gyamfi-Bannerman 2017). In line with the published literature, our study shows lower rates of caesarean section amongst teenage pregnancies (Maravilla et al. 2017) although the reasons for this could not be elucidated.

Our study shows remarkable differences in terms of maternal and paediatric outcomes in comparison with other published series. Approximately 80% of teenage pregnancies are unintended, whereas in our population this figure was only 27.8% (Leftwich & Ortega Alves 2017).

Pregnancy and giving birth significantly increases the chances that teenage mothers will become high school dropouts and as many as half have to go on welfare. Our sample shows a high rate of completed secondary-level education, employment and higher education.

In the UK it has been reported that about half of all teenagers with children are single parents, with another 40% cohabitating as a couple and only 10% married (UK Census 2001). According to US reports, Teenage fathers are frequently in a romantic relationship at the time of birth, but many do not stay with the mother and this often disrupts their relationship with the child. Being a single mother is a risk factor for poverty, mental health issues and may also reduce educational opportunities (Goossens et al. 2015). In Belgium, about one out of four mothers are solely responsible for the education of her children (Struffolino & Mortelmans 2017). Our sample shows only 15.3% of single mothers and only 26.4% of the mothers are not with the father. Paternal involvement has certain benefits for the child such as cognitive development, health, education and the development of

peer relationships. In our sample, children growing up in the absence of their father have less medical follow-up but this finding was not significant ($p = 0.065$). In our population, an unintended pregnancy was a risk factor for suboptimal prenatal care as well as the absence of the father during and after pregnancy. However, when corrected for paternal absence during pregnancy, paternal absence after pregnancy is no longer significant. Remarkably, 31.6% of relationship break-ups (before or after giving birth) were due to the pregnancy.

Nearly 1 in 4 teenage mothers will experience another pregnancy within two years of having their first. The likelihood decreases with the level of education of the young woman – or her parents – and increases if she is married (Kalmuss & Namerow 1994). In our sample, 59 of the patients (81.9%) had at least one other pregnancy.

When compared with the first pregnancy, a second one leads to higher risk of complications such as preterm births, mental health problems, and developmental problems among children (Maravilla et al. 2017). It is for these reasons that our hospital promotes the introduction and use of contraception within teenage mothers. 26% refused contraception in the immediate post-partum period, 31.6% of them due to pregnancy planning. In the long-term follow-up period, another 31% stopped contraception in order to plan for another pregnancy. An additional effort should be made to explain the importance of contraception and the risks of short delays between two pregnancies (McCarthy et al. 2014, Norton et al. 2017).

Poor academic performance in the children of teenage mothers has also been noted, (Goossens et al. 2015) with many of the children being held back a grade, scoring lower on standardized tests, and/or failing to graduate from secondary school. Our study was too small and covered too small a time period to determine the school pathways in more detail, nevertheless, all children in our study were in school (kinder garden or primary school). Two children with autistic spectrum disorders were in special needs educational systems.

When compared with published data, our population has remarkably low rates of obstetrical complications, unplanned pregnancies, lone parenting, school dropouts and birth spacing. We therefore presume that our sample is different from those populations found in the literature. One could suspect that a bias was introduced by the selection of individuals, thereby ensuring that the sample obtained was not representative of the population intended to be analyzed. Out of 342 patients, only 72 patients (21.05%) satisfactorily completed the questionnaire. Interestingly, another 12 patients were contacted but refused to participate. The main reason for refusal (8 patients) was a lack of knowledge of one of the three languages the used in our questionnaire (French, Dutch or English). Although, learning a second language is easier at a young age and immersion learning may be a more effective way, these young women didn't learn any of the Belgium official language.

ages over a period of at least 5 years. Language is an indispensable tool for social integration, education, employability and involvement in the education of their child (Bowen 2001, Jacobs et al. 2006, Dustmann & Fabbri 2003).

The language requirements of French, Dutch or English necessary to participate in our study may have created a sampling bias. Another possible example of sampling bias includes migration bias, by excluding those subjects who may have moved away from the study area. 75.44% of the population sample could not be reached due to incorrect or outdated contact details. We cannot therefore exclude the possibility that some members of the population were less likely to be included than others, resulting in a biased sample. Individuals of particular interest for our research questions (e.g. marginalized young mothers) may be under-represented in our study, and others, with certain protective factors, may have been over-represented.

In many developed countries, young age at first intercourse and lack of use of contraceptive methods (or their inconsistent and/or incorrect use; the use of a method with a high failure rate is also a problem) may be factors in teenage pregnancy. On the other hand, the teenage birth rate is very high in Bulgaria and Romania. As of 2015, Bulgaria had a birth rate of 37/1.000 women aged 15–19, and Romania of 34 (Eurostat 2017). The teenage birth rate of these two countries is even higher than that of underdeveloped countries like Burundi and Rwanda (World Bank 2017). 20.8% of our population sample was Romanian and 6.93% Bulgarian, where teenage pregnancy is both frequent and planned; and social stigma is very low. It could be assumed that this cultural trait might be preserved when moving to Belgium.

Adolescent mothers are more likely to have postpartum mental health disorders compared to an older population. Developmental disabilities and behavioral issues are increased in children born to teenage mothers. Despite our interest in maternal and child psychosocial outcomes, our retrospective study design did not permit us to investigate these issues.

The literature links several of the possible adverse outcomes of teenage pregnancies as for unintended pregnancies, such as maternal mental health disorders, relationship instability, education and employment difficulties; and mental and physical health issues for the child (Baron et al. 2018, Barton et al. 2017, Bexhell et al. 2016, Goossens et al. 2015, Leftwich & Ortega Alves 2017, Maravilla et al. 2017). Furthermore, unplanned pregnancies are at a higher risk for a late uptake of prenatal care (Barton et al. 2017, Bexhell et al. 2016). Our data confirms a lack of prenatal care for unplanned pregnancies. The literature presumes that this is due to a later acknowledgement of the pregnancy (Baron et al. 2018). The paternal absence amongst unintended teen mothers could represent the relation instability but does not indicate the support of a father's presence (Barton et al. 2017). Surprisingly, more teenage mothers success-

fully finish their education. However, there is no difference in school drop-outs nor employment. School drop-outs are usually quite specific for young populations and of special interest to various human rights organizations. The postnatal maternal and paediatric care does not differ between unplanned and planned pregnancies. However, as stated before, this does not reveal the presence of maternal and paediatric (mental) health disorders. Despite the fact that the utility of SAJ/SPJ is non-significant overall, they were far more involved when the pregnancy was unplanned. We hypothesise that this could become significant when studied in a larger population and as such, this may indicate an important psychosocial vulnerability for the child (Baron et al. 2018, Bexhell et al. 2016).

Many studies focus on the prevention of unintended pregnancies, but research is lacking in describing several minority groups, such as teenage mothers (Barton et al. 2017). Within the literature, as well as within our own population, we found several similarities between teenage pregnancies and unplanned pregnancies but also some contrasts. Noting that 80% of teenage pregnancies is unplanned (Leftwich & Ortega Alves 2017), we would recommend investigating the cross-links between both and the related pregnancy, maternal and paediatric outcomes.

Inherent to a retrospective study is recall bias. Studies have shown that mothers remember rather well, the enrollment of their pregnancies and the early life of their children. Nonetheless, answers may show social acceptance rather than reality. Finally, contacting patients by phone is easier and less time-consuming for researchers and patients than interviews. However, the disadvantage is the lack of building of trust, as such personal and in-depth questions are more easily perceived as intrusive.

CONCLUSIONS

Pregnant teenagers face many of the same pregnancy related issues as other women, however there are some additional socioeconomic concerns. Most continental Western European countries have very low teenage birth rates. Teenage pregnancy in developed countries, such as Belgium, is usually unintended and carries a social stigma.

In contrast, teenage pregnancy in less developed countries is more frequent, often occurs within marriage and most are planned. However, in these poorer societies, early pregnancy may combine poverty with malnutrition and poor health care, increasing the risk of medical complications.

Our study suggests that migrant teenage mothers have the advantage of both: the wealth of a developed country and the low social stigma related to the country of origin.

However, more research needs to be done to further investigate this hypothesis.

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Contribution of individual authors:

All the authors contributed to the article, all participated to the literature search and medical writing. All are answerable for published reports of the research.

Caroline Kadji & Juan Tecco came up with the idea of the manuscript.

Caroline Kadji extracted from the hospital's database, the relevant sample for our study.

Lotta Coenen & Pauline Bellekens wrote the first draft.

Lotta Coenen worked on the statistics with the statisticians.

Andrew Carlin & Juan Tecco was written the final draft.

This publication has been approved by all co-authors, as well as by responsible authorities where their work has been carried out.

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FRENCH TRANSLATION AND LINGUISTIC VALIDATION OF A NEW PATIENT REPORTED OUTCOME INSTRUMENT: THE BODY-Q: A DESCRIPTION OF THE PROCESS

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SUMMARY

Background: Bariatric surgery or reconstructive body contouring surgery performed after weight loss, has the potential to have a major impact on one's body image, health-related quality of life (HRQOL) and mental wellbeing. Many researches show interest in measuring this impact using generic instruments that unfortunately are not specifically oriented toward bariatric or surgery patients. The BODY-Q is a new patient-reported outcome (PRO) instrument designed to measure patient perceptions of weight loss and/or body contouring. In this article, we describe the methods used to translate and culturally adapt the French version of the BODY-Q.

Material and method: We followed the recommendation for translation process established by the International Society for Pharmacoeconomics and Outcome Research (ISPOR) and the World Health Organisation (WHO). This process included two forward translations, one backward translation, a review by a panel of expert and cognitive debriefing interviews with patient. Our aim was to ensure a conceptual and culturally valid translation.

Results: This translation process led to a conceptually and culturally equivalent French version of the Body-Q. Backward translation comparison to the English original version led to the identification of 16 differences necessitating re-translation. The expert panel offered support to identify inadequate expressions and proposed changes to the translations. The cognitive debriefing interviews with 15 patients contributed to minor changes in the translation.

Conclusions: This thorough method of translation and cultural adaptation allowed us to develop a conceptually and culturally valid French translation of the BODY-Q.

Key words: translation - patient - reported-outcome - self image - psychological changes - bariatric surgery

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INTRODUCTION

This article is at the crossroads of psychiatry, bariatric and plastic surgery as the surgery has such an important influence on self-image. Prior bariatric surgery, patients have difficulties to visualize the psychological and physical changes beyond the fact that they will lose weight. This is why it involves an interdisciplinary team (surgeon psychiatrist, endocrinologist, psychologist, dietician, nurses...) to evaluate and follow the patient all along the process. In Belgium there is a Royal decree that stipulate that the surgery needs to be approved by the healthcare team to be reimbursed. The success is measured in lost pound while psychological aspects of success tend to be neglected. Evaluation of outcomes from the patient perspective is becoming increasingly important in clinical research, especially in reconstructive surgery since many procedures aim to directly alter one's appearance, body image and/or health-related quality of life (HR-QOL). Many studies have included patient-reported outcome (PRO) instruments, but often the tools used were not designed for surgery patients (Hensel et al. 2001, Song et al. 2006, Lazar et al. 2009, Bolton et al. 2003, Cintra et al. 2008, Gusenoff et al. 2008, Blomqvist et al. 2000, Coriddi et al. 2011, Singh et al. 2012).

Bariatric surgery, with the rapid and massive weight loss, can leave the body with substantial amounts of excess hanging skin. Excess skin may have both physical and psychological consequences, including skin problems, body pain and distortions of body image. The goals of post-bariatric body contouring procedure are to restore physical comfort and body image. However, many authors (Trempe et al. 2015, Jabir 2013, Kitzinger et al. 2012, Reavey et al. 2011) point out the lack of dedicated PRO instruments to measure improvements in outcomes following bariatric and reconstructive surgery.

To address this absence, Klassen AF, Cano SJ, Alderman A, et al. (2016) designed a PRO instrument specifically oriented towards weight loss and body contouring. The BODY-Q measures three main concepts: appearance, HR-QOL, and experience of health care (Klassen et al. 2014, 2016) via 18 independently functioning scales. It also includes a checklist of symptoms specifically related to obesity. The BODY-Q was developed following international recommendations for item generation, item reduction, and psychometric evaluation (Aaronson et al. 2002, US Food and Drug Administration Guidance 2015a, Patrick et al. 2011a, Patrick et al. 2011 b, US Food and Drug Administration Guidance 2015 b). Rasch (1993) Measurement Theory analysis was used

for item reduction and to examine reliability, validity, and ability to detect change.

The BODY-Q is unique compared to other PRO in that it includes 10 scales to measure appearance-related concerns. Each BODY-Q scale is functioning independently and scored on a scale from 0 (worse) to 100 (best), without total score.

The BODY-Q as a specific tool, when used in clinical practice, provides a way for patients to raise their concerns to their surgeon, psychiatrist and members of the healthcare team. With a complete overview of the patient's concerns, the BODY-Q can be used to follow patients over their entire weight lost and body contouring process. With such a tool, it would be possible to compare findings across countries and bring a whole new scientifically validated knowledge to the bariatric and body contouring surgery patients.

The goal of our study was to produce a French version of the BODY-Q. Adaptation of a questionnaire in another language and culture requires high quality translation and linguistic validation. Qualitative interviews with patients are also needed to assess full understanding of the wording of items, instructions and response options.

In order to ensure the development of a high-quality French translation of the BODY-Q, we followed the guidelines for translation and cultural adaptation set forth by The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the World Health Organization (WHO) (Wild et al. 2005, WHO 2016).

MATERIAL AND METHOD

Our aim was to develop a conceptually and culturally equivalent translation rather than a literal translation and secure an equivalent French version of the BODY-Q.

Step 1: Permission from authors and recruitment

We obtained permission to use the BODY-Q from the developers (Klassen et al. 2016) and we started to recruit translators and expert panel participants. The group was asked to use a simple and clear wording in order to be understandable for the largest number of patients.

Step 2: Forward Translation

Two translators, both fluent in English with French as mother tongue, produced an independent forward translation of the original items. The first translator was a professional and the second was a health professional with experience working with the target patient population.

Step 3: Forward Translation review

Both translators discussed the translations and agreed on a reconciliation version (French version 1). The aim was the production of a conceptually equivalent translation of the original questionnaire keeping in mind an easy and simple language to understand.

Step 4: Backward translation

A professional translator who was a native English speaker and bilingual in French produced a backward translation (French to English) based on the French version 1, without access to the original English version. The objective was to determine from the backward translation any misunderstandings, mistranslations or inaccuracies in the intermediary forward version of the questionnaire.

Step 5: Backward translation review

The backward translation was then sent to the BODY Q developers (Drs. Klassen and Pusic) for review and comparison with the original version. All differences were discussed, re-translated and shown again to the developers. This process continued until a satisfactory result was reached and led to French version 2.

Step 6: Expert Panel discussion

The expert panel is composed by the three translators, a plastic surgeon specialist in body contouring and a psychologist. They met to discuss the French version 2. All participants were native French speakers and fluent in English, except for one translator who was native English speaker and fluent in French.

The aim of this discussion was to review the translation to identify and resolve any final unclear expressions. This resulted in French version 3 for pre-testing.

Step 7: Cognitive debriefing Interviews

The objective of this step was to test the translated questionnaire on a group of patients from the target population to determine whether it was acceptable, understandable in the way it was originally intended by the developers, and if the language used is accurate, clear and non-ambiguous.

To complete this objective, 10 cognitive debriefing interviews were performed with patients exploring or seeking body contouring surgery, and patients who had had body contouring. Participants were recruited in Cliniques Universitaires Saint Luc, Belgium throughout January 2016. There was no incentive offered. The interviews were done after the consultation with the surgeon in the hospital. Semi-structured interviews using the think aloud approach were performed by the psychologist and notes were taken.

Participants were asked to read the French version of the BODY-Q questionnaire to identify any items, instruction and response options that they felt were not appropriately worded and to propose different expressions. The interviewer questioned participants to determine any difficulty in their understanding of the questionnaire and to verify the patient's interpretation of all items as well as the instructions, time frame and response options. Findings were used to make final changes to version 3, leading to French version 4.

Cognitive debriefing interviews with five additional patients were performed to review the French version 4.

Step 8: Harmonization and reconciliation

Findings of the first and second round of cognitive debriefing interviews were used to correct the version 4 leading to French version 5.

Step 9: Final version

French version 5 was proofread independently by the clinician and the psychologist, resulting in the final French version of the BODY-Q.

Step 10: Final report

Report is written on the development of the translation.

RESULTS

Translation and cultural adaptation of the BODY-Q led to the development of a conceptually and culturally equivalent French Version. Examples of the changes made during the translation process are described below:

In Step 3:

The two forward translators had several discussions about the different phrasing and the wording in French, since French is a very complex language with many words that can express the same or very close signification. The goal was to choose the simplest words that could be understood by the majority of the patients. The translators encountered a difficulty in the translation of “body contouring”. In French, this word is very technical and not very often used. The expert panel and the healthcare team helped to find an easier phrasing that reflects the knowledge and the experience of the patient about his surgery. The equivalent wording chosen was “surgery of the silhouette”.

In step 5:

When developers of the BODY-Q reviewed the back translation, they identified 16 differences that appeared to have a different meaning from the original English version. Those items were re-translated until they were deemed acceptable.

For example, in the Appearance-Related Psychosocial Distress scale, the item “I worry that I am ugly” was back translated as “I am afraid that I am ugly”. In French the word “afraid” is commonly used in the spoken language as a less powerful meaning of “worry”. The developers of the BODY-Q judged that use of “afraid”, as having a different conceptual meaning than “worry”. It was changed to stay as close as possible to the conceptual meaning. The expert panel and the patients found the revised item to be easily understandable.

Furthermore, the item “I have little interest in doing things” was back translated as “I have little interest in activities”. The translators interpreted “things” to be “activities”, however the back translation was judged to be different by the BODY-Q developers and therefore was re- translated.

In Step 6:

The expert panel identified 24 discrepancies. There was one important change as the translation process was not completely satisfactory in term of French expressions. In the Satisfaction with Body scale, the panel found that the translation of “size” was too literal to satisfy the quality process. In the sentence: “the size (i.e., weight) of your body”, the word “size” in French has different meanings and can refer to dimensions such as: height or width independently. The combination of “size” and “weight” in the same sentence was particularly confusing in French as it referred to two different concepts. The expert panel reached a consensus on an easily understandable wording using a French word close to “build” in English. This choice was confirmed in the patients’ interviews, as participants found the revised item easy to understand.

In step 7:

We performed 10 cognitive debriefing interviews with two post bariatric patients, three pre-body contouring and five post body contouring patients (Table 1).

Table 1. Participant to cognitive interviews characteristics

	Patients post bariatric surgery	Patients pre-body contouring surgery	Patients post body contouring surgery
First round of cognitive interviews	(n=2)	(n=3)	(n=5)
Gender			
Male	1	1	4
Female	1	2	1
Age	59.5 (57-62)	50 (36-66)	43.4 (35-55)
BMI	27.9 (26.9-29)	28.3 (23.7-34.3)	30.86 (23-45.9)
Second round of cognitive interviews	(n=1)	(n=2)	(n=2)
Gender			
Male	1	2	2
Female	0	0	0
Age	57 (57)	47 (37-57)	61.5 (55-68)
BMI	21.8 (21.8)	26.5 (25.6-27.7)	25.95 (24.8-27.1)

Three minor changes to the translation were required after the cognitive debriefing interviews. In the Social Function scale, the word “gatherings” from the item “I feel at ease at social gatherings with people I know”, was considered to be inappropriate to several patients. They reported that “gatherings” in French referred to a big crowd. Therefore, the word was conflicting the last portion of the question “people I know”. To address this issue “social meetings” was suggested to replace “gatherings”. However, some participants felt that “meetings” in French was used more in professional contexts and “social” was not commonly used to describe a group situation with people.

Finally, we proposed to simplify the sentence by using the French word for “group” and participants felt this option was more understandable.

Moreover, in the Appearance-Related Psychosocial Distress scale, the translation of the item “I feel unhappy about how I look” gave a negation in the French translation, equivalent to “I feel not happy”. Patients reported a difficulty answering the questionnaire as they had to take into account the double negation between “I feel not happy” and the response option equivalent in French to “not agree”. The problem was that if we changed these phrases, this would have led to a change in the scale quotation. Indeed, taking out the double negation would have led to the opposite understanding. We found another word, less commonly used in French but easy to understand for the entire participants group, that allows us to avoid the negation in the item.

In the second round of cognitive debriefing interview, we interviewed one post bariatric surgery, two pre-body contouring and two post body contouring patients. This phase confirmed all the changes made in the translation process.

Overall, participants were very pleased with the questionnaire as it adequately reflected their concerns before and after surgery. They highlighted the fact that the scars scale assessment was very important as it is a major concern for patients given how extensive scars can be following body contouring.

DISCUSSION

Different tools have been used to assess the patient outcomes post body contouring surgery. Commonly, generic PRO instruments have been used, resulting in contradictory reports of outcomes in the literature (Singh et al. 2012, Staalsen et al. 2015). The BODY-Q is the most comprehensive PRO instrument designed to date for body contouring patients. As such, the BODY-Q provides a new perspective to research on the patient outcomes in bariatric and reconstructive surgery and its use may lead to more scientific and clinically relevant results (Singh et al. 2012, Tremp et al. 2015).

We applied the ISPOR and WHO translation and cultural adaptation guidelines to develop a French conceptually equivalent translation of the BODY-Q. Attaining a

high-quality translation was crucial to enable its use in French especially in a context where specific PRO instruments are needed in the domain of plastic surgery. Consultation of patients via cognitive debriefing interviews during the translation process was very useful to determine correct utilization of the French expressions and wording, as well as their full understanding.

During the cognitive interviews, patients raised a difficulty in the reading of the questionnaire. They found it difficult to answer the questionnaire straight away and described that they had to read the question several times before answering. Their trouble completing the scales was widely due to the fact that among the 10 scales some used different response options. For instance, the response options for 6 scales were “disagree/agree”, while the remaining scales had varying possibilities (two scales with bothered/not bothered, one scale with dissatisfied/satisfied, one with all the time/never).

As the patients got used to the questionnaire, they reached a certain habit in the pattern of answering the questions, so it could have been difficult to break this pattern each time the possible answer changed.

The solution was to sort the scales in order to present all the scales with response option “satisfied/dissatisfied” together followed by the two scales with the “bothered/not bothered” response options and the remaining scales. We had no complaints following this sorting in the second patient interview.

Several participants reported the Appearance-Related Psychosocial Distress scale to be disturbing given the scale’s negative connotation compared to the other positively worded scales. In order to avoid any confusion, the Appearance-Related Psychosocial Distress scale was placed first. This way, the participants remained fully focused.

We recommend this sorting if a clinician wants to use 10 scales of the BODY-Q during the same consultation.

CONCLUSION

We translated BODY-Q into French and tested the translation with a group of pre- and postoperative body contouring patients, following the ISPOR and WHO methodologies.

The expert panel meetings and cognitive debriefing interviews with patients were very useful for ensuring the translation and was relevant and meaningful to patients. The French version of the BODY-Q is suitable in assessing outcomes in post bariatric and body contouring surgery in the French-speaking population.

Contribution of individual authors:

Perle Rillon, François Château, Anne Klassen, Elena Tsangaris, Pirson Geneviève & Christine De Coninck all made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data.

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THE THERAPEUTIC ALLIANCE - ITS IMPACT ON ANTIDEPRESSANT THERAPIES IN MAJOR DEPRESSIVE CONDITIONS AND ON THE OVERALL HEALTH

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SUMMARY

Background: Based on our 2012 study and a review of the literature on the therapeutic alliance we asked ourselves different questions: does the alliance exert a real influence on the evolution of depressive affects, the rate of remission and the physical and global health?

Subjects and methods: In a two-year study, forty people with major depressive disorder are randomly assigned to groups that receive a SSRI (escitalopram) or a SNRI (duloxetine), each group receive concomitant ASA (100 mg) or a placebo. Sociodemographic data are recorded and patients under went regular assessments with the Hamilton depression scale (HDS) and Clinical Global Impression (CGI) scale, the Helping Alliance Questionnaire (HAQ) and the Short Form Health Survey (SF-12).

Results: There is no significant difference in efficacy between the two antidepressants or between antidepressant treatment with and without ASA. However, subgroup comparisons reveal that the duloxetine + ASA (DASA) subgroup showed a more rapid improvement in HDS score as early as 2 months ($t=-3.114$, $p=0.01$), in CGI score at 5 months ($t=-2.119$, $p=0.05$) than the escitalopram + placebo (EP) subgroup. Regardless of the treatment arm, the remission rate at 2 years is 50%. Among patients in remission a majority, 65%, have a high level of alliance in opposition to nonresponders who have found mostly a low level of alliance ($\chi^2 = 6.296$, $p=0.012$). HAQ scores are not correlated with HAD scores, but a correlation is found with remission rates ($r=0.316^*$). At all times, HAQ scores are correlated with physical health.

Conclusion: Our findings suggest that a noradrenergic agent combined with ASA is more effective in treating depression than a serotonergic agent alone. A good alliance improves effectiveness of anti-depressant treatment of 1.85 and leads to an improvement of the physical health rather than directly on the depressive feelings.

Key words: depression - antidepressant drugs - alliance - physical health

* * * * *

INTRODUCTION

Starting the treatment of depressive patients remains a therapeutic challenge. From 2012 to 2014, we carried out a comparative study to compare the efficacy of a SNRI (duloxetine) and a SSRI (escitalopram) and their combination with either a placebo or 100 mg of acetylsalicylic acid (ASA). The initial results published in 2017 (Zdanowicz et al. 2017) show that the association of SNRI and ASA improves the HDS score (Hamilton Depression Scale) at 2 months ($t=-3.114$, $p=0.01$) the CGI (Clinical Global Impression) at 5 months ($t=-2.119$, $p=0.05$) and the remission rate ($\chi^2=6.296$, $p=0.012$) compared to the SSRI + placebo group. This suggests that a noradrenergic agent combined with an acetylsalicylic acid is more efficient than a serotonergic agent alone. Based on the same study, we wondering the influence of the therapeutic alliance on health indicators such as the HDS, the perception of the therapeutic alliance by the patient and the clinician on the basis of the "Helping Alliance Questionnaire" (HAQ) and the patient's overall health (SF12 i.e. "The 12-item Short Form Health Survey"). Since the emergence of the concept of therapeutic alliance, it has been used increasingly in medical literature. Its definition has been widely altered and reshaped over the years. The most common involves the existence of an affective link bonding the therapist and the patient along with an

agreement on the objectives and the resources which are necessary for a correct implementation of the treatment. In 1979, Downing & Rickels suggested that some quite different factors from pharmacological properties, such as the therapeutic alliance, can affect the response both to a placebo and drugs. In 1996, Krupnick et al. studied the effect of the therapeutic alliance on psychotherapies and pharmacological treatments on the basis of a multi-centre study carried out within the framework of the "National Institute of Mental Health (NIMH) treatment of depression collaborative research program (TDCRP)". The patients ($n=225$) had been split into 4 groups: psychotherapy, cognitive and behavioural therapy, undergoing a pharmacological treatment (imipramine) and placebo. The study demonstrates a significant relationship between the quality of the alliance and the response, and variability in responses to treatments, whatever their modality (odd ratio to 3). Thus, this interest in the alliance revealed that it turns out to be the best pronostic and predictive, known factor of therapeutic responses to many treatments, yet vastly underestimated in pharmacologic studies. It contributes therefore directly to the success of the management of patients with depression (De Bolle et al. 2010). Finally, it has been demonstrated over the years that a relationship exists between organic and psychiatric diseases, although it is often underestimated (Mantelet 2003, Cottencin 2009). The physical symptoms of depression are often

badly investigated and unfortunately wrongly attributed. And yet physical comorbidities related to depression have been rightly defined (Cottencin 2009, Coulehan et al. 1990) and are mostly interpreted as a consequence of the patient's thymic condition. However, studies carried out on animals and human subjects, have shown that emotional conditions, in particular depression and stressful situations, are related to an alteration of neuronal, hormonal and immunological conditions (Schleifer et al. 1984). In this perspective, based on our 2012 study, we questioned ourselves as to the role of the therapeutic alliance on depression, its treatment and remission rate; but also, on the patient's overall health.

SUBJECTS AND METHODS

Subject

A 2-year study is carried out on a group of 40 patients. Inclusion criteria were as follows: presence of a major depressive condition defined by the DSM IV items; it must be the patient's first or second depressive episode; no symptoms of depression during the preceding two years; no history of other psychiatric disorders on Axis I of the DSM-IV-R; no history of gastritis, or gastric or esophageal ulcers; aged between 18 and 63 years. Patients taking depressogenic drugs (e.g. beta blockers, morphine derivatives) were excluded, and no formal psychotherapy took place for the duration of the study. In total, 40 patients completed the study and sign a written consent, validated by the ethics committee (Belgium, n° B03920072846). The antidepressant + placebo group (n=20) comprised a duloxetine + placebo (DP) subgroup (n=11) and an escitalopram + placebo (EP) subgroup (n=9); antidepressant + ASA group (n=20) comprised a duloxetine + ASA (DASA) subgroup (n=8) an escitalopram + ASA (EASA) subgroup (n=12).

Methods

During the remission stages, defined by the absence of symptoms of the major depressive condition (DSM IV), medication is discontinued unlike the monitoring that goes on for another 2 years. For patients who left the study, the last score obtained was recorded for the remaining assessments (LOCF). Patients are firstly evaluated by "The Mini International Neuropsychiatric Interview" in order to rule out any previous or present psychiatric disorder. The "Helping Alliance Questionnaire (HAQ)" (Luborsky et al. 1996) evaluates the doctor's relationship of trust in the patient and vice versa. Socio-demographic data are gathered, such as the age, sex, social status (defined according to the patient's monthly salary) and the number of homemakers. At 0, 0.5, 1, 1.5, 2, 3, 6, 12, 18, and 24 months, patients were assessed with the 17-item Hamilton depression scale (HDS). The clinical global impression (CGI) scale was completed at each visit as well as the SF12 ("The 12-item Short Form Health Survey") (Ware & Keller 1996) questioning both the overall physical health (pain,

everyday physical functioning, etc ...) and the sanity (vitality, the patient's social functioning, everyday mental functioning and well-being). The SF12 is filled in by the patient while the psychiatrist fills in the HDS and the CGI. Parametric statistical analysis are carried out using the SPSS25 while taking into account the type 1 and 2 errors. No post-hoc test was carried out. Pearson correlation analysis was carried out for possible covariates. Qualitative variables were compared with the Chi-squared test, and means were compared using Student's t-test. Significance levels were set at $p > 0.95$ and $p < 0.05$. The data is presented as an average \pm the standard derivation.

RESULTS

Demographic data

The study is conducted with 7 men and 33 women. The mean age is 40.33 ± 14.37 ; the average salary is $1,800 + 723\text{€}$ and the average number of people at home $2.7 + 1.5$. Both groups are statistically similar in terms of income ($t=0.086$, $p=0.932$). There is no correlation between the age and the HDS except in the first month ($p=0.026$, $r=-0.352$). Comparisons of the ASA and placebo groups reveals a significant difference in terms of age (ASA group 46.6 years old; placebo group 34.25 years old; $t=2.98$, $p=0.05$) but there is no significant correlation between the age and HDS score. No significant difference is observed between the duloxetine group and the escitalopram group.

Therapeutic alliance and intensity of the depression

The mean HDS score is 23.83 ± 3.2 (Figure 1). No correlation has been shown between the HDS and HAQ scores. There is no difference in average in the HAQ score for the patients with one recurrence or not.

Therapeutic alliance and response to the treatment

Of the 40 patients, 21 responded within 3 months (50% decrease in HDS score), 20 patients were in remission at 6 months and 1 patient had relapsed at 2 years (Table 1). Taking an anti-depressive molecule is thus associated to a remission rate of around 50%. Basing ourselves on the therapist's HAQ results for the 40 patients, with a minimum of 60 and a maximum of 92 we obtain an average of 77.10% on the therapist's HAQ. This one is used as a "clearcut" to transform our quantitative into a qualitative alliance scale, splitting the HAQ data into 2 categories: low and high alliances. Out of those 50% remission rate, 35% are patients taking an antidepressive molecule with a low therapeutic alliance; yet their association with a good alliance increases this rate to 65%. Establishing a good therapeutic relationship would thus increase the efficiency of the antidepressive treatment by 1.85 (Table 2).

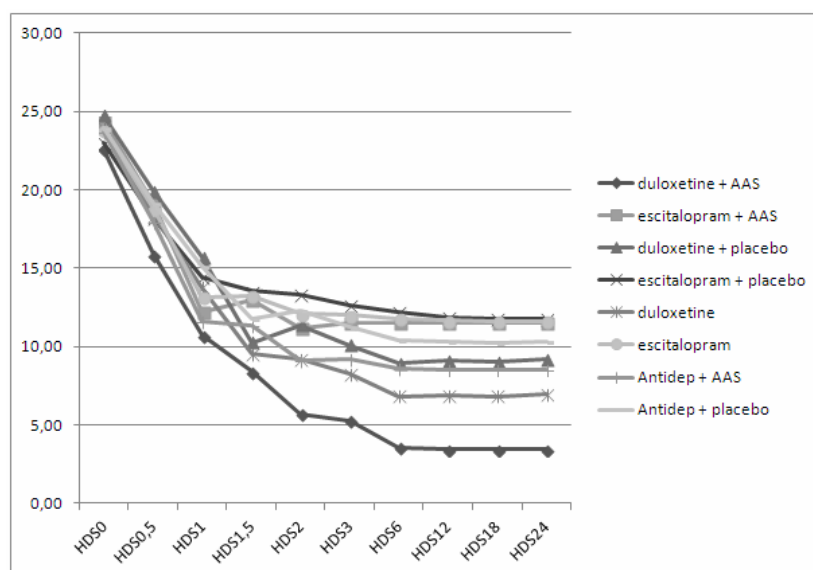


Figure 1. Evolution of the Hamilton Depression Scale (HDS) during the study according to the treatment type

Table 1. Response to treatment, remission and relapse

	n	Responders	Remission	Relapse
		%	%	
Total	40	21	20	1
Duloxetine + AAS	8	4	8	0
Escitalopram + AAS	12	8	2	0
Duloxetine + placebo	11	7	6	1
Escitalopram + placebo	9	2	4	0
Duloxetine	19	11	14	1
Escitalopram	21	10	6	0
Antidep + AAS	21	10	6	0
Antidep + placebo	20	9	10	1

Table 2. Correlations between remission and therapeutic alliance

		Remission Rate		Total
		No remission	Remission	
Therapeutic Alliance	Low alliance	14	7	21
	High alliance	6	13	19
Total		20	20	40

Table 3. Correlation between the Short Form Health Survey (SF-12) including physical health (PH) and mental health (MH) and the Helping Alliance Questionnaire (HAQ)

	HAQ patient	HAQ therapist
PH0	-0.035	0.309*
PH6	0.281	0.442**
PH12	0.197	0.489**
PH18	0.189	0.476**
PH24	0.220	0.530**
MH0	-0.154	0.319*
MH6	0.237	0.066
MH12	0.225	0.127
MH18	0.222	0.109
MH24	0.215	0.111

** La corrélation est significative au niveau 0.01 (bilatéral);

* La corrélation est significative au niveau 0.05 (bilatéral)

The differences in distribution for the patients in remission or not, crossed with the patients with a good therapeutic alliance or not, have a chi-square of 4.912 ($p=0.027$) resulting in a significant difference in distribution between the remission rate and the clinician's HAQ.

Therapeutic alliance and overall health

First of all, it should be noted that in a previous study (Zdanowicz et al. 2011) our patients' physical and mental health was worse than the health of the controls in good health (physical health 36.74/51.14, $t=6.353$, $p<0.000$; mental health 35.10/51.51, $t=5.846$, $p<0.000$). At the end of our study, the patients reporting an improvement in terms of physical health (36.74 \rightarrow 39.09, $t=-2.032$, $p=0.049$) and mental health (35.10 \rightarrow 40.81, $t=-2.476$, $p=0.018$) still retain a significant difference versus the health of healthy controls (physical health 39.09 / 52.39;

Table 4. Correlations between Hamilton depression scale (HDS), clinical global impression (CGI) scale and the Short Form Health Survey (SF-12)

	HDS0	HDS6	HDS12	HDS18	HDS24	CGI0	CGI6	CGI12	CGI18	CGI24
PH0	-0.442*	-0.357*	-0.338	-0.341	-0.337	-0.144	-0.297	-0.350*	-0.350*	-0.351*
PH6	-0.255	-0.478**	-0.472**	-0.482**	-0.488**	0.032	-0.482**	-0.476**	-0.476**	-0.468**
PH12	-0.397*	-0.502**	-0.501**	-0.507**	-0.501**	0.017	-0.463**	-0.524**	-0.524**	-0.510**
PH18	-0.421*	-0.499**	-0.508**	-0.508**	-0.500**	0.001	-0.467**	-0.524**	-0.524**	-0.509**
PH24	-0.380*	-0.519**	-0.522**	-0.527**	-0.519**	0.014	-0.479**	-0.534**	-0.534**	-0.536**
MH0	0.150	0.053	0.043	0.047	0.046	0.138	-0.103	-0.037	-0.037	-0.057
MH6	-0.170	-0.388*	-0.364*	-0.360*	-0.359*	0.223	-0.479**	-0.472**	-0.472**	-0.495**
MH12	-0.133	-0.385*	-0.422*	-0.419*	-0.407*	0.280	-0.507**	-0.530**	-0.530**	-0.549**
MH18	-0.174	-0.416*	-0.446**	-0.443**	-0.433*	0.297	-0.534**	-0.554**	-0.554**	-0.566**
MH24	-0.171	-0.425*	-0.451**	-0.450**	-0.440*	0.302	-0.537**	-0.570**	-0.570**	-0.583**

*** La corrélation est significative au niveau 0.001 (bilatéral); ** La corrélation est significative au niveau 0.01 (bilatéral);
 * La corrélation est significative au niveau 0.05 (bilatéral)

$t=4.659$; $p<0.000$; mental health 40.81 / 52.70; $t=3.965$; $p<0.000$). By looking into the influence of therapeutic alliance on the patient's physical health and mental sanity (Table 3), we notice a significant correlation between the improvement of the patient's physical health and the clinician therapeutic alliance throughout the study. We can't objectivize a significant relationship between both the patient's and the clinician's HAQ's, on the one hand, and the improvement of the patient's sanity, on the other hand. Besides, there is a correlation between the patient's physical health and sanity on the one hand, and the intensity of his depression and his clinical improvement on the other hand (Table 4) significant from the sixth month of the treatment.

DISCUSSION

It must first be pointed out that because of the limited size of our sample, we cannot allow ourselves to generalize our conclusions. However here are our observations.

After two years of study, we objectivize a 50% remission rate with patients suffering from a major depressive condition. By analysing the influence of the therapeutic alliance on this remission rate, 35% are taking an antidepressant molecule alone, the remaining 65% result from the taking of an antidepressant combined with a good therapeutic alliance. The alliance seems to multiply by 1.85 the efficiency of the antidepressant. Based on the HAQ, the SF12 and the HDS, no correlation is found between the HDS score and the HAQ. A significant relationship is showed between the remission rate and the HAQ. From the point of view of overall health, the clinicians' therapeutic alliance seems directly correlated, at every stage of the study, to the perception of the patient's physical health and improvement. No correlation of the same kind is made to the patient's sanity. The alliance thus affects the physical health more than the subject's psychological health, which turns out to be fairly surprising. Finally, a significant correlation between the patient's physical

health and the HDS score is objectivized. Starting from these different assumptions, our hypothesis would be that the therapeutic alliance, through its influence on the patient's physical health perception, would make it possible, indirectly, to obtain a significant increase of the remission rate. As a result, the gain in remission would be, indirectly, related to the improvement of the patient's physical health, in particular thanks to the tie that binds the clinician's HAQ to the HDS (Zdanowicz et al. 2018). Symptoms and ties binding psychiatric disorders and organic diseases (Mantelet 2003, Cottencin 2009, Coulehan et al. 1990) as well as the impact of the physical health on the depression of elderly people (Berkman et al. 1986) may reinforce our hypothesis that perhaps, just like the geriatric patients in whom depression seems to be secondary to the presence of chronic pain inducing a progressive deterioration of the autonomy, the adult patient firstly experiences a certain physical malfunction prior to a decreased autonomy, leading to the expression of a depressive table. The thymic condition of elderly people could be a reaction to the deterioration of their physical health, the opposite of what is generally claimed in adult subjects. On this base, we could understand the close link that unites depression and physical health. Knowing that therapists' evaluations of therapeutic alliance are predicting therapeutic progress, the alliance could be directly related to the evolution of the symptoms, and, as a result, the effect of the treatment of the depression, although there may be an unavoidable inter-subject variability between the patients.

CONCLUSION

Our results suggest that the therapeutic alliance perceived by the clinician plays a much bigger part than could have been thought at the beginning. In addition to being a predictive and prognostic factor in the response to many forms of treatment, it influences the patient's perception on his physical health in an indirect way, increasing remission rate significantly by multiplying

the efficiency of the antidepressant by 1.85. In conclusion, the management by the psychiatrist would require a psychological aspect as well as a physical aspect. The quality of that relationship will thus be the decisive factor in the prognosis of the patient's depression. Our results reinforce the assumptions made by Krupnick et al. in 1996 on the role of therapeutic alliance in results of psychotherapy and pharmacotherapy. However, because of the limited size of our sample, it is difficult to extrapolate our results. It would be interesting to continue investigating the impact of this therapeutic alliance on our daily practice.

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Contribution of individual authors:

Aurore Sourdeau & Nicolas Zdanowicz each made substantial contributions to the design of the study, and/or data acquisition, and/or the data analysis and its interpretation.

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PATIENT'S AND GENERAL PRACTITIONER'S PERSPECTIVES REGARDING DISTURBED EATING

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SUMMARY

Objectives: We wanted to investigate the patient's expectations on the general practitioner's (GP) responsibilities in screening and follow up of disturbed eating behaviour. Then, we looked for remediation for some of the mentioned shortcomings in family medicine. We also examined if online aid (offered by the non-profit organisation "Eetexpert.be") is already known and used.

Subjects and methods: Anonymous patient questionnaires were gathered at 4 treatment centres for eating disorders or were collected with help of the Flemish patients organisation for eating disorders (Vlaamse Vereniging Anorexia Nervosa en Boulimia Nervosa). Later, online enquiries were sent to Flemish GPs.

Results: Out of 123 patients responding to the questionnaire, 44 found their GP to have had an important supportive role in their healing process. Active listening and targeted referral were among the most appreciated interventions by those patients. 71 GPs replied the online enquiry. Only 1 out of 5 knew about the free online assistance of "Eetexpert.be". Responders suggested several additional barriers to care.

Conclusions: In Flanders there is a contrast between expectations and needs of patients on one hand compared to the services provided by GPs on the other. Reassuringly, all responding physicians were open to more education and support regarding eating disorder treatment.

Key words: eating disorder - general practitioner - qualitative research

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INTRODUCTION

Eating disorders, with an estimated prevalence of 2.3% for adult patients in Belgian GP practices (Ansseau et al. 1999), are one of the five most common psychiatric disorders in primary health care. In the daily general practice multiple problems are experienced in dealing with patients with disturbed eating behaviour in terms of screening, diagnosis, treatment, adequate referral and follow-up. Since detecting eating disorders in general practice at an early stage is associated with a better outcome, this is unfortunate. Our objectives were firstly, to gain insight into the role of the general practitioner from a patient perspective with the aim of mapping out any shortcomings in the quality of care and being able to better align the care provided by the general practitioner with the expectation of the patient with an eating disorder. Secondly, we wanted to question the GP's on their opinions concerning help for eating disorders in primary care and if the support from „Eetexpert vzw“ reaches them.

SUBJECTS AND METHODS.

The qualitative research on patient's perspective was based on an anonymous survey conducted with eating disorder patients in four Flemish eating disorder centres (Centrum voor Eetstoornissen UZ Gent, UZ Leuven, Psychiatrische Kliniek Broeders Alexianen Tienen and

eetklinik Paika UZ Brussel) and via the Flemish association Anorexia Nervosa and Bulimia Nervosa (ANBN). Patients from the age of 16 years were included in the study. No restrictions were imposed on the type of eating disorder or on gender. The data collection ran from November 2015 to January 2016 in Flanders, the most populated and Dutch speaking part of Belgium. The study was approved by the Ethics committee of UZ Brussel. The incomplete surveys were excluded before applying statistical analysis.

The GP's inquiry via an online survey (LimeSurvey) was diffused digitally in Flanders by vzw Eetexpert, the GP organization Domus Medica and ICHO (the Inter University Centre for GP training). It came with an information page and informed consent form. Answers were collected between 1 September 2017 and 31 December 2017.

RESULTS

123 respondents completed the survey. The majority of patients (76.9%) consulted their doctor for complaints about their eating disorder, usually in the context of underweight or weight fluctuations, absence of menstruation, hair loss, fatigue and depression.

In less than half of the cases (45.2%), the GP assessed the underlying eating problem, and when it was, it was more frequently in case of anorexia nervosa (44.4%) than bulimia nervosa (15.4%). The majority of

patients (74.1%), of whose general practitioner was aware of their eating problem, were eventually referred to second and/or third-line care, usually to the psychologist (37.2%), followed by a specialized centre for eating disorders (22.1%) and the dietician (20.9%).

For 39.3% (n=44), the general practitioner played an important supporting role in the healing process, 31.1% (n=36) noted shortcomings and 28.6% (n=32) indicated to be disappointed in the general practitioner. Patients who were referred and actively followed by their GP experienced this as an important support in their healing process. The qualities of GPs that were most appreciated by the respondents were listening comprehension (83.7%), followed by targeted referral to specialists (77.2%) and providing sufficient time during the consultation (70.7%). More than half of them (56.9%) want a regular follow-up by the GP. If the patients feel misunderstood, if there is only attention for body weight and / or insufficient time is given, eating disorder patients will not quickly approach their doctor. Shame, not wanting to give up the eating disorder and denial can also cause serious delay in the use of specialized help for eating disorder patients. The majority of respondents (81.3%) noted that the doctor should explicitly ask about eating disorders, this confronting attitude is experienced by patients as acknowledging their problems and as a doctor's competence. For adolescents, it is important to emphasize professional secrecy.

71 GPs completed the survey. 67.6% indicate they have an active role in the care for patients with disturbed eating behaviour. Barriers for adequate care were given: poorly accessible specialized care, lack of knowledge on personalized care and lack of time. 16.9% of participating general practitioners were aware of the support material offered by "Eetexpert vzw". All responding physicians were open to supplementary training, the need for step-by-step plans was expressed.

DISCUSSION

74.0% (n=91) of patients noticed that generally the GP minimalizes or inadequately recognizes the problems accompanying eating disorders. Most of the barriers mentioned above in the result section concur with previous findings (Linville 2010).

The GP survey was the first in Flanders. Response rates in both groups were unfortunately low and so lack statistical power, so results are descriptive. Furthermore,

the doctors who responded could have been those more interested in eating disorders. Nevertheless, many of the barriers given by the GP's were similar in other regions.

CONCLUSIONS

Based on the results of this study, it can be stated that there is currently a mismatch between the expectations and needs of the patient and the services that some GPs actually offer. Adjustments can cause both to become allies in the fight against eating disorders.

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Contribution of individual authors:

Dieter Zeeuws presented this material at the 7th Biennial Cambridge International Conference on Mental Health 2019. He wrote this manuscript based on previously unpublished work (except a poster at the DGPPN Kongress Berlin 2018) in Dutch by Karolien Cocquereaux. The patient questionnaires were part of her thesis to obtain the degree of master in medicine. The GP's inquiry were documented in her master of family medicine thesis. Liesbeth Santermans reviewed this manuscript.

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MOBILE CRISIS TEAM IN THE BRUSSELS REGION: FACTS AND FIGURES

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SUMMARY

Background: A reformation of psychiatry was set up in Belgium with the establishment of mobile crisis teams.

Subjects and methods: We performed a retrospective analysis of the patients referred to the mobile team "Pharos" in the period between December 2013 and December 2018.

Results: The number of patients is growing over the years and the most common referral reasons are suicidal thoughts and depressive mood. We have a high percentage of inclusions, maybe because the main referrers are GPs. Alcohol withdrawal at home is feasible and safe.

Conclusion: Many psychiatric crisis situations can be managed at home with support of mobile teams, but further research is needed to provide evidence on outcome and cost effectiveness.

Key words: mobile team - outcome - alcohol withdrawal at home

* * * * *

INTRODUCTION

Since 2011 a reformation of psychiatry was set up in Belgium, with the establishment of mobile crisis teams. These teams provide short term, intensive home treatment to people who are experiencing acute mental health problems. Mobile teams can help to reduce the number of hospital admissions per year and offer a safe alternative to the traditional in-patient model with significant cost savings (Sjolie et al. 2010).

The mobile crisis team "Pharos" started in november 2013 and is located in the Brussels region. The territory they cover is situated in the north, west and south of Brussels (a region called "Halle-Vilvoorde") and includes 500.000 inhabitants. The team is multi-disciplinary, consisting of a psychiatrist, a psychologist, a social worker and different bachelors and masters having experience in mental health care. Patients must be referred to the team by a doctor (e.g. general practitioner (GP), psychiatrist). Patients must always be informed and willing to cooperate with the team. The number of interventions varies depending on the severity of the crisis and the maximum treatment duration is 4 weeks. Our team works 6 days/7, but there is a 24h telephone permanence. At the time of the first demand patients are analyzed in terms of intervention indications: is there a psychiatric crisis? Is the patient 16 years or older? Is the patient living in the area served by Pharos? Is the patient willing to cooperate? Often a second analysis is done during a home visit. Whether or not a patient will then be included, is discussed in team.

The last few years we also proceeded to assisted alcohol withdrawal at home. This involves psycho-

social support, substitute medication regimens and daily monitoring of the patient (to check for symptoms of withdrawal and subsequently advise on use of medication). We also aim to refer patients to ambulant treatment for relapse prevention. Patients referred to Pharos for an alcohol detoxification must meet eligibility criteria. Severe withdrawal (delirium tremens, seizures in the past), abuse of other substances, absence of a carer, severe health problems and serious psychiatric illness (such as an acute psychosis) are contraindications. Literature on management of alcohol detoxification in the community is scarce, but it shows that detoxification at home is safe, is cheaper than residential care and it increases acceptability of treatment (Nadkarni et al. 2017, Stockwell et al. 1991). There seems to be no difference in efficacy in home detoxification in comparison to inpatient care (Stockwell et al. 1991).

Since literature on mobile teams is rather scarce we present the following facts and figures of the Pharos team.

SUBJECTS AND METHODS

We performed a retrospective analysis of the patients referred to Pharos in the period between December 2013 and December 2018. The following items were analyzed: number of patients, percentage of inclusions, person who refers, reason for referral, ratio male-female and outcome. Secondly we performed an analysis of the patients referred for alcohol withdrawal at home in the period August 2018 until April 2019. Ratio male-female, safety and completion rates were analyzed.

RESULTS

The total number of patients referred to Pharos in the period December 2013 until December 2018 was 1530, of which 1256 were included (82%). 274 patients were excluded or were seen once and orientated to other (mental) health services. Reasons for exclusion were mostly lack of cooperation of patients, living outside the area served by Pharos, chronicity of the pathology and absence of a crisis situation, elevated risk of aggression and acute suicidal behavior in which safety at home cannot be guaranteed. During the years the number of patients kept growing: 179 in 2014, 287 in 2015, 333 in 2016, 344 in 2017 and 369 in 2018. The sex ratio was 37% males versus 63% females. Main referrers are GPs (40%), emergency psychiatrists (16%), psychiatrists working at the psychiatric unit in a general hospital (7.5%), ambulant psychiatrists (7.5%) and psychiatrists working in a psychiatric hospital (4.5%). Other requests come from psychologists, social services, families, patients,... So most of the referrals (53%) come from outside the mental health sector. Main reasons for referral are suicidal thoughts (29%), depression (28%), adaptation disorder (15%), alcohol abuse (14%) and psychosis (8%). After or during treatment by Pharos 15% of the patients needed to be hospitalized: 4% in a psychiatric hospital, 10% in a psychiatric unit of a general hospital and in 1% forced hospitalization was necessary. The other 85% of the patients were referred to their GP (13%), to an ambulant psychiatrist (13%), ambulant psychologist (10%), mobile team for chronic treatment at home (7%),... About 5% had no further follow-up. In 10% of the cases the treatment by Pharos was aborted unilateral by the patient. In 90% treatment stopped in mutual agreement.

From August 2018 to April 2019 twentyfour patients were referred and included for alcohol withdrawal at home. Nine were female (37.5%) and fifteen were male (62.5%). Mean age was 48 years. Two patients were excluded after the first home visit because of insufficient motivation. One patient was advised to do an inpatient detoxification. Twelve patients completed the detoxification and were abstinent after treatment completion by Pharos. Seven patients continued drinking and two patients were hospitalized at the psychiatric unit of a general hospital because of relapse during treatment by Pharos. None of these patients experienced severe detoxification related adverse effects. So alcohol withdrawal at home seems to be feasible and safe as already concluded in previous studies (Nadkarni et al. 2017, Stockwell et al. 1991).

DISCUSSION

The number of patients is growing over the years, which could mean that the need for home treatment is high. GPs are now more accustomed with the mobile teams which make them refer more patients. It could also indicate a good patient and referrer satisfaction.

Patient satisfaction was high in our population in concurrence with several other studies.

Some of our patients did not accept an inpatient treatment but completed detoxification at home, which points out the importance of giving certain eligible patients this possibility. It will increase acceptability of treatment and will lead to a greater number of patients to be reached. This seems to be the case not solely for alcohol dependence, but for other psychopathology as well.

Our care rate is relatively high (82% inclusions), probably because the demand comes from the health sector (mostly GPs or psychiatrists). They can make a good estimation on the kind of intervention needed. A study by Deschietere et al. found that most of the inclusions in their mobile team were requested by the health sector. When the requests came from patients, their families or other non health care workers the inclusion rates were lower (Deschietere 2019).

The most common referral reasons were suicidal thoughts (29%) and depressive mood (28%) and main referrers are GPs (40%). This is in line with a retrospective study of the activities of a home-based crisis team in North Cork that showed low mood as the most common referral reason (40%) and GPs as the most important referrers (56%) (Lalevic et al. 2019).

The male/female ratio in our population was 37%/63%. It is well known that women are more likely to use mental health services than men. The ratio male/female for alcohol withdrawal at home was 37.5/62.5%. This is in line with a review of Nadkarni et al. that showed a predominance of males in almost all studies (Nadkarni et al. 2017). 50% of our patients completed detoxification and were abstinent. The review of Nadkarni showed detoxification completion rates from 50% to 100%. They did not conclude on effectiveness because of the heterogeneity of outcome measures (Nadkarni et al. 2017). In our population abstinence was only evaluated in a clinical interview at the end of treatment, so we cannot make any conclusions on the outcome. Neither was there a longer term follow-up to evaluate if abstinence was sustained. Randomised controlled trials with formal outcome measures and long term follow-up are needed to evaluate on the effectiveness of community detoxification.

CONCLUSION

We can conclude that many psychiatric crisis situations can be managed at home with support of mobile teams, but further research is needed to provide evidence on outcome and cost effectiveness.

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All data were collected by the Pharos team.

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Contribution of individual authors:

Liesbeth Santermans managed the literature search, data interpretation and she wrote the article.

Nathalie Vanderbruggen, Dieter Zeeuws & Cleo L. Crunelle reviewed the manuscript.

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MANAGEMENT OF ARFID (AVOIDANT RESTRICTIVE FOOD INTAKE DISORDER) IN A 12-YEAR-OLD ON A PAEDIATRIC WARD IN A GENERAL HOSPITAL: USE OF MIRTAZAPINE, PARTIAL HOSPITALISATION MODEL AND FAMILY BASED THERAPY

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SUMMARY

Background: Avoidant Restrictive Food Intake Disorder (ARFID), at the cross roads of eating and feeding disorders, is sometimes called an "umbrella diagnosis" as it covers a certainly large and rather heterogeneous list of eating symptoms. It came with the DSM5 (2013) but still, there are no clear guidelines re diagnosis and treatment.

Purpose: Through this case, we aim to report not only a presentation of ARFID, but also how this relatively new and emerging diagnostic category has been identified and managed on a Pediatric Ward, in a General Hospital.

Subject and methods: This study reports the case of a 12y old girl Irish girl with ARFID treated by a multi-disciplinary team on a Pediatric Ward in a general hospital. A literature review regarding ARFID was concomitantly carried on, in order to consider the current therapeutic options recommended.

Results: 3 admissions on a pediatric Ward were necessary for this patient with ARFID, who was successfully managed with a partial hospitalization model, Family Based Treatment (FBT) and Mirtazapine.

Conclusions: The dynamic around the management of this condition is the occasion to discuss the other therapeutic options suggested these days, and more specifically the different pharmacological molecules that have also been used in young patients with ARFID and the importance of involving a multi-disciplinary team.

Key words: Avoidant Restrictive Food Intake Disorder (ARFID) - child psychiatry - Mirtazapine - partial hospitalization model - Family Based Treatment

* * * * *

INTRODUCTION

The notion of ARFID was brought in the DSM 5 (2013); at the cross roads of eating and feeding disorders, it is characterized by inadequate nutritional or caloric intake leading to unintentional weight loss, nutritional deficiency, supplement (including enteral feeding) dependence, and/or significant psychosocial impairment. 3 subgroups were identified depending on the eating pattern that leads to ARFID symptoms and therefore motivates the food avoidance, each with distinct associated features:

- those with limited variety associated with the sensory features of eating (e.g. finicky or picky eating);
- those with limited intake that were associated with poor appetite or limited interest in eating;
- those whose avoidance of eating had occurred in response to a specific event and is associated fear of negative consequences from eating (e.g. gagging, choking or vomiting).

DSM 5 made clear that individuals with ARFID can only be diagnosed in the absence of weight or shape concerns. That being said, patients with ARFID may experience poor body image related to being visibly smaller in height and/or weight, by their same-age peers (Vargas 2018).

Furthermore, the feeding or eating disturbance cannot be explained by lack of available food or by an associated culturally sanctioned practice. The eating disturbance cannot occur exclusively during the course of anorexia nervosa (AN) or bulimia nervosa (BN), nor can it be attributable to a concurrent medical condition or be better explained by another mental disorder.

Though specific numbers are hard to track, Katzman et al. recently (2019) identified that the prevalence of ARFID among children and adolescents ranges from 1.5% to 23% among eating disorder day treatment and inpatient treatment settings. They also established that children and adolescents with ARFID are younger, include a greater proportion of boys (although still predominantly girls) and have a longer duration of illness compared with patients with AN. Their studies also showed that patients with ARFID compared to those with AN, appeared to have a greater likelihood of comorbid and /or psychiatric illness (obsessive compulsive disorder, generalized anxiety, autistic spectrum disorder, learning disorder and cognitive impairment).

In order to make a diagnosis of ARFID, it is highly recommended to get a thorough developmental, feeding, nutritional and psycho-social history to fully understand how a patient's presentation impacts their current physical and psychological well-being, though currently, there is no empirically validated treatment for ARFID.

SUBJECTS AND METHODS

This study reports the case of a 12y old Irish female patient with ARFID admitted on 3 occasions on a Pediatric Ward in a General Hospital and treated by a multi-disciplinary team. Concomitantly, between March 2018 and May 2019, a literature search based on electronic bibliographic databases as well as other sources of information (grey literature) was conducted in order to investigate the current ARFID treatment modalities and to guide our therapeutic path especially around psychopharmacology.

RESULTS

First Presentation and Admission to the Pediatric Ward

Alayah is a 12-year-old Irish girl who lives with both her parents and who is a high achiever pupil, currently in 5th class in National School. She is a popular girl with a lot of friends. She has a lot of hobbies and is a fantastic athlete. She though admits that she always wants to be “the best” and explains that sometimes she “puts herself under pressure”. Alayah has no psychiatric nor medical personal history. There are medical or psychiatric family antecedents. Her Mum has had 2 children from a previous marriage (1 boy who is 26y old and 1 girl who is 22y old) who now live independently. Both Alayah’s parents are working and Alayah is very close to them and to her siblings who are worried about the fact she is not eating and losing weight.

2 weeks prior to her first hospital admission, she was referred to the Emergency Department (ED) in Wexford General Hospital (WGH) Ireland, by her GP for severe constipation and Movicol (manufactured by Norgine Limited, New Road, Hengoed, Mid Glamorgan, CF82 8SJ, U.K.) was prescribed. But after 2 weeks, the GP refers Alayah to the ED as she has lost 2kg (weight: 41.2kg, height: 161.7 cm, BMI 15.8 which is at the 15th percentile) and is deteriorating as she cannot eat solids, vomits after solids and has no appetite. She is reported to drink water but to complain of nausea and cramps in the abdomen while having no energy. She also reports severe constipation, dizziness, crushing fatigue and body

aches. At that stage, the Pediatric team decides to hospitalize Alayah in order to run different tests. No organic cause to Alayah’s symptomatology is identified (her medical examination and tests results are normal and only the reduced food intake appears problematic. Testing for celiac disease is negative); a referral to Liaison Psychiatry is made.

During the first psychiatric evaluation of the patient, parents report that Alayah has always been a very fussy eater, that she had suffered from constipation since infancy. Her BMI has always been below the 20th Percentile. Mum reported how Alayah “tends to eat one food for a period of time and then moves onto another food”. Alayah explains how she dislikes the smell of foods and being surrounded by other people eating while eating at school. Parents and Alayah report constipation has a significant impact on Alayah’s intake as it greatly reduces her appetite. This leads to an irregular eating pattern with further exacerbates the constipation.

The parents say that Alayah’s reaction towards constipation is initially to stop eating her meals for a day or two, before restarting eating small portions of food. Alayah explains that she has been ‘badly constipated’ for the past month and that she feels constantly nauseous. She reports that she is afraid to eat because she thinks she would get sick. She explains that last Saturday, she ate some pizza at a birthday party but felt sick and vomited it afterwards. While on Movicol, she experienced some liquid stools/fecal incontinence which were very embarrassing, especially as she was doing gymnastics.

She denies any history of binge eating, self-induced vomiting or use of laxatives (apart from Movicol), diuretics or diet pills. She also expresses the fact that she has no issue re body image and that “if anything, I am too thin as you can see my bones and I would like to put on some weight”. She presents euthymic, not psychotic and not suicidal and apart from the fear of “being sick” if she eats, she has no psychiatric symptom. This presentation is consistent with a diagnosis of a restrictive/avoidant food intake disorder; this is discussed and explained to the patient and her family (Table 1).

Table 1. Growth History (12.03.18 - 17.07.2018)

Location	1 st Hospital Admission	2 nd Hospital Admission	Hospital Discharge	1 st Child Psychiatry Review	Final Child Psychiatry Review
Date	12.03.18	27.03.18	01.06.18	12.06.2018	17.07.2018
Age (years and months)	12 years 1 month	12 years 1 month	12 years 4 months	12 years 4months	12 years 5 months
Weight (kg)	41.2 (46.81 st centile)	39.4 (38.21 st centile)	45.0 (59.10 th centile)	43.8 (53.98 th centile)	42.4 (46.02 nd centile)
Height (m)	1.618 (92.2 nd centile)	1.618 (92.2 nd centile)	1.618 (88.5 th centile)	1.618 (88.5 th centile)	1.618 (87.1 st centile)
BMI (kg/m ²)	15.7 (13 th centile)	15.1 (6 th centile)	17.2 (33 rd centile)	16.7 (<25 th centile)	16.2 (17 th centile)

Subsequently, Alayah is discharged from the Ward (after 3 days in WGH) and referred for outpatient department (OPD) follow-up both in Pediatrics and in Child and Adolescent Mental Health Services (CAMHS) with a view of starting Family Based Treatment (FBT) also sometimes referred to as the Maudsley method.

Second Admission on the Pediatric Ward

2 weeks later, following an OPD pediatric review, Alayah is re-admitted on the Ward. Her weight has dropped to 39.4 kg and her BMI is now 15 which is on the 6th percentile. On medical examination, the temperature was 37.2°C, the respiratory rate 16 breaths per minute and the oxygen saturation 98% while the patient was breathing ambient air; the blood pressure and pulse were 111/71 and 64 beats per minute during the day but her heart rate dropped to 50 beats per minute during the night. Her abdomen is soft and a bit tender. Sexual development was classified as Tanner stage 2; the remainder of the examination and the para-clinical (blood, urine, ECG) investigations were normal. The hemoglobin level, hematocrit, platelet count, red-cell indexes and results of liver and renal-function tests were normal as were blood levels of glucose, calcium, magnesium, total protein, globulin, and thyrotropin (Thomas et al. 2017). As Alayah has not yet been seen in CAMHS, a re-referral to Liaison Psychiatry is made.

Alayah's sleep has deteriorated and she feels exhausted all day long. She has been eating very little at home and is gagging (but not vomiting) each time she puts food in her mouth. She says her constipation has not improved despite the use of Movicol directed by the Consultant Pediatrician.

A multi-disciplinary approach is then decided with the Pediatric team, the Liaison Psychiatry Consultant and the Dietician, though a prudent referral to an inpatient CAMHS (specialized in Feeding/Eating disorders) is also made (unfortunately no bed would become available so no transfer was organized).

Whilst Alayah is on the Pediatric Ward, we intent to help her make meaningful gains in her weight, stabilize physically so that she could possibly be taken off the waiting list of the inpatient CAMHS and be managed in the community.

The strategy focused on increasing appropriate feeding behavior and decreasing maladaptive patterns. In that regard, it is crucial that everyone in the multi-disciplinary team is "on the same page". It is also essential to involve the parents in the care plan for consistency and sustainability of the results (FBT).

Meal plans are established and reviewed weekly with the dietician; they are calculated to cover Alayah's nutritional needs and help her restore a healthy weight. Besides increasing the food intake, the meal plans also progressively include various "new foods" for Alayah. This is first difficult for the patient who was very anxious about "having to eat more" and trying "new

foods", but progressively her level of stress decreases and she engages very well in this program. She even makes suggestions in order to make the meal more comfortable for herself.

A 1:1 special nurse remains with the patient when her parents are not available. Indeed, it is essential that Alayah is accompanied and supported, especially around meal times.

Several psychiatric appointments (including family sessions) are scheduled weekly, always associating a member of the Pediatric team, and aim to minimize the stress (psycho-education of parents and staff) and reduce medicalization (validate the psychological component of the patient's condition) to provide a neutral environment for Alayah (Albahari & Rabie 2018).

Also in order to keep the stress as low as possible, we tried to provide Alayah with a familiar environment. So, planned and gradual breaks from the hospital are organized so that she spends time at home, with her family, her friends and her pets. With the psycho-education provided, parents become more confident and they feel quite empowered and comfortable managing Alayah out of hospital. Her breaks out of hospital start to be regular and longer (a few hours in the beginning that are progressively extended to a full day and subsequently several nights and days out of the Ward), and help her to remain connected with her usual activities and friends. For example, she went on a school trip with the other pupils, but had to eat her full lunch, closely monitored by her teacher. This type of outing certainly stimulates her appetite and helps her to remain socially included. This can be considered as a partial hospitalization model as it falls on the continuum of mental healthcare between residential treatment and outpatient treatment. It includes individual and family intervention (FBT model), medication management, nutritional counselling and meal supervision. In the future group counselling should be a great and beneficial addition.

At this stage, the parents are not keen on a pharmacological option.

Alayah gradually improved (weight=45kg, BMI=17.2: 33th centile) and was discharged from hospital after 2 months of treatment. The relay is taken by her local CAMHS, from which she requests to be discharged after 3 reviews. CAMHS advised a follow up with the GP (weight monitoring) and Primary Care Psychology (ongoing support).

Third Admission on the Pediatric Ward

5 months later, Alayah attends an outpatient Pediatric review and her weight has dropped again (weight=39.2kg, BMI = 14.8: 3rd centile). The family is very worried and a decision of admission for physical observation and stabilization is made. Medical examination and para-clinical investigations are normal. A new referral to Liaison Psychiatry is issued.

Table 2. Growth History (06.11.18 - 21.05.2019)

Location	31 st Hospital Admission	Pediatric Review	Pediatric Review	Pediatric Review	Pediatric Review
Date	06.11.18	20.11.18	24.12.18	15.01.19	21.05.19
	Start Mirtazapine				
Age (years and months)	12 years 9 months	12 years 9 months	12 years 10 months	12 years 11 months	13 years 3 months
Weight (kg)	39.2 (24.51 st centile)	41.2 (33.72 nd centile)	45.0 (50 th centile)	46.0 (52.79 th centile)	49.5 (61.79 th centile)
Height (m)	1.627 (84 th centile)	1.627 (84 th centile)	1.63 (83.6 th centile)	1.63 (82.4 th centile)	1.65 (84.6 th centile)
BMI (kg/m ²)	14.8 (3 rd centile)	15.6 (8 th centile)	16.9 (24 th centile)	17.3 (29 th centile)	18.2 (40 th centile)

To the psychiatrist, Alayah essentially complains of constipation, nausea and abdominal cramps mostly at night. She explains that she gradually “slipped back” into her old habits of eating very small amount of food. She says she is constipated and that she cannot eat during the day (fear of being sick), but that she feels “ravenous” in the evening and eats only then. Subsequently she sleeps quite badly, often wakes up and spends hours on the toilet during the night. She says this is impacting on her concentration and that she feels tired and stressed during the day, which prevents her from eating before the evening and so the cycle continues.

Parents explain that they could not “stick to an eating routine” as they have been travelling abroad and that Alayah has refused to attend the GP to get her weight monitored. No contact was made with the Primary Care Psychology Services.

The diagnostic of ARFID is reiterated and a multi-disciplinary care plan similar to the previous one (partial hospitalization and FBT) is put in place for 2 weeks after which she continues to attend multi-disciplinary interventions in WGH as an outpatient.

This time, the patient and her family are agreeable to try medication. Various options are considered but Mirtazapine is started (7.5 mg nocte).

Mirtazapine enhances serotonergic and noradrenergic neurotransmission and also has some anticholinergic and antihistaminic effects (Hsiu-Wen & Tien-Chun 2011). It promotes appetite and weight gain, decreases nausea and vomiting and improves gastric emptying, which helps a lot with feeding issues (Gray et al. 2018). It also improves sleep and reduces anxiety (Mushtaq 2018). Of course, it is an off-label approach in the pediatric population but it was reported to have been successfully used in at least 2 other ARFID cases in children (Thomas et al. 2017, Tanidir & Hergüner 2015).

For Alayah, this worked a treat and helped her in many ways. Indeed, she reported sleeping much better at night time (falling asleep faster and not waking up during night time) and feeling less tired and less stressed during the day. She also noted that she did not feel nauseous anymore and that she was actually hungry

during the day. She started to eat more regularly and her constipation became less symptomatic.

As per table 2, once on Mirtazapine and while benefiting from the multi-disciplinary care plan, Alayah’s weight perked up and her BMI reached and remained in the healthy range. 6 months after starting the Mirtazapine, it is still early days, but she certainly got into a healthy eating routine and does not avoid food anymore (weight =49.5kg, BMI =18.2, 40th centile). She has restarted gymnastics and continues to attend multi-disciplinary reviews in WGH (pediatrician, dietician, psychiatrist and psychologist) (FBT) as an outpatient.

DISCUSSION

Psychopharmacology in ARFID

ARFID is a relatively new diagnosis category in psychiatry and to date, literature describing this disorder and guiding pharmacological treatment is limited. It certainly appears as a multi-faceted disorder that requires a multi-disciplinary approach.

Currently, the best clinical approach seems to focus on specific symptoms that may contribute to the condition and to identify and treat comorbid psychiatric conditions that may be exacerbating the patient’s symptoms of food avoidance/restriction and overall distress. Concurrent anxiety disorders are the most prevalent but major depressive disorder is also common among patients with ARFID (Nicely et al. 2014).

From a psycho-pharmacological point of view, there are no established guide-lines. In a case of ARFID, the first aim is generally to restore a healthy weight for the patient and also to reduce the level of stress/anxiety connected to the food intake. Targeted symptoms that may be treated with medication include severe situational anxiety about eating, as well as decreased appetite or early satiety resulting from chronic undernourishment (Thomas et al. 2017). It is important to specify that using a pharmacological agent should always be carefully considered and associated to other treating approaches (including behavioral treatment and FBT) and multi-disciplinary interventions.

Benzodiazepines (e.g. Lorazepam) can be considered for some extremely tense patients in the (very) short term in order to reduce food-related anxiety; for example, when introducing the meal plan system. Cyproheptadine has been identified as safe and effective for use in young children with eating difficulties related to low appetite (Bryant-Waugh 2019). Olanzapine at a low dosage has been used in order to reduce anxiety, stimulate the appetite and facilitate the eating process in young patients with ARFID. One recent study even mentions the benefit of using D-cycloserine to assist in exposure interventions in anxiety disorders (Sharp et al. 2017).

In a Pediatric population, Selective Serotonin Reuptake Inhibitors (e.g. Fluoxetine, Sertraline) are usually the first line treatment for anxiety and depression, though because of some of their potential side-effects, especially at the beginning of the treatment (nausea, vomiting, reduced appetite), they could exacerbate the difficulties in a patient with ARFID and actually contribute and/or complicate to the feeding/eating issues.

In this case, we decided to use Mirtazapine as a pharmacological adjuvant in the treatment of ARFID, because it was actually ticking a 'lot of the boxes' as it helped not only regarding anxiety and sleep but also reduced her nausea, helped her feel hungry and improved her stomach emptying process.

CONCLUSIONS

In 2013, the DSM 5 introduced the concept of ARFID which covers a rather large and heterogeneous list of eating/feeding symptoms; therefore, it is sometimes considered as "an umbrella diagnosis". The complexity of this pathology resides in its various presentations and aspects (even though some subgroups were identified, ARFID remains a rather imprecise entity). Its diagnosis and treatment must involve a multi-disciplinary team and a poly therapeutic input in order to address these multiple facets; the pediatric treatment seems obvious but so is the behavioral treatment, the dietetic approach, the mental health (psychiatry/psychology) input as well as individual, family and group treatment. Psychopharmacology can be very useful in some cases but requires to be thoroughly considered.

One crucial imperative is that "everybody participating must be on the same page". It is particularly important to "train the trainer" in order for consistency and sustainability of the results. Therefore, beside working with the patient, it is essential to also work with the staff and the family in order to reduce their stress levels and provide a neutral environment in which the patient will work on restoring a healthy weight.

Different treatment modalities can be put in place in order to optimally support the patient but also to help his rehabilitation and his connection to the real world. In

our case, Alayah started to be fully hospitalized on a Pediatric Ward, but progressively, she started to spend gradual planned and regular time at home, with her family and even in school, while coming back to the clinic for days of intensive multi-disciplinary interventions (Partial Hospitalization Model). These outings are extremely motivating for the patient and the family, and can help to reduce the anxiety and minimize the medicalization of ARFID. It is also helping to build confidence in how to manage situations out of hospital, both for the parents and the patient.

Finally, a multi-disciplinary outpatient follow-up 'seals the deal' and helps monitoring the progress and adjusting the interventions while keeping the patient in a healthy place.

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LANGUAGE IN MILD DEPRESSION: HOW IT IS SPOKEN, WHAT IT IS ABOUT, AND WHY IT IS IMPORTANT TO LISTEN

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SUMMARY

Background: Our previous research demonstrated that mild depression (MD) is characterized by patterns of atypical language use such as inverted word order, greater repetition, increased use of reflexive/personal (e.g. myself) or negative/indefinite (e.g. nobody) pronouns, verbs in past tense, and other lexico-grammatical, stylistic and syntactic indicators (how the patient speaks). We now investigate the role of semantic features (what the patient speaks about) in diagnosing (why it is important to listen) affective states.

Subjects and methods: 201 written narratives from 124 patients with MD and 77 healthy controls (HC), including 35 cases of normal sadness (NS), were studied using principle component lexis analysis. Statistical data evaluation was performed with SPSS-25 ($p < 0.05$, significant) and included the Cohen's kappa for inter-rater reliability, nonparametric methods to measure between-group differences (Mann-Whitney U-test, Pearson Chi-square test, Kruskal-Wallis, one-way ANOVA), and discriminant analysis for modeling of semantic variables related to affective diagnostic types.

Results: Component lexis analysis revealed an exaggerated usage of semantic categories describing existential and family values in the texts of MD patients compared to HC. However, there were fewer cognitive and altruistic categories presented in patients' self-reports. The most substantial between-group difference was the lesser semantics of self-realization in MD patients, as well as their significantly lower ranking of social status' priorities. Communicative and hedonic values in MD speech displaced and predominated in ranking over the values of social status, versus the opposite relationship in HC speech. The discriminant model revealed a set of semantic indicators significantly distinguishing the MD, HC and NS groups (96.3%; Wilks' $\lambda = 0.001$, $p < 0.001$, $r = 0.996$).

Conclusions: Linguistic structure and content of patients' verbalizations may serve as diagnostic markers of MD. Evaluation of psychosocial themes within the content of narratives should enable a better understanding of MD pathogenesis and emphasize the importance of monitoring social difficulties during treatment.

Key words: affective disorders - mild depression - component analysis - language - semantic categories

Abbreviations: HC - entire group of healthy controls; MD - mild depression; NH - normal healthy participants with euthymic state; NS - normal sadness

* * * * *

INTRODUCTION

Mild depression (MD) has been registered in 15% of the population (Shim et al. 2011) and demonstrates a continuous, gradual growth of disease incidence over recent decades (Wittayanukorn et al. 2014). MD often represents a maladaptive response of the individual leading to excessive reactions to environmental stressors (Kessler 1997), which causes personal and professional difficulties (Paykel et al. 2005), and brings an elevated risk of unemployment (Birnbaum et al. 2010) and social isolation. Indeed, the onset of MD is often precipitated by negative life events (Bagot et al. 2014, Paykel 2003), and social defeat stresses (Liu et al. 2017), leading to the adjustment disorder after chronic exposure (Hammen 2005). The continued exposure to stress

factors can initiate a recurrent course of depression (Liu & Alloy 2010, Monroe & Harkness 2005), bringing anhedonia, reduced quality of life (Yang et al. 2015) and increased suicidality risk (Holmstrand et al. 2008).

The pathogenesis of MD entails distortions in affective (e.g. sad mood) and cognitive (e.g. negative thought content) components presented only through patients' language, while in severe forms of depression also compounded by observable signs of motor component (e.g. slow bodily movements). However, there is a lack of objective tests to recognise MD, and its diagnosis can include subjective elements. Previous research shows that language can serve as a specific diagnostic marker of clinical depression (Anreassen & Pfohl 1976, Bernard et al. 2016, Bucci & Freedman 1981, Smirnova 2013, Trifu et al. 2017). In particular, MD patients demon-

strate atypical patterns of language use, which differ from those in a euthymic state or normal sadness (NS) as a non-pathological reaction to adverse life circumstances (see for literature overview and study details, Smirnova et al. 2013, 2018). Pennebaker et al. (2003, p. 548) postulated that “the styles in which people use words” as well as “the content of what they say” and “language per se” represent valid depictions of a patient’s affective symptoms. Our recent study showed that written narratives of MD patients differed in a number of respects from those of euthymic controls or individuals suffering from NS. The MD narratives were longer, of rather descriptive style, and marked by various features such as repetitions, increased use of personal pronouns, and verbs in continuous/imperfective and past tenses, consistently characterized by switching to the self-focusing style and to retrospective ruminations, expressed in the past tense (Smirnova et al. 2018).

The cognitive theory of depression describes dysfunctional thought patterns focusing on three areas of experience: the self, personal future, and the world (Beck 1995). In the event-congruency hypothesis, a match of the nature of stress factors and individual personal vulnerability substantially heightens the risk to develop depression (Beck 1987). Furthermore, intrapersonal conflicts contributing to the onset of stress-related depressions are exacerbated by the changing value systems and degraded social support of post-industrial societies (Targ 1976) in the era of “socially prescribed perfectionism” (Hewitt & Flett 1991). For example, contemporary social media popularize overly critical self-evaluation (Frost et al. 1990), and unrealistic or unattainable aspirations for self and others, all of which set the stage for decreased emotional well-being and depression (Hewitt & Flett 1990, 1991, Yang et al. 2015). Street et al. (2001) highlighted four psychosocial determinants of depression: (i) cognitive style resulting in a lack of positive intrapersonal and interpersonal communication, (ii) behaviors and the impact of environmental stressors, (iii) the individual’s pursuit of unrealistic goals and a perceived lack of control, and (iv) self-focus and self-reinforcement. The connection of these factors with language was introduced by Barnard’s observation (2009) that MD patients express ruminative and avoidant thought patterns and perceive word meanings selectively, focusing on the meanings of certain things, while neglecting other meanings. Luria (1975) defined the spoken or written word as “a special form of reflection of reality”, such that language establishes a secondary linguistic reality, e.g. whereby adding subjective meanings that bring deevaluation of self-realization, enables a person create a new, depressive reality. Language can thus establish the pathological basis for the formation of novel maladaptive meanings.

The key semantic component of depressive thought has the meaning of «internal threat» (Glukhareva 2000, Mikirtumov 2004), which undermines the integrity of

self-image and brings guilt-feelings and ruminations, where meanings of life can be lost (Hedayati & Khazaei 2014, Stillman et al. 2009). Following up Luria, Rudnev (2002) states that depression entails a revised linguistic representation of reality, where meaning is either decreased, absorbed by one universal negative meaning, or transitive in the sense that loss of value of one thing generalizes to all things, the so-called «objectlessness of melancholy».

In this study, we proceed from our earlier report on lexico-grammatical, stylistic, and syntactic indicators of language in depression (how patient speaks) (Smirnova et al. 2018), to a study of an analysis of the semantic characteristics of the content of patients’ language in relation to attenuated life meanings and values (what patient speaks about). As such, we test the hypothesis that these differences in language content also serve as a diagnostic marker (why it is important to listen to patient’s language), significantly distinguishing the affective states of MD, NS and euthymia.

SUBJECTS AND METHODS

201 participants were examined at the University’s Department of Psychiatry after giving written informed consent to participate in a study approved by the University Ethics committee). This group is identical to the study populations from our recent publication (Smirnova et al. 2018). The entire group included 124 patients with diagnosis of MD, who were of mean (SD) age 42 (12) years. In this MD group, 94 (76%) were females, 57 (46%) single or divorced, and 66 (53%) had a college or university degree. Their ICD-10 categories were: F32.0 (n=27; 22%), F41.2 (n=26; 21%), F43.20 (n=29; 23%), F43.21 (n=23; 19%), F43.22 (n=19; 15%). We also recruited 77 age-matched healthy controls (HC) of mean (SD) age 40 (12) years, of whom 61 (79%) were female. Of the 77 HCs, 42 participants were designated as normal healthy (NH) and 35 qualified as being in a state of normal sadness (NS), based on reporting current life problems and low mood. The ICD-10 categories of the NS group were: Z56 - Problems related to employment and unemployment (n=7; 20%), Z59 - housing and economic circumstances (n=14; 40%), Z60 - social environment (n=4; 11%), Z63 - primary support group, including family circumstances (n=10; 29%). The total Hamilton Depression Rating Scale-21 score for the MD group (Mean (SD)) was 14.3 (2.2), which differed significantly from that of the HC (3.03 (0.89)), NS (3.77 (0.65)) and NH (2.40 (0.50)) groups (ANOVA $F(2, 198)=4,110.05$, $p<0.001$, $\eta^2=0.976$), with significant paired between-groups differences after post hoc Bonferroni correction ($p<0.05$; $\alpha=0.05$), $p<0.001$.

There were 201 narratives (written self-reports on the topic «The current state of life and future expectations») investigated by the research team, consisting of a psychiatrist (DS), linguist (ES) and clinical psychologist (NK).

Table 1. Semantic categories and themes presented in the written narratives of individuals with mild depression, normal sadness and healthy participants

Semantic categories and themes	Descriptive statistics - n (%)			Between-group comparison			Effect size Cohen's f
	MD (n=124)	Control group		MD vs HC *	Kruskal-Wallis One-way ANOVA	Effect size	
		HC (n=77)	NH (n=42)				
<i>Existential category</i>	124 (100%)	65 (84%)	38 (49%)	27 (77%)	20.55	0.319	26.47
To be free	12 (10%)	10 (13%)	8 (19%)	2 (6%)	5.52	0.165	10.38
To live	124 (100%)	64 (83%)	38 (42%)	26 (74%)	22.38	0.334	30.50
To love	73 (59%)	29 (38%)	18 (42%)	11 (31%)	3.64 [#]	0.134	4.80 [#]
<i>Family category</i>	124 (100%)	59 (76%)	32 (76%)	27 (77%)	8.10	0.200	8.07
To pass on the best to one's children	121 (98%)	54 (70%)	27 (64%)	27 (77%)	8.74	0.208	10.71
To live for the sake of one's family	104 (84%)	58 (75%)	31 (74%)	27 (77%)	2.58 [#]	0.113	2.66 [#]
To help relatives	120 (97%)	52 (68%)	29 (69%)	23 (66%)	9.10	0.212	9.18
<i>Self-realization category</i>	34 (27%)	42 (55%)	26 (62%)	16 (46%)	55.60	0.525	57.94
To perfect oneself	12 (10%)	33 (43%)	21 (50%)	12 (34%)	46.70	0.482	49.53
To realize oneself	14 (11%)	38 (49%)	23 (55%)	15 (43%)	64.44	0.566	65.77
To realise opportunities	9 (7%)	33 (43%)	21 (50%)	12 (34%)	52.83	0.512	55.76
<i>Social status category</i>	20 (16%)	36 (47%)	22 (52%)	14 (40%)	42.64	0.460	44.11
To be successful	2 (2%)	16 (21%)	11 (26%)	5 (14%)	21.40	0.326	24.60
To make a career	11 (9%)	28 (36%)	19 (45%)	9 (26%)	36.19	0.424	41.28
To achieve high social status	11 (9%)	26 (34%)	17 (40%)	9 (26%)	34.89	0.416	37.98
<i>Communicative category</i>	20 (16%)	30 (39%)	17 (40%)	13 (37%)	13.25	0.256	13.30
To be together with a significant other	7 (6%)	24 (31%)	15 (36%)	9 (26%)	23.72	0.343	25.06
To feel needed by others	10 (8%)	8 (10%)	2 (5%)	6 (17%)	0.32 [#]	0.040	3.89 [#]
To enjoy friendship	11 (9%)	11 (14%)	11 (26%)	2 (6%)	2.90 [#]	0.120	10.46
<i>Hedonic category</i>	28 (23%)	23 (30%)	15 (36%)	8 (23%)	1.33 [#]	0.081	2.99 [#]
To derive pleasure	4 (3%)	19 (25%)	13 (31%)	6 (17%)	21.57	0.328	25.04
To be happy	5 (4%)	17 (22%)	11 (26%)	6 (17%)	15.87	0.280	17.39
To have sensations	26 (21%)	18 (23%)	13 (31%)	5 (14%)	0.16 [#]	0.028	3.25 [#]
<i>Cognitive category</i>	8 (6%)	19 (25%)	8 (19%)	11 (31%)	15.28	0.275	17.79
To know oneself	8 (6%)	10 (13%)	2 (5%)	8 (23%)	13.62	0.260	25.58
To know God	2 (2%)	1 (1%)	1 (1%)	0 (0%)	0.12 [#]	0.024	1.21 [#]
To understand life	4 (3%)	16 (21%)	6 (14%)	9 (26%)	12.38	0.248	13.92
<i>Altruistic category</i>	4 (3%)	18 (23%)	12 (29%)	6 (17%)	19.79	0.314	22.24
To help others	2 (2%)	13 (17%)	7 (17%)	6 (27%)	16.04	0.282	15.97
To do good to others	1 (1%)	7 (9%)	4 (10%)	3 (9%)	8.53	0.206	8.53
To improve the world around one	2 (2%)	9 (12%)	9 (21%)	0 (0%)	9.32	0.215	26.14

* p<0.05 significant; [#] n.s. non significant p>0.05; HC: The entire healthy control group; NH: Normal healthy participants with euthymic state; NS: Normal sadness; MD: Patients with mild depression

Detailed analysis of lexico-grammatical, lexico-semantic and syntactic features of the texts are presented in our recent paper (Smirnova et al. 2018). We now focused on semantic features of the text, which were evaluated using component lexis analysis (Mikirtumov 2004). This hierarchical analysis consisted of three stages: 1) determining for each utterance the keywords, known as lexical-grammatical items, i.e. the smallest semantic units, 2) combining the keywords into semantic ranks (known as lexical-semantic groups), which are based on the common semantic meaning, and finally 3) codifying the semantic ranks into semantic themes, and then into semantic categories, known as semantic extra-items or arch-items. We used the classification of fundamental semantic themes and categories to standardize themes and categories obtained at the final stage of component analysis (Kotlyakov 2013; Table 1). Each language sample was scored by the profile of semantic themes and categories presented in the text. For example, we analyzed the MD utterance “I was useless and did not help anybody, neither my daughter, nor my grandchildren” according to a consensus-based opinion of the three team members, following the defined stages of the component lexis analysis: 1. Keywords “useless”, “help”, “daughter”, “grandchildren”. 2. Semantic ranks “help/aid” and “relatives”. 3. Semantic theme “To help relatives” and Semantic category “Family”. Each of the three researchers rated all the texts using component analysis and by codifying semantic arch-items. While one rater (DS) was unavoidably informed about the clinical state of the participants, the other two raters were blind regarding the group assignment. The simple majority (two out of three raters) resolved any conflicts regarding semantic categories.

All statistical analyses were performed with the IBM SPSS Statistics 25 (IBM Corp. 2017). An inter-rater reliability (the Cohen's Kappa, k) was assessed to determine consistency between the three raters in coding the semantic features. Differences between groups were evaluated using the nonparametric Mann-Whitney U-test, Pearson Chi-square test, and Kruskal-Wallis, one-way ANOVA, depending on the variable type and number of groups compared. Values of $p < 0.05$ were

deemed to be statistically significant. Mathematical modeling of discriminant analysis (λ -Wilks; method Standard) was applied to establish the level of significance in relation to between-group differences and included semantic categories and themes as independent variables.

RESULTS

The average inter-rater reliability on semantic categorization between the two blind raters was high: $k = 0.834$, $p < 0.001$, 95% CI (0.802-0.857). Component lexis analysis showed that texts of patients with MD significantly differed from written reports of HC and NS participants in the majority of examined semantic categories and themes (Table 1).

Semantic categories describing existential and family values were exaggerated in the narratives of MD patients compared to HC, while cognitive and altruistic categories were mentioned significantly less often in MD patients' texts, in line with the rest of categories. However, selected themes such as “to love” from the existential category, “to live for the sake of the family” from the family category and “to know God” from the cognitive category, did not show statistically significant differences between MD, HC and NS groups. The most substantial between-group difference, according to the size-effects, was the lesser representation of self-realization in MD patients, as well as their significantly lower ranking of social status' priorities. Communicative and hedonic values in the MD group were displaced and prioritized in ranking over the values of social status, which was the opposite finding to that in the HC group (Table 1, 2).

The discriminant analysis revealed that our mathematical model significantly characterized the study sample such that the set of semantic categories and themes distinguishes affective states of MD, NS and euthymia in NH with a probability of 96.3% (Figure 1). The spread of canonical discriminant functions demonstrated significant differences between MD, NS and NH (96.3%; test of functions 1 through 2: Wilks' $\lambda(180) = 0.001$, $p < 0.001$, canonical correlation $r = 0.996$).

Table 2. Ranking of Semantic categories presented in the texts of patients with mild depression and healthy participants

Study groups Semantic Category	HC		MD	
	№ Ranking	n (%)	№ Ranking	n (%)
Existential	1	65 (84%)	1 >	124 (100%)
Family	2	59 (76%)	2 >	124 (100%)
Self-realization	3	42 (55%)	3 <	34 (27%)
Social status	4	36 (47%)	5	20 (16%)
Communicative	5	30 (39%)	6	20 (16%)
Hedonic	6	23 (30%)	4	28 (23%)
Cognitive	7	19 (25%)	7 <	8 (6%)
Altruistic	8	18 (23%)	8 <	4 (3%)

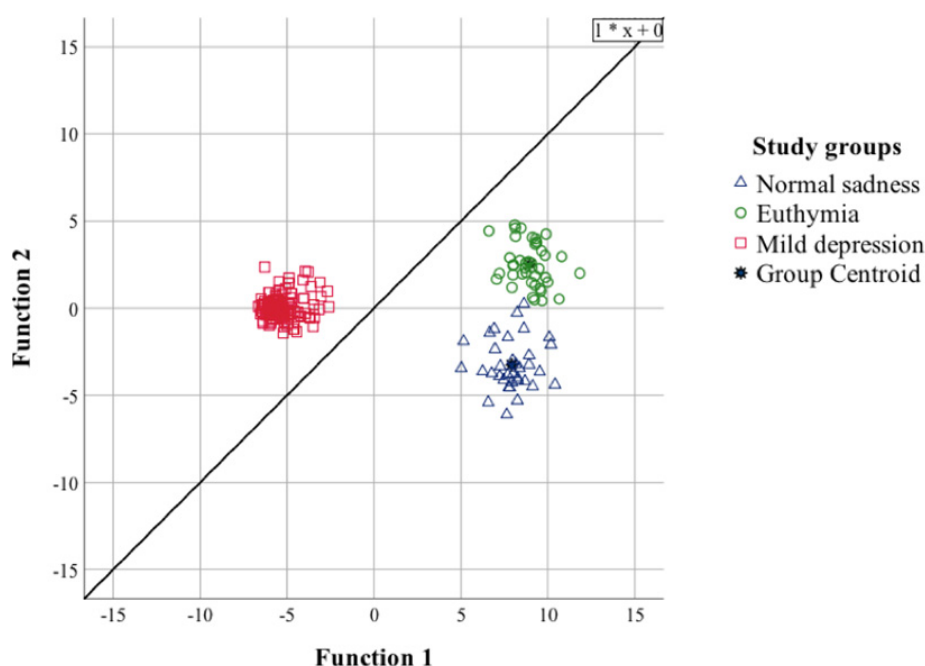


Figure 1. Canonical discriminant functions. Discriminant model of the diagnostic types of mild depression, normal sadness and euthymia, based on component lexis analysis of narratives

DISCUSSION

The topic for written reports of our study participants «The current state of life and future expectations» was chosen to investigate those psychosocial themes and life priorities that tend to be emphasized by MD patients in the contextual framework of experiencing their depressed mood. Consistent with our previous analysis of language style (Smirnova et al. 2018), we found that narratives of MD patients differ significantly from those in NS and euthymia according to the spectrum of semantic categories and themes presented in the written content, i.e. semantic features correlated with an affective component. This finding supports the proposition that language can serve as a diagnostic marker of clinical depression (Anreassen & Pfohl 1976, Bernard et al. 2016, Bucci & Freedman 1981, Smirnova 2013, Trifu et al. 2017), and gives important new information about the linguistic basis of the distortion in the spectrum of semantic categories in MD; some were over-prioritized, and others were significantly reduced (Barnard 2009, Pennebaker et al. 2003, Rudnev 2002). Thus, the new finding of significantly attenuated semantic representation of categories of self-realization and social status, along with a lower ranking of social status in the MD group, is consistent with other findings that depression is associated with professional disabilities (Paykel et al. 2005) and unemployment (Birnbaum et al. 2010). These social deficits arise from impaired intrapersonal and interpersonal communication (Street et al. 2001), where lower life meanings lead to selective neglect of previously held priorities more in accord with euthymia (Barnard et al. 2009, Rudnev 2002, Hedayati & Khazaei 2014, Stillman et al. 2009). These changes

exacerbate the increased social distance by switching to a more self-focusing style (Pennebaker et al. 2003), accompanied by a tendency for unhealthy criticism of self, other people, and external events (Beck 1995, Monroe & Harkness 2005, Stillman et al. 2009). In MD, this self-focusing style with reduced societal values enables avoidance of traumatic circumstances, which further compromise integration into society, often due to a sense of failure to have achieved the unrealistic standards typical of modern societies (Hewitt, Flett 1990, 1991). However, narratives of the MD patients had an elevated occurrence of family category, and the communicative category supplanted social status values in ranking, while remaining significantly lower in comparison to HC. This re-prioritization might be attributed to a search for support from the primary social group as a compensatory strategy in response to the decreased sense of social well-being due to experiencing social pressure and psychosocial stressors, perceived or real (Beck 1987, Hedayati & Khazaei 2014, Kessler 1997, Stillman et al. 2009, Yang et al. 2015).

The fewer instances of hedonic category in the MD group has an obvious association with symptoms of anhedonia (Yang et al. 2015). The concomitantly lower content related to altruistic and cognitive categories reflects the problems to prioritize the high level of values in the hierarchy of needs (e.g. morality, faith) following the difficulties with the basic needs of safety (e.g. resources, employment) (Hedayati & Khazaei 2014), which also seems at odds with the self-focusing strategies typically observed in depression (Pennebaker et al. 2003). That certain semantic themes such as “to love” from the existential category, “to live for the sake of the family” from the family category and “to know

God” from the cognitive category did not significantly differ between MD, NS and HC groups points to them as life priorities that are resilient to or independent of depressive mood. Thus, the most prominent differences between MD, NS and HC lie in the area of decreased social values within self-realization and social status («to realize oneself», «to realize opportunities», «to make a career»), also include low cognitive and altruistic intentions and, conversely, exaggerated existential («to live») and family («to pass on the best to one’s children», «to help relatives») semantics.

CONCLUSIONS

Features of language structure and of content may represent objective diagnostic markers of MD. Precise evaluation of psychosocial themes specified in the content of patients’ verbalizations or writings might also impart a better understanding of the pathogenesis of MD, which often starts as a maladaptive reaction to social stressors, then exacerbated by further social difficulties arising due to the depression itself. In the absence of reliable biomarkers or test for MD, linguistic analysis (listening to what the patient says) may afford accurate monitoring of the dynamics of affective state during treatment.

Limitations of the study

We studied written narratives, which may not relate simply to natural speech flow in MD. Our classification systems for semantic categorization is based on earlier investigations of Russian language speakers and, being inseparable from life values and priorities, might be specific to the Russian mentality. Therefore, the cross-cultural validity of this analysis must be confirmed by further investigation. Future research would benefit from application of expanded semantic approach, through implementation of a questionnaire specifically designed for diagnosis of MD. Such a questionnaire based on analysis of semantic categories and psychosocial topics, while also probing relationships between salient stress factors and individual vulnerabilities of life values and priorities, might reveal optimal targets for psychotherapeutic interventions.

Contribution of individual authors:

Daria Smirnova, Elena Sloeva & Gennadii Nosachev designed the project.

Daria Smirnovaa & Gennadii Nosachev collected the data.

Daria Smirnova, Elena Sloeva, Natalia Kuvshinova & Gennadii Nosachev analyzed the data with advice from Dmitry Romanov & Paul Cumming.

Daria Smirnova & Paul Cumming wrote the first draft of the manuscript, and revised upon input from the other co-authors.

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BIPOLAR DISORDERS AND BIPOLARITY: THE NOTION OF THE "MIXITY"

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SUMMARY

The notion of "mixity" of the dysphoric phases of the bipolarity includes the most insidious symptoms of the bipolar spectrum of mood disorders: the overlapping between depression-restlessness-irritability-grief-tension-anxiety can cause worsening of the mood disorders and in the most acute phases may cause increased risk of major behavioural disruption including murder and suicide. The early utilization of the rating scale on mixed states, "GT-MSRS", which can demonstrate the level of "mixity" of the mood disorder, can prevent this.

Key words: bipolar spectrum disorders – early diagnosis – mixed states – mixity - mixed state rating scale – GTMSRS

* * * * *

INTRODUCTION

The dysphoric component of mood (mixed states) is quite frequent among all the subtypes of the bipolar spectrum. Mixed states include approximatively 30% of all mood spectrum disorders (Tavormina 2010, 2013, Akiskal 2000, Perugi et al. 2014), however, they are pathologies which are often underestimated or, worse, not diagnosed or treated inappropriately (Agius 2007, Tavormina 2007, 2018).

Emil Kraepelin was among the first psychiatric nosologists who described the mixed states. In his 1921 treatise "Manic-Depressive Insanity" Kraepelin stated that "very often we meet temporarily with states which do not exactly correspond either to manic excitement or to depression, but represent a mixture of morbid symptoms of both forms of manic-depressive insanity". He thus specified six types of mixed states, based on various combinations of manic and depressive mood, thought, and behaviour. These were: depressive or anxious mania, excited depression, mania with poverty of thought, manic stupor, depression with flight of ideas, and inhibited mania.

As we can see, Kraepelin's description is absolutely correct, so that the modern classifications of the bipolar disorders and mixed states are similar (Akiskal 1996, 2000, Tavormina 2007) (Tables 1, 2).

As Akiskal wrote, the depressive expressions of bipolar disorders have long been neglected; it is crucial to exam the different clinical expressions of bipolar depression including, among others, retarded depression, agitated and/or activated depression, mood-labile depression, irritable-hostile depression, atypical depression, anxious depression, depressive mixed state, and resistant depression (Akiskal 2005).

Clinicians find great difficulties in making a correct diagnosis of the mood disorders which they are assessing, above all when mixed states are present: this is because the patients mainly focus their own symptoms on depressive uneasiness (inducing the clinicians to frequently prescribe antidepressants drugs alone or together

with benzodiazepines), inducing them to prescribe these inadequate treatments and not take note of the real problem of increasing dysphoria caused by these treatments (Tavormina 2018).

CLINICAL CONSIDERATIONS

The following are the main symptoms of the mixed states are (Tavormina & Agius 2012): depressed mood together with irritability, anhedonia and widespread apathy, reduced ability to concentrate and mental over-activity, a sense of despair and suicidal ideation, hyper/ hypo- sexual activity, insomnia, comorbidity with anxiety disorders (PAD, GAD, OCD, soc ph.), various somatisation symptoms (mainly: gastrointestinal disorders, headaches), disorders of appetite, substance abuse (alcohol and/or drugs), delusions and hallucinations, antisocial behaviour. At least two or more of them need to be present (Tavormina & Agius 2012). How many times the news we can hear or read contains reports of murders, murders-suicides, familiar massacres, rapes, substance abuse connected with violence, etc.: very often a bipolar mood disorder illness, untreated or mistreated, is responsible of these facts.

The "mixity" of depressive phases (that are the most insidious symptoms of overlapped depression-restlessness-irritability) can cause increased risk of suicidality (Akiskal 2007): the intensity of these symptoms can be shown using the rating scale for mixed states "GT-MSRS", (Tavormina 2014), an easy rating scale to administer to the patient structured in eleven items (and 7 sub-items), to demonstrate the level of the mixity (a score from 2 to 6: medium-light level; a score from 7 to 12: medium level; a score from 13 to 19: high level); (Tavormina 2014, 2015).

METHODS

All the points of mixity symptoms are contained inside the rating scale "GT-MSRS", structured in eleven items, eight of them subdivided in sub-items (Tavormina 2014) (Figure 1).

Table 1. Akiskal's schema of bipolar spectrum (Akiskal & Pino 1999)

- Bipolar ½:** schizobipolar disorder
Bipolar I: core manic-depressive illness
Bipolar I½: depression with protracted hypomania
Bipolar II: depression with discrete spontaneous hypomanic episodes
 (*Bipolar II, "sunny" bipolars* - hypomanic periods (2-3 days) characterized by cheerfulness and jocularity, people-seeking, increased sexual drive and behavior, talkativeness and eloquence, confidence and optimism, disinhibition and carefree attitudes, reduced sleep need, eutonia and vitality, and over-involvement in new projects).
Bipolar II½: depression superimposed on cyclothymic temperament
 (*Bipolar II½: Unstable, "darker" BP II* - dysphoric, irritable hypomania superimposed upon an inter-episodic cyclothymic temperament ("roller-coaster" course often misinterpreted or misdiagnosed as borderline personality disorder). Often comorbid with panic disorder and social phobia, as well as, bulimia and borderline personality disorder).
Bipolar III: depression with induced hypomania (i.e., hypomania occurring solely in association with antidepressant or other somatic treatment)
Bipolar III½: prominent mood swings occurring in the context of substance or alcohol use or abuse
Bipolar IV: depression superimposed on a hyperthymic temperament
 (*Bipolar IV: VERY DANGEROUS condition* - depression superimposed on a stable hyperthymic temperament: exuberant, articulate and jocular, overoptimistic and carefree, overconfident and boastful, high energy level, full of plans and activities, ... with broad interests, over involved, uninhibited and risk-taking, and an habitual short sleeper. And suddenly slip into deep (often) treatment-resistant depression. This is an extremely DANGEROUS condition because hyperthymic individuals are intolerant of any degree of depression, and certainly poorly tolerate the affective dysfunction associated with a depressive mixed state. Many mysteries about suicide, and suicides that one reads about in the newspaper (ie, "an extremely successful and happy person, who had everything, put the gun in his mouth") may well belong to this category).

"G.T. Mixed States Rating Scales", or "G.T. MSRS"		Yes	Not
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<i>Self-administered rating scale -</i>			
Has there ever been a period of time during last three months when you frequently were and/or presented/felt ...		Yes	Not
1) Hyperactivity (euphoria) quickly alternating with periods of psychomotor retardation (apathy)?		
If Yes, for how many days/weeks?		
2) Depressed mood together with irritability and/or internal tenseness?		
If Yes, for how many days/weeks?		
3) Substance abuse (alcohol and/ or drugs)?		
If Yes, for how many days/weeks?		
4) Disorders of appetite?		
If Yes, for how many days/weeks?		
5) A sense of despair and suicidal ideation?		
6) Anhedonia and widespread apathy?		
7) Delusions and hallucinations?		
8) Hyper or hypo-sexual activity?		
If Yes, for how many days/weeks?		
9) Insomnia (or sleep fragmentation) or hypersomnia?		
If Yes, for how many days/weeks?		
10) Reduced ability to concentrate and mental overactivity?		
If Yes, for how many days/weeks?		
11) Gastrointestinal disorders (colitis, gastritis), headaches, and various somatic symptoms (muscular tenseness; tachicardia)?	
If Yes, for how many days/weeks, and what of those symptoms?		
		\$\$\$\$\$\$\$\$	
<i>Additional points -</i>			
Could it be considered that, at the age of about 18-20 years (if you are more than 20 years old; if you are younger, please consider the answer as "during actual last years"), you were:			
(choose only one of these three following answers)			
- a person of very lively character-hyperactive and extremely cheerful ?		<input type="checkbox"/>
or			
- a person who always tended to be tense and irritable ?		<input type="checkbox"/>
or			
- a person always tended to be taciturn, solitary and melancholy, and also with anxiety symptoms (panic, phobia between persons, claustrophobia) ?		<input type="checkbox"/>
		\$\$\$\$\$\$\$\$	
"G.T. Mixed States Rating Scales" - Scores			
- The " <i>Additional Points</i> " help to focus about the Temperaments of the patient (hyperthymic temperament for the first point; cyclothymic temperament for the second point; depressive-anxious temperament for the third point).			
There is a Mixed states diagnosis if at least two YES answers are present ;			
- Give <i>Double scores</i> in the points 1-2-3-4-8-9-10-11 if at least 50% of the month is involved;			
- Level: <i>Medium-light level of mixed state</i> : from 2 to 6 scores;			
- Level: <i>Medium level of mixed state</i> : from 7 to 12 scores;			
- Level: <i>High level of mixed state</i> : from 13 to 19 scores.			
The positive result following to "G.T. MSRS" will conduct to do a generic diagnosis for mixed states sub-types of bipolar spectrum disorders, following Akiskal's scheme (The evolving bipolar spectrum: Prototypes I, II, III, IV. Psychiatr Clin North Am. 1999) or Tavormina's scheme (A study of the incidence of bipolar spectrum disorders in a private psychiatric practice. Psichiatria Danubina 2007) for bipolar disorders.			
The clinician will need of special care to do the correct sub-diagnosis of sub-group of mixed state.			

Figure 1. The rating scale "GT-MSRS" for mixed states (Tavormina 2014)

Table 2. Tavormina's schema of bipolar spectrum (Tavormina & Agius 2007)

Acute mania	
1 - Bipolar I	(→ dysphoric mania)
2 - Bipolar II	(→ rapid cycling bipolarity, mixed dysphoria)
3 - Cyclothymia	(→ rapid cycling bipolarity)
4 - Irritable Cyclothymia	(rapid cycling bipolarity)
5 - Mixed Dysphoria	(depressive mixed state)
6 - Agitated Depression	(→ depressive mixed state)
7 - Cyclothymic temperament	(→ Mixed Dysphoria, depressive mixed state, rapid cycling bipolarity, agitated depression, bipolar I-II)
8 - Hyperthymic temperament	(→ Agitated Depression, Irritable Cyclothymia, bipolar II)
9 - Depressive temperament	(→ brief rec. depr, agitated depression)
10 - Brief recurrent depression	(→ dysthymia, major depressive episode, agitated depression)
Unipolar Depression	

The presence of hyperactivity (or euphoria) quickly alternating with periods of apathy (or psychomotor retardation) is the matter of the first item; these symptoms are frequently present in the diagnosis of rapid cycling bipolarity and irritable cyclothymia. The presence of depressed mood overlapped with irritability and/or internal tenseness is the matter of the second item; these symptoms are frequently present in the diagnosis of mixed dysphoria and agitated depression. The presence of substance abuse (alcohol and/or drugs) and disorders of appetite are the matters of the third and fourth items: these symptoms are usually present in very unstable mood diagnosis (mixed dysphoria, agitated depression, irritable cyclothymia). Anhedonia and widespread apathy, and a sense of despair with suicidal ideation (5th - 6th items), are frequently present in the depressive phases of the instability (agitated depression; recurrent depression). Delusions and hallucinations (7th item), less frequent than other symptoms, might be found in all type of mood disorder mixed states. The presence of hypersexual activity or hypo-sexual activity are typical of the dysphoric-hyperthymic phases of the mood (the hyper-sexual activity) or of the depressive-agitated phases of the mood (the hypo-sexual activity). In the 9th item we find the insomnia (or sleep fragmentation), usually present in the agitated phases of the mood (mixed dysphoria, agitated depression, irritable cyclothymia) and instead the hypersomnia is typical of the depressive-agitated phases of the mood (recurrent depression, cyclothymia, agitated depression). The presence of mental overactivity and the reduced ability to concentrate (10th item) are the most typical symptoms of all mood mixed states diagnosis: these symptoms will be reduced by mood-stabilisers and then may disappear when the patients go into recovery. The last item is the 11th, the presence of somatisations (gastrointestinal disorders, such as colitis and gastritis; headache; muscular tenseness; tachycardia; atypical dermatological problems), in several conditions these may be the main clue which could help the psychiatrist to identify mixed states early, so that the clinician can diagnose them correctly and quickly.

The four diagnoses of "Recurrent Depression" and "Major Depression" emerged in the first validation study on "GT-MSRS" (Tavormina 2015) scored within the "medium level" of this rating scale, showing how the symptoms of mixity (in these examples: anhedonia; insomnia/hypersomnia; mental overactivity; hypo-sexual activity; sense of despair; somatisations) are diffused within all mood disorder sub-types, including "Recurrent Depression" and "Major Depression". In consequence of this, the prescription of mood stabilisers together with antidepressants, even in patients with a diagnosis of major depression or recurrent depression, is crucial for a good treatment.

FINAL EVALUATIONS AND CONCLUSIONS

Very often patients with bipolar disorders received a correct diagnosis after on average 25 years of illness (McCombs et al. 2007, McCraw et al. 2014, Akiskal-Benazzi 2005, Tavormina 2018). Clinicians find great difficulty in making a correct diagnosis of the mood disorders which they are assessing, above all when mixed states are present: this is because the patients mainly focus their own symptoms on depressive uneasiness, inducing the clinicians to frequently prescribe inadequate treatments such as antidepressants drugs alone or together with benzodiazepines, thus increasing dysphoria (Tavormina 2016, Agius et al. 2007). A correct approach to the diagnosis of bipolarity can be done using the rating scale "GT-MSRS".

The following significant sentence of Hagop Akiskal (from the Conference: "Melancholia: beyond DSM, beyond neurotransmitters" – May 2–4, 2006, Copenhagen) needs to be reflected on: "Melancholia as defined today is more closely aligned with the depressive and/or mixed phase of bipolar disorder. ... Given the high suicidality from many of these patients, the practice of treating them with antidepressant monotherapy needs re-evaluation".

And also: mixed states occur in an average of 40% of bipolar patients over a lifetime; current evidence supports a broader definition of mixed states consis-

ting of full-blown mania with two or more concomitant depressive symptoms (Akiskal et al. 2000).

All this means is that it is essential to remark once again what has been described in previous papers: that the "instability of mood", more than the "depression", is the main issue which the clinician needs to deal with in a patient with mood disorder; this relates to the important notion, that the depressive episode is only one phase of a broader "bipolar spectrum of mood" (Tavormina 2007, 2012, Akiskal 2000). In consequence of this, when considering bipolarity the notion of the mixity becomes the conceptual reference point of the diagnostic process.

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THE EMOTIONAL AND PSYCHOLOGICAL BURDEN OF THE "BURNOUT" IN FAMILIES OF PSYCHIATRIC PATIENTS

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SUMMARY

People, who assist patients with chronic health problems for work, voluntary or for family reasons, may be affected by burnout. This is defined as an excessive reaction to stress caused by one's environment that may be characterized by feelings of emotional and physical exhaustion, coupled with a sense of frustration and failure. A person who assists a suffering person, beyond the professional role, is indicated generally by the term "caregiver". The definition of Burnout in families is fairly recent, because the psychology of trauma has ignored a large segment of traumatized and disabled subjects (family and other assistants of "suffering people") unwittingly, for a long time. The burnout of secondary stress is due to one's empathic ability, actions through disengagement, and a sense of satisfaction from helping to relieve suffering. Figley (1995) claims that being a member of a family or other type of intimate or bonded interpersonal relationship, one feels the others' pain. Closely associated with the suffering of the family caregiver is the concept of compassion fatigue, defined as a state of exhaustion and disfunction-biologically, psychologically, and socially - as a result of prolonged exposure to compassion stress and all that it evokes. In families, this can be the cause of serious conflicts and problems, quarrels, verbal and physical aggression, and broken relationships. The intervention on families requires practice and effectiveness approaches performed by experienced professionals. Some approaches focus more specifically, such as those that adopt a cognitive/behavioural technique with direct exposure, implosion methods, various drug treatments and family group psychotherapy. One of the most common models of intervention is based on the principle that the observation unit for the understanding of the disorder is not the single individual but the relationship between individuals.

Key words: burnout - caregiver - family members - compassion fatigue

* * * * *

INTRODUCTION

The family care of a person affected by a chronic disabling disease can be characterized by a complex system of experiences, emotions, changes, opportunities, fatigue and stress (Stajduhar & Cohen 2009). Such experiences can occur in those ones who "assist" a series of events, sometimes unexpected, and they can generate several feelings and emotions, which can be simple and immediate, such as apprehension and alarm, or more complex and specific such as anger, despair, sense of abandonment and loneliness, impotence, inability. The consequences, often inevitable, on their current and future personal stories and on process of care were often poorly estimated and little valued, although they prove to be onerous and debilitating (Ursini & Nardini 2007). A person who assists a suffering person, beyond the professional role, is indicated generally by the term "caregiver". This term refers to a person who takes care of an addict and / or sick and / or disabled subject. The caregiver may be "a person who helps to meet the needs of a depending individual" (Johnson et al. 2016), or "a person who intervenes in diagnosing, preventing and treating illness and / or disability" (Nielsen et al. 2016). Caregivers can be divided into professional and non-professional subjects. The members of the families of the disabled person are included in this second group. "Conceptually, the term" burnout "in families may seem odd" observed Figley, in 1998 (Figley 1998). "After all, the dictionary

definition of Burnout is a noun meaning "termination of the powered portion of a rocket's flight upon exhaustion of the propellant" (Random House Dictionary). Similarly, burnout families can be considered as a signal that a family member is "left without gas". The definition of burnout in families is fairly recent, because the psychology of trauma has ignored a large segment of traumatized and disabled subjects (family and other assistants of the "suffering people") unwittingly, for a long time (Franza et al. 2012). This resulted "in other words, that caregivers ... have been ignored, while suffering, being in the right, for the love of a traumatized person" (Figley 1998). According to the model of the Maslach " burnout does not only affect the parties engaged in specific social and health professions, but all those who care for people or working in close contact with people for long periods of time, it points out, however, the specificity for all the helping professions" (Maslach 1982).

BURNOUT IN THE ORGANIZATIONAL STRUCTURES

Several complex personal and business affairs can produce burnout. In any form of work and care there are potential sources of stress; some organizational structures can create more stress and tension, while others can provide more stimulation and offer the possibility of a greater personal involvement, resulting in a greater gratification (McTiernan & McDonald 2015). Organizational structures can be represented by business,

education and the family systems where personality, motivations, interlocutors of the subject, dynamics of the organizational structure, the hierarchy and the type of activity constantly interact. Business and families' organizational structures are subject to malfunctions that affect the development of inadequate lifestyles and burnout in their members. Among the several critical factors there overworking, total disorganization of the structure, ambiguity of the role of each component of the system, a dysfunctional hierarchical structure, the lack of attention to human resources and, finally, economic difficulties are listed. The traumatic factors can also cause high stress in family system. Therefore, the important difference is that they cannot escape from the "refuge" of their house while they are trying to have a close contact with their loved one sick daily. In all organizational structures, and particularly in health care structures, the customer is hosted, heard, cared, and finally, discharged for by professionals. At the end of the care pathway there is the customer's separation. The detachment stage cannot be in the family. The family system experiences a continuous cycle. For this reason, the family members are more exposed to high levels of stress.

FACTORS OF VULNERABILITY IN HOUSEHOLD

Several family vulnerability stress factors in relative caregiver have been described. Among the main factors of vulnerability in family members there are anxiety and depression (Sander et al. 2003, Davis et al. 2009, Sady et al. 2010). There is a significant relation between patient and caregiver emotional status, not only for patients. Patient and caregiver's anxiety and depression develop in concordance and they were found to be higher in family caregivers than in a non-caregiving population (Yan et al. 2019, Haun et al. 2014). Patients with depression highly impact on the caregiver burden, while burden is also discussed to influence caregivers' depression (Krug et al. 2016). Younger families have increased risk of burnout (Stancin et al. 2010), and when financial problems and the poor social support, and poor social network (Aitken et al. 2009, Taylor et al. 2002) are added, the usual daily life is greatly impaired. Other risk factors in household are the low socioeconomic status (Bøe et al. 2018, Anderson et al. 2005, Urbach & Culbert 1991) and the conflict within the care team (Ganesalingam et al. 2008).

COPING STRATEGIES IN THE FAMILY

When the traumatized family's components have high levels of stress, the whole family environment remains involved. This family can be described as "family with burnout". Because of a low self-esteem, the family's member begins to think not to be able to provide the necessary assistance: he/she is not able to do his/her homework and solve any daily difficulties. The family members are no longer able to control the space,

they lose control of their role, and feel be "invaded" by their work (Tsaras et al. 2018). The stress response is coping. The individual chooses a specific way in which to deal with the stressful stimulus. Each family develops its own coping strategy to manage the "family turmoil". When this attempt to restore a balance fails, the family develops the crisis. For, example, a highly disabling disorder child constitutes a major violation to the family homeostasis. However, the family seem to possess a greater degree of protection because it tends to be more prone and motivated to tolerate a higher level of stress. The family system acts also as an osmotic system. A set of different coping behaviours is known as "coping strategy". The most common coping strategies in families focused on the emotions described in the literature as the refusal and the removal or the avoidance, these families often seek refuge in forms of abuse (alcohol and drugs). The use of anxiolytics and hypnotics drugs in the "traumatized family " is very high, more than double than the general population (Stevens et al. 2015, Enoch 2011, Hall et al. 1994). Family members suspend the relationships with the surrounding world avoiding to give explanations. Divorce can be seen with a sense of escape from the situation and a coping mechanism focused on emotions. The decision to divorce can be, in turn, a source of guilt and anxiety to social rejection (Rajani et al. 2019, Shrubbs 2013). Also, the faith is a coping mechanism oriented on emotions and is often the basis for an effective coping. A possible explanation is that the aid with prayer leads to a state of calm, emotional rest, that makes family members to think more clearly about how to adapt and solve their problems (Superdock et al. 2018, Krägeloh et al. 2015) The interruption and abandonment of the workplace have been studied in literature as a coping strategy centred on the problem. But this technique rather than reduce, increases stress. A family member who leaves the job becomes more isolated socially and with the deteriorating economic situation. The search of social support, often charities, is a coping strategy of problems frequently used and which has a positive impact on our own stressful life (McGilton et al. 2018, Burton et al. 2016, Claxton-Oldfield 2016).

THE HOPE COPING STRATEGY

While demoralization is a common form of "normal suffering" for people, and their family, who have chronic medical illnesses or disabling psychological diseases, the hope is an important coping strategy for family members because it helps them to make sense of life and cope with their current situation (Smith et al. 2019). Its definition is difficult as it is complex, multifaceted, multi-dimensional and prone to oversimplification. Hope is described as an emotion, an experience, a need, a characteristic, a state or a dynamic process with affective, functional, contextual, temporal, and relational dimensions. However, hope can be a good coping strategy to help family members to fight the burnout. In

this context the psychotherapy (for example, individual, group psychotherapy) can help family members to recognize and reach the awareness of their suffering (Griffith & Dsouza 2012). Thus, the family and its members give meaning to their work and cooperate with each other. It is the crucial part of the experience of the family and a prominent appearance in each story, regardless of the clinical situation, the relationship with the patient and the personality of the family member (Sampson et al. 2014, Milberg & Strang 2011).

INTERVENTION STRATEGIES IN FAMILIES

Psychoeducational interventions are techniques that provide information about the disease, help the individual to learn and develop problem-solving techniques; they do acquire strategies and coping skills, improve communication, deal with conflicts, reduce hypercriticism, hyper-emotional, and hostility towards the patient (Chi et al. 2015, Fiorillo et al. 2011, Magliano et al. 2006). Furthermore, they reduce sick family member's expectations, increase the social support networks, and reduce the family burden. In this area, it is inserted the role of the health care workers and, in particular, psychotherapist. They may, in fact, provide the information and the basis on the strategies and techniques to improve patient management. They can identify the primary and support caregiver and, finally, use a communicative and flexible approach especially in the family where compliance and acceptance of the disease is poor (Sin et al. 2017). In a recent study the authors assessed the effectiveness of a psychoeducational intervention in young people who had a family member with a mental health disorder such as depression, anxiety, and/or substance abuse. The program was based on a series of literacy and coping programs. The research concluded that over 90% of the youth reported an improved use of positive coping strategies from pre-to post intervention (Riebschleger et al. 2019). Some specific interventions aim to foster all the goals that are essential to improve the living conditions, including defining and planning goal, emotional perception, effective communication for negotiation, practical interpersonal and intrapersonal problem-solving (for example, structured psychoeducational and salutogenetic approach) (InteGRO) (Veltro et al. 2018). The intervention on families requires family psychotherapeutic techniques performed by experienced professionals. One of the most common models of intervention is based on the principle that the observation unit for the understanding of the disorder is not the single individual but the relationship between individuals. As a general principle for health professionals we can show that when a family member has a post-traumatic reaction, social support among family members can prevent the post-traumatic stress disorder and the secondary disorders to the stressors. Unfortunately, many family members have difficulty in providing mutual aid and may engage in an endless battle in search of strategies to solve a crisis.

There is not "a culture that is committed to consider the patient, the operator and their needs and pay attention to family relationships, social and organizational" (Anastasiadou et al. 2015). Furthermore, there are numerous evidences that the administration of self-management interventions improves outcomes for people with severe mental illness and that this intervention can help family members to manage the care burden of their sick family (Lean et al. 2019). Healthcare professionals must be aware that with his work, he/she is part of a system with rules and balances and he/she has to test the changes imposed by the disease. He must learn to hone the skills of listening and observing, before acting, in order to capture the necessary information to identify the mode of intervention more suitable and effective. He must learn not to make judgments, because it is unnecessary to determine "who is wrong or who is right" and "who is good or bad," since the story and the balance of the family system are not known. It's essential to "photograph" the situation, to understand the problems and strengths of the system. The achievement of this purpose is to make it necessary to build an efficient system of support, formed by people aware of the importance of their role and adequately training, that can allow to exploit the individual skills and able to understand the peculiarities of discomfort working. Therefore, the operator has to learn to observe and listen not only the patient, the family, but also himself, in order to grab his potentialities, but also his limits, to prevent or at least reduce the risk of burnout. Verhaeghe STL et al. (2007) in a review have concluded that families' members do not receive the indispensable attention and that health workers often meet the needs of family members in an inadequate and superficial manner, although there is a general consensus that the involvement of "traumatized" families is important and have a positive effect on families, patients and the entire healthcare system and perhaps pharmacotherapy for those termed unsuccessful with psychotherapy. Finally, it must be pointed out, that the presence of psychiatric symptoms, such as depressive or anxious symptoms, that meets the criteria of the international diagnostic classifications (DSM and ICD) requires a pharmacological intervention.

CONCLUSIONS

The research conducted on the psychological reactions of the family members of "traumatized" patients has been precious and valuable. The scale of problems is clearer. Research has shown that family members are particularly vulnerable: partners, children, families with economic problems and doctors. A support from health experts reduces stress by encouraging the members to work together effectively. Conflicts with health caregivers should be avoided as they cause stress. Work on families becomes part of a rehabilitation process. Support patterns and long-term care that can alleviate the burden in family members are urgently needed. Future research should be directed to the mode of reaction of

the family system and addressed to each member of the family. It may also be important to investigate the typical ambivalence among family members on the patient trauma; e.g., the associated hope and despair, factors that influence each other. The research on the genesis and evolution of the reaction of the family members to trauma and the onset of the next steps appear to be necessary. Certainly, not all the aspects of the problem were evaluated and further research is needed to allow the creation of intervention programs more effective and targeted.

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PSYCHOPATHY IN ADOLESCENCE: CAUSES, TRAITS AND RISK BEHAVIOURS

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SUMMARY

Psychopathy is a personality disorder defined by a specific set of behaviours and personality traits evaluated as negative and socially harmful. The modern conception of Psychopathy was introduced by Cleckley in "Mask of Sanity" (1941), and refined by Hare with the construction of the PCL (1980, 1991), a gold standard instrument for the evaluation of the disorder. Manipulation, deception, grandeur, emotional superficiality, lack of empathy and remorse, impulsive and irresponsible lifestyle, persistent violation of social norms and expectations (Cleckley 1976, Hare 2003) are some behavioural aspects that characterize psychopathic subjects. With this work we intend to study in depth the causes, the traits, in particular the so-called callous-unemotional and risk factors that lead a teenager to become a psychopathic subject. The diagnostic tools useful for the assessment and for the possibilities of intervention that can be put into practice will also be described.

Key words: psychopathy - adolescence - DSM-5 - traits - assessment

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INTRODUCTION

The word psychopathy literally means "mental illness" (from psyche, "mind" and pathos "suffering"). According to Cleckley (1976) and Hare (1991, 1993), a psychopath is an individual who presents antisocial behaviour, but at an interpersonal level he is at the same time engaging and emotionally detached, centered on himself and looking for new sensations, insensitive but intelligent and talkative, devoid of remorse and empathy but capable of seduction in order to satisfy his narcissistic need for social dominance and omnipotent interpersonal control. Psychopathy is not a behavioural disorder (BD) or an antisocial personality disorder (ASPD). Although psychopaths, like antisocials, lack genuine emotional ties with others and remorse, but behave in emotional coldness, combined with those of a particular seduction and manipulation, with utilitarian purposes; they become predators, sadists and conceal very violent acts. All this constitutes the peculiar outcome of an affective and interpersonal deficit common with the Antisocial Personality Disorder.

Robert D. Hare (2009) distinguishes psychopaths in three categories:

Primary psychopaths

Primary psychopaths, considered by the author to be true psychopaths. Normally they are neither violent nor extremely destructive, but sociable, fascinating and verbally expert. They present themselves as calm individuals and masters of themselves; however, they are in fact cruel, manipulative, selfish and deceitful (Levenson et al. 1995). They are excellent actors and manage to arouse emotions in their interlocutors, without however experiencing any of them in their regard (Bartol 1995).

Secondary psychopaths

Secondary psychopaths, on the other hand, have severe emotional problems; their delinquency is attributed to the social isolation that characterizes them (Bartol 1995). Although the primary psychopath is the true psychopath, it is the secondary psychopaths that are most frequently in contact with the law.

Dissocial psychopaths

Dissocial psychopaths show aggressive and antisocial behaviours that they have learned in the context of their evolutionary environment. In particular they are characterized by a greater tendency to be impulsive and markedly angry.

Adolescence: constitutional and psychosocial factors predisposing to psychopathic disorder

Constitutional factors play an important role in the etiology of dissocial and aggressive behaviours of children and adults (Eley et al. 1999, Slutske et al. 1997). In the developmental age, antisocial and aggressive behaviours have been associated with poor verbal skills (Lahey et al. 1995, Moffit & Silva 1988, White et al. 1994), with high neuroticism and low constriction (Tremblay et al. 1994), to attention deficit hyperactivity disorder (ADHD) and autonomic hypo-activity. Even in adults, multiple psycho physiological correlates to aggressive, antisocial and violent behaviours have been found. The most stable factor is the poor arousal capacity of SNA. Other research has shown a reduced negative emotional reactivity in subjects with ASPD since childhood as also the functioning of mirror neurons seems to be lacking in such subjects. With respect to language, psychopaths do not appear capable of using their profound semantic meaning, resulting in lexically poor and difficulty recognizing shades of meaning.

Table 1. Distinctive factors of the an affective trait in children and the emotional detachment of Psychopathy

An affective tract	Emotional detachment
Disinterest in the feelings of others	Lack of empathy
Absence of feelings of guilt	Lack of guilt or remorse
Disinterest in school duties	Difficulties in accepting the Responsibilities of one's actions
Show little emotion	Superficial affects
They do not keep their promises	
They cannot form a stable group of friends	

Another line of research has highlighted a set of common personality characteristics in the conduct disorders of some groups of children, adolescents and adults. These characteristics (see table 1), considered basic temperament traits and named in the "an affective trait" child and in the adult "emotional detachment", are related to the persistence of aggressive behaviour over time and to psychopathy (Frick 1998, Frick et al. 2000).

PREDICTORS OF PSYCHOPATHY: CALLOUS TRAITS - UNEMOTIONAL

From the late 1990s onwards, literature has identified a constellation of callous-unemotional traits that, if present from school age, associated with conduct disorder, may be able to predict psychopathy in adolescence and in adulthood (Frick & Ellis 1999, Frick & Moffitt 2010). In the DSM-5 the callous- unemotional traits were inserted for the first time as diagnosable traits. In particular, the profile of the callous-unemotional child / adolescent, which emerges from the DSM-5, is that of an individual with conduct disorder who has shown at least three of the following characteristics in one or more of the social relationships over the last 12 months characterizing his life: 1) Lack of remorse and / or guilt; 2) Lack of empathy; 3) Lack of concern about one's performance in the school environment or in other relevant activities (depending on age). 4) Superficial affectivity. The profile of these children is identical to that of adult psychopaths with phenotypic manifestations present in different ways. For example, we will hardly find a child with strong psychopathic traits to deceive an adult by cheating him or inducing an investment that will probably bring him to ruin, but we could observe a child capable of lying with a bewildering shamelessness about violent and often premeditated acts as can be the physical and psychological submission of a peer or an animal. Such children and adolescents are distinguished, in fact, from their other peers with externalizing disorders such as attention deficit with hyperactivity disorder (ADHD), oppositional - provocative disorder or conduct disorder without comorbidity with psychopathic traits, for emotional coldness, rationality and premeditation of their acts, thus connoting their aggressiveness as proactive or premeditated and calculated aggression rather than as an act of impulse and emotional reactivity. Although the prognosis of these children is significantly negative

compared to that of peers with other behavioural disorders (Frick & Viding 2009), intervening on these traits as early as possible could be the key to a more effective intervention. The predilection for new and dangerous activities, the scarce sensitivity to punishment, the reduced emotional reactivity in the face of negative stressful stimuli characteristic of subjects with CU traits elevated are consistent with a temperamental style that can be defined as poorly "impressionable and scary" (low fearfulness) and characterized by low avoidance of damage, poor behavioural inhibition and very brave. Many studies aimed at analyzing normal development in children correlate the temperamental style described above with low scores to the evaluation of the development of a moral conscience. This correlation is in line with those theories that suggest that social morality and the internalization of social norms are partly dependent on the arousal negative evoked by the punishments that result from incorrect behaviour. The guilt and anxiety that is generally associated and / or precede the carrying out of an unlawful act can be attenuated if the child has a temperament in which the negative arousal connected to punishment is attenuated. The presence of a weakened negative arousal could also play a critical role in developing empathic responses to the suffering of others. In summary, children with conduct disorder and elevated CU traits tend to have a marked propensity towards new and dangerous situations, are poorly sensitive to punishment and show poor emotional activation in response to potentially stressful negative stimuli. Furthermore, their behavioural problems seem to be poorly correlated to environmental factors, such as the presence of an inadequate parental educational style and a deficit in the provision of services.

ASSESSMENT OF PSYCHOPATHIC TRAITS IN AGE GROUPS

Currently the most used tools in child psychiatry to evaluate psychopathy are represented by Psychopathy Checklist Revised Youth Version (PCL-YV, Forth et al. 2003) and the Antisocial Process Screening Device (APSD, Frick & Hare 2001). The PCL-YV is a semi-structured clinical interview, which requires 60 to 90 minutes for the administration, mainly used in forensic samples of adolescents (12-18 years). The PCL-YV includes 20 items, only 4 of these are related to the CU

sections. The APSD, on the other hand, is a tool aimed at measuring the same behavioural traits evaluated by the Psychopathy Checklist-Revised (PCL-R, Hare 1991) with the exception of some eliminated as deemed inappropriate for children (eg: parasitic lifestyle) or modified to be more adapted to the developmental age. Previously known as PSD, it was initially aimed at evaluating psychopathic traits exclusively through the judgment of parents and teachers (APSD Parent-version and APSD Teacher-version) and only later a self-report version was also used (APSD Youth-version). Frick, himself emphasized the need to develop a self-report version of the APSD, both because the reliability and validity for the evaluation of various psychopathological areas increases in subjects in the developmental age with increasing of age (Kamphaus & Frick 1996), both because children with severe behavioural problems often come from highly "dysfunctional" families with a high psychiatric burden and therefore not always reliable. Moreover the analyzed traits concern not only "overt" behaviours that can be easily caught by external observers but also "covert" behaviours that can be detected above all by the interested subject and escape from others because they poorly grasp the inner aspects of the other or because they are poorly expressed (Loney & Frick 2003). The APSD is a structured clinical interview consisting of 20 items, currently present in three versions (self-report, parents, teachers) and aimed at children over 6 years old. The score for each item ranges from 0 (never true), 1 (sometimes true) to 2 (very often true). The factorial analysis carried out on the data relating to a non-clinical sample of 1136 children / adolescents led to the identification in the APSD of 3 dimensions: Callous-Unemotional Dimension (6 items) Narcissistic Dimension (7 items), Impulsiveness Dimension (5 items). In order to overcome the psychometric limitations of the aforementioned Frick scale, the Inventory of Callous Emotional Traits (ICU, Frick 2003) was developed. The rating scale was based on the developments of the 6 items of the CU subscale of the APSD. The ICU is a rating scale of 24 items, all related to the CU dimension present in the three assessment tools; self-report, parents and teachers. The score for each item ranges from 0 (never true), 1 (sometimes true), 2 (very often true) to 3 (very often true). Each item is formulated within the questionnaire, both in a positive and negative sense. The first test of the psychometric properties of the ICU questionnaire was performed in a large non-clinical sample of 1443 German adolescents, using exclusively the self-report version (Essau et al. 2006). The factorial analysis carried out led to the identification of 3 dimensions: Callosity Dimension (11 items) Indifference Dimension (8 items), Emotional Dimension (5 items). There is currently only one other study in literature in which this questionnaire was used, again in the self-version, in a sample of young prisoners (Kimonis et al. 2008).

CONCLUSIONS

At a very early age it is possible to change the behavioural patterns of psychopaths reducing their aggression and impulsiveness, teaching them strategies to suit their needs adequately. In this perspective, the role of families and schools, which have the responsibility, is fundamental to identify and report suspicious behaviour without experiencing guilt or self-accusation. It is necessary to pursue research in this field to promote a greater understanding of the disorder and identify targeted interventions to be applied in the developmental age.

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THE “IMPERFECT BEAUTY” IN EATING DISORDERS

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SUMMARY

Not only philosophers, but also artists and scientists have always struggled to find a universal definition of beauty. Not even Darwin could find an answer to the question: are there any parameters of beauty that we can apply to every species. Nobody can give a valid definition for the perception of beauty in others. Can a definition in subjective terms be achieved? If I say something is beautiful, it only means that it is beautiful for me, but it does not mean that is necessarily beautiful for everyone else. Beauty is a subjective experience, but it is not only a perceptive experience! According to the Treccani Dictionary of Italian Language, beauty can be defined as: something capable of pleasing the soul through the senses and become an object worthy of contemplation. Developmental biologists say that when people talk about how beautiful a person is, they tend to highlight those qualities that make them more or less attractive. These qualities can be, for example, if and how much I look like their father or mother. Does this mean there can be universal parameters of beauty for the human species? According to Professor Semir Zeki, there are universal parameters of beauty and the easiest way to define them is in a negative way. This means that whoever has his eyes in a different position, compared to where the eyes are placed in a nation or race, cannot be called beautiful. According to this, could there be a model of beauty in our society?

Today's society gives a considerable importance to appearance, it is even thought that being "beautiful" can achieve happiness, love and success. Mass media show icons of perfection and ideals of beauty almost unattainable and makes us to believe that achieving them would make us feel fulfilled; therefore underestimating other values such as happiness, family, friendship and beauty. There is less and less space for self-acceptance and developing other qualities, whereas we invest more into treatments of various kinds to change our body, considering it as an object we can manipulate, or as a tool to achieve goals. Particularly young people, today, are conditioned by the myth of beauty and by the canons imposed by newspapers, TV and the media, which demands virtual beauty without originality. According to this canon, women must always be slim but firm and sinuous, with flowing bleached hair, perfect make-up, smooth skin, full lips and long nails. On the other hand, men are forced to resemble the football players: muscular, but not too much, without a belly and marked abdominal muscles, tall, well-shaved, fragrant, or even shaving their whole body. According to Charmet: "We live in a continuous casting, with boys feeling inadequate and ugly". Adolescence is then considered a period full enthusiasm but also of torment, such as long struggles in front of the mirror with the different ways of "decorating" a suddenly new body. This is a particularly fertile ground for the onset of pathologies such as depression, dysmorphophobias, eating disorders and other pathologies. They become 'mutants', because they change and adapt to the current fashion; nowadays these changes affect not only women, but also men. Pathologies are also in the rise among increasingly younger people, aged 10 to 20 years old. In addition, there are new pathologies, such as orthorexia (the obsession for healthy eating) or drunkorexia (a combination of fasting/binge eating with alcohol abuse). Often, these are associated with other psychiatric disorders or serious physical complications. However, only a small percentage of people suffering from these conditions ask for help.

Key words: imperfect beauty - eating disorders – anorexia - bulimia

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INTRODUCTION

*"Beauty has as many meanings
as there are moods to a man"*

Oscar Wilde

For centuries philosophers and writers have tried to define beauty, unsuccessfully. After all, there are so many types of beauty: the beauty of a landscape, a painting, a body, a face, music, the beauty of architecture and even mathematical formulas. In each culture, the type of education received has a strong influence in what someone would consider beautiful. Beauty is something that can create a sensation of great pleasantness, of admiration or aesthetic enjoyment and which can also produce the desire to communicate one's pleasure to others. We can think of beauty as a diamond, in the sense that if we turn it around, we can discover new facets, each of which shines with a different colour. When we look at an object or hear a sound, we are inevitably influenced by our personal experience. This

is why each of us has a different definition of beauty, which also makes others understand who we are. The culture of beauty has ancient roots: Greeks linked beauty of the body to that of the soul; Policleto even created a code to define the ideal proportions that a person should have to be considered beautiful. Greek artists had the task of reproducing statues of emperors or military leaders in an unrealistic way, with idealized features, creating not only attractive bodies, but also enhancing other qualities and virtues. The Greek expression "kalòs kai agathòs" (beautiful is good) denotes the ideal of human perfection: an equation between the two terms. Beauty is considered a divine gift. For Plato, beauty was "the splendor of Truth"; and Kant was convinced beauty was a characteristic of the morally good. To understand beauty from an evolutionary point of view, we need to consider its expressions throughout human evolution. Furthermore, we have to place it in the context of individual subjectivity and behavior, since beauty and aesthetic are fundamentally a social

experience. Starting from these considerations, beauty can have a particularly relevant effect in our relationship with others and the world, such as to extend the model and the feeling of oneself. Just as well, a frightful experience can generate a minimization of that self. If we take this evolutionary and neuro-phenomenological perspective in an attempt to understand beauty, it is difficult to agree with the thinking that "as far as beauty is concerned, one is simply spectator, passive, in a state of wonder". As stated by Umberto Galimberti (2002). As long as beauty is identified with an external canon, we will not be able to feel it in ourselves for what it can actually do: extend and increase our possibilities, our actions and our conception of ourselves. With beauty we are faced with a constantly repeated impulse, which every time presents itself as new. As unique and capable of presence, that is to be there and to know we are, we tend to the fullness of our expression and we are virtually inhabited by the capacity for creation and beauty, above all by the desire for beauty. Is our society obsessed with physical beauty?

The era we are leaving behind us has taught us to judge people by their physical appearance: it is a mantra that many repeat and apply despite the fact that they have simultaneously developed strong fashion trends in informal and casual clothing. The impact that physical beauty has on our lives is very powerful: just think of the impact beauty can have on well-being or on one's success at work or school. It is because of these reasons many people tend to spend lots of energy and even money on finding a more pleasant physical appearance. Our society is obsessed by the idea of beauty. We can probably even say that the two greatest obsessions of our time are the idea of competitiveness (understood as perfection) and the idea of beauty. Adorno (2009) argued: beauty is not the beginning of a platonian purity: the first step is not to place beauty with perfection, nor with purity, nor with order or harmony, if so it would be too simple. If beauty was a matter of harmony or purity it would be easy to pursue, it would be an almost Pythagorean concept of beauty. "Beauty can pierce us like a pain": if the writer Thomas Mann, with these words, celebrated beauty for his ability to unleash strong emotions in those who admire it, today it could even represent a risk, especially for the women.

Women internalize these ideals of thinness by considering them the point of reference with which to judge themselves, while males tend to admire a young, thin and muscular body. We live under the looming of two distorted toxic categories of our times: one is the category of beauty and the other of happiness that become the imperatives of the action in individuals. We are only legitimized to exist on the basis of two conditions: that of beauty and that of the happy. Society, the dominant culture, teaches that beauty is thinness, that weight is inversely proportional to self-confidence, and that image and appearance count more than being yourself. An exasperated attention is increasingly developed towards corporeity, to the point that the image seems to become

more and more the only channel to express individual identity. Contemporary society attaches considerable importance to the body image, which must attain to rigid aesthetic standards, be sculpted in all its forms, present a young, toned but lean appearance. From here we can see the rise of various significant social pathologies and phenomena, ranging from the boom of aesthetic surgery to the pandemic anorexia, and from the endless number of beauty products to the obsession for beauty farms and wellness centers.

THE IMPERFECT BEAUTY

Social adaptation and personality is affected, particularly in adolescence, by the relationship one has with one's own image and by the perception of one's body, which is remarkable in terms of the impression it produces on others. In young people, ability for introspection is intense, image is subjected to scrupulous attention and the comparison with peers is continuous, as well as identification with an ideal physical standard. Youth is the age when everything is done, sometimes unconsciously, to be up to standard or models that are baked in series. Clothing, footwear, gestures, phrases, social behaviour, make many young people products of cultural and physical imitation. Advertising in itself is nothing more than a series of models that are aesthetically unachivable, making the existential crisis of those who are not up to standards even more profound. Nowadays, beauty industry has become a remedy for every imperfection, every defect, and those who limit themselves to being normal risk feeling inadequate compared to the rest of humanity. The acceptance of oneself, of one's own limits can only come, and not always, with maturity and experience, but considerations of this kind are not taken into account in the world of young people and are increasingly ignored by adults. The illusion of immortality in young people, forgetting the relativity of a value that is destined to weaken and that could make others underestimate much more significant and lasting. Yet today, in a society full of corporeality and beauty they are exalted to exhaustion, a term that the greatest fear becomes that of not feeling beautiful enough. A flood of negative images falls on the heads of the boys "in the time of the pack" (Charmet 2013). "First they felt guilty, now they feel ugly and there is nothing worse" (Charmet 2013). Today's kids don't like what's good for me. According to Charmet: "In adolescence the problem has always been far from the mind with the body, but until a few years ago the boy was assaulted by guilt to discover the sexual and aggressive instincts of the body, now he rejects it, he is ashamed and shame is far worse than guilt. Guilt is easier to solve. Meanwhile, it concerns, it works, a word, it does not involve the value of the self. Shame on the other hand strikes deeply, gives no chance ". In boys who feel ugly, it is the body that is put on the bench. Don't like it, so you punish it or try to make it adequate. This explains the physical fact of attacking, *affabando*

or sformandolo. Or wait for those young people who retire to their own bedroom and send their avatar into the world. Or, again, of those who inflict wounds. The theater becomes the refuge, the film experiences the emotions that cannot be tolerated in life (Juli 2018), the reactions that occur most frequently are: eating disorders, social withdrawal, self-harm, depression, dysmorphophobia. Just as the body is transforming, there is a work in progress and we patiently need to wait for the result. Actually, no one is allowed the image of their body, even using the mirror. The reflected image, in fact, is not superimposable, but symmetrical: the right becomes the left and since the two parts are not perfectly identical, the image I see in the mirror is not my own. So mirrors say only half the truth, half of what you see and what others see. The myth of Narcissus says precisely it is impossible for the body to grasp its image. Just like Montale writes in *Travestimenti*: "a glance in the mirror is enough to believe you are someone else"; and Barbey d'Aureville: "The mirrors in my wardrobe are like large lakes where I can see my ideas navigate, along with my image"; Yeats in the poem *Two trees* (in *Poems*) warns: "Do not look at the bitter mirror that the demons put before us, passing ..." Yet one of the main functions of this tool of many meanings is precisely to provide a concrete basis for the aesthetic self-assessment of one's person, or rather of one's appearance. The relationship with the image of our body is something we have to build over time, and at the same time changing our relationship with reality changes what we see. The body is the vehicle of existence, having a body means joining a defined environment, approaching certain objects and interacting with it continuously (Merleau-Ponty 1979). In fact, our relationships with others are decisive, because their positive or negative interest for some aspects of our body leads to a modification of our image, which accentuates or removes what it feels accepted or rejected. Indeed, no one can constitute an ego without a "you", so it is true that our body image is related to the body image of others. We are phenomena offered to for viewing; and being is first of all being visible. Although bodily dissatisfaction is rooted among the youngest, in its extreme form it is considered an essential component of the implementation of pathological behaviors. In fact, dissatisfaction with one's own body can be associated with a distortion of the body image which, in turn, is closely linked to altered eating behaviors (Juli 2017). At present, we do not know if the role of bodily dissatisfaction: if it provokes or worsens the onset of eating disorders, or whether this is previous to the disorder itself or secondary to changes in cognitive functions determined by fasting (in anorexia), or binge eating (in bulimia). However, several studies including that of Bruch H. (1978) suggest a close correlation between dissatisfaction and the onset of eating disorders. Eating disorders are serious psychiatric diseases, they are not fads or whims, they are not attitudes, there is basically an alteration of the body scheme that precedes it. People always see themselves as fat even

when they are very thin, it is a sort of hallucination. Seeing themselves as always fat, they adopt several ways to lose weight like restricting food or doing a lot of physical activity, or to adopt compensation methods such as in bulimia. There are triggers (for example a diet) and root causes (existential problems). To diagnose an eating disorder, it is not enough to focus on the physical form in reality, but there is an important internal discomfort. The supply of food we have today contrasts with the obsessive model of thinness that is proposed to us. Food is the first relationship that puts us in touch with the world and it highlights the existence of emotions. Change must aim for inner transformation, working on emotions, the way we eat and the type of food we eat. Food represents an emotional block for everyone. The DSM V defines nutrition disorders as: "Nutrition and nutrition disorders are characterized by a persistent eating disorder or by behaviors associated with nutrition that determine an altered consumption or absorption of food and that significantly damage physical health or psychosocial functioning" (DSM-V 2013). From an epidemiological point of view, eating disorders, although more frequent in the female sex, up to 9/10% of the cases correspond to the male sex. It seems that between the two sexes there are no big differences in the clinical manifestations. In Italy three million young adults are suffering from an eating disorder, a phenomenon often underestimated both by those who suffer from it and family members, and which constitutes a real social epidemic: 95.9% are women, 4.1% are men. Suffering from an eating disorder, in addition to the negative consequences on the organic level, involves important effects on the social functioning of the person, with serious undermining on the quality of life; limiting their relational, working and social capacities. According to Freeman (2002) among the main factors that differentiate males from females, there is the "awareness", instead of the "feeling" of being fat or obese (women "feel" fat, men "know they are fat"), the use of diets to achieve sporting goals and to prevent family conditions such as diabetes or cardiovascular diseases. According to the World Health Organization (2018), anorexic and bulimic disorders are among the major causes of death among teenagers, a real social alarm. Among these are: Orthorexia, the exaggerated attention to food quality in order to feed themselves in a healthy way, the Drunkorexia, a new and dangerous eating behavior that consists of eating little, even fasting, in order to compensate for the caloric intake of alcoholic beverages; and is characterized by the abuse of physical exercise, hyper-protein and anabolic diets; Pregorexia, the eating disorder that afflicts pregnant women who do not want to gain weight during pregnancy and undergo prolonged training and low-calorie diets. When the disorder starts, it causes an alteration of the body pattern and lead the patient to see himself fat even when he is very thin. This becomes a sort of perennial hallucination that has nothing to do with fashion or whims.

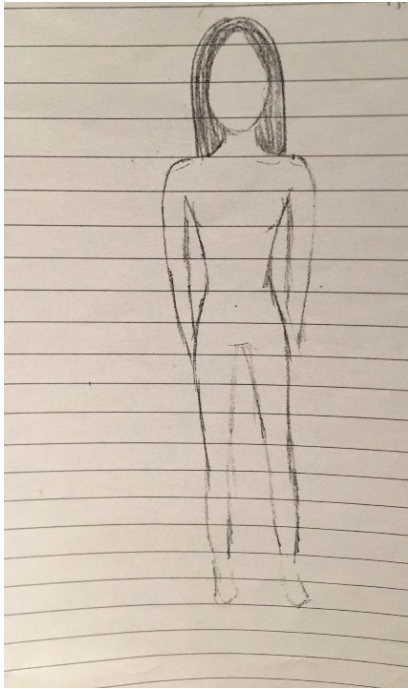


Figure 1. How I wish to be

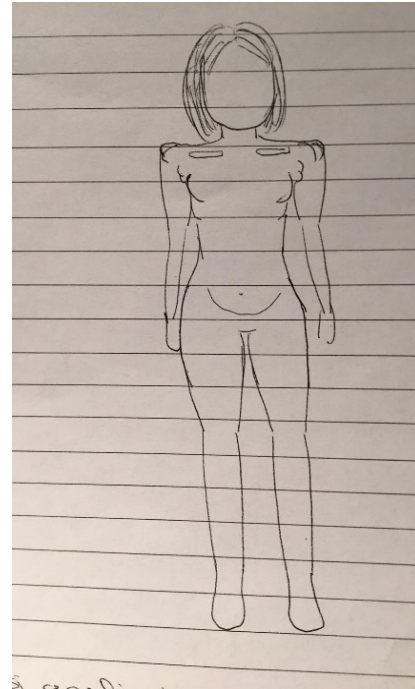


Figure 2. How I am

In the context of studies on eating disorders, body image was analyzed above all regarding the perceptive aspects of the body experience, such as, for example, the estimation of body size. In the following drawings, Amily, who was affected by a Restorative-type 30-year Anorexia Nervosa (anthropometric parameters: 1.70 h and 46 Kg) reports "How I wish to be" and "How I am". In both figures we can see the lack of facial features: it is a completely empty face. In the image we can see clear signs on her body of the phobic points, defined as: "Full of flesh" (breast, belly and hips), the upper and lower limbs are drawn at times, especially in the figure "How I wish to be" the upper limbs are hidden, and the lower ones together with the feet can be glimpsed; this means that the parts of the body that put us in contact with the world have disappeared from the internal image that she has of herself, it is as if the links with the world (hands, feet, eyes, mouth) have dissolved. The abandonment of the body corresponds to a dismissal towards life and the bonds that one has with it. This is like the "arm wrestling" that patients do with their own body: wanting to bend them to laws that are not their own, not to listen to them anymore, not to respect them, humiliate them through a desire for uninterrupted coercion (Figure 1, Figure 2).

CONCLUSIONS

Society has never asked women to be independent, or cultured, or to achieve successful goals in life; however, he always demanded them to be beautiful. In fairy tales, it makes no difference if the protagonist is a princess or a peasant girl. What is important is that her beauty takes your breath away. Media offer models that are often unattainable, where the beauty of the body

becomes an object for worship, and all those who do not have it are excluded. Conforming to these aesthetic parameters has become one of the obsessions of our time, striking new generations the most, who are more interested nowadays in the obsessive care of physical appearance. It is a phenomenon not only concerning women, because men too have entered into the mentality of touch-ups, creams and wax. However, allowing oneself to be conditioned by these models can lead to not living to the fullest, not appreciating one's body's characteristics, not grasping its potential, because in each of us there is a potential to be exploited, even if we do not correspond to the imposed standards of beauty. Beauty canons vary over time; in fact it is conceived differently according to historical periods. For example, Venus can be remembered for her prosperous breasts and its accentuated curves.

Nowadays Venus would not exactly correspond with the beauty that society imposes given that she would be a size 38. Girls who try to "respect" these canons often exaggerate, trying to reach perfection, damaging their body and falling into anorexia, thinking of not being up to it or not being enough. There is no perfect model of beauty but only a different way of seeing things because "it is not beauty what is beautiful, but what is pleasing", so there is no objective beauty that everyone agrees on. Fortunately, in recent years we have witnessed the emergence of trends that encourage diversity: curvy fashion bloggers, commercials featuring real women. It is important to focus our attention on primary prevention, providing young people with protective factors. Parents and schools also have the duty of creating a protection in the minds of children, of building an 'antidote' culture as opposed to the penetration capacity of models proposed by mass media.

For example, a father should be able recognize the physical prowess of a child, to value it, and a mother to point out that that big nose of his fifteen year old daughter is a hallmark of the family, the profile of the grandfather to which everyone is loyal. Even physical education teachers can do more: work on beauty models, discuss constructive diets, shed light on the effects of supplements and propose an intelligent usage of gyms. It is necessary to offer the skills for a "counterculture" of the body. Learning to know ourselves for who we really are, exploring our most authentic dreams, being able to reach a sincere awareness of oneself and of others, helping us to accept all the complexity of the human soul and not to hide behind deceptions imposed from outside: this important faculty of the psyche can guide us to more satisfying relationships and a fully happy life.

Meanwhile, we can remain a little distant from the ideals of beauty that magazines, models, facial tissues and advertising campaigns propose to us, recognizing that we cannot reach them, without giving ourselves to cosmetic surgery. In a certain way, nowadays the power to be both beautiful and ugly is in the hands of each of us, rather than in the eyes of others. And to confront daily our normality/imperfections leads us to adopt incorrect eating behaviors, depression and medical conditions such as anorexia and bulimia. We should roll up our sleeves, young and old, and accept and appreciate ourselves for what we are inside, for our imperfections and our peculiarities. Our external appearance can serve us for a good first impression, but what leaves the most profound impression in others must be our personality, the secret traits of our character, our temperament, our way of doing, our looks and gestures. What makes the difference must be our inner uniqueness and not a stereotypical shell to contemplate! What is beauty? Beauty is love for yourself, that perfect balance between psyche, heart and body that only us can care for and decide to accomplish as we wish.

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STRATEGIC TRAINING: THE MAGIC WORLD OF CHANGE

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SUMMARY

"Before convincing the intellectual part of the mind it is necessary to touch and prepare the heart", an aphorism by Blaise Pascal (Vozza 1995), refers to one of the most important functions of strategic training, not only being successful in making communicative messages correctly and rationally understood, but also involving its addressee, above all by making one enter into emotional syntony with the communicative content. To understand the precious wealth of knowledge that has over time brought the necessary skills to do strategic training, it is necessary to find its roots by taking a step back in time. It is necessary to go as far as the fifth century BC, with Protagoras and its persuasive efficacy, with a rapid historical excursus passing by Aristotle and his Sophistic communication techniques to arrive at about 2000 years later, passing through social psychology, up to the Palo Alto strategic school. Among its various activities, the Genius Academy Centre for Research and Psychological Studies has decided to push two strategic training projects aiming to increase the level of well-being perceived by the addressee and encouraging the desired change. One of the two strategic training projects, A "Journey" in a journey, conceived by the writer, started in 2013. The educational and therapeutic value are amplified by optimizing the suggestions and stimuli of the journey. Another strategic training project for future aeronautical professionals, which gives a great contribution to the traditional technical training, is an innovative psychological programme specifically designed to prepare, not only for technical operational challenges, but also for numerous psychological challenges deriving from working in a particular environment such as the airport.

It is specifically designed to study and improve the travel experience of people in airport transit and aims to raise the level of traveller's well-being, through a series of highly innovative interventions in specifically provided areas with the use of digital reality in coping and helping with anxiety and fear of flying.

Key words: strategic training – change – academy - airport

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INTRODUCTION

"Words were originally magical", said Freud (De Shazer 1994), because the human mind is organized in such a way that some words, written or spoken, have a more powerful effect than others. Some phrases or words, stimulate certain brain perceiving elements better than others by inducing the production of neurotransmitters responsible for activating feelings of well-being, discomfort, fear or excitement depending on the emotions evoked. A reader or a listener who experiences such emotional states can be literally fascinated by what one hears or reads. "Before convincing the intellectual part of the mind it is necessary to touch and prepare the heart", this aphorism by Blaise Pascal (Vozza 1995) refers to one of the most important functions of strategic training, not only being successful in making communicative message correctly and rationally understood, but also involving its addressee, above all by making one enter into emotional syntony with the communicative content. In order to make a formative communication of this type possible and practicable, it is necessary to develop that ability to enter in emotional harmony with the people to whom the communication is addressed and to make them perceive positively what one wants to communicate.

WORDS HERITAGE

To understand the precious wealth of knowledge that has over time brought the necessary skills to do strategic

training, we need to find its roots by taking a step back in time. It is necessary to go as far as the fifth century BC, with Protagoras and its persuasive efficacy, the first one who used the persuasive efficacy of language. His art was characterized by asking questions instead of proposing affirmations, questions structured in a very precise succession in order to induce answers in the interlocutor towards the direction imagined by the persuader. Protagoras did not oppose the point of view of his interlocutor but guided him, through answers he himself provided to the questions, in order to discover alternative images of reality. Unlike the metaphor, which evokes, but leaves the interlocutor free to construct a meaning and to interpret it subjectively, the aphorism, balancing analogical and logical effects of language, nails a deliberate effect (Reale 2006, Schiappa 1991). The rhetoric of Protagoras, in which the main aim was to persuade one's interlocutor, was later countered by the dialectic of Socrates, where instead of dialogue was oriented towards the search for truth. Socrates' method of investigation, based on reason, has left an important trace throughout the Western World. Proceeding in our historical continuum, to the research of Milton Erickson and Carl Rogers, (1901-1980) we give tribute of the studies on hypnosis and hypnotic language as well as an activity of systematization of suggestive communication techniques within the therapeutic dialogue. To C. Rogers (1902-1987) we owe the identification of a model of clinical communication aimed at creating empathy through a specific mirroring technique, defined by him as mirroring. In these years, we are witnessing

an evolution of studies and research, in particular it is necessary to mention the fruitful work of the Californian research group of the Mental Research Institute of Palo Alto. Palo Alto research group marks an epochal turning point, starting a new season for the study of language and its effects, especially if we consider that until this period, studies had mainly dealt with the structure and meaning of language. "It is impossible not to communicate", says the first axiom of the "Pragmatics of Human Communication" by P. Watzlawick (1967), from which we can deduce that communication constitutes an essential condition of human existence for which all defined interpersonal situations between two or more people are communicative. But if the possibility of not communicating is true, then one can choose whether to do it in a strategic way, in order to be able to guide and manage communication effectively, with a specific purpose, rather than randomly, and then to suffer the effects.

STRATEGIC TRAINING

Two Practical Application Experiments in the World of Tourism and the Airport World

In the light of the above arguments, strategic training does not end with the conclusion of the communicative exchange, but it can also continue later and trigger a series of chain mechanisms, which effects continue to work overtime and in the mind of the interlocutor. Among its various activities, the Genius Academy Centre for Research and Psychological Studies has decided to push two strategic training projects aiming to increase the level of well-being perceived by the addressee and encouraging the desired change. One of the two studies is aimed at the individual's bio-psycho-social betterment, and the fascinating perspective of using the opportunities offered by a trip as a catalyst for important changes, has found, in the past years, an important place. In the project A "Journey" in a journey, conceived and created by the writer from the 2013, the educational and therapeutic value of change, derives from the idea of contextualizing the growth training project by optimizing the suggestions and stimuli of a journey, where the individual can be predisposed to enter precisely in a suspended space, during which beneficial changes could happen, both psychophysical and psychosomatic (Spurio 2018). Another strategic training project, still work in progress but definitely promising, has started thanks to the collaboration between Alitalia and Genius Academy, signed in September 2018. It is a project for future aeronautical professionals, which gives a great contribution to the traditional technical training. This is an innovative psychological programme specifically designed to prepare, not only for technical operational challenges, but also for numerous psychological challenges deriving from working in a very particular environment such as the airport.

In the field of the research work studied for the airport world, The GHA project has recently born, an acronym that defines another work of research born by the tested partnership between Genius Academy and Genius Handling. It is a project born with the aim of studying and bettering the behaviour of people travelling (airport tourism). It is an activity designed to study and to improve the travel experience of people in airport transit and aims to raise the level of traveller's well-being through a series of highly innovative interventions in specifically provided area also with the use of digital reality, for example helping in anxiety and fear of flying. The intervention and research project born in March 2019, is also made possible by the presence of Genius Handling, as a company in around 50 European airports.

CONCLUSION

The Sixth Continent

With reference to the journal "The Economist" (2014) the set of global airports and people who pass through them, has been defined "The Sixth Continent". At the end of 2017, the "flying" passengers will have exceeded 4 billion per year (approximately the inhabitants of Asia, the most populous of the 5 continents), adding 7.4% compared to 2016, according to the data presented last June by IATA (International Air Transport Association, 2017), in 20 years it will be 7.2 billion. Therefore, the future of this sector is not only played on the safety of flights, but also on the development of hubs, which will best accommodate travellers, entertain them, help them relax and feel calm, and cope with states of anxiety and fears related to transit in "free" areas in which the difficulties are many. The airport areas have been defined by Marc Augé (2009) as the land of undefined places, opposed to anthropological places, because they are spaces without the pre-requisite of being identitarian, relational and historical.

In 20 years, there will be more than 7.2 billion passengers globally in transit at airports. One more reason to consider international airports as a destination in itself. Airports have become a third dimension that begins from the point of departure and ending at arrival.

Therefore, airports, the Sixth continent, are the spaces in which the world with all its diversity is enclosed, one of the last challenging frontiers for the researcher who loves to dedicate time and research to the study, growth and positive change of the human being.

The researcher who is always in search of innovation and knowledge, in order to use his/her professionalism, needs to be present with their work in contexts far from the non-realistic atmospheres of centres for research, closer to real life, where people come face to face with each other and find one another. This happens, for example, during the experience of A "Journey" in the Journey, where the suspended time space of a travel is the setting for innovative and interesting situations of

parallel discovery of one's inner world, and where the sensation and emotion evoked by the places visited are associated with specific psychological programmes like seminars, social dreams, individual and group psychotherapy. This also happens in those "Lands of no one" belonging to everyone e.g. airports - spaces of individuality that intersect without entering into a relationship, driven by the frenetic desire to consume or to accelerate daily operations: a gateway to change.

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EVALUATION OF THE QUALITY OF REHABILITATION TREATMENT IN NEURODEVELOPMENTAL DISORDER

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SUMMARY

Complex disability is very difficult to manage. It usually subtends very serious clinical pictures, because it affect several body systems, or because it is associated with intellectual disability and behavioral disorders. Often affected patients are unable to communicate their basic needs. All these factors combine to make the management of these patients very complex, and those who care for them realize how important it is to find a way to detect their state and to identify their potential capabilities.

Developing appropriate rehabilitation programs for these patients requires additional effort and an assessment capacity that is as objective as possible. Few scales cited in the literature are capable of evaluating these aspects in patients with complex disabilities, among them the Barthel Index (Mahoney & Barthel 1965) and the Vineland Adaptive Behavior scale II (Sparrow et al. 2005). The majority of these scales often tend to depict the data regarding the disease to a degree of severity that precludes adequate individual rehabilitation program development. There is a dire need for a more appropriate instrument, an observational grid that is capable of identifying the potential of this patient population and evaluate the effectiveness of rehabilitation interventions provided.

The aim of the study is to evaluate the efficacy of rehabilitation interventions in a group of patients with IQ <32 (determined by the Vineland II scale) using an evaluation tool created ad hoc called D-Rubrics, designed with the intent to identify "micro-differences" between baseline (T0) and post-rehabilitation (T1). The goal is part of a more long term-term objective which involves developing an effective assessment tool for patients with complex disabilities. Such an assessment tool should be practical, easy to administer and useful in both clinical and research settings.

Key words: rehabilitation – interventions – scale - neurodevelopmental disorders - disability

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INTRODUCTION

Complex disability is characterized by the co-presence of clinical symptoms and multisystemic signs, often severe, and usually associated with the patient's inability to communicate verbally.

Although the benefits of a range of disability-focused therapies have been well studied, little remains known about how they work, let alone how to monitor these benefits in a precise and reliable way (Poquérousse et al. 2018). This justifies the need for specific assessment systems capable of addressing such complex and difficult issues. In daily practice, rehabilitation facilities manage complex clinical situations and are required to establish the most appropriate and specific rehabilitation-educational interventions for individual users. This process requires the action of a multidisciplinary team, and quantitative instruments that are as objective and reliable as possible. Both of these are fundamental aspects essential when assessing the patient's condition, as well as in evaluating any changes and responses to the interventions proposed. Evaluation scales exist in the literature, most of which are designed to be concise and simple to complete, aspects which often result as inadequate for the special needs of patients with complex

disability. The results often tend to demonstrate an extremely severe condition, without any possibility of either differentiating individual abilities, or, most of all, of highlighting the potential, even if modest, that patients with complex disability may possess.

For example, the "Barthel Index", BI (Mahoney & Barthel 1965), is a widely used scale in many practice areas, that provides a quantitative measure of patient performance in the context of activities of daily life (ADL: Activities of Daily Living). The same argument applies to other evaluation scales such as the "Functional Independence Measure" (FIM) scale (Granger et al. 1986), which aims to provide a quantitative index of a person's degree of disability, and the "Supervision Rating Scale" (SRS) (Boake 1996) which provides an indication of the subject's need to be monitored and supervised.

Other scales exist which are more comprehensive and explanatory, but they are very complex and require a significant amount of time as well as the presence of highly qualified personnel to complete. These scales do not allow for frequent and flexible verification, both important prerequisites in clinical-rehabilitative practice. This is the case of the "Vineland II" scale (Vineland Adaptive Behavior) (Sparrow et al. 2005), designed to

assesses adaptive behaviors in those activities that an individual usually performs to meet the expectations of personal autonomy and social responsibility as compared to a cohort of the same age and cultural context. Specifically, it aims to measure adaptive behavior in the following domains: communication, everyday life skills, socialization and motor skills.

The lack of sensitivity of measurement tools in severe disability is well documented in the literature: in 1989 Shah and colleagues proposed a scale capable of implementing the sensitivity of the Barthel Index by expanding the number of categories used to record improvement in each subscale, while simultaneously revising the scoring method, thus developing the "Modified Barthel Index", or MBI (Shah et al. 1989). Despite these improvements, over the years even the latter scale was deemed not very sensitive in assessing patients with severe and complex disabilities.

This introduction allows us to highlight the need for an evaluation tool capable of measuring the functional status / level of independence of a patient at any given time. The systematic nature of this process would allow for appropriate planning of rehabilitation-educational interventions, and the effectiveness of these interventions could be assessed by re-verification utilizing same instrument.

In 2012 our rehabilitation facility, the Serafico Institute, was included in a research study promoted by A.R.I.S. (Religious Association of Socio-Health Institutes), AGE.NA.S. (National Agency for Regional Health Services) and eight Italian IRCCS and sponsored by the Ministry of Health, entitled: "*Study of the developmental prospects of rehabilitation services aimed at satisfying the demand for health and functional independence of disabled subjects with emphasis on sustainability of central and regional policies in the health care sector and the integration between social welfare and health*".

The research study in question led to the formation of a permanent, multi-regional observatory, later extended nationally, whose responsibilities include monitoring rehabilitation needs, responses and expenditures in the evaluation forms available to the centers involved, while empowering these centers to guarantee and verify essential levels of assistance provided in each region.

The Serafico Institute's contribution to the study was in providing comprehensive assessment on a group of 10 boys between the ages of 14 and 18 with varying degrees of intellectual disabilities. The assessment was conducted using the Vineland functional scales for adaptive behavior (Sparrow et al. 1984) and the Praxia Examination (Scuccimarra et al. 2004) in two different time periods: before treatment, and at 6 months post-onset of treatment. Any changes detected during the treatment period were documented and all treatments conducted were assessed both in a quantitative and qualitative manner. In addition, competencies in ADL performance were identified via compilation of an *ad*

hoc checklist developed by the promoters of the project and referred to as the "Basic ADL Exam" which included four macro areas of evaluation: dressing, feeding, personal hygiene and transfers/mobility. Each area contained a number of specific items to assess. For each of these items the skill level of the individual patient could be assessed via a 0 to 4-point scoring system, (from "0" corresponding to 0% of task completion, to "4" corresponding to between 75% to 100% of task completion). We immediately realized that in order to guarantee maximum accuracy in the scores provided it became important to introduce a greater level of detail in the individual ADL items proposed for each of the four macro areas indicated so that the actual abilities of each subject in each item assessed could be more appropriately identified.

Our search for a more precise and valid assessment instrument oriented us towards utilizing a unique methodology involving the application of assessment grids referred to as rubrics (Cawley 2013). Upon further research, we adopted various checklists purchased from www.YourTherapySource.com, an online resource for special education, pediatric occupational and physical therapy publications used in the clinical setting.

Specifically, the following checklists were purchased:

- for the clothing macro area: the Dressing Skills Rubrics (2011);
- for the feeding macro area: the Meal Time Rubrics (2011);
- for the personal hygiene macro area: the Personal Hygiene Rubrics (2011);
- for the movements macro area: Mobility Rubrics (2011).

The instruments were well received by the staff involved in the project who appreciated its ease of application in both educational and rehabilitation areas. The multidisciplinary work group formed during the study suggested that an evaluation tool of this nature would be invaluable for the entire patient population with complex disability residing in the institute. Following an initial assessment of the instrument's applicability to different types of complex disability, the study group formulated several proposals for adapting the instrument to assess patients with very severe illness as well as for those patients with visual deficits. An initial draft of a specialized task analysis resulted (analysis of abilities / activities) that was introduced in all living groups, followed by a period of staff training regarding assessment and documentation procedures, where meticulous observation for precise detection of ability was emphasized. These aspects served as core elements in developing the actual ADL assessment project now referred to as D-Rubrics.

The primary aim of this study is to analyze preliminary data obtained from compilation of the current version the D-Rubrics with the goal of establishing concurrent validity of the instrument.

We expect a strong correlation between this new assessment tool and the MBI, which is validated and assesses the same construct. We did not take the BI into consideration given its very low sensitivity in severe disability.

The secondary aim of this study is to evaluate any differences between the values obtained from the above-mentioned instruments (D-Rubrics versus MBI) administered at baseline (T0) and following rehabilitation intervention, already a fundamental cornerstone of the Serafico's practice model, but patient-specific using specific items targeted for reevaluation at T1. We expect that only the D-Rubrics tool will highlight differences in the scores observed between T0 and T1, while no differences in scores will emerge by the other measure.

SUBJECTS AND METHODS

Subjects

A power analysis was used to estimate the adequate sample size for the repeated measures analysis of variance. A total sample size of 189 subjects allowed us to highlight, at a threshold of $\alpha = 0.05$ and with a power (1-beta) of 0.8, an average of the effect (Effect size f) equal to 0.25 standard deviations, as described by Cohen (1988).

In consideration of the small size of the sample used, the study is classified as a pilot and, if the expected results will be confirmed, will eventually be extended to a greater number of patients.

For this study, the inclusion criteria were as follows: age 18 and over, QI less than 70 (valuated by Vineland II) and SRS (Supervision rating scale) ≥ 4 .

The group studied (n) consisted of 33 patients, 28 male, 5 female, with ages ranging from 18 to 40 years (Mn 27.12; Sd 7.40), classified secondary to DSM-V diagnostic criteria: Autism spectrum disorders (ASD) ($n=8$), Intermittent Explosive Disorder (IED) ($n=10$), dual ASD and IED diagnosis ($n=6$) and other behavioral disorders ($n=10$). QI was evaluated via assessment using Vineland II and demonstrated the following distribution: a score of 20 for $n=32$ patients (classified as having profound intellectual disability), and a score of 31 for $n=1$ patient (classified as severe intellectual disability) (Mn 20.32; Sd 1.89). Every patient in the group presented a pathological syndrome affecting neurodevelopment, $n=5$ patients with a definite genetic diagnosis (Down Syndrome, Angelman Syndrome, Dravet Syndrome, Fragile X syndrome and WAGR syndrome), $n=2$ patients with cerebral palsy, and the remaining $n=26$ patients without a definite diagnosis.

All patients in the study were classified as independent for ambulation.

D-Rubrics

This evaluation grid is structured to permit the user to assign a numerical score to the ability to perform the components of a specific ADL task.

The grid is divided into 4 main groups, referred to as "macro areas", each related to different aspects of the basic activities of daily living: feeding, personal care, dressing, mobility.

These macro areas are further divided into sub-groups, or "items", which define very specific activities (for example: "bringing food to the mouth with the hands"). Each item belonging to a macro area is broken down further into a series of "components" describing the individual actions that the patient is required to perform to complete the sequence required by the item. For example, for item 1 in the macro area of Feeding ("Bringing food to the mouth with the hands"), the patient's ability to "grab the food in question" is assessed first, followed by the ability to "maintain the food between the fingers without dropping it", etc...).

Each component is assigned a score ranging from 0 to 4, and defined as follows:

- 0 - corresponds to "totally dependent";
- 1 - corresponds to "important physical assistance and/or verbal cues required to complete the task (gestures or icons/symbols)";
- 2 - corresponds to "slight physical assistance and / or verbal cues required to complete the task (gestures or icons/symbols)";
- 3 - corresponds to "capable of performing the action but the quality of the performance, the attention level and participation are inconsistent";
- 4 - corresponds to "independent and appropriate task performance".

The scores assigned to each "component" of an item are then added up, and the total obtained allows the evaluator to quantify individual performance relative to the "item" in question. The individual total scores of each item are added up and the totals generate a numerical value for the macro area in question. The higher the numerical value, the greater the patient's level of independence in that macro area.

Modified Barthel Index (Shah et al. 1989)

The Barthel Index explores items related to mobility, transfers, ambulation, personal hygiene, feeding, and bowel and bladder control. Scores of 0, 5, 10 or 15, are assigned based on the degree of independence demonstrated by the subject performing the single action.

The resulting score measures the level of assistance that the patient requires in order to perform the activities of daily living in question.

The minimum value possible ("0") indicates complete dependence, while the maximum value possible ("100") represents complete independence.

Due the diversity of the population being studied a more sensitive scale was deemed necessary to ensure accuracy in evaluating competence in this specialty area of rehabilitation. The Modified Barthel Index was identified as more sensitive when compared to the original

Barthel Index. The MBI provides a detailed scoring system, with shorter numerical intervals between competence levels (scoring distributions: 0, 2, 5, 8, 10; or 0, 1, 3, 4, 5; or 0, 3, 8, 12, 15).

The scoring of the MBI is no more difficult to score than the original Barthel Index, nor does it increase completion time for trained assessors. In addition, its use improves internal consistency and provides improved discrimination of functional ability.

Vineland II (Sparrow et al. 2005)

This scale evaluates level of adaptive behavior, which is necessary when forming a diagnosis of intellectual disability disorder and, in agreement with DSM-5 criteria (Diagnostic and Statistical Manual of Mental Disorder, fifth edition). It is also required for establishing the severity of the disorder.

Consequently, according to the diagnostic criteria for intellectual disability, patient performance which is at least 2 standard deviations lower than the reference group will be sufficient for making a positive diagnosis.

This instrument consists of 4 scales, or "domains," with each domain divided into 11 subdomains:

- Communication (Receptive, Expressive and Written).
- Daily Living Skills (Personal, Domestic and Community).
- Socialization (Interpersonal Relationships, Play and Leisure Time, Coping skills)
- Motor skills (gross motor and fine motor).

Compilation of these scales was carried out by designated personnel based on the type of scale. The compilation of the D-Rubrics, the Barthel Index and the Modified Barthel Index were carried out by a selected group of assistants/carers and were supervised by the assessment team composed of the following members: pedagogist/educational specialist, psychologist, various rehabilitation specialists, occupational therapist, physiatrist and neurologist (from this point referred to as the rehabilitation team).

The Vineland-II was completed by a psychologist trained in test administration and scoring of the assessment.

Procedure

This observational study was approved by the local ethics committee of the Umbria Region (Italy). Informed consent was obtained from parents and/or guardians of the patients involved in the study following full disclosure of the study's purpose and possible implications. Data was collected once informed consent was obtained.

Prior to actual data collection 10 assistants/carers on staff were identified and received specific training in item analysis and scoring procedures. Each staff member was assigned a patient in the study and was responsible for completing both the D-Rubrics and the

Modified Barthel Index for the assigned patient at two different times: at baseline (T0) and at three months post-intervention (T1).

In accordance with the Serafico Institute's practice model, upon completion of the initial evaluation phase (T0) the rehabilitation team established a specialized rehabilitation treatment plan for each patient, focusing on those skills identified as having potential to improve. Each treatment intervention lasted for three months; at the end of the intervention phase the carers/assistants completed the entire evaluation protocol for a second time.

Statistical Analysis

Descriptive statistics including mean and standard deviation were performed for all scales analyzed. To analyze the Internal Consistency of each macro area comprising the D-Rubrics (feeding, dressing, personal care and mobility), Chronbach's alpha values were calculated with a value of ≥ 0.70 being considered acceptable (George & Mallery 2003). In terms of concurrent validity Spearman's rank correlation coefficients were calculated for these preliminary results in order to examine the strength of the relationship between D-Rubrics macro areas and total score with those subscales that take into consideration the same activities and total score of the Modified Barthel Index. For example, the D-Rubrics Feeding macro area was compared to the MBI Feeding subscale, and the D-Rubrics Mobility macro area was compared to the MBI Transfers, Mobility and Stair Climbing subscales. A coefficient ≥ 0.70 was considered adequate. Finally, in order to investigate the sensitivity of the D-Rubrics in demonstrating the differences in performance between pre- and post-rehabilitative interventions, Repeat Measure Analysis were run for all measures. For all statistical evaluations $p < 0.05$ was considered indicative of significant differences. The Statistical Package for Social Science (IBM SPSS Version 21) was used for conducting all data analysis.

RESULTS

Mean levels of each D-Rubrics macro area and total score as well as of each subscale and total scores of MBI are reported in Table 1.

As shown in table 1 Cronbach's alpha of each D-Rubrics macro area was calculated to analyze internal consistency. It was excellent for all macro areas ranging from 0.986 to 0.918.

In Table 2 data regarding Spearman's rank correlation between the D-Rubrics macro areas and total score and MBI subscales and total score are reported. Data showed correlation from moderate to strong between the single D-Rubrics macro areas and the MBI subscales that assess the corresponding ability. Only the Mobility subscale showed a slightly lower than 0.70 correlation. A close correlation also emerged between the Total scores of D-Rubrics and the MBI total score.

Table 1. Descriptive statistics means and standard deviations for D-Rubrics macroareas and MBI subscales and total scores. Cronbach's alpha of D-Rubrics macroareas

	Totale Sample		Cronbach's α
	Mn \pm Sd	Min - Max	
D-RUBRICS			
Feeding	49.63 \pm 28.62	1.60-100	0.939
Personal Care	35.44 \pm 26.24	0-93.42	0.961
Dressing	45.43 \pm 31.91	1.67-100	0.986
Mobility	73.30 \pm 24.45	7.42-100	0.918
Total	48.68 \pm 27.19	2.29-98.61	
MBI			
Feeding	6.09 \pm 2.55	0-10	
Personal Hygiene	1.71 \pm 1.60	0-4	
Bathing Self	1.71 \pm 1.60	0-4	
Toilet	5.12 \pm 2.54	0-8	
Bowel Control	6.29 \pm 3.96	0-10	
Bladder Control	6.44 \pm 4.00	0-10	
Dressing	5.76 \pm 2.71	0-10	
Ambulation	11.09 \pm 2.58	0-15	
Chair/Bed Transfers	13.00 \pm 2.65	3-15	
Stair Climbing	6.32 \pm 2.92	0-10	
Total	63.21 \pm 21.83	6-94	

MBI: Modified Barthel Index

Table 2. Spearman's rank correlation to explore the Concurrent Validity of the D-Rubrics

MBI	D-RUBRICS	Feeding	Personal Care	Dressing	Mobility	Total
Feeding		0.758**				
Personal Hygiene			0.807**			
Bathing Self			0.753**			
Toilet			0.843**			
Bowel Control			0.851**			
Bladder Control			0.814**			
Dressing				0.761**		
Ambulation					0.669**	
Chair/Bed Transfers					0.740**	
Stair Climbing					0.676**	
Total						0.879**

** p<0.001; MBI: Modified Barthel Index

Table 3 demonstrates the Mean and SD at T0 and T1 of each single scale of D-Rubrics and MBI, the respective delta scores (Δ) and the results of Repeat Measure Analysis.

The Repeat Measure Analysis highlighted significant differences between T0 and T1 in specific macro areas of the D-Rubrics following rehabilitation intervention. The measures demonstrated slight differences in two areas, in feeding ability (F=11.14; p=0.002), in personal care ability (F=12.75; p=0.001) as well as in the Total score (F=8.79; p=0.006). The differences between pre- and post-interventions of the Mobility macro area was also near statistical significance (p=0.06). It was not possible to perform the Repeat Measure Analysis for any of the MBI subscales having reported the same scores in both cases ($\Delta=0$).

DISCUSSION

In the complex disability field, the literature provides limited data regarding appropriate evaluation methods. This study arises from an awareness of the lack of instruments capable of detecting and measuring patients' clinical-functional status and any changes which result, however minimal, over time, with the goal of monitoring the effectiveness of rehabilitation interventions.

One of the main goals of this study was to analyse preliminary data regarding the validity, reliability and sensitivity of a new assessment tool designed to evaluate and detect changes in functional status / level of independence following rehabilitation intervention of patients with complex disability. A strong limitation of this study is the small sample size, yet this is justified

Table 3. Repeat Measure for D-Rubrics macroareas and MBI subscales and total scores

	T0 Mn ± Sd	T1 Mn ± Sd	Δ	F	p
D-RUBRICS					
Feeding	49.63±28.62	50.68±28.22	1.05	11.14	0.002
Personal Care	35.44±26.24	36.08±25.86	0.64	12.75	0.001
Dressing	45.43 ±31.91	45.73 ±31.69	0.30	1.85	0.183
Mobility	73.30±24.45	73.62±24.43	0.32	3.87	0.060
Total	48.68±27.19	49.17±26.96	0.50	8.79	0.006
MBI					
Feeding	6.09±2.55	6.09±2.55	0	-	-
Personal Hygiene	1.71±1.60	1.71±1.60	0	-	-
Bathing Self	1.71±1.60	1.71±1.60	0	-	-
Toilet	5.12±2.54	5.12±2.54	0	-	-
Bowel Control	6.29±3.96	6.29±3.96	0	-	-
Bladder Control	6.44±4.00	6.44±4.00	0	-	-
Dressing	5.76±2.71	5.76±2.71	0	-	-
Ambulation	11.09±2.58	11.09±2.58	0	-	-
Chair/Bed Transfers	13.00±2.65	13.00±2.65	0	-	-
Stair Climbing	6.32±2.92	6.32±2.92	0	-	-
Total	63.21±21.83	63.21±21.83	0	-	-

MBI: Modified Barthel Index

by the fact that developing systematic and reproducible programs with patients with complex and severe disabilities is complicated. Another limitation is represented by the brief period for follow-up, which was designed to obtain a preliminary idea of the instrument's ability to capture minimum variations even in a short amount of time. Despite these limitations, the results have demonstrated some very interesting data revealing excellent internal consistency, proof that the D-Rubrics is capable of measuring the abilities in question and does it in a coherent and reliable manner.

Even the data regarding the Spearman's rank correlation between the D-Rubrics and the MBI demonstrated a moderate to strong correlation, indicating that the construct measure of the D-Rubrics is comparable to the construct measure of the MBI, a measure which is already validated and widely utilized in the field of disability assessment.

The data were collected at the baseline (T0) and following a 3-month period of educational/ rehabilitation intervention (T1). The interventions included in the routine treatment plan focused on those aspects / items identified via D-Rubrics as having the greatest potential for improvement. This allowed for an exploration of the instrument's sensitivity to change and also proved the insensitivity of the MBI to measure minute differences in functional status of those patients who demonstrate very little improvement their abilities (Δ score=0). The D-Rubrics reaches significant sensitivity particularly in the macro areas of feeding, personal care, and in the total scores. Statistical significance is not obtained in the mobility

macro area, most likely because patients show exceptionally high scores at T0. In this case it is possible to hypothesize that the patients in question have already reached their maximum level of performance at baseline, considering previous rehabilitation interventions carried out in the institute.

For the dressing macro area, the data are far from reaching statistical significance. This may depend on the complexity of the skill components involved in the ability to dress oneself. The degree of dexterity and fluidity required by the motor prerequisites necessary to dress oneself is high, and 3 months of rehabilitation intervention is most likely insufficient to achieve any appreciable result.

Despite the limitations of the study the data obtained were extremely encouraging. Future studies are being planned to prove the consistency of these results over time and with a larger patient population.

CONCLUSIONS

This study identifies the urgent need for an evaluation scale capable of establishing the clinical condition of patients prior to educational/rehabilitative intervention with a high degree of sensitivity, as well as identifying even minimal improvements post-intervention. The D-Rubrics scale seems to represent a very solid evaluation tool for use in complex disability, with an acceptable degree of sensitivity and excellent internal consistency.

A larger cohort of patients with a longer follow-up period is required to confirm the data presented.

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Contribution of individual authors:

Moreno Marchiafava, Chiara Bedetti & Silvia Ilicini: study conception and preparation.

Silvia Ilicini & Sandra Cicuttin: identification and acquisition of the original assessment instrument, adaptation of the original assessment instrument, drafting and manuscript translation.

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NEW TECHNOLOGIES FOR ART THERAPY INTERVENTIONS TAILORED TO SEVERE DISABILITIES

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SUMMARY

Individuals with multiple disabilities can have a wide range of characteristics depending on the combination and severity of the disabilities, such as intellectual disability, mobility issues, sensorial impairment, language issues and brain injury. New technologies can help therapists find an alternative way to engage and interact with clients by opening a communication window and starting to build the therapeutic relationship.

The need to use more customized technological tools led us to develop the Painteraction system, an intuitive tool based on Augmented Reality that allows clients to be immersed in their own images. Just by moving their bodies individuals are able to make drawings and receive visual feedback, both from themselves and their therapists, as it appears on the screen.

The pilot testing of Painteraction was performed on 21 inpatients at Istituto Serafico (Assisi, Italy) with severe/multiple disabilities in order to explore and assess reaction and responsiveness in a semi-structured art therapy setting. The sample was formed by 14 males and 7 females (N=21) between the ages of 7 and 35. All participants attended three twenty-minute individual art therapy sessions which were approximately one week apart.

Through direct and indirect (video recordings) observation of the sessions, it appeared that the specific Augmented Reality tool introduced in the art therapy setting was easily accepted by most of the clients involved and generally allowed the development of an interpersonal therapist-client relationship.

The present study therefore gave us the opportunity to test new digital tools in the challenging setting of severe/multiple disabilities and observe the huge potential of new media to empower clients to express themselves and their creativity, and ultimately overcome mental and physical barriers.

We propose that Augmented Reality tools are particularly well-suited to art therapy and create an equally suitable therapeutic environment to address specific client needs.

Key words: severe disability - multiple disability - art therapy - augmented reality - Painteraction

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INTRODUCTION

The present paper aims to present the results of the pilot test of an Augmented Reality tool in an art therapy setting on individuals with severe/multiple disabilities.

The complexity of interventions with this population resides in the wide range of their characteristics, depending on the combination and severity of their impairments.

Every person with multiple disabilities presents a unique challenge.

Art therapy is a mental health profession that uses the creative process of art-making to foster personal development and improve the psychological, affective, cognitive and relational well-being of individuals. It is based on the premise that the creative process generated in artistic self-expression, when practised by a professionally trained art therapist, fosters the growth and development of a sense of self. This type of therapy involves a tripartite relational structure: client with art image; client with art therapist; art therapist with art image (European Federation of Art Therapy EFAT 2018).

The availability of digital technology has increased opportunities for creative expression and communication exponentially. Art therapists have reflected upon the opportunities for incorporating digital technology as a useful intervention tool in clinical sessions (Carlton 2014, Choe 2014, Darewych 2015, Malchiodi 2009, Orr 2012, Peterson 2010).

In Augmented Reality (AR) virtual elements are used to build upon the existing environment. Clients can see their own body in an imaginary context while feeling inside the "real" world. It has been claimed that the virtual environment enables a synthesis of the actual and the imaginary (Vincelli 1999). In AR the combination of an existing environment, one's own body and imaginative and artistic elements creates dream-like experiences in a safe environment. What happens on the screen represents the achievement of the tripartite relational structure: client and therapist with art image on the screen. It is easier for the client to accept the presence of the therapist, to look at him/her on the screen, to start interacting together and even accept physical contact rather than having to engage directly in the "real" world through eye contact etc. From this

perspective the screen can be seen as a sort of “third space” (Ogden 1994) where the relationship between client and therapist can be safely developed. This reminds us of Winnicott’s “potential space” which is an intermediate area between the inner world, the “inner psychic reality” (fantasy), and “actual or external reality” (Ogden 2004). Winnicott states that: “It is a space where we can develop psychologically, to integrate love and hate and to create, destroy and re-create ourselves”, thus promoting the development of the self and facilitating psychological growth (Winnicott 1997). This shared dreamlike space incorporated within an immersive and interactive environment shows great potential for enhancing the efficacy of art therapy (Hacmun 2018).

We hypothesize that the use of a tailored tool can allow for a less invasive relational approach, combining a playful environment with an art therapy intervention. The new technological tool presented in this paper, Painteraction, has strong clinical experience and allows a highly customized approach to the specific needs and skills of each client. According to our hypothesis, using the tool in an art therapy setting allows the fine-tuning of the intervention to the needs of the client. The resulting approach is respectful, playful and can improve social relationships, body movement and creative expression in people with severe/multiple disabilities.

METHODS

The present pilot test aimed at exploring and assessing reaction and responsiveness to specific digital tools by a population affected by severe/multiple disabilities in a semi-structured art therapy setting.

A qualitative piece of research was run to evaluate reactions through direct observation of avoidance or acceptance of the proposed activities during each session.

The study explored the following two research questions:

- How do people with severe/multiple disabilities experience digital technology as a clinical intervention tool in art therapy?
- Do technological tools in an art therapy setting improve the opportunities to establish a relationship with therapists?

The study was conducted at the Serafico Institute in Assisi (Italy), a specialized inpatient facility providing rehabilitation services to individuals with multiple disabilities (mainly intellectual and sensorimotor). Extensive clinical documentation regarding diagnosis is required prior to admission.

The sample was formed by 14 males and 7 females (N=21) between the ages of 7 and 35. All subjects had severe/profound intellectual disability according to Vineland Adaptive Behaviour Scales criteria (Carter et al. 1998). Just two of them were verbal (N=2). Among

the non-verbal subjects, just one communicated via Augmented and Alternative Communication while others communicated by pointing at images, objects, words and symbols.

Therapists and clients involved had not met before the beginning of the pilot test. Clients had never used the proposed technological tools before the beginning of the pilot test, and had never received any training on the use of the specific tools involved and generally on AR.

All participants attended three twenty-minute individual art therapy sessions which were approximately one week apart in a dedicated room at the Istituto Serafico. The pilot testing took place from September to December 2018.

Each session was facilitated by one art therapist and two Major Degree Psychology students. Sessions were adapted to each individual’s level of cognitive and physical ability and were structured in the following three segments: warm-up activity, digital art therapy intervention and closure activity. Each session started with a check-in feeling chart and closed with a check-out feeling chart (Figure 1).



Figure 1. Feeling charts

In the warm-up activity the digital tool Painteraction allowed physical warm-up and user engagement. The digital art therapy intervention was preceded, if possible, by free drawing on paper with pastels. Client’s drawings or images selected by clients were used in the last digital activity, which involved body expression. The check-out feeling chart was proposed at the closure of each session. Check-in and check-out feeling charts were completed either verbally or by pointing to two different smiley faces (sad or happy). Feeling charts were considered as a qualitative measurement of a client’s acceptance/avoidance of the proposed session and as a marker of the willingness to participate in the second and third sessions. Each session was video recorded.

Permission to proceed with this study was reviewed and granted by Istituto Serafico Board. Participation in this study posed no potential risks to participants’ well-being beyond those normally encountered in everyday life.

TOOLS: PAINTERACTION

A new technological tool named Painteraction was recently developed at Atlas Centre, Italy from an original idea by Donnari (2015), (Pazzagli et al. 2018).

Key elements of Painteraction are:

- Intuitive understanding of “how it works” and ease in managing the tool: the device provides a natural user interface that allows users to interact intuitively with voice and gestures without any intermediary device, such as a controller.
- Screen acts like a mirror reproducing the real room where the action happens, with AR that enhances the real world.
- Visual feedback of movements that can catch the client’s attention and help him/her to immediately understand how the software works.
- Sensorial integration: movement, visual feedback and sound. Motion responsive technology provides the integration of different sensorial inputs.
- Different applications for a tailored treatment. Painteraction offers a range of applications that allow the therapist to better understand which approach is tailored to the needs and skills of the specific client.
- Data recording. Data stored in a cloud can be retrieved by researchers to perform assessment and evaluation. Data can also be used for supervising the therapists.

The Painteraction setting consists of a television screen, a personal computer and a Kinect, a motion sensing input device (Figure 2).



Figure 2. Painteraction setting

There are five interactive applications:

Trails: Luminous trails are generated by hand movements. The client and therapist can see themselves on the screen and receive visual feedback from their hand movements. Sound feedback can be added to the trails.

Paint: By simply using hand movements, it is possible to draw by picking colours from a menu. Colours can also be associated with basic emotions represented by emoticons. The colour lines are transparent and

behind the drawing it is possible for therapist and client to see themselves on the screen. A sound effect can be added to the colours.

Physics: The application allows interaction with a virtual ball bouncing around in response to full body motions.

Vowels: Vowels emitted by a user are sensed and transformed into coloured shapes which appear on the screen close to the user’s mouth. It is also possible to make drawings with one’s own voice.

Avatar: After choosing a background (one’s own drawing or a chosen image), the client can see his/her own body immersed in the image. A detail of the image or a favourite character can be used as a personalised avatar and can be moved by one’s own body. It can be used for storytelling or as a real life simulation tool.

A website was designed to manage the access and privilege levels of different kinds of users. Therapists and researchers can retrieve data and videos of the sessions from the website and receive a visual recap of the time spent using each application.

RESULTS

18 clients rated the first and following sessions positively. Three clients expressed avoidance by refusing to remain in the setting during the first and the second session. A third session was not proposed to these subjects. Therapists generally reported, as shown in the video recordings of the sessions, that the clients adopted a positive attitude towards the proposed activities.

The warm-up was generally enjoyed and helped engage 15 clients and establish a good atmosphere. Three clients were clearly not interested in the warm-up activity during the first session and did not want to repeat it in the following sessions.

Just 4 subjects could perform free drawing while the others were willing to choose favourite images from the internet by pointing at the computer screen (Figure 3, 4). Digital art therapy intervention based on personal drawings or favourite images was appreciated by the 18 remaining clients.



Figure 3. Free drawing on paper



Figure 4. Immersion in the client's drawing.

DISCUSSION

The primary research question for the study was: How do people with severe/multiple disabilities experience digital technology as a clinical intervention tool in art therapy?

Throughout the study, participants had the opportunity of experiencing a different kind of intervention that could be individually customized, thus facilitating non-verbal interaction. The technological tool gave the clients the opportunity to have their first engagement of a visual-sensory nature. The visual approach seemed effective for all 18 clients who completed the three sessions. According to our experience the use of the screen and the AR tool was a very effective way to start the session; we noticed that it caught clients' interest and focus. We experienced also that such a tool facilitated the development of an interpersonal relationship between therapists and client. Physical touch, body movement, free drawing (on paper or on the screen) were afterwards easily accepted by all 18 clients.

Clients expressed a clear appreciation of the possibility of being immersed in their own drawings or in images of their choice. In the video recording, facial expressions show joy and amusement. After the initial phases all 18 clients willingly used the final immersive tool. Three people were able to make free drawings on paper. Three clients chose images and characters from their favourite cartoons and animated them in real life with the therapists. Two clients chose the photo of their favourite singer and animated it by singing their favourite songs. The possibility of introducing sounds and music was always proposed as an opportunity to test individual acceptance and tailor the following sessions to their sensorial preferences. Just 8 people accepted music and sounds during the session.

The second research question was: Do technological tools in an art therapy setting improve the opportunities to establish a relationship with therapists? Therapists were generally impressed by the ease of acceptance of the proposed activities during the sessions, considering they had no previous contact with these clients. The possibility of having fun together seemed a powerful way of establishing relationships and getting close to

new clients. Clients were generally surprised by the potential of this technological tool, and it was described as magical. The tool was greeted with interest and curiosity by these 18 clients, at no point creating anxious reactions or facial expressions denoting fear. Interest and appreciation was also expressed in check-out feeling charts and by the fact that all 18 clients chose to participate in all three sessions proposed.

CONCLUSION

The present pilot test aimed at exploring and assessing a specific digital tool for clients with severe/multiple disabilities. Considering direct and indirect (video recordings) observation of the sessions, the specific AR tool introduced in the art therapy setting seemed to be easily accepted by most of the clients involved and generally allowed the development of an interpersonal therapist-client relationship.

The main elements that facilitated the art therapy sessions seemed to be:

- The possibility of individual personalization of the tool;
- The element of surprise generated in the client;
- The possibility of experiencing themselves in a safe and playful environment;
- The possibility of overcoming disability barriers, e.g. the possibility of drawing just by moving their bare hands;
- The possibility of integrating different sensorial channels (visual, hearing, touch);
- The possibility of expressing free individual preferences by choosing favorite images and characters to interact with.

Although there was a general appreciation of the experience by both clients and therapists, the present study has several limitations.

Since this pilot testing was the first application of this technological tool in a severe/multiple disability context, we adopted a heterogeneous sample regarding age, sex and diagnosis. Another limitation linked to the testing phase is the limited amount of time of each session and of the entire study.

The evaluation was based on qualitative observations.

Considering the favourable results, the next steps we can foresee are:

- Clinical trial on a homogeneous randomized sample with a control group.
- Quantitative research based on measurements and standardized tools to assess the positive effect of the proposed digital art therapy intervention.
- Longer time to practise (at least one year, once per week) and follow-up assessment six months after the conclusion of the clinical trial.

In the future we wish to investigate mirror neuron system activation during art therapy sessions with Painteraction and generally sensorimotor activation and improvement.

In conclusion, the present study gave us the opportunity to test new digital tools in the challenging setting of severe/multiple disabilities, and to observe the huge potential of new media in empowering clients to express themselves and their creativity in overcoming mental and physical barriers. In summary, we propose that art therapy is particularly well-suited for employing AR tools that create a therapeutic environment that can address clients' specific needs. The integration and implementation of new digital media in art therapy interventions is crucial for the evolution of the field. We believe that new technologies have the potential to enhance and expand classical art therapy approaches.

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Contribution of individual authors:

Simone Donnari & Giovanni Fatuzzo: design of the study, interpretation of data, manuscript writing.

Valentina Canonico: design of the study, manuscript writing.

Chiara Bedetti & Moreno Marchiafava: revising manuscript.

Marina Menna: design of the study.

Sandro Elisei: design of the study, interpretation of data.

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THE EFFECT OF MOZART'S MUSIC IN SEVERE EPILEPSY: FUNCTIONAL AND MORPHOLOGICAL FEATURES

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SUMMARY

Music is a very important factor in everyday life, involving mood, emotions and memories. The effect of music on the brain is very debated. Certainly, music activates a complex network of neurones in auditory areas, mesolimbic areas, cerebellum and multisensory areas. In particular, music exerts its effects on the brain of patients with epilepsy, having a dichotomous influence: it can either be seizure-promoting in musicogenic epilepsy or antiepileptic. Several studies have shown that seizure-prone neural networks may be stimulated by certain periodicities while other frequencies may prevent seizure activity. There are a lot of data in the literature about the so-called "Mozart effect" (Rauscher et al. 1993). In previous studies we observed that in institutionalized subjects with severe/profound intellectual disability and drug-resistant epilepsy, a systematic music listening protocol reduced the frequency of seizures in about 50% of the cases. In this study we are conducting a survey on the observation of what happens to the brain of patients suffering from drug-resistant epilepsy through electroencephalographic investigations, brain MRI and behavioural analysis before and after six months of listening to Mozart music (Sonata K.448). The first step is to present the data of the first patient under investigation.

Key words: EEG - epilepsy - intellectual disability - autism - MRI

* * * * *

INTRODUCTION

Data literature has revealed much evidence supporting the positive effects of music in neurological disease, including Parkinson's disease, senile dementia, sleep disorder, depression and epilepsy. Since 1952 Gheerbrant found a relaxant effect in Mozart's music on native Indians during his expedition to the Amazon region (Gheerbrant 1952). Since then, many reports have been published on the effects of Mozart's music, named "Mozart effect" (Rauscher et al. 1993). The expression "Mozart effect" refers to an increase or normalisation of higher brain function associated with listening to Mozart's music (Grylls et al. 2018). In epilepsy this effect was first characterised by Hughes et al, who observed a decrease in electroencephalographic epileptiform activity in 23 patients out of 29 while they were listening to Mozart's music (Hughes et al. 1998). After this work some authors have studied electroencephalographic activity before, during and after listening Mozart's Music (Turner et al. 2004) and its effects on the seizure frequency in children (Lin et al. 2010, Lin et al. 2011, Grylls et al. 2014, D'Alessandro et al. 2017, Bedetti et al. 2019). Regarding seizure frequency, a randomized controlled study carried out over 24 months in children with initial unprovoked seizures

revealed that those children who were under musical treatment had a 76.8% reduction in epileptic seizures compared to the 37.2% reduction of the children in the control group (Lin et al. 2014). Studies of Lin et al. have confirmed previous sporadic and anecdotal observations (Lahiri & Duncan 2007, Kuester et al. 2010) and overall have stimulated further investigations on this subject.

Understanding why music, and in particular Mozart's music, have this positive effect is very difficult.

Data literature shows that music listening improves neuronal connectivity in specific brain regions and musical activities promote neural plasticity and induce grey and white matter changes in multiple brain regions, especially frontotemporal areas (Wan et al. 2010, Schlaug et al. 2015, Vaquero et al. 2016).

The approach to music, both as a passive listening activity and as direct use of musical instruments, is able to influence the functionality of numerous brain areas. From several studies in literature we can see the involvement of brain areas that go beyond the classical structures connected to sensory perception (Habibi et al. 2018), in particular the structures appointed to interconnect intra-and inter-hemispheric brain areas to be called into question (Moore et al. 2014), including the corpus callosum (Schlaug et al. 1995, Lee et al. 2003).

Among the mechanisms that can explain this link with music and the development of brain structures dedicated to interconnection, we find not only the activation of the areas assigned to perception and secondary integration to musical listening, but also the ones for the activity of "abstraction" of the emotional meaning that the brain performs in response to the complex auditory stimulus (Sachs et al. 2018).

Musical processing involves a complex network of neurones in auditory areas, mesolimbic areas, cerebellum and multisensory areas, so music can be used in the fields of cognitive neuroscience, auditory perception, memory, sensorimotor processing, brain plasticity and mirror neuron system. The brain, like music, generates waveforms that may create harmony or disharmony (Maguire 2016).

Mozart's music in particular seems to act through different mechanisms. Studies on the organisational structure of the neocortex of the brain showed that nerve cells are highly structured in longitudinal cell columns, forming an organisational unit (Mountcastle 1957, Rakic 1988). Hughes et al. noted that Mozart's music is also highly organized (Hughes et al. 1998), with a unique, repetitive structure. Considering that the cerebral cortex and Mozart's music have a similar arrangement, they may communicate to each other, normalising the suboptimal functioning of the cortex (Liao et al. 2015).

Mozart's music, compared to that of other composers, shows long-term periodicity, so melody repetition is more frequent than in other musical works (Hughes 2001). These characteristics may resonate with the structure of the cerebral cortex (Liao et al. 2015).

Other authors suggested that mirror neurons are involved in the antiepileptic effect, activating through music listening and regulating neuronal activity (Molnar et al. 2006, Buccino et al. 2005).

Lin et al. observed that, in sixty-four epileptic children, there was a significant reduction of epileptiform discharges during and right after listening to Mozart's music (sonata K448 and K545); at the same time, in the majority of the patients, a reduction in heart rate

was observed representing the autonomic function; so the authors conclude that there is a possible increase in parasympathetic tone during the exposure to music (Lin et al. 2013).

Dopamine may also play a role in the effect of music on epilepsy. Reflex epilepsy and in particular musical epilepsy are connected to the other side of the effect that music can have on the brain. This phenomenon can be explained by the different roles of dopamine receptors: the D2 receptors activation is associated with an anti-epileptic effect, the activation of selective D1 receptors lowers the seizure threshold and induces epilepsy (Al-Tajir & Starr 1990).

Taking into consideration everything that has been said, this work aims to verify whether after an intervention with Mozart's music (sonata K448) we can identify changes in seizure frequency through EEGs, in the brain structure and functionally through brain MRI and on the behavioural level through the administration of specific scales.

For this survey the model is communicated by describing a single case report.

SUBJECT AND METHODS

This project has been approved by the Ethics Committee of the Umbria Region (prot. Number 13236/18/ESS). An informed consent form was signed before the study began. A 27-year-old boy affected by profound intellectual disability, $QI=20$ evaluated by Vineland II (Sparrow et al. 2005), autism spectrum disorder, intermittent explosive disorder, drug-resistant epilepsy with atonic and tonic-clonic seizures (EEG characterized by very frequent and generalised epileptiform discharges), microcephaly, facial and limbs dysmorphisms. Figure 1 shows a brain MRI of the patient characterised by a reduction of the cranium diameters, diffuse cortical atrophy, dysmorphic corpus callosum (reduced volume at the level of the body), malacic areas in the frontal and occipital lobes bilaterally, reduced representation of the subcortical white matter, slight left ventricular prevalence.

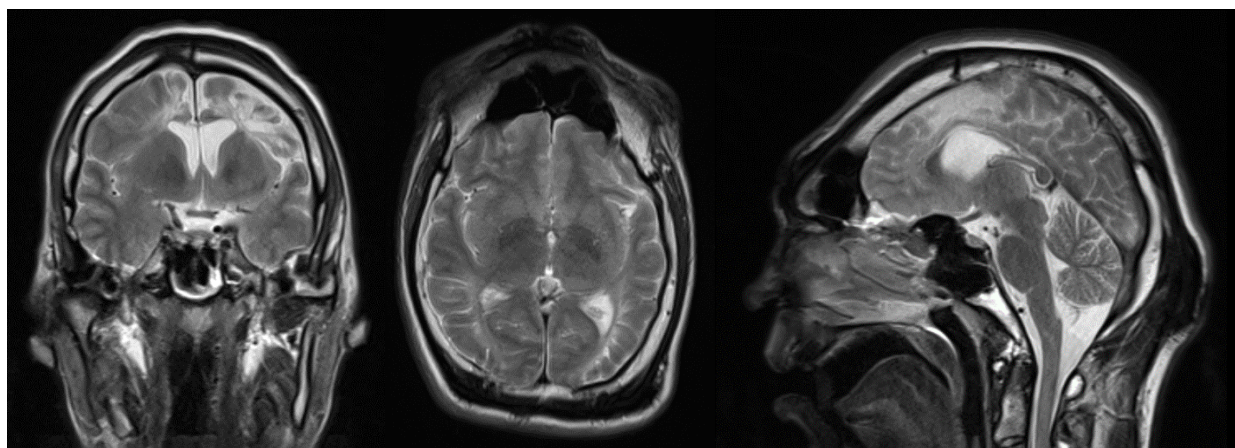


Figure 1. A T2 weighted MRI of the brain in the coronal, axial and sagittal view (from right to left)

He was subjected to EEG (duration: 180 minutes in the waking state) and brain MRI before (baseline: T0) and after (T1) a six-months-long period of listening to music 30 minutes a day (Mozart's piano sonata K448). Then we detected differences in epileptiform activity and in brain MRI between baseline and T1. Even the seizure frequency (seizure/month) had been monitored 6 months before and during the 6-months-period of listening to music. For the behavioural aspects we used the Brief Psychiatric Rating Scale (BPRS) and the Modified Overt Aggression Scale (MOAS).

As regards changes on the EEG, we programmed the measurement of the number of epileptic discharges between an exam performed before the music period and an exam performed immediately after the music period. The seizure frequency has been calculated like total of seizures 6 months before compared with total of seizures during the music period of 6 months listening to Mozart. We also measured the monthly average in the number of seizures of the previous six months and of the six months during music listening.

To perform the MRI it was necessary to sedate the patient with midazolam 0.35 mg/Kg mg i.v. and then with propofol (2 mg/Kg i.v. for the induction and 8 mg/Kg/h for maintenance).

The two brain MRI exams were obtained using a Siemens (Erlangen, Germany) 3T Verio MRI scanner with a 12-channel head coil. Anatomical images were obtained using a T1-weighted sagittal magnetisation-prepared rapid gradient echo (MPRAGE) series (repetition time [TR] 1900 ms, echo time [TE] 2.52 ms, slice thickness 1 mm), from which it was obtained a linear volumetric measurement of the dimensions of the corpus callosum. We followed the Hofer's criteria which divided the corpus callosum into 5 sections/regions: region I as the most anterior segment covers the first sixth of the corpus callosum and contains fiber projecting into the prefrontal region; the rest of the anterior half of corpus callosum is region II, which contains fiber projecting to premotor and supplementary motor cortical areas. Region III was defined as the posterior half minus the posterior third and comprises fiber projecting into the primary motor cortex; region IV, the posterior one-third minus posterior one-fourth refers to primary sensory fiber. Callosal parietal, temporal and occipital fiber cross the corpus callosum through region V which is defined as the posterior one-fourth (Hofer & Frahm 2006), (Figure 2).

The DTI sequence was acquired using a single shot echo planar imaging with a 12-channel head coil (TR 12200 ms, TE 94 ms, 2 mm thickness, isotropic voxels) from the foramen magnum to the vertex (whole brain acquisition). The diffusion gradients were applied along 30 non-collinear directions with two effective b values: 0 and 1000 s/mm². Image data processing was performed with the FSL 6.0 software package (FMRIB Image Analysis Group, Oxford, UK).

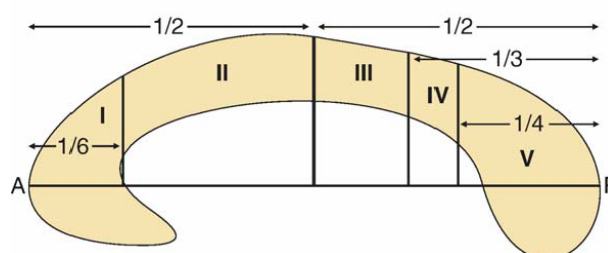


Figure 2. Sagittal section of the corpus callosum and subdivision into its functional components, according to Hofer's criteria (Hofer & Frahm 2006).

Diffusion data were corrected for motion and distortions caused by eddy current artifacts; the FMRIB's Diffusion Toolbox was used for local fitting of diffusion tensors. Two regions of interest (ROI) were defined for each exam (pre and post-music period): the first one included the entire corpus callosum displayed on the sagittal anatomical image, with a thickness of 6 mm on the midline; the second one included only the V portion of the corpus callosum, region made up of callosal parietal, temporal and occipital fiber (Hofer et al. 2006), with the same thickness on the midline. For each ROI the average FA and MD with the respective standard deviation (SD) were calculated with FSL. The first measurement was made the day before the beginning and the second was made the day after the end of the six months of music listening. A measurement of the tractography from the corpus callosum was also performed before and after the music period.

For the behavioural aspects we used the Brief Psychiatric Rating Scale (BPRS) that is a rating scale which may be used to measure psychiatric symptoms (24 items) such as depression, anxiety, hallucinations and unusual behaviour; each of the 24 items is rated 1-7, in an increasing order of gravity. The scale is one of the oldest, most widely used scales to measure psychotic symptoms (Overall & Gorham 1962). We also used another method for the evaluation of the behaviour, in particular the aggressive one, which can be performed through the use of an internationally validated scale, which is the Modified Overt Aggression Scale (MOAS), a versatile and prompt compilation tool for the caregiver and for health professionals. It evaluates four different forms of aggressiveness (verbal, physical towards objects, physical towards third parties, physical towards oneself) (Yudofsky et al. 1986).

Professional cares assessed the behaviour of the patients through blinded administration of these scale both before and after the musical listening period.

RESULTS

There was a significant decrease in the frequency of generalized epileptiform discharges on 180 min-awake-EEG performed on the last day of listening to music (160) compared to the 180 min-awake-EEG performed

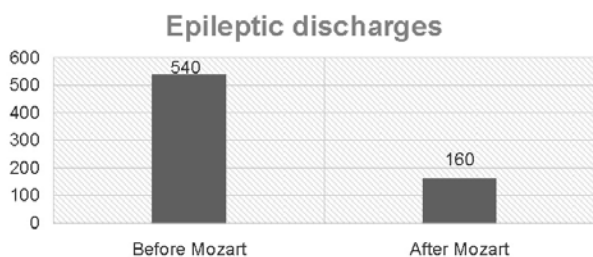


Figure 3. Comparison of the number of epileptic discharges counted manually through the 180 min-awake EEG performed the day before the beginning of period of listening to music (Before Mozart: equal to 540) and the last day of the period of listening to music (After Mozart: equal to 160)

the day before the beginning of listening to music (540). Epileptic discharges were counted manually (Figure 3). During the music listening period no pharmacological changes have been made.

The total number of seizures in the 6 months prior to listening to music was 176, while that of the six months during which the patient was listening to music was 94 (a reduction of 46.6%).

As shown in figure 4 even the seizure frequency (calculated as a monthly average in the 6 months before and during music listening) presents a marked reduction with a 6 month average percentage of reduction of 53.4%.

In particular, tonic-clonic seizures have been reduced to a greater extent than atonic ones, respectively 54.1% and 29.7% (Figure 5).

The analysis through brain MRI consists in calculating the volume of the corpus callosum according to a linear model, that divides the structure in 5 regions according to Hofer's criteria based on the connections between different areas. The same measurement was made before and after the musical listening period (Table 1).

Table 1 shows how the linear volumetric measurements of the corpus callosum are substantially unchanged between the T0 control and the T1 control.

Table 1. Corpus callosum measurement according to Hofer's criteria (Hofer & Frahm 2006), which divides the structure into 5 regions based on the connections within the different brain areas. The table shows the values of the 5 sections before and after the period of music listening

Corpus callosum sections	I	II	III	IV	V
Before music	9.5	19.1	9.5	4.7	14.3
After music	9.5	19.1	9.5	4.8	14.3

Table 2. Region Of Interest (ROI) for the volumetric measurement of the corpus callosum and of the only V portion expressed in average (Mean) and standard deviation (DS). FA=fractional anisotropy. MD= mean diffusivity

	Before Music		After Music	
	Mean	DS	Mean	DS
ROI Corpus callosum (whole)				
MD	0.001397	0.000566	0.001538	0.000866
FA	0.366932	0.240215	0.253316	0.101850
ROI Corpus Callosum (V posterior)				
MD	0.001299	0.000393	0.002398	0.000537
FA	0.472133	0.214866	0.306006	0.119977

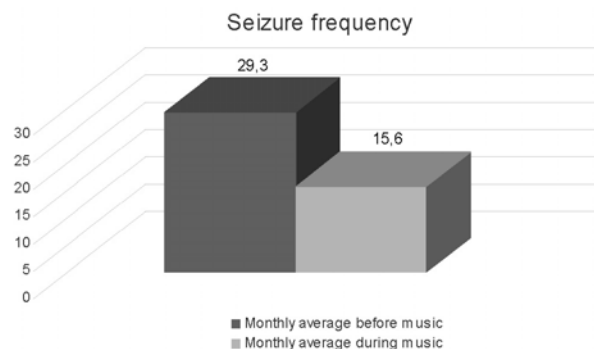


Figure 4. Seizure frequency: monthly average of seizures comparing the 6 months before (black column) and during (grey column) the period of listening to Mozart's music

The volumetric analysis of the corpus callosum was also conducted through the definition of Region of Interest (ROI) contouring the corpus callosum on a brain sagittal image and obtaining a measurement of fractional anisotropy (FA) and mean diffusion (MD) for a thickness of 6 mm for both the whole structure of corpus callosum and only the V portion. The same measurement was made before and after the musical listening period (Table 2).

The Corpus callosum data showed in Table 2, detect a reduction in FA and an increase in MD for both the whole corpus callosum and only its V portion.

The corresponding images obtained through DTI before the listening to music period (Figure 6) and after the listening to music period (Figure 7) provide a visual feedback of the performed study.

The behavioural aspects were assessed using two scales: the BPRS and the MOAS. The first, 24 items scale, useful to evaluate psychiatric symptoms such as elation/euphoria, agitation/aggression, irritability/lability and unusual behaviour; each of the 24 items is rated 0-7, where 0=not assessed, 1=absent and 2-7 in increasing order of gravity. The second scale measures the aggressiveness of the patients (verbal, physical towards objects, physical towards third parties, physical towards oneself) giving a score from 0 to 4 with increasing gravity.

Table 3 shows a reduction (from 88 to 73 equal to 17.1%) in the total score of the BPRS after the period of music listening. Considering the individual scores a reduction was observed for the items: hostility (from 7 to 5), elevated mood (from 6 to 5), bizarre behaviour (from 6 to 5), blunted affect (from 6 to 5), emotional withdrawal (from 6 to 5), tension (from 7 to 6), uncooperativeness (from 7 to 5), excitement (from 6 to 5), distractibility (from 6 to 4), motor hyperactivity (from 6 to 5), mannerism and posturing (from 7 to 6). Values equal to "0" were assigned based on the severity of the patient's intellectual state which does not allow the evaluation of these items. No items have increased.

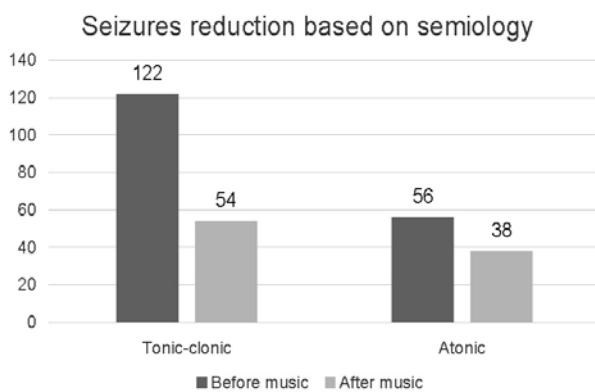


Figure 5. Reduction of seizures frequency in the six months before (black columns) and during (grey columns) music listening distributed by tonic-clonic and atonic semiology

Table 3. Single and total scores obtained from the administration of Brief Psychiatric Rating Scale (BPRS) before and after the period of listening to music

BPRS	Before Music	After Music
Somatic Concern	0	0
Anxiety	0	0
Depression	0	0
Suicidal	1	1
Guilt	0	0
Hostility	7	5
Elevated mood	6	5
Grandiosity	0	0
Suspiciousness	0	0
Hallucination	1	1
Unusual thoughts content	0	0
Bizarre Behaviour	6	5
Self Neglect	6	5
Disorientation	3	3
Conceptual disorganisation	6	6
Blunted affect	6	5
Emotional withdrawal	6	5
Motor Retardation	1	1
Tension	7	6
Uncooperativeness	7	5
Excitement	6	5
Distractibility	6	4
Motor hyperactivity	6	5
Mannerism and Posturing	7	6
Total	88	73

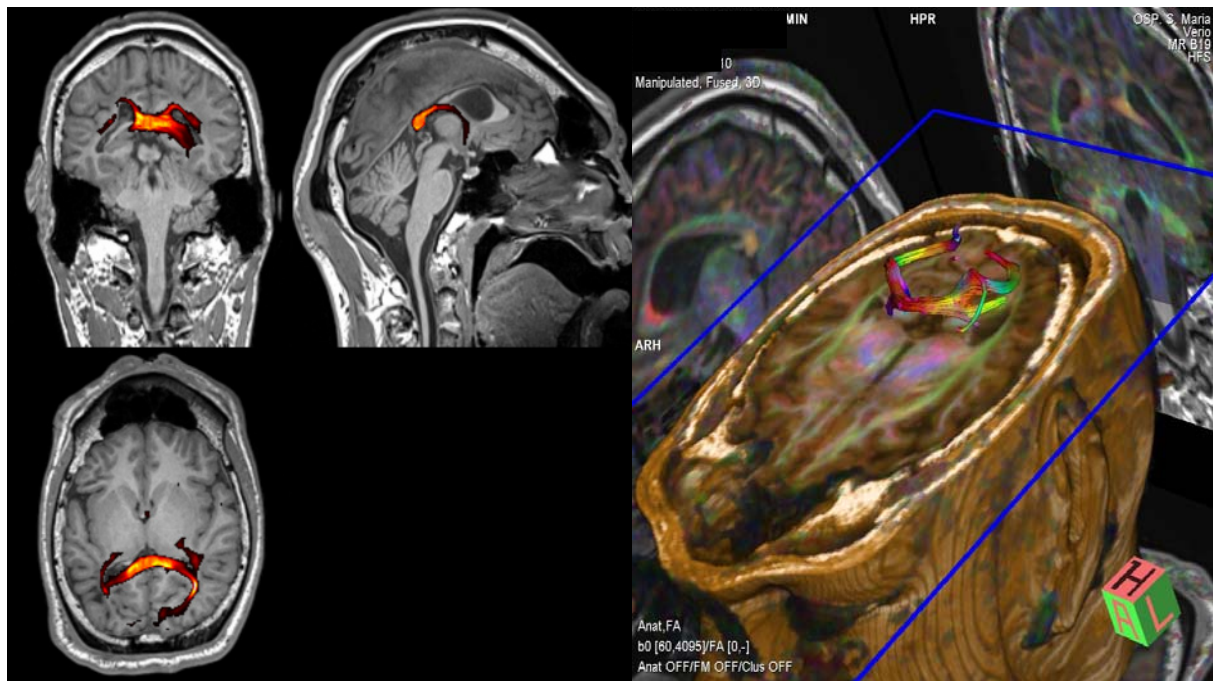


Figure 6. Pre-music MRI exam: to the left bundles of splenium fiber of the corpus callosum (DTI sequence: TR 1.22 ms; TE 94 ms; thk 2 mm; directions: 30), superimposed on anatomical images (3D T1-weighted images: TR: 1900 ms; TE: 2.52 ms; thk: 1 mm). On the right the 3D reconstruction

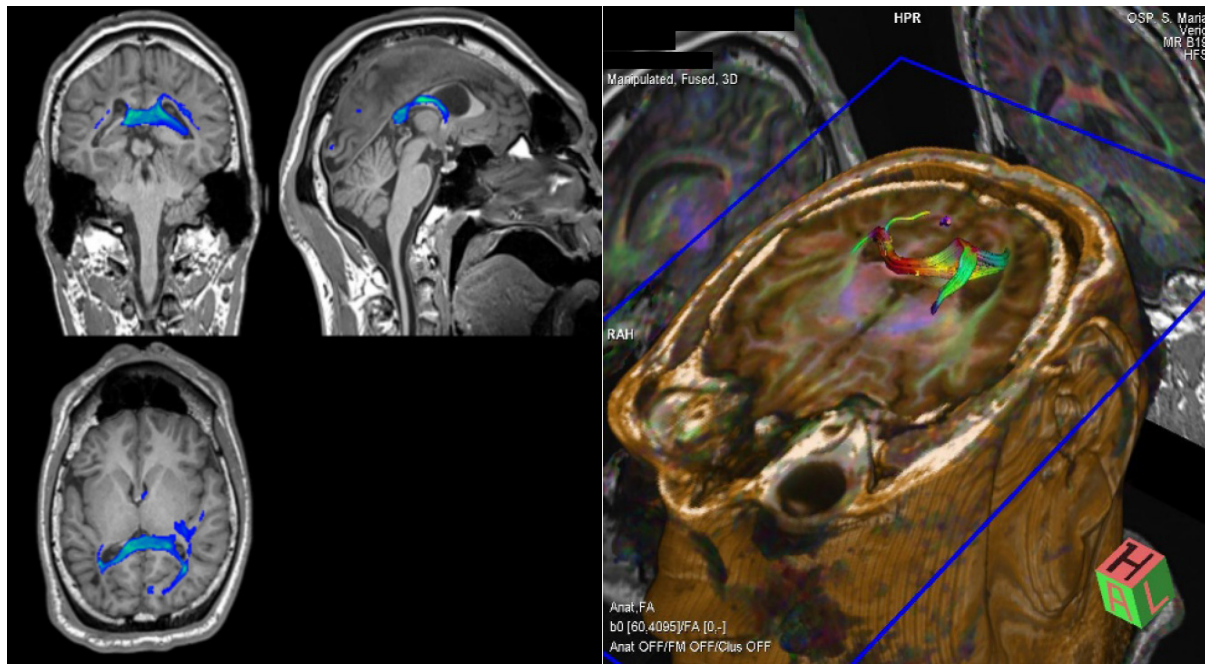


Figure 7. Post-music MRI exam: to the left bundles of splenium fiber of the corpus callosum (DTI sequence: TR 1.22 ms; TE 94 ms; thk 2 mm; directions: 30), superimposed on anatomical images (3D T1-weighted images: TR: 1900 ms; TE: 2.52 ms; thk: 1 mm). On the right the 3D reconstruction

Even the MOAS shows an improvement of behavioural aspects, in particular of the aggressiveness, which has been reduced by almost 50%, especially for the items of verbal aggression (from 4 to 2), aggression against property (from 2 to 1) and self-aggression (from 4 to 2) (Table 4).

Table 4. Single and total scores obtained from the administration of Modified Overt Aggression Scale (MOAS) before and after the period of listening to music

MOAS	Before Music	After Music
Verbal Aggression	4	2
Aggression against property	2	1
Self-aggression	4	2
Physical aggression	4	3
Total	14	8

DISCUSSION

The purpose of this work was to analyse what happens in the brain when Mozart's music (Sonata K448) is systematically administered, for a period of 6 months. This purpose has been achieved by carrying out assessments before and after the musical listening period. In particular we observed and analysed the electroencephalographic characteristics, the frequency of epileptic seizures, brain MRI data (volumetric measurement of the corpus callosum and its connections), and the behavioural aspects (through the administration of two scales: the BPRS and the MOAS).

The analysis of EEG aspects obtained by manual counting of generalized epileptic discharges between the

track performed before and after the music listening session shows a marked reduction (70.4%) in line with the literature data that shows reduction in epileptic activity on the EEG, in particular of generalized ones, during and after the administration of Mozart's music (Turner et al. 2004, Lin et al. 2010, Lin et al. 2011, Lin et al. 2014, Grylls et al. 2014). Equally in agreement with the literature data, our research presents a reduction in the frequency of epileptic seizures during the 6 months of listening to music, in particular for tonic-clonic seizures, compared to atonic ones, notes for the poor response to pharmacological treatments (Kelley & Kossoff 2010).

Brain MRI data concerning the volumetric acquisitions of the corpus callosum show linear data that can be substantially overlapped between before and after listening music period, it is possible that the already damaged structure (atrophy of the body, MRI Figure 1), is not able to show significant variations, considering also that the presence of drug-resistant epilepsy contributes to the damage of brain structures such as the corpus callosum.

The measurement through FA and MD at T0 e T1 shows the reduction of FA and the increase of MD. This data can be interpreted in line with some network activity studies with analysis of FA and MD carried out on patients suffering from migraine, through which it is hypothesised that the reduction of FA reflects the shrinkage of neuronal and glial cells or the gain of directional organisation (Mandl et al. 2008, Coppola et al. 2014, Coppola et al. 2016). However these data obtained from the study of a single patient, with a strongly compromised cerebral development, are presented as an

example and they cannot be attributed neither statistical nor clinical value yet. A correct interpretation can only be extrapolated when the analysis is conducted on the whole group of our patients.

The behavioural aspects show an improvement that mainly concerns the significant reduction of aggression (measured by the MOAS). Even though the BPRS have highlighted a reduction of hostility, elevated mood, bizarre behaviour, blunted affect, emotional withdrawal, tension, uncooperativeness, excitement, distractibility, motor hyperactivity, mannerism and posturing. All aspects are very difficult to control in a patient with autism spectrum disorder and gain greater value even in the context of a relatively short follow-up period.

CONCLUSIONS

The study was designed to develop a method of investigation and presented the preliminary data of the first patient analysed. It shows very positive data and in line with the literature regarding the marked reduction of epileptic discharges to EEG after the listening period of the Mozart's music and the sharp reduction in the frequency of seizures during this period.

Brain MRI data need, for a correct clinical interpretation, the implementation of the sample, also in consideration of the gravity of the clinical picture studied.

The behavioural aspects showed a good outcome with reduction of aggressive behaviours and with reduction of motor stereotypes with the attainment of less distractibility and greater collaboration, after the listening to music period, in a patient with autism spectrum disorder.

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Contribution of individual authors:

Chiara Bedetti, Massimo Piccirilli, Patrizia D'Alessandro & Domenico Frondizi: conception and preparation of the study.

Chiara Bedetti, Massimo Principi & Antonio Di Renzo: acquisition of data and their interpretation.

Antonella Baglioni, Marina Menna & Moreno Marchiafava: preparation of the study.

Sandro Elisei, Massimo Piccirilli, Marilena Gubbiotti, Antonella Baglioni & Marina Menna: revision of the manuscript.

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URINARY AND BOWEL DYSFUNCTION IN AUTISM SPECTRUM DISORDER: A PROSPECTIVE, OBSERVATIONAL STUDY

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SUMMARY

Background: Vesico- sphincter and bowel dysfunction have been frequently detected in Autism spectrum disorder (ASD) patients, but to date no consistent information exist on adults affected by the disease. We evaluated the prevalence and types of bladder and bowel dysfunction (BBD) in young and adult patients affected by ASD.

Subjects and methods: Twenty- seven adults and 20 children/teens with ASD and a matched group of typically developing subjects were enrolled. Daily pads use and episodes of urinary incontinence (UI) were recorded in a 3- day voiding diary. Patients underwent also the measurement of post-void urinary residual volume and 3- day bowel diary. In addition, type and duration of the pharmacological agents assumed by the patients were accurately recorded.

Results: Any type of UI was observed in 85.1% of adults and in 90% of children/teens. In adults, nocturnal enuresis (NE, 62.9%) and diurnal intermittent UI (37%) were the most frequently observed bladder dysfunction while in children/ teens were NE (75%) and diurnal continuous UI (40%). In all patients was demonstrated a significant relationship between urinary symptoms and pharmacological agents, particularly NE and clotiapine ($p < 0.004$) and periciazine ($p < 0.008$).

Conclusions: Young and adult patients with ASD present with a high prevalence of BBD and concomitant antipsychotic medications could to play a contribution in induction and/or maintaining of BBD.

Key words: Autism spectrum disorders - bladder and bowel dysfunction - antipsychotic medication

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INTRODUCTION

Autism spectrum disorders (ASDs) are multifactorial neurodevelopmental conditions, which include impairments in social communication and interaction, and restricted, repetitive patterns of behaviour, interests, or activities (American Psychiatric Association 2013). Comorbid psychiatric and medical morbidities are frequently observed, including social anxiety disorder, attention-deficit/hyperactivity disorder, and intellectual disability (Simonoff et al. 2008, Mannion & Leader 2016, Matson & Shoemaker 2009). The most frequently reported medical conditions are immune system abnormalities, gastrointestinal disorder, mitochondrial dysfunction, sleep disorders, and epilepsy (Mannion & Leader 2016). Although the prevalence of ASD has been more frequently described in children, as being 1 out of 68 children worldwide (Lee et al. 2017), few data exist on epidemiologic data of ASD in the adult age, which would be an important information considering that the disorder is a long-lasting condition which can persevere throughout life. One important clinical aspect, more often under-diagnosed and under-reported is represented by the presence of vesico-sphincter and bowel dysfunction in the affected subjects. Some previous reports described the presence of urinary incontinence, faecal incontinence and constipation in subjects in the paediatric age (Niemczyc et al. 2018), but to date no consistent information exist on adults affected by the disease. We evaluated

bladder and bowel dysfunction in a group of subjects affected by ASD in order to clearly identify their urologic and gastro-intestinal status. A comparison with typically developing (TD) subjects was also performed.

SUBJECTS AND METHODS

A prospective, observational study was conducted at the Serafico Institute of Assisi, "InVita" Research Centre. The experimental procedures were performed according to the Declaration of Helsinki and approved by the local Ethics Committee (CEAS No. 3308/18). Included patients were 27 adults (aged ≥ 18 years) and 20 children/teens (aged from 5 to 17 years), all with confirmed ASD according to DSM-V (American Psychiatric Association 2013) and International Classification of Diseases-10 (ICD-10) criteria (Cambridge: New York Cambridge University Press). Patients' familiars/caregivers and control subjects provided written informed consent. The study included also a control group consisting of TD subjects, which were matched to patients for sex and age. Exclusion criteria for both patients and TD subjects were neurological diseases, congenital lower urinary tract diseases, previous surgical intervention in the pelvis and lower urinary tract, any previous pharmacological treatment for urinary disturbances during the last 3 months. BBD were evaluated according to the standards of the International Continence Children Society (Austin et al. 2013) and the Inter-

national Continence Society (Abrams et al. 2002). Urinary incontinence (UI) was classified as: diurnal, continuous, or intermittent UI. Nocturnal enuresis (NE) was also investigated and classified as primary or secondary NE, and mono or non-mono symptomatic NE. Daily pads use was recorded in a 3-day voiding diary by patients' familiars or caregivers. For continent patients and for those with UI but able to void spontaneously by reaching the toilet, caregivers were adequately instructed to detect the following voiding symptoms: straining, interrupted stream, hesitancy, post-micturition dribble. Patients underwent also urinalyses and cultures and kidney and bladder ultrasound, with the measurement of post-void urinary residual volume (PVR). PVR was measured immediately after a spontaneous micturition in continent patients or in those with intermittent UI; in patients with continuous UI, the presence of urine in diapers was checked at least every hour during daytime and, after detecting a micturition, PVR was promptly measured. In cases of PVR \geq 150 ml, an additional measurement was performed. These procedures have been previously described (Gubbiotti et al. 2019). With regards to bowel evaluation, a 3-day bowel diary was used to record stool frequency and daily events of faecal incontinence (FI). Type and duration of the pharmacological agents assumed by the patients were accurately recorded in order to detect any possible relationships between urinary and bowel symptoms and drugs assumed. Pharmacological agents were classified into 6 different classes: antidepressant drugs (AD), barbiturates (BRT), mood stabilizers (MS), antipsychotic drugs (APD), benzodiazepines (BDZ), and antiepileptic drugs (AED). Before commencing the study, TD subjects completed the Social Communication Questionnaire (SCQ; Berument et al. 1999) in order to exclude autistic symptoms. Only subjects with a SCQ score \leq 14 (subclinical) were included in the evaluation. TD subjects also were asked to complete the 3-day voiding and bowel diary and they underwent kidney and bladder ultrasound with measurement of PVR and urinalyses and culture. Any pharmacological treatment assumed by controls was accurately recorded.

The primary aim of the study was to evaluate prevalence and types of BBD in young and adult patients affected by ASD. Secondary aims were: to compare urinary and bowel dysfunction identified in ASD patients with those presented by TD subjects; to identify any possible relationship between urinary and bowel symptoms and the pharmacological treatment assumed by the patients.

Statistical Analysis

The Mann-Whitney U test was performed to compare continuous non-parametric variables. The associations between categorical variables were tested by χ^2 test with Yates' continuity correction or Fisher's exact test. All values in the text and tables are expressed for facility as mean \pm SD. All calculations were carried out with IBM-SPSS® version 25.0 (IBM Corp., Armonk, NY, USA, 2017). A two-sided P value of <0.05 was considered significant.

RESULTS

Thirty-eight males and 9 females affected by ASD were prospectively included in the study. Twenty-seven patients aged \geq 18 years, and 20 aged from 5 to 17 years (mean age \pm SD was 25.3 \pm 10 years). Overall, 41/47 (87.2%) patients presented with any type of incontinence, which was detected in 23 adults (85.1%) and in 18 children (90%). In adults, NE and diurnal intermittent UI were the most frequently observed bladder dysfunction, identified in 17 (62.9%) and 10 (37%) patients, respectively. In children/teens, any type of UI was detected in 18/20 (90%) cases, with primary NE being observed in 15 (75%), and diurnal continuous UI in 8 (40%). Voiding disturbances, such as delaying, interrupted stream and abdominal straining during voiding were observed in 4 (14.8%) adult males and in only 1 (5%) children, who also showed a confirmed high PVR (300 ml). FI was detected in 9/27 (33.3%) adults and 8/20 (40%) children/teens; constipation was observed in 19/27 (70.3%) adults and in 13/20 (65%) children/teens (Table 1).

Table 1. Bladder and Bowel Dysfunction in 27 adults and 20 children/teens affected by ASD, and in 47 typically developing (TD) subjects

	Total (n=47)	Adults (n=27)	Children/Teens (n=20)	TD subjects (n=47)
	No (%)	No (%)	No (%)	No (%)
Any incontinence	41 (87.2)	23 (85.1)	18 (90)	2 (4.2)
Nocturnal enuresis n (%)	34 (72.3)	17 (62.9)	15 (75)	0
Diurnal continuous incontinence n (%)	21 (44.6)	6 (22.2)	8 (40)	0
Diurnal intermittent incontinence n (%)	13 (27.6)	10 (37)	1 (5)	2 (4.2)
Faecal incontinence n (%)	18 (38.2)	9 (33.3)	8 (40)	0
Voiding symptoms				
Delaying n (%)	5 (10.6)	4 (14.8)	1 (5)	0
Interrupted stream n (%)	5 (10.6)	4 (14.8)	1 (5)	0
Straining n (%)	5 (10.6)	4 (14.8)	1 (5)	0
Hypoactive bladder	2 (4.2)	2 (7.4)	0	0
Constipation n (%)	30 (63.8)	19 (70.3)	13 (65)	5 (10.6)

Table 2. Relationships between BBD and pharmacological agents in 27 adults and 20 children/teens affected by ASD

	Adults (n=27)	p	Children/Teens (n=20)	p
Intermittent Urinary Incontinence	Clotiapine	0.03	Periciazine	0.09
	Periciazine	0.08		
Nocturnal Enuresis	Clotiapine	0.04	Periciazine	0.09
	Periciazine	0.08	Clotiapine	0.07
Faecal Incontinence	Clotiapine	0.01		

With regards to TD subjects, SCQ scores were within normal ranges in all cases. Only 2 (4.2%) woman complained of intermittent urge UI, and 5 (10.6%) patients presented with constipation (Table 1). No other BBD were detected.

Forty-two patients were under psychotropic pharmacological agents, which were assumed alone or in multi-drug combination regimen. The number of the different drugs assumed ranged from 1 to 5. The most frequently adopted pharmacological agents were antipsychotics (APD) followed by mood stabilizers (MS) and benzodiazepines (BDZ).

A significant relationship was observed between the use of clotiapine and FI ($p < 0.01$), and between clotiapine and NE and intermittent UI, in adults ($p < 0.04$ and $p < 0.03$, respectively). A trend to a significant association between periciazine with NE and intermittent UI in both adults and children/teens ($p = 0.08$ and $p = 0.009$, respectively) (Table 2). No significant relationships were identified between pharmacological agents assumed by the patients and voiding symptoms.

DISCUSSION

The present study showed a high prevalence of BBD in subjects affected by ASD, with any type of urinary incontinence being the most frequently observed dysfunction in both adults and children. Herein we confirm the previously observed high rates of primary, non-monosymptomatic NE (62.9%), diurnal UI (37%) and faecal incontinence (33.3%), in adult patients with ASD (Gubbiotti et al. 2019), but in the present study these dysfunctions have been investigated in a larger number of patients and a more detailed investigation of the pharmacological agents assumed by the patients was included. Indeed, frequency and types of UI in adults with ASD have been rarely investigated in previous studies; to the best of our knowledge, only Fortuna and co-workers identified the dysfunction in 4.7%, 19.4% and in 22.2% of ASD cases aged from 18 to 29, 30 to 40, and > 40 years, respectively (Fortuna et al. 2015). Also patients affected by other diseases presenting with severe intellectual disabilities show high rates of urinary incontinence, similar to those detected in our ASD patients, as those with Angelman syndrome (Laan et al. 1996). In our study, also children/teens presented with elevated rates of NE, diurnal UI and FI, which were somewhat higher as compared to those previously described (Niemczyk et al. 2018). The high proportions of BBD detected in both young and adult patients with ASD in our study can be

attributed to the presence of severe intellectual disability and great mood alterations (i.e. anxiety, euphoria/elevated mood), as previously identified, (Gubbiotti et al. 2019), which are all expression of an altered cerebral connectivity hypothesized to contribute to the development and maintaining of ASD (Fuentes et al. 2014). What should deserve particular investigation when studying BBD in patients with ASD, is the eventual contribution given by the concomitant oral drugs assumed by these patients due to their frequent neuro-psychiatric impairment. In our study, a significant association was found between clotiapine and FI, and between clotiapine and NE and intermittent urinary incontinence in adults. In addition, and a trend to a significant association between periciazine with intermittent UI and NE was identified in both adults and children/teens. Pharmacological agents that alter the normal circuits underlying urinary continence expose patients to the risk of urinary leakages. Actions of these drugs can be exerted at the level of the urinary system, particularly the autonomic nervous system and, as a consequence, in some cases urine output increases, in some others a physical or cognitive function can be affected. In a recent study, significant associations were identified between UI and selective serotonin reuptake inhibitors (SSRIs), and between UI and antipsychotics (Mauseth et al. 2018). Antipsychotics are dopamine receptor antagonists and can thereby lead to UI. On the other hand, antipsychotics could be hypothesized to reduce the risk of urinary incontinence due to their anticholinergic effect (Tsakiris et al. 2008). Thus the contribution of antipsychotics as drugs inducing urinary incontinence is not definitely elucidated. Another important point to take into account is the dose-effect relationship, which unfortunately in our study has not been investigated.

Finally, in our study voiding disturbances were detected in a small proportion of cases, specifically in 14.8% of adult males and in 1 (5%) children, and no case presented with a damage of the upper urinary tract. Whether voiding disturbances could be related to coexistent vesico-sphincter dysfunction, cognitive impairment or drugs' intake needs to be fully investigated.

CONCLUSIONS

Young and adult patients affected by ASD present with high prevalence of bladder and bowel dysfunction, with UI as the most frequently observed dysfunction. Concomitant antipsychotic medications appear to play a great contribution in induction and/or maintaining of BBD in patients with ASD.

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Contribution of individual authors:

Marilena Gubbiotti & Antonella Giannantoni: contributed to conception and design, collected data, contributed to the analysis and interpretation of data, drafted the manuscript.

Chiara Bedetti & Moreno Marchiafava: collected and interpreted data.

Sandro Elisei: manuscript revision.

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MATHEMATICS ANXIETY AND COGNITIVE PERFORMANCE IN ADOLESCENT STUDENTS

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SUMMARY

Several studies highlight that many students feel negative feelings about mathematical learning and that the mathematics anxiety seems to play a central role in mathematical performance. More specifically students with higher level of maths anxiety are less efficient in mathematical tasks. The aim of this study was to investigate the relationship between specific mathematics anxiety as assessed by AMAS, trait and state anxiety as assessed by STAI-Y, and mathematical skills assessed through the ABCA tests in a sample of 83 adolescent students (78.3% males) without diagnosis of dyscalculia and cognitive disorder attending their first year of secondary school. Results showed that 38% of the students referred high level of maths anxiety. Independent T-test revealed that female students referred a higher level of maths anxiety as well as of trait and state anxiety than male ones, while there were no differences in the mathematics performance. The simultaneous multivariate linear regression analysis showed that maths anxiety was influenced by trait anxiety and in its turn has an impact on the high level mathematics performances (i.e. arithmetic facts). Understanding the relationships between maths anxiety and maths learning and performance may have relevant implications in clinical, educational and didactic practice.

Key words: mathematics anxiety - cognitive performance - mathematics performance - adolescents

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INTRODUCTION

In the last years studies have highlighted that high percentages of students, regardless of their culture, experience negative feelings in educational settings, such as anxiety, in particular about mathematics learning (Blazer 2018, Luttenberger et al. 2019). A recent study on 15-16 year-old students, in which 34 Organisation for Economic Co-operation and Development (OECD) countries participated, shows that more than 30% of students of secondary school report tension and nervousness while doing maths homework and maths problems, another 59% refer concern that mathematics will be tricky for them (OECD – The Organisation for Economic Co-operation and Development 2018). These findings underline how the anxiety related to mathematical learning can be considered a widespread problem. What do we mean by maths anxiety (MA)? Fennema and Sherman (1976; p. 326) defined MA as “feelings of anxiety, dread, nervousness, and associated bodily symptoms related to doing mathematics” and it seems to have several implications in learning and using mathematics in educational as well as in daily context (Pechter et al. 2017, Kohn et al. 2013). The MA seems to be consisting of two dimensions, cognitive and affective (Wigfield & Meece 1988): the first dimension refers to the concern about mathematics performance and the possible failure, while the affective dimension refers to the feeling of nervousness in a testing context (Liebert & Morris 1967).

To better understand the antecedents that influence the incidence of MA, several studies have focused on personal aspects like gender and trait anxiety, the tendency to perceive high-stress situations as threatening (Hembree 1990, Pechter et al. 2017). Most studies about gender and MA indicate that female students referred higher levels of MA than male (Else-Quest et al. 2010, Devine et al. 2012, Primi et al. 2013). About the link among trait anxiety and MA the findings of a meta-analysis (Hembree 1990) showed a close relationship between maths and trait anxiety from $r=0.24$ to $r=0.54$, highlighting that they are separate but related constructs (Aschcraft 2002). A more recent research demonstrated how trait anxiety together with gender explained a high percentage of variance in MA (Pechter et al. 2017). In contrast with the aforementioned studies, Grežo and colleagues (2018) didn't find any link between trait anxiety and MA assuming that the latter could be a complex construct better explained through personality traits as well as environmental and contextual variables. Among contextual variables we could consider the setting in which the mathematics performances are measured, the feelings of nervousness, tension and the arousal of the autonomic nervous system related to the particular moment, the so-called state anxiety (Spielberg & Sydeman 1994).

As previously mentioned, MA has an effect on learning and using mathematics. Many studies show that the MA plays a central role in mathematical performance (Baloglu & Koçak 2006, Sad et al. 2016). More

specifically students with a higher level of MA are less efficient in mathematical tasks that are included in basic arithmetic computation but especially in high-level computing skills (Ashcraft & Kirk 2001, Maloney et al. 2011, Cates & Rhymer 2003). MA seems to have an impact on the resources of working memory (WM), the cognitive functioning involved in specific aspects of high-level mathematical skills as processing and retrieval of arithmetical facts and method (Ashcraft & Kirk 2001, Ashcraft & Krause 2007). About the link between MA and mathematical performance, literature is conflicting. Most of the studies, as previously underlined, prove the theory that MA tends to affect the performance related to maths; further studies, on the contrary, show that the poor maths performance and the repeated failures could be the predictor of higher level of MA (Ma & Xu 2004, Birgin et al. 2010). This variety of data might support the “Reciprocal Theory” suggesting the bidirectional relationship between MA and mathematics ability; becoming aware of one's difficulties could increase the state of anxiety related to maths and in turn, higher level of MA could have an effect in poor maths performances, creating a vicious circle (Carey et al. 2016). This relationship seems to change based on the context in which the maths ability is measured, e.g. in a relaxed evaluation-free situation, students with high MA reach the same performance level of students with lower MA (Ashcraft & Faust, 1994). Longitudinal studies are needed to better explain this relationship. Furthermore, some studies are focused on the difference in this relationship (MA and maths performance) between genders. Hembree in his meta-analysis (1990) displayed that the MA was more predictive of maths performance in male than female participants, in particular of basic maths ability as suggested by Miller & Bichsel (2004). More recent studies have found that MA predicts maths performance more in girls than boys (Devine et al. 2012, Reali et al. 2016), while other studies didn't find any differences between genders, in particular on applied mathematical performance (Miller & Bichsel 2004). These inconsistent data suggest the need for further studies.

Few studies have investigated this link between MA and mathematics achievement in adolescents (Trezise & Reeve 2015, Passolunghi et al. 2016), most have been carried out on children or young adults (Wu et al. 2012, Ramirez et al. 2013).

Starting from the aforementioned data, the aims of our study were: (1) to analyse the prevalence of the MA and the difference in MA level between gender in a group of 14-15 year-old Italian students, the age group which was less considered, in particular in the studies about the link between MA and mathematical performance; (2) to investigate the role of trait and state anxiety, assessed before and after the mathematics tasks, on variance in MA. Considering the complexity of the construct highlighted by previous studies (Hembree 1990, Peachter et al. 2017, Grežo et al. 2018), MA

variance could be explained not only by trait personality (trait anxiety) but also by contextual variables such as the state anxiety assessed both before, i.e. the state of tension one feels prior to starting a test, and after, i.e. the state of tension one feels after the awareness of how the tests were carried out (3). To explore the link between anxiety and different mathematical abilities, more specifically the effects of the maths, trait and state anxiety on mathematics performance. In a performance context the state anxiety could play a role not only as predictor of MA but also to explain the variance in the mathematics performances. Finally (5) to investigate the gender difference in the relationship between MA and maths performance.

SUBJECTS AND METHOD

Subjects

The subjects were 101 students attending the first class of secondary school, who were enrolled through convenience sampling. The inclusion criteria were (a) absence of diagnosis of dyscalculia and cognitive disorder, (b) having good knowledge and fluency of the Italian language and (c) all assessment tools needed to be entirely completed. Since they didn't meet the inclusion criteria, 17 students were excluded from the study, therefore the final sample was composed of 84 students (78.6% males and 21.4% females).

Procedure

The students and their parents have been informed about the research and data has been collected. Before the study, both mothers and fathers signed in the informed consent form to participate. No incentives were given, and all participants could withdraw at any time. The study was approved by the CEAS, the local ethics committee of the Umbria Region (Italy).

All participants completed the self-report questionnaires and the standardised mathematics test individually in the classroom during school hours. In a first moment the students filled in all measures that assessed, in order, trait, maths and state anxiety; later they completed the three different types of mathematical tests (in this order: 1) written calculation A; 2) written calculation B and 3) arithmetical facts); lastly, the state anxiety one was compiled again. The students before starting the tests had been informed that the mathematics performance was evaluation-free.

Measures

Abbreviated Math Anxiety Scale (AMAS)

AMAS (Hopko et al. 2003), is a self-report consisting of 9 items that evaluate using a 5-point Likert scale from 1 “strongly agree” to 5 “strongly disagree”) related to two aspects of MA measured by the sub-scales Learning Maths (5 items) and Maths Evaluation An-

xiety (4 items). Final score can range from 9 to 45, higher scores indicate high MA. In this study we used the Italian version (Primi et al. 2014) that showed good internal consistence (Cronbach's alpha 0.85); the mean of the normative sample was 23.6 (Sd=8.1; IC 99% 22.18-25.02).

State and Trait Anxiety Inventory (STAI-Y)

STAI-Y (Spielberg 1989) is a self-report composed of 40 items that measure using a 4-point Likert scale ranging from 1 (Not at all) to 4 (very much so) two types of anxiety in adult people, 20 items assessing state anxiety, anxiety about a specific moment or event and 20 items assessing trait anxiety as a personal characteristic. In previous studies STAI-Y has been also used with adolescents (Castro-Sanchez et al. 2018). The Italian version of the STAI – Y (Pedrabissi & Santinello 1989) was used, showing good internal consistency and adequate test-retest reliability.

ABCA 14-16

ABCA 14-16 (Baccaglioni-Franket al. 2013), was used to assess the students' mathematical skills in secondary school. The ABCA is composed of a battery for the assessment of mathematical ability and allows to identify a profile of each student related to mathematical skills comparing the percentile scores to the cut-off criteria of the normative sample: <40th percentile: severe difficulties; 40th-70th percentile: sufficient skills; >70th percentile: optimal ability.

The specific paper and pencil mathematics sub-tests used in this study were:

- **Written Calculation A:** to examine the child's application of the procedures needed to complete written computational operations as addition and subtraction.
- **Written Calculation B:** to examine the child's application of the procedures needed to complete written computational operations as multiplication and division.
- **Arithmetical Facts:** to investigate how students have stored combinations of numbers and whether they are able to access them automatically, without purposive calculation procedures. The items include addition, subtraction, and multiplication.

For each sub-subtest responses are scored for correct answers. The raw scores were subsequently transformed into a percentile scores.

Statistical Analyses

First, descriptive statistics were calculated in terms of means and standard deviations for all variables studied and an independent t-test was performed to investigate the differences in maths, trait and state anxiety and in the single mathematics performance between genders; effect size was measured using Cohen's d, in which levels were small ($d \geq 0.2$), medium ($d \geq 0.5$), and large ($d \geq 0.8$) (Cohen 1988).

Second, to understand the role of trait and state anxiety in the MA variance, multivariate linear regression analysis was run in the whole group. Third, simultaneous multivariate linear regression analysis was run to explore the role of the single anxiety scales (maths, trait and state) on the mathematics performance scores, separately, on written calculation A scores, written calculation B scores and arithmetical facts scores. These last analyses have been carried out on the whole group and separately by gender groups. All analyses were performed using SPSS, release 18 (SPSS Inc., Chicago).

RESULTS

Descriptive statistics of the all measures assessed for the whole sample and separated for gender are reported in Table 1. So, 38% of the students indicate that they experience some level of specific anxiety for maths, reporting higher AMAS test scores than the upper endpoint of 99% confidence interval of the Italian normative sample mean (Primi et al. 2013).

The independent t-test highlighted some differences between genders, in particular female students reported higher levels of specific MA ($t=-3.04$; $p=0.003$; $d=0.8$), higher levels of trait anxiety ($t=-2.46$; $p=0.016$; $d=0.6$) and a higher level of state anxiety assessed after the mathematics performances than male students; from a medium to a large effect size; no difference between genders in state anxiety was assessed before the performance. Regarding the single mathematics tasks, the entire group showed several difficulties, in particular the mean percentile scores achieved in written calculation A and B, which were lower than the cut-off criteria of 40th percentile. At the arithmetical facts test the group achieved sufficient mean scores (>40th percentile). The t-test did not show differences between genders in any task.

Table 2 shows the results of the multivariate regression analysis. Data highlighted that the regression model with MA as dependent variable and trait and state anxiety (Before and After) as independent variables was highly significant ($R^2=0.26$; $F_{(3,80)}=9.47$; $p<0.001$). The model accounted for 26% of the variance (R^2) specifically, only trait anxiety ($\beta=-0.318$; $SE=0.091$; $t=-2.36$; $p=0.02$), significantly predicted MA whereas state anxiety, assessed both before and after the performance, did not.

In Table 3 the results of the regression analysis are reported separately for each single mathematics task of the whole group. In Section 1 data showed that the model explained 14% of the variance of scores achieved in the written calculation A task ($R^2=0.14$; $F_{(2,81)}=6.50$; $p=0.002$). In detail, only state anxiety was significantly linked to worse performance in this specific test ($\beta=-0.264$; $SE=0.308$; $t=-2.35$; $p=0.021$), whereas MA was not. The same data resulted from focusing on the male students' group ($R^2=0.16$; $F_{(2,62)}=4.05$; $p=0.011$), while in the girls' group overall model this link was not significant.

Table 1. Descriptive statistics and independent T test for gender with means and standard deviations for anxiety measures and mathematic performance task percentile scores

	Totale Sample Mn ± Sd	Gender		t	p	d
		Male; Mn ± Sd	Female; Mn ± Sd			
Anxiety Measures						
AMAS Tot	21.67±6.33	20.62±5.87	25.5±6.63	-3.040	0.003	0.8
STAI Trait	39.95±9.33	38.68±8.67	44.61±10.39	-2.460	0.016	0.6
STAI State (Before)	36.38±9.90	35.39±10.06	40.0±8.59	-1.770	0.080	-
STAI State (After)	39.31±11.05	37.63±10.26	45.44±11.96	-2.760	0.007	0.7
Math Performance						
Written Calculation A	37.05±27.05	37.77±26.62	34.39±29.19	0.468	0.641	-
Written Calculation B	25.38±29.78	25.39±30.10	25.33±29.42	0.008	0.994	-
Arithmetical Facts	41.26±30.57	43.23±30.41	34.06±30.96	1.130	0.262	-

p: <0.05 significant difference; d: ≥0.2 small effect size; ≥0.5 medium effect size; ≥0.8 large effect size; AMAS = Abbreviate Math Anxiety Scale; STAI = State and Trait Anxiety Inventory

Table 2. Results of regression analysis with MA as depend variable and Trait and State Anxiety as predictors

AMAS Tot	F	gdl	R	R ²	β	SE	t
Section 1	9.47**	3.80	0.512	0.26			
STAI Trait					0.318	0.091	2.36**
STAI State (Before)					0.085	0.087	0.626
STAI State (After)					0.190	0.068	1.60

* p<0.05; ** p<0.01; AMAS = Abbreviate Math Anxiety Scale; STAI = State and Trait Anxiety Inventory

Table 3. Results of regression analysis separately for individual mathematics performance scores as depend variables: (1) Written calculation A; (2) Written calculation B and (3) Arithmetical facts

	F	gdl	R	R ²	β	SE	t
(1) Written Calculation A							
Section 1	4.43**	3.80	0.378	0.14			
AMAS Tot					-0.199	0.507	-1.680
STAI Trait					0.092	0.424	0.631
STAI State					-0.317	0.384	-2.25*
(2) Written Calculation B							
Section 2	2.21	3.80	0.277	0.08			
AMAS Tot					-0.237	0.579	1.920
STAI Trait					-0.087	0.485	-0.572
STAI State					0.025	0.173	0.863
(3) Arithmetical Facts							
Section 3	5.28**	3.80	0.407	0.17			
AMAS Tot					-0.332	0.565	-2.83**
STAI Trait					0.000	0.473	-0.002
STAI State					-0.137	0.428	-0.989

* p<0.05; ** p<0.01; AMAS = Abbreviate Math Anxiety Scale; STAI = State and Trait Anxiety Inventory

Section 2 highlighted that the overall model was not significant ($R^2=0.08$; $F_{(1,82)}=2.21$; $p=0.094$). The same results have been found both in male and female participants. The anxiety scales did not link with the written calculation B scores variance.

Finally, regarding the arithmetical facts (Section 3), the last test that was performed, the results of the regression analysis showed that the overall model explained 17% of the variance ($R^2=0.17$; $F_{(3,80)}=5.28$; $p=0.002$), more specifically, MA was the only variable that was significantly linked to the arithmetical performance ($\beta=-0.332$; $SE=0.565$; $t=-2.83$; $p=0.006$) whereas trait and state anxiety were not. The same was true for the male students' group ($R^2=0.135$; $F_{(3,62)}=3.23$; $p=0.028$) but not for the female's group.

DISCUSSION

The main aims of this study were the understanding of the antecedents of MA and its relationship with the basic and high-level mathematics performances in a sample of adolescent students of a technical-professional Italian secondary school. Until today, literature has been mostly focused on children and young adults (Wu et al. 2012, Ramirez et al. 2013), less in adolescents. This is a transitional age also on an educational level, during which the stabilization of the knowledge occurs as well as the one of the beliefs, the emotions and also the behaviours for learning and studying in general and towards specific learning subjects in particular (i.e. mathematics). About mathematics, adoles-

cence is a period of life in which the experiences one has made that are related to maths learning during primary school could have an influence on the feelings one experiences and on the approach to the study of this specific subject. In turn, the negative feeling towards mathematics may have an influence in the cognitive performance related to mathematics skills, so as to give consistency to the assumptions of the “reciprocal theory” (Carey et al. 2016); in this sense it has been important for us to investigate this issue in this specific age group.

Our findings, according to previous studies (Luttenberger et al. 2019, OECD 2018), confirm the high percentage of the presence of the specific MA also in the adolescent students and higher level of MA as well as of trait anxiety in females compared to males. Furthermore, in line with Peachter and colleagues (2017), our results highlights the close relationship between MA and trait anxiety; The MA variance of 26% is explained by the presence of trait anxiety while it does not seem to be influential by context-related anxiety, or rather the state anxiety that was assessed before and after the maths performance, in this case probably because the students knew that their performance would not have been evaluated by their teachers.

As of the mathematics performances our sample proves to be in shortfall. In almost all the tasks, the students have proved insufficient without showing differences between females and males, perhaps due the difference in the number of components of the two groups. This difference in the number, one of the main limits of this study, makes the results referring to males more consistent than the ones referring to females.

Many studies focused on the relationship between MA and mathematical performance, particularly in the high-level computing performance (Ashcraft & Ridley 2005, Devine et al. 2012, Ma 1999). Our findings show that MA is linked only to arithmetical facts while it is not linked with basic maths performance (written calculation A and B). In the first task completed by the students, written calculation A, 14% of the maths performance variance is explained only by state anxiety; perhaps the physiological anxiety related to the particular moment may have affected this specific performance, because it was the first, but not the subsequent ones, since state anxiety tends to modulate over time. With reference to the written calculation B test, no link may have emerged between the performance and MA probably because there is not a great variability in the obtained results, in fact the whole group has obtained rather low scores in a homogeneous way.

The specific MA is linked to the arithmetical facts task that assessed the students’ stored combinations of numbers and their ability to access them automatically. This task assessed more advanced maths competence involving higher levels of cognitive functioning and working memory processes that seem to be affected by MA, in particular the retrieval of the automatism process. Moreover, some information required by this task may be recently acquired and, as suggested Raghobar

and colleagues (2010), the acquisition of new maths skills may depend on visual-spatial WM, therefore it is more exposed to the interference of anxiety in its retrieval and processing, causing many computing mistakes. This specific relationship is present in the male’s group but not in the female’s group; in our sample the MA is only linked to the male group’s maths performance; even if the female students show higher level of MA than male ones, it does not seem to interfere with the mathematics performance, differently from most of the previous studies (Devine et al. 2012, Reali et al. 2016) that found a stronger relationship between MA and maths performance in girls than boys, but most likely we did not find the same results due to the low number of females.

This study has some limits, i.e. the already mentioned difference between the number of males and females, which makes the males’ results more consistent than those of the females. A second one is that the sample comes from a single educational institute therefore, in order to generalise the results, a more representative cohort of students coming from other kinds of educational institutes is needed. Finally, this study has been conducted only in a relaxing evaluation-free setting, thus, since the link between MA and maths performance seems to change according to the assessment context, a school-evaluation setting will be needed for a greater generalisation of the results and to study this link. Moreover, an assessment in school-evaluation context may also better explain the role of the contextual variable on the MA variance.

CONCLUSION

The present study confirms that also in Italy adolescent students, like in other countries (OECD 2018), have some levels of specific MA and importantly this one is closely related to the mathematics performances that do not seem to be affected by other anxiety forms. Few studies have focused on this link in the Italian context, therefore this study tries to fill this gap. Understanding the link between MA and mathematics performances may have relevant implications in clinical, but above all in educational and didactical practice, giving teachers food for thought to implement new teaching strategies to try reducing anxiety in the school context.

In order to better understand this relevant issue, longitudinal studies are in progress, in particular future studies will focus on the assessment of MA and maths performance also in a school-evaluation situation.

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Contribution of individual authors:

Livia Buratta: substantial contribution to the conception of the study, to its design and to data collection, statistical contribution and interpretation of data, writing of the manuscript.

Massimo Piccirilli: contribution to the conception of the study, interpretation of data and manuscript revision.

Gianni Alberto Lanfaloni: contribution to the conception and preparation of the study, to data collection and data interpretation.

Silvia Ilicini: contribution to the preparation of the study and data collection.

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CLINICAL UTILIZATION OF THE RATING SCALE OF MIXED STATES (GT-MSRS) IN A PSYCHIATRIC INPATIENT UNIT: A RETROSPECTIVE STUDY

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SUMMARY

Mixed states are often underdiagnosed, with important consequences in terms of worsening prognosis, frequent admission to the hospital, higher suicide risk and poorer quality of life. For this reason, we analyzed retrospective data from patients admitted in the Psychiatric Hospital from January 1st to April 30th 2019 to identify clinical features of the mixed states by administering the G.T. MSRS scale. Within the 90 subjects of the sample, the large majority (75%) met criteria for mixed state. Of those only 16 were discharged with a diagnosis of Affective Disorder, however 26 (30.9%) were prescribed a mood stabilizer. This study shows that there is a high prevalence of mixed states in the inpatient unit admission, which is demonstrated both from the prescription of mood stabilizers, and confirmed by the diagnosis of mixed states rated with the scale. The scale can be a useful instrument to detect early in the course of the hospitalization the presence of mixed state, in order to guide a tailored psychopharmacological treatment, and improve prognosis.

Key words: mixed state - bipolar spectrum - unitary psychosis - mixed state rating scale - tailored treatment

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INTRODUCTION

Mixed affective states, defined as the coexistence of depressive and manic symptoms, are complex presentations of manic-depressive illness that represent a challenge for clinicians at the diagnosis, classification, and pharmacological treatment levels. In the updated DSM-5 version, published in May 2013, Mixed States are classified as Specifiers of Bipolar Disorders or Major Depressive Disorder and it applies when a person experiences both symptoms of depressed mood and mania (though one or the other would be considered predominant) within the same episode.

According to the theory of "unique psychosis", first postulated by Neumann (1874-1884), we can find different psychopathological pathways that are probably modulated by the personality structure on which the affective disorder is implanted and by its intrinsic possibility of experiencing anger (dysphoria) alongside pain and euphoria. Affective disorders are considered therefore the result of a "process" that can be implanted on different "structures" of personality and which will be modulated by them (Wiener 1983).

This is the reason why, according to this theory, bipolar disorders are always underestimated, especially if we consider subthreshold forms, with important consequences in terms of prognosis and quality of life. As for any other psychiatric diagnosis, in fact, correct identification of mixed states has important clinical relevance for both timely diagnosis and planning adequate treatment. In contrast, the inability to recognize this clinical entity exposes the patient to significant risks, and

especially for the possible worsening of symptoms due to iatrogenic damage as a consequence of inappropriate therapy.

A change in the classification system that takes into account subthreshold bipolarity represents a challenge for clinicians, researchers, and regulators, who may use it as a base for a corresponding change in psychopharmacological choices. Treatment guidelines do not usually recommend specific treatment for mixed states (Stahl 2016). As a consequence, the selection of medication is usually based on individual factors and short and long-term safety and tolerability. It is largely recognized, however, that mixed manic/depressive presentations in bipolar disorder have a poorer pharmacological response compared with pure episodes, and combination therapy is often required.

The aim of this study is to identify mixed states in an inpatient unit sample, to check the prevalence of those symptoms by using the G.T. Mixed States Rating Scale ("G.T. MSRS"), (Tavormina 2014). The "G.T. MSRS" has been designed to detect mixed states in order to improve the clinical effectiveness of psychiatrists and to prescribe a correct treatment.

SUBJECTS AND METHODS

The medical records of all patients, aged more than 18 years, consecutively admitted to a Male-only inpatient Psychiatric Unit of Hospital from January 1st 2019 to April 30th 2019 were revised to assess the presence of symptoms of mixity, utilizing the G.T. Mixed states rating scale, by two trained psychiatrists (AC, GE).

Exclusion criteria were the presence of psychotic symptoms due to medical condition (e.g. Parkinson disease, brain tumor) and mental retardation.

The "G.T. Mixed States Rating Scale", or "G.T. MSRS", is a self-administered rating scale structured with 11 items (7 among them include also sub-items). The response to each question would be "YES" or "NO". A "YES" answer would score 1 (or 2 if the symptom scored on items 1-2-3-4-8-9-10-11 is present for 50% of the month), a "NO" answer would score zero. Scores can range from 0 to 19, with a higher score meaning a more severe mixed state presentation. If a patient is positive (meaning having a total score equal or more than 1) on the "G.T. MSRS", this will suggest a "generic" diagnosis for a mixed state in the bipolar spectrum, based on the Akiskal's or Tavormina's full-spectrum scheme (Akiskal & Pinto 1999, Tavormina & Agius 2007). Subsequently, the clinician will need to carefully make a correct sub-diagnosis of the sub-groups of mixed state. A Medium-light level of mixed state is defined with scores ranging from 2 to 6; a Medium level of mixed state is defined if the score is 7 to 12; a High level of mixed state is defined if the score ranges 13 to 19.

RESULTS

The total sample included 90 subjects, with an age that ranged from 20 to 72 years old (mean 49, SD=17). Subjects were grouped into 4 sub-groups based on the discharge diagnosis: schizophrenia-spectrum psychosis for 38 subjects (45.2%), affective disorder for 16 (19%), personality disorder for 16 (19%) and "others" (which included adjustment disorders, obsessive compulsive disorder, substance abuse) for 14 (16.8%).

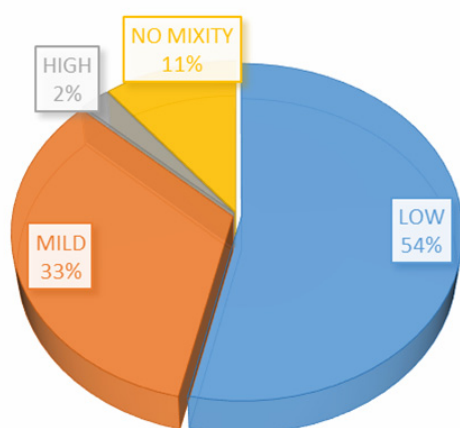


Figure 1. Level of mixity

In our sample, 75 patients (89.2%) met criteria for mixed state: 45 met criteria for low level of mixity, 28 for mild level of mixity, 2 for high level of mixity (Figure 1). Specifically, the majority of subjects discharged with a schizophrenia spectrum psychosis disorder

diagnosis had a mixed state (29 patients), of which 21 met criteria for low level of mixity and 8 met criteria for mild level of mixity (Figure 2). All subjects discharged with an affective disorder had mixed state, 12 of them met criteria for low level of mixity and 4 met criteria for mild level of mixity (Figure 3). The large majority of patients with a discharge diagnosis of personality disorder (14 out of 16) showed a mixed state, 12 met criteria for mild level of mixity and 2 met criteria for high level of mixity (Figure 4); all subjects diagnosed with "others" diagnosis met criteria for low level of mixity (Figure 5).

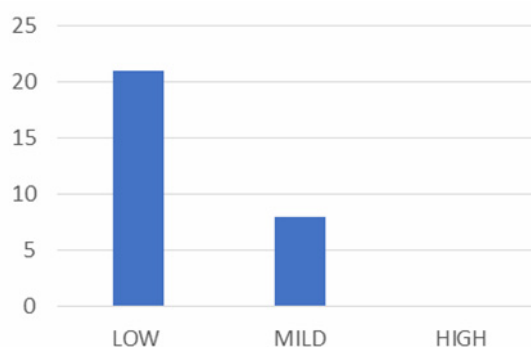


Figure 2. Level of Mixity in pt. with Schizophrenia Spectrum Psychosis Disorder diagnosis at discharge

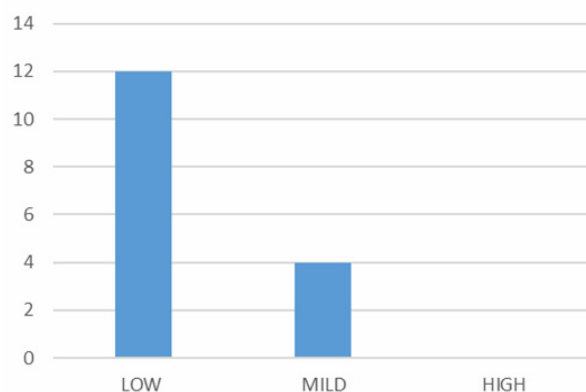


Figure 3. Level of Mixity in pt. with Affective Disorder diagnosis at discharge

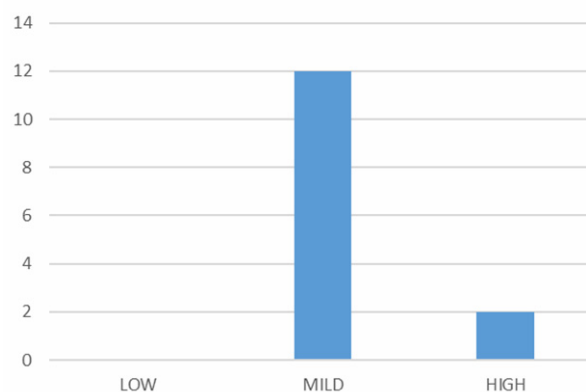


Figure 4. Level of Mixity in pt. with Personality Disorder diagnosis at discharge

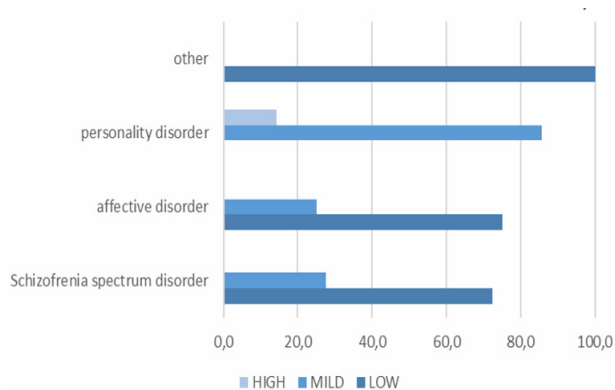


Figure 5. Level of Mixity: summary chart

Twenty-six patients (30.9%), within all the 75 that met criteria for mixed state, had prescribed a mood stabilizer during their hospitalization, but only 16 had a diagnosis of Affective Disorder (Bipolar Disorder or Major Depression) at the discharge; in particular, we found a high prevalence of mixity in patient with personality disorder. It often happens that mixed symptoms are underestimated because the patients referred frequently present anxiety or somatic symptoms that influence the clinicians to prescribe only antidepressants or benzodiazepines. For this reason, we have highlighted that an early detection of mixed states could help avoid misdiagnosing or mistreating patients with these symptoms. As we said before, treatment guidelines do not usually recommend specific treatment for mixed states. As a consequence, the choice of medication is usually based on clinical experience, individual factors and short and long-term safety and tolerability.

DISCUSSION

In our study, we found that the majority of subjects admitted to an inpatient psychiatric unit met the criteria for mixed state diagnosis, which was not always reflected in the discharge diagnosis, confirming our hypothesis of the limitation of the DSM-5 diagnosis, compared to the affective spectrum.

Mood stabilizers and atypical antipsychotics are recommended to treat mixed episodes, but data is limited to sub-analyses or post hoc analyses of populations of patients with both manic and mixed episodes. It is interesting to note that the majority of those subjects who met the criteria for mixed states diagnosis had been prescribed a mood stabilizer, validating the results of GT-MSRS scale. Even though there are already two validating studies on the usefulness of "GT-MSRS" (Tavormina 2015, 2017), the limitations of this study suggest that additional studies are needed to understand what is the best treatment option for mixed states.

A question that often arises in the psychiatric debate is how to describe the nature of mental disorders, in terms of either nosological entities or unitary psychosis.

Since psychiatric disorders reflect affective imbalances, we have considered the hypothesis that the concept of the unitary psychosis helps us to think that there is a unitary affective ground in the psychosis, in which the psychotic symptoms fit within different phenomenological frameworks.

CONCLUSIONS

Despite the limitations of this study, interesting results have been obtained with this retrospective study: the rating scale "G.T. MSRS" can be a valid instrument that helps clinicians to identify the "mixity" symptoms of the mood, in order to prescribe a tailored treatment. To detect mixed states is very important in terms of prognosis, suicide risk, side effects and quality of life. Given the high prevalence of mixed state in the inpatient unit population, the G.T. MSRS scale could be an easy tool to detect "mixity" symptoms in mood disorders early in the course of hospitalization, in order to prescribe mood regulator drugs as soon as possible, avoiding the utilization of antidepressants alone, or the use of benzodiazepines for long periods (Tavormina 2016). Further studies are needed to identify a tailored treatment, considering the mixity features.

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Contribution of individual authors:

Alba Cervone projected and designed the study, and also wrote the manuscript.

Alba Cervone, Giuseppe Cimmino, Francesco Paolo D'Ostuni & Giulia Esposito visited patients and carried out clinical work.

Alba Cervone, Francesco Paolo D'Ostuni, Giulia Esposito & Manlio Russo interpreted the data.

Giuseppe Tavormina created and validated the Mixed State Rating Scale, and reviewed the study.

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DYSPHORIA DIMENSIONS: A PRELIMINARY INPATIENTS STUDY TO DIFFERENTIATE BORDERLINE PERSONALITY AND BIPOLAR DISORDER SPECTRUM

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SUMMARY

Background: Differentiating Borderline Personality Disorder (BPD) from Bipolar Disorder (BD) represents a very difficult challenge for clinicians. Dysphoria could be a possible key to differentiate these disorders. We currently define dysphoria as a complex and disorganized emotional state with proteiform phenomenology, characterized by a multitude of symptoms. Among them irritability, discontent, interpersonal resentment and surrender prevail. These dimensions can be detected using the Neapen Dysphoria Scale - Italian version (NDS-I). Dysphoria role in BPD has been highlighted by the recent theorization of the Interpersonal Dysphoria Model, according to which dysphoria could represent the "psychopathological organizer" of the BPD. On the other side, dysphoria role in BD has not yet been established. This is simply considered as an aspect, and not fundamental, of the symptomatology characterizing BD, especially in mixed states patients. The phenomenological analysis of the dimensional spectrum of dysphoria within BPD and BD could provide a valuable aid in the differential diagnosis between BPD and BD.

Aims: The aim of this paper is to verify if the dimensional spectrum of dysphoria differs between Borderline Personality Disorder (BPD) and Bipolar Disorder Spectrum (BD) through an observational comparative study

Subjects and methods: In this study, 65 adult patients, males and females between the ages of 18 and 65, were enrolled from the Psychiatric Service of the Santa Maria della Misericordia Hospital in Perugia (PG), Italy, from January 1st 2018 to April 30th 2019. We have formed 2 groups. A BPD group composed of 33 patients (19 female patients, representing approximately 57.6 % of the sample) and a BD group composed of 32 patients (18 Female patients, representing approximately 56.2% of the sample). Patient's comorbid with BD and BPD have been excluded from the study. After a preliminary assessment to exclude organic and psychiatric comorbidity, and after at least 72 hours from hospitalization, we administered them the Neapen Dysphoria Scale - Italian Version (NDS-I), a specific dimensional test for dysphoria. Starting from the dataset, with the aid of the statistical program SPSS 20, we have carried out a comparison between disorders groups selected and their NDS-I total score and subscales (irritability, discontent, interpersonal resentment, surrender); For this we have used the Mann-Whitney U test, a nonparametric test with 2 independent samples, by setting a significance level $p < 0.05$.

Conclusions: This study allowed us to explore and analyze dysphoria dimensions expressions in BPD and BD. Despite the small sample analyzed, the results show a significant different dimensional spectrum expression of the dysphoria between the two disorders. In particular, Irritability and Interpersonal Resentment dimensions show greater interest in BPD than BD spectrum. Further studies with a larger and stratified sample are needed to confirm these results.

Key words: dysphoria - borderline personality disorder - bipolar disorder - NDS-I - neapen dysphoria scale italian version

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INTRODUCTION

Differentiate Borderline Personality Disorder (BPD) from Bipolar Disorder (BD) represents a very difficult challenge for clinicians.

Despite many clinicians and researchers claim that the DPB belongs to the spectrum of bipolar disorder (Akiskal 2004, Perugi et al. 2013), several studies have been carried out in the attempt to find a valid diagnostic instrument that could easily distinguish these two disorders.

To date there are not genetic, imaging or blood tests that have provided such accuracy values to be considered biomarkers of differentiation between BPD and BD (Paris & Black 2015).

Our principal aim is not providing a clinical instrument to obtain this differentiation but analyzing the quantitative and qualitative expression of dysphoria dimensions within these disorders that can be useful in the next future to helping clinicians to obtain a possible clinical tool for a differential diagnosis (Moretti et al.

2018). Only studying these variations of dysphoria dimension between BPD and BD patient groups we can think to move forward in the direction to considering dysphoria dimensional spectrum analysis a possible key feature to differentiate these two disorders.

Our group have already studied the possible different expression of dysphoria dimensions in three different psychopathological disorders (Moretti et al. 2018), but the three samples was too small for a valid and generalized conclusion.

This time, using a similar paradigm, we want to enlarge the samples by focusing on BPD and BD and observing the expression of their dysphoria patterns.

DYSPHORIA

A Possible Definition

The word "dysphoria" came into English from the Ancient Greek word $\delta\upsilon\sigma\phi\omicron\rho\iota\alpha$ (dysphoria), which means "excessive pain". The Greek word itself is a compound

noun: it's made up of two Greek words $\delta\upsilon\sigma\text{-}$ (dus-, "bad") and $\phi\acute{\epsilon}\rho\omega$ (phérō, "I bear, carry").

Its usage in heterogeneous clinical areas contributes to the lack of clarity and imprecision that hovers around the specific meaning of the term itself.

Usually, the term is used to indicate a generic state of dissatisfaction and affective instability, characterized at the same time by anxiety and depression, without any specific feature. This wide range of situations in which this term is applied often implies an implicit and shared meaning, with no need of definition.

We have already tried to define dysphoria, in our previous work (Moretti et al. 2018), as a complex and disorganized emotional state with proteiform phenomenology characterized by a multitude of symptoms: irritability, discontent, interpersonal resentment and surrender (Starcevic et al. 2007, 2013). Dysphoria appears to be an unstable and unpredictable "entity". Generally, we consider it as a temperamental tract, but its manifestation arises in response to environmental stimuli, especially to adverse ones, from which it is often modulated.

Dimensions of Dysphoria

Generic traits apart, dysphoria could be characterized exquisitely by three specific components: tension, irritability and urge (D'Agostino et al. 2016).

Tension is a condition of strong emotional pressure caused by deflection of the mood, chronic and undefined unhappiness and extremely extended and persistent discontent, which leads the subject to surrender. In addition, there is a persistent state of oppressive, often ambivalent, painful expectation of the present and the future.

Irritability refers to a state of constant and annoying restlessness, worry and incessant anxiety. Similar to a sensation of adversity towards the world that leads the subject to assume a suspicious, hostile and resentful attitude towards the environment and the people around him.

Urge, finally, is characterized by impatience and intolerance, by an irresistible need to act, which often leads to the appearance of self-harm behaviour. The action, in the dysphoric patient, is always a violent action; violence not necessarily with a physical meaning, but rather referred to the great intensity of emotions that invest the subject. The patient tries to get out from his discomfort state through the action, thus trying to modulate, in some way, the dysphoric state.

NDS-I a New Clinical Tool for a New Dysphoria Approach

As reported in our last work (Moretti et al. 2018), to differentiate various dysphoria dimensions, we need a new test capable to detect the shades of dysphoria spectrum. In our opinion, the best test suited for this job seems to be, in our opinion, the Neapen Dysphoria Scale - Italian Version (NDS-I). It has been translated and adapted in Italian by D'Agostino et al. in 2016 and

represents the Italian version of the homonymous NDS introduced in Australia by Starcevic et al. in 2007. This auto-administered test consists of 24 items in Likert scale from 0 to 4. At the end of the test it is possible obtain a specific Total Score, that provides a rough assessment of the degree of dysphoria, and additional scores divided into 4 subscales that represent the dimensions of the dysphoria (irritability, discontent, personal and interpersonal resentment, renunciation / surrender). The test has not any cut-off and represents a dimensional, non-nosographic tool. That means, hopefully, that it might show the severity of the symptomatology and above all if some domains are more involved than others. Unfortunately, it has not been validated yet on a large scale. Although the psychometric properties are excellent for the healthy population, they have not been verified yet in the pathological population (D'Agostino et al. 2016).

Dysphoria Phenomenology in Borderline Personality and Bipolar Disorder Spectrum

Many clinicians and researchers considered dysphoria as a nonspecific psychopathological phenomenon inscribed in a multitude of psychiatric disorders (D'Agostino et al. 2017) including, for example, Bipolar Disorder (BD), in particular Mixed-States, Major Depressive Disorder (MDD), Post-Traumatic Stress Disorder (PTSD), Feeding and Eating Disorders (FED), Personality Disorders where Borderline Personality Disorder (BPD) occupies a privileged position, but also in others generic neurological and medical disorders.

This point of view represents a superficial generic vision of the dysphoria's manifestations, especially if we focus on its different dimensional expression in these various disorders.

Considering BPD dysphoria appears to be a characterizing and disabling psychopathological element. BPD patient suffers continuous disturbances of his affective sphere. These disturbances are characterized by behavioral reactions often disproportionate and inadequate compared to the real gravity of the stimulus event. Dysphoria fits between subjective perception and behavioral response.

Dysphoria replaces the normal neuromodulatory mechanisms that leads a healthy subject to separate the real distance between the severity of the external objective event and the severity of the representation of the same event to provide an adequate response. Thus, we can imagine that if these modulator mechanisms fail, or become dysregulated, the inability to control one's emotions prevails. These can be so amplified as to make the subject a slave to his emotions and to their continuous variability base on environmental stimuli. In severe cases, the subject, who over time has learned to identify him-self with the emotional reactions elicited by external event, ends up losing the boundaries between the Self and the object (Moretti et al. 2018).

In BD disorder, dysphoria seems play an important role during maniac phase and in the Mixed-State. This one seems very similar to BPD (Perugi et al. 2016), often is very difficult to differentiate these disorders only with clinical interview. Dysphoria phenomenology for BD is unknown yet. Our aim is trying to study its spectrum to highlighting any differences compared with BPD,

Borderline Personality and Bipolar Disorder: A Comparison

Looking at the recent scientific literature we must highlight the difficulty that many researchers and clinicians have in marking a clear demarcation line between Borderline Personality and Bipolar Disorder Spectrum.

Despite the very large number of studies on this topic the scientific community has yet to clarify if BPD represents a part of the wider Bipolar Spectrum (Perugi et al. 2013), or if it has its own phenomenology. It is even less clear the comorbidity interrelation between these two nosographic identities; epidemiological comorbidity data shared by many authors tends not to correspond: some authors sustain a 20% prevalence (Fornaro et al. 2016, Frias et al. 2016), others show a prevalence as close as 14% (Brieger et al. 2003), some other declares a prevalence as low as 3.6% (Di Giacomo et al. 2017). Because of these differences, some author supports the extreme conviction that a dichotomic vision of these two disturbs is not useful in the everyday clinical practice.

The difference shown in the data above probably reflects the difficulty clinicians have in clinically differentiating symptoms overlapping between BPD and BD, e.g. mood instability or impulsivity (Vöhringer et al. 2016). In addition to this we would remark how difficult could be making a differential diagnosis in the short times required, for example, in an inpatient clinic. In fact, in a psychiatric ward, it is hard to immediately differ these two disorders in a patient with a new onset right because of this overlapping. In 2016 editorial three characteristics were considered to be fundamental in order to differentiate BPD and BD: childhood sexual abuse, repeated self-harm, depersonalization (Ghaemi 2016). Particularly the author supported the presence of childhood sexual abuse in the patient history as an important factor helping the clinician in the diagnosis of BPD compared to BD.

Certainly, traumatic events, not only sexual ones, significantly contribute in the development of BD, but this is not the only element involved and many patients do not have such a history, mainly because reluctant to talk about it, but also because they didn't have such traumatic events. It is important to consider as well one more difficulty when facing patients with traumatic event in their history: the overlapping symptoms between BD and PTSD.

This summary wants to show the necessity of finding new tools that could help clinicians easily differentiating patients affected by these two disturbs in order to start a correct and prompt treatment (Bassett et al. 2017).

To do so, many authors, suggest the use of tests in addition to clinical interview which is still to consider the gold standard (Vöhringer et al. 2016, Mneimne et al. 2017, Di Giacomo et al. 2017).

Our aim is to show how the clinical dimension of dysphoria could be a helpful tool, useful in differentiating BPD and BD, as already shown in our preliminary work (Moretti et al. 2018).

Aims

The primary goal of this work, starting from the positive results of our previous work (Moretti et al. 2018) with a larger patient's sample, is to verify if the dimensional spectrum that composes dysphoria differs between Borderline Personality Disorder (BPD) and Bipolar Disorder Spectrum (BD) through an observational comparative study.

SUBJECTS AND METHODS

In this study, 65 males and female patients affected by Borderline Personality Disorder (BPD) and Bipolar Disorder Spectrum (BD) between the ages of 18 and 65, were enrolled from the Psychiatric Unit of the Santa Maria della Misericordia Hospital in Perugia, Italy, from January 1st 2018 to April 30th, 2019. We have formed 2 groups. A BPD group consisted of 33 patients (19 female patients, representing approximately 57.6 % of the sample), and a BD group consisted of 32 patients (18 female patients, representing approximately 56.2% of the sample).

Once eligible patients were identified, we proceeded carrying out their history and clinical information, through clinical interview and using other clinical tools like Structured Clinical Interview for DSM-5-Clinical Version (SCID-5-CV) to detect major psychiatric disorders, the Structured Clinical Interview for DSM - II (SCID-II) and Minnesota Multiphasic Personality Inventory - 2 (MMPI-2), to detect personality disorders.

After selecting patients with BPD or BD, those who had other medical, psychiatric comorbidities and current history of substance use were excluded from the study to avoid confounding factors.

Patients agreed to give their informed consent according to the current EU regulations on privacy through an information talk and related information form, with the possibility for patients to withdraw at any stage of the study.

Once the consents were obtained we continued administering the NDS-I test to the patients, prior instructing them in its correct compilation. NDS-I test was given to patients at least after 78 hours from the hospitalization, to avoid that the disorder's burst phase could alter test results. After that, we collected and re-pro-

cessed the patients tests in a specific database. Since the NDS-I test is a dimensional tool there is no cut-off, therefore, its goal is not to define whether a subject is dysphoric, but rather showing which dysphoria domains are more relevant. To do that we extrapolated the scores of the individual items expressed on the Likert scale and we calculated the scores of the four subscales as indicated by D'Agostino et al. 2016.

The data obtained have been reported in a specific database. Because of the small size of the samples, it has been decided to avoid the division by gender and to consider males and females indiscriminately within the reference group. Starting from the dataset, with the aid of the statistical program SPSS 20, we obtained data showing the comparison between the two groups selected and NDS-I total score and subscales.

Finally, we took the scores of NDS-I subscales and total scores for each group and then we compared these values. We did it using the Mann-Whitney U test, a nonparametric test with 2 independent samples, by setting a significance level $p < 0.05$.

RESULTS

At first, we obtained graphs from data. From these we tried to highlight some differential dimensional aspects between the expression of the total score and the various subscales of the NDS-I between BPD and BD patient's groups.

In Figure 1 we can see how the group of BPD patients has a higher total score, therefore a higher declared degree of dysphoria, compared to the other group in line with our predictions.

In Figure 2 we have analyzed the dimension of irritability. In this dimension, BPD group showed a greater grade of irritability compared with BD patients.

In Figure 3 we can observe a substantial overlap between the two disorders groups linear diagram regarding the discontent dimension.

In Figure 4, analyzing the interpersonal resentment, we noticed a very important difference between the expression of this dimension in the BPD group compared with BD group, larger than a previous study (Moretti et al. 2018).

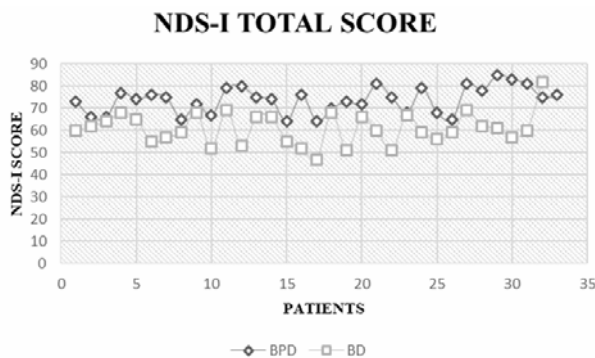


Figure 1. Comparison between groups of patients and the NDS-I Total Score

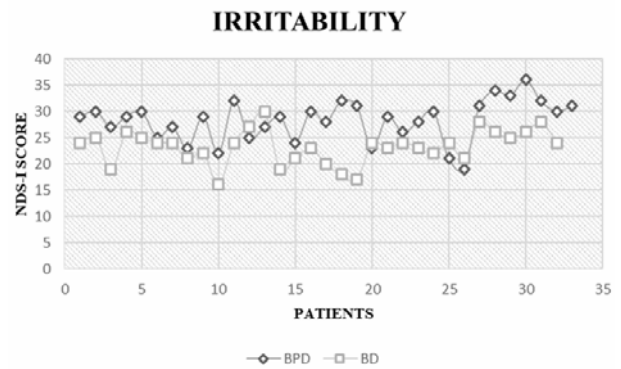


Figure 2. Comparison between groups of patients and the NDS-I Irritability Subscale Score

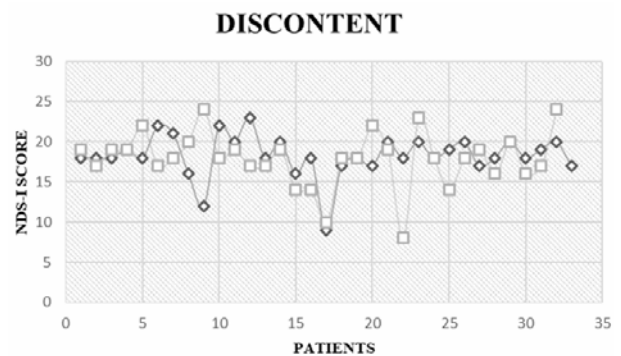


Figure 3. Comparison between groups of patients and the NDS-I Discontent Subscale Score

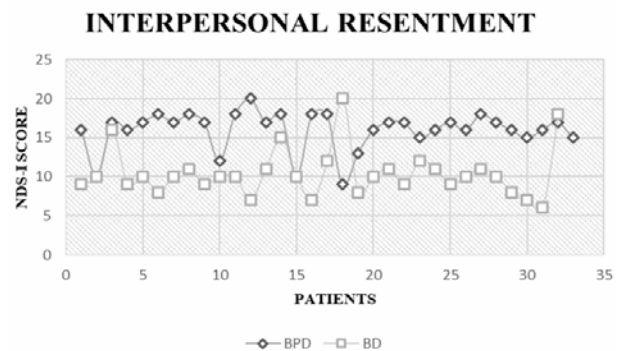


Figure 4. Comparison between groups of patients and the NDS-I Interpersonal Resentment Subscale Score



Figure 5. Comparison between groups of patients and the NDS-I Surrender Subscale Score

Table 1. Arithmetic mean of the scores of the NDS-I test with reference to the BPD and BD groups

	Borderline Personality Disorder	Bipolar Disorder
NDS-I Total Score Mean	73.72	60.81
Irritability Score Mean	28.24	23.22
Discontent Score Mean	18.30	12.35
Interpersonal Resentment Score Mean	15.96	10.44
Surrender Score Mean	11.21	9.25

Table 2. Confrontation between BPD and BD groups using U Mann-Whitney test with a significance level $p < 0.05$

	NDS Total Score	NDS Irritability	NDS Discontent	NDS Interpersonal Resent	NDS Surrender
U di Mann-Whitney	98,500	172,000	479,000	121,500	326,000
Sig. Asint. 2 tails (significance level)	0.000	0.000	0.514	0.000	0.008

In Figure 5, we observe a significant prevalence of the surrender dimension in BPD patients compared to BD group. In this case data appears more widespread and clinically not worthy of value.

In Table 1 we have translated and resumed in numerical language what we have analyzed until now, arithmetic means it's been calculated to show the same differences saw in graphs analysis. In particular, if we pay attention to means values for each subscale, the different dysphoria expression is easily understandable in these two disorders, even if only qualitatively.

At last, data obtained with Mann-Whitney U test, resumed in Table 2, shows that the two disorders group presents a different distribution of the values within the individual subscales. The differences in the statistical analysis confirm the qualitative observation previously made. We observe a very strong significant statistically difference in BPD group regarding NDS-I Total score, Irritability and Interpersonal Resentment subscales compared with BD group.

Study Limitations

This paper shows several limitations. First, the very low amount of data from the literature about NDS-I test. This limits our observations to our sample, making any review and meta-analysis impossible to prove or deny our results.

The second limitation concerns the small number of samples taken into consideration, thus the impossibility of carrying out a gender differential analysis. For this reason, the study does not presume to be exhaustive and complete, rather as a preliminary work to be implemented over time. Consequently, data obtained must not be considered definitive but suggestive for future works. Future work must aim to improve gender sample to observe the reproducibility of our results in a large divided sample composed by BPD and BD male and female patients.

Referring to the small number of samples, we decided to utilize the U Mann-Whitney test instead T Student Test because we were at limit boundaries of

normal statistical population, but there was too much difference between two groups. Gender and age were too widespread. Next studies must consider this problem and make more homogeneous samples.

The third limitation concerns the NDS-I test. This test, as already mentioned in a precedent work (Moretti et al. 2018), has not been validated yet in Italy and its psychometric properties have been evaluated exclusively in a sample of healthy subjects. This test was selected to respond to the studies aim to analyze dysphoria dimensions construct and there is no other test currently validated by the literature with these characteristics.

Finally, it must be considered that in a clinical setting it is often difficult to observe symptoms phenomenological continuity over time. In this regard, NDS-I should be administered several times during the hospitalization, but also in the psychiatric territory services once the patient has been discharged, to detect significant variations in this continuity. In this study, due to the short hospitalization of enrolled patients, a re-test could not be performed. Next works must take in account this important aspect.

CONCLUSIONS

This study allowed us to explore dysphoria' expressions in patients affected by Borderline Personality and Bipolar Disorder. Despite the small samples size differences between means of the two groups values obtained through NDS-I subscales were statistically significant ($p < 0.05$). These preliminary data showed that BPD patients have a greater pervasiveness and severity dysphoria symptoms compared to BD patients. In particular, Irritability and Interpersonal Resentment dimensions show greater interest in BPD than BD spectrum.

Although it has been reported in a recent study that the self-report measures presented a limited value for the differential diagnosis (Fowler et al. 2019), NDS-I could be a good adjunct tool for clinical diagnosis and follow-up to prevent possible relapses.

Indeed, in this case we have proposed NDS-I test as an aid to differential diagnosis between BPD and BD, but the utility of this type of instrument could be in patient's follow up with the aim of detecting a possible early relapse. This possible use as secondary prevention instrument must be studied yet, but if our predictions will be confirmed by other studies this test could have obvious positive implications on patient's management, not only for diagnostic stage. NDS-I test being a dimensional tool does not pretend to objectify the patient's experience. The result must always be interpreted based on the subjective experience of the person facing the clinician, even within a dimensional approach.

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Contribution of individual authors:

Massimo Claudio Bachetti conceived and designed the study.

Massimo Claudio Bachetti & Giulio Spollon wrote the first draft of the manuscript.

Massimo Claudio Bachetti & Francesca Brufani performed statistical analyses.

Massimo Claudio Bachetti, Francesca Brufani, Giulio Spollon & Patrizia Moretti visited patients and carried out clinical work.

Massimo Claudio Bachetti, Francesca Brufani & Giulio Spollon conducted testing.

Massimo Claudio Bachetti, Francesca Brufani & Patrizia Moretti discussed results,

Massimo Claudio Bachetti, Francesca Brufani, Giulio Spollon & Patrizia Moretti supervised the writing of the manuscript; all authors approved the final version of the manuscript..

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CIRCADIAN RHYTHMS DISRUPTIONS AND EATING DISORDERS: CLINICAL IMPACT AND POSSIBLE PSYCHOPATHOLOGICAL CORRELATES

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SUMMARY

Background: A link between abnormalities in circadian rhythms and the development of eating disorders was extensively hypothesized, mainly in consideration of the influence of the circadian clock on eating behavior. The present review is aimed at summarizing the evidence about biological rhythms disruptions in eating disorders, possibly clarifying their impact on the psychopathological profile of such patients.

Methods: Electronic database MEDLINE/PubMed/Index Medicus was systematically searched for original articles examining the prevalence of circadian rhythms disruptions in eating disorders (anorexia nervosa, bulimia nervosa, binge eating disorder).

Results: Studies included in the review confirmed the hypothesis of a high prevalence of circadian disruptions in eating disorders. The analyzed research mainly focused on sleep-wake cycle, rest-activity abnormalities and hormonal secretion, whilst literature about other circadian rhythms was scanty. Altered biological rhythms presented higher association with specific psychopathological features, but such relationship was assessed in few studies.

Conclusions: Circadian rhythms disruptions were confirmed to be relevant aspects in the context of eating disorders. Further research is needed in order to clarify the role of biological rhythms in such illnesses, in the attempt to address adjunctive treatment strategies with the possible focus of circadian abnormalities.

Key words: circadian rhythms - biological rhythms - eating disorders - anorexia nervosa - bulimia nervosa - binge eating disorder

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INTRODUCTION

Eating disorders (EDs) are complex psychiatric conditions that involve patients' global functioning and present a complex etiopathogenesis, encompassing both psychological and biological aspects (American Psychiatric Association 2013). Over the last decade, several studies focused on circadian rhythms and their alterations in patients suffering from EDs. Circadian rhythms disruptions already demonstrated to play a significant role in several psychiatric disorders, possibly being correlated to their pathophysiology (Cretu et al. 2016, Allegra et al. 2018). The hypothesis of a possible disruption in biological rhythms also in EDs arises from the fact that the circadian pacemaker is connected with metabolic and hedonic centers, controlling both feeding and other activities (Mendoza 2018). Subsequently, all circadian rhythms, i.e. sleep-wake rhythm, activity levels, social patterns, hormonal secretion, and not only those related to eating behaviors, can potentially be altered in patients affected by EDs. It was hypothesized that patients with abnormalities in eating attitudes display predominantly phase-delayed circadian rhythms of various behavioral and neuroendocrine factors, and that the timing of key rhythms involved in food intake and metabolism would be altered (Goel et al. 2009). This was already demonstrated in animal models, where changes in food intake resulted in a fragmentation of sleep and a reduction of slow wave sleep (Lauer & Krieg 2004). In addition, circadian disruptions may represent not only relevant symptomatological features

in EDs, but also possible modulators of some clinical aspects of such disorders, which could be i.e. demonstrated by the link between insomnia and poorer treatment outcomes (Allison et al. 2016). Notwithstanding the potential interest of circadian disruptions in EDs, an extensive assessment of their impact on this complex group of disorders is still lacking. Subsequently, the aim of the present review is to summarize the evidence about circadian abnormalities in the main EDs, focusing on their prevalence and possible influence on clinical and psychopathological features.

METHODS

We conducted a systematic search of the electronic database MEDLINE/PubMed/Index Medicus using the following search string: (((anorexia nervosa) OR bulimia nervosa) OR binge eating) OR eating disorders) AND (((circadian rhythms) OR biological rhythms) OR sleep-wake cycle). Two independent investigators (GM and FB) performed the literature search, title/abstract screening and full text screening. The reference list of selected articles underwent further screening in order to search for additional literature. We included in the present review original studies reporting data about the prevalence and the possible clinical impact of circadian rhythms disruption in the main EDs, namely anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED). Only research conducted in the past 15 years was considered for inclusion (screening period: 1st January 2004 - 31st May 2019). Articles presenting

hypotheses without empirical investigation, reviews, letters to the editor, case reports and studies concerning animal models were excluded. No language restriction was applied.

RESULTS

Literature search results

The database search initially yielded 672 records. Among these, 21 were selected after performing title-abstract screening. Further evaluation led to the exclusion of 3 articles. Two more papers were deemed eligible for inclusion in the review after hand-screening of relevant references. Subsequently, the full text examination identified 20 papers which were included in the present review.

Content results

Hormonal circadian patterns

Patterns of circadian hormone secretion in patients with EDs were evaluated in ten of the included studies, with the measurement of blood and salivary levels at different times of the day (Misra et al. 2005, Germain et al. 2007, dos Santos et al. 2007, Germain et al. 2009, Germain et al. 2010, Monteleone et al. 2011, Galusca et al. 2012, Ostrowska et al. 2013, Galusca et al. 2015, Germain et al. 2016). Thirteen hormones were taken into account in the selected articles (see Table 1), mainly regulating food intake and appetite. The circadian rhythm of such molecules was significantly decreased/absent or dysregulated in subgroups of patients affected by EDs, with frequent abnormalities in their daily mean blood/salivary concentration. An exception was demonstrated for orexigenic neuropeptide 26RFa, which showed a circadian profile similar in BN and controls, whilst it was significantly decreased in all-type AN (Galusca et al. 2012). A similar result was found for obestatin and ghrelin, which showed abnormalities only in AN patients but not in BN (Germain et al. 2010). Studies considering also constitutional thinness demonstrated that some abnormalities were detectable as well in these subgroups for the analyzed hormones (Germain et al. 2007, Germain et al. 2009, Germain et al. 2016).

Sleep-wake rhythm

Sleep-wake disruptions in EDs were examined in eight of the included studies, by analyzing sleep architecture (Tzichinsky & Latzer 2006, Sauchelli et al. 2015, Tanahashi et al. 2017, Asaad Abdou et al. 2018, Kandeger et al. 2018, Roveda et al. 2018) and sleep quality (Lundgren et al. 2008, Sauchelli et al. 2015, Tromp et al. 2016, Tanahashi et al. 2017). Different measures of assessment were used, including objective (i.e., actigraphy and polisomnography) and subjective (i.e., self-administered questionnaires) instruments. Sleep abnormalities appeared to be significantly more frequent in patients with EDs (Lundgren et al. 2008, Sauchelli et

al. 2015, Tromp et al. 2016, Asaad Abdou et al. 2018). Studies considering obese patients with and without BED showed that patients with BED did not present sleep architecture abnormalities when compared to obese subjects (Roveda et al. 2018), with the whole obese group showing more significant sleep disturbances. Despite this, in another study the BED subgroup demonstrated abnormalities in specific parameters, such as minutes of wakefulness during sleep (Tzischinsky & Latzer 2016). One study, using a structured questionnaire and polisomnography, also demonstrated higher rates of parasomnias and daytime hypersomnia in AN and BN, as well as abnormalities in indexes such as sleep latency, sleep efficiency and arousal (Asaad Abdou et al. 2018). When comparing different AN subtypes, binge eating-purging type presented with worse sleep quality, abnormal sleep duration and more disrupted circadian rhythm (Sauchelli et al. 2015, Tanahashi et al. 2017). Furthermore, insomnia and sleep parameters abnormalities were linked to a higher severity of depressive symptoms in EDs (Asaad Abdou et al. 2018) and presented an indirect influence on disordered eating attitudes (Kandeger et al. 2018).

Chronotype/circadian preference

Four of the selected studies analyzed patterns of activities in EDs, with a particular focus on circadian preferences (Natale et al. 2008, Harb et al. 2012, Roveda et al. 2018, Kandeger et al. 2018). Studies assessing chronotype found a significant association with eveningness, both when the sample was composed of patients with all-type EDs (Natale et al. 2008) and only with diagnosis of BED (Harb et al. 2012). In this subgroup of patients, levels of daytime activity also resulted to be reduced (Roveda et al. 2018). On the other side, a study assessing eating patterns and diurnal preference in a sample of students did not find any significant correlation between chronotype and disordered eating attitudes (Kandeger et al. 2018).

Other circadian rhythms

One study assessed circadian eating patterns and mood variations among patients with diagnosis of BN, by means of self-administered instruments (Lundgren et al. 2008). Dysregulated eating behaviors presented a significant circadian component, with the prevalence of night-time eating and morning anorexia. Similarly, mood variations across the day were strongly prevalent, with a higher rate of depression during the evening/night.

DISCUSSION

The results of the present review, as expected, demonstrated high rates of biological rhythms dysregulation in patients with EDs, when considering sleep/wake cycle, activity patterns/chronotype and hormone secretion. Abnormalities in the circadian concentrations of the studied hormones, especially molecules controlling food intake (i.e. NYY, GLP-1, leptin, ghrelin, obestatin,

Table 1. Summary of the included studies assessing circadian rhythms in EDs

References	Study Design	Sample	Analyzed circadian rhythm	Circadian rhythm assessment measure(s)
Asaad Abdou et al. 2018	Observational, prospective, cross-sectional study	23 females with AN or BN (age 18-45) 20 controls matched for age and sex	Sleep architecture	Structured Sleep Disorder Questionnaire PSG
Kandeger et al. 2018	Observational prospective study	383 students (60.1% females), mean age 21.1 (± 0.1), who were screened for disordered eating attitudes (4.2% met the criteria)	Chronotype/circadian preference, sleep architecture	MEQ, Insomnia severity index
Roveda et al. 2018	Observational, prospective, cross-sectional study	8 obese females 8 obese females with BED	Rest-activity circadian rhythm and sleep architecture	Actigraphy and Actiwatch Sleep Analysis Software
Tanahashi et al. 2017	Observational, prospective, cross-sectional study	12 AN binge eating-purging type 8 AN restricting type	Sleep quality and sleep architecture	PSQI
Germain et al. 2016	Observational, prospective, cross-sectional study	10 restrictive type AN women 5 binge-purging type AN women 15 recovered restrictive type AN women 4 BN women 10 constitutional thinness women 7 healthy obese women 10 normal weight women	Plasmatic IL-7 rhythm	24-hour sampling of IL-7 (12 measurements), leptin and cortisol (6 measurements)
Tromp et al. 2016	Observational prospective study	574 young adults, 12% with EDs (screened positive at ESP)	Sleep quality and daytime functioning	SLEEP-50 questionnaire subscales for sleep apnea, insomnia, circadian rhythm disorder and daytime functioning
Galusca et al. 2015	Observational, prospective, cross-sectional study	23 AN young women 22 CT young women 14 normal weight age-matched controls	Plasmatic NPY and α MSH rhythm	24-hour sampling of NPY, α MSH (12 measurements), leptin, GH and cortisol (6 measurements)
Sauchelli et al. 2015	Observational, prospective, cross-sectional study	48 AN patients 98 healthy weight controls	Sleep quality, sleep architecture	PSQI
Ostrowska et al. 2013	Observational, prospective, cross-sectional study	86 females (13-18 years) with AN and 21 healthy subjects (13-17 years)	Melatonin rhythm	Melatonin blood samples (2 measurements)
Galusca et al. 2012	Cross-sectional study	19 restrictive AN women 10 binge-purging AN women 14 CT women 10 bulimic women 10 normal-weight age-matched controls	Orexigenic neuropeptide 26RFa rhythm	24-hour sampling of 26RFa (12 measurements), leptin, GH, cortisol (6 measurements)
Harb et al. 2012	Cross-sectional study	100 subjects (77% females), mean age 39.5 (± 11.7) years, 66% overweight. 43% presented binge eating, 27% abnormal eating attitudes/behaviors, 18% night eating behavior.	Chronotype/circadian preference	MEQ

Notes: α MSH = Melanocyte stimulating hormone type α ; AM = Anti-meridian; AN = Anorexia nervosa; BDI = Beck Depression Inventory; BED = Binge Eating Disorder; BN = Bulimia nervosa; CT = constitutional thinness; EDs = Eating disorders; ESP = Eating Disorder Screen for Primary Care; GH = Growth hormone; GLP-1 = Glucagone-like peptide 1; IGF-1 = Insulin-like growth factor-1; IL-7 = Interleukin-7; EAT = Eating Attitude Test; EDI-2 = Eating Disorders Inventory-2; MEQ = Morningness/eveningness questionnaire, reduced version; MEQr = Morningness/eveningness questionnaire; NEQ = Night eating questionnaire; NPY = Neuropeptide Y; PM = Post-meridian; PSG = Polisomnography; PSQI = Pittsburgh Sleep Quality Index; PYY = Peptide YY

Table 1. Continues

References	Study Design	Sample	Analyzed circadian rhythm	Circadian rhythm assessment measure(s)
Monteleone et al. 2011	Cross-sectional study	8 AN females 8 age-matched controls	α -amylase and cortisol salivary levels	Salivary samples 15, 30, 60 min from awakening and at 10 AM, 12 AM (before lunch), 4 PM, 6 PM, 7 PM and 8 PM (before dinner)
Germain et al. 2010	Cross-sectional study	22 restrictive type AN women 10 binge-purging type AN women 16 normal-weight BN women 9 age-matched control subjects	Plasmatic ghrelin, obestatin, and PYY rhythm	24-hour sampling of leptin, GH, cortisol, obestatin, total and acylated ghrelin, and PYY (12 measurements)
Germain et al. 2009	Cross-sectional study	15 restrictive type AN young women 9 young women restored from AN 10 CT 9 control subjects	Plasmatic obestatin and ghrelin rhythm	24-hour sampling of leptin, GH, cortisol, obestatin, total and acylated ghrelin (6 measurements)
Lundgren et al. 2008	Observational prospective study	31 females, diagnosis of BN	Eating behavior (nighttime patterns and morning anorexia) Sleep quality Circadian mood variations	NEQ, EDI-2, BDI
Natale et al. 2008	Observational, prospective, cross-sectional study	270 females: 146 recruited in a EDs treatment centre, 240 controls	Chronotype/circadian preference	MEQr
Dos Santos et al. 2007	Prospective transversal controlled study	12 female patients with diagnosis of AN (10 restrictive type, 2 bulimic type, age: 15-35) 13 age-matched healthy and ovulatory females	24-hour salivary cortisol rhythm	Multiple salivary cortisol determinations (9 AM, 5 PM, 11 PM)
Germain et al. 2007	Observational, prospective, cross-sectional study	12 AN young women 10 age-matched CT 7 age-matched normal weight	Plasmatic PYY, GLP-1, ghrelin, leptin and GH rhythm	24-hour sampling of PYY, GLP-1, ghrelin, leptin GH, cortisol (every 4 hours measurements)
Tzischinsky & Latzer 2006	Observational, prospective, cross-sectional study	36 obese patients (divided in obeses with and without BED) 25 normal weight controls	Sleep architecture	Mini actigraphs, self-reported questionnaires (Mini-Sleep Questionnaire, Standard Technion Clinical Sleep Questionnaire) and sleep diary
Misra et al. 2005	Observational, prospective, cross-sectional study	22 AN females (12-18 years) 18 age-matched healthy controls	Plasmatic ghrelin, GH, cortisol rhythm	Blood samples every half hour for 12h at night

Notes: α MSH = Melanocyte stimulating hormone type α ; AM = Anti-meridian; AN = Anorexia nervosa; BDI = Beck Depression Inventory; BED = Binge Eating Disorder; BN = Bulimia nervosa; CT = constitutional thinness; EDs = Eating disorders; ESP = Eating Disorder Screen for Primary Care; GH = Growth hormone; GLP-1 = Glucagone-like peptide 1; IGF-1 = Insulin-like growth factor-1; IL-7 = Interleukin-7; EAT = Eating Attitude Test; EDI-2 = Eating Disorders Inventory-2; MEQ = Morningness/eveningness questionnaire, reduced version; MEQr = Morningness/eveningness questionnaire; NEQ = Night eating questionnaire; NPY = Neuropeptide Y; PM = Post-meridian; PSG = Polisomnography; PSQI = Pittsburgh Sleep Quality Index; PYY = Peptide YY

orexigenic neuropeptides), were shown in a relevant number of the considered studies, confirming the hypothesis of a significant biological load in the etiopathogenesis of EDs, which should thus be considered psychoneuroendocrine diseases as historically defined (Brambilla et al. 2001). The differences in circadian hormone profiles shown between AN restrictive and binge-purging subtype could present possible implications in the differential diagnosis of such subgroups

(Germain et al. 2010). Moreover, the distinct profile that some studies demonstrated for AN when compared to constitutionally thin patients (Germain et al. 2007, Germain et al. 2009, Germain et al. 2016) suggests a possible link between specific psychopathological features and hormone secretion abnormalities, which should be further clarified in future studies. This could be evaluated also in consideration of the direct effect that some of the abnormally secreted hormones,

i.e. somatotrophic axis hormones, might play on specific symptomatological features, such as mood and anxiety (Brambilla et al. 2018). The presence of sleep disorders and diurnal preference variations in patients with EDs was as well expected, in consideration of the influence that such biological features show on eating attitudes and on their implication on general health status (Kandeger et al. 2018). Furthermore, the relationship between altered sleep and eating features was already demonstrated by the characterization of forms of disordered eating and sleeping, i.e. the night eating syndrome (NES) (American Psychiatric Association 2013). Sleep disorders were demonstrated to be prevalent in all-type EDs, which could also suggest that sleep/wake cycle dysregulation could represent a common risk factor for such illnesses (Allison et al. 2016). Noteworthy, few studies further investigated the possible influence of altered sleep and diurnal preference on distinct psychopathological features (Lundgren et al. 2008, Asaad Abdou et al. 2018, Kandeger et al. 2018). Evening chronotype, which was frequently showed by patients with EDs, was associated in previous studies with specific disturbances of mood, alertness and, more recently, with dissociative experiences (Selvi et al. 2017), which could represent one of the psychopathological underpinnings of altered eating behaviors (Castellini et al. 2019). Further research on the symptomatological correlates of circadian disorders in EDs could help identifying core features, which could be at the basis of behavioral disturbances in this complex group of illnesses connecting them to specific biological correlates, as already demonstrated for emotional dysregulation, disturbances of body image and vulnerability to interpersonal stress (Anderson et al. 2018, Monteleone et al. 2018, McLean & Paxton 2019). Moreover, widening the research interest to further biological rhythms, i.e. social activity patterns, as already demonstrated for mood disorders, where extensive interviews were developed at this aim (Allega et al. 2018) could add significant evidence to the impact of circadian disruptions in EDs and provide new possible therapeutic targets. This review presents limitations. First, the small sample sizes of the included studies contributed to a possible risk of bias in most of the considered research. In addition, the heterogeneity of the measures used for the assessment of circadian rhythms abnormalities, particularly for what concerns sleep, for which subjective instruments were mainly used, might represent a major flaw of previous literature. Furthermore, the present review did not take into account nor other possible manifestations of EDs, such as NES, which could present relevant implications in terms of connection with biological rhythms alterations (Allison et al. 2016), neither studies which did not assess hormones in their circadian profile, possibly excluding further literature of interest (Brambilla et al. 2018).

CONCLUSIONS

Circadian disruptions were confirmed to be prevalent features in eating disorders, but the literature on the topic is still scanty, focusing only on specific biological rhythms. Further research is needed in order to clarify the psychopathological correlates of such abnormalities, their implication on differential diagnosis and their role as possible risk factors, also in the attempt to address adjunctive treatment strategies.

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Contribution of individual authors:

Giulia Menculini, Francesca Brufani, Valentina Del Bello & Patrizia Moretti conceived and designed the review.

Giulia Menculini & Francesca Brufani performed the literature search.

Francesca Brufani wrote substantial part of the introduction.

Giulia Menculini wrote substantial part of methods.

Giulia Menculini & Valentina Del Bello wrote substantial part of results.

Giulia Menculini discussed results.

Patrizia Moretti & Alfonso Tortorella corrected the first draft of the manuscript.

Alfonso Tortorella supervised all phases of the study design and writing of the manuscript.

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THE HUMOR IN THERAPY: THE HEALING POWER OF LAUGHTER

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SUMMARY

Although humour is a key element of human communication, and, for this reason, it is also present in therapeutic contexts, its use in this sense still remains largely untapped. The purpose of this article is to increase curiosity and broaden the reflection on the use of humour in the psychotherapeutic relationship. The first part is dedicated to a short review of the main theories on the origins of laughter. The second part will examine those studies reporting a beneficial effect of humour on physical well-being, while the third part will review those studies describing how humour can help improve psychological well-being. The fourth part will further explore the clinical effects of humour in the therapeutic relationship. Both the positive and negative effects of humour in the therapeutic relationship will be discussed. In addition, some brief examples are included.

Key words: humour – psychotherapy - therapeutic alliance

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What Causes an Entertained Reaction?

The explanatory models that attempted to tackle this issue were the following: the Incongruity-Resolution Theory, the Superiority Theory, and the Relief Theory.

The Incongruity-Resolution Theory

The act of laughing is part of a "mental game set-up" where what occurs is real and unreal at the same time. Humour is a game with a climax, an unexpected and illogical element (Fry 2001) that occurs when the stimulus is congruous and incongruous at the same time, deviating from the recipient's perspective. There are two stages: the initial portion, the central "object stage", and an implicit element that does not make sense, which is revealed in its paradoxical nature at the climax of the joke. Freud (1905) defined this element "unreasonable" or "meaningless", and identified its characteristics: contraposition between proper meaning and absurd, union of two contrasting representations and joyous judgement. Bateson (2006) in *The Position of Humour in Human Communication* refers to the reversal of the figure-ground and to paradox, as paradigm of the humorous act. Something becomes comedic when the meaning of an expression is interpreted as "proper", even though it was meant to be construed "figuratively", or when there is contradiction between words and body language. These meta-communicative passages discriminate and qualify reality: "what occurs makes us laugh." Incongruity is determined subjectively, that is, it must not go beyond what the recipient is comfortable dealing with, or be felt as threatening (Provine 2003). Koestler's "bisociation" theory has had a strong impact on clinical psychology (Koestler, cit. Forabosco 1987). Bisociation is a creative act: two elements belonging to two different registers are perceived as connected and incompatible at the same time. The cognitive field broadens (Arieti 1976) with problem solving or cognitive resolution functions, subverting the rules, motives, values and ideas: "the temporary abandonment of

conscious control frees the mind from certain constraints required to regulate common reasoning, but which may hinder creative impulses; at the same time, different, more primitive mental organization processes are established" (Forabosco 1987).

Psychoanalytical theories

Psychoanalytical theories stress the essential role of humour as a tension reliever. Ever since the famous essay by Freud of 1905, *Jokes and Their Relations to the Unconscious*, jokes have been identified as part of the unconscious language. Freud identifies the contraposition between proper meaning and absurd, union of contrasting representations and the presence of joyous astonishment in the origin of laughter. Libidinal and aggressive impulses - which are sent back to the unconscious due to their unacceptability - are recovered through jokes, which would allow our mind to express what is inexpressible through linguistic, semantic and conceptual artifices. The enjoyment depends upon "psychic economy", by overcoming the internal or external obstacle and expressing our libidinal or aggressive impulses in a socially acceptable way. Even more, jokes are a moment of personal and narcissistic elevation, associated with the enjoyment resulting from intellectual activities and from self-affirmation. Freud reveals its relational nature: it takes two people to tell a joke, and three for it to be appreciated (Lothane 2007).

The Superiority Theory

The Superiority Theory identifies jokes as the psychological need to laugh about the misfortunes of others to assert our superiority (Chaloult & Blondeau 2017, Martin 2007), obtaining a narcissistic gratification and a triumph of ego.

Humour, Pain and Physical Disorders

In popular language, "Cheer up, you'll get over it" highlights the healing power of laughter. Research

shows a reduction of pain and discomfort after listening and/or watching funny or relaxing comedy videotapes rather than neutral materials, especially in people with a high sense of humour (Cogan et al. 1987, Hudak et al. 1991). Humour decreases discomfort due to overcrowding (Aiello et al. 1983). For people that undergo surgery, watching comedy films after surgery reduces the quantity and intensity of lamentations and drugs request (Rotton et al. 1996), provided that the patient picks out the film. Laughing decreases pain in residential children and seniors, stress perceived during dental surgery, cardiovascular risk, and anxiety before a negative event (Schneider et al. 2018, Gelkopf & Kreitler 1996, Trice & Price Greathouse 1986). The mechanism concerns the production of catecholamines - responsible for the cerebral production of endorphins - an increased level of adrenaline and noradrenaline, slower breathing, and a reduction of blood pressure and muscular tension (Fry & Salameh 1987, Berk 1983 in Provine 2013). Echoing the research that indicated a decrease of Immunoglobins A in stressful situations, Marting & Dobbin (1988) indicate a significantly higher level of Immunoglobins A in the saliva (S-igA) of persons with high humour scores (Gelkopf & Kreither 1996, Fry & Salameh 1987, Martin & Dobbin 1988). Lefcourt (1990) describes a strengthening of the immune system. Berk (1989) finds a reduction of the stress hormone. However, due to some methodological flaws, the results of these studies cannot be deemed as entirely valid (Provine 2013).

Humour and Emotions: What Are the Effects?

Many studies attest the beneficial effect of humour in managing stress and reducing negative emotions. In stressful situations, it regulates the emotional response, mitigates the effects caused by stressful materials, and reduces occupational stress (Martin & Lefcourt 1983, Martin et al. 1993). Positive humour (affiliative humour and self-enhancing humour) is negatively related to burnout levels (Tümkaia 2007). In depressed senior patients, it increases personal satisfaction and resilience to negative events (Konradt et al. 2013), and it has a protective effect on parents of hospitalized children (Schneider et al. 2018, Lamas 2015). Laughing reduces aggressive behaviour (Prerost 1987), and yet it improves performance in soldiers with a sense of humour in stressful situations (Bizi et al. 1988). Humour produces a cognitive-affective shift, with consequent decrease of arousal (Abel 2002, Martin et al. 1983). People with a high sense of humour experience less anxiety and sadness, employ issue-related and emotion-focused coping strategies, and receive more social support (Fry 1995, Martin & Lefcourt 1983, Yovetich et al. 1990). Humour is negatively related to neuroticism (Deaner & McConatha 1983). Not all studies support these assumptions. According to Porterfield (1987), humour does not mitigate negative life experiences, and, on the contrary, it can help develop prejudice and distorted behaviour, or it can be used against other people, even

though it can directly mitigate depression. Both the appreciation and the production of humour reduce depression, as measured by the Beck Depression Inventory (Deaner et al. 1993). In agreement with the constructs of low self-esteem, impairment and personal vulnerability, people with high depression levels, as measured by the Beck Depression Inventory, enjoy cartoons with other people in them the most, although the differences between the experimental group and the control group are not significant. In case of Obsessive-Compulsive Disorder, it is counter-productive. There is a correlation between humour and perceived social cohesion, reduction of social fear and fostering of healthy work relationships (Sultanoff 2013, Fry 2001).

Humour and Therapy: Preliminary Considerations

Freud defined humour as “a refined and special skill”. Whether or not this skill should be used in psychological therapy, is a controversial subject. Men are born with an innate ability to laugh, but humour in psychotherapy requires a careful analysis. Although there are many articles on this subject, they are mainly anecdotal, and even Humour - the magazine published by the Multidisciplinary International Society for Humour - has published very few research plans. The AATH (American Association for Therapeutic Humour) defines it as: “any intervention that promotes health and wellness by stimulating a playful discovery, expression or appreciation of the absurdity or incongruity of life’s situation. This intervention may enhance health or be used as a complementary treatment of illness to facilitate healing or coping, whether physical, emotional, cognitive, social or spiritual” (Sultanoff 2000, cit. by Franzini 2001).

People with a sense of humour are perceived as socially appropriate, intelligent and capable of solving problems (Francescato 2002). If we combine these characteristics with empathy, acceptance and commitment, aren’t we describing a therapist? Maturity and flexibility, naturalness, emotional connection, good professional experience, empathy and positive regard, as well as moral and ethical sense are what describes a “good therapist”, whether s/he uses this tool or not (Scarinci et al. 2018, Leus et al. 2017, Sultanoff 2013, Salameh 1987).

Kubie (1971), one of the most prominent opponents to the use of humour, states: “Humour has its essential place in life. Let us leave it where it is, and take note that there is an area of life where it can have a marginal role, or maybe no role at all: psychotherapy.” The author paved the way to a reflection: how consciously and “therapeutically” employed is humour? Therapists consider themselves as humour appreciative, rather than active humourists (Lefcourt & Martin 1986), and have little awareness of a communication method they widely use (Gibson & Tantam 2018). International literature (Scarinci 2018, Chaloult & Blondeau 2017, Franzini

2001) reports the lack of specific training, despite humour being used in therapy. Franzini (2001) suggests adding it to specialist training, and recommends its use in supervision, as element to strengthen the supervisor-supervisee relationship. Salameh (1987), created a Humour Immersion Training with numerous exercises and role-plays.

In therapeutic practice, it has been considered: expression of nearness, positive feedback, coping ability to mitigate the effects of stressful events, cognitive skill to shift away and distance oneself from negative events, and ability to grasp paradox (and therefore change). Laughing is considered essential to recover the healthy and constructive parts of oneself, by accessing a meta-position that allows distancing negative emotions. In all these forms, it is construed as a useful tool (Gibson & Tantam 2018, Scarinci et al. 2018, Cann et al. 2008; Querini & Lubrani 2009, Abel 2002, Martin & Lefcourt 1983, Arieti 1976).

Ventis (2001) suggests its use as stand-alone technique to desensitize when treating phobias; Prerost suggests the Humorous Imagery Situation Technique (HIST; Prerost 1994), useful to reduce anxious symptoms in averagely depressed patients (Ciera et al. 2015). Although these studies are promising, it is hard to employ humour as a stand-alone technique. Research on its efficacy highlight a positive correlation between humour and effectiveness, both in the therapist and in patients, although severe patients report a lower level of subjective perception (Ponchielli 2018). In conclusion, it is essential to analyse in depth the use of humour in therapeutic relations, the only feasible path in a psychotherapeutic context.

The Five Uses of Positive Humour

Humour in clinical use (metaphor, narrations, film production, therapist's self-derision, jokes or gags and imaginative techniques), (Scarinci 2018, Taber et al. 2011, Fry 2001, Prerost 1994) is precious: during the assessment phase; to build/monitor the therapeutic alliance; for cognitive development, emotional adjustment and as a model.

During the assessment phase, it is important to observe if and how the patient adds light elements to the narration, showing his level of insight and the use of more mature defence mechanisms (Chaloult & Blondeau 2017). During the second session, a patient expresses her insight through this gag: "I am constantly unhappy. I should have been a poet... The Leopardi of the South." It is essential to understand the personal, ethnic and religious characteristics, as well as the attachment quality. An insecure attachment leads the patient to appreciate humour less, and to use it less as a stress management and interpersonal distance adjustment strategy. A negative vision of oneself and of the other person, perceived as distant, unpredictable or hostile requires particular caution. People with an insecure attachment are least likely to resort to an affiliative

style, favouring maladaptive behaviours (Cann et al. 2008). Kelly (1955) suggested the use of a dedicated assessment tool: a type of self-characterization where the patient has to write a "humorous sketch", as if they were the character of a comedy. Self-characterization is a tool to assess the patient's personality, affective and relational aspects, and central topics, whose analysis can be performed "along three structural dimensions: focused contexts, storytelling and content" (Scarinci 2018), causing the topics the patient is willing to joke about to emerge. It is essential to preserve the primary topic of personal suffering and anything related to it (Chaloult & Blondeau 2017).

To build and preserve the therapeutic alliance, it helps the patient perceive a greater emphatic connection, it fosters a shared construction of the issue, and it may highlight ambivalent requests. "Psychotherapy as a relationship is unique, and the methods by which they build intimacy in the therapeutic alliance are generally different from the methods by which they build intimacy in other types of relationships. Although humour is present in both personal and clinical relationships, its use in therapy is selective and for the benefit to the client" (Sultanoff 2013).

Let us analyse the following case

During the first session with A., the therapist finds out he has already had a first session with five other therapists. Believing that A.'s behaviour needs to be furthered explored, the therapist tries to probe around, asking what did not go well with the previous first sessions. A. tells her he did not like the other therapists, and that, in any case, he "has trust issues". The therapist notices how painful A.'s emotional position is: his need to get help and the impossibility to get it; she decides to use a joke, and, pretending to stroke an imaginary beard, she says: "You and I, Mr. A, are in serious trouble!" The joke, accompanied by a big smile, throws him off for a few seconds; then his face lights up, and he smiles back heartily, asking the therapist, "What can we do?". The use of plural is the first hint of cooperation and parity in building a human and therapeutic alliance to define a shared goal and reach pain resolution.

In this context, humour created nearness, made the therapist accessible and authentic, and made the patient relax before the daunting task of opening up before a stranger (Chaloult & Blondeau 2017, Taber et al. 2011, Trenkle 2009, Martin 2007). The playful mode highlighted a nodal point of its use, returning it in a way that allowed content to overcome the patient's defence, creating a first hint of balanced therapeutic alliance, and conveying amiability. This movement regulates distance, transference and balance between the primary and the secondary process (Fabian 2017).

The third contribution is the development of new perspectives and standpoints, and the improvement of the problem solving ability and of creativity. Humour is useful to explain both some therapeutic passages and the

way things work to the patient, preventing the boredom of “persistent repetition of concepts and explanations”, and to foster recollection (Ellis 1976).

To this end, let us see G. 's case

G is a young woman with anxiety issues that cause her to vomit before going to work. With this patient, it was hard to share a working assumption, because she simply wants to be freed from her anxiety, without having to give up the idea of “I have to do everything right, or other people will judge me for it”, so she thinks she can't ever fail. Her attitude toward others is absolutely not judgemental. G. struggles to accept that this dysfunctional idea may be the source of her malaise, and does not understand the negative implications of her way of thinking. Then, the therapist tells a funny story to explain her patient's standpoint: the Mother Superior of a convent meets the nun in charge of cooking, and praises a dish, calling it a “great dish”, but when the nun tells her the plate is for her, the Mother Superior says, “What? This little thing?” If told with the right gestures, the story is light and funny. G. laughs: “You are right, it is me, the other way around. I'm just like that!”

The fourth use involves affect regulation (Chaloult & Blondeau 2017, Scarinci et al. 2018, Gelkopf & Kreidler 1996). In the REBT (Rational Emotional Behaviour Therapy), humour helps restructuring dysfunctional and catastrophic contents, and the negative implications on the personal value - REBT's goal (Ellis 1976) - to show new ways to react to activating situations. The last aspect involves the positive reinforcement value that the therapist can portray by acting as a model and reinforcing an attitude with a light vision of life.

Ventis (1987) warns us to “remember that the use of humour and laughter in therapy is not a goal in itself, but one option for facilitating therapy”, making it clear that it must be applied according to the same principles that guide all therapeutic interventions (Gibson & Tantom 2018, Richman 2001, Dimmer et al. 1990), based on the therapeutic stage, the type of topic discussed, the needs and the level of emotional understanding of the patient.

Negative Humour

Just like many other therapeutic interventions, humour can have negative effects and pose some risks (Haig 1986), when it is used to humiliate or diminish self-esteem, and attack the patient's intelligence and well-being (Chaloult & Blondeau 2017, Franzini 2001, Kubie 1971). It is contraindicated: in those patients that have suffered humiliation, intimidation or who can feel diminished; those patients with paranoid or narcissistic traits (Salameh 1987); in those cases when it is ill-suffered by the patient or the therapist (Martin et al. 2003); if it prevents awareness (Kubie 1971) or if it is premature with respect to the therapeutic progress, alliance and patient's insight capacity. In therapists, it affects the “required confidentiality” (Kubie 1971) and

it can hide conscious or unconscious negative counter-transference emotions, breaking the therapeutic alliance and triggering a paranoid or distancing reaction (Chaloult & Blondeau 2017, Fabian 2017, Salameh 1987).

Let us review R. 's case

R, 65 years old, is in therapy for anxiety and depression. His obsessive, narcissistic and controlling behaviour make him a very complicated patient, who struggles to emotionally connect to other people, who only receive his reprimands or complaints. One day, the therapist breaks her foot, and shows up at the office in a cast. R., who usually waits for her in the parking lot to start the session right away, looks unhappy not to find her in her usual place, and loquaciously tells her how impolite this is. Without giving importance to his interlocutor's conditions, he starts complaining. While the therapist struggles between the crutches, her purse, her keys, one of her crutches falls. The sound interrupts R., who, angered, brings his hand to his sides, “Can you reach it yourself... You know...” The therapist, visibly annoyed, stops him, sarcastic: “Sure! Don't worry... I wouldn't want you to hurt your back.” This sarcastic and aggressive comment breaks the therapeutic alliance, which must be re-discussed in session (Martin et al. 2003).

A joke is negative when it is not relevant to the therapeutic goal (Pierce 1994), when it is excessive (Ellis 1976), when it only rewards the therapist in a narcissistic way (Chaloult & Blondeau 2017, Schneider et al. 2018) or when it is a mutual form of captatio benevolentie. It must not be used to shift the focus from unpleasant topics and emotions, to prove that the therapist or the therapy is “not dangerous” (Pierce 1994). The illusion created by humour hides the lack of therapy.

Let us review M. 's case

M. is a patient with Binge Eating Disorder, Class 2 obesity, sent to therapy by the dietician, because he does not comply with the diet; he proves to be friendly and cooperating, right from the start. Once therapy starts, the therapist realizes the she often feels gratified, but the patient does not make any progress. In supervision, she realizes M. and her are “indulging” each other in an illusion, maintained by the use of humour as shield to avoid tackling any emotional topic. When she understands this mechanism, the therapist takes the lead again. Laughing can be a way to flee from pain, to mask the issues, a seductive mode that bridges the gap with the therapist.

Let us review G. 's case

G. is an intelligent and experienced man, proud of his career, in therapy for Pathological Gambling. He has two sides: on one side, he is a valid and skilled man, and on the other side, he is an out-of-control person, who gambles in the most run-down places, Dr. Jekyll and Mr. Hyde. His fabling skills are disruptive and make the sessions lighter. Often, when they reach a topic that is

too emotionally daunting, G. finds a way to add a joke or a story, something that slows progress down to avoid tackling the difficult core. This aspect has been discussed during therapy. Turning the emotional axis upside down places back the patient in a safe area, and “neutralizes” the therapist, seducing him with positive emotional aspects to maintain G.'s false split ego, and, at the same time, portraying his impossibility to change.

It is the opinion of this author that keeping personal traits out of therapy is like tending for a bee (something notoriously impossible!). And so, laughter, jokes and gags have become part of the way I do therapy. Out of this came the decision and the obligation to further analyse its use, because, if the idea of doing therapy while having fun is fascinating, the need to explore and improve the use of this technique in the therapeutic style is absolutely essential.

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EATING DISORDERS: THE ROLE OF CHILDHOOD TRAUMA AND THE EMOTION DYSREGULATION

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SUMMARY

Background: The present retrospective case-control study is aimed at evaluating the presence of childhood traumatic factors and the difficulty in regulating emotions, within a sample of patients with eating disorders compared to the group of healthy controls.

Subjects and methods: We included 65 people assessed for eating disorders, 40 patients and 25 healthy controls, who were given two tests: the Childhood Trauma Questionnaire-Short Form (CTQ-SF) to investigate the presence of traumatic events and the Difficulties in Emotion Regulation Scale (DERS) to assess the emotional regulation.

Results: People with eating disorders showed higher average scores, and therefore greater severity than the control group, in all the domains explored, both considering traumatic experiences and emotional dysregulation. The domain emotional neglect showed the closest correlation with eating disorders (average scoring 15.9 vs 9.9 of healthy controls), followed by emotional abuse (12.2 vs 7.8), physical neglect (8.2 vs 6.6), physical abuse (8.3 vs 6.6) and sexual abuse (7.2 vs 5.6). In the same way, the emotional dysregulation was greater among people with eating disorder than healthy controls, concerning every items explored by DERS, as clarity (average scoring 14.8 vs 11.4), awareness (17.1 vs 11.7), goals (16.3 vs 12.9), strategy (22.0 vs 14.7), non acceptance (17.4 vs 12.1) and impulse (16.5 vs 11.4).

Conclusions: Childhood traumatic experiences and emotional dysregulation result significantly higher in people with eating disorders than healthy controls.

Key words: eating disorders - childhood trauma - emotional dysregulation

* * * * *

INTRODUCTION

Eating disorders (ED) are a group of heterogeneous clinical conditions, characterized by an altered food intake that results in an impairment of psychological or physical health. The major clinical entities classified within the DSM V are Anorexia Nervosa (AN), Bulimia Nervosa (BN), Binge Eating Disorder (BED), and Not Otherwise specified Eating Disorder (NOSFED) (APA 2013). ED would be an expression of dysfunctional individual and relational patterns, supported by emotional and behavioral dysregulation (Cimbolli et al. 2017). Moreover, childhood trauma is associated with a high level of emotional dysregulation, dissociation and behavioural problems. Dissociation can be seen as a failed regulatory strategy, used to cope with emotions, which exceed the resistance skills of a person. A "traumatic event" is a stressful event, which is stronger than individual resistance (van der Kolk 1996). The relationship between psychological trauma and eating disorders has been investigated by clinicians and researchers, who observed a higher rate of traumatic history in individuals with eating disorders than the general population (Brewerton 2007). Typical behaviours of eating disorders (for example severe food restriction, binge eating, elimination behaviours) are aimed at escape and avoidance cognitions and emotions related to the trauma, thus promoting maintenance of the eating disorder and symptoms related to trauma. The

association between other serious adverse experiences (for example, emotional abuse in childhood) and psychopathology of eating disorders has also been investigated (Trottier & MacDonald 2017). Specifically, child sexual abuse (CSA) could be a strong predictor of development of eating disorders such as bulimia or binge eating symptoms. Patients with ED may often have superimposed symptoms such as anxiety, depression and post-traumatic stress disorder. In particular, some characteristic symptoms of PTSD can also be found in patients with eating disorders. Behaviours such as purging, could be a manifestation of dissociation, to avoid or regulate symptoms resulting from a post-traumatic stress disorder. In other words, the maintenance of atypical eating behaviours could be the expression of a maladaptive response related to a previous trauma. Therefore, physical and sexual abuse in children increases the likelihood of an eating disorder, which can promote the onset of mental disorders (Armor et al. 2016).

SUBJECTS AND METHOD

The present sample consists of sixty-five patients, recruited from the psychiatric hospital clinic and other eating disorders centres in the area, evaluated to investigate the presence of EDs. Specific tests have been administered for eating disorders, such as Eating Attitude Test (EAT), Bulimia Test - Revised (BULIT-R),

Binge Eating Disorder (BES) and, later, Childhood Trauma Questionnaire-Short Form (CTQ-SF) and Difficulties Emotion Regulation Scale (DERS) to investigate the presence of traumatic experiences in childhood and the difficulty in regulating emotions, respectively. CTQ-SF consists of 28 items, exploring five different traumatic domains, such as Emotional abuse, Physical abuse, Sexual abuse, Emotional neglect and Physical neglect. Instead, DERS consists of 36 multiple choice items, containing six evaluation subscales (Non acceptance, Goals, Impulse, Awareness, Strategies, Clarity). The socio-demographic and clinical characteristics of the subjects were then analysed by using descriptive statistical analysis and the average score differences between the affected subjects and the healthy control group by using the Student's t-test, considering significant test results with $p < 0.05$.

RESULTS

The sample was composed by sixty-five subjects, nine males and fifty-six females, with an average age of 39.3 years. 40 people were affected by ED and 25 people were not affected. The most frequent ED diagnosis was BED, followed by NOSFED (Table 1).

Table 1. Diagnosis distribution of Eating Disorders

	Subjects	Percentage
Binge Eating Disorder (BED)	17	42.5%
Not Otherwise Specified	15	37.5%
Eating Disorder (NOSFED)		
Anorexia nervosa (AN)	6	15.0%
Bulimia nervosa (BN)	2	5.0%
<i>Total</i>	<i>40</i>	<i>100.0%</i>

The analysis of average score differences between Eating Disorders (ED) and Healthy Controls (HC) showed more severe childhood traumatic experiences in the first group than in the second one. The difference was statistically significant in the items emotive abuse and emotive neglect (Table 2).

Table 2. CTQ-SF average score differences between Eating Disorders (ED) and Healthy Controls (HC)

	ED	HC	p value
Emotive Abuse	12.2	7.8	$p < 0.05$
Physical Abuse	8.3	6.6	
Sexual Abuse	7.2	5.6	
Physical Neglect	8.2	6.6	
Emotive Neglect	15.9	9.9	$p < 0.05$

In the same way, difficulties in emotion regulation was significantly greater for patients with Eating Disorders (ED) than Healthy Controls (HC), concerning every item explored by DERS test (Table 3).

Table 3. DERS average score differences between Eating Disorders (ED) and Healthy Controls (HC)

	ED	HC	p value
Summary	104.1	74.6	$p < 0.05$
Non acceptance	17.3	12.1	$p < 0.05$
Goals	16.3	12.9	$p < 0.05$
Impulse	16.4	11.3	$p < 0.05$
Awareness	17.1	11.7	$p < 0.05$
Strategy	22.0	14.7	$p < 0.05$
Clarity	14.9	11.4	$p < 0.05$

DISCUSSION

The presence of traumatic childhood experiences was significantly greater in the group of subjects suffering from eating disorders than in the control group; in particular every domain explored by CTQ-SF showed a higher average score in the group of affected subjects. These results appear substantially in agreement with several evidences in the literature. Tagay (2014) showed that in a sample of patients with eating disorders, potential traumatic events were present in almost all cases. Other studies state that the probability of developing an eating disorder is more than three times greater for people who have suffered any kind of child abuse than the general population; BED and BN seem to have a stronger association with childhood traumatic experiences than other EDs (Caslini et al. 2015). There is still limited evidence regarding the individual types of abuse in relation to specific eating disorders, however, AN and BN would seem to be more related to emotional abuse than other types of abuse (Molendijk et al. 2017). Furthermore, several studies confirm that child sexual abuse and child physical abuse, are configured as risk factors for the development of eating disorders (Moulton et al. 2015). Difficulties in regulating emotions are also related to eating disorders (Fox & Power 2009); there is evidence in the literature that disorganized eating behaviours can be configured as attempts to deal with negative emotions (Cooper et al. 2004, Corstorphine et al. 2006). Some evidences have shown that emotional dysregulation can follow traumatic events and become the link between them and eating disorders, resulting in anger, dissociative experiences, impulsiveness and compulsiveness (Burns et al. 2012, Trottier & MacDonald 2017). This study has several limitations, due, for example, to the low sample size and to the analysis of eating disorders as a whole. However, in agreement with several scientific evidences, we can retrospectively state that people suffering from eating disorders show traumatic experiences and emotional dysregulation rates, significantly higher than healthy controls.

CONCLUSIONS

Childhood traumatic events and difficulties in regulating emotions are configured as risk factors for

development of eating disorders. Given the frequency and involvement of increasingly younger patients in eating disorders, it seems necessary to continue studying, more specifically, the relationship between childhood traumatic experiences, emotional dysregulation and eating disorders on larger samples.

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Contribution of individual authors:

Filippo Brustenghi, Francesca Alice Fiore Mezzetti, Cristina Di Sarno, Cecilia Giulietti & Patrizia Moretti wrote the first draft of the manuscript.

Filippo Brustenghi & Cecilia Giulietti wrote substantial part of the introduction.

Filippo Brustenghi & Francesca Alice Fiore Mezzetti wrote substantial part of methods.

Filippo Brustenghi, Cristina Di Sarno & Cecilia Giulietti wrote substantial part of results.

Filippo Brustenghi & Cecilia Giulietti discussed results.

Patrizia Moretti & Alfonso Tortorella corrected the first draft of the manuscript.

Patrizia Moretti supervised all phases of the study design and writing of the manuscript.

Filippo Brustenghi, Francesca Alice Fiore Mezzetti, Cristina Di Sarno, Cecilia Giulietti & Patrizia Moretti supervised the writing of the manuscript.

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DYSPHORIA DIMENSIONAL MODEL FOR FEEDING AND EATING DISORDERS: A PRELIMINARY STUDY

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SUMMARY

Background: Anorexia Nervosa (AN), Bulimia Nervosa (BN) and Binge Eating Disorder (BED) are severe psychiatric illnesses which represent the main expression of Feeding and Eating Disorders (FED). Clinicians agree that emotional and behavioural dysregulation play a crucial role in FED. Dysphoria could help us to better understand these components. Indeed, we define dysphoria as a generic state of dissatisfaction and emotional instability, without any specific features. Among the multitude of symptoms, we find that irritability, discontent, interpersonal resentment and surrender prevail. These dimensions correspond to the four subscales of Neapean Dysphoria Scale - Italian version (NDS-I). Dysphoria role in FED has not yet been investigated. Using this test, we can characterize dysphoria both in quantitative and qualitative terms. Accordingly, domain evaluation could discriminate these disorders allowing us to assess possible differential phenomenological expressions.

Aims: The aim of this paper is to understand in which way the dimensional spectrum that composes dysphoria differs between Anorexia Nervosa, Bulimia Nervosa and Binge Eating Disorders through an observational comparative study.

Subjects and methods: The enrolled sample (30 patients) is represented by patients with a history of FED (AN, BN or BED). Patients were males and females between the ages of 13 and 45 with a good knowledge of Italian language. Patients with severe cognitive impairment (MMSE <19) and civil incapacitation were excluded. Patients were recruited from the Psychiatric Service of the Santa Maria della Misericordia Hospital in Perugia (PG), and other residential and semi residential structures specialized in FED treatment (FED specialized center at Palazzo Francisci in Todi (PG), Nido delle Rondini in Todi (PG), BED (Binge Eating Disorders) center in Città della Pieve (PG) and ambulatory services for FED in Umbertide (PG)). We administered them the Neapean Dysphoria Scale - Italian Version (NDS-I), a specific dimensional test for dysphoria. Starting from the dataset, with the aid of the statistical program SPSS 20, we have carried out a comparison between disorders groups selected and NDS-I total score and subscales (irritability, discontent, interpersonal resentment, surrender). For this we have used the Mann-Whitney U test, a nonparametric test with 2 independent samples, by setting a significance level $p < 0.05$.

Conclusions: This study allowed us to better understand and characterize the most common Eating Disorders. Beyond that, despite the small sample size, we found in our analysis statistically significant difference in the expression of various dysphoria dimension spectrum inside our 3 groups.

Key words: dysphoria - anorexia nervosa - bulimia nervosa - binge eating disorder- NDS-I

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INTRODUCTION

Anorexia Nervosa (AN), Bulimia Nervosa (BN) and Binge Eating Disorder (BED) are severe psychiatric illnesses which represent the main expression of Feeding and Eating Disorders (FED).

These affect 13% of girls and women and are marked by chronicity, relapse, distress and functional impairment (Stice et al. 2019). In AN, BN and BED there is a persistent alteration of eating behaviour, such as restricted intake in AN or bingeing and purging (f.e. self-induced vomiting and/or abuse of laxatives, diuretics and physical hyperactivity or extreme dieting), as well as excessive concerns about body shape and body weight (Gravina et al. 2018). About that we can differentiate BN from BED because in the first one binge eating is accompanied by a loss of control, over eating and attempts to prevent weight gain (Kaltiala-Heino et al. 2003).

Clinicians agree that emotional and behavioural dysregulation play a crucial role in FED (Cimballi et al. 2017). In this regard, it is widely documented that emo-

tion regulation difficulties influence the etiology and maintenance of FED (Racine et al. 2018). Emotion dysregulation across multiple dimensions is common to AN, BN and BED but there are important limitations of existing research: reliance on self-report, small/widely varying samples and few longitudinal studies (Jason et al. 2015). To better investigate these eating disorders, we can focus on the possible affective comorbidities found, such as bipolar disorder, depression, anxiety and personality disorder.

Many factors impact on the course of FED, and among these, personality characteristics play a key role. Personality disorders are highly common in patients with FED, with a prevalence of cluster C in AN, cluster B in BN and BED (Rotella et al. 2016). In support of this, the perfectionism, a central feature of DOC, is a fundamental cognitive process also in AN (Levison et al. 2018). The subject establishes strict rules of conduct that aim to achieve an ideal body weight. In this way, he builds self-confidence, therefore we find traits of narcissistic personality too (Barajas-Iglesias et al.

2017). While in AN there is an over-controlled personality and cognitive rigidity, in BN and BED we have typical features of the borderline personality as impulsiveness and affective lability. Patient with BN is pervaded by instability and psychomotor activation that find the culmination in the binge episode. Initially it is relieved, then it is followed by a sense of guilt and self-depreciation and the implementation of compensatory behaviour (Thibeaut et al. 2018). In BED, there is a condition of pure discontrol; impulsivity seems to be a predictive factor for the development of overweight and obesity (Gaudio et al. 2017).

The knowledge of temperamental traits and of their relationship with specific ED is relevant for the design of specifically targeted intervention (Rotella et al. 2017).

Dysphoria could help us to better understand FED. Indeed, we define dysphoria as a generic state of dissatisfaction and emotional instability, without any specific features. It's generally considered a temperamental trait, but its phenomenological expression is in response to environmental stimuli (D'Agostino et al. 2016). Alongside this general description, dysphoria can be distinguished in three specific dimensional components: tension, irritability and urge. Tension is a condition of strong emotional pressure, chronic unhappiness and discontent which leads the subject to surrender. Irritability refers to a state of a constant and annoying restlessness, worry and anxiety. The subject is suspicious and hostile towards people around him. Finally, urge is characterized by impatience and intolerance, by an irresistible need to act, with often self-harm behaviours. Action is violent in the sense of the intensive emotions that invest the subject (Moretti et al. 2018). Among the multitude of symptoms, we find irritability, discontent, interpersonal resentment and surrender prevail. These dimensions correspond to the four subscales of Neapen Dysphoria Scale - Italian version (NDS-I). Dysphoria role in FED has not yet been investigated. Using this test, we can characterize dysphoria both in quantitative and qualitative terms. Accordingly, domain evaluation could discriminate these disorders allowing us to assess possible differential phenomenological expressions. The aim of this paper is to understand in which way the dimensional spectrum that composes dysphoria differs between Anorexia Nervosa, Bulimia Nervosa and Binge Eating Disorders through an observational comparative study.

SUBJECTS AND METHODS

Subjects

In the present prospective study, have been enrolled patients (30 patients) with an history of FED (AN, BN or BED). Patients were males and females between the ages of 13 and 45 with a good knowledge of Italian language. Patients with severe cognitive impairment (MMSE <19) and civil incapacitation were excluded. They were recruited from the Psychiatric Service of the Santa Maria della Misericordia Hospital in Perugia (PG),

Umbria, Italy, and other residential and semiresidential structures specialized in FED treatment of our region (FED specialized center at Palazzo Francisci in Todi (PG), Nido delle Rondini in Todi (PG), BED (Binge Eating Disorders) center in Città della Pieve (PG) and ambulatory services for FED in Umbertide (PG)). All selected patients signed their informed consent prior to inclusion in the study.

We present preliminary data because our study is still in progress; we are recruiting patients with the objective of collecting at least 100 of them. Our aim is also to re-administer the test one month after the first evaluation.

Methods

All patients had administered the Neapen Dysphoria Scale – Italian Version (NDS-I), a specific dimensional test for dysphoria (D'Agostino et al. 2016). This psychometric test indicates not "how much" but "how" the subject is dysphoric (Moretti et al. 2018). We can use it thanks to D'Agostino and his working group, who translated it from the homonymous NDS introduced in Australia by Starcevis (Starcevis et al. 2007). This auto-administrated test consists of 24 items in Likert scale from 0 to 4. At the end of the test is possible to obtain a specific Total Score which gives a rough assessment of the degree of dysphoria and other 4 additional scores which represent the dimensional subscales of dysphoria. These are irritability, discontent, interpersonal resentment, renunciation/surrender. The test hasn't any cut-off because it represents a dimensional, non-nosographic tool.

Starting from the dataset, with the aid of the statistical program SPSS 20 (Statistical Package for Social Sciences), we have carried out a comparison between disorders groups selected and NDS-I total score and subscales. For this we have used the Mann-Whitney U test, a nonparametric test with 2 independent samples, by setting a significance level $p < 0.05$.

Statistical analyses

Patients enrolled in the study were 30, divided in 3 groups of 10: Anorexia Nervosa, Bulimia Nervosa and Binge Eating Disorder. All of them gave an informed consent according to the current EU regulations on privacy through an information talk and related. After that, we instructed patients about the correct compilation of the test and we administrated NDS-I. Finally, we collected the data in a specific database and we started our analysis. Just because is a preliminary study with only 30 patients, we decided to avoid the division by gender by considering males and female in the same way. Starting from the dataset, by using the statistical program SPSS 20, we have obtained graphs showing the comparison between disorders groups and NDS-I total score and subscales. In order to provide a quantitative imprint, we have calculated arithmetic means of each

subscale for each group of patients. The comparison between groups has been possible by considering two groups at time: we used the U Mann-Whitney test, a nonparametric test with 2 independent samples, by setting a significance level $p < 0.05$.

RESULTS

Analyzing the graphs obtained we tried to put in evidence, both for the total score and for the subscales, some differential dimensional aspect.

In Table 1 we can see that there aren't significant differences between NDS Total Score and NDS subscales if we compare patients with AN and BN by using Mann-Whitney U test Anorexia vs Bulimia with a significance level $p < 0.05$.

In Table 2 instead, comparing the scores between AN and BED patients, we find that the NDS-I Interpersonal Resentment Subscale Score is higher in BED patients with a statistically significant difference ($p = 0.022$). The data was obtained with the Mann-Whitney U test (Anorexia vs BED) with a significance level $p < 0.05$. There aren't any other significant data in the differences between the two groups.

In Table 3, comparing BN and BED patients, some difference can be remarked: NDS-I total score is higher in BED patients with statistically significant differences ($p = 0.038$).

On the other hand, the difference between the total scores means of the two groups shows no significant differences ($p > 0.05$).

In Table 4 we have translated in numerical language the differences between groups. The arithmetic mean of the total score on the NDS-I test and the related subscales, show what we have previously expressed: BED

patients have a greater level of dysphoria and an interpersonal resentment major than others in a meaningful way.

We can represent by graphs the analysis of the data to highlight some differential dimensional aspects (Figure 1, 2, 3, 4, 5).

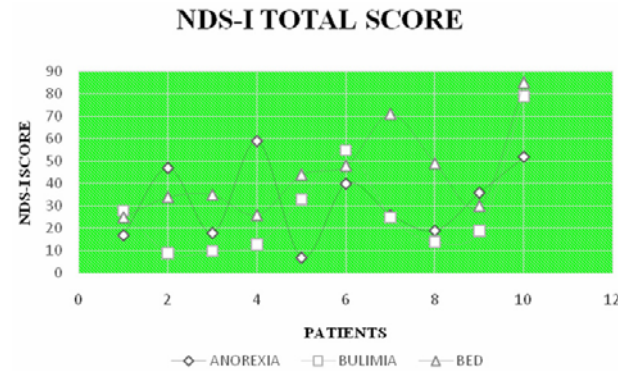


Figure 1. Comparison between groups of patients and the NDS-I total score

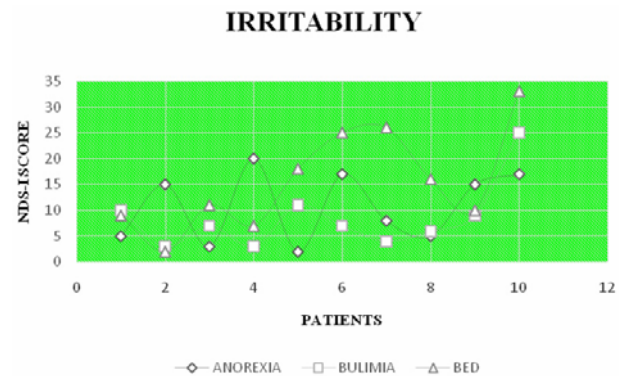


Figure 2. Comparison between groups of patients and the NDS-I Irritability Subscale Score

Table 1. Statistical comparison between AN and BN total scores and subscale scores

	NDS-I Total Score	NDS-I Irritability	NDS-I Discontent	NDS-I Interpersonal Resentment	NDS-I Surrender
U di Mann-Whitney	40,500	42,000	49,000	45,500	31,000
Sig. Asint. 2 tails	0.473	0.544	0.939	0.731	0.149

Notes: NDS = Nepean Dysphoria Scale-Italian Version

Table 2. Statistical comparison between AN and BED total scores and subscale scores

	NDS-I Total Score	NDS-I Irritability	NDS-I Discontent	NDS-I Interpersonal Resentment	NDS-I Surrender
U di Mann-Whitney	33,500	34,500	29,000	20,000	44,000
Sig. Asint. 2 tails	0.212	0.241	0.111	0.022	0.648

Notes: NDS = Nepean Dysphoria Scale-Italian Version

Table 3. Statistical comparison between BN and BED total scores and subscale scores

	NDS-I Total Score	NDS-I Irritability	NDS-I Discontent	NDS-I Interpersonal Resentment	NDS-I Surrender
U di Mann-Whitney	22,500	25,000	35,500	25,500	33,000
Sig. Asint. 2 tails	0.038	0.058	0.271	0.063	0.198

Notes: NDS = Nepean Dysphoria Scale-Italian Version

Table 4. Arithmetic mean of the total score on the NDS-I test and the related subscales for the 3 study groups

	Anorexia	Bulimia	Bed
NDS-I Total Score Mean	31.1	28.5	44.7
Irritability Score Mean	10.7	8.5	15.7
Discontent Score Mean	8.6	9.9	13.3
Interpersonal Resentment Score Mean	4.2	4.8	8.3
Surrender Score Mean	7.9	5.4	7.4

Notes: NDS = Nepean Dysphoria Scale-Italian Version

DISCONTENT

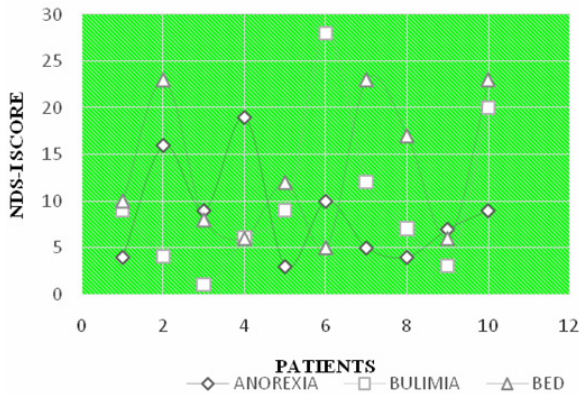


Figure 3. Comparison between groups of patients and the NDS-I Discontent Subscale Score

INTERPERSONAL RESENTMENT

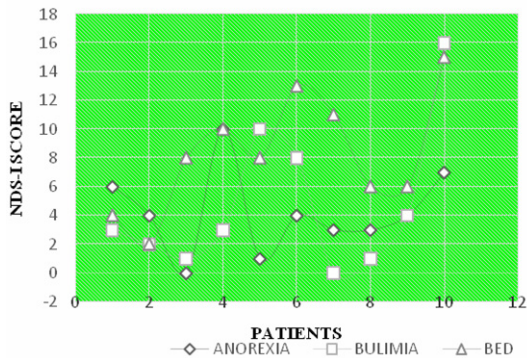


Figure 4. Comparison between groups of patients and the NDS-I Interpersonal Resentment Subscale Score

SURRENDER

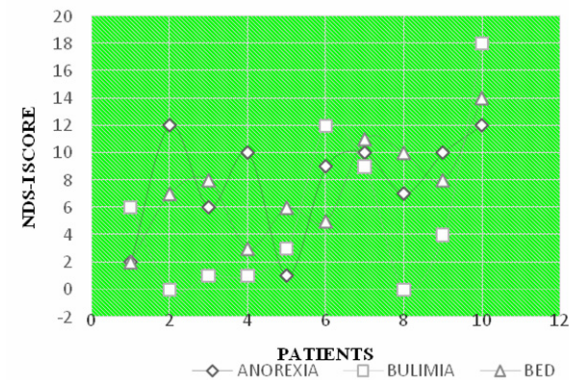


Figure 5. Comparison between groups of patients and the NDS-I Surrender Subscale Score

CONCLUSIONS

The present study, through a transeographic-dimensional approach, helps us to explore, despite the small sample, dysphoria and its expression. It allowed us to better understand and characterize the most common Eating Disorders. Between means of values obtained, some differences were statistically significant: in particular BED patients had a higher score of dysphoria and an interpersonal resentment greater than BN and AN patients. These differences, if confirmed by the increase in the sample size, could be good clinical indicators of differential diagnosis and longitudinal surveillance in order to capture possible relapses or transition from one category to another. We expect to enlarge the sample to confirm our results and provide to the clinicians a better instrument to perform early diagnoses and intervention.

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Contribution of individual authors:

Roberta Lanzi, Massimo Claudio Bachetti & Patrizia Moretti conceived and designed the study.

Roberta Lanzi wrote the first draft of the manuscript.

Roberta Lanzi & Massimo Claudio Bachetti performed statistical analyses.

Roberta Lanzi, Cecilia Giulietti & Margherita Rosi visited patients and carried out clinical work.

Patrizia Moretti & Alfonso Tortorella supervised all phases of the study. All authors approved the final version of the manuscript.

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INFULENCE OF SEX HORMONES AND INFLAMMATORY PROCESSES ON COGNITION IN SCHIZOPHRENIA

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SUMMARY

Background: In the literature we can find evidence that sex hormones are involved the alterations of cognition in schizophrenic patients. Another factor, which may have an impact on cognitive domains in this clinical group inflammatory processes.

The objective of this review was to explore studies, in which the role of both immunological factors and sex hormones on cognitive functions in schizophrenia are analyzed.

Methods: The search of papers covering this topic in PubMed and Google Scholar was performed.

Results: Endocrine factors like: testosterone, estrogen, as well as immunomodulatory are observed to play a role in cognitive functioning in schizophrenia.

Conclusions: More studies are necessary to confirm these possible co-relations.

Key words: immunological processes - sex hormones - cognitive functions - schizophrenia

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INTRODUCTION

Cognitive deficits in schizophrenia are important symptoms, which may be mild to moderate and are mostly related to negative symptoms (Keefe et al. 2006). There are different factors which may have an influence on neuropsychological functioning by schizophrenic patients. One of them is medication. According to a number of studies atypical antipsychotic drugs are regarded as being superior to the typical ones in terms of their impact on cognitive functions (Meltzer and McGurk 1999, Klasik et al. 2011). Another condition that may modify this domain in schizophrenia is drug abuse (Wobrock et al. 2013). In the literature we can also find reports focusing on the influence of serum hormone levels and cognitive functioning in schizophrenia (Bratek et al. 2015, Moore et al. 2013, Li et al. 2015). Yuan et al. (2016) in a study involving first episode schizophrenia patients found that testosterone and estradiol may protect cognitive function against recession. It is possible that some changes in sex hormone levels in men and women suffering from schizophrenia may lead to certain differences in cognitive functioning (Bozikas et al. 2010). The immunopathogenesis of schizophrenia was postulated already in the 90-ties (Holden et al. 1997). Since then a number of publications have appeared to support this hypothesis (Muller & Schwarz 2006, Na et al. 2014, Bedrossian et al. 2016, Dickerson et al. 2016, Karanikas 2011, Suvisaari & Mantere 2013). Levels of interleukins IL-2 and IL-4, IL-6 and other inflammatory markers were found to be increased of schizophrenic patients (Watanabe et al. 2008). The objective of this review was to explore studies, in which the role immunological and endocrine factors on cognitive functions in schizophrenia are analyzed.

METHODS

This review was focused on the impact of sex hormones and inflammatory processes on the cognitive functioning of schizophrenic patients. In order to achieve this result PubMed and Google scholar were searched (effective date 30.07.2019). During our search we used following terms: (cognitive functions (Title/Abstract) OR schizophrenia (Title/Abstract)) AND sex hormones (Title/ Abstract) OR inflammatory markers OR memory OR attention OR neuropsychological symptoms OR AND (humans (MeSH Terms) AND English (lang).

RESULTS

Sex hormones and cognitive functions in schizophrenia

A number of research results show, that there is a correlation between the levels of sex hormones and the cognitive functioning in schizophrenic patients. According to Ko et al. (2006), there is an association between serum levels of estrogen and reduced performance in cognitive function, especially verbal performance and executive functioning in schizophrenic women of reproductive age. Yuan et al. (2016) observed that endogenous testosterone and estradiol are protective factors against the recession of cognitive functions in the first episode of schizophrenia. In another study, performed in the population of older female schizophrenic patients, it was found, that estrogen interacts with the dopaminergic system and in this way it affects cognition (Searles et al. 2018). In the study by Halari et al. (2004), which investigated the effects of serum levels of oestrogen, progesterone, testosterone and cortisol on neuropsychological functioning and psychopathology in schizophrenia

it was found that oestrogen and age was co-related with lower intensity of positive symptom scores, and in the analysis of differences between men and women, cortisol was associated with poor performance on information processing in men. Moore et al. (2013) analyzed the correlation between hormone levels (testosterone, estrogen, and prolactin), cognitive function and general symptoms of chronically ill male patients with schizophrenia or schizoaffective disorder. A correlation was found between circulating testosterone levels and the performance on verbal memory, processing speed, and working memory in examined subjects. Rubin et al. (2015) postulated that oxytocin, the level of which does not change during the menstrual cycle, may have a stronger positive impact on some cognitive domains than estrogens in schizophrenia. According to McGregor et al. (2017) the protective action of estrogens in schizophrenia, which affects also cognitive functioning, is correlated with the functional outcome of the disease. The results of the study by Gurvich et al. (2018) revealed that in females with schizophrenia, menstrual cycle irregularity predicted significantly poorer cognitive performance in the areas of psychomotor speed, verbal fluency and verbal memory.

Inflammatory markers and cognitive functions in schizophrenia

There is a group of research findings suggesting that inflammatory processes are associated with worse cognitive performance in schizophrenia. Possible mechanism of this process are: microglial activation, monoaminergic imbalance, brain abnormalities and the kynurenine pathway (Ribeiro-Santos et al. 2014). Negative associations between inflammatory markers and general cognitive abilities were found in the study by Hope et al. (2015). The role of peripheral inflammation might and cognitive deficits in schizophrenia and bipolar disorder were also discussed by Misiak et al. (2018). Kogan et al. (2018) found evidence that the increased inflammation is correlated with cognitive deficits and worse daily functioning in schizophrenic patients (Kogan et al. 2018). Dunne et al. (2017) found that the cytokines IL-10 and MDC are associated with the social cognition in schizophrenia. Bora et al. (2019) discussed the role of the elevated CRP and reduced BDNF levels in schizophrenia in the cognitive functioning in schizophrenia. According to the authors, due to small effect sizes of the observed correlations further studies are needed to confirm this phenomenon.

Implications for treatment

Clinical reports show benefits from augmenting anti-psychotic treatment with estrogens or selective estrogen receptor modulators. Different mechanism of action of these drugs are discussed (Bratek et al. 2016). Although literature data referring to the role of hormones and inflammatory markers is not very rich, we have obser-

vations that some hormones, like estrogen may have and anti-inflammatory effects, which may be advantageous in the treatment of cognitive deficits (Weickert et al. 2016).

CONCLUSIONS

Due to limited literature data the suggestions for the therapy of cognitive dysfunction in schizophrenia must be cautious and more research studies are necessary to confirm these possible co-relations.

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Contribution of individual authors:

Krzysztof Krysta; design of the review, literature researches and analyses, interpretation of data, manuscript writing.

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ROLE OF COPPER AND KETAMINE IN MAJOR DEPRESSIVE DISORDER - AN UPDATE

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SUMMARY

Major depressive disorder is one of the most important psychiatric issues worldwide, with important prevalence of treatment-resistant depression (TRD). Non-monoaminergic agents are currently in the spotlight. Objective was to explore for information about mechanisms of action of ketamine, its connections with copper and possible importance for TRD treatment. There are at least few possible pathways for ketamine action in depression in which copper and other divalent ions may show a vital role. There is urgent need for more studies to gather information about correlation between ketamine, copper and antidepressive features of these agents.

Key words: ketamine - copper - major depressive disorder - NMDA

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INTRODUCTION

Major depressive disorder (MDD) is one of the key public health problems worldwide. It has a negative influence of personal life, work life, education also sleeping, eating habits, and general health (Hasin et al. 2005). About one third of depressed patients experience treatment-resistant depression (TRD) despite broad use of monoaminergic antidepressants (Ionescu et al. 2015). The definition of TRD varies worldwide – some authors define TRD as failure in achieving remission with two or more adequate antidepressant trials (McIntyre et al. 2014). The number of patients not able to have good response to conventional treatment makes need of non-monoaminergic antidepressive agents of prime importance.

KETAMINE

Ketamine, which is commonly used to induce anesthesia, is a dissociative agent used in psychiatry to trigger a fast antidepressive and antisuicidal effects (Larkin et al. 2011). What is more, ketamine shows a rapid antidepressant effect in patients with TRD (Diamond et al. 2014). In view of increased response compared to traditional antidepressant treatment, ketamine seems to be an auspicious drug in TRD with prevalent pharmacodynamic effect of the N-methyl-D-aspartate receptor (NMDAR) antagonism. Ketamine promotes fast antidepressant effect - it starts within hours of administration and is mediated by alteration in glutamate transmission (Berman et al. 2000). However, there are more suggested mechanisms of action highlighted later in this paper. (S) – ketamine has a much greater affinity for the NMDAR, and (R) – ketamine has a greater opioid receptors affinity (Morgan et al. 2012). One of the first clinical studies on ketamine's

potential antidepressant effects was conducted over a decade ago. The study was double blinded, performed on eight patients during the depressive episode (seven suffering from MDD, one bipolar), randomized to receive either a subanesthetic dose of ketamine (0.5 mg/kg) or saline placebo. Four patients reported an antidepressant response to ketamine, evaluated a reduction of at least 50% on the Hamilton Depression Rating Scale (HAM-D) (Berman et al. 2000). Other researches iterated this ketamine-associated antidepressant reaction in clinical trials with single and repeated administrations under open-label, double-blind, placebo-controlled, and double-blind active comparator conditions via parallel arm or crossover treatment paradigms, but notably in treatment-resistant depression (Newport et al. 2015). Ketamine could be taken into consideration as the model glutamatergic agent, in particular because it is the best known and - to date - the most effective of the glutamatergic agents (Kishimoto et al. 2016). The molecular mechanisms underlying ketamine's antidepressant effects is being revealed by recent studies concerning the properties of ketamine and its metabolites (Lener et al. 2017).

COPPER

Copper (Cu) has been linked to mental disorders as for example autism and epilepsy. So far, researches measuring copper levels in patients' blood or hair with depressive disorder showed contrary results. To obtain a versatile approximation of the correspondence between body burden of copper and depressive disorder and examine the possible role of copper in mental health, there was a systematic review and meta-analysis performed. Gathered studies found that patients suffering from depression had higher blood levels of copper than the control group without depression (Ni et al. 2018).

NMDAR AND DIVALENT IONS

One of the most opulent ionotropic glutamate receptors in the human brain are the NMDARs (McBain et al. 1994). Binding the synthetic agonist NMDA, for instance glutamate, with the co-agonist glycine (Shleper et al. 2005) opens cation channel, which causes entry of calcium and sodium ions into the intracellular space. An excitatory postsynaptic potential could be induced by the activation of NMDAR by glutamate. Assembling evidence implies that the NMDAR has an important role in the treatment and neurobiology of major depressive disorder (Dang et al. 2014). Extracellular magnesium ions inhibit NMDARs, when negative membrane potential is attendant (Nowak et al. 1984). There are many elements such as magnesium and zinc ions, which are involved in the etiology of depression due to effect on biological pathways by modulating the NMDAR activity (Sowa-Kućma et al. 2013, Peters et al. 1987). Copper is another divalent ion having a major influence on NMDA receptor. It is reported to inhibiting NMDAR channels with the half maximal inhibitory concentration close to 20 mM. Although, the significance of values presented in the varied researches was rather wide and the molecular mechanism underlying inhibition of NMDAR activity is largely unclear (Trombley et al. 1996). Copper at doses >30mM prevalently blocks the NMDAR, however there are some studied that notifies that copper can facilitate this receptor at lower concentrations (Marchetti et al. 2014). This aspect may concern metal activity in synaptic and non-synaptic sites. The NMDARs undergo desensitization (Mayer et al. 1989) which leads to deplete toxic calcium over-extension of cells during intervals of prolonged glutamate raisings. High glycine concentration is neurotoxic as it essentially slows desensitization kinetics, namely blocking glycine reuptake increases NMDAR mediated neuronal excitability (Chen et al. 2003). Some authors divulged that NMDARs are likewise adjusted by cellular prion protein (PrP^C) (Khosravani et al. 2008, You et al. 2012).

COPPER AND PRP^C

PrP^C is a molecule which includes copper binding sites with fluctuates varying from the femtomolar to the micromolar range (Jackson et al. 2001). Transformation of PrP^C into the abnormal β -sheet-rich scrapie conformation (i.e. PrP^{Sc}) has been affiliated with prion diseases (Kingsbury et al. 1983). Changes in PrP^C conformation is induced by binding of copper ions (Wong et al. 2003). This fact may have significant consequences for the regulation of NMDARs and progress of depression. Lack of PrP^C in mice causes depressive-like behavior (Gadotti et al. 2012). It can be cured with the NMDAR antagonists, which suggests that the absence of PrP^C may enhance the receptor's activity. You et al.

(2012) suggested that chelation of copper ions adjusts native NMDARs in rat and mouse hippocampal neurons. What is more, glycine chelates of copper ions (Martin et al. 1971) by extension balance between agonist level and copper concentration is essential. Copper-dependent cooperation between the NMDAR subunit and PrP^C regulate receptor complex for glycine, conducting to non-desensitizing currents insignificant to glycine concentration (Ślupski et al. 2018). Nonetheless, it is essential to remember that higher levels of copper are also toxic on account of the generation of free radicals (Simpson et al. 1988). Copper inflects also AMPA-receptors, which are glutamate-gated cation channels that intercede the majority of fast central excitatory transmission (Weiser et al. 1996) and calcium channels (Jeong et al. 2003).

FOCUS ON GLUTAMATE PATHWAY

Acute stress multiplies extracellular glutamate in the medial prefrontal cortex (mviaPFC) and hippocampus, and this has conducted to the presumption that glutamate-mediated excitotoxicity through activities at extrasynaptic N-methyl-D-aspartate receptors (NMDARs) is accountable for the atrophy of neurons in these CNS parts (Popoli et al. 2011). However, ketamine is an NMDAR channel blocker, it causes a paradoxical erupt of glutamate in the rodent PFC (Moghaddam et al. 1997). Dose-dependent increases in glutamate cycling by increased glutamate signaling is assisted by MRS studies in rodents and humans (Chowdhury et al. 2017). Essentially, these studies explain that the burst of glutamate is exponential (within minutes) and evanescent, which is crucial to ration the excitotoxic effects of ketamine (Chowdhury et al. 2017, Moghaddam et al. 1997). The cellular trigger for this burst of glutamate is thought to involve blockade of NMDAR on tonic firing GABA interneurons, leading to disinhibition of glutamate transmission (Duman et al. 2016). Tonic activity of GABA interneurons would take into consideration removal of the Mg²⁺ block of the NMDAR channel, thus increasing vulnerability of these interneurons to ketamine occlusion in contrary to less active glutamate neurons. Recent slice electrophysiology studies show that ketamine incubation declines inhibitory postsynaptic currents (IPSCs) on hippocampal principle neurons, sustaining this theory (Widman and McMahan 2018). The muscarinic receptor antagonist scopolamine also causes rapid antidepressant actions in patient suffering from MDD. It is reliant on blockade of M1 receptors on GABAergic interneurons in the mPFC and disinhibition of glutamate transmission (Wohleb et al. 2016). Activity-dependent synapse formation is dependent on AMPAR activity, BDNF release, and stimulation of the mTORC1 signaling pathway, and it is caused by the ketamine-stimulated transient glutamate burst (Duman et al. 2016, Lepack et al. 2014, Li et al. 2010).

NMDA-INDEPENDENT MECHANISM OF ACTION

Another suggested pathway of ketamine action should be brought to light, as NMDA-independent action has been identified in animal study.

G_{α_s} plasma membrane redistribution induced by ketamine increased pairing of G_{α_s} and adenylyl cyclase and through this mechanism increased intracellular cyclic adenosine monophosphate (cAMP) (Czysz et al. 2014). Furthermore, enhanced intracellular cAMP increased phosphorylation of cAMP response element-binding protein (CREB), which respectively increased BDNF expression. Intracellular cAMP induced by ketamine remained increased even when NMDAR was not present, which indicates an NMDAR-independent effect (Wray et al. 2018). Besides, 10 μ M of the ketamine metabolite (2R,6R)-hydroxynorketamine (HNK) which has no affinity to NMDAR also induced G_{α_s} redistribution and increased cAMP. These results indicate a new mechanism of action in depression, mediated by acute ketamine treatment that may support ketamine's strong antidepressant effect. It seems that the translocation of G_{α_s} from lipid rafts is a plausible characteristic of antidepressant action that might contribute to further diagnosing process or for drug development (Zanos et al. 2016).

DISCUSSION

Focusing on ketamine seems to be even more vital issue as ketamine may become a basis for transformative treatment with powerful impact on stigma of depression and may serve as a first agent from entirely new class of antidepressants. This approach is based on the hypothesis that both efficacy and tolerability can be better preserved with selectively targeting elements of ketamine's effects (Krystal et al. 2019). Ketamine and copper are both antagonists of NMDA receptor. Copper interacts also with PrP^C pathway (Wong et al. 2003). The evidence deliberated may testify the synergistic interaction between copper and ketamine pharmacodynamic activity being of particular importance in mood disorders. During the observation of copper serum levels in patients treated with ketamine important information about connections between NMDAR antagonistic agents and trace elements antagonistic to that receptor may be provided. It is essential to carry out further investigations referred to copper and ketamine in pharmacotherapy of depression - copper levels may be associated with the therapeutic response to ketamine in TRD and copper supplementation may increase the response rates in depressed subjects.

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Jakub Słupski & Anita Słupska: manuscript writing, literature research, data analysis and interpretation.

Wiesław J. Cabała: design of the study, data analysis, manuscript redaction.

Łukasz P. Szałach, Adam Włodarczyk, Natalia Górską & Joanna Szarmach: literature research, data interpretation.

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EVOLUTION OF RELIGIOUS TOPICS IN SCHIZOPHRENIA IN 80 YEARS PERIOD

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SUMMARY

Background: Environment and culture are shown to be an important factor influencing characteristics of psychotic symptoms. Content of hallucinations and delusions is a projection of internal processes on external world. Religion plays a central role to lives of many people, but in schizophrenia religious experience and spirituality is confounded by psychotic symptoms. The aim of this study was to find how content of hallucinations and delusions interact with cultural conditions, that were changing over the decades.

Subjects and methods: 100 of case histories from 2012 were randomly selected. From the medical record, content of hallucinations and delusion was extracted and categorized. Data from 2012 was compared with previous study by the authors, obtaining perspective of 80 years of history in the one hospital.

Results: Religious content of delusions and hallucinations appeared in 26% of patients. Diversity of the religious and spiritual themes in schizophrenia has been gradually decreasing. Many minor religious entities and figures such as "saints" and "angels" disappeared in 2012. Although, occurrence of contact with God and other religious figures was similar as in previous years, number of "visions" abruptly decreased. All of the religious content was culture-specific.

Conclusions: Religious topics express general plasticity over a time, following cultural changes in society.

Key words: schizophrenia - auditory hallucinations - delusions - religious topics

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INTRODUCTION

Entanglement of religion, spirituality and psychotic symptoms is neither rare nor easy clinical issue (Mohr & Pfeifer 2009, Walker 1991, Menezes & Mereira-Almeida 2010). Religious phenomenology is an area of human existence, which is inaccessible to scientific methods, based on experiment, intersubjectivity and possibility of falsification. Experiencing religion is radically subjective and individual. Beliefs are often rigid and, by definition, unprovable.

Although, knowledge about underlying neurobiological causes of schizophrenia is increasing and biochemistry of the brain became susceptible to pharmacological treatment, there is still an explanatory gap between neuroscience and phenomenology of the patients (Mishara & Fusar-Poli 2013). Karl Jaspers, the founding father of phenomenological approach in psychiatry, differentiated in delusion its form (way in which it is experienced) and the content (Bürgy 2007). According to Jaspers, the content itself is of secondary importance, underestimating that aspect of delusion. Delusion is a phenomenon, which goes beyond the natural, even extensive, contextual understanding of patients (Walker 1991). Delusions are the products of disturbed neurobiological processes, creating new, immediate meanings of the external objects. In phenomenological method, the crucial step of understanding (during the diagnostic investigation) and

differentiating delusions from delusion-like ideas, is a "effortful perspective taking (transcending default self-perspective - ethnic, cultural, and individual diversity is embrace" (Mishara & Fusar-Poli 2013). Investigating the relation between social, cultural as well as historical context and psychotic symptomatology might be a fruitful field of research.

Patient with psychosis is immersed in the cultural environment and historical context, which frames form and context of psychotic symptoms (Al-Issa 1995). Both hallucinations and delusions might be influenced both by cultural differences and dominance of certain topics and areas of life (Kent & Wahass 1996). Moreover, politics of different countries might contribute to development of certain themes of delusions (Kim et al. 1993). Viswanath & Chaturvedi (2012) in their review showed several mechanisms of interactions between culture and psychopathology: a) pathogenic effects – culture is a direct causative factor in forming or generating illness; b) patho-selective effects – tendency to select culturally influenced reaction patterns that result in psychopathology; c) patho-plastic effect – culture contributes to modeling or shaping of symptoms; d) patho-elaborating effects – behavioral reactions become exaggerated through cultural reinforcements; e) patho-facilitative effects – cultural factors contribute to frequent occurrence; f) patho-reactive effects – culture influences perception and reaction.

Another aspect of external impact on psychotic symptoms, namely historical perspective, was evaluated in several studies (Skodlar et al. 2008, Stompe et al. 2003, Mitchell & Vierkant 1989). Results obtained in these researches showed differences in patients' experiences, which reflect socio-economical and cultural changes over decades, within the same country. Authors suggest that content of positive symptoms was a concretization of internal, pathological processes projected on external reality (Stompe et al. 2003, Krzystanek et al. 2012). Examples of delusions connected with advent of new technologies (such as Internet), shows that the new elements are integrated into delusional content, if they are present in a milieu of patients (Bell et al. 2005).

Religion and spirituality are important factors in life of many patients with schizophrenia. According to Mohr et al. (2007) religion plays a central role in life of 45% patients. Cook (2015), in his review, found that typically 20–60% of patients reports some kind of religious content in delusions and hallucinations. This type of delusions is associated with the higher score in psychotic symptoms' scales and the longer duration of untreated psychosis (Siddle et al. 2002, Mishra et al. 2018). Religion from a psychological point of view is a common coping mechanism (Koenig 2009). It explains the unexplainable, giving the meaning to events and experiences, which seems to be meaningless and connected with senseless loss or suffering. Facing psychotic symptoms, poverty, social exclusion, patients with schizophrenia, similarly as general population, use religion as coping mechanism (Mohr et al. 2007). However, religion can have both positive and negative impact on a course of the disease. On the one hand, religion may be a source of meaning, serenity and religious commandments, influencing behavior. On the other, factors like an exclusion from community, a promise of afterlife after suicidal attempt, a loss of faith and other spiritual experiences may consist exacerbating or even precipitating factors for the onset of schizophrenia (Huguelet & Mohr 2009, Menezes & Almeida 2010).

In the current study, authors aimed to explore an historical aspect of delusions and hallucinations. We focused on the content of positive symptoms, their changes and fluctuations over a period of 80 years (from 1932 to 2012). This research was designed as an exploration of patients' phenomenological perspective, due to a shortage of this kind of approach in literature of the topic.

SUBJECTS AND METHODS

In the study, authors conducted a retrospective analysis of 100 medical histories of in-patients diagnosed with schizophrenia. All of the patients were admitted to the State Neuropsychiatric Hospital in Lubliniec (Poland) during 2012. In case, if an admission exceeded the end of December 2012, the data from the beginning of 2013 was considered, too. This particular year was chosen as a continuation of earlier study conducted in

the Hospital in Lubliniec (Krzystanek et al. 2012). In the previous research, case histories from the years of 1932, 1952, 1972 and 1992 were selected, and the starting point (1932) is the year from when the complete paper records of patients were able to collect.

The study sample was randomly selected by an administrative worker responsible for managing an archive. The archivist was not a part of the research group and she was informed only about inclusion criteria: in-patients suffering from schizophrenia admitted in 2012 with equal number of men and women. This approach was applied to eliminate the selection bias. Mean age of the patients was 45.5 ± 14.2 , including 50 men and 50 women.

First step of the analysis was an extraction of both delusions and hallucinations from case histories. Authors aimed to separate the elements to obtain simplest structures of patients' reports, yet having an informational value. Subsequently, the obtained data was categorized by the topics. The following categories of topics were distinguished: religious figures (i.e. "God", "Christ", "Pope"), events (i.e. "The end of world") and other religious themes (i.e. places of cult or activities such as prayer). Certain elements were also divided by the subjective relation, perceived by patients ("contact", "vision", "identification"). Term "religious content" was understood in a broad sense, both as religiousness (referring to a certain tradition, doctrine and religious community) and spirituality (concerned with transcendence and meaning) (Mohr et al. 2007).

Finally, results from 2012 were compared with previous study. Complete data encompassed period of 80 years, measured in 5 time points separated by 20 years intervals.

RESULTS

Total number of all topics extracted from the study sample was 237. Among them, authors found 57 religious elements counted after decomposing complexed patients' relations on primary subjects. Religious content of delusions appeared in 26% of case histories. Global category encompassing contact with deity and divine mission was third most common theme in the total number of positive symptoms' elements. Second most common religious element was a representation of evil, personified as the devil, what is congruent with catholic beliefs. Table 1 present most prevalent elements of hallucinations and delusions in the case histories. "Contact with God" as a topic was exceeded by the number of persecutory delusions deriving from earthly sources.

Nearly all of the religious themes were associated with Catholicism, what reflects the dominance of this religion among the polish population (95.8%, according to the official record). A topic of reincarnation appeared only in one patient. Moreover, in the context of the case history analysis, reincarnation didn't derive from personal beliefs of the patient, but was rather a cultural or more – a pop-cultural motif.

Table 1. Religious content among all positive symptoms subjects. Presented as percentage of the theme in total number of positive symptoms

Positive symptoms subject	Percentage of all positive symptoms
Persecutions by other people	14.5
Persecutions by family	8.3
Contact with deity, divine mission	6.3
Poisoning	6.6
Machines & Technologies	4.4
Body	3.9
Institutions and secret services	6.1
Persecutions by neighbours	3.5
Persecutions by medical personnel	3.1
Psychotropic drugs	3.1
Satan/demons	3.1

Another trend in the material is a general decrease of religious themes diversity. It is especially visible in Table 2, regarding figures such as Holy Spirit or Saints. Number of this figures dropped to zero in 2012. In case

of saints, study showed stable decrease since 1932. Also in the Table 3, figure of “angels” is absent, both in visions and in form of contact. Disappearance of this theme started in 1992 and continues in 2012.

Authors found a trend of decreasing prevalence of divine visions among the subjects. Table 2 shows rapid decline of this theme in 2012. There were only few visions of God and Holy Mary. Mother of Christ is a very important figure for polish Catholics, personifying divine care and hope, appearing in revelations during important moments of polish history. As it is visible in Table 4, Częstochowa (the shrine to Mary) rarely, but constantly appear in positive symptoms. Speaking of delusional identification, Table 2 shows disappearance of this phenomenon in relation to nearly all figures, except for “Identification with God” and “Identification with Jesus”. Religious figures in this context are the concretization of patient’s grandiosity delusions, i.e. *“I feel that I am an incarnation of Jesus. People expects that I will resurrect them or heal them. I am happy with it. My mother must be divine, if she gave birth to Messiah.”*

Table 2. Incidence of major Catholic figures in delusions and hallucinations of the patients. Results are expressed as percentage of patients presenting each figure. They were differentiated according to the relation of patient with deity

Positive symptoms subject	1932	1952	1972	1992	2012
Vision of God	17	6	14	16	3
Vision of Mary	6	6	8	6	2
Vision of Christ	10	6	8	4	0
Vision of Holy Spirit	3	2	3	0	0
Names of saints	6	2	3	1	0
Contact with God	3	0	10	5	5
Contact with Mary	4	4	7	3	5
Contact with Christ	1	6	6	1	3
Contact with Holy Spirit	2	2	3	0	0
Contact with saints	4	4	6	1	0
Identification with God	5	2	1	3	1
Identification with Mary	1	0	2	2	0
Identification with Christ	6	2	2	2	1
Identification with saints	2	2	0	0	0
Being saint	2	0	3	4	0

Table 3. Incidence of transcendental themes and minor religious or spiritual figures. This category include also representations of evil and apocalyptic motives. Results are expressed as a percentage of patients presenting each element in positive symptoms

Positive symptoms subject	1932	1952	1972	1992	2012
Afterlife	1	4	2	4	2
Heaven	1	4	2	3	1
Hell	3	4	3	1	1
Eternal damnation	0	0	0	1	0
Visions of Satan/devil	8	4	6	6	5
Visions of angels	4	2	4	0	0
Contact with devil	7	4	3	2	5
Contact with angel	3	2	3	0	0
Contact with ghosts	7	4	5	1	1
Black magic/Satanism	1	0	1	0	0
End of the world	1	6	5	1	4

Table 4. Incidence of religious themes connected with Catholic rituals, tradition and the Bible. Results are expressed as a percentage of patients presenting each element in positive symptoms

Positive symptoms subject	1932	1952	1972	1992	2012
Church	2	6	5	1	3
Cross, Holy Water	4	2	1	1	3
Mass	0	2	6	1	0
Prayer	3	0	1	2	3
Pope	2	0	0	3	1
Priest	0	0	2	1	0
Czestochowa (shrine)	1	0	0	2	1
The Bible	0	0	1	2	1
Biblical prophecy	0	0	0	2	1
Biblical citation	0	0	2	4	1
Biblical events	6	2	2	3	1
Crucifixion	0	0	0	0	1
Sin/Religious guilt	0	0	0	0	2
Exorcism	0	0	0	0	1

Although, figures of angels and saints disappeared in study sample, occurrence of devil is constant, similarly to data from earlier study (Table 3). Interestingly, every case of apocalyptic visions in delusions was connected with devil or Satan. This kind of delusions was especially catastrophic and ominous, i.e. *“Stronger and stronger radiations were directed toward me. Devils were released from hell to destroy everything, all Poland, all the world”*. Devil in that case may be perceived as a concretization or an attempt to explain high level of psychotic anxiety and fear.

Table 4 presents an incidence of physical objects (symbols) and places connected with the topic of religion. This category includes also clergy. Though those elements are relatively rare content of positive symptoms, nevertheless amount of this type of representation is stable over time (except for “Biblical events”). Among new topics, non-existing in previous years, in 2012 we found “crucifixion”, “sin”, as an expression of sense of guilt and “exorcisms”.

DISCUSSION

In 2012, there were 26 patients presenting religious themes in hallucinations and delusions. That prevalence locates within a range of typical incidence of this phenomenon (20-60%) as presented by Cook (2015). Grover et al. (2014) showed even a higher percentage. The mentioned studies are, to our knowledge the only two studies on this particular subject. Due to wide interval between the lowest and the highest rates further epidemiological research is needed in this area.

Interestingly, we found constant decrease of religious “visions”, with relatively stable number of “contact” with divine figures. Both types of delusional content were connected with separate modalities. This finding may be explained in two ways. First, it is a general change and form of natural evolution of psychopathological manifestation of the symptoms’ content. This

change may be described as a shift from passivity toward active interaction with the delusional figures. Second explanation is connected with weak point of our study – it depended on the patients’ clinical records not on the personal examining of subjects. Hypothetically, the psychiatrists fulfilling the clinical files did not ask patients about their “visions”. It is not possible to discern these two factors basing on our material.

Suhail & Cochrane (2010) showed the difference between Western and non-Western cultures in prevalence of visual and auditory hallucinations. Authors compared British group, Pakistani immigrants in England and Pakistani group in their home country. Pakistani immigrants’ group was more similar to White British group than to second Pakistani group. Authors ascribe this result to temporary environmental impact. Mueser et al. (1990) proposed two hypotheses to explain that findings: a) a significant cultural impact on the content of positive symptoms; b) a worse access to medical facilities and treatment. In case of our data from the State Hospital in Lubliniec, both hypothesis might be true. On the one hand, during 80 years both environmental and cultural conditions have been radically changing. On the other hand, in this period of time, significant changes happened in psychopharmacology and social consciousness of psychiatric disorders. It is important to keep in mind that in 1932 and 1952 there was no antipsychotic drugs yet (actually chlorpromazine was introduced to American, not Polish market right in 1952). Mishra et al. (2018) showed that duration of untreated psychosis was correlated with more religious content of delusions, thus it could be a factor influencing a characteristic of schizophrenia symptomatology.

In our study, we found obvious decrease in diversity of religious themes. Figures of Holy Spirit, saints and angels were absent in 2012. Especially, number of saints occurring in the material gradually decreased from 1932. Impoverishment of religious themes in psychotic

symptoms might be an effect of a process of secularization of general population. Believing in saints and angels is now more and more folkloristic or “esoteric” than the canonical catholic doctrine, so that is more prone to change. Suhail & Ghauri (2010) showed that number of minor religious figures in delusions (parallel, but of Islamic origin) is connected with patients’ level of religiosity. Both Skodlar et al. (2008) and Stompe et al. (2003) showed fluctuating character of religious delusions prevalence. They connect it with cultural attitude towards religion in different times and with change of interest between generations.

Although the number of other minor religious entities declined, the amount of representations of devil or Satan remained stable. In the material devil may play a very specific role. In our understanding, it is concretization of anxiety, guilt and other negative emotions. Moreover, all of diabolical figures were connected with catastrophic visions. It can reflect derealization and decomposition of patients’ inner world. Rhodes and Jakes (2004) proposed a model derived from cognitive linguistics, in which metaphor is used by people reporting difficult psychosocial experiences, to make their experience understandable. In case of psychosis, those metaphors and metonymies might contribute to creation and maintenance of delusions. Devil can be an example of the metaphorical thinking. Ange Drinnan & Tony Lavender (2006) in their qualitative study suggested that all the religious content of delusions have background in personal histories. As a consequence, patients attribute (as well as God and other religious themes) their usual experiences to devil.

Figure of Holly Mary was a second most common major figure in the sample. It may reflect polish regional specificity. She is perceived by fundamental groups of polish society as the Queen of Poland. There are several shrines with holy pictures of Holly Mary and the closest one to the study Hospital in Lubliniec is in Czestochowa. There is also a religious practice of prayers to Mary and pilgrimage to Czestochowa, and asking for healing of diseases, including psychiatric disorders. However, no information about such practices was found in the analyzed material. Again, in our interpretation the occurrence of Holly Mary in psychotic symptoms can be a religious attribution of internal need for care and attention.

Only in 2012, authors found theme of exorcism in the sample. It was referred as a special kind of prayer, solution to patient’s anxiety and difficult life situation. Patients, even in developed Western countries, hold superstitions, which may be surprisingly common. In the study by Pfeifer (1994), 37.6% patients from Switzerland believed that their condition is influenced by evil forces. Over 30% of them were looking for help in rituals, prayers and exorcisms. Similar believes might explain high occurrence of the figure of Holly Mary in the symptoms as a representation of hope for divine intervention and healing the disease.

Major limitation in our study was already mentioned, namely, on the basis of case histories, authors can’t exclude a confounding factor, which are psychiatrists’ attention for certain topics. Data come only from one psychiatric hospital. Next problem is a subjectivity of a diagnosing process and our arbitrary selection of important information from patients’ clinical files. During the period of 80 years the knowledge about schizophrenia and diagnostic criteria have been constantly changing. Publication of the first version of DSM coincided with our second time point measurement (1952), but surely DSM was not applied yet in that year in Poland. Last issue is that the clinical files we used were often incomplete, and contained only general but not detailed information about patient’s symptomatology. In the end, the study had a qualitative character and some of the religious topics were too rare to draw a final conclusions.

CONCLUSIONS

Religious topics express general plasticity over a time, following cultural changes in society. Religious content of delusions appeared in 26% of case histories.

In the study, impoverishment of religious themes in psychotics symptoms was shown.

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SHORT-TERM KETAMINE ADMINISTRATION IN TREATMENT-RESISTANT DEPRESSION PATIENTS: FOCUS ON ADVERSE EFFECTS ON THE CENTRAL NERVOUS SYSTEM

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SUMMARY

Major depressive disorder (MDD) is a recurrent, incapacitating psychiatric illness which will be the second most disabling disease worldwide by the year 2020. There is a rising promise in a N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine, which may be used in the treatment of resistant depression. Many of the studies are in favor of the drug, even in single dose application, with effects appearing in minutes to hours from administration. However, there is a need to evaluate the benefits and risks regarding psychomimetic, psychiatric, neurologic, and cognitive adverse effects of ketamine administration. The most distressing symptoms which appear most frequently during ketamine administration are dissociative symptoms, which can be quantified as a CNS adverse drug reaction. Results generally show that a single infusion of ketamine is efficacious and well-tolerated, while dissociative symptoms tend to abate within 2 hours after ketamine administration. As studies show single doses of ketamine should be definitely considered as an option in TRD patients with/without suicidal thoughts, even though it could not provide remission, or the effect could be temporary, but improving patients' quality of life by reducing depressive symptomatology should be a major asset while considering this particular procedure, particularly in inpatients.

Key words: ketamine – MDD - treatment resistant depression - central nervous system - safety

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INTRODUCTION

Major depressive disorder (MDD) is a recurrent, incapacitating psychiatric illness which will be second most disabling disease worldwide by the year 2020 (Martínez-Cengotitabengoa & González-Pinto 2017). Almost one-third of the MDD patients do not achieve remission suffering from treatment-resistant depression (TRD) (Correia-Melo et al. 2017). It also is associated with substantial mortality (American Psychiatric Association 2000). There is a great need to develop treatments which could rapidly relieve or significantly decrease MDD symptomatology. There is a rising promise in used since early 1960s for anesthesia purposes, a N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine (Haas & Harper 1992). The mechanism of action of ketamine is different from majority of prescribed antidepressants with selective serotonin reuptake inhibitors being the most frequently given by physicians (Cohen et al. 2017). The proposed mechanism of action is to affect glutamate (major excitatory neurotransmitter in mammalian brain (Włodarczyk et al. 2017), increasing brain-derived neurotrophic factor (BDNF) release, stimulating synaptogenesis. There are strong data that expression reduction of BDNF is associated with MDD (Guilloux et al. 2012, Lusher & Fuchs 2015).

The aim of this paper is to evaluate the benefits and risks regarding psychomimetic, psychiatric, neurological, cognitive adverse effects of ketamine, as we called 'Central Nervous System (CNS) adverse drug effects' of single-doses of ketamine in MDD patients.

KETAMINE USE IN DEPRESSION

Ketamine is a racemic mix of S-ketamine and R-ketamine. With drug development an enantiomer, intranasal S-ketamine, is in clinical use being approved by The Food and Drug Administration in March 2019 (Food and Drug Administration, Highlights Of Prescribing Information, 2018). The S-ketamine is more potent NMDA antagonist, more potent agonists of μ -opioid receptor and less potent sigma receptor agonist than R-ketamine (Andrade et al. 2017a), which can show its advantage over ketamine regarding more analgesic, more anesthetic, less psychomimetic and other adverse effects, therefore it is preferred acting as psychiatric drug. The majority of studies although are based on ketamine racemic mix intake due to its more common availability (Correia-Melo et al. 2017, Segmiller et al. 2013).

Since the first study by Berman et al. (2000) with ketamine administered intravenously there were several other researches exploring ketamine predominantly in TRD treatment with ketamine (Andrade et al. 2017a, Feifel et al. 2017). Many of them are in favor of the drug, even in single-use, with effects appearing in minutes to hours from administration (Correia-Melo et al. 2017, Feifel et al. 2017, Kim & Mierzwinski-Urban 2017, Möhler 2012) lasting mostly up to 7-14 days, interestingly often with antisuicidal effect (Al-Shirawi et al. 2017, Kim & Mierzwinski-Urban 2017). Chiefly, ketamine in intravenous doses is administered in 0.5 mg/kg in 40 minutes (Feifel et al. 2017), nonetheless, there is also evidence for faster infusions (Correia-Melo et al. 2017). Doses below 0.5 mg/kg of ketamine seem

Table 1. Comparison between ketamine route/dose safety

Route	Dose	Comment
Intravenous	0.5 mg/kg	no serious adverse events (SAE), most studied way of administering
Intranasal	50 mg	no SAE, adverse events disappeared after max 4h.
Sublingual		no significant studies found on single-dose administration
Subcutaneous		no significant studies found on single-dose administration
Intramuscular	0.25 mg/kg; 0.5 mg/kg	no SAE, results similar in both doses, may appear painful

Table 2. Comparative incidents of neuropsychiatric adverse effects in studies with ketamine/ esketamine in different routes of administration (Berman et al. 2000, Diazgranados et al. 2010, Shiroma et al. 2014, Singh et al. 2015, Sos et al. 2013, Loo et al. 2016, Murrough et al. 2013)

Most common adverse effects		
Adverse events were:		
<ul style="list-style-type: none"> ▪ well tolerated ▪ ephemeral ▪ they return to baseline within 0.5-4 hours after administration ▪ no serious adverse events were reported 	Psychomimetic	loss of concentration, vivid dreams, dysphoria, anxiety and disorientation, hallucinations, thought disorder
	Dissociative	altered body perception, alter time perception, depersonalization, derealization

Table 3. Safety scales

Questionnaire	Symptoms assessed	Time
CADSS	Dissociative domain	ca. 15 min
BPRS+	Psychotic domain	ca. 10 min.
MCCB	Cognitive domain	60-90 min.

to be less effective than standard 0.5 mg/kg (Andrade 2017b, Xu et al. 2016). In studies comparing one to series of administrations of ketamine, it was stated that repeated ketamine infusions provide longer time of positive response (Segmiller et al. 2013). In a study by Hu et al. (2016), single dose of intravenous ketamine with placebo comparison, there response and remission rates were significantly higher for ketamine, respectively 92% vs. 57% and 77% vs. 14%. Moreover, even widely prescribed for anxiety, sleep disturbances, anxiety or behavioral disinhibition etc., benzodiazepine (Haas & Harper 1992), were compared (midazolam) vs. ketamine in single-dose. Although nearly one-fifth of the patients experienced dissociative symptoms, the antidepressant results were in favor of ketamine (64% of ketamine-patients vs 28% midazolam-patients with response rates), measured with Montgomery-Åsberg Depression Rating Scale (MADRS), after 24 h of infusion one or the other. The results did not differ in groups after 7 days from infusion (Murrough et al. 2013). Sublingual (oral) form of ketamine in dose 10 mg, given in bipolar depression, appeared to be better tolerated and similarly efficacious on mood and cognition in comparison to intravenous ketamine (Lara et al. 2013), unfortunately as well as in subcutaneous route literature lacks significant data on single dose of ketamine. Single dose of intranasal form of ketamine also appeared to be more efficacious than placebo, while administering ketamine intramuscularly in a dose up to 0.5 mg/kg showed significant benefit in depression (Andrade 2017b) (Table 1).

NEUROPSYCHIATRIC ADVERSE EVENTS ASSOCIATED WITH NERVOUS SYSTEM DISORDERS

The last sentence brings an important concern of ketamine not only about its efficacy but also its tolerability and safety issues. The most distressing symptoms which appears most frequently during ketamine intake are dissociative symptoms (Xu et al. 2016), which can be established as a CNS adverse effect. The most used and valuable questionnaires tend to be Clinician Administered Dissociative States Scale (CADSS) and brief psychiatric rating scale (BPRS) or four-item BPRS positive symptoms subscale (BPRS+), neurocognitive functioning, using the MATRICS consensus cognitive battery (MCCB) (Kim & Mierzewski-Urban 2017, Short et al. 2018). In a large, double-blind, multi-center study of esketamine (nasal form) taken as an add-on to oral antidepressant treatment, showed that adverse events were mild to moderate, where most common adverse events reported in the esketamine plus antidepressant group were: dysgeusia, vertigo, dissociation, somnolence, and dizziness, each reported for less than 7 per cent of patients in the antidepressant/placebo group In that same study it dissociation was measured by CADSS and it was noted that there appeared to be a reduction in the value of symptoms reported with repeated esketamine intake over time (Daly et al. 2019) (Table 2).

Although, dissociative symptoms have been observed as positive indicator for a better antidepressant effect of ketamine (Correia-Melo et al. 2017), still they might be distressing (Segmiller et al. 2013). Results generally show that a single infusion of ketamine is efficacious and well-tolerated, while dissociative symptoms tend to disappear in a maximum of 2 hours from ketamine intake (Feifel et al. 2017, Kim & Mirzewski-Urban 2017). As to cognition significant improvements

Table 4. Management for best practice

Patient qualification	Treatment resistant depression	
Assessment	safety during ketamine intake	BPRS+, CADSS, MCCB
Observation and follow-up	safety after ketamine intake	Montgomery-Åsberg Depression Scale
Intervention	if significant adverse event appears	Small dose of benzodiazepines, e.g. lorazepam 1mg p.o.

in some domains were observed (processing speed, verbal learning, and visual learning) of neurocognitive performance but not in others (working memory and reasoning) measured between baseline and seven days after treatment with intravenous single-dose ketamine (Kim & Mirzawinski-Urban, 2017). As for anxiety which could be also a CNS group adverse effect, if per clinical evaluation it would be significant, as it appeared in one study with part stoppage of drug infusion, single dose of 1 mg lorazepam would stop excessive anxiety symptoms (Feifel et al. 2017). Mostly, the adverse effects of ketamine tend to be mild to moderate, short-term, but when some patients experience a severe intensity of adverse effects they are not regarding CNS adverse effects group (Short et al. 2018, Xu et al. 2016).

In a several studies with ketamine hydrochloride from single up to twelve infusions per study, where groups were various in terms of patient number were compatible with each other in terms of CNS adverse effects (summarized in table 2) (Berman et al. 2000, Diazgranados et al. 2010, Shiroma et al. 2014, Singh et al. 2015, Singh et al. 2016, Sos et al. 2013, Loo et al. 2016, Murrough et al. 2013). For example, in a study with 15 patients suffering from major depression disorder carried by Loo et al. (2016), a relationship between dose and patients' response was observed between dissociative psychomimetic effects and ketamine treatment regarding all routes, but higher peak scores in the intravenous group. Analysis of CADSS scores showed no noteworthy effect for route at 40 minutes or 240 minutes after injection. CNS effects reported included mild depersonalization, derealization, altered body perception and altered time perception. Peak effects occurred up to 15 minutes after injection, resolving without intervention by 40 minutes after injection for every participant, every dose and every route of administration. Items rated from the BPRS and Item 1 of the Young Mania Rating Scale (Elevated Mood) revealed no evidence of treatment emergent mania at any time point, across routes of administration and doses. No clinically significant change in BPRS or CADSS was observed in the midazolam condition, across all routes of administration (Loo et al. 2016). In other study on a larger group (66 depressive patients) by Singh et al. (2016), during the double-blind and open-label phases, dissociative symptoms (measured by CADSS) were observed shortly (up to 40 minutes) after start of the infusion and resolved by 3 hours post-infusion maximum. The acuteness of dissociative symptoms reduced with repeated dosing. No delusions or hallucinations were observed during the study. BPRS scores returned

to primary values at the 3-hour after infusion assessment in the two ketamine frequency groups in both the double-blind and open-label phases. Other evidence is showing similar results saying the BPRS score returned to a basal by less than an hour (Diazgranados et al. 2010, Sos et al. 2013), 120 minutes after infusion ends (Berman et al. 2000, Shiroma et al. 2014) or in one study in 240 minutes (Shiroma et al. 2014). In the last-mentioned study also indicates that ketamine most common adverse event were those related to Central Nervous System 'each infusion included feeling strange or unreal (58.3%), abnormal sensations (54.2%) (Murrough et al. 2013) (Table 3).

However, with scarce data on ketamine use in TRD and recent approval of esketamine nasal spray for patients with TRD who experienced remission or response after esketamine treatment, the evidence for the long-term continuation treatment applies to esketamine nasal spray in addition to oral antidepressant treatment and is known to be both clinically effective in short-term intervention as well as in the long-term maintenance treatment for preventing relapse (Daly et al. 2019).

As studies show single doses of ketamine should be definitely considered as an option with strong evidence for its safety in TRD patients with/without suicidal thoughts (Table 4).

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SERVICES FOR PATIENTS WITH INTELLECTUAL DISABILITY AND MENTAL HEALTH PROBLEMS IN POLAND

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SUMMARY

Background: Poland is a democratic, sovereign state in Central Europe, member of the European Union. The healthcare in Poland is delivered to patients mainly through a public contributor called the National Health Fund, supervised by the Ministry of Health. The care for people with disabilities, including intellectual disabilities in Poland is coordinated by the Governmental Program on Activities for People with Disabilities and their Integration with the Society. The system of care for people with intellectual disability in Poland is constitutionally guaranteed. The aim of this review was to analyze the different forms of care for persons suffering from intellectual disability and mental health problems in our country.

Methods: Analysis of available documents on the policy and organizations of systems of services for this group of patients was performed.

Results: Non-governmental organizations play an important role in taking care of people with disabilities. In Poland there are no special psychiatric services dedicated for patients with intellectual disabilities. The comorbid psychiatric disorders are treated in general psychiatric wards or hospitals or in outpatient settings. Offenders with intellectual disabilities in the penitentiary system are referred to therapeutic settings in wards for convicts with non-psychotic mental disorders and intellectual disabilities. Training of medical students and young doctors offers only very limited basic knowledge on intellectual disability within psychiatry curriculum. There is no separate specialty in mental health in intellectual disability within psychiatry.

Conclusions: The main conclusion of this review is that the specialist working with persons suffering from intellectual disabilities in Poland face many challenges regarding the need to introduce positive changes in this field.

Key words: intellectual disability - mental health - comorbidity - special education - rehabilitation - national program

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INTRODUCTION

Poland, properly Republic of Poland, is a democratic, sovereign state in Central Europe. In 2003, Poland signed the accession treaty in Athens, which constituted the legal basis for accession to the European Union, becoming its member on May 1, 2004. At the same time Poland became one among the most populated countries and biggest in terms of area within the union (6th country for both criteria in EU, 36th and 69th country in the world) (Eurostat 2017). Current population is estimated to be 36 million 600 thousand people with sex ratio of the total population 0.93 (men < women). Mean life expectancy is on the level of 76 years of age (with significant sex difference: 72.1 - men, 80.3 - women) (GUS 2011a). Poland is classified by the World Bank as high-income economy, 8th largest within the union itself, and 23rd worldwide in terms of GDP). Poland passed the political and economic transition in 1990s, but the general overview of the system gives the impression, that the transition of the Polish healthcare system is still ongoing and requires many efforts to overtake other European countries. Health expenditures equal 4.67% GDP (36. place among all 44 countries investigated by the Organization for Economic Co-operation and Development) with 6,6 hospital beds per 1000 inhabitants (7th position within EU), and 2.3 physicians per 1000 inhabitants (the lowest number in the whole EU). The

healthcare in Poland is delivered to patients mainly through National Health Fund (NHF), supervised by the Ministry of Health. This public insurgency agency is active from 2013 and is paid for the employs (and their offspring) from health insurance contribution, paid by employers to the Polish budget. According to Article 68 of the Polish Constitution, everyone has a free access to health care. According to the data from PwC Poland (2016) there are 800 hospitals in Poland with about 220 000 hospital beds, which gives almost six sick beds per thousand citizens. According to PwC Poland, this rating belongs to one of highest rates in Europe. The rating is in contrast with the level of budget financing of public healthcare. The expenditures from the national budget is much lower than in European countries and equals 4.7% gross domestic product (GDP). Unless 43% of GDP is allocated to the treatment in hospitals the financial situation of the big hospitals is dramatically bad. The level of financing of public healthcare from public resources in Poland is one of the lowest in Europe (Nieszporska 2017). The situation is complicated by the general lack of physicians, especially specialists, that decreases the availability of medical service in public health sector. According to Global Health Observatory data, Poland is a country with one of the lowest ratio of physicians per 1000 inhabitants (2.22 in 2012). The financial results of Polish hospitals are bad and the stable deterioration of their income is

observed. The situation can be explained by aforementioned low Polish budget financing, old infrastructure of most of hospitals and centralized health system monopolized by the National Health Fund (Nieszporska 2017). Many hospitals, like psychiatric hospitals change their profile from short to long-term care. Some hospital wards turn into one-day clinics. In many cases, due to the restructuration of the health care system and pour governmental financing, hospitals that plunged into debt were closed down. The public healthcare system in Poland coexists with a private health care. Because of long waits in public out-patient clinics, many patients decide to pay the full cost of the service in private medical centers and doctors' offices. Private sector comprises mostly the basic health services, private sanatoria, rehabilitation clinics, specialists and long-term treatment service. Still, there are a few private hospitals in Poland, that results from relatively low funding of treatment procedures covered by NHF.

Different types of disabilities affect 4.9 million people living in Poland (GUS 2011b). A large group within this population are persons with intellectual disability, however the estimation of its exact number in our country faces methodological limitations like the lack of a homogeneous statistical definition of a disabled person (Antczak et al. 2018).

According to the Report on Disability published by the World Health Organization in 2011, it is estimated that the worldwide number of people with all types of disabilities stands at around 1 billion or about 15.6% of the total population, of which 2.2% has serious difficulties in functioning (WHO 2011). In Poland, there is no precise data on the number of people with mental retardation. According to data from 2009 (GUS 2011b), the number of persons with disabilities was 5.1 million, which represents 16% of the population aged 15 years and older. It is estimated that the percentage of the persons, who are intellectually disabled is: mild impairment 80%, moderate 12%, deep 7% profound 1% of cases (APA 1994). A number of persons with intellectual disability suffer from comorbid psychiatric disorders, however no systematic studies on this topic were carried out. In Poland there are also no published data about available beds for this population of patients, death rates, and costs of treatment their treatment.

The purpose of this review is to analyze accessible data on the comorbidity of mental health and intellectual disability in Poland and to discuss the availability of the forms of treatment and rehabilitation for the MHID population.

METHODS

We searched for documents on mental health and intellectual disability in Poland in following databases: PubMed, Google Scholar, Scopus, and Web of Science. As far as the keywords are concerned, we focused on "intellectual disability", "mental retardation", "mental health", "psychiatric disorders", "psychiatric comorbi-

dity", in all four databases. Texts of the legal acts were retrieved from Polish Government Legislation Centre. The source of statistical data were mainly publications of the Central Statistical Office. Data on the forms of treatment and rehabilitation in Poland were found on internet services specializing in disabilities in Poland: <http://www.niepelnosprawni.gov.pl/>, as well as web pages of institutions providing care of ID persons in our country.

RESULTS

The results of the research we grouped according to the topic and are presented below in following sections.

National policy on Mental Health and Intellectual Disability (MHID)

The care for people with disabilities, including intellectual disabilities in Poland is coordinated by the Governmental Program on Activities for People with Disabilities and their Integration with the Society. The program includes activities of ministries, offices and other organizational units in the field of various spheres of life of people with responsibilities for the implementation of tasks in the field of social assistance and social support within the scope adopted by the laws belong to the units of government administration and local self-government (Kulesza-Rozeslaniec 1997). One of the basic elements of the care for children and young people with intellectual disabilities is special education, which is guaranteed by several legal acts.

According to the Regulation of the Ministry of National Education of 18 January 2005, the following forms of education can be distinguished:

- special kindergartens and special departments in generally accessible kindergartens;
- special schools of all types, including apprenticeship schools, and special branches in mainstream schools;
- youth educational centers;
- youth social therapy centers;
- special educational and upbringing centers;
- special educational centers;
- centers enabling children and young people with a deep degree of intellectual disability, as well as children and young people with mental disabilities with comorbid disabilities to the implementation of:
 - obligatory annual pre-school preparation;
 - schooling obligation;
 - the obligation to learn (Belza 2011).

Implementation of human rights and legal problems

Applying human rights in the field of care for persons with intellectual disability in Poland is regulated by international and local standards. However we miss publications, which would analyze, how these rights are

implemented in practice. One such document is the WHO report (2018) on the rights of persons with intellectual disabilities staying in institutions. The main conclusions from the report were: more information should be provided about activities and resources, including vocational trainings, available to these persons in the community. They should also be supported to make their own decisions and exercise their legal rights. Others conclusions were that efforts should be made to encourage deinstitutionalization and support the involvement in community life in order to prevent isolation from society (WHO 2018). A common legal problem among persons with intellectual disability is the fact that many of them, especially in the long term care centers have limited or no legal capacity to make decision on their own, including the consent for treatment (Firkowska-Mankiewicz & Szeroczyńska 2005). This attitude is the result of fact that in without using these legal form of admission to a general hospital would be practically impossible, except for emergency situations. The limitation of their legal capacity is a consequence of the situation that there are no other legal forms of support for these persons to make decisions about their psychiatric and somatic treatment, as well as about their personal, legal, financial and other affairs. So decisions must be often made by a person, who is the legal representative in decision-making. An attempt to change this situation are is the Self Advocacy movement. It is a way of engaging people with intellectual disabilities in social life and including them to influence the politics of their local community and act on their own matters. The self-advocacy movement in Poland is based on three main pillars of legal and civic education, the creation of local self-advocacy groups and their cooperation with PSONI and with local authorities (Zakrzewska-Manterys 2016).

Diagnosing intellectual disability

Diagnosis of intellectual disability in Poland is made with the use of following tools: The Cattell Infant Intelligence Scale, Polish version (Kostrzewski 1961), Terman-Merrill Stanford-Binet Test - this test does not have Polish norm, so it is used only as a supportive tool (Stelter 2010), Polish adaptation of WISC-R (Maczak et al. 1997), Raven's Progressive Matrices (Jaworowska & Szustrowa 2000), Leiter International Performance Scale (Jaworowska et al. 1996), Columbia Mental Maturity Scale (Ciechanowicz 1990). Additionally, other neuropsychological test are used like, The Denver Developmental Screening Test, Bayley Scales of Infant Development, Brunet-Lézine Scale, Munich Functional Developmental Diagnostics (Stolarska & Kaciński 2007, Maczak et al. 2007).

Diagnosis of comorbid psychotic, affective and other psychiatric disorders id made mainly based on the interview and medical history. Specific tools like Psychiatric Assessment Schedule for Adults with Developmental Disability (PASS-ADD) (Costello et al. 1997), and methods like Characteristics of Assessment Instruments for

Psychiatric Disorders in Persons with Intellectual Developmental Disorders (CAPs-IDD) (Zeilinger et al. 2013), Glasgow Depression Scale for People with a Learning Disability, Glasgow Anxiety Scale for People with an Intellectual Disability, Glasgow Depression Scale–Carer Supplement (Sullivan et al. 2018) are not widely used in Poland.

Therapeutic services for persons with intellectual disabilities

Political transformation in Poland after 1989 and related changes in the legislation and social policy of the State in favor of people with disabilities, prepared the basis for creating and implementing a new direction and programs of action for these people, and consequently the need to establish many aid institutions, which have a decisive impact on changing their life situation (Krysta et al. 2014). The system of care for disabled people adopted in Poland is now constitutionally guaranteed. Taking care of people with disabilities in Poland on the level of human rights and combating discrimination is a serious challenge for the State. This is why non-governmental organizations play an important role in this respect by undertaking grassroots initiatives in the field of advocacy of interests, creating programs for equalizing the chances of these people and their right to a dignified and happy life, as well as full participation in social life. In Poland, since the 1990s, there have been numerous, non-governmental organizations aimed at the care, assistance and support of children and adults with intellectual disabilities. A model example for this is the activity of the Polish Association for People with Intellectual Disability (Mrugalska 2006). It is the largest non-governmental, self-help, non-profit social organization in Poland, focused on providing help, care and support people with intellectual disabilities and their families in a comprehensive manner, taking into account the needs of these people at every stage of their lives. The activity of the Association covers the entire territory of the Republic of Poland, through a network of registered and actively operating field offices (Kościelska 2014, Ostrowska 2014). The activity of the Polish Association for People with Intellectual Disability and other institutions and associations are programs, which include tasks in the scope of identifying needs concerning the life and situation of these people, including the number of people with intellectual disabilities in all age groups, the scope and type of necessary forms of help and care. Based on the information gathered and needs identified, they undertake comprehensive, multi-specialist assistance and support of these people in equalizing opportunities, while ensuring the conditions necessary for their dignified and happy life and full and satisfying participation in social life. It is a comprehensive activity, covering the issues of health, care, rehabilitation and education, vocational training, preparation for work, housing in the form of facilities adapted to specific forms of support, family

support, shaping positive social attitudes, development of human resources, care for the observance of the rights of persons with intellectual disabilities, taking into account international legal acts regulating the rights of these people. They create for this purpose specialized facilities and forms of care adapted to each type of activity, they are among others: Early Intervention Centers (OWI), Rehabilitation and Education Centers (OREW), Occupational Therapy Workshops (WTZ), Occupational Activation Centers (ZAZ), as well as other facilities dealing with social rehabilitation, employment, leisure activities such as Centrum DZWONI, rehabilitation meetings, individual support for families in difficult life situations (Krysta et al. 2015). Implementation of the adopted forms of care and programs of activities directed to people with intellectual disability, takes place in cooperation with institutions subject to individual departments in the ministries, responsible for health, education, social policy support and care (Krysta & Krysta 2015).

The detailed objectives and forms of activities of different types of centers

Early Intervention Center (OWI). It is an institution whose activity is focused on early, multidisciplinary, comprehensive, coordinated and continuous assistance to a child at risk of disability, with developmental disorders. It covers the care of children with moderate, severe and profound intellectual disabilities. The Early Intervention is based on multidisciplinary work that provides the services of a team of professionals. The referral to OWI is made by doctors specializing in hospital departments and specialist clinics, as well as other specialists, among them a psychologist, speech therapist, physiotherapist, educator who make an early diagnosis of the child's physical and mental condition, assess his emotional state and development opportunities. They also determine how to proceed and the form of care. OWI conducts many forms of activity through psychological, pedagogical, speech therapy, help and support as well as the necessary individual education of parents, when the need arises.

Center for rehabilitation, education and care (OREW). The idea of establishing and creating OREW derives from the great determination of the parents of deeply, multi-disabled children who remained in the previous political system completely on the margins of social life. The Center's program of activities is focused on comprehensive, multidisciplinary and comprehensive education and stimulation of children and youth with intellectual disabilities and co-morbidities. Parents also receive support and educational help, enhancing their parental skills (Kastory-Bronowska and Pakuła 2004).

Workshops of Occupational Therapy (WTZ). The Workshop perform tasks defined by the Government which specifies types of tasks in the field of occupational and social rehabilitation of disabled persons, which may be commissioned to foundations and non-governmental organizations. The Workshops' activity is

addressed to adults with moderate and severe intellectual disabilities. Rehabilitation carried out in WTZ is a long-term process. It is a series of activities in particular organizational, therapeutic, psychological, technical, training, educational and social, aimed at achieving, with the active participation of these people, the highest possible level of their functioning, quality of life in social integration (Miształ 2005). The rehabilitation conducted in the Workshops is a comprehensive activity aimed at restoring the damaged skill of the participant, or improving their functions, it prepares the participants of the Workshop to independently manage their lives in the everyday life. Rehabilitation in WTZ is carried out using various types of training and occupational therapy techniques. The place for conducting classes within the framework of therapy are multi-purpose studios, where disabled people can perform activities according to their capabilities, without the feeling of rejection and alienation. Here, they gain autonomy, which is a chance for their adult life. Among the most-created laboratories, the most popular are: plastic horticulture and various techniques, household, painting, computer tailor, knitting, ceramic, locksmith, everyday life skills workshop, but also other workshops according to the participants' interest (Krysta et al. 2012). WTZ's also carry out large-scale social rehabilitation, the aim of which is to involve people with intellectual disabilities into social life and to give them the opportunity to participate fully in it, participate in various cultural sporting events (Krysta & Krysta 2017).

The Employment Consulting Center (DZWONI). It is an innovative solution for implementing supported employment. The aim of DZWONI's activity is comprehensive activity supporting the skills of people with intellectual disabilities in moving on the labor market, based on the assisted employment model. It is a model consisting in combining activities directed at a person with a disability and its environment as well as employers and associates. The Center employs vocational counselors, psychologists, pedagogues, work trainers supporting people with intellectual disabilities in access to work. Supporting includes help in finding a job, taking up employment as well as help in maintaining a prepared job (Maślanka 2008).

Occupational Activation Center (ZAZ). It is created to employ people with disabilities, including those with severe and moderate disabilities. Participants of Occupational Therapy Workshops using the Advising Center's support have the opportunity to work in the Vocational Rehabilitation Institution with the possibility of transition to the open labor market (Krysta and Krysta 2017).

Currently, most of the occupational therapy workshops are conducted by entities from the non-public sector (82% of WTZ's), and the vast majority of them, including the most dynamically developing, is run by seven non-governmental organizations. Local government institutions are much less likely to create WTZ's. Only slightly more than one third of all WTZ (36%) are

run by organizers, who have created a more extensive system of social support for people disabled (at least 2 different forms of institutional support) (Ulman 2012). The majority of WTZ's operating in Poland (57%) are not designed for groups of participants, which would be dominant due to the type of their disability. 43% of them focus on one type of disability (40% of which are institutions mainly focusing on people with intellectual disabilities). It is worth noting that specialization in a given type of disability is more often the domain of WTZ operating in large urban centers, where the offer of support for people with disabilities is greater. The second most numerous group among WTZ participants are persons suffering from psychiatric disorders. A number of WTZ participants are persons with comorbid intellectual disability and psychiatric disorder, but there are no available data how large this population is.

15% of all WTZ's are conducted by denominational organizations. Another 3% of WTZ is being conducted by religious associations (parishes, monasteries, archdiocese). Less than every twentieth WTZ (4%) is run by the economic entity. Most often these are social economy entities. Public sector entities are responsible for 18% of WTZ's. They are primarily municipal local governments, social assistance centers - or social welfare homes (4%). First of all, it is worth noting that the market of WTZ's is focused to a large extent around seven non-governmental organizations (forming at least 5 WTZ) that they organize or they co-organize through their regional branches. In total, 26 organizations (practically only NGOs) run more than 1 WTZ - in total they organize 239 WTZ (35%), attended by 37% of all WTZ participants.

The organizations that run the WTZ centers are respectively:

- Polish Association for People with Mental Disabilities (PSOU): 80 WTZ centers, 3 318 participants;
- CARITAS: 60 WTZ centers, 2 176 participants;
- Society of Friends of Children (TPD): 26 WTZ centers, 874 participants;
- Brother Albert Foundation: 12 WTZ centers, 586 participants;
- Polish Society for Combating Disability: 7 WTZ centers, 230 participants;
- Invalides and Disabled People Foundation "MERCY" in Kalisz: 6 WTZ centers, 190 participants;
- Polish Association of the Blind: 6 WTZ centers, 214 participants.

In big cities the contribution of the associations may differ from that observed on a national level, for example in Warsaw the most important MGO's are: Catholic Association of the Disabled of the Archdiocese of Warsaw (2 WTZ). Foundation for Helping People with Intellectual Disabilities "Dom", Association of Parents and Guardians of the Mentally Impaired People "Faith and Hope", Social Welfare Home "At the Early Spring", PSONI, Association "Open Door" (Morysińska 2014).

Physical health of persons with intellectual disability

The young population with intellectual disabilities have many physical health problems (Young-Southward et al. 2017). However current results of activities aimed at improving the health of young people with intellectual disabilities in Poland are not fully satisfactory (Krawczyńska et al. 2013). Their physical fitness according to available reports is insufficient (Wieczorek 2008). Inadequate diet and lack of proper physical activity, which may be the result of a lack of awareness, are serious health risk factors (Matuszak 2014). They often have an increased BMI (Pop et al. 2007). In 2003 a questionnaire survey concerning physical activity was carried out among students aged 15-17 of with mild intellectual disability, in the region of Upper Silesia. It was found that only every second girl and over 62% of boys take a moderate physical activity during their free time. Their peers without disabilities schools are more active in both gender groups (Baranowski 2013). Studies on obesity in children and adolescents with intellectual disability indicate a wide scale of the phenomenon, which often has a social background. This may be one of the conditions for the difficulties in the treatment and rehabilitation of this population (Matuszak et al. 2010). Increased risk for comorbid medical conditions in persons with intellectual disability is also reported in studies from other countries. Reichard & Stolze (2011) found that persons with intellectual disabilities are more likely to have diabetes, arthritis cardiovascular disease and asthma. As the population of people with intellectual disabilities ages, we observe a substantial increase in the rates of chronic conditions and their relative impact on health (Krahn and Fox 2014, Reichard et al. 2011, Bratek et al. 2017).

Psychiatric services for persons with intellectual disability and comorbid psychiatric disorders

In Poland there are no special psychiatric services dedicated for patients with intellectual disabilities. The comorbid psychiatric disorders are treated in general psychiatric wards or hospitals or in outpatient settings (Boguszewska et al. 2008). The persons staying in the long-term care institutions are usually visited by a consultant psychiatrist every 2-3 months. In case of a more serious challenging behavior of psychotic exacerbation, they are referred to a local general hospital. Bobińska et al. (2009) in their analysis list the most frequent reasons for hospital admissions: aggression, appearance or worsening of psychotic symptoms, worsening or change of behavior. In their opinion the direct causes of hospitalizations are determined by environmental reasons, among which conflicting relationships and lack of personal support were the most common. Psychotic decompensations are the most frequent among patients with mild level of intellectual disability, behavior disorders among those with a more serious disability (Bobińska et al. 2009a). In one third of the

admitted patients repeated hospitalizations are observed, and women are more frequently represented in this group (Bobińska et al. 2009b). It is very common that the environmental background is the factor leading to a deterioration being a reason of a hospitalization (Bobinska et al. 2008). Some changes in this situation are expected in the course of the implementation of the National Program of the Mental Health Care, which postulates the creation of so called Centers of Mental Health, which would be responsible for the development of community psychiatry services for different groups of psychiatric patients. At the moment preparations for the pilot phase of this reform are being done (Wciórka et al. 2014). Children with intellectual disability and comorbid psychiatric disorders are treated in inpatient and outpatient departments of child and adolescent psychiatry. However, the accessibility to such services are still limited due to too small number of specialists and psychiatric hospitals and wards for children (Tabak 2014).

Services for offenders with intellectual disability

Polish law excuses a defendant if an offense committed in a state of insanity. Past offenders and suspected or potential future offenders with mental health problems or an intellectual or developmental disability may be referred by the court to specialist secure units caring for mentally ill offenders. The court may make a decision on the stay in a psychiatric institution only to prevent an offence of significant social harmfulness (Kmieciak 2013, Heitzman & Markiewicz 2017).

The total number of hospital beds for offenders in psychiatric institutions in Poland in 2013 was 2132: Units with a basic degree of security - 1162 beds. Units with enhanced security level - 777 (730 for men and 47 for women) Units with the maximum degree of security - 193 (only men) (Markiewicz 2013).

Polish Ombudsman, Adam Bodnar has been focusing on the problem of offenders with intellectual disabilities since 2015. According to him in Poland there is a lack of systemic solutions regarding the treatment of persons with mental or intellectual disabilities who are participants of criminal proceedings (Bodnar 2017). He initiated a research program to analyze the situation of a group of patients with intellectual disabilities in Polish penitentiary system. As part of the research project, the situation was verified for a group of persons deprived of their liberty (convicted and remand prisoners), who have been diagnosed with moderate intellectual disability, and prisoners with mental or intellectual disability to whom doubts arose as to guaranteeing them the right to defense in criminal proceedings and premises for continued detention in prison isolation. Most convicts with intellectual disabilities are referred to a therapeutic system in a ward for convicts with non-psychotic mental disorders intellectual disabilities. The aim of the interventions are preventing the aggravation of pathological features of personality, restoring mental balance and shaping the ability of social coexistence and preparation

for independent living. However this system misses certain elements like special education or addiction treatment services for this group of prisoners. One of the conclusions of the above program was that from the point of view of the effectiveness of a modern penitentiary system, the attitude to the offenders with intellectual disability requires deep transformations. In present, the current practice in our country cannot be effective (Brzostymowska et al. 2017). It is emphasized the need to increase the financing of prison health care and the number of medical personnel, as well as to improve the material and living conditions and sanitary conditions in the prevention of suicidal behavior and improve the health of people in custody and convicts (Kurlak 2017).

Training of specialist working with person with intellectual disability

The main university in Poland training specialists working with the persons with intellectual disability is The Maria Grzegorzewska University in Warsaw.

The main goal of the University is training future teachers, including specialists working in special education system. But the program of the University offers also Interdisciplinary Trainings for those graduates of social sciences, humanities, medicine, art or technical sciences who combine their career aspirations with broadly understood activities for the benefit of people with disabilities or intend to pursue a research career in disability research and are interested in continuing their studies (Głodkowska & Gasik 2017). Except for this there are departments of oligophrenopedagogy in 9 other Polish Universities training mainly teachers for special schools.

Training of medical students offers only very limited basic knowledge on intellectual disability within psychiatry classes. The curriculum of specialty in psychiatry also gives little coverage on this topic. There is no separate specialty in mental health in intellectual disability within psychiatry. Patients with MIDH are usually taken care of by general specialists.

DISCUSSION

The model of care for patients with intellectual disability in Poland has certain strengths. One of them is a complex system of different forms of services designed for different age groups and focusing on different forms of activities. EIC's and OREW's concentrate on the support for children with intellectual disability and their families. These institutions are run mainly by NGO's and other non-government institutions. Education of children and young people is provided by a network of a state-provided special education system. This system consists of special primary schools and secondary vocational schools. Adult persons with intellectual disability may take advantage of the offer of WTZ's and OAC's. These are also run by NGO's, local government and church institutions. Concerning

the education system, the main strength is the well prepared staff of teachers being trained by a network of university degree colleges, with a long tradition and good quality of teaching, with a special contribution of the Maria Grzegorzewska University, which is a leader not only in training of specialists, but also in scientific research on intellectual disabilities in Poland. Concerning the care for patients with comorbid psychiatric disorders the advantage is a relatively good access to general psychiatry specialists, who mostly take care of MHID patients in Poland, as there are no psychiatrists specializing in the treatment of comorbid psychiatric disorders and intellectual disability. Except for a regular outpatient care, an access to inpatient treatment in general psychiatry wards is also guaranteed. However they are not run by the state, but mostly NGO's.

The model of care of patients with intellectual disability in Poland also has certain weaknesses. In Poland MHID patients are treated in general psychiatric hospitals and outpatient and services. There are no special units dedicated for them, and no specialized treatment and rehabilitation programs. One of the negative phenomena is the fact, that many psychiatric drugs, including second generation antipsychotics are not refunded for persons with intellectual disability, which results in a common prescribing of traditional neuroleptics like haloperidol, causing many side-effects. The changes in this field are limited by the fact, that in our country there are no published statistical data about the comorbidity of intellectual disability and psychiatric disorders. There are also no available publications on pharmacological treatment, number of hospital beds, outpatient consultation, comorbidities, mortality etc. in this population.

There is a need to prepare and publish guidelines for Polish doctors, on proper diagnosing and treatment of persons with intellectual disability, with the focus of their special needs. A good example could be Canadian guidelines, which put emphasis on following aspects of care: a person-centered approach to care, proper communication, engagement in a shared decisions with patients and their caregivers. These guidelines postulate also a creation of interprofessional health care teams of different specialists. The Authors of these guidelines, Sullivan et al. (2018) advise also to review regularly the indications, dose, effectiveness, and side-effects of medications, and to monitor such parameters like weight, WCR, BMI, vision and hearing impairments and challenging behaviors. Concerning the treatment of comorbid psychiatric disorders, they propose the use of disorder-specific psychotropic medication accompanied with other possible interventions (Sullivan et al. 2018). There is a need to translate into Polish, validate and use questionnaires developed for people with ID, which are used in other countries. As some authors postulate the need to introduce new diagnostic guidelines (Bertelli et al. 2016), we should follow the research on this topic and introduce the results in our clinical work. It is also very important to increase the availability of modern

pharmacological treatment methods including the use of second generation antipsychotics. We should also make efforts to introduce new methods taking advantage of new technology like telemedicine and virtual reality (Krysta et al. 2017).

CONCLUSIONS

The main challenges in the care of persons with intellectual disability include the changes in the mental care system. At the moment there are no special services either in the inpatient hospital system or in the outpatient care. There is an expectation that the newly introduced national Program of the Mental Health Care, which will focus on the community psychiatry will improve the accessibility for specialist help for patients with intellectual disability with comorbid psychiatric disorders. Another challenge is the reform of the penitentiary system, which will change the present attitude to offenders with intellectual disability. The system of training medical students and young doctors also needs to be reformed as now very little time in the teaching curriculum is devoted for patients with intellectual disability. A better interdisciplinary co-operation of specialists in different fields is also necessary to improve the effectiveness of care.

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Krzysztof Krysta & Janina Krysta: design of the review, literature researches and analyses, interpretation of results, manuscript writing.

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RISK FACTORS FOR NONCOMPLIANCE WITH ANTIPSYCHOTIC MEDICATION IN LONG-TERM TREATED CHRONIC SCHIZOPHRENIA PATIENTS

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SUMMARY

Background: The attitudes of schizophrenic patients toward medications directly impact the treatment compliance. Although noncompliance represents a serious concern in long-term schizophrenia treatment, a detailed information on the factors that impair compliance is still limited. The present study aims to assess the factors related to noncompliance with antipsychotics agents, in long-term treated chronic paranoid schizophrenia patients.

Subjects and methods: Two groups of such patients (total number $n=162$) were analyzed and compared: 1). patients with symptomatic remission on haloperidol ($n=32$), clozapine ($n=40$) or olanzapine ($n=45$), and 2). drug resistant patients ($n=45$). The mean duration of the disease was 19.3 years.

Results: Altogether, in our patient sample, a better drug attitude was found in the olanzapine and clozapine groups. Our findings have also revealed that worse attitude toward antipsychotics correlated with an earlier onset of schizophrenia, younger patient age, shorter duration of the disease, higher burden of symptoms, treatment with a typical antipsychotics, and higher severity of akathisia.

Conclusion: Our results suggest that detecting factors that influence the patient's attitude toward medications might be helpful for designing targeted educational strategies in chronic schizophrenia patients (particularly those with the high risk of noncompliance), and further trials are warranted to explore this topic.

Key words: schizophrenia - compliance - drug attitude - antipsychotics - long-term treatment

* * * * *

INTRODUCTION

Lack of compliance to therapeutic agents is one of most important problems of contemporary medicine. In psychiatry, the crisis of compliance is one of the hot spots in every discussion on the decreasing treatment effectiveness during recurrent schizophrenia episodes, and in the development of drug resistance. For example, the results of our recent telemedicine study, showed that the compliance rate, among schizophrenic patients with symptomatic remission, in the first month of the treatment was 44.6%, and had been decreasing over the subsequent 6 months (Krzystanek et al. 2015).

Schizophrenia is a chronic, progressive disease, and if its treatment is not continued, the schizophrenic process maintains in progress, resulting in chronic symptoms and reduction of brain volume (Vita et al. 2015). Diminishing number of neurons, together with declining number of receptors, decrease the possibilities of favorable treatment outcomes. Altogether, the good prognosis in schizophrenia is augmented by an adequate therapeutic compliance, in every single patient (Vita et al. 2015).

The basic component of compliance is an attitude of each patient toward taking the medication. This attitude represents a combination of different factors, such as the

patient's knowledge, education, judgement or prejudice, society stereotypes, stigma, philosophy of life, culture, age, gender, income level, duration of schizophrenia, etc. (Kuroda et al. 2008). For instance, patients from different cultures may be characterized by various levels of drug acceptance, schizophrenia insight, and stigma (Mohamed et al. 2014).

One of the possibilities to improve the medication compliance is to explore the patient's attitudes, and possible reasons for noncompliance. This may lead to designing some helpful and better targeted management strategies, suitable for clinical practice. Therefore, the primary goal of our study was to identify factors associated with the medication acceptance (as an important part of the patient's attitude), in long-term treated chronic paranoid schizophrenia patients. For this reason, we first, evaluated mental state of patients with symptomatic remission, treated with a classical antipsychotics – haloperidol, or one of the atypical antipsychotics – olanzapine or clozapine; second, assessed the same parameters, in the subgroup of patients without remission, who were treatment resistant, and third, explored the patients' attitudes toward the antipsychotic treatment with three different agents (haloperidol, clozapine, and olanzapine). Subsequently, we compared these attitudes

between the patients with symptomatic remission (SR) (on these three antipsychotics), and the ones, who were resistant to antipsychotic medications (RES).

SUBJECTS AND METHODS

Patients

A total of 162 schizophrenic patients were included into the study. The mean age of patients was 46.1 years, the average onset of the disease was at the age of 27.4 years, and the mean duration of the disease was 19.3 years. The symptomatic remission patients (SR) were recruited from outpatient clinics, and the treatment resistant patients (RES) were residents of social houses in the area of Silesia (Poland).

The study was approved by the Ethical Committee of the Medical School of Silesia in Katowice. All patients signed their written, voluntary informed consent.

The basic study sample characteristics are given in Table 1.

The study patients were diagnosed with paranoid schizophrenia (according to ICD-10 criteria) and treated in monotherapy with haloperidol (HAL, n=32), clozapine (CLO, n=40) or olanzapine (OLZ, n=45) for at least 6 months.

In our study, the patients included into the subgroup with symptomatic remission (SR) of schizophrenia met the following inclusion criteria (Andreasen et al. 2005, van Os et al. 2006): they had Positive and Negative Syndrome Scale (PANSS) score of three or less, simultaneously on all eight items: delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), passive/apathetic social withdrawal (N4), lack of spontaneity and flow of conversation (N6), and their symptom severity criteria had been achieved for the minimum period of 6 months.

The patients included into the subgroup that was resistant to the treatment (RES, n=45) did not have any substantial remission in the history of their disease, and they were treated (upon the duration of the study) with more than one antipsychotic drug, including the first generation long acting injectable antipsychotics. The main exclusion criteria were: schizophrenia-like symptoms of organic origin, psychoactive substance abuse and concomitant mental disturbances.

Procedures

Clinical status of patients was assessed by using the following clinical scales: Drug Attitude Inventory (DAI-10), Positive and Negative Syndrome Scale (PANSS), Negative Symptom Assessment Scale (NSA-16), Simpson-Angus Extrapyramidal Symptoms Scale (SAS) and Barnes Akathisia Rating Scale (BARS).

Statistical analysis

Due to lack of normal distribution the non-parametric Kruskal-Wallis test was used. To show more detailed differences between groups post hoc analysis was performed. Two tests were used: the more rigorous HSD Tukey test and liberal NIR test.

RESULTS

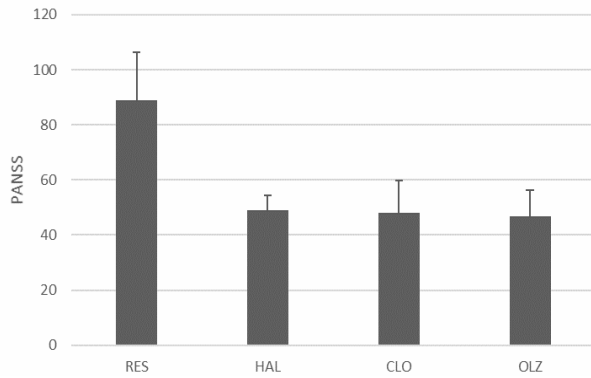
Main results

The highest intensity of schizophrenia symptoms in PANSS was present in treatment resistant schizophrenia patients (Figure 1). Pearson's correlation test showed that the PANSS results correlated with NSA-16 score ($R=0.76$, $p=0.001$) in the RES group of patients with shorter schizophrenia duration ($R=-0.84$, $p=0.0001$), and with NSA-16 results in the haloperidol group ($R=0.63$, $p=0.0001$), clozapine group ($R=0.85$, $p=0.001$) and olanzapine group ($R=0.56$, $p=0.0001$).

Table 1. Characteristics of the study subgroups

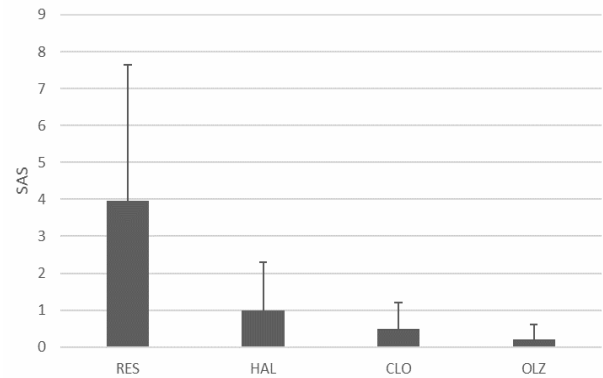
Patient's characteristic	Symptomatic remission (SR) patients			Treatment resistant (RES) patients (n=45)
	Antipsychotic (n – number of patients in the group)			
	Haloperidol (n=32)	Clozapine (n=40)	Olanzapine (n=45)	
Gender				
females	15	15	21	29
males	17	25	24	25
Age*				
years (\pm SD**)	52.3 (\pm 9.6)	43.5 (\pm 7.1)	41 (\pm 12)	22-65
min-max***	37-65	34-53	22-61	22-65
Age of schizophrenia onset*				
years (\pm SD)	31 (\pm 8.5)	25.9 (\pm 8.2)	26.9 (\pm 6.1)	27.4 (\pm 7.9)
min-max	22-38	18-41	20-39	18-45
Duration of the disease*				
years (\pm SD)	20.6 (\pm 11.9)	19.6 (\pm 6.4)	16 (\pm 7.9)	23.1 (\pm 11.5)
min-max	6-40	6-29	1-31	4-50
Hospitalisations*	15.6	6.3	4.5	11.7

* arithmetic mean; ** standard deviation; *** minimum and maximum values



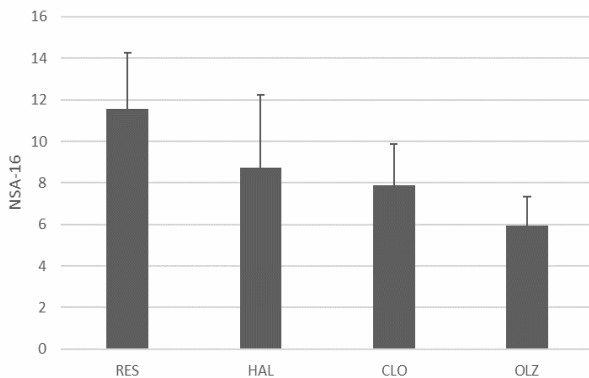
Results expressed as arithmetic means with standard deviation (SD); Kruskal-Wallis test: $H_{3,162}=94.9$, $p=0.0001$, $\eta^2_p=0.7$; RES – treatment resistant patients (n=45); HAL – patients on haloperidol (n=32); CLO – patients on clozapine (n=40); OLZ – patients on olanzapine (n=45)

Figure 1. Global PANSS results in schizophrenia patients



Results expressed as arithmetic means with standard deviation (SD); Kruskal-Wallis test: $H_{3,162}=52.6$, $p=0.00001$, $\eta^2_p=0.36$; RES – treatment resistant patients (n=45), HAL – patients on haloperidol (n=32); CLO – patients on clozapine (n=40); OLZ – patients on olanzapine (n=45)

Figure 3. SAS results in schizophrenia patients



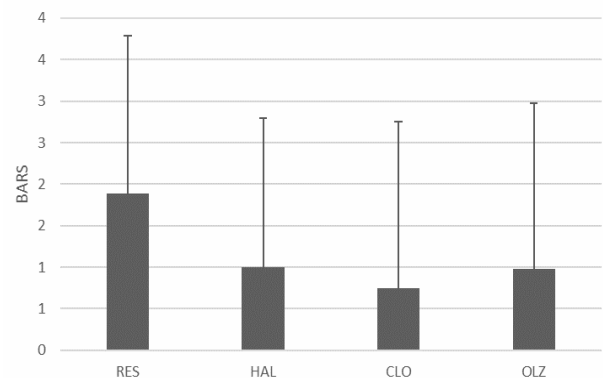
Results expressed as arithmetic means with standard deviation (SD); Kruskal-Wallis test: $H_{3,162}=84.7$, $p=0.00001$, $\eta^2_p=0.53$; RES – treatment resistant patients (n=45); HAL – patients on haloperidol (n=32); CLO – patients on clozapine (n=40); OLZ – patients on olanzapine (n=45).

Figure 2. NSA-16 scale results in schizophrenia patients

The highest intensity of negative symptoms was shown in RES group, and the lowest in olanzapine group (Figure 2). All the results were significantly different ($p<0.05$ in Kruskal-Wallis (H) test and in the post-hoc analysis – HSD Tukey and NIR tests).

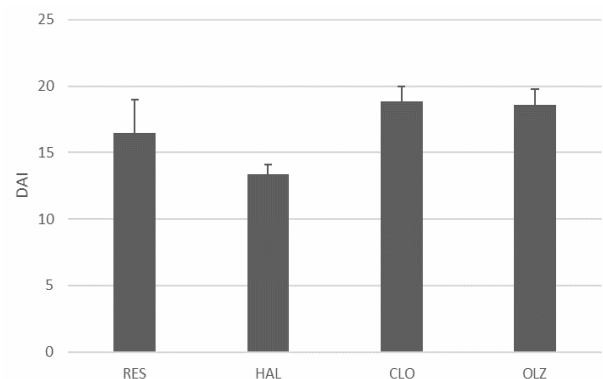
In RES group, higher NSA-16 result correlated with global PANSS result ($R=0.76$, $p=0.0001$), longer duration of the disease ($R=0.39$, $p=0.009$) and SAS score ($R=0.34$, $p=0.02$). In the haloperidol group the intensity of negative symptoms correlated with global PANSS score ($R=0.63$, $p=0.0001$), duration of the disease ($R=-0.84$, $p=0.0001$) and SAS result ($R=0.55$, $p=0.001$). In clozapine group, higher NSA-16 result correlated with schizophrenia duration ($R=-0.43$, $p=0.005$) and with BARS score ($R=0.77$, $p=0.0001$).

Intensity of extrapyramidal symptoms and akathisia were mild in all the study subgroups. The results are shown in Figures 3 and 4.



Results expressed as arithmetic means with standard deviation (SD); Kruskal-Wallis test: $H_{3,162}=21.4$, $p=0.0001$, $\eta^2_p=0.05$; RES – treatment resistant patients (n=45); HAL – patients on haloperidol (n=32); CLO – patients on clozapine (n=40); OLZ – patients on olanzapine (n=45)

Figure 4. BARS results in schizophrenia patients



Results expressed as arithmetic means with standard deviation (SD). Kruskal-Wallis test: $H_{3,162}=86.3$, $p=0.00001$, $\eta^2_p=0.64$; RES – treatment resistant patients (n=45), HAL – patients on haloperidol (n=32); CLO – patients on clozapine (n=40); OLZ – patients on olanzapine (n=45)

Figure 5. DAI results in schizophrenia patients

Factors associated with compliance and non-compliance to medications

Patients' drug attitude differed in the analyzed subgroups, as presented in Figure 5. The worst attitude was expressed by the patients treated with haloperidol (this was even worse than in those, who were resistant to treatment). In the post-hoc analysis, the DAI results between groups were statistically different in all the study groups, except from the subjects, treated with olanzapine or clozapine (HSD Tukey test $p=0.8$, NIR test $p=0.4$).

The analysis of correlations in the haloperidol group showed that the worse drug attitude relates to the earlier schizophrenia onset ($R=0.64$, $p=0.0001$), younger patient's age ($R=0.63$, $p=0.001$) and higher score on PANSS ($R=-0.49$, $p=0.004$) and on BARS ($R=-0.6$, $p=0.0001$). In the RES group, higher results in DAI scores correlated with earlier schizophrenia onset ($R=0.4$, $p=0.008$). In clozapine patients, the worse attitude toward the antipsychotic was connected with shorter duration of the disease ($R=-0.6$, $p=0.0001$) and lower BARS score ($R=-0.67$, $p=0.0001$).

DISCUSSION

Main findings

In the present study, we report that in the patients with long-term treated chronic schizophrenia there was no difference in the severity of symptoms, between the patients in symptomatic remission (SR), regardless of the antipsychotic medication use (classical versus atypical). However, the patients treated with olanzapine had the lowest severity of negative symptoms.

The severity of negative symptoms was correlated with the duration of the disease, in all the study subgroups, except from the one, treated with olanzapine. This indicates that the treatment with olanzapine is related to a lower frequency of negative symptoms, and also, with a possible arrest of the development of these symptoms. The patients with long-term schizophrenia treated with atypical antipsychotics displayed the best compliance with the treatment. In contrast, the worst attitude toward the medication was noted in younger patients, treated with haloperidol, with an early onset of schizophrenia, severe disease symptoms, and severe akathisia.

The patients treated with clozapine had worse compliance with the antipsychotic at the beginning of treatment. In case of olanzapine, no differences in compliance with the medication, related to the disease duration, time of onset, severity of symptoms, or medication intolerance were observed.

No relations were found between the drug attitude and the negative or parkinsonian-like symptoms, in any of the study groups.

Comparison with prior studies

Numerous studies have indicated the importance of the role of positive attitude toward the treatment for the outcome of schizophrenia. Patients who understand their disease process, and accept the gains from the treatment achieve better therapeutic success, and are capable to fulfill their life aims (Lysaker et al. 2004).

Awareness of the disease has the great impact on the drug attitude, better insight and acceptance of the long-term treatment regime. All those factors contribute to a better compliance and prevention of schizophrenia relapse (Lysaker et al. 2004, Kako et al. 2014).

Long-term study of Murawiec and Boutros (2012) showed that better attitude toward the drug, assessed with DAI, correlated with reduced number of days spent in the psychiatric hospitals. It was also proved that higher scores in DAI corresponded with the therapeutic adherence in schizophrenia patients (Yang et al. 2012). The EUFEST study confirmed the usefulness of DAI score as the predictor of the treatment effectiveness in the first episode of schizophrenia (Gaebel et al. 2010).

As the lack of compliance has become the crucial problem of contemporary psychiatry, an attempt to identify the risk factors for negative drug attitude appears to be helpful for finding strategies to improve patient outcomes. The worst attitude toward the antipsychotic treatment in our study group was expressed by the patients receiving a classical neuroleptic (haloperidol), and by the treatment resistant ones. According to our results, the worse compliance was observed in younger age subjects, and with early onset of the disease. Similarly, Chandra et al. (2014) showed that poorer compliance relates to early age of schizophrenia onset and younger age of patients. The study of Chandra et al. was operating on another inclusion criteria: the patients were suffering from schizophrenia for no longer than 6 months and were in acute psychotic state, but his results are consistent with our study. In Chandra's study, the lack of compliance and worse drug attitude was related to higher PANSS severity. Brain et al. (2013) indicated the same correlation – the higher severity of positive symptoms was the predictor of non-adherence. In the presented study the worse drug attitude was observed in patients with more intensive schizophrenia symptoms and with shorter duration of the disease. Our results replicate the observation from CATIE study, where patients with lower PANSS score at the beginning of the study expressed better attitude toward drug (Lieberman et al. 2005). As in the study of Chandra et al. (2014) we also showed that bad attitude to the drug was related to the severity of antipsychotic side effect – akathisia.

The interdependence of the earlier onset of schizophrenia and the worse drug attitude indicates the importance of early education in young schizophrenia patients. The better acceptance of the disease improves the attitude to the treatment and improves live competence (Mintz et al. 2003).

In the subsequent study Mintz et al. showed that better insight in schizophrenia symptoms improves their reception by patients (Mintz et al. 2004). Moreover, the CATIE study showed that the improvement of insight in schizophrenia correlates with the better compliance (Lieberman et al. 2005).

Among the results of the present study the interesting finding was that though the intensity of negative symptoms both in the treatment resistant patients and in subjects treated with haloperidol was higher than in clozapine and olanzapine groups, the drug attitude did not correlate with negative symptoms. Because the negative symptoms in the study correlated with severity of extrapyramidal symptoms, their character may be secondary to the antipsychotic treatment. The relation between the negative symptoms and drug attitude during longer time periods requires further studies.

In the treatment resistant patients, negative symptoms were worsening with the longer duration of schizophrenia. In contrast, in the symptomatic remission (SR) groups, the intensity of negative symptoms decreased with the duration of the disease. This may bring some optimism in terms of the long-term treatment outcomes in chronic schizophrenia, providing that the patients remain compliant with the treatment.

The drug attitude in the study group was better in patients treated with atypical drugs. It is worth reminding that proscribing typical neuroleptics is indicated as the main reason of poor adherence in the treatment of schizophrenia, beside the poor insight and lack of therapeutic alliance between patient and his therapist (Dassa et al. 2010).

Strengths and limitations

Strengths

To our knowledge, the present study is one of very few studies that explores several clinical parameters of patients with long-term treated chronic schizophrenia. In contrast, the majority of published studies on schizophrenia have been focused on early phases of this disease.

In addition, in our study, we investigated a homogenous group of schizophrenic patients, in symptomatic remission, who were treated with different antipsychotics for many years. In this way, the results of this study can be relevant to different clinical situations, encountered in a daily management of such patients.

Limitations

We are aware of some important limitations of our study, such as lack of reliable methods for direct assessment of the patient compliance with medications (this is common in studies exploring drug adherence). In particular, the DAI-10 scale, which we used, can only indirectly indicate whether or not the patient will be taking a given medication. For instance, a patient may

be perfectly educated about schizophrenia symptoms, and about the importance of therapeutic adherence, and may even express the best drug attitude in front of an examiner. However, in the real world, he or she might still be noncompliant. Although there is no perfect way to assess the drug compliance, the DAI-10 still remains the most reliable tool in clinical practice.

Our study included patients of similar age, who had comparable duration and onset of schizophrenia. However, we were unable to involve patients with a similar number of hospitalizations. For this reason, there is a concern that differences in the number of hospitalizations could potentially impact the schizophrenia course, and thus, might be a source of bias in interpreting of the study data.

Since in the present study, one classic and two atypical antipsychotics were used, it might be impossible to generalize the study results to therapy with other antipsychotic agents. Nevertheless, the antipsychotics used in this study are common in psychiatric practice, and thus, they should be representative in terms of their clinical efficacy, safety, and mechanisms of action.

Clinical implications

The results of this study provide at least two valuable messages for clinicians. First, it is possible to identify risk factors, predicting undesirable attitude toward medications, such as: earlier onset of schizophrenia, younger patient age, shorter duration of the disease, higher severity of symptoms, treatment with typical neuroleptics, and higher severity of akathisia. Patients with such characteristic should be specifically supervised to improve their treatment adherence. Second, the study findings indicate that olanzapine is well received by patients with chronic schizophrenia and has particularly beneficial impact on exacerbation of negative symptoms in such patients.

CONCLUSIONS

An analysis of clinical parameters, and attitudes toward medication, in a group of patients with chronic schizophrenia allows to identify factors that might increase risk of undesirable attitude to pharmacologic treatment, and in turn, also a worse adherence to treatment. Antipsychotic medications, despite their similar clinical efficacy in treatment of schizophrenia symptoms, have been differently perceived by patients. Among the analyzed study medications, atypical antipsychotics (olanzapine and clozapine) were best perceived by the patients. In particular, using olanzapine was beneficial for improvement of negative symptoms, and good tolerability of the treatment. Moreover, taking olanzapine might arrest the development of negative symptoms in patients with chronic schizophrenia.

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MAGNESIUM AND KETAMINE IN THE TREATMENT OF DEPRESSION

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SUMMARY

Depression affects over 121 million people annually worldwide. Relatively low remission rates among depressive patients enforce the search for new therapeutic solutions and an urgent need to develop faster-acting antidepressants with a different mechanism of action occurs. The pathomechanism of depression postulated by the monoamine hypothesis is limited. The results of abnormalities in glutamate and γ -aminobutyric acid (GABA) systems in the brains of people with mood disorders allowed to develop new theories regarding pathophysiology of these disorders. Glutamatergic transmission is influenced by magnesium and ketamine through glutamatergic N-methyl-D-aspartate receptor (NMDAR) antagonistic effects.

Magnesium and ketamine have a common mechanism of action in the treatment of depression: an increase in GluN2B (NMDAR subunit) expression is related to the administration of both of the agents, as well as inhibition of phosphorylation of eEF2 (eukaryotic elongation factor 2) in cell culture and increase of the expression of BDNF in the hippocampus. Combination of ketamine and magnesium in a normal magnesium level presents a superadditive effect in depression treatment. Analysed substances affect the GABAergic system and have anti-inflammatory effects, which is correlated with their antidepressant effect.

The synergistic interaction between the pharmacodynamic activity of magnesium and ketamine may be of particular importance for patients with mood disorders. Further research is needed to determine the relationship between magnesium levels and ketamine treatment response mainly in the attempt to establish if the magnesium supplementation can change ketamine treatment response time or present superadditive effect.

Key words: magnesium - ketamine - depression

* * * * *

INTRODUCTION

Depression affects over 121 million people annually worldwide, being a common cause of disability, social disfunctions, family life disruptions and work environment problems (Gelenberg 2010, Tizabi et al. 2012). Current pharmacological treatment for depression includes a wide range of drugs, unfortunately with a homogeneous mechanism of action mainly related to the regulation of the monoamine system. Relatively low remission rates (approximately one third of patients do not achieve remission due to this treatment) among depressive patients, numerous side effects and delayed onset of action enforce the search for new therapeutic solutions, there is an urgent need to develop faster-acting antidepressants with a different mechanism of action (Gaynes et al. 2009, McIntyre et al. 2014). The last two decades of research on the neurobiological foundations of depression have been dominated by the study focused on the glutamatergic system (Sanacora et al. 2008). Glutamatergic transmission is influenced by magnesium and ketamine through glutamatergic N-methyl-D-aspartate receptor (NMDAR) antagonistic effects (Berman et al. 2000, Murck 2013, Zarate et al. 2006). The synergistic interaction between the pharmacodynamic activity of magnesium and ketamine may be of particular importance for patients with mood disorders.

DEPRESSION - A NEW POINT OF VIEW

The pathomechanism of depression postulated by the monoamine hypothesis is limited. It was reported that monoamine deficiency did not reliably indicate depression in healthy people and did not significantly increase the symptoms of depression in untreated patients (Duman et al. 2016). The results of abnormalities in glutamate and γ -aminobutyric acid (GABA) systems in the brains of people with mood disorders allowed to develop new theories regarding pathophysiology and treatment of these disorders. It was observed that GABA levels in the cortical areas of patients with depression are reduced (Godfrey et al. 2018, Price et al. 2009). Reduction in the level of glutamate metabolites in the central frontal cortex in MDD was observed as well (Moriguchi et al. 2018). In contrast, acute stress increases extracellular glutamate amount in the medial prefrontal cortex and hippocampus indicating that excitotoxicity of glutamate acting on NMDAR is responsible for neuronal damage (Popoli et al. 2011).

MAGNESIUM DEPENDENCY IN DEPRESSION

The importance of magnesium ions for the biochemical processes of an organism cannot be overestimated. This element is indispensable for the catalytic

activity of about 300 enzyme proteins as well as being a micronutrient of considerable importance for the proper functioning of the central nervous system, therefore its fluctuations can be a risk factor leading to mental disorders (Schwalfenberg et al. 2017). Low levels of magnesium with high levels of calcium and glutamate in the hippocampus may cause changes in the functioning of synapses which may lead to the development of depression (Serefko et al. 2016).

Magnesium blocks NMDAR in a voltage-dependent manner; when its concentration is too low there is an abnormal influx of calcium into the cells resulting in the release of intracellular glutamate that causes depolarization and can lead to neuronal dysfunction (Murck 2013, Sowa-Kućma et al. 2013). However, it is worth noticing the effect of magnesium is not only related to NMDAR antagonism. Magnesium indirectly increases α -Amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid-ergic (AMPAergic) activity, increases the expression of brain derived neurotrophic factor (BDNF), suppresses hippocampal kindling, modulates protein kinase C (PKC), affects P-glycoprotein which alters the hypothalamic-pituitary-adrenal axis (Murck 2013). Magnesium is also important for the functioning of serotonergic, noradrenergic, dopaminergic, and γ -aminobutyric acid-ergic (GABAergic) systems and has anti-inflammatory activity. All the above-mentioned mechanisms are associated with its antidepressant effect (Cubała et al. 2016, Sanacora et al. 2008, Singewald et al. 2004).

In preclinical studies it was observed that feeding mice on a low magnesium diet is associated with an increase of depressive-like behavior in the forced swim test (FST), similar behavior was observed in rats (Singewald et al. 2004, Spasov et al. 2008). Cotreatment with magnesium and some antidepressants, such as imipramine, fluoxetine, citalopram, tianeptine, and bupropion, results in a synergistic antidepressant effect similar to FST (Szewczyk et al. 2018, Poleszak et al. 2005). Antidepressant activity of magnesium in combination with glutamatergic N-methyl-D-aspartate (NMDA) antagonists was observed in mice, therefore magnesium supplementation may be an effective method of reducing the NMDA antagonist dose (Poleszak et al. 2007). One animal study hypothesized about magnesium potentially being a cofactor which would increase the effect of ketamine. The results of this study did not confirm the usefulness of magnesium as a supportive treatment for ketamine in depression in mice (Razmjou et al. 2016). The issue calls for further investigation.

The concentration of magnesium in serum may be a potential marker in patients with depression as multiple studies have observed a relationship between depression and magnesium levels, but obtained results are not homogeneous. Most studies exhibit low magnesium levels in the course of depression (Cheungpasitporn et al. 2015, Frizel et al. 1969, Islam et al. 2018), however, there are also studies presenting high magnesium concentration in patients' blood (Cubała et al. 2013, Styczeń et al. 2013).

Studies indicate the antidepressant properties of magnesium and/or potential usage of magnesium as an additive to antidepressant treatment (Cardoso et al. 2009, Poleszak et al. 2005). Response to antidepressant treatment in patients with higher levels of magnesium was observed (Camardese et al. 2012). Another study showed an increase in intracellular magnesium concentration after treatment with amitriptyline or sertraline (Nechifor 2009). Tarleton et al. (2017) demonstrated a decrease in depression symptoms after just a two-week period of magnesium supplementation, also relationship between low magnesium intake and depression was observed (Tarleton & Littenberg 2015). Rapid (in the duration of less than 7 days) antidepressant effect associated with the response to magnesium treatment was shown (Eby & Eby 2006). Magnesium treatment was as effective as imipramine in two-week randomized study in a group of elderly patients with hypomagnesemia/type 2 diabetes (Barragan-Rodriguez et al. 2006). In the contrast to aforementioned research, in the Mehdi et al. (2017) study no improvement in the symptoms of depression after magnesium supplementation was observed, lack of antidepressant effect was also reported in a randomized clinical trial in a group of patients with postpartum depression (Fer et al. 2017).

KETAMINE AND ITS ANTIDEPRESSANT PROPERTIES

Ketamine is an intravenous anesthetic presenting a wide spectrum of pharmacological effects, including sedation, catalepsy, analgesia, and sympathetic stimulation (Kishimoto et al. 2016, Kurdi et al. 2014). Recently, it is increasingly used in psychiatry due to the fact that a single injection of ketamine shows a rapid antidepressant effect (Berman et al. 2000, Kishimoto et al. 2016, Zarate et al. 2006). Ketamine is an NMDAR antagonist, but it shows different mechanism of antidepressant action as well. The immediate effect of ketamine is the blockade of the postsynaptic GluN2B NMDA receptors (glutamate ionotropic receptors NMDA type subunit 2B)- these receptors activate the eukaryotic extension factor-2 (eEF2) which decrease BDNF levels. By blocking NMDA receptors containing GluN2B, ketamine can prevent phosphorylation of eEF2, increase BDNF levels and promote AMPA receptors in the synapses, increasing synaptic connectivity. Preclinical studies show that ketamine causes a glutamate burst by blocking NMDAR on GABA interneurons, which results in its indirect action. GABA interneurons are more sensitive to ketamine because their tonic activity removes magnesium ions from channel, allowing ketamine to block NMDAR. Ketamine reduces the inhibition of glutamate release and results in increased stimulation of AMPA glutamate receptors which activates a signaling cascade that raises BDNF levels. Local release of BDNF stimulates tropomyosin kinase B receptor (TrkB), resulting in the activation of mammalian target of

rapamycin complex 1 (mTORC1) which increases synaptic plasticity (Murck 2013, Duman et al. 2019, Krystal et al. 2019). Ketamine also presents an effect on the normalization of proinflammatory cytokines in mice, in particular interleukin 1 beta (IL-1 β), tumor necrosis factor α (TNF- α) and interleukin 6 (IL-6) (Tan et al. 2017). Human studies confirm the reduction of proinflammatory cytokines (TNF- α) after infusion of ketamine, which was associated with the reduction of depressive symptoms in treatment-resistance depression (Chen et al. 2018, Szałach et al. 2019).

It has been reported that the administration of ketamine provides antidepressant effects in rodents, i.e. multiple infusions of ketamine in rats exposed to the forced swim test reverted chronic stress-induced depressive behavior (Parise et al. 2013).

The effectiveness of ketamine in the treatment of depression has been confirmed in meta-analyses and systematic reviews (Coyle & Laws 2013, Serafini et al. 2014). The antidepressant efficacy was demonstrated within a few hours after administration of ketamine in randomized, placebo-controlled, double-blind studies for unipolar and bipolar depression (Berman et al. 2000, Kishimoto et al. 2016, Zarate et al. 2006, Diazgranados et al. 2010). Significantly higher rate of relapse in patients randomized to the placebo, compared with patients randomized to esketamine nasal spray was observed (Daly et al. 2018). Single intravenous infusion of ketamine led to a rapid (80 min) and sustained (up to 7 days) antidepressant response (Berman et al. 2000, Zarate et al. 2006). An open study showed that six intravenous infusions of ketamine over 12 days were safe and effective for ten patients with drug-resistant depression, with an average relapse time of 19 days (Aan het Rot et al. 2010). In the study of 24 patients with treatment-resistant depression (TRD), the mean time to relapse was 18 days (Murrough et al. 2013).

KETAMINE AND MAGNESIUM RELATIONS IN DEPRESSION TREATMENT

Magnesium and ketamine have a common mechanism of action in the treatment of depression. An increase in GluN2B expression is related to the administration of both ketamine and magnesium (Chatterjee et al. 2012). Magnesium and ketamine inhibit phosphorylation of eEF2 (eukaryotic elongation factor 2) in cell culture and increase the expression of BDNF in the hippocampus, which increases synaptogenesis (Slutsky et al. 2010). Administration of magnesium and ketamine leads to synaptic strengthening, measured by the increase in slow wave sleep in humans (Murck 2013). It was observed that sensitivity of ketamine increases in the state of magnesium depletion (Begon et al. 2001). Combination of ketamine and magnesium in a normal magnesium level has a superadditive effect in depression treatment (Orser et al. 1997). Ketamine directly or indirectly increases magnesium levels in the brain by

activating a non-NMDA glutamate receptors (Murck 2013). Ketamine and magnesium also affect the GABAergic system and have anti-inflammatory effects, which is associated with their antidepressant effect (Chen et al. 2018, Cubała et al. 2016, Sanacora et al. 2008, Szałach et al. 2018).

CONCLUSIONS:

Decreased levels of magnesium are reported to cause changes in the functioning of synapses which may lead to the development of depression, therefore concentration of magnesium may be treated as a potential marker in patients with depression (Cheungpasitporn et al. 2015, Frizel et al. 1969, Islam et al. 2018). Studies indicate the antidepressant properties of magnesium and/or its potential usage as an additive to antidepressant treatment (Barragan-Rodriguez et al. 2008, Eby & Eby 2006, Tarleton et al. 2017). Ketamine presents a rapid antidepressant effect due to which it is increasingly used in psychiatry (Coyle & Laws 2015, Serafini et al. 2015). Its rapid action and effectiveness in depression makes it promising for patients who are refractory to treatment (Aan het Rot et al. 2010, Daly et al. 2018, Murrough et al. 2013). Studies on the complexity of antidepressant action of ketamine contribute to the development of knowledge about the pathogenesis of depression (Duman et al. 2019, Krystal et al. 2019, Murck 2013).

In summary, magnesium and ketamine are involved in many key mechanisms of the pathophysiology of depression. The presented data may indicate a synergistic effect between the pharmacodynamic activity of magnesium and ketamine in the treatment of depression. Further research is needed to determine the relationship between magnesium levels and ketamine treatment response mainly in the attempt to establish if the magnesium supplementation can change ketamine treatment response time or present superadditive effect.

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EFFICACY OF KETAMINE IN BIPOLAR DEPRESSION: FOCUS ON ANHEDONIA

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SUMMARY

Bipolar depression (BD) is among the most severe psychiatric disorders. A significant number of patients do not achieve an entirely symptom-free state and experience residual sub-syndromal depression. Most of the treatment options approved for bipolar depression give no rapid symptom improvement. Ketamine is an anaesthetic medication that acts as an antagonist of the NMDA receptor and has antidepressant potential. Due to its unique way of action, ketamine seems to be crucial for the treatment of anhedonia. This review paper aims to provide an overview of the efficacy of ketamine infusions in bipolar depression with a focus on anhedonia. Literature suggests that intravenous ketamine 0.5 mg/kg over 40min weekly could be useful in the treatment of bipolar depression with prominent anhedonia, but there is still a small number of studies that examine the efficacy of ketamine infusions in BD. In conclusion, ketamine should be considered as a valuable treatment option for patients with BD and anhedonia.

Key words: ketamine - Bipolar depression - anhedonia

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INTRODUCTION

Ketamine is an anaesthetic medication that acts as an antagonist of the NMDA receptor with an antidepressant potential. Although ketamine enantiomer es-ketamine has been recently registered for treatment-resistant depression (TRD), there is still a small body of evidence and treatment guidelines, and there is a need for further research (Fuontoulakis et al. 2017). While various pharmacological treatment options are available, there are still unsatisfied needs, including the lack of consistent evidence of improvement in anhedonia. Ketamine due to its unique way of action seems to be crucial for the treatment of anhedonia (Lally et al. 2014).

BIPOLAR DEPRESSION

Bipolar depression (BD) is among the most severe psychiatric disorders. Depression is the most prevalent state throughout the life of bipolar patients. A significant number of patients do not achieve an entirely symptom-free state, and experience residual subsyndromal depression (Serafini et al. 2018). The most frequent residual symptoms include anxiety, sleep disturbances, depressed mood, work difficulties, fatigue, and anhedonia. These patients have a higher risk of early relapse, lower levels of social and psychological functioning, and higher rates of physical morbidity and also mortality. Thus, effective treatment plays here a significant role. Over half of patients with bipolar depression suffer from anhedonia (Paykel 2009).

Most of the treatment options approved for bipolar depression give no rapid symptom improvement. Delayed antidepressant effect (symptom response time is approximately 3-4 weeks) leads to poorer quality of life,

increased suicidal risk (Machado-Vieira et al. 2008) and lower remission rates. About the third of the patients do not respond to antidepressant treatment (Machado-Vieira et al. 2010). There is a need for a novel, more rapidly acting treatment options for BD.

ANHEDONIA

Anhedonia is defined as a decreased subjective experience of pleasure (Pelizza & Ferrari 2009, Ribot 1987, Snaith 1993). Anhedonia is associated with more severe forms of depression, less effective treatment (Spijker et al. 2001, Uher et al. 2012) and can be a predictor of suicide completion (Fawcett et al. 1990). Anhedonia is a trans-nosographic condition reported in several psychiatric disorders (De Berardis et al. 2015, Di Nicola et al. 2013, Hatzigiakoumis et al. 2001, Millan et al. 2014, Pettorruso et al. 2014a), including alcohol, and substance abuse (Martinotti et al. 2008) and neurological disorders (Pettorruso et al. 2014b).

Anhedonia can be divided into consummatory and motivational components. Consummatory aspect is associated with subjective pleasure, e.g., enjoying an activity and motivational aspect – with anticipating of and driving towards rewarding stimuli, e.g., planning activity (Der-Avakian & Markou 2012).

A variety of neurotransmitters are potentially involved in the hedonic capacity of the human brain, including dopamine, opioids, glutamate, serotonin, acetylcholine, cholecystokinin. Dopamine plays an essential role in the brain reward system, but glutamate also has a significant role in this system, especially with the motivational part (Hauber et al. 2000). Serotonin has a recognised effect on the modulation of dopamine and opioid release and therefore could have a regulatory role

in the rewarding process (Yan 2000) Opioid antagonists on the contrary decrease reward behaviour (Van Wolfswinkel et al. 1998). The role of stress hormones seems to be also important in anhedonia development, especially dynorphine (released by corticotropin-releasing hormone), which reduces the release of dopamine thus limiting the ability to feel pleasure (Knoll & Carlezon 2010).

Self-report scales or questionnaires, e.g., The Fawcett-Clark Pleasure Scale (FCPS) (Fawcett et al. 1983) or Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al. 1995) are most commonly used to measure anhedonia. Most of them measure subjective experience of hedonic impact (i.e., liking) but some also focus on reward motivation (i.e., wanting) – eg. The Temporal Experience of Pleasure Scale (TEPS) (Gard et al. 2006) differentiating between anticipatory and consummatory experience of pleasure (Romer 2010) Several studies indicate that depressed patients with major depressive disorder (MDD) and BD show more deficits in motivational than consummatory reward behaviours (Treadway & Zald 2011, Sherdell et al. 2012). Understanding the mechanisms of the motivational component of anhedonia seems to be crucial to successful anhedonia treatment. Dopaminergic signalling is correlated with anticipation, motivation, and learning related to pleasure but not with its consumption (Salamone & Correa 2012, Wise 2004). There is no robust evidence for dopaminergic signalling deficits in patients with depression (Dunlop & Nemeroff 2007). Pharmacological treatment studies gave some evidence for dopaminergic dysfunction in depression (Corrigan et al. 2000, Goldberg et al. 2004) and the effectiveness of dopamine modulating drugs (Argyropoulos & Nutt 2013). However, it is still unclear whether dopaminergic-enhancing agents or standard treatment gives a faster improvement of anhedonia in depression. Self-reported anhedonia levels are usually reported as the last symptom to improve with selective serotonin reuptake inhibitors.

Literature data analysis might help in explaining the difficulties in anhedonia treatment as well as the reason for limited data in that field (Lally et al. 2015, Strauss & Cohen 2017). Standard medication for depression has little impact for the alleviation of anhedonia (Nutt et al. 2007), and anhedonia often is the last symptom improved by selective serotonin reuptake inhibitors (SSRIs) (Boyer et al. 2000, Shelton & Tomarken 2001).

KETAMINE

Ketamine is an anaesthetic medication that acts as an antagonist of NMDA receptor, may act as a partial agonist of dopamine D2 receptors, may also increase the dopamine level in the striatum and may activate signalling cascades including the AMPA/kinase receptor system (Aan Het Root et al. 2012, Kapur & Seeman 2001, Vollenweider et al. 2000). Existing literature suggests that glutamate levels and NMDA receptor mRNA expression are abnormal in patients with major de-

pressive disorder and bipolar affective disorder and long-term antidepressant treatment reduces NMDA receptor mRNA transcription (Boyer et al. 1998, Paul et al. 1994, Sanacora et al. 2008). It is widely accepted that NMDA receptors also are required for learning and memory formation, and for synaptic plasticity induction (Trofimiuk et al. 2019). Those findings led to the experimental use of ketamine for the treatment of depression. Results of studies of ketamine use as an antidepressant in humans were promising. Preclinical studies and clinical trials revealed the rapid antidepressant effect of ketamine (Al Shirawi et al. 2017, Alberich et al. 2017, Correia-Melo et al. 2017, Daly et al. 2018, Murrough et al. 2013, Segmiller et al. 2013, Zarate et al. 2012).

SAFETY OF KETAMINE USE

Infusions of intravenous (i.v.) ketamine in patients with depression was found to be generally safe and well-tolerated (Alberich et al. 2017). It was found that ketamine induces transient changes in hemodynamic measures elevating blood pressure and/or heart rate. Also, psychotomimetic symptoms and dissociative symptoms showed small, but significant elevations during the ketamine infusions. These symptoms usually all resolve within four hours post-infusion. The most common side effects are drowsiness, dizziness, poor coordination, blurred vision, and feeling strange or unreal. Low-dose ketamine could rapidly and safely reduce core symptoms of depression within 24-72 h of single and continuous infusions; however, adequate medical support and monitoring should be present to optimise patient safety (Wan et al. 2014).

Controversy exists regarding the illicit use of ketamine. Ketamine is known as a club drug with a brief dissociative and euphoric effect lasting up to 2 hours and thus must be administered in controlled settings. Ketamine abuse may lead to dysfunction of important bodily functions, including cardiovascular, respiratory, gastrointestinal, reproductive, genitourinary, and immune systems. Habitual abuse of ketamine may result in significant urinary bladder dysfunction and renal impairment - ketamine cystitis - as well as the cognitive impairments (Li et al. 2011).

KETAMINE AND ANHEDONIA.

Recent evidence suggests that antidepressant agents which target the glutamatergic system, e.g., ketamine, may provide more rapid onset improvement of anhedonic symptoms in MDD (Bechtholt-Gompf et al. 2010, Paul & Skolnick 2003, Walter et al. 2009). The mechanism underlying the efficacy of ketamine in depression is believed to be related to enhanced neuroplasticity. Changes in the metabolic activity of the hippocampus, dorsal anterior cingulate cortex and orbitofrontal cortex in combination with altered activity in reward processing pathways and increased glucose metabolism,

have been observed in individuals treated with ketamine. Additionally, ketamine indirect targets the dopaminergic system by altering glutamatergic signalling pathways. Ketamine also has been shown to increase the concentration of dopamine in the central nervous system, resulting in reduced D2 receptor expression as a potential compensatory mechanism to excessive dopamine stimulation (Cao et al. 2019).

Given the apparent role of dopaminergic and glutamatergic signalling in mediating anhedonia and reported pharmacological effects, ketamine may be ideally suited to ameliorate anticipatory anhedonia in currently depressed patients specifically (Lally et al. 2014).

KETAMINE IN BD TREATMENT

A small number of clinical trials and case reports of bipolar patients with ketamine treatment are present to date (Berman et al. 2000, Correia-Melo et al. 2017, Diazgranados et al. 2010, Lara et al. 2013, Lally et al. 2014, Permoda-Osip et al. 2014, Rybakowski et al. 2017, Zarate et al. 2012) (Table 1).

Six studies used intravenous ketamine administered 0.5 mg/kg over a time period of 40 min. (Berman et al. 2000, Diazgranados et al. 2010, Lally et al. 2014, Permoda-Osip et al. 2014, Rybakowski et al. 2017, Zarate et al. 2012). In one case report, 0.25 mg/kg of ketamine was administered over a time period of 10 min. (Correia-Melo et al. 2017). One case report investigated the efficacy of sublingual ketamine administered 10 mg/5 min every 2-3 days or weekly (1-20 doses per patient) (Lara et al. 2013). Four studies applied a single infusion of ketamine versus placebo.

All reviewed studies identified a rapid and robust antidepressant effect. Ketamine was always statistically significantly superior to placebo. The average response rate was 51% (ranging between 35% and 79%). The antidepressive effect was observed at one day and seven days post-infusion, and this is consistent with ketamine's pharmacokinetic properties. Some studies showed the anti-depressive effect of ketamine treatment up to 14 days after a single infusion. This data suggest that weekly administration of ketamine could be the most effective. Response after ketamine infusion occurred significantly more frequently in male than in female with BD (Coyle & Laws 2015, Rybakowski et al. 2017).

The safety and tolerability of ketamine treatment were satisfactory. No serious adverse events (SAEs) were observed. Minimal adverse events (AE) were noted in all studies, predominantly during ketamine infusion: dissociative symptoms, dizziness or faintness, nausea, dry mouth, headache. In both (ketamine and placebo) group appeared during infusion ($\geq 10\%$): feeling woozy or loopy, feeling lethargic or drowsy, cognitive impairment, fear of anxiety, nausea, dizziness, odd sensations, blurred vision, headache. Most of AE resolved completely by 60 minutes post-infusion.

KETAMINE IN ANHEDONIA TREATMENT

One study revealed rapid, the significant anti-anhedonic effect of ketamine (administered i.v. 0.5 mg/kg/40min) in 1, 3, 7 and 14 days post ketamine infusion. Furthermore, anti-anhedonic effects of ketamine remained significant even when controlling for the level of depressive symptoms, suggesting that ketamine has a unique role in ameliorating anhedonia levels independent of other depressive symptoms. More significant anti-anhedonic response was associated with lithium than valproate intake (Lally et al. 2014).

DISCUSSION

The impressive antidepressant effect of ketamine cause growing clinical use in depression treatment. Although there is a low body of evidence for use ketamine in depression treatment recently, The International College of Neuro-Psychopharmacology in Treatment Guidelines for Bipolar Disorder in Adults recommended the use of ketamine in combination with mood stabilizers in acute bipolar depression with comorbid anxiety treatment (4th level of recommendation) (Fountoulakis et al. 2017).

The most studied pharmacological interventions with respect to their effects on anhedonia were SSRIs, SNRIs, melatonergic MT1/MT2agonists, 5-HT2C-antagonists, NDRIs, SNRIs, and MAOI-A. It appears that available antidepressants have varied beneficial effects on anhedonia. Effectiveness of antidepressants on anhedonia seems to be related to their neurobiological effects on dopamine neurotransmitter systems (Treadway 2016). Researchers have also demonstrated an association between stress-induced anhedonia and reduced levels of hippocampal brain-derived neurotrophic factor (BDNF) (Burstein et al. 2017). Ketamine as an antidepressant agent that targets the glutamatergic system may provide more rapid onset improvement of anhedonic symptoms in MDD than other antidepressants.

Ketamine is also used as a recreational drug. The difference between clinical and recreational use is dose and frequency. Medical use is usually single 35mg dose which is repeated at the same dose days or weeks later in opposite to recreational use when doses can go up to several grams per day (Singh et al. 2017).

Basing on literature data patients with BD and anhedonia should be considered to ketamine treatment: intravenously 0.5 mg/kg over 40 min. weekly. Anhedonia studies had several limitations that need to be addressed by future research (small sample size, lack of placebo control for ketamine). Further researches should also focus on long term efficacy, misuse potential, suicidal thoughts and anhedonia.

Table 1. Main characteristics of case series, controlled and open randomised trials on the ketamine use in bipolar depression

Author	Study	Total patients	Sex (male)	Age mean	Comorbidity	Concomitant medication
Berman et al. 2000	Randomized, double-blind, placebo controlled, crossover study	9	4	37±10	Panic disorder	Drug free 2 weeks
Diazgranados et al. 2010	Randomized, double-blind, placebo controlled, crossover, add-on study	18	6	47.9	Anxiety disorder	Lithium or Valproic acid
Zarate et al. 2012	Randomized, double-blind, placebo controlled, crossover study	15	7	46.7±11.2	No	Lithium or Valproic acid
Permoda-Osip et al. 2014	Open study	42	10	48±11.5	No	Lithium, Valproate, Quetiapine, Carbamazepine, lamotryginę, arypiprazol, topiramate
Rybakowski et al. 2017	Open study	53	13	47±12.6	No	Lithium, Valproate, Quetiapine, Carbamazepine, lamotryginę, arypiprazol, topiramate
Lally et al. 2014	Randomized, double-blind, placebo controlled, crossover study	36	15	46.69	No	Lithium or Valproic acid
Lara et al. 2013	Open Case study	14	5	37.2±11.9	Panic attacks, chronic insomnia, GAD	Carbamazepine, oxcarbamazepine, lithium, topiramate, paliperidone, venlafaxine, duloxetine, SSRIs, divalproex, arypiprazole, nortriptyline, quetiapine, clonazepam, lamotrigine, mirtazapine, bupropion, metylfenidate
Correia-Melo et al. 2017	Retrospective chart review	27	17	51.0	OCD, Social phobia, PTSD, GAD, Panic disorder, ADHD, Agoraphobia, BDZ use, Cardiovascular disease, Endocrine disease, Cancer	No data

Table 1. Continues

Author	Ketamine administration	Number of doses	Measurment scales	Remission	Response	Adverse events
Berman et al. 2000	i.v., 0.5 mg/kg/ 40 min.	1	HDRS, BDI, VAS, BPRS	No data	50%	Positive symptoms in BPRS
Diazgranados et al. 2010	i.v., 0.5 mg/kg/ 40 min.	1	MADRS, HDRS, BDI, VAS, BPRS, CADSS, YMRS	31%	44%	no
Zarate et al. 2012	i.v., 0.5 mg/kg/ 40 min.	1	HDRS, BDI, BPRS, CADSS	30%	79%	Confusion, lethargy, cognitive deterioration, nausea, headache, blurred vision, fear or anxiety
Permoda-Osip et al. 2014	i.v., 0.5 mg/kg/ 40 min.	1	HDRS	40%	52%	no
Rybakowski et al. 2017	i.v., 0.5 mg/kg/ 40 min.	1	HDRS	26%	51%	Transient increase in blood pressure, depersonalisation
Lally et al. 2014	i.v., 0.5 mg/kg/ 40 min.	1	MADRS, SHAPS			no
Lara et al. 2013	Sublingual, 10 mg/5 min	Every 2-3 days or weekly; (1-20 doses)	HDRS	57%	35%	Mild agitation
Correia-Melo et al. 2017	i.v., 0.25 mg/kg/ 10 min.	1	MADRS, CGI	37%	48.1%	Mild severe dissociative symptoms

CONCLUSION

Literature suggests that ketamine is effective in the treatment of bipolar depression, but there is still a small number of studies devoted to ketamine treatment in BD. Further proof-of-concepts surveys are warranted to demonstrate the impact of ketamine on anhedonia in bipolar depression.

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Contribution of individual authors:

Maria Gałuszko-Węgielnik: literature research and analysis, manuscript writing with input of all authors.

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COULD PROBLEMS IN THE BEDROOM COME FROM OUR INTESTINES? A PRELIMINARY STUDY OF IBS AND ITS IMPACT ON FEMALE SEXUALITY

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SUMMARY

Introduction: Female sexuality may be affected by many somatic and psychological factors. Somatic conditions have impact on psychological well-being. We assumed that chronic disease like Irritable Bowel Syndrome (IBS), when producing the long-term distress, may greatly influence sexual functioning.

Aim: The aim of this study was to determine whether the severity of IBS influences sexual functions of women and take into consideration other factors like Small Intestinal Bacterial Overgrowth (SIBO) comorbidity and duration of IBS.

Subjects and methods: Study patients were recruited by contacting IBS patients at Gastroenterology Ward of Clinical University Centre in Katowice. The survey consisted of 3 parts. The first part were socio-demographic questions. The second part was polish translation of Female Sexuality Functions Index (FSFI) questionnaire. The third part consisted of questions about the patient condition, pharmacotherapy and Irritable Bowel Syndrome Severity Score (IBSSS) questionnaire. 307 women were included in the study and completed the questionnaire. 143 participants were diagnosed with IBS. The mean age of participants was 27 (IQR=23-33). 29% of the patients (n=41) had severe, 47% (n=68) moderate and 24% (n=34) mild IBS.

Results: The prevalence of sexual dysfunctions was greater in women with IBS (48%) than in healthy control group (23%) ($p<0.001$). The median of FSFI was: 30.1 (26.3-32.8) for healthy control group, 30 (23.5-32.6) for mild IBS, 26.2 (22.2-31.6) for moderate and 24.4 (20.1-28.9) for severe.

Conclusion: IBS decreases all domains of women sexual activity. Severity of sexual dysfunctions relate to intensity of IBS symptoms. All physicians treating IBS-patients should take sexual dysfunctions into their clinical consideration.

Key words: irritable bowel syndrome - sexual dysfunctions - sexual health - gastrointestinal diseases

Abbreviations: IBS - Irritable Bowel Syndrome; FSD - Female Sexual Dysfunctions; QoL - Quality of Life; FSFI - Female Sexual Functioning Index; IBSSS - Irritable Bowel Syndrome Scoring System; IQR - Interquartile Range

* * * * *

INTRODUCTION

The amount of research on the topic of Irritable Bowel Syndrome's (IBS) impact on female sexuality is scarce. Fortunately, in the last decade female sexual dysfunctions (FSD) in chronic illnesses have become an important research topic. FSD have a tremendous influence on women's quality of life while having also a great impact on health care expenses (Verschuren et al. 2010). Sexual functions are an essential factor when it comes to quality of life and nowadays sexual health is perceived to be a human right. Despite the fact that the prevalence of female sexual dysfunctions in premenopausal women around the world is high and around 40%, patients and health care professionals are often uncomfortable discussing sexual health (Mc Cool et al. 2019).

Female sexual functions are affected by many various factors, from psychosocial ones, through drugs side effects, obstetric history, hormone level disorders, ending on chronic conditions such as diabetes, hypertension and hyperlipidaemia (Krakovsky & Grober 2018). Diseases that cause sexual dysfunctions usually impair body image and feeling of attractiveness, restricting patient's mobility and activity (Palacios et al. 2009).

Irritable Bowel Syndrome (IBS) is one of most common chronic gastrointestinal tract conditions. In ROME IV criteria IBS is defined by the presence of abdominal pain with altered stool frequency, its form and its relation to defecation (Soares 2014, Longstreath et al. 2016). It affects around 5-20% of world population with women being more often affected (2:1 when compared to men) (Defrees & Bailey 2017). Nonetheless, it's estimated that due to the IBS symptoms only around

35% of patients will seek medical care (Ziółkowski et al. 2012, Endo et al. 2015).

While being perceived to be a benign condition, IBS is associated with decreased quality of life (QoL) and an increase in healthcare use (Mönnikes 2011). Studies have shown that patients suffering from IBS make two to three times more health care appointments than in healthy general population. Additionally, IBS patients QoL has been shown to be lower than QoL of patients with various chronic diseases and is comparable to QoL impairment of patients with depression or GERD (Gralnek et al. 2000, El-Serag et al. 2002). Furthermore 38-100% of IBS patients suffer from anxiety disorder and clinical depression (Hausteiner-Wiehle & Henningsen 2014, Woodman et al. 2016). Moreover, IBS patients with depression have a significant decrease in QoL domains like: body image, health worry, social relations, sexual and relationship (Kopczyńska et al. 2018).

Taking together all aforementioned factors: IBS being as the most common chronic GI tract condition, the proved connection between many different chronic illnesses and sexual dysfunctions and the limited research on that topic, we have decided to investigate the possible link between IBS and FSD to shed more light on the important problem. We assumed the presence of IBS symptoms entails a significant somatic stress that may influence the sexual functions of women.

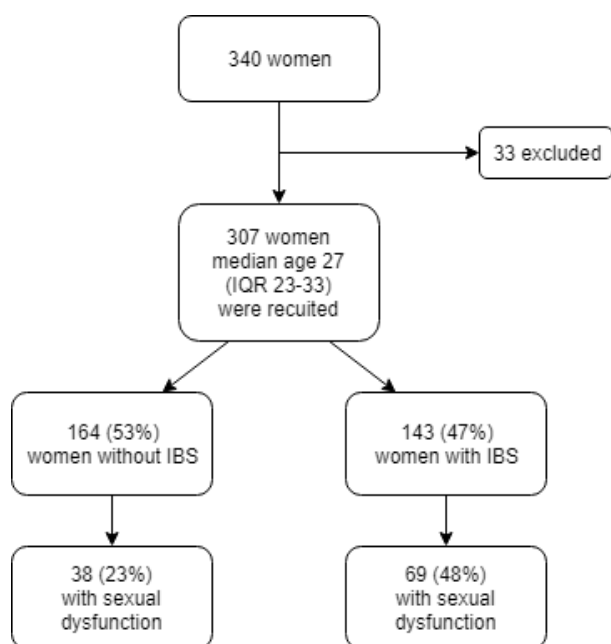


Figure 1. Patients' flow-chart

SUBJECTS AND METHODS

A cross-sectional study among Polish women diagnosed with IBS (n=164) and healthy control group (n=164), was conducted between March 2018 and April 2019 in cooperation with Gastroenterology Ward in Central University Hospital in Katowice. The fully self-

administered questionnaire was given to the patients at random while waiting for their routine medical check-ups in out-patient clinic. The exclusion criteria were: age below 18 and over 50 years old, occurrence of a neoplasm and/or any severe chronic disease, lack of a sexual partner and lack of sexual activity. 33 women were excluded from the study and final study group consisted of 307 women aged 19-50 years old. The characteristics of study and control groups were statistically equal (Figure 1).

The survey consisted of 3 divisions with a total of 37 questions. The first part contained socio-demographic characteristic. The second part included polish version of Female Sexual Functioning Index (FSFI), developed by Drosdzol-Cop et al. in 2009. The original FSFI is an internationally validated questionnaire developed by Rosen et al. in 2000. It consists of 19 questions which evaluate six following domains of women's sexual functioning: desire (questions 1 and 2; score range 1-5), arousal (questions 3, 4, 5,6; score range 0-5), lubrication (questions 7, 8, 9, 10; score range 0-5), orgasm (questions 11, 12, 13; score range 0-5), satisfaction (questions 14, 15, 16; score range 1-5) and pain (questions 17, 18, 19; score range 0-5) over past 4 weeks. The total result ranges between 2-36 where lower score correlates with worse sexual functioning and the result below 27 indicates the presence of sexual dysfunctions. The third part consisted of IBS related questions (duration since IBS diagnosis, drugs taken by the patient, symptomatic reaction to alcohol consumption, comorbidity of Small Intestinal Bacterial Overgrowth (SIBO) and Irritable Bowel Syndrome Scoring System (IBSSS). IBSSS is a self-administered, validated questionnaire created by Francis et al. in 1997 aiming to determine the severity of IBS's symptoms. The survey consists of five questions (each with a score range 0-100): presence and severity of abdominal pain, number of days with pain for every 10 days, presence and severity of abdominal distention, patient's satisfaction with bowel habit and patient's opinion on how IBS affects his/her life. The final score ranges 0-500 and divides patients into four groups: remission phase (0-74 points), mild IBS (75-174 points), moderate IBS (175-300 points) and severe IBS (>300 points).

The university Ethics committee waived the requirement for informed consent due to anonymous and non-interventional nature of the study.

All data analyses were conducted using StatSoft Statistica version 13.0 PL software and P value <0.05 was considered as significant. Qualitative variables are presented as a percentage and/or as an absolute value. Quantitative variables are presented as a median and an interquartile range. Shapiro-Wilk test was used to verify distributions of the groups, and between-group differences were investigated using non-parametric tests (U Mann-Whitney or Kruskal-Wallis). To measure qualitative variables chi-square test was used.

RESULTS

The median age of the participant was 27 (IQR=23-33). The analysis was conducted on 307 women of which 143 suffered from IBS and served as a studied group and 164 healthy women became our control group. General characteristic of the group is presented in Table 1.

Table 1. General characteristics of the subjects

Characteristic	Number of patients	%
Age	27	IQR 23-33
Marital status		
Married	129	42
Not married	178	58
Educational status		
Primary School	6	2
High School	132	43
University and above	169	55
Accommodation		
Village	68	22
City < 50k	58	19
City > 50-200k	64	21
City > 200k-500k	43	14
City > 500k	74	24

In the study group mild IBS was observed in 34 patients (24%), moderate in 68 (47%) while 41 presented severe IBS (29%). 31 (22%) participants were diagnosed with small intestinal bacterial overgrowth (SIBO) and 112 (78%) were not. Specific characteristic of the study group is presented in Table 2.

Our data analysis revealed that IBS in women is responsible for significant decrease both in FSFI global score in its specific domains (Table 3 and Figure 2).

Table 3. Impact of IBS on female sexual activity by FSFI's domains

	Without IBS	With IBS	P
FSFI	30.1 (26.3-32.8)	26.4 (22.3-31.3)	<0.001
Desire	4.2 (3.6-5.4)	3.6 (3.0-4.8)	<0.050
Arousal	5.1 (4.2-5.7)	4.5 (3.6-5.4)	<0.001
Lubrication	5.9 (4.5-6.0)	5.1 (4.2-6.0)	<0.010
Orgasm	5.2 (4.2-5.6)	4.4 (2.8-5.6)	<0.010
Satisfaction	5.2 (4.4-6.0)	4.8 (3.6-5.6)	<0.050
Pain	5.6 (4.4-6.0)	4.4 (3.6-4.8)	<0.001

Table 4. Impact of IBS's severity on female sexual activity

	Mild	Moderate	Severe
FSFI	30 (23.5-32.6)	26.2 (22.2-31.6)	24.4 (20.1-28.9)
Desire	4.8 (3.0-4.8)	3.6 (2.7-4.8)	3.6 (3.0-4.2)
Arousal	5.1 (4.2-5.4)	4.5 (3.6-5.4)	4.5 (3.3-4.8)
Lubrication	5.1 (4.5-5.7)	5.4 (4.5-6.0)	4.8 (3.9-5.7)
Orgasm	5.6 (4.4-6.0)	4.4 (2.8-5.6)	3.6 (2.8-5.2)
Satisfaction	5.2 (4.4-6.0)	4.8 (4.0-5.6)	3.6 (3.2-4.8)
Pain	4.4 (4.0-5.6)	4.4 (3.6-4.8)	4.4 (3.6-4.8)

Table 2. General characteristics of study group

Characteristic	Number of patients	%
IBS		
Mild	34	24
Moderate	68	47
Severe	41	29
SIBO		
Yes	31	22
No	112	78
Decrease in symptoms after alcohol intake		
Yes	47	33
No	96	67
Time since IBS diagnosis (years)		
Under 1	16	11
1-3	46	32
4-5	28	20
More than 5	53	39

Furthermore, there was a significant difference (<0.001) between the number of women with sexual dysfunctions (FSFI ≤26) in the study group (n=69, 48%), comparing to the control group (n=28, 23,2%). Those results are presented in Figure 3.

The equally interesting results were observed when we compared female sexual activity versus the severity of IBS using IBSSS. We proved the significant difference in medians of FSFI's between results in women with mild IBS and severe IBS (p<0.001). The significance of the difference between mild and moderate, and moderate and severe decrease of sexual activity were respectively p<0.07 and p<0.08. Detailed results are presented in Table 4.

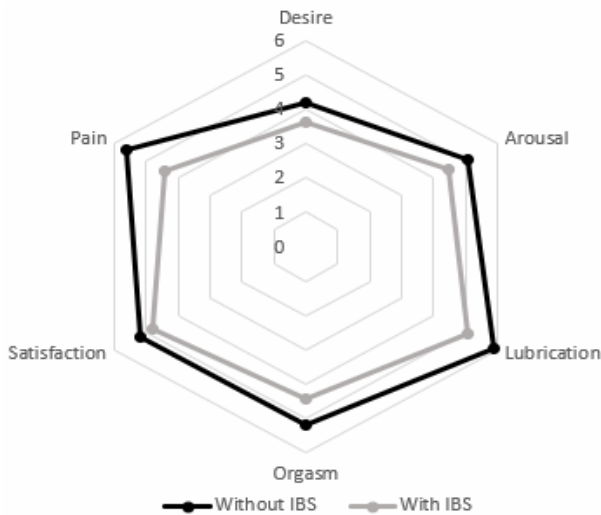


Figure 2. Impact of IBS on female sexual activity measured by FSFI's domains

Moreover, we found a few statistically significant differences between FSFI's domains scores in each severity group of IBS (Figure 4). The most significant decrease was noted between mild and severe IBS ($p < 0.001$) and mild and moderate IBS ($p < 0.01$) in orgasm domain. In satisfaction domain the decline was proved between mild and severe IBS ($p < 0.001$) and moderate and severe IBS ($p < 0.01$), while in arousal it was only proved between mild and severe ($p < 0.01$).

Likewise, the number of patients with sexual dysfunctions increased when compared to the severity of IBS symptoms and peaked at 61% in the severe disease. The results are presented in Figure 5.

SIBO comorbidity, duration of IBS and alcohol consumption didn't produce any significant associations when it comes to female sexual function, although 29% patients reported symptoms alleviation after consuming alcohol.

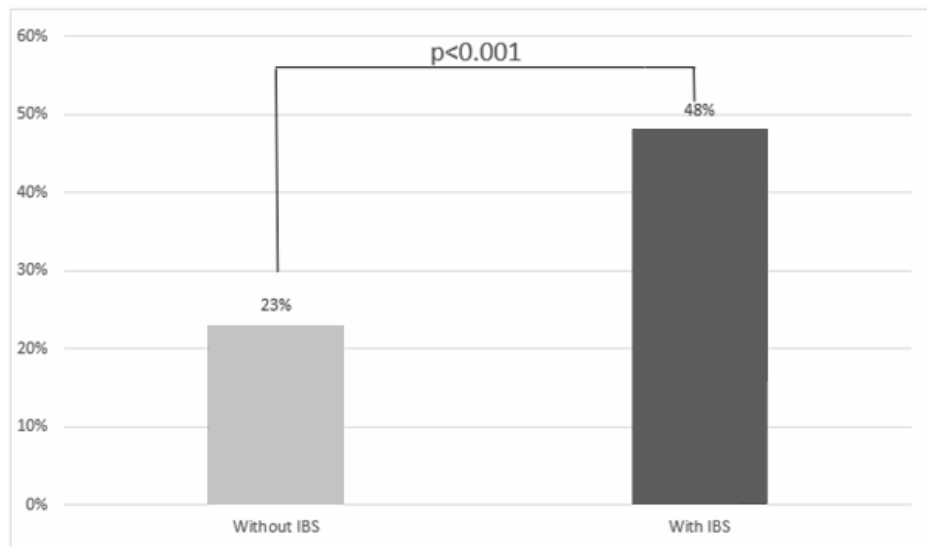


Figure 3. Occurrence of sexual dysfunctions in women with IBS and without IBS

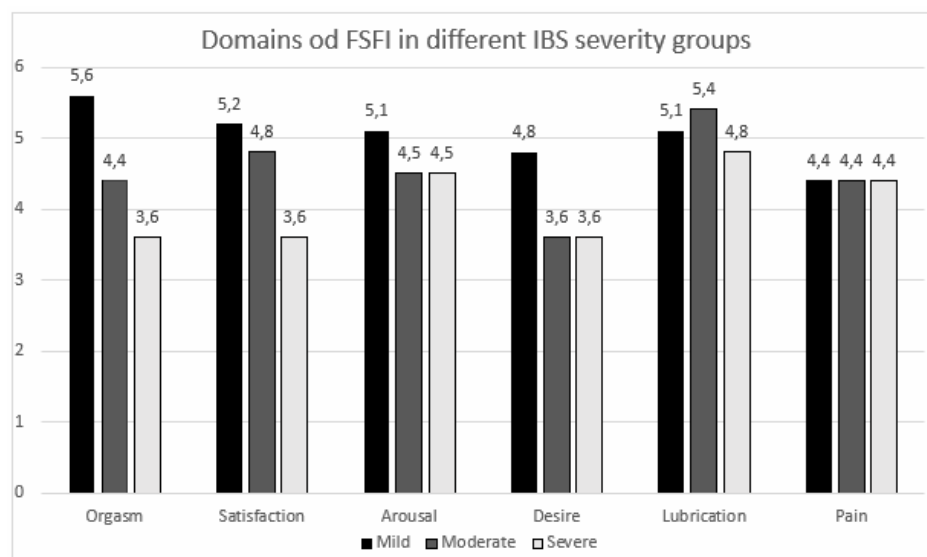


Figure 4. Changes in domains of FSFI in each severity group of IBS

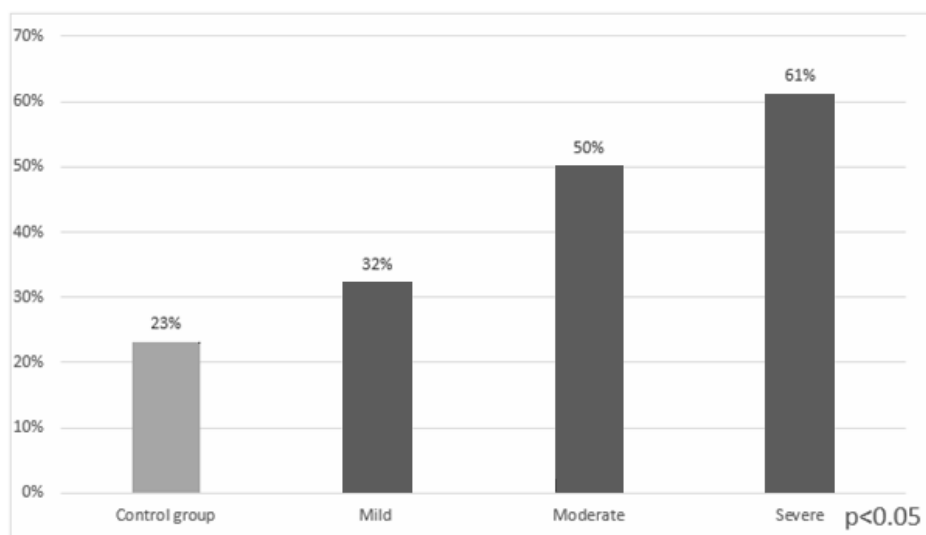


Figure 5. Impact of IBS's severity on prevalence of female sexual dysfunction

DISCUSSION

Irritable bowel syndrome's impact on female sexual functions is still poorly researched. Most of the available research was conducted in the last century and usually referred to a broader spectrum of symptoms. Our work focused on sexual functions and tried to establish the prevalence of FSD in IBS and alleged negative effect of IBS on sexual life.

The prevalence of IBS in general population is around 5-20% and its symptoms like pain, diarrhoea, constipation and bloating may produce a great psychological distress to the patient. IBS influences on perception of attractiveness, health worry, and other domains of life including psychosocial interactions and sexual relationships, which is shown by IBS-patients' decrease in QoL. Moreover, 38-100% IBS patients have a comorbidity of anxiety or major depressive disorder.

The frequency of sexual dysfunctions in IBS ranges from 14.3-43.3% and up 45.2% in constipation-predominant IBS. Our results were close to those observations with the prevalence of 48% (Corney & Stanton 1990, Fass et al. 1998, Schmulson et al. 1999), although we didn't take into consideration the subtypes of IBS. When prevalence of sexual dysfunctions was compared with the IBSSS, the occurrence of FSD increased with the severity of the disease. Unfortunately, we couldn't find any reports on that topic.

In our research FSFI was used to measure sexual functioning. We've managed to prove the decrease of the median score when compared our research group with control group and in each more severe group. Fass et al. 1998 reported decrease of sexual drive as the most common sexual dysfunction and in his study pain was more often observed in women than in men. In our study we demonstrated the significant decrease in each domain of woman sexual functioning: desire, arousal, lubrication, orgasm, satisfaction and pain. Whorwell et

al. 1986 listed dyspareunia as a crucial component of IBS with 63% of patients being affected by it with none in his control group, while Fass et al. 1998 proposed decreased libido to be the most common sexual dysfunction in IBS (Whorwell 1986, Fass et al. 1998).

Pain accompanying sexual activity may relate to anatomy of innervation of sexual organs. Pelvic hyperalgesia through similar innervation as a GI tract was thought to be important in development of hypersensitivity. Splanchnic afferent nerves are the same for female inner reproductive system and distal parts of GI tract (Rapkin & Mayer 1993). In turn, a mechanism of decreased libido is abundant in a group of chronic diseases and may reflect psychological stress related to the patient's situation and its impact on his functioning (Campbell et al. 1989).

Our results seem close to both Fass's and Whorwell's findings and though we are unable to state the prevalence of specific sexual dysfunctions our research showed that the incidence of pain and decreased sexual desire was bigger in IBS women, comparing to the control group. Although, pain sensitivity did not change in proportion to the severity of IBS. In the light of previous and present research covering visceral hypersensitivity it seems that IBS patients may be more susceptible to other chronic pain disorders, including dyspareunia.

Furthermore IBS patients present higher levels of anxiety and depression, and the comorbidity between IBS and stress-induced psychiatric disorders is considered to be between 30 and 50%. Those psychiatric long-lasting conditions result in low grade inflammation, causing an increase in intestinal permeability and affect the neuroimmunological response (Popa & Dumitrascu 2015). Moving forward this impairment of mental health may lead to decrease in arousal and desire resulting in impaired sexual satisfaction and FSD. In fact, Forbes et.al postulated that sexual dysfunctions,

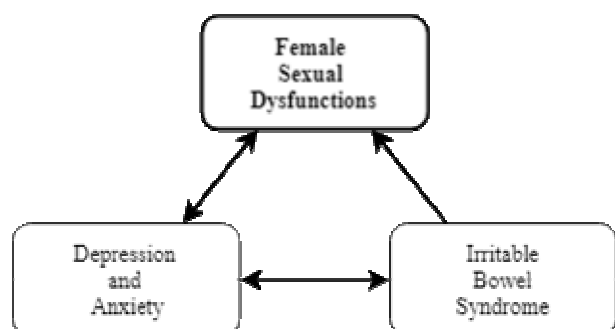


Figure 6. Proposed vicious cycle of IBS, depressive/anxiety disorders and FSD

anxiety and depression share the same underlying latent psychological vulnerability (Luftey et al. 2009, Forbes et al. 2016, Basson & Gilks 2018). IBS, anxiety and/or depression and sexual disfunction may create a vicious cycle of conditions that potentiate each other (Figure 6).

Primary care physicians and gastroenterologists should take into account a great possibility of developing sexual dysfunctions in their IBS female patients. Physicians should inquire them, educate and when sexual dysfunctions occur refer them to a sexologist to maintain their good quality of sexual life.

The limitations of our study should be underlined. The study group should be bigger and consist from subtypes of IBS. The impact of pharmacotherapy on IBS and sexual symptoms should be considered, too.

CONCLUSIONS

IBS decreases all domains of women sexual activity. Severity of sexual dysfunctions relate to intensity of IBS symptoms.

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Contribution of individual authors:

Piotr Sławik: design of the study, literature research and analysis, data interpretation, manuscript writing.

Mateusz Szul: design of the study, literature research and analysis, data interpretation, statistical analysis.

Marek Krzystanek: data interpretation and manuscript redaction.

Marek Waluga: design of the study.

Anna Fuchs: data interpretation.

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THE RELATION BETWEEN EMOTIONAL INTELLIGENCE AND INTERNET ADDICTION IN KATOWICE HIGH SCHOOL STUDENTS

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SUMMARY

Background: Emotional intelligence (EI) is described as the capacity to be aware of, control, and express one's emotions, and to handle interpersonal relationships judiciously and empathetically. It is considered as one of the most important predictors of success, quality of relationships, and overall happiness. Dynamically changing environment of the youth and young adults in recent years may influence their EI development, affecting their lives significantly. The purpose of this study was to analyse the way how the Internet is used by high school students, to determine the amount of time they spend on the Internet, identify the level of EI and to explore if there is any correlation between those factors.

Subjects and methods: 1450 high school students from Katowice, at the age from 18 to 21 years took part in an anonymous survey consisting of three parts: The Trait Emotional Intelligence Questionnaire – Short Form (TEIQue-SF), Internet Addiction Test and authorial test giving information about the way of spending time online. The questionnaires were collected from May 2018 to January 2019.

Results: 1.03% of the respondents fulfilled the Internet addiction criteria. Students at risk for addiction (33.5%) turned out to be a larger group. A statistically significant correlation between TEIQue-SF and Internet Addiction Test score ($P < 0.0001$, $r = -0.3308$) was observed. Another significant correlation was found between TEIQue-SF score and amount of time spend on the Internet ($p < 0.0001$, $r = -0.162$).

Conclusion: A significant part of high school students used Internet excessively. Such behaviours were positively correlated with lower EI test results.

Key words: emotional intelligence - Internet addiction - high school students

* * * * *

INTRODUCTION

We currently live in the era of the Internet and the ubiquity of mobile devices that allow an easier access to many resources, including information, entertainment and communication. Using them allows one to improve the standard of living, and their multi-tasking offers vastness of possibilities. However, despite their benefits, they also carry many risks.

Along with the increase of the Internet accessibility, which can now be used almost in any place, at anytime, anywhere in the world, the IA problem is growing. Depending on the severity of the addiction, it may cause various degrees of negative effects on personal and family life, interpersonal relations, emotional disorders, problems in fulfilling duties and many others. One of the symptoms is the so-called 'losing sense of time on the web' - the time that is not used for work or study and for one of the subtypes IA, i.e. Internet gaming disorder - the phenomenon of tolerance (the need to spend more and more time on computer games to achieve the same "high") which Jorgenson et al. (2016) mention in her work. In this case, adolescents and young adults are particularly vulnerable group in our society.

There are many risk factors for IA. Khoshakhlagh and Faramarzi (2012) in their work report that anxiety, obsessive-compulsive, aggression, phobia, hypochondria disorders, and emotional intelligence (EI) were the most significant predictors of Internet addiction. Our attention was mainly drawn to emotional intelligence, whose relationship with IA is reported in many publications. Salovey and Mayer (1990) defined EI as 'a set of skills hypothesized to contribute to the accurate appraisal and expression of emotion in oneself and in others, the effective regulation of emotion in self and others, and the use of feelings to motivate, plan, and achieve in one's life.' It follows that EI is essential for proper functioning in society, and its irregularities cause serious disorders.

There are gender-wise differences in the values of the above factors. According to Saraiva et al. (2018) women show a higher EI level and a lower level of IA compared to men, which confirms their inverse relationship. Strittmater et al. (2015) in her work noticed that PIU (Problematic Internet Use) players are more often boys/men who also have problems in dealing with peers, whereas female Internet users are more often "non-gamers", however, they exhibit greater exposure to depressive disorders. Both groups have shown a higher

level of disorders, i.e. depression, ADHD, behavioural disorders and more self-harming tendencies towards oneself compared to the average Internet user.

Not insignificant are the fear and depression mentioned above, as Lee et. al. 2014 showed in their research. The occurrence of these factors in childhood shows a significant relationship with the manifestation of IA in adolescence (Rammazi et al. 2018). Many works also provide information on an increased risk of depression for people with IA in later years of their lives. According to research conducted by Khoshakhlagh and Faramarzi (2012), women are much more exposed to depressive disorders. Numerous studies also confirm correlation between increased level of stress and IA.

As can be seen, the issue of EI and IA and their correlation is extremely complex and there are many other factors that also affect them. In our research we decided to check whether there is a relationship between IA and EI in the studied population. We also tried to determine if the amount of time spent on the Internet and what activities it is devoted to have an impact on adolescent IA.

SUBJECTS AND METHOD

1450 people were invited to participate, of whom 1200 were included in the study. 250 were rejected due to incomplete filling-in of the questionnaire or marking only the highest or lowest values in the TEIQ-SF test. The study group consisted of 539 (44.9%) women and 661 (55.1%) men aged 18 to 23 with an average number of 19.6 ± 0.8 years. The people were recruited in 33 upper-secondary schools in Katowice from May 2018 to January 2019. Among the respondents, the largest group were learners of technical secondary schools - 681 (56.7%) pupils. 500 (41.7%) of students attended high school, and 19 (1.6%) - vocational school.

The study was approved by the Head of the Department of Education and Sport in Katowice and headmasters of the institutions. Anonymous questionnaires were distributed during general education classes. The participants were familiarised with the subject and principles of the study and were informed about voluntary accession to it. The course was supervised by the teachers of particular classes in cooperation with the persons conducting the research.

In the study, the questionnaire consisted of four parts:

- A short questionnaire gathering basic information about the respondent, such as gender, date of birth and the type of school they attend.
- Questionnaire evaluating emotional intelligence - TEIQue-SF by K.V. Petrides (Siegling et al. 2015) adapted to Polish standards by Agata Wytykowska (Szczygieł et al. 2015). The scale is based on the long form of the TEIQue (Petrides and Furnham 2003) and consists of 30 items. It includes two items from each of the 15 facets of the TEIQue organised under four-factors: well-being, self-control, emotio-

ality, and sociability. Items were selected primarily on the basis of their correlations with the corresponding total facet scores, which ensured broad coverage of the sampling domain. They are either positive (15 items; e.g., "On the whole, I'm a highly motivated person.") or negative (15 items, e.g., "I often find it difficult to see things from another person's viewpoint"). Items were responded to on a 7-point Likert scale where 1 means strongly disagree and 7 means strongly agree. The result is obtained after summing the scores from positive sentences, and the reversed score from negative sentences. The higher the score, the higher the IE feature of the unit.

- Internet Addiction Test questionnaire (IAT), by Kimberly Young (adapted by Paweł Majchrzak and Nina Ogińska-Bulik to Polish conditions, 2007). It was created based on DSM-IV diagnostic criteria for pathological gambling. The questionnaire consists of 20 questions regarding various behaviours and feelings related to the use of the Internet, referring to, i.a., negligence of duties because of the Internet, as well as the control over the time spent on the Internet. There are possible answers from 1 to 5, indicating the frequency of each phenomenon (1 - rare, 5 - always). The sum of points falls within the range of 20 - 100. A score equal to or greater than 40 indicates the risk of Internet addiction, and a score equal to or greater than 70 indicates respondent's excessive use of the Internet.
- Author's questionnaire collecting information on the amount of time spent on the Internet. The sheet includes the number of hours spent on the Internet by the student on a school day and on a day off from school. The respondents also determined how many hours of that time they used the Internet on mobile devices (e.g. smartphone, tablet). The respondents determined how much time on average during the day they devote to the mentioned sub-items by selecting 1 of 8 possible time intervals (a-no time whatsoever, b - 1-15 minutes, c - 16-30 minutes, d - 31-60 minutes, e - 1-2 hours, f - 2-3 hours, g - 3-4 hours, h > 4 hours).

RESULTS

Due to missing answers in the tests TEIQ and IAT, 250 people were removed from the analysis. After counting them out, the research group consisted of 1200 people, of which 539 (44.9%) were women. 500 (41.7%) students attended high school, 681 (56.7%) technical college and 19 (1.6%) - vocational school. The average age of the respondents was 19.6, $SD=0.8$ (Table 1).

An inverse correlation was found between the results of tests surveying emotional intelligence and Internet addiction in our research group (Figure 1.) with a score of $P<0.0001$ and $\rho = -0.317$. The normal distribution of IAT and TEIQ results in the study group with the Shapiro-Wilk test $p<0.05$ was rejected, therefore Spearman's rank correlation was used to investigate the relationship between IAT and TEIQ results (Table 2, 3).

Table 1. Participants sociodemographic, TEIQ and IAT test scores (n=1200)

Gender	
Women	539 (44.9)
Men	661 (55.1)
Age (years), Arithmetic mean (SD)	19.6 (0.8)
Type of high school	
High school	500 (41.7)
Technical secondary school	681 (56.7)
Vocational school	19 (1.6)
Average time spent in the internet during week (hours), Arithmetic mean (SD)	4.5 (2.67)
Average time spent in the internet during weekend (hours), Arithmetic mean (SD)	5.8 (3.32)
Average score from TEIQ, Arithmetic mean (SD)	4.62 (0.8)
Average score from IAT, Arithmetic mean (SD)	38.19 (12.31)
Participants who get < 40 from IAT	765 (63.7)
Participants who get ≥ 40 from IAT	409 (34.1)
Participants who get > 70 from IAT	26 (2.2)

Abbreviations: SD = Standard deviation; TEIQ = Trait Emotional Intelligence Questionnaire; IAT = Internet addiction test; Data are presented as number (percentage) of patients if not stated otherwise

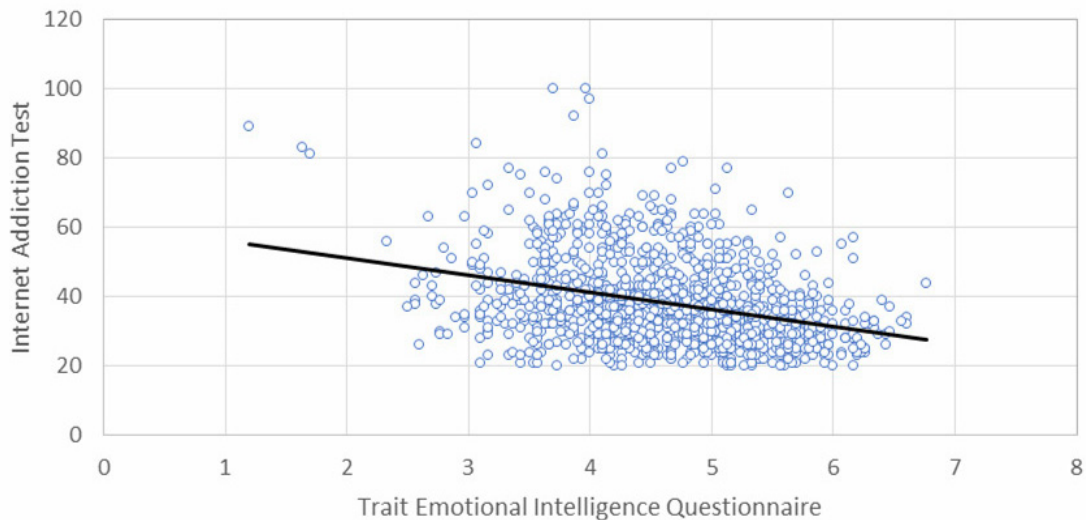


Figure 1. Correlation coefficient between Internet Addiction Test score and Trait Emotional Intelligence Questionnaire test score (n=1200, $p < 0.0001$, $\rho = -0.317$)

Table 2. Differences between gender (n=1200)

	Women	Men
Average score from TEIQ, Arithmetic mean (SD)	4.46 (0.78)*	4.75 (0.79)*
Average score from IAT, Arithmetic mean (SD)	37.77 (11.51)	38.52 (12.92)
Participants who get ≥ 40 from IAT	183 (33.95)	226 (34.19)
Participants who get > 70 from IAT	7 (1.3)	19 (2.87)

Abbreviations: SD = Standard deviation; TEIQ = Trait Emotional Intelligence Questionnaire; IAT = Internet addiction test; Data are presented as number (percentage) of patients if not stated otherwise; * = statistically significant difference ($P > 0.05$)

Table 3. Differences between types of school

	High school	Technical secondary school
Average score from TEIQ, Arithmetic mean (SD)	4.58 (0.8)	4.66 (0.8)
Average score from IAT, Arithmetic mean (SD)	38.67 (11.19)*	37.81 (12.90)*
Participants who get ≥ 40 from IAT	186 (37.2)	218 (32.01)
Participants who get > 70 from IAT	6 (1.2)	19 (2.79)

Abbreviations: SD = Standard deviation; TEIQ = Trait Emotional Intelligence Questionnaire; IAT = Internet addiction test; Data are presented as number (percentage) of patients if not stated otherwise; * = statistically significant difference ($P < 0.05$)

Table 4. Indicators of emotional intelligence, well-being, self-control, emotionality and sociability on the basis of Trait Emotional Intelligence Questionnaire test

	Arithmetic mean	Standard deviation	Median	Interquartile range	Minimum	Maximum
Emotional intelligence	4.62	0.8	4.63	4.10-5.17	1.20	6.77
Well-being	4.54	1.32	4.67	3.67-5.50	1.00	7.00
Self-control	4.53	1.03	4.50	3.83-5.17	1.17	7.00
Emotionality	4.72	0.85	4.75	4.13-5.38	1.00	7.00
Sociability	4.66	1.03	4.67	4.00-5.33	1.00	7.00

The results of the TEIQ test of people at risk of the Internet addiction (IAT>40) and people addicted to the Internet (IAT>70) were compared with people who obtained less than 40 points in IAT. The Shapiro-Wilk test rejected the normal distribution of the TEIQ results in the group that obtained less than 40 points from the IAT test and the Kruskal-Wallis test was used due to the small number of people with the addiction to Internet. A statistically significant difference was found between these groups $p<0.005$.

DISCUSSION

The percentage of people with addiction in each study depends on the used test, used cut-off point and socio-cultural factors. Our results showed that 2.2% of respondents overuse the Internet and 34.1% are at risk of the overuse. "Internet Addictive Behavior in Adolescence: A Cross-Sectional Study in Seven European Countries" (Tsitsika et al. 2014), which also used an IAT test and the same cut-off point, shows symptoms of addiction in 1% of respondents and risk of addiction in 12.7%. A telephone survey conducted in Germany with use of Chen Internet Addiction (Rumpf et al. 2014) revealed probable Internet addiction at the level of 1.0% (CI 0.9–1.2) among the entire sample, 2.4% (CI 1.9–3.1) in the age group 14–24, and 4.0% (CI 2.7–5.7) in the age group 14–16. In a study conducted in Poland (Tabak & Zawadzka 2017), using Young's Diagnostic Questionnaire, 11.6% of respondents met the criteria of addiction and 8.2% were threatened with Internet addiction. The participants were 376 students, aged 14–19 (M=16.04; SD=0.9).

The average score of TEIQue-SF test for the group was 4.62 SD=0.8 (women=4.46 SD=0.78, men=4.75 SD=0.79) (Table 4). The average result for people with Internet addiction was 3.71, SD=1.03 and for those at risk of addiction 4.39, SD=0.7. The average age was 19.6 (SD=0.8). In a study conducted in Poland (Szczygieł et al. 2015) on participants aged from 18 to 29 years (M=22.69; SD=2.40), the average score of TEIQue-SF test was 4.83 (SD=0.79) for men and 5.06 (SD=0.70) for women. High school students 14 to 16 years old in Kanyakumari District, India, had the median score of TEIQue-SF at the level of 4.65 for boys and 4.53 for girls (Lawrence & Deepa 2013). In a similar study conducted on high school students aged

on average 15.2 (SD=2.9) in Sparta the median of TEIQue-SF test was 4.9 (SD=0.6) for boys and 4.8 (SD=0.7) for girls. The differences in test results may be caused by the age difference of the respondents (Chen et al. 2016), parental education, geographical origin, socio-economic status or even birth order (Akbar et al. 2011).

The results of our study show a moderate, inverse relationship between Internet addiction and the level of emotional intelligence ($p<0.0001$, $\rho=-0.317$). Students from 13–18 years of age (M=16.2, SD=1.45) residing in several communities in Central and Eastern Ontario were part of the study that examined the relationship between emotional intelligence (EI) and several addiction-related behaviours (gambling, using the Internet, and playing video games). The analysis revealed that EI is a moderate to strong predictor of addiction-related behaviours (Parker et al. 2008). Results of the study on undergraduate students aged 18-24 studying at Kharazmi University indicated that all the components of emotional intelligence are significantly, negatively correlated to the Internet addiction (Far et al. 2014). Despite the fact that many studies have shown no connection between emotional intelligence and Internet addiction (Maddi et al. 2013, Waldo et al. 2013), pooled results of thirteen studies regarding connection between Internet addiction and emotional intelligence revealed a moderate and inverse relation between Internet addiction and emotional intelligence (Ranjbar and Bakhshi 2018).

People with a high emotional level are more likely to enjoy their life and achieve long-term goals due to the greater awareness and control over their own and other people's emotions (Salovey and Mayer 1990). Study on students from colleges in Delhi showed that low emotional intelligence was associated with a higher level of anxiety and a higher likelihood of Internet addiction (Juneja and Sethi 2015). Individuals with poor affect regulation abilities may struggle with regulating distressing emotions due to difficulty in identifying subjective emotional states, and a limited ability to communicate these feelings to others. As a result, these individuals are unable to obtain the help or comfort needed from other people. It may also be possible that adolescents, who spend considerable amounts of using the Internet, do not develop good interpersonal abilities (Parker et al. 2008).

The self-medication model (Khantzian 1997) indicates that people can compensate for “deficiencies” in their real lives, such as poor relationships with people, lack of satisfaction with their achievements or negative emotions such as anxiety, through the use of the Internet. The computer network allows them to escape from the reality. People get pleasure out of the sense of control and connection with other users (Leung 2004). People with lower emotional intelligence are more likely to become addicted because they have less satisfying life in general.

Low levels of emotional intelligence are associated with weaker self-control. People with low emotional intelligence will be more susceptible to abandon their daily duties, associated with learning, working and interacting with others, for temporary online pleasure (Kim et al. 2017).

- The weak part of the study was that the students who were absent from classes did not participate in the research.
- Some of the completed questionnaires (250) were missing and were not taken into account.
- The cross-sectional study does not establish a causal connection, but only a correlation.
- The findings are also limited due to the research tools used in the study.

Using a broader range of assessment strategies (e.g. performance based or observer ratings) should provide more reliable results.

CONCLUSIONS

The results show that there is a risk of Internet addiction among students of upper-secondary schools. There is also a link between Internet abuse and emotional intelligence. They seem to confirm findings of other authors, demonstrating that the people who have problems with managing their own emotions and coexisting with others are more vulnerable to addiction.

In the current situation, when the Internet is entering the lives of almost every person from an early age, it is very difficult to predict the effects that it has on individual people and the society of future generations. In order to better understand the problem, it is necessary to conduct research not only on the mechanism and consequences of Internet addiction, but also on the way in which “ordinary” Internet use affects people and whole communities.

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CLOZAPINE: PROMISING TREATMENT FOR SUICIDALITY IN BIPOLAR DISORDER

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SUMMARY

Bipolar disorder is associated with the highest risk of completed suicide of all mental disorders. The suicide mortality of people with bipolar disorder is approximately 25 times higher than the general population. No approved pharmacological strategies for suicidality in bipolar disorder have been introduced so far. There is evidence for anti-suicidal effect of clozapine in schizophrenia. Clozapine with its unique pharmacology, anti-aggressive and anti-impulsive properties is potentially an effective strategy for suicidality in bipolar disorder.

Key words: clozapine - bipolar disorder - suicidality - treatment resistance

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INTRODUCTION

Suicidality in bipolar disorder is a major issue (Schaffer et al. 2015, Carter et al. 2003). Suicide accounts for 15% to 20% of deaths among bipolar disorder patients (Baldessarini et al. 2006, Goodwin & Jamison 1990). Absolute rates of suicide in bipolar disorder are about 0.4% per year. This is 20 fold greater than population rates and translates into risks at long term follow-up between 3-6% (Baldessarini et al. 2006).

Naturalistic studies suggest that suicide rates are lower in patients who receive long-term treatment (Angst et al. 2002). Especially lithium may have particular efficacy. The findings from different centres are consistent and the treatment effect is large Tondo et al. 2001, Toffol et al. 2015). A study of a large Swedish data base has confirmed lithium effect in reducing suicide attempts by 30%; the same effect was not seen with valproate (Song et al. 2015). Both lithium and valproate treatment were associated with 90% reduction in completed suicide.

The key issue in pharmacotherapy of suicidality is its potential effect not only as a syndromolitic intervention, but also as symptom-domain treatment regardless the diagnosis. Although there are no approved interventions for suicidality in bipolar disorder, there is body of evidence on anti-suicidal effect of clozapine in patients with schizophrenia and it is suggested that this strategy can also be useful in patients with bipolar disorder.

CLOZAPINE AS MOOD STABILIZER

Although clozapine lacks regulatory approval for use in any phase of bipolar disorder it is used in treatment resistant bipolar disorder (TRBD) in US since 1989 (Nielsen et al. 2012). It reduces symptom severity in manic and mixed episodes and decreases the need for use of concomitant psychotropic drugs (Nielsen et al. 2012, Chang et al. 2006). There is some evidence to

support efficacy in rapid cycling bipolar disorder when standard treatments have failed. (Calabrese et al. 1991, Chen et al. 2005).

Use of clozapine in bipolar disorder is significantly associated with a reduction in psychiatric admissions, psychotropic comedications, and hospital contact for self-harm and overdose (Nielsen et al. 2012), which suggests that clozapine has strong mood-stabilizing properties. Clozapine has been shown to be useful in treatment of TRBD, decreasing the number of hospitalizations and improving symptomatic and functional improvement (Li et al. 2015). It has anti-manic and possibly an antidepressant effect described in one case report (Green et al. 2000, Banov et al. 1994, Calabrese et al. 1996). There is also evidence for use of clozapine in rapid cycling bipolar disorder (Calabrese et al. 1991, Chen et al. 2005).

According to British guidelines, clozapine is worth considering as a treatment option in cases of resistant bipolar I disorder, including rapid cycling (Goodwin et al. 2016). It is also recommended for treatment-resistant bipolar disorder in the latest version of The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders (Grunze et al. 2013). The latest Canadian guidelines for the treatment of BD suggest using clozapine as the third-line treatment for acute mania and as an additional agent for the maintenance treatment of bipolar I, treatment-resistant mania (Yatham et al. 2009).

SAFETY ISSUES

The risk-benefit profile in long term clozapine treatment of bipolar disorder needs to be assessed carefully. Most common side-effects of clozapine are sedation, hypersalivation, constipation, postural hypotension, hypertension, tachycardia, weight gain, fever, seizures, nausea, nocturnal enuresis, gastro-oesophageal reflux disease. It can also increase triglyceride and cholesterol

levels. Clozapine is strongly linked to hyperglycaemia, impaired glucose tolerance and diabetic ketoacidosis. The risk of diabetes appears to be higher with clozapine than with other SGAs and conventional drugs, especially in younger patients. Clozapine appears to increase plasma levels of insulin in a clozapine level-dependent fashion. Patients on clozapine should be closely observed for signs or symptoms of myocarditis, particularly during the first 2 months of treatment. Clozapine is also linked to cardiomyopathy. Anticholinergic effect of clozapine can worsen cognitive functions (Abel et al. 2018)

Clozapine can cause serious, life-threatening adverse effects, of which agranulocytosis is the best known. Early US data suggested a mortality rate of 0.012%. Risk can be well managed by the approved clozapine monitoring systems. Risk of fatal agranulocytosis is less than 1 in 8000 patients treated. Other uncommon adverse effects are colitis, delirium, eosinophilia, heat stroke, liver enzymes abnormalities, interstitial nephritis, pancreatitis, parotid gland swelling, pericardial effusion, pneumonia, stuttering, thromboembolism, skin reactions and thrombocytopenia. It is worth noticing that overall mortality of patients with schizophrenia is lower for those on clozapine than in schizophrenia as a whole. Risk of fatal pulmonary embolism is estimated to be around 1 in 4500 patients treated. Careful monitoring (full blood count, lipids, weight, glucose, blood pressure, ECG) can help avoiding most of adverse effects. Many of the adverse effects of clozapine are dose dependent and associated with speed of titration. Adverse effects also tend to be more common and severe at the beginning of therapy. To minimize these problems it is important to start treatment at a low dose and to increase dosage slowly (Abel et al. 2018).

There is some evidence that clozapine improves treatment adherence in comparison to FG drugs (Rozenheck et al. 2000), through greater and more regular clinical supervision coinciding with mandatory blood testing.

CLOZAPINE AS AN ANTI-SUICIDAL AGENT

Suicide accounts for 15% to 20% of deaths among bipolar disorder patients (Baldessarini et al. 2006, Goodwin et al. 1990). The ratio of suicidal attempts among bipolar disorder patients is much lower (~ -3:1) than in the general population (~30:1); however, the attempts are highly lethal (Baldessarini et al. 2006). Suicidal acts appear mostly in association with severe depressive or mixed states. Independent associations have been found for female gender, previous criminality, parental psychiatric disorders and low family income (Webb et al. 2014) Aggression and impulsivity may also be associated with suicide attempts (Oquendo et al. 2000, Oquendo et al. 2004).

For today there are no approved pharmacological interventions for suicidality in bipolar disorder. Clozapine has been shown to have specific anti-suicidal

properties in patients with schizophrenia (Meltzer et al. 2003, Hennen et al. 2005, Ciapperelli et al. 2000). Some authors have suggested that clozapine's anti-suicidal properties could extend beyond schizophrenia to bipolar disorder (Carter et al. 2003, Meltzer et al. 2000). This effect was described in one case report (Vangala et al. 1999). Anti-suicidal effect seems to be independent of that which provides psychotic symptom relief. Interestingly, psychotic symptoms do not predict a better response to clozapine in bipolar patients compared to schizophrenic patients Ciapperelli et al. 2000) and the doses required for optimal effect in bipolar disorder may be less than those used for treatment-resistant schizophrenia (Fehr et al. 2005) although it demands further study.

There is also some evidence that clozapine reduces suicidal behaviours in severe borderline personality disorder (Benedetti et al. 1998). Possible mechanisms of reducing suicidality with clozapine probably involve the simultaneous modulation of dopamine, norepinephrine, and serotonin (Meltzer et al. 2000), regulation of the hormone system (pregnenolone, cortisol) (Marx et al. 2006) and intracellular systems – dependent modulation of N-methyl-D-aspartate (NMDA) receptor expression, brain-derived neurotrophic factor up-regulation, and regulation of the arachidonic acid cascade (Leveque et al. 2000, Spivak et al. 2003). According to Youssef, pregnenolone alterations may be relevant to the neurobiology of suicide in schizophrenia and bipolar disorder and may constitute a common path for the anti-suicidal effect for clozapine and lithium (Youssef et al. 2015).

Despite being the first drug to demonstrate a reduction in suicidal behavior in a large RCT, clozapine is used with only 1.5% of bipolar patients (Nielsen et al. 2010), suggesting a substantial underutilization of this valuable drug.

ANTI-IMPULSIVE AND ANTI-AGGRESSIVE PROPERTIES OF CLOZAPINE.

Clozapine reduces violence and aggression in patients with schizophrenia and other psychiatric disorders (Frogley et al. 2012). There is also evidence that clozapine can reduce aggressive behavior in patients with bipolar disorder with psychotic symptoms (Kowatch et al. 1995) Clozapine's anti-aggressive effect seems to be specific and greater than both: antipsychotic and sedative effects, although definitely more studies are needed in this field (Frogley et al. 2012). Clozapine effectively reduces aggression against self, including physical mutilation (Chengappa et al. 1999, Swinton 2001) in severe cases of BPD. Many of these patients may have experienced psychotic or quasi-psychotic symptoms; however, (Parker 2002) has shown that clozapine reduces aggression whether directed at self or others in BPD patients, independently of changes in psychotic-type symptoms. The patients' aggression also rapidly reoccurred if clozapine

was discontinued and improved when reinstated. There is also evidence for reduction of aggression in post-traumatic stress disorder with psychotic symptoms (Wheatley et al. 2004).

Clozapine has complex receptor-binding affinities for D₂ and D₄, but also 5-HT_{2A}, receptors could underpin its anti-aggressive effects which may in part be mediated by an anxiolytic as opposed to an exclusively antipsychotic effect (Becker et al. 2003, Gallitano-Mendel et al. 2008). Elevated plasma noradrenalin (NE) levels in patients treated with clozapine may also play a role in its anti-aggressive and anti-suicidal properties (Nielsen et al. 2010) Probably a number of pathways are involved and might include reduced substance misuse and impulsivity, increased monitoring and surveillance compliance, increased treatment concordance, and a generally better outcome (Volavka & Citrome 2008).

ROLE OF CLOZAPINE IN SUBSTANCE USE DISORDERS

As mentioned before there is evidence for clozapine reducing substance abuse. It may limit the use of cannabis (Brunette et al. 2011), alcohol (Chau et al. 2010), both combined (Green et al. 2003) and poly-substance abuse including cocaine (Zimmet et al. 2000) in comparison to FG and other SG antipsychotics. It even appears that clozapine treatment is associated with reduced cigarette smoking (Mc Evoy et al. 1999), although this remains contentious (de Leon et al. 2005). Some authors suggest that clozapine should be evaluated for reducing abuse of alcohol and other substances in bipolar disorder patients (Zhornitski et al. 2010).

TITRATION RATE

An interesting aspect of clozapine use in TRBD is the titration rate. According to clinical guidelines and drug information the rate of 12.5-25 mg/d is optimal. Following this regimen, it takes 2-3 weeks until reaching the target dose. Ifteni et al. based on their study suggest that rapid titration max 100 mg/day is safe, correlates with shorter hospitalization and smaller doses of benzodiazepines used in this group of patients (Ifteni et al. 2014).

One study reported ultra-rapid titration of clozapine (max 150 mg on the first day) in four patients with treatment-refractory mania with psychotic features. The authors observed very rapid antimanic and antipsychotic effect during the first week of treatment. The dose of clozapine on discharge was relatively low (100 mg/d, 150 mg/d, 300 and 400 mg). None of the patients developed life-threatening adverse effects such as neutropenia, symptoms suggestive of myocarditis, neuroleptic malignant syndrome, or delirium. The authors recommend rapid titration of clozapine, after an initial test dose of 25 mg, if this is well tolerated, especially in young patients in whom adequate control of symptoms is urgent, particularly for inpatients having severely agi-

tated mania with psychotic symptoms requiring physical restraints and seclusion, with no response to high doses of antipsychotics generally given in parenteral form or ECT (Aksoy et al. 2015).

Chengappa et al. 2002 suggest that the rapid mood-stabilizing effect of clozapine might be connected with its anti-aggressive effect and that anti-aggressive benefits of clozapine continues to occur for months after the rapid titration phase. The benefits of rapid clozapine titration should be always balanced against the potential for an increased risk of hypotension, seizures, myocarditis and delirium (Abel et al. 2018).

CONCLUSION

Although no approved drug for suicidality in bipolar disorder is available, there is a body of evidence for clozapine as a mood stabilizer and it should be considered as a treatment strategy especially in treatment resistant patients with suicidality.

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THE PREVALENCE OF SEASONAL AFFECTIVE DISORDER AMONG THE BLIND AND PATIENTS WITH SERIOUS VISUAL IMPAIRMENT

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SUMMARY

Background: Seasonal affective disorder (SAD) is an interesting disorder in which depression should occur at a particular time of a year, each year and it should disappear at a specific time of the year. While the prevalence of SAD among generally healthy individuals is well known, the information about the prevalence of this disorder among the blind and visually impaired patients is very limited. The aim of the study was to investigate the prevalence of SAD among the blind and people with serious visual impairment in Polish population.

Subjects and methods: 250 blind or seriously visually impaired individuals and 258 healthy controls were assessed with the usage of Seasonal Pattern Assessment Questionnaire (SPAQ). In research group survey was conducted with the Computer Assisted Telephone Interview (CATI) technique. In control group the questionnaire was distributed via Internet. The results were analysed with the usage of statistical package - Statistica 13.1.

Results: The results revealed that among people suffering from SAD there is statistically significant difference in SPAQ scores between completely blind and seriously visually impaired people.

The study shows that in the control group age is negatively correlated with score in SPAQ score, while in the study group age is positively correlated with SPAQ score. The data show that there is a difference in occurrence of SAD between men and women.

Conclusion: The study has shown a significant difference in occurrence of SAD between study and control groups. What is more the analysis has indicated major difference in the occurrence of SAD between men and women from the study group. Taking into consideration the fact that this is the second analysis of this type in Europe further investigations are needed.

Key words: seasonal affective disorder - visual impairment - blindness

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INTRODUCTION

Seasonal affective disorder (SAD) is a recurring major depression with a seasonal pattern. According to the *Diagnostic and Statistical Manual of Mental Disorders DSM-5*, depression should occur at a particular time of a year, each year and it should disappear at a specific time of the year (Lam et al. 2001). Moreover the patient should demonstrate minimum 2 episodes of depression in the previous 2 years and the number of seasonal episodes should be larger than non-seasonal episodes (Lam et al. 2001).

It is possible to distinguish 2 different types of SAD - winter-type and summer-type SAD.

The symptoms of winter seasonal pattern disorder usually occur during autumn and winter months and improve with the arrival of spring or early summer. The most common symptoms of winter-type SAD include lack of energy, low mood, slowing down, anxiety and reduced motivation to act (Zauderer & Ganzer 2015, Roecklein & Rohan 2005). These patients feel tired despite sleeping more than healthy people, they have problems with concentration. Their appetite may be increased leading to weight gain (Rosenthal et al. 1987). Apathy, sadness and lack of motivation in patients with SAD contribute to the impairment of functioning at work and in social relations (Roecklein & Rohan 2005).

People with summer seasonal pattern disorder experience SAD during summer. Moreover the symptoms are reversible. They have poor appetite leading to weight loss, insomnia, agitation, restlessness, anxiety, and even episodes of violent behaviour (Melrose 2015, Dan & Oren 2014). Another important thing is the severity of SAD. Some people present milder symptoms and this form is known as subsyndromal (sSAD) (Lam et al. 2001).

The pathogenesis of SAD is not fully understood, however, it is known that the presence of SAD is influenced by many factors, both biological and physical. Formerly the scientists thought that one of the most important factors was geographic latitude (Magnússon & Stefánsson 1993), however nowadays numerous studies suggest that impact of latitude on the prevalence of SAD is minimal (Magnússon et al. 2000). What is more, many studies indicate that genetic factor can play a role in the development of SAD (Ho et al. 2018).

The prevalence of SAD among generally healthy individuals is well known and it ranges from 1.5% to 9% (Thaler et al. 2011). SAD occurs 4 times more frequently in women than in men (Magnússon & Partonen 2005). It is more common among young people rather than older ones (Magnússon & Partonen 2005). However the prevalence of SAD among the blind and visually impaired patients is not investigated, with this study being the first in Poland and the second in Europe about this subject.

The aim of the study was to investigate the prevalence of seasonal affective disorder among the blind and people with serious visual impairment in Polish population and to find out if there are any differences in prevalence of SAD between healthy and blind or visually impaired people.

SUBJECTS AND METHODS

We have assessed 258 healthy individuals and 250 blind or seriously visually impaired patients, who were aged 18 or above, with the usage of Seasonal Pattern Assessment Questionnaire (SPAQ) and with authors' questionnaire, which task was to assess what kind of visual deficit subjects from the study group have. It consisted of detailed questions concerning sense of light, field of view and disability class; full version of the questionnaire is presented as a Table 1. In order to obtain the data of the study group CATI (Computer Assisted Telephone Interview) technique was introduced, with the help of School and Educational Centre for Blind Children in Laski. All together, 4 pollsters conducted over 65 hours of telephone interviews and did 750 phone calls.

After successfully collecting 250 records, study group was divided into 2 main subgroups: the blind and persons with serious visual impairment. Data from both subgroups were compared with each other as well as with control group, and the results from other studies.

Statistical analysis of gathered data was performed using legal statistical package Statistica 13.1. There were used only nonparametric tests, because Shapiro-Wilk test revealed that distribution of SPAQ score is nonparametric.

RESULTS

Study group consisted of 117 women and 133 men. Mean age in this group was 41 (± 13.8) years. 129 was seriously visually impaired (with disability class), but with sense of light, and 121 were completely blind and without any sense of light. Median of obtained scores in SPAQ was 5 points (IQR=6). Control group consisted of 176 women and 82 men. Mean age in this group was 37 (± 14.0) years. No one had visual impairment. Median of obtained scores in SPAQ was 9 points (IQR=8). Full demographic data are shown in the Table 2.

Table 1. Author's questionnaire

Question	Possible answers
Are you completely blind or seriously visually impaired?	Completely blind Seriously visually impaired
What is your vision deficit in dioptres in your right eye? (question only for seriously visually impaired people)	Numerical value I don't know
What is your vision deficit in dioptres in your left eye? (question only for seriously visually impaired people)	Numerical value I don't know
Do you have a narrow field of view	Yes No
To what extent do you have a narrow field of view? (question only for people with narrow field of view)	Ca. 20 degrees Ca. 30 degrees I don't know
Is your blindness or visual impairment acquired?	Yes No
Has your blindness or visual impairment occurred after fifth year of age? (question for people with acquired blindness of visual impairment)	Yes No
Can you see strong light?	Yes No
Can you determine the direction of strong light? (question for people with perception of strong light)	Yes No
Have you ever taken antidepressants prescribed by a doctor?	Yes No

Table 2. Demographic data

Parameter	Men	Women
Quantity (N)	133	117
Mean age (years)	40.11 \pm 13.82	43.05 \pm 13.78
Median of SPAQ score (points)	4 (IQR=7)	6 (IQR=6)
Completely blind (%)	53	50
Serious visual impairment (%)	47	50

First of all the data showed that 36 people out of 250 from the study group, which is 15%, reached score 11 or more in SPAQ questionnaire, what meets the criteria of SAD. While as many as 33 persons, which is 14%, obtained between 8 and 10 points in SPAQ what meets the criteria for sSAD.

Interesting thing is that in general polish population the occurrence of SAD is of about 4% and in case of sSAD it is established to 10 %.

In addition Mann-Whitney U test revealed, that among individuals with 8 or more points in SPAQ, the blind have higher scores than people with serious visual impairment, but with sense of light and the difference is statistically significant ($p < 0.01643$), as shown on a Figure 1.

What is more Mann-Whitney U test proved, that in both study ($p < 0.0016$) and control groups ($p < 0.00001$)

the fraction of people with seasonal affective disorders is greater among women, what is presented on Figure 2.

Furthermore the study have found that blind woman with a score of 8 or more points in SPAQ have higher scores in SPAQ than women with serious visual impairment ($p < 0.008$). Among men this difference was not statistically significant.

In addition to this, Spearman rank correlation coefficient revealed that in control group age is negatively correlated ($p < 0.001$; $R = -0.2116$) with SPAQ score, which means that younger patients received higher scores.

On the other hand Spearman rank correlation coefficient revealed that in the study group age is positively correlated ($p < 0.018$; $R = 0.1491$) with SPAQ score. The correlations are shown on the Figure 3 and Figure 4 respectively.

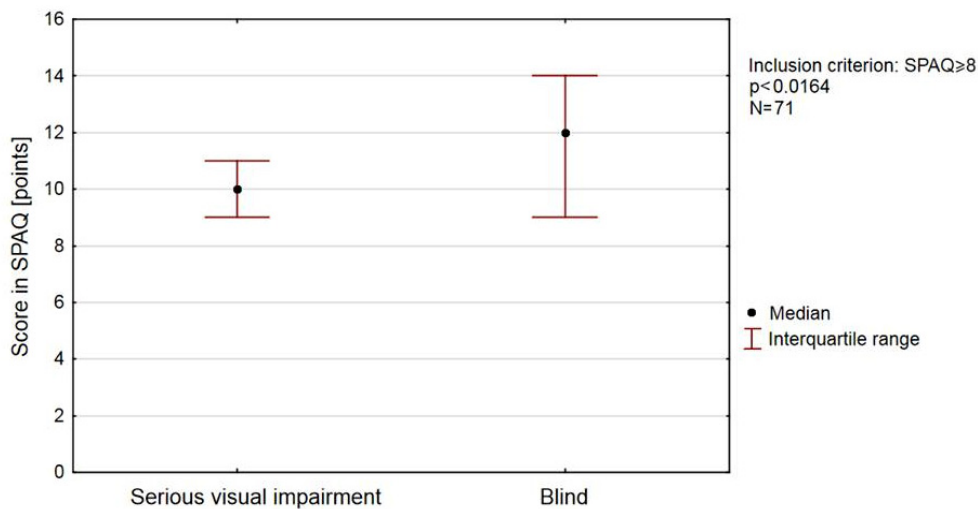


Figure 1. Difference in SPAQ scores between two subgroups of the study group

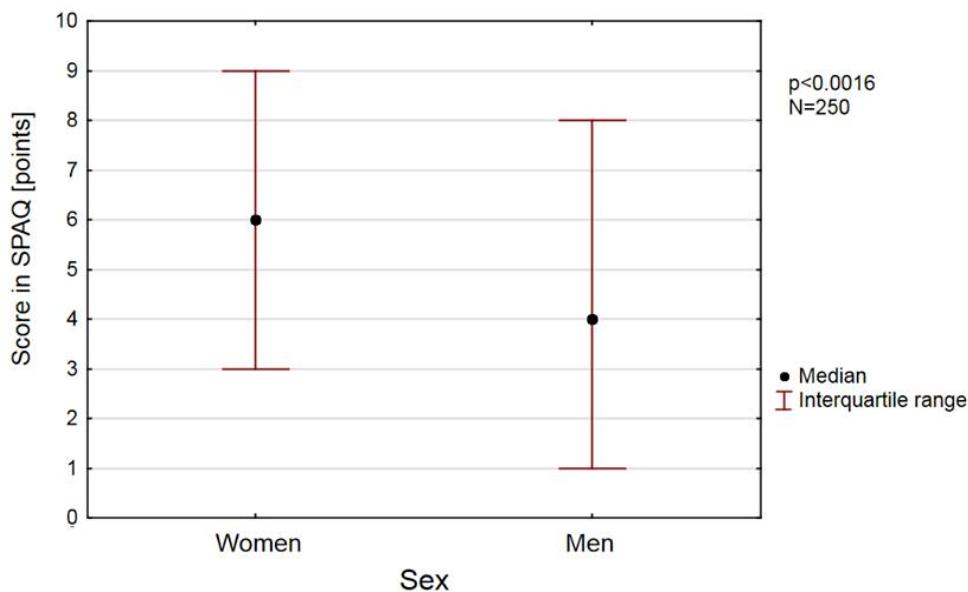


Figure 2. Difference in SPAQ scores between women and man of the study group

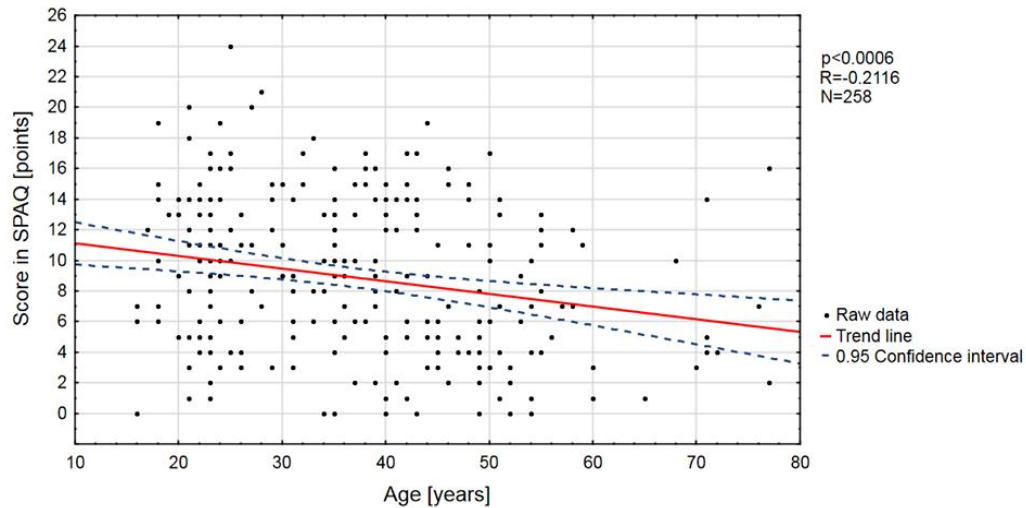


Figure 3. Correlation between age and SPAQ score in the control group

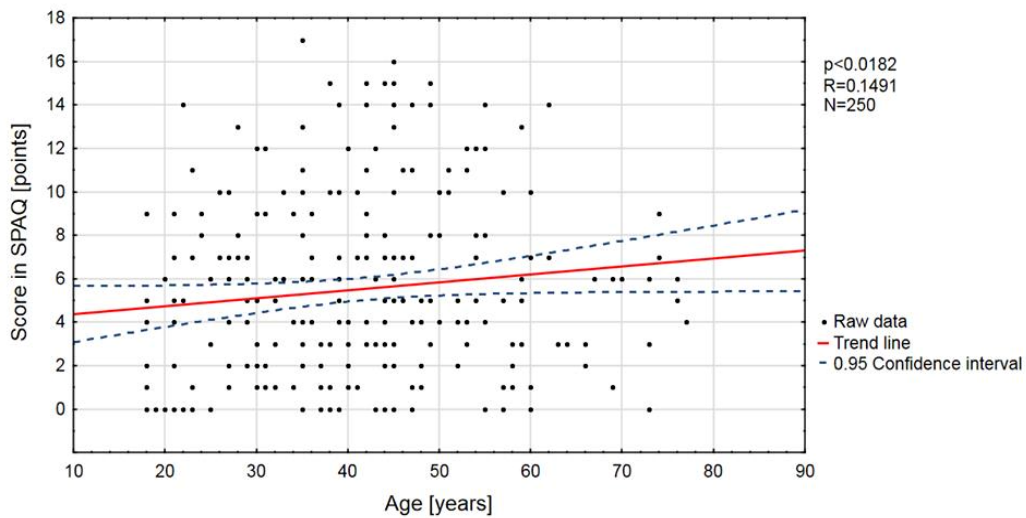


Figure 4. Correlation between age and SPAQ score in the study group

DISCUSSION

Although seasonal affective disorder is a common depressive disorder, the data about its prevalence among the blind or persons with serious visual impairment are very limited (Melrose 2015). To our knowledge this is the first study on this subject in Poland and only the second in Europe (the first one conducted in Denmark). The data obtained in this study indicate that the prevalence of seasonal affective disorder is significantly higher among the study group than in the control. Moreover there is a statistically significant difference in the prevalence of SAD between the blind and persons with serious visual impairment. Since photoperiodic information can be transferred via a pathway extending from the retina to the retino-hypothalamic tract, the suprachiasmatic nuclei, the superior cervical ganglia, and the melatonin-producing pineal gland, the dysfunction of retina may result in deregulation of secretion of melatonin what matches the results of other studies (Oren 1991). Contrastingly in the other European study

on this subject the results suggested that there is no difference in the prevalence of SAD among the blind and seriously visually impaired persons (Madsen et al. 2016). However we think it possible that melatonin secretion is deregulated to the greater extend among the blind because reduced amount of bright light reaches their retino-hypothalamic tract and thus their pineal gland. Nevertheless it is only a hypothesis and this difference in the prevalence still needs to be investigated.

The difference in prevalence of SAD among the study and control groups may also be caused by deregulation of circadian rhythm and thus melatonin secretion (Winkler 2006). We believe that the circadian rhythm is deregulated to the greater extend among the study group causing abnormal secretion of melatonin and in turn resulting in greater frequency of SAD among this group. Imbalanced production of melatonin most probably increases number of serotonin reuptake receptors, which results in decrease of serotonin level and causes symptoms of depression (Święcicki 2007). The reason why some people may experience SAD in the summer

may be connected with too much sunlight, which also leads to the modulation of melatonin production, however this subject exceeds the topic of this study (Lingjaerde & Reichborn-Kjennerud 1993, Wehr et al. 1987).

Many studies indicate that noradrenaline can also play the role in the pathogenesis of SAD, with its level inversely correlated with the level of depression in untreated SAD (Checkly et al. 1993). There are also reports that dopamine is being involved in the occurrence of SAD (Lam & Levitan 2000). The data on the genetics of seasonal affective disorders show a familial contribution to the development of SAD and that genetic variant related to serotonergic transmission, the 5-HTTLPR gene promoter polymorphisms, is associated with SAD (Sher et al. 1999). It is very probable that in some cases subjects from the study group also have this genetic variant what further contributes to the higher prevalence of SAD, however this hypothesis exceeds the topic of this study.

The data show that in the study group the prevalence of subsyndromal SAD was also significantly higher than in the control group what matches the results of other studies (Magnússon & Stefánsson 1993). The analysis also shows that women in both study and control groups are more prone to developing SAD. This is most probably connected to the genetic predisposition as well as hormonal fluctuations, which may act as a trigger to depression (Albert 2015). Furthermore blind women are more susceptible to developing SAD than seriously visually impaired women, what supports our hypothesis that deregulation of melatonin secretion is greater among the blind. Interestingly the data show that there is no difference between blind and visually impaired men. This suggests that genetic predisposition and hormonal fluctuations have greater impact on the prevalence of SAD than the difference in the amount of light, which falls on the retina between the blind and visually impaired persons.

The study also shows that age is negatively correlated with SPAQ score, which means that younger people received higher scores in the questionnaire, and it matches the results of other studies (Roeklein & Rohan 2005). On the other hand, in the study group age is positively correlated with SPAQ score, which means that the older the patient the higher the score he obtained. This correlation may be connected to the fact that the blind and seriously visually impaired live with decreased quality of life, thus along with time it is more probable to develop SAD, however this topic needs to be further investigated (Renaud & Bédard 2013).

This study has its limitations, which are connected to the fact that data for the study group were gathered via CATI technique and not by a face-to-face interview with the subjects. This technique was imposed because the Polish Association of the Blind (PZN) refused to cooperate with us thus making it impossible to assess the blind and visually impaired people in person. Their decision was motivated by the lack of time and place to conduct the study, as PZN hasn't got its own quarters

and their meetings are very scarce. In the end we have teamed with The Educational Centre in Laski, with whom we've been gathering the data for 2 years. Moreover the data for the control group were gathered via Internet survey what on the one hand allows reaching greater amount of persons but on the other creates a problem of bias based on a self-report. The validity of SPAQ is also a subject of discussion since it is acceptable as a scanning tool and not as a diagnostic, however it was the only possible option to use while gathering data via Internet and telephone interviews (Magnusson 1996).

CONCLUSION

The aim of this research was to investigate the prevalence of seasonal affective disorder among the blind and people with serious visual impairment in polish population. The study also tried to find reasons for any differences in prevalence of SAD between healthy and blind or visually impaired people. The study has shown a significant difference in occurrence of SAD between study and control groups. Moreover the blind achieved higher average score in SPAQ than visually impaired persons. It may support the thesis that retinal dysfunction can play a role in the pathogenesis of some cases of SAD. What is more the study showed major difference in the occurrence of SAD between sexes. Women achieved higher score in SPAQ than men which means women are more susceptible to develop SAD. Moreover blind women suffer from SAD more often than women with serious visual impairment. Since this is only the second study about this subject in Europe this topic is fairly unknown to the public thus this problem might be belittled. That is why it is crucial to raise awareness about the fact of high prevalence of SAD among the blind and people with serious visual impairment. Only then it will be possible to have effective treatment and in consequence to improve the quality of life of the blind and seriously visually impaired persons suffering from SAD.

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Contribution of individual authors:

Bartłomiej Kurczab: design and conception of the study, data analysis, and literature searches.

Aleksandra Ćwiek: design and conception of the study, collection and analysis of data.

Anna Witkowska: design of the study, data collection.

Krzysztof Kramarczyk: data collection, literature searches.

Karolina Drzyzga: design and conception of the study, literature searches.

Krzysztof Kucia: design and conception of the study.

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SHORT-TERM KETAMINE ADMINISTRATION IN TREATMENT-RESISTANT DEPRESSION: FOCUS ON CARDIOVASCULAR SAFETY

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SUMMARY

Ketamine is an anaesthetic and analgesic agent that demonstrates the antidepressive effect in major depression. Several administrations routes, dosing schemas and esketamine are investigated in basic and clinical research with particular focus on treatment-resistant depression (TRD) where drug demonstrates its efficacy where very limited alternatives are available. The majority of ketamine studies in TRD treatment reported no serious adverse events regardless the administration route or regimen. However, the most commonly observed adverse events following ketamine administration in antidepressive doses include general, psychotomimetic, dissociative and hemodynamic ones. The side effects are mild or moderate, well-tolerated and transient.

This paper discusses the risks regarding cardiovascular safety in MDD patients in short-term ketamine administration with particular focus on the effect on blood pressure and adverse drug reactions mitigation measures.

The increase in systolic (SBP) and diastolic (DBP) blood pressure is dose-dependent and begins shortly after administration peaking at around 30 to 50 minutes with SBP and DBP rise from 10% to 50% above predose values and resolving at approximately 2 to 4 hours after the dose administration. These changes generally are primarily asymptomatic. The elevations in SBP and DBP are observed on each dosing day with multiple administration schema.

The treatment with ketamine and esketamine is contradicted in subjects at risk of an increase in blood pressure or intracranial pressure. The current evidence indicates the blood pressure should be assessed prior to dosing with ketamine and hypertensive individuals shall receive effective lifestyle/pharmacologic management prior to treatment. Blood pressure should be monitored after dose administration until blood pressure returns to acceptable levels. If blood pressure remains elevated acute blood pressure management shall be delivered. In patients experiencing symptoms of hypertensive crisis immediate emergency care must be provided.

The unmet need for improved pharmacotherapies for TRD means the use of ketamine and esketamine is warranted therapeutic option in patients who fail to achieve a sustained remission of depressive symptoms with drugs with monoamine-based mechanisms of action. Adequate safety measures must be applied when using ketamine/esketamine in TRD subjects with particular focus on somatic comorbidities as the transient drug effect on cardiovascular system is demonstrated and of clinical significance.

Key words: ketamine - MDD - treatment resistant depression - cardiovascular system - safety - adverse drug reactions - blood pressure

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INTRODUCTION

Ketamine is an anaesthetic and analgesic agent that received particular interest in 2000 when Berman et al. published the results of their clinical trial demonstrating the antidepressive effect of the drug in major depression (Berman et al. 2000, McGirr et al. 2015, Rosenblat et al. 2019). With a global burden of mood disorders on humans and the limitations of the monoaminergic antidepressants available ketamine research and use flourish with recent FDA approval for intranasal esketamine in TRD (treatment-resistant-depression) use.

Ketamine is a racemate of its R- and S-enantiomers exhibiting different pharmacodynamics with majority of basic and clinical research pointing out to esketamine showing 3- to 4-fold higher affinity to phencyclidine site of the NMDA receptor than R-ketamine, corresponding with its potency in terms of anaesthesia and analgesia (Kohrs & Durieux 1998) and more favorable tolerability profile with regard to its psychotomimetic side effects (Mathew et al. 2012, Paul et al. 2009).

The mechanisms associated with ketamine antidepressant action are unclear. Still, its mode of action is

different from monoaminergic antidepressants (Chiriță et al. 2015). Subanaesthetic ketamine and esketamine doses trigger a intracellular cascade that induces synaptogenesis and dendritic spine formation (Duman et al. 2012) impacting three signalling pathways hypothetically employed in a glutamate hypothesis of major depression including the brain-derived neurotrophic factor (BDNF) pathway, the mammalian target of rapamycin (mTOR) signalling pathway and AMPA receptors (Abelaira et al. 2014).

The aim of this paper is to evaluate the risks regarding cardiovascular safety in MDD patients in short-term ketamine administration with particular focus on the effect on blood pressure and adverse drug reactions mitigation measures.

KETAMINE USE IN MAJOR DEPRESSION

The seminal proof-of-concept study with ketamine demonstrated that a single, subanaesthetic dose of intravenous drug exerts a rapid and persistent antidepressive effect in major depression (Berman et al. 2000). The subsequent basic research data and clinical trials

confirmed that ketamine is effective for patients with TRD (Coyle & Laws 201, McGirr et al. 2015, Short et al. 2018) and, in somehow isolated manner, reduces the intensity of suicidal thoughts in patients with TRD (Diazgranados et al. 2010, Price et al. 2009, Price et al. 2014, Short et al. 2018).

The mechanism of ketamine action in major depression is distinct from the monoaminergic antidepressant treatments. Ketamine affects fast excitatory glutamate transmission, increases BDNF release, and stimulates synaptogenesis. The pharmacodynamics of ketamine and esketamine is well demonstrated with its clinical antidepressive effect appearing in minutes to hours post administration in line with glutamate hypothesis of major depression.

Ketamine is administered via different routes including intravenous (IV), intramuscular (IM), intranasal (IN), inhalation (nebulization), epidural, subcutaneous, transdermal, intra-articular, sublingual and oral formulations (Le Nedelec et al. 2018).

In majority of clinical reports available in the literature on patients with major depression, ketamine is used as a racemic mixture for single, intravenous 40-minute infusion in a dose equal to 0.5 mg/kg (Berman et al. 2000, Diazgranados et al. 2010, Zarate et al. 2006, Zarate et al. 2012b, Short et al. 2018). There are also studies with multiple ketamine administrations with several IV infusions (Murrough et al. 2013b, Shiroma et al. 2014, Singh et al. 2016, Short et al. 2018) with recent studies on intranasal esketamine in acute and maintenance treatment of TRD (Daly et al. 2018, Daly et al. 2019, Fedgchin et al. 2019, Popova et al. 2019). The FDA approved nasal esketamine spray demonstrates its antidepressive effect in the acute and maintenance treatment of TRD at doses of 56 or 84 mg coadministered with an oral antidepressant (Daly et al. 2019).

KETAMINE USE IN MAJOR DEPRESSION – CARDIOVASCULAR ADVERSE DRUG REACTIONS

The majority of ketamine studies in TRD treatment reported no serious adverse events regardless the administration route or regimen. The most commonly

observed adverse events following ketamine administration in antidepressive doses include general, psychotomimetic, dissociative and hemodynamic ones. The side effects are mild or moderate, well-tolerated and transient as all of them cease within 4 hours post administration (Short et al. 2018) (Table 1).

However, there is the clinically significant effect on blood pressure in normotensive individuals. The transient peak increases in systolic (SBP) and diastolic (DBP) blood pressure were reported during the infusions with ketamine and esketamine as well as being observed when alternative administration route was investigated. Animal studies suggest that the increase in blood pressure produced by ketamine is due to selective activation of central cardiac stimulating mechanisms leading to an increase in cardiac output. The blood pressure levels exceeding 180/100 mmHg or heart rates exceeding 110 beats per minute in approximately 20-30% of the patients exposed to drug are reported (Short et al. 2018).

The increase in SBP and DBP is dose-dependent and begins shortly after administration peaking at around 30 to 50 minutes with SBP and DBP rise from 10% to 50% above predose values and resolving at approximately 2 to 4 hours after the dose administration. These changes generally are primarily asymptomatic. The elevations in SBP and DBP are observed on each dosing day with multiple administration schema (Daly et al. 2018, Daly et al. 2019, Fedgchin et al. 2019, Popova et al. 2019).

The blood pressure elevation rates are higher among subjects with a history of hypertension than in those without such a history. Thus, the exposure to ketamine and esketamine treatment is associated with meaningful effects on heart rate and, in particular, on blood pressure for some patients.

SAFETY PRECAUTIONS

It is of prime importance qualifying and monitoring patients' safety when using ketamine with particular focus on cardiovascular risks. The treatment is contradicted in subjects at risk of an increase in blood pressure or intracranial pressure, in particular with known aneurysmal vascular disease and with known history of intracerebral hemorrhage (Short et al. 2018).

Table 1. Ketamine associated adverse drug reaction in the treatment of treatment-resistant depression

Type	Symptom	Comment	Timeframe
General	headache blurred vision, dry mouth, dizziness, anxiety, nausea, vomiting, faintness, sleep disorders, cognitive decline, restlessness, euphoria, increased sex drive, constipation, dysgeusia, hypoaesthesia at site of administration	transient	returns to normal up to 4 hours post-dose
Psychomimetic	paranoia, hallucinations, delusion, thought disorder	transient	returns to normal up to 4 hours post-dose
Dissociative	altered body and time perception, depersonalisation, derealisation	transient	returns to normal up to 4 hours post-dose
Hemodynamic	increase HR, increase SBP and DBP	transient	returns to normal up to 4 hours post-dose

Patients with cardiovascular and cerebrovascular conditions are to be evaluated and stabilized prior to treatment initiation with exclusion of subjects with unstable or poorly controlled hypertension, history (within 6 weeks) of cardiovascular event, including myocardial infarction (MI), ischemic stroke or transient ischemic attack, hemodynamically significant valvular heart disease or New York Heart Association Class III-IV heart failure of any etiology.

Patients with a history of an MI should be clinically stable and cardiac symptom free prior to drug administration (Table 2).

Table 2. Patients with a history of an MI

Transient blood pressure increases are observed with ketamine/esketamine on treatment days. The maximum value was reached at 40 minutes after the start of administration in most cases and typically returned to the predose.
Few patients experience treatment-emergent transient hypertension, defined as a systolic blood pressure of 180 mm Hg or higher and/or a diastolic blood pressure of 110 mm Hg or higher.
No clinically significant change in electrocardiographic findings was observed to date.

KETAMINE USE IN MAJOR DEPRESSION – CARDIOVASCULAR ADVERSE DRUG REACTIONS MITIGATION MEASURES

CVD ketamine adverse drug reaction in the treatment of treatment-resistant depression is presented in table 3.

Table 3. CVD ketamine adverse drug reaction in the treatment of treatment-resistant depression

Common	temporary tachycardia; increase in blood pressure and heart rate
Rare	arrhythmia; bradycardia

Ketamine may cause transient increases in SBP and/or DBP lasting approximately 1 to 2 hours. The current evidence indicates the blood pressure should be assessed prior to dosing with ketamine and hypertensive individuals shall receive effective lifestyle/pharmacologic management prior to treatment. Blood pressure should be monitored after dose administration until blood pressure returns to acceptable levels. If blood pressure remains elevated acute blood pressure management shall be delivered. In patients experiencing symptoms of hypertensive crisis immediate emergency care must be provided (Table 4).

Table 4. Ketamine/esketamine adverse drug reactions in TRD

Author	Intervention	Response
Berman et al. 2000	ketamine i.v. Infusion (single)	significantly greater scores on the BPRS scale, especially the positive symptoms. Scores returned to baseline by 120 min after infusion.
Zarate et al. 2006	ketamine i.v. Infusion (single)	elevations in blood pressure, euphoria, dizziness, and increased libid; adverse effects occurring more frequently with placebo than ketamine were gastrointestinal distress, increased thirst, headache, metallic taste, and constipation. The majority of these adverse effects ceased within 80 minutes after the infusion.
Diazgranados et al. 2010a	ketamine i.v. Infusion (single)	adverse events associated only with ketamine ($\geq 10\%$ of subjects) included tachycardia and increased blood pressure; two subjects who experienced increased blood pressure and tachycardia returned to normal within minutes after the infusion. No adverse event was significantly different from placebo at 80 minutes or thereafter. No significant changes occurred in electrocardiography, respiratory, or laboratory values during the study.
Diazgranados et al. 2010b	ketamine i.v. Infusion (single)	replicable to the previous study
Zarate et al. 2012b	ketamine i.v. Infusion (single)	no significant changes occurred in electrocardiogram, respiratory, or laboratory values during the study.
Sos et al. 2013	ketamine i.v. Infusion (single)	mild increases in blood pressure, emotional blunting and euphoria; majority of these effects ceased within 30 minutes after the ketamine infusion.
Murrough et al. 2013a	ketamine i.v. Infusion (uo to 6)	mild transient changes in blood pressure were observed on the infusion day; the infusion was discontinued for two patients in the ketamine group because of hemodynamic changes; in one case, a blood pressure elevation (peak, 187/91 mm Hg) unresponsive to beta-blocker therapy resulted in infusion termination after 30 minutes. The blood pressure normalized within 10 minutes of infusion cessation. In the other case, there was transient but pronounced hypotension and bradycardia that resolved without sequelae and was followed by overnight observation in the hospital.

Table 4. Continues

Author	Intervention	Response
Murrough et al. 2013b	ketamine i.v. Infusion (single)	sixteen participants (67%) did not experience any clinically significant change in vital signs during any of the ketamine infusions; eight participants (33%) experienced elevated BP and/or heart rate according to pre-defined study criteria at least once during the series of infusions; one participant experienced elevated BP during the first infusion that did not respond satisfactorily to administration of antihypertensive medication, resulting in discontinuation of the infusion and study exit (maximum BP: 180/115); BP of that participant stabilized shortly after discontinuation of the ketamine infusion.
Shiroma et al. 2014	ketamine intranasal administration (single)	none of the patients experienced arrhythmia or required respiratory support during the infusions; one normotensive 32-year old patient experienced a single episode of rise in blood pressure (180/92) that required 10 mg of IV labetalol; blood pressure rapidly returned to baseline and remained normal until discharge.
Lapidus et al. 2014	ketamine intranasal administration (up to 6)	intranasal ketamine was associated with small increases in systolic BP (mean increase of 7.6 mm Hg at 40 min compared with baseline); four participants experienced treatment emergent increases in systolic BP >130 mm Hg after ketamine, and three participants experienced systolic BP >130 mm Hg after placebo. No patients had diastolic BP >100 mm Hg. There were no clinically significant elevations in BP or heart rate that required intervention, and all hemodynamic changes resolved by 4 hours after infusion. No association was found between hemodynamic changes and antidepressant response to ketamine (all $p < 0.05$).
Singh et al. 2015	esketamine i.v. Infusion (twice)	no clinically significant changes in laboratory tests, electrocardiograms, or physical examinations were observed; the only clinically significant vital sign abnormalities were a case of irregular breathing and a case of transient high blood pressure (both with esketamine 0.40 mg/kg dosing), which resolved within 2 hours without intervention.
Loo et al. 2016	esketamine i.v. Infusion (single)	transient increases in heart rate, systolic and diastolic blood pressure were observed with peak incidence 5–10 min after ketamine injection in the IV group, and 10–15 min after ketamine injection in the IM and SC groups; across groups, increases in heart rate did not exceed 120% of baseline, except in three participants (one each in IV, IM and SC groups); increases in mean arterial pressure (MAP) did not exceed 120% of baseline, with the exception of four participants (n=2, IV; n=2, IM).
Singh et al. 2016	ketamine i.v. Infusion (2-3/week/4 week)	no clinically significant changes in laboratory tests, pulse oximetry, and ECG were observed during the study.
Daly et al. 2018	esketamine intranasal (twice/week)	most of the esketamine-treated participants manifested transient elevations in blood pressure (maximum mean change: systolic, 19.0 mm Hg; diastolic, 10.3 mm Hg) and heart rate (maximum mean change: 9.4 bpm) on dosing days; maximum blood pressure values were observed in most cases at 10 or 40 minutes after the dose (systolic: 199 mm Hg; diastolic: 115 mm Hg); elevated values typically returned to the value observed before dosing by 2 hours after the dose; dose effect was not observed for heart rate, although the greatest mean increases from baseline during both periods were observed in the 84-mg esketamine group.

CONCLUSIONS

Ketamine and esketamine demonstrate rapid antidepressant effect in TRD patients. The drug exhibits good overall tolerability profile. The unmet need for improved pharmacotherapies for TRD means the use of ketamine and esketamine is warranted therapeutic option in patients who fail to achieve a sustained remission of depressive symptoms with drugs with mono-

amine-based mechanisms of action. Adequate safety measures must be applied when using ketamine/esketamine in TRD subjects with particular focus on somatic comorbidities as the transient drug effect on cardiovascular system is demonstrated and of clinical significance. However, the evidence for its safety in TRD patients is strong with adequate treatment regimen being used.

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Contribution of individual authors:

Joanna Szarmach: study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript.

Wiesław Jerzy Cubała: drafting of manuscript, critical revision.

Adam Włodarczyk: analysis and interpretation of data.

Mariusz S. Wiglusz: critical revision.

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CADASIL AND BIPOLAR AFFECTIVE DISORDER

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SUMMARY

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a rare monogenic disorder caused by mutations in the NOTCH3 gene. The clinical features are primarily neurological, which include recurrent transient ischaemic attacks, strokes, and migraines. However, psychiatric manifestations which mainly include mood disturbances have also been reported in CADASIL. Manic symptoms and bipolar disorders are rarely documented in CADASIL and existing reports generally lack detailed descriptions of the psychiatric evaluation.

We discuss a case of Bipolar Affective Disorder (BD) in a British woman with a family history of CADASIL.

This case provides insight into the diagnosis and management of BD as well as the possible underlying aetiologies that should be considered. The similarities between BD and CADASIL in terms of imaging, genetic, and therapeutic aspects raise the possibility of common dysfunctional pathways. BD in CADASIL may warrant greater consideration by both psychiatrists as well as non-psychiatric specialists and further studies are required to understand the pathological significance.

Key words: CADASIL - Bipolar Affective Disorder - EUPD

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INTRODUCTION

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a rare inherited cerebrovascular disease that develops due to mutations in the NOTCH3 gene on chromosome 19p13.1 (Di Donato et al. 2017).

The clinical features, age of onset, and progression of CADASIL are variable. Clinically, it is characterised by mid-adulthood onset, primarily with neurological features including recurrent subcortical ischemic events with white matter hyper-intensities visible on magnetic resonance imaging (MRI) and migraine with aura (Dichgans et al. 1998). This is often accompanied by a varying degree of cognitive decline. Although the clinical features have a neurological preponderance, CADASIL is also characterised by psychiatric manifestations, reported in approximately one third of patients in CADASIL cohorts (Adib-Samii et al. 2010). These mainly include, mood disturbances, anxiety disorders, and personality disorders, with psychotic symptoms also being described (Chabriat & Bousser 2007). Most patients are affected by major depression, with other important psychiatric conditions such as bipolar affective disorder (BD) rarely being described otherwise (Valenti et al. 2008). The reported frequency of BD in CADASIL patients varies widely in the literature from 2% in one meta-analysis (Valenti et al. 2008) to 26% in a retrospective cohort study (Valenti et al. 2011). BD, especially BD type II, is difficult to diagnose correctly and is often underdiagnosed. As many as 40-50% of cases are misdiagnosed as unipolar depression (Benazzi 2007), which may be related to heterogeneity in the disorder. In

the CADASIL literature, the diagnostic criteria used for BD are often inconsistent or unreported, which may account for the discrepancies. This highlights a need for clinicians to be aware of the possible psychiatric manifestations of CADASIL, as well as the need for psychiatrists to consider CADASIL as a differential diagnosis.

Despite the significant morbidity of BD in CADASIL, the frequency is likely to be underestimated (Chabriat & Bousser 2007). Although CADASIL is increasingly recognised in the neurological literature, fewer studies go beyond solely reporting on the existence of the associated mood disturbances such as BD among its cardinal symptoms (Valenti et al. 2008). Comparable imaging and genetic findings exist between BD and CADASIL, which raises the possibility that the two disorders share common pathogenic mechanisms. In this report, we discuss a case of BD in a British woman with a family history of CADASIL. Thus, we expand on the clinical approach to BD and the diagnosis of CADASIL.

CASE PRESENTATION

Having obtained full informed consent, we describe a case of a 41 year old British woman, who was admitted to the Acute Day Treatment Unit (ADTU). Prior to her admission to ADTU, there had been an episode of her having taken an overdose. She gave a history of alleged emotional and sexual abuse and described having pervasive features of Emotionally Unstable Personality Disorder (EUPD). Additionally, on careful history taking, it transpired that she had been experiencing a number of episodes of manic and hypomanic symptoms which usually lasted around 4-7 days and were followed

by longer periods of depressive symptoms. Additionally, there were mixtures of manic, hypomanic, and depressive symptoms. Her misuse of alcohol was much more apparent during manic/hypomanic periods. She further stated that she often took to alcohol to 'bring herself down' during her manic/hypomanic periods. She was taking 100 mg of Sertraline daily and 200 mg of Quetiapine daily. Indeed, she had noticed when she was on a higher dose of Sertraline (200 mg daily), she experienced more frequent manic/ hypomanic episodes with rapidity of cycling. She was diagnosed with EUPD and BD (rapid cycling type), with a differential diagnosis of BD type II. She was well aware that her father died of diagnosed CADASIL, having had a major stroke in his 50s. She was also aware that her paternal grandmother also had a stroke at a relatively young age. Furthermore, she knew that CADASIL is an autosomal dominant genetic condition and that she had a 50% chance of inheriting it. This was clearly troubling her and she was keen to have genetic testing to check if she had CADASIL. On her request, and with the assistance of her GP, we arranged for the genetic testing from the regional genetic service who carried out the test after counselling.

Fortunately, she was found not to have inherited the CADASIL gene.

DISCUSSION

CADASIL is a rare monogenic disease caused by mutations in the NOTCH3 gene on chromosome 19p13.1 that can present with a range of symptoms including: stroke, migraine with aura, cognitive impairment, and psychiatric disturbances. The most frequently reported psychiatric disturbances are mood disturbances (9–41%) (Valenti et al. 2008), including BD. BD is a heterogeneous disorder and the continuum/spectrum approach to mood disorders has been introduced to account for this as the research on BD subtypes continues to expand. Our current case of BD was suspected to be a manifestation of CADASIL based on the family history of the condition. However, this significant differential diagnosis was excluded by genetic testing that was initiated following psychiatric evaluation. This case has highlighted the dynamic process involved in the diagnosis of BD as well as issues surrounding the psychiatric manifestations of the suspected underlying organic aetiology of CADASIL.

A small number of case reports have explored the presentation of mood disorders in CADASIL. CADASIL presenting with symptoms of mania have been discussed in case reports by Kumar & Mahr (1997) and Park et al. (2014). Leyhe et al. (2005) and Wang et al. (2017) have elaborated on cases with hypomanic and depressive features. Gamakaranage & Chang (2012) previously described a CADASIL patient with personality changes (including mood swings and aggressive behaviour) but without manic features. In a number of

these reports, a detailed description of the psychiatric work-up and treatment was not included (Gamakaranage & Chang 2012, Kumar & Mahr 1997).

Similarities in the genetic findings have been described between BD and CADASIL. While we do not suggest that these illnesses are equivalent, understanding the correlations of BD with CADASIL provides insight into dysfunction within gene networks common to both disorders. BD is reported to have a high degree of heritability but is thought to be a multifactorial disease, stemming from environmental contributions and multiple genes that have not yet been identified (Craddock & Sklar 2013, Muller-Oerlinghausen et al. 2002). Previous genetic linkage analyses investigating NOTCH3 as a candidate gene for BD have yielded negative results (Ahearn et al. 2002). However, more recently, integrative approaches have identified gene-expression associations between the Notch signalling pathway and BD (Pedroso et al. 2012). It may be the case that patients with BD exhibit less distinct downstream dysfunction in the Notch3 signalling pathway in comparison to CADASIL.

The association of BD with CADASIL provides insight into the organic basis and possible therapeutic avenues for psychiatric illnesses once widely considered to be functional disorders lacking an observable disease process. MRI has revealed an increased prevalence of white matter hyper-intensities in patients with BD compared to normal controls (Altshuler et al. 1995), which has been used as an endophenotype in the disorder (Sarıççek et al. 2016). The white matter lesions affecting the fronto-limbic and fronto-striatal pathways may contribute to developing BD in later life. Notably, these imaging findings in BD resemble those reported in CADASIL (Di Donato et al. 2017) and the Notch pathways have also been suggested as a causative factor (Mahon et al. 2010). Most of these white matter hyper-intensities are thought to arise from focal cerebral ischemia (Thomas et al. 2002) which suggests that ischaemic episodes may contribute to the pathophysiology of both disorders. However, it must be noted that BD and other mood disorders that may arise in CADASIL could be a consequence of the disabling neurological function reported in many cases.

The arteriopathy of CADASIL is characterised by the progressive degeneration of vascular smooth muscle cells (VSMCs) in cerebral vessels (Bergmann et al. 1996). The anticonvulsant valproate has been shown to promote anti-apoptotic effects on human VSMCs in vitro through the Notch3/c-FLIP signalling pathway, with comparable in vivo effects on the signalling in the rat brain (Yuan et al. 2009). Furthermore, elevated plasma levels of inhibitory Notch ligands have been found in BD compared to healthy controls, suggesting that the Notch signalling pathway may be aberrantly attenuated in these disorders (Hoseth et al. 2018). Lithium may exert its mood stabilising effects by activating Notch signalling through the inhibition of

glycogen synthase kinase-3 β (Espinosa et al. 2003, Hoseth et al. 2018). These findings highlight the possible relevance of these medications in the treatment of CADASIL and reducing the burden of white matter lesions in BD.

The diagnosis of BD, particularly BD type 2 is difficult, often being mistaken for unipolar depression. This may lead to inappropriate management and negative health outcomes including poor quality of life and suicide risk (Nasrallah 2015). Patients with CADASIL initially demonstrating only neurological symptoms may pose a further challenge to diagnosis. Pooled data from CADASIL case series that documented the presence of mood disorders showed that BD was reported in 9/451 (2%) of patients (Valenti et al. 2008). However, in these studies, psychiatric disorders in general were poorly characterised, usually lacking the usage of precise diagnostic criteria and thorough psychiatric evaluation (Valenti et al. 2008). Assessment of mood disorders in CADASIL using the DSM-IV semi-structured interview has demonstrated a higher frequency of BD than previously reported (Valenti et al. 2011). This raises the possibility that the diagnosis of BD may have been largely missed by non-psychiatric specialists in these larger series of patients (Valenti et al. 2011). Conversely, in psychiatric patients, CADASIL as a disease is likely to be underdiagnosed. If the affective symptoms present during psychiatric assessment without neurological deficits, the underlying diagnosis of CADASIL may not be recognised (Leyhe et al. 2005).

CONCLUSION

Altogether, based on these findings and with our clinical case in mind, it is therefore reasonable to emphasise that a thorough psychiatric evaluation should be carried out in patients with suspected CADASIL. Indeed, the possibility of this disease should be explored further by psychiatrists when assessing individuals presenting with features of psychiatric disorders such as BD who give a family history of strokes at an earlier age.

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Contribution of individual authors:

Rashid Zaman conceived the idea of the paper and wrote the case report and revised the manuscript.

Hong Kai Lim & Zachary A. Millar reviewed the literature and wrote the first draft.

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PHARMACOLOGICAL THERAPIES IN BIPOLAR DISORDER: A REVIEW OF CURRENT TREATMENT OPTIONS

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SUMMARY

Background: Bipolar disorder is a mental illness characterised by periods of elevated mood alternating with periods of depression. Long-term relapse prevention in bipolar disorder is challenging, with a significant number of patients relapsing following the initial stabilisation of mood. Initial treatment of the condition is complex and usually occurs in secondary care. Whilst there is no known cure for bipolar disorder, several therapies have been found to be effective in both managing acute episodes and sustaining long-term remission. The key pharmacological therapies in bipolar disorder are lithium salts, antiepileptics and antipsychotics and these will be the focus of this review.

Aim: This review seeks to outline the key common pharmacological therapies used in the treatment and relapse prevention of this condition.

Methods: A MEDLINE search was performed, and the available literature was subsequently analysed, including meta-analyses, reviews and original clinical trials.

Results: Management strategies can be subdivided into treating acute presentations of mania and depression and maintaining long-term remission. The extensive side effect profile of several antipsychotics means that there are certain patient groups for whom they may be intolerable or contraindicated. Lithium emerges as a highly efficacious maintenance therapy but retains the burden of therapeutic drug monitoring. Antiepileptics play a crucial role in maintaining remission but are linked to serious, albeit rare, side effects.

Conclusion: Despite the efficacy of the medications discussed in this article, their underlying mechanisms of action remain to be fully elucidated. Nonetheless, these key therapies continue to be essential tools in the management of bipolar disorder.

Key words: bipolar disorder - lithium - antiepileptics – antipsychotics -relapse prevention

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INTRODUCTION

Bipolar disorder is a severe mental illness characterised by periods of elevated mood (mania or hypomania), depression and mixed episodes. It affects 1-2% of the population worldwide, transcending nationality, ethnicity and socioeconomic status (Grande et al. 2016).

Bipolar disorder comprises several subtypes. Bipolar I disorder is characterised by at least one manic episode with or without a history of depressive episodes. Bipolar II disorder is characterised by one or more episodes of depression and by at least one episode of hypomania, but no evidence of mania (NICE 2018). Hypomania differs from mania in several ways: symptoms need only last 4 days; there are no psychotic features; there is no significant impairment in occupational or social functioning; and hospitalisation is not required. Episodes may also be mixed, in which depressive and manic or hypomanic symptoms co-exist or rapidly alternate. In addition, rapid-cycling bipolar disorder is defined as the experience of 4 or more mood episodes within a 12-month period. These may be depressive, manic, hypomanic or mixed.

The management of bipolar disorder can be divided into two distinct phases: management of an initial episode (which may precipitate the diagnosis of bipolar disorder) and long-term management to prevent relapses. These two phases require different treatment strategies and coordination between primary and secondary care.

This distinction is also important when the different pharmacological therapies used to treat bipolar disorder are considered.

The oldest and, arguably, the most effective of these therapies is lithium. Salts of lithium (lithium carbonate and lithium citrate) have been used for 70 years in bipolar disorder. Initially they were observed to have an antimanic effect, only becoming established as a maintenance therapy twenty years later. Whilst the efficacy of lithium is established, its popularity has declined more recently. As lithium is a naturally-occurring substance, it cannot be patented by pharmaceutical companies. It is believed by some that this lack of commercial incentive has been a key factor in its decline (Bauer 2018). Another stumbling block with lithium is the necessity for therapeutic drug monitoring, which must occur three-monthly as a minimum once the drug has been titrated accordingly (NICE 2018).

Antipsychotics have come to the fore in more recent years following the discovery of the atypical antipsychotic, clozapine. This drug was a valuable advance in the field as it had a far lower incidence of extrapyramidal side effects (EPS) than its predecessors. A family of second-generation atypical antipsychotics have since become common treatments in bipolar disorder. Whilst these are very efficacious drugs, their multimodal mechanism of action confers an extensive side-effect profile. The tolerability of this group of drugs to the individual patient thus becomes an essential consideration.

Antiepileptics are the third class of drug that are commonly used in the management of bipolar disorder. They share a common mechanism of action by inhibiting sodium signalling in CNS neurons and therefore dampen global neurotransmission. The two key antiepileptics valproate and lamotrigine are widely used as mood stabilisers and are able to maintain remission in a variety of patient groups. They also show efficacy in managing other facets of bipolar disorder, with valproate demonstrating antimanic properties while lamotrigine is useful in managing bipolar depressive states. These benefits, however, must be balanced against their off-target activity, which can be life-threatening in a small minority of cases.

LITHIUM

History

Since its introduction in 1949, lithium has become a mainstay of psychopharmacology. Some have even hailed it the 'aspirin of psychiatry'. As well as its antimanic and prophylactic actions, it also displays antidepressant, anti-suicidal and neuroprotective effects (Bauer 2018). As such, it could be argued it more closely resembles a psychiatric 'cure-all'! Indeed, this is cemented by its status as the longest standing psychotropic medication in clinical practice.

Lithium carbonate was first used in 1949 by John Cade to treat mania. He initially noted the calming effect of the drug and other behavioural changes in laboratory animals, before going on to test his hypothesis on ten patients (Tondo et al. 2019). Its main use however, as a maintenance therapy for bipolar disorder, was not realised until 1968. Two Danish psychiatrists, Schou and Baastrup were pioneers in establishing its safety and its widespread use in the modern-day treatment of various psychiatric disorders.

Psychopharmacology

Its mechanism of action is thought to be derived from its ability to disrupt magnesium binding sites on proteins. Many proteins are regulated by magnesium binding and this confers a plethora of potential mechanisms through which lithium may operate (Kato 2019). Inhibition of inositol monophosphate (IMP) and the subsequent depletion of inositol from neurons is thought by many to be its key mechanism of action. This reduces signalling through the inositol phospholipid pathway. This theory has been supported with both in vitro and in vivo experiments. For example, in IMAP2 knockout mice experiments, the affected mice showed behavioural changes and an increase in rearing behaviours compared to the control group. Another popular theory is that lithium acts through inhibition of glucose synthase kinase 3 β (GSK-3 β). GSK-3 β has many substrates on which it acts and so the possibilities with regards to lithium's mechanism of action are

equally broad. Both theories are well-evidenced, and one can reasonably speculate that they may be working in tandem. Alternatively, another candidate protein that is regulated by magnesium binding could feasibly underlie lithium's effects.

Indications

It is interesting to note that the primary use of lithium today is long-term relapse prevention in bipolar disorder, whereas other drugs have superseded it as an antimanic agent. It can be used as an adjunct in mania where two different antipsychotic medications have failed to adequately control symptoms (NICE 2018).

Efficacy

Lithium's evidence base in terms of its efficacy as a maintenance therapy is well-established. A network meta-analysis (Miura et al. 2014) also showed lithium to be the most effective maintenance treatment and supported its continued use as the first-line drug. This is reflected by its status as the first-line drug in many guidelines internationally. These include not only the NICE guidelines, but also the CANMAT, CIND and Japanese Society of Mood Disorders guidelines (Kato 2019). There is also a strong body of evidence that lithium has robust anti-suicidal properties. A meta-analysis of studies investigating suicide rates found that suicide was 82% less frequent whilst on lithium treatment in terms of suicides per 100 patient-years (Tondo et al. 2001).

Side Effects & Contraindications

Lithium is associated with a variety of initial side effects including tremor, nausea, fatigue, increased appetite, increased white blood cell count, polydipsia and polyuria. Some of these side effects (thirst and tremor) tend to subside over the initial few weeks of treatment (Tondo et al. 2019). However, the narrow therapeutic index of lithium may be considered to be its main drawback. This is the ratio of the toxic concentration of a drug to its therapeutic concentration (and is approximately 3 for lithium). This makes lithium toxicity, which can be life-threatening, a realistic concern where therapeutic drug monitoring is not employed effectively. Blood lithium concentration must be measured one week after starting therapy, one week after every dose change and weekly until levels are stable. Thereafter, levels must be measured three-monthly. BMI, kidney function, calcium and thyroid function tests must be measured six-monthly. In addition, lithium prescription must always be by brand name and with a consistent salt-form, as the bioavailability of each preparation varies widely (NICE 2018).

Owing to its near-complete renal excretion (minor contributions include sweat and faeces), lithium is contraindicated in those with clinically significant renal

impairment (NICE 2018). Equally, those with low sodium levels should not receive lithium as the kidneys treat lithium similarly to sodium (Hedya & Swoboda 2019). Sodium depletion can lead to excessive lithium reabsorption and subsequent toxicity. In the same way, diabetes insipidus is a contraindication for lithium therapy as the kidneys cannot produce a concentrated urine.

Lithium also has multiple effects on the physiology of the thyroid gland. Most important among them is the inhibition of the synthesis and release of the thyroid hormones, namely tri-iodothyronine (T3) and thyroxine (T4). This reduction in thyroid hormone secretion increased the production of thyroid-stimulating hormone (TSH), causing thyrocyte proliferation and goitre (Kibirige et al. 2013). Goitre is observed in approximately 40% and hypothyroidism in 20% (Lazarus 2009). However, treatment with levothyroxine is effective and hypothyroidism is not an absolute contraindication to lithium therapy. Whilst those that develop hypothyroidism upon commencing lithium can continue the drug, those with untreated or untreatable hypothyroidism cannot be prescribed it for these reasons.

Lithium is also contraindicated in patients with cardiac disease associated with rhythm disorders. This can be explained by the similarity of lithium to other cations such as sodium and potassium which govern the membrane potential of excitable cells. Regression analyses of electrocardiography parameters have shown that long-term lithium use was associated with atrial and ventricular instability (even at therapeutic doses) compared to healthy controls (Altinbas et al. 2014). Understandably, Brugada syndrome (which can cause ventricular arrhythmias) is an absolute contraindication to lithium therapy. A literature review of the use of drugs in Brugada syndrome patients lists lithium as a class IIa drug. Class IIa drugs are defined as those drugs in which the weight of evidence is in favour of a pro-arrhythmic activity (Postema et al. 2009). Additionally, it is thought that lithium can unmask Brugada syndrome, even at subtherapeutic doses (Chandra & Chandra 2009).

Overall, lithium is a very effective drug but is inappropriate for many patients due to its wide-ranging physiological effects. Perhaps another important factor limiting its use is a lack of incentive for pharmaceutical companies to promote it due to the fact it is a natural substance and therefore cannot be patented. Newer, trendier compounds have overtaken it in the US. Additionally, some authors have described a 'lithium stigma' due to the perception that lithium is only a drug for the severely mentally ill, with antipsychotics and anti-epileptics being less taboo (Tondo et al. 2019). However, the efficacy of lithium in relapse prevention cannot be understated. As well as there being an international consensus on its use, it has also stood the test of time, continuing to be the first-line drug as a maintenance therapy 70 years since its inception.

ANTIPSYCHOTICS

History

It is widely attributed that Paul Ehrlich's quest for a novel antimalarial in the late 19th Century brought to light the clinical significance of early phenothiazine derivatives (Zirkle 1973). Their utility as negative psychomotor modulators, however, did not become apparent until the advent of chlorpromazine in the late 1950s. Initially explored for its actions at histamine receptors, it was subsequently found to have drastic tranquilising effects on acutely manic patients (Winkelman 1954).

The benefits of chlorpromazine and similar traditional antipsychotics however was countered by the high incidence of tardive dyskinesia and unwanted dystonic reactions (Denham & Carrick 1961). This problem was only answered several decades later by the development of clozapine, an atypical drug which displayed markedly reduced incidence rates of extrapyramidal effects in comparison to traditional antipsychotics (Baldessarini & Frankenburg 1991). The success of clozapine has spurred the development of several novel second-generation drugs which are routinely used in the management of bipolar disorder today.

Psychopharmacology

While the molecular mechanisms of bipolar disorder are slowly being unravelled, there still exists a large gap between the neurobiological understanding of the condition and the mechanism of action of antipsychotics. Atypical antipsychotic drugs are believed to be effective in the management of mania by primarily antagonising the effects of dopamine at D2 receptors, an effect shared with typical antipsychotics (Seeman 2004). However, neuroimaging studies have demonstrated that the atypical drugs clozapine and quetiapine display low affinities for the D2 receptor and only engage the receptor for brief periods of time, which is believed to contribute to their lower incidence rates of EPS (Seeman & Tallerico 1999).

Several atypical drugs also display antagonism at multiple receptor sites, giving an incredibly complex mechanism of action. Olanzapine has been shown to display antagonism at 5-HT_{2A}, 5-HT_{2C}, H1 and muscarinic receptor subtypes (Bymaster & Felder 2002, Reynolds 2011, Yatham et al. 2005). Both 5-HT_{2A} and 5-HT_{2C} receptors have been shown to play crucial roles in the regulation of mood, and as such it is postulated that this antagonism underpins the efficacy of several atypical drugs in ameliorating depressive episodes (Berg et al. 2008).

Indications

The UK's National Institute for Clinical Excellence (NICE) advocates the use of atypical antipsychotics

for the management of all aspects of bipolar disorder including acute manic episodes, mixed episodes, depression and maintenance regimes (NICE 2019). As per the guidelines, a choice of either the typical antipsychotic haloperidol or one of three atypical drugs (olanzapine, quetiapine, or risperidone) is deemed an appropriate first line treatment (Anderson et al. 2012) (Table 1).

Table 1. Summary of NICE guidance on the use of antipsychotics in the management of bipolar disorder

Condition	Preferred antipsychotic treatment
Acutemanias and mixed episodes	Haloperidol OR Olanzapine OR Risperidone OR Quetiapine
Depression	Quetiapine OR + Olanzapine OR Olanzapine + Fluoxetine
Relapse prevention (min. 4 weeks after manic episode)	Haloperidol OR Olanzapine OR Risperidone OR Quetiapine
Acute mania while on antidepressant	Antidepressant should be terminated, then treat as per acute manic episode

Efficacy

A significant body of research lends weight to the notion that both typical and atypical antipsychotics display therapeutic benefits over placebo in the treatment of mania (Derry & Moore 2007, Smith et al. 2007). In comparison to monotherapy with mood-stabilisers, there appears to be a greater role for atypical antipsychotics in the management of mania. In particular, the atypical drug olanzapine has been shown to exhibit superior antimanic effects over lithium without the need for regular blood monitoring (Niufan et al. 2008). The typical antipsychotic chlorpromazine, however, only showed a clear benefit over lithium in more severe cases (Prien et al. 1972).

It should be noted that current NICE guidance also permits the use of the first-generation antipsychotic haloperidol in the management of acute mania. A meta-analysis by Scherk and colleagues found that haloperidol was more effective than both olanzapine and quetiapine in providing symptomatic relief in acutely manic patients. This was demonstrated by measurable differences in the Young mania rating scale (YMRS) scores between the two drug classes, the main parameter used to quantify the degree of mania experienced during the study. However, the overall efficacy between atypical and typical antipsychotics was deemed similar due to the higher incidence of adverse effects leading to increased trial non-compliance in the haloperidol group (Scherk et al. 2007). As such, it is important that clinicians take tolerability into account when deciding commencing initial treatment for mania.

Depressive episodes are one of the most common presenting complaints of bipolar disorder and as such form a cornerstone symptom in the aetiology the disease (Cruz et al. 2010). Unlike mania, however, only two antipsychotics are licensed in the UK for combating bipolar depression. Both quetiapine and olanzapine have been shown to have significant positive impacts in alleviating and maintaining remission of depressive episodes in bipolar patients (Gao et al. 2005). This beneficial effect also extends to patients with treatment-resistant unipolar depression but is inferior to the therapeutic effect of antidepressants for non-refractory cases of major depressive disorder (Amato et al. 2018).

Selective serotonin reuptake inhibitors (SSRIs) may also feature in the overall management of bipolar depression when combined with an atypical antipsychotic. A growing body of work has highlighted that dual therapy with olanzapine and fluoxetine produces measurable improvements in overall mood beyond those provided by monotherapy with olanzapine alone (Tohen et al. 2003). Animal studies have found that this combination therapy is able to significantly enhance catecholamine signalling in the prefrontal cortex, however the resultant effect of this in ameliorating mood in human subjects remains to be explored (Zhang et al. 2000).

Side Effects & Contraindications

While initially designed to combat the debilitating, extrapyramidal symptoms experienced by patients taking traditional antipsychotics, the multimodal mechanism of action of the atypical drugs has invariably led to novel off-target effects.

Atypical antipsychotics are believed to cause greater metabolic dysregulation than their traditional counterparts, leading to higher rates of truncal obesity and weight gain in patients taking these drugs (Reynolds & Kirk 2010). Indeed, several studies have noted that olanzapine and clozapine are associated with the worst metabolic profile, with this undesirable effect being positively correlated with the length of treatment and lack of previous antipsychotic exposure (Bak et al. 2014, Correll et al. 2015). In contrast, aripiprazole has been consistently associated with a low incidence of weight disturbance and may even be beneficial in inducing weight loss in a select subset of bipolar patients (Barzman et al. 2004).

Various mechanisms have been proposed for this action, including the modulation of NPY signalling and 5-HT₂ antagonism in the feeding centres of the hypothalamus (Kirk et al. 2006, López-Alonso et al. 2007). The latter is supported by the notion that 5-HT₂deficient mice have been shown to demonstrate voracious eating and rapid weight gain (Tecott et al. 1995). The role of the H₁ receptor in satiety has also received significant attention in recent years and was

explored in a landmark study by Kim and colleagues. Strikingly, the study detailed that the satiety-inducing effects of leptin are reduced upon administration of atypical antipsychotics, with the degree of dampening being correlated with the affinity of the drug with H1 receptors (Kim et al. 2007). This is believed to occur despite an increase in circulating leptin levels, thus reflecting the propensity of these drugs to concurrently induce a degree of leptin resistance which further fuels weight gain (McIntyre et al. 2003).

Atypical drugs are largely contraindicated in those with evidence of cardiac conduction anomalies. This is attributable to the ability of the drugs to lengthen the cardiac QTc interval, which can be detected with regular ECG monitoring (Zemrak & Kenna 2008). The mechanism for this prolongation is yet to be fully elucidated but is believed to involve antagonism of a type of inwardly-rectifying potassium channel (hERG) which plays a critical role in myocyte repolarisation (Nachimuthu et al. 2012). Antagonism of these ion channels may lead to a sudden death by inducing a broad-complex polymorphic ventricular tachycardia (Ray et al. 2009). Ziprasidone has been shown to have the worst cardiac profile and as such care should be exercised when combining it with other treatments known to prolong the QT interval such as SSRIs (Vieweg 2003).

ANTIPILEPTICS

History

The marketing of phenobarbital as an anti-seizure drug in the early 19th century hailed the beginning of a long era of antiepileptic drug discovery (Smith et al. 2007). Since then, the creation of the antiepileptic drug development programme (ADD) has enabled several conventional therapies to come to the forefront of mainstay medical treatment. Within this programme, novel compounds are tested against a battery of animal seizure models to determine their overall efficacy and suitability in clinical practice (Kupferberg 1989).

Modern-day antiepileptics were developed around the turn of the millennium with the aim of reducing the amount of off-target effects and drug-drug interactions with prevalent medications (Porter et al. 1984). An example of this new class of antiepileptic includes lamotrigine, which alongside the older anticonvulsant valproate plays a crucial role in the management of bipolar disorder.

Psychopharmacology

Sodium valproate follows a characteristic pharmacokinetic profile, displaying near-complete absorption upon oral administration (Perucca et al. 1978). The drug then rapidly equilibrates between CSF and blood before being eliminated through both urine and faeces (Schobben et al. 1980, Woodbury 1980). In a similar fashion, administration of lamotrigine leads to maxi-

mal plasma concentrations within three hours of ingestion with an estimated bioavailability of 98% (Goa et al. 1993).

Both drugs exert therapeutic effect by modulation of voltage-gated sodium channels. The open-channel inhibition displayed by lamotrigine is believed to stabilize the resting membrane potential of presynaptic glutamergic neurons, leading to reduced excitatory neurotransmitter signaling (Stahl 2004). In contrast, valproate-induced inhibition of sodium channels has been shown to reduce neuronal burst firing and induce long term adaptive changes in overall ion channel levels (McLean & Macdonald 1986, Yamamoto et al. 1997). Furthermore, animal models have highlighted the secondary effect of valproate in increasing inhibitory GABA transmission, which may play a role in reducing the severity of bipolar symptoms (Johannessen 2000). One proposed mechanism for this effect is by inhibition of succinic semialdehyde reductase, an enzyme that plays an important role in the degradation of GABA (Ghodke-Puranik et al. 2013).

Indications

As per the NICE guidelines for the management of bipolar disorder, both lamotrigine and valproate are indicated as mood stabilizing treatments to prevent future relapses. Valproate is further licensed as a third-line treatment for the management of mania where antipsychotics and lithium have shown poor efficacy or are contraindicated. Conversely, lamotrigine is also indicated as monotherapy for the management of bipolar depression and unlike valproate does not require regular blood tests to assess hepatic function (Calabrese et al. 1999).

Efficacy

There exists a significant body of evidence to support the efficacy of both valproate and lamotrigine as mood stabilizing agents. Lambert and colleagues highlighted that when compared to the traditional mood stabilizer lithium, valproate maintained a similar rate of illness remission over an 18-month timeframe (Lambert & Venaud 1995). Similar results have been shown by lamotrigine, which is also able to maintain remission in pregnancy with minimal teratogenic activity (Newport et al. 2008).

Several meta-analyses have highlighted the anti-manic properties of valproate (Macritchie et al. 2003). This effect is believed to be synergistic with antipsychotics, with a similar rate of adverse effects as antipsychotic monotherapy alone (Müller-Oerlinghausen et al. 2000). Furthermore, work by McElroy and colleagues highlighted that orally loading valproate in acutely manic patients significantly improved overall outcomes. It is thought that this effect is due to a rapid reduction in the time taken to reach the effective therapeutic concentration by administering high doses of the drug (McElroy et al. 1993).

Conversely, lamotrigine has been proven to be successful in the management of bipolar depressive states. Dose-dependent improvements in the Hamilton Rating Scale for Depression (HRSD) and Montgomery-Asberg Depression Rating Scale (MADRS) upon lamotrigine administration is well documented in the literature (Calabrese et al. 1999). This benefit is believed to be correlated with the magnitude of the depressive episode, as patients that displayed a more severe phenotype showed a greater response to lamotrigine treatment (Geddes et al. 2009).

Side Effects & Contraindications

The side effect profile of sodium valproate is well defined and extensive. Of note, excessive weight gain plays an important factor in valproate discontinuation and poor treatment adherence. While the mechanism surrounding this unfavourable effect is unknown, it is hypothesized to involve both increases in insulin secretion and deficiencies in components of the fatty acid metabolism cycle (Breum et al. 1992, Kanemura et al. 2012). A rare but potentially serious complication of valproate is that of hyperammonemic encephalopathy. This condition is characterized by a raised plasma ammonia level, falling GCS and vomiting and is thought to be attributable to the inhibition of urea cycling by valproate metabolites (Brusilow 2002, Coulter & Allen 1980). Early treatment with L-carnitine has been shown to improve outcomes in patients with valproate-induced encephalopathy (Segura-Bruna et al. 2006).

Unlike valproate, the modern anticonvulsant lamotrigine is not associated with excessive changes in body mass (Biton et al. 2001). Instead, cutaneous side effects on the toxic epidermal necrolysis spectrum form a significant proportion of the unwanted effects of the drug. Of these, Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are regarded as the most serious dermatological complications. Both SJS and TEN form a continuum of disease, with SJS being characterized by mucosal blistering lesions with $\leq 10\%$ cutaneous desquamation while TEN is defined by a $\geq 30\%$ detachment of the skin (Messenheimer 1998). The pathogenesis of these type IV hypersensitivity reactions remains to be fully elucidated, however it is postulated that aberrant lymphocytic activity plays a crucial role in their aetiology (Sánchez-Borges 2008).

Pregnant females and females of child bearing potential serve as important contraindications to the administration of valproate due to the risk of foetal malformations (Vajda & Eadie 2005). Valproate is believed to exert its teratogenic effect through inhibition of foetal histone deacetylase (HDAC), a key enzyme involved in the storage of DNA (Lloyd 2013). Other notable contraindications to valproate include severe hepatic failure and hematological malignancies (Coyle

et al. 2005, Peterson & Naunton 2005). In a similar fashion to lithium, lamotrigine serves as a relative contraindication in patients with Brugada syndrome, largely due to its ability to inhibit cardiac sodium channels at high doses (Strimel et al. 2010). Clinicians should therefore be aware of the risks of lamotrigine in patients with a familial history of sudden death and adjust the therapeutic dose accordingly.

CONCLUSION

This paper has sought to highlight the key aspects of the key major bipolar disorder treatments while also attempting to unravel the complex mechanisms surrounding their therapeutic effect. It is clear that lithium and antipsychotics have a crucial role in the management of bipolar disorder and display tremendous efficacy as the primary maintenance and antimanic treatments respectively. Lamotrigine and anti-psycho-tics have also been shown to combat bipolar depression as monotherapies, with the latter also being used in combination with an antidepressant. Of course, these beneficial effects should always be balanced against any off-target effects to ensure high levels of patient compliance. Regular blood monitoring for patients undergoing lithium therapy is also essential to closely monitor drug levels and thus prevent toxicity. The antiepileptic valproate is effective as a mood stabiliser and as an antimanic agent however is contraindicated in females of reproductive age due to its teratogenic profile. The adverse effects of weight gain and hepatotoxicity associated with valproate can be diminished by switching to lamotrigine, however this must be balanced with an increased risk of cutaneous syndromes. Alternative pharmacotherapies and psychotherapy are likely to play a greater role in patients with co-existing arrhythmias, which serves as a relative contraindication for all three drug classes. As new treatments develop, further study will be needed to integrate them with the current first-line drugs discussed in this review.

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Amol Joshi: background research and writing of conclusion, antiepileptic and antipsychotic sections.

Alexander Bow: background research and writing of abstract, introduction and lithium sections.

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DEAF PSYCHIATRY: A REVIEW OF THE DIFFICULTIES AND THE EFFECT OF AN INQUIRY ON CURRENT PRACTICE

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SUMMARY

Communication is a huge difficulty in researching Deafness in psychiatry and in practically assessing and treating deaf patients. This paper aims to review the difficulties surrounding the assessment and treatment of deaf patients, using a review of the current literature on audio-visual hallucinations as an example. It will also include a summary of the published inquiry into the care and treatment of Daniel Joseph (a profoundly Deaf man), and a review of the Department of Health consultation document and NHS England responses to that inquiry as evidence of why these difficulties have relevance in everyday practice. In structuring the paper in this manner, the author hopes to review the current state of healthcare provided for Deaf individuals within psychiatry, and what still needs to be done.

Key words: Deaf – communication - hallucinations

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INTRODUCTION

The terminology surrounding deafness is widely accepted to fall into two categories: the uppercase “Deaf” and lowercase “deaf”. The lowercase version (“deaf”) refers to individuals who have hearing loss and use oral methods of communication, whereas the uppercase version (“Deaf”) refers to a cultural community that does not view their Deafness as a disability and uses sign language as their primary method of communication. This paper is focused on the mental health of the latter group.

The biggest problem facing the assessment of the mental health of Deaf patients arises because of the communication barriers in place. Not only is there a different language being used by the patient, but there may also be the issue of language dysfluency – a lack of proficiency in any particular language, primarily due to early language deprivation (Angelmyer 2018). There is also a lack of appropriate assessment tools tailored specifically to deaf patients (Ram 2015). This extends to the treatment for deaf patients due to the lack of evidence based psychotherapy available. One aspect of communication barriers includes the difficulty of assessing acute psychosis, which will be explored in the form of a literature review of audio-visual hallucinations as a specific example in Deaf patients. The ramifications of these difficulties in practice will be addressed through an overview of the Daniel Joseph inquiry (Merton Sutton and Wandsworth Health Authority and Lambeth Southwark & Lewisham Health Authority, 2000), and the Department of Health’s consultation document (Britain 2002) and NHS England response (Department of Health 2005) to that inquiry.

EXAMPLES FROM THE LITERATURE

When searching for literature concerning the assessment of hallucinations in Deaf individuals, there was little distinction found between the uppercase “Deaf” and the lowercase “deaf”; instead there seemed to be a split between congenitally deaf patients and those whose deafness arose later in life. In congenitally deaf patients with psychosis, auditory hallucinations presented as common phenomena (du Feu 1999) that seem to lack the auditory properties that hearing patients may be able to describe e.g. loudness, pitch and intonation. However, gender and identity were able to be distinguished (Bellugi 1975, cited in Perrone-Bertolotti 2014). In some cases, the voice hallucination may actually present as signed or lip read communication, or through somatic perceptions such as vibrations felt in certain positions within the body (Atkinson 2006). The range of modalities in which these hallucinations may be felt highlights the difficulties in thoroughly assessing the presence of ‘voices’ in their full range of presentations. It has been suggested that there are methodological shortcomings in the linguistically appropriate assessment of hallucinations in deaf patients for reasons such as the use of interview tools developed for hearing people and that there is a lack of control for degree of hearing loss, preferred communication mode and language fluency levels (Landsberger 2011, Atkinson 2006).

The reason why these difficulties are relevant in clinical practice is succinctly summarised by Glickman in his review of problems in the assessment of mental status in Deaf persons (Glickman 2007). He describes how in the mental state examination, clinicians look for evidence of abnormalities of language that may indicate

thought disorder, but that this is made more problematic because making sense of language patterns in prelingually deaf patients who do not receive adequate exposure to sign language is challenging. It is very difficult to determine whether language problems are due to mental illness, language deprivation, both, or other factors. In a case study, Glickman outlines how even with a proficient interpreter, understanding such patients can be extremely difficult.

Glickman also weighs in on the nature of auditory hallucinations in deaf patients. Although many deaf individuals may not be able to understand speech, they may hear that speech is occurring (Glickman 2007). This is even more true of individuals who use devices such as cochlear implants. This residual hearing may allow some deaf people to form representations of the auditory consequences of articulation, which may then be misattributed to voice-hallucinations (Atkinson 2006) with uncertainty about mode of perception (Atkinson 2007). The idea of subvocal articulation/inner speech being the root of deaf hallucinations has since been further developed by Perrone-Bertolotti et al., who also raised the issue that within research, questionnaires studying hallucinations in deaf people need to be designed to avoid audiocentric biases (Perrone-Bertolotti 2014). Throughout the literature, there is the recurring motif that identification and characterisation of auditory hallucinations in deaf individuals is extremely challenging, especially in a healthcare system that is tailored to the hearing population. It is therefore unsurprising that Daniel Joseph's case arose, greatly impacting the perception of Deaf services in the UK.

THE INQUIRY AND ITS INFLUENCES

It is usual in the UK health system that, when serious incidents occur, an inquiry is held, so that its findings become the evidence base for development of mental health policy in order that the risks identified can be minimised in future. One such published inquiry concerns the serious incident in which Daniel Joseph was involved.

Daniel Joseph is a profoundly Deaf man with severe mental illness who was found guilty of manslaughter of his landlady on the grounds of diminished responsibility in 1998. His case led to an inquiry into the care provided for Deaf individuals in the UK, which found there was a range of incidents leading to the index offence that demonstrated the lack of coordination between services (Merton Sutton and Wandsworth Health Authority and Lambeth Southwark & Lewisham Health Authority 2000). The inquiry panel recognised many points of improvement that largely hinged on a need for greater coordination between Deaf services and a clear, regularly updated list of specialist services available to all clinicians. This was due to one of the factors hindering Daniel's treatment being confusion over what services the National Deaf Service offered,

with many other teams expecting them to deliver the equivalent of a community child and adolescent mental health service for Deaf patients. They additionally identified the need for a better educational network for Deaf children, better multidisciplinary working, and the need to develop emergency assessments of mental health in the community, with a greater capacity within forensic placements for suitable individuals. In the case of serious incidents, the inquiry panel highlighted the importance for all staff involved to undergo a review but also have external support available and be encouraged to use reflective practice in a 'no blame' environment. This need for reflection has continued to be relevant in healthcare and triggered the development of subsequent government reviews.

'A Sign of the Times' (Britain 2002) is a Department of Health consultation document produced in part as a response to the Daniel Joseph case. In this consultation document the difficulty of Deaf patients presenting to a mental health service that is primary organised on the basis of hearing patients was highlighted. The seven mental health standards set out by National Service Framework for Mental Health were reviewed and the challenges faced in delivering those standards for Deaf individuals were identified. It was suggested that one of the existing challenges in current Deaf services is the resource intensity needed for multiple agencies across the UK to liaise with each other. The difficulty in developing an organised network of new services was also emphasised. This was due to units arising largely due to the passion and dedication of individuals in geographically scattered areas rather than a national approach. This increased the personal inconvenience and travel costs for Deaf individuals. One of the largest areas of deficit in Deaf services was (and is) psychiatric intensive care, which current services are not commissioned to provide. Another issue raised is the difficulty Deaf patients have in accessing a number of mainstream services e.g. recognition of mental health problems in primary care, counselling post diagnosis of cancer and legal information leaflets. There is even less access for assessment and treatment of Deaf individuals in prisons. 'A Sign of the Times' additionally emphasised the need for more BSL interpreters if mental health promotion initiatives are to be delivered, and it was suggested that there was need for greater employment of Deaf people in health and social care, and increased training of specialist staff.

The NHS England document titled 'Mental Health and Deafness' (Department of Health 2005) provides best practice guidance for the treatment of Deaf patients with mental health needs which is built on 'A Sign of the Times' and the Daniel Joseph inquiry. Its recommendations echoed much of those presented by 'A Sign of the Times' with an additional breakdown of the specific services that could benefit from enhancement. For example, it recommended the increased integration of communication technology into primary and secondary

care, e.g. email and minicoms, and the current SIGN (a charity) development of a program that translates questions and advice into BSL. It also suggested the possibility of Gateway Workers for directing Deaf individuals to the relevant mental health services and piloting of Health Living Centres that act as a “one-stop shop” for healthcare for Deaf patients. A greater use of specialist community practice nurses could enhance local services. Specialist advice should also be sought when performing prison inreach for Deaf patients.

DISCUSSION

The inquiry and subsequent responses have identified the most important problems within the Deaf services currently available and suggested some potential interventions. However, the scattered nature of the services and their limited availability not only increases the personal inconvenience and the travel costs of the Deaf patients, as suggested by ‘A Sign of the Times’ (Britain 2002), but it also does the same for professionals carrying out assessments of Deaf patients, thereby increasing the time it takes for patients to be assessed and treated. The issue of succession planning is also mentioned by ‘A Sign of the Times’ (Britain 2002) and is still very relevant, in that, particularly for specialist consultant psychiatrists, there is very limited recruitment of new trainees who may be able to sustain a service. This not only contributes to the paucity of resources but also to a stagnation in the quality of Deaf services available since ‘something is better than nothing’.

While the recommendations may address the current deficits in mental health services, they do little to suggest how the scattered range of specialist services might be unified into a coherent national network that is self-sustainable. In the current economic climate, the NHS is under strain and so a delayed development of services is understandable, but further investigation of whether these suggestions have been implemented needs to be carried out. There needs to be a push towards greater Deaf awareness and training for healthcare staff, and a greater number of interpreters because communication is so important in all aspects of mental health.

CONCLUSION

So what now?

Communication underpins all aspects of healthcare, ranging from public health awareness of Deafness, to the practicalities of assessment, treatment and management options available for Deaf patients. ‘A Sign of the Times’ (Britain 2002) quotes the following statistics:

“The Royal National Institute for Deaf People estimate that there are over eight million people in the UK with hearing loss, most often associated with

ageing and that the first and preferred language of over approximately 75,000 Deaf people in Britain is British Sign Language (BSL).”

If Deaf people are not considered as a percentage of the British population but as individuals who can benefit from the presence of a robust mental health system that can deliver the expected standard of care, then the evidence bases and the healthcare protocols need to be expanded to adequately meet those needs. The current literature provides evidence for the difficulties in assessing Deaf patients in a common presentation of psychosis, and the Daniel Joseph inquiry provides evidence for the need to overcome those difficulties. These challenges exist in Deaf psychiatry but also outside of that specialty, with many of the same themes echoed in treating patients in an ever more multi-cultural environment. While it may be unrealistic to meet many of the recommendations made by the referenced documents immediately, there at least needs to be a “tried and tested” protocol for accessing the appropriate Deaf services when necessary in order to ensure the best possible healthcare for those patients.

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PHYSICAL HEALTH CHECKS IN PATIENTS ON ANTIPSYCHOTIC MEDICATION

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SUMMARY

Schizophrenic patients have traditionally suffered from high rates of cardiovascular disease and early mortality. NICE guidelines suggest that several physical health measures be monitored regularly in these patients, and particularly those on antipsychotic medication, which has a wide side-effect profile that may potentiate the risk of cardiovascular disease and other comorbidities. This general practice audit aimed to determine the rates of physical health monitoring in primary care in patients on antipsychotic medication for over a year for psychotic symptoms or schizophrenia. The search was conducted in three different general practices in March 2019, yielding 19, 8 and 30 patients respectively, with a total of 57 patients.

This audit aims to record and analyse rates of monitoring of a range of physical health measures recommended by NICE guidelines over the past year. The results demonstrated that physical health monitoring was poor amongst all the practices audited, especially that of prolactin and waist circumference. We recommend that these rates of monitoring be improved, through implementing templates or the delivery of targeted education to general practitioners and nurses.

Key words: audit - antipsychotic medication - cardiovascular side effects - cardiovascular risk - psychosis - schizophrenia - hyperprolactinaemia

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INTRODUCTION

Patients suffering with schizophrenia have long been known to be a disadvantaged group, with a shorter life expectancy than the general population (Šimunović Filipčić & Filipčić 2018), and higher rates of cardiovascular disease, which have remained elevated over the last decade (Rødevand et al. 2019).

Furthermore, this population is also at higher risk of diabetes, obesity and suicide (Cordes et al. 2017). Therefore, physical health monitoring plays an important role in identifying individuals with or at risk of cardiovascular disease or metabolic disorders, and modulating this risk.

NICE recommends that schizophrenic patients undergo an annual health check that is comprehensive, including weight, waist circumference, pulse and blood pressure, fasting blood glucose, HbA1c, blood lipid profile. An assessment of nutritional status, diet and level of physical activity is also to be noted ('Psychosis and schizophrenia in adults: prevention and management | NICE Guidance').

These checks are particularly important for those on antipsychotic medication, which improve outcomes for patients (Stafford et al. 2015). However, this class of medications may lead to many and varied side effects including extrapyramidal symptoms, hyperprolactinaemia, sexual dysfunction, cardiovascular side-effects, hypotension, hyperglycaemia and weight gain (Wolfgang & Ukok, n.d.). For this reason, the BNF recommends that monitoring of full blood count (FBC), urea and electrolytes (U&Es), liver function

tests (LFTs), blood lipids, fasting blood glucose, and blood pressure is required at least annually after the antipsychotic is prescribed.

These particular physical health measures, recommended by both NICE and the BNF, play a key role in monitoring the varied side effects of antipsychotic medication, and thus preventing poor health outcomes for affected individuals. For instance, FBC must be monitored regularly as clozapine may cause agranulocytosis which can lead to sepsis and death (Węclewicz & Wiciński 2018). U&Es and LFTs must be regularly measured as antipsychotic use can result in derangements in electrolyte balance (Yang et al. 2018) and liver function, with the risk of rare but severe hepatic injury (Marwick et al. 2012).

Antipsychotic use may also lead to an elevation in prolactin levels, which can cause gynaecomastia, galactorrhoea, infertility and amenorrhoea (Haddad & Wieck 2004). These effects are little researched in psychiatric patients, but highly prevalent, with some studies reporting prevalence rates of up to 45% for amenorrhoea in women treated with conventional antipsychotics (Peuskens et al. 2014). The effects of hyperprolactinaemia include long term osteoporosis, a recognised cause of significant morbidity. Although at present there are few studies looking at the effects of osteoporosis in psychiatric patients, the potential for deleterious long-term consequences of antipsychotic medication cannot be ignored and should reinforce the need for adequate monitoring of prolactin in these at risk groups.

Furthermore, an increased risk of developing type II diabetes mellitus with antipsychotic use (Whicher et al.

2018) is evident, especially with commonly used atypical antipsychotic agents such as olanzapine. As such, fasting blood glucose and HbA1c must be monitored to identify those at risk of diabetes early, in order to slow or halt progression through conservative measures, or else control the condition to prevent serious complications, such as peripheral neuropathy, nephropathy and retinopathy (Faselis et al. 2019).

Atypical antipsychotic medication use increases the risk of metabolic syndrome, including a rise in obesity (Mahendran et al. 2010) and hyperlipidaemia (Mhalla et al. 2018), another risk factor for cardiovascular disease. Blood lipid levels, weight, and waist circumference (a more accurate marker of cardiovascular disease risk than BMI) (Savva et al. 2010) should therefore be monitored annually. Blood pressure should also be monitored as there is a high prevalence of hypertension in the schizophrenic population (Bushe et al. 2005). Lifestyle advice is crucial in modifying these cardiovascular disease risk factors, including advice about diet and exercise.

Given the elevated risk of cardiovascular disease and early mortality in schizophrenic patients, alongside the side effects of antipsychotics which may further increase this risk, it is clear that careful physical health monitoring of this population is crucial in improving their long-term health outcomes. According to NICE guidelines ('Psychosis and schizophrenia in adults: prevention and management | Guidance | NICE') primary care should monitor the physical health of patients with psychosis or schizophrenia when the responsibility is transferred from secondary care, and then at least annually. This audit aims to look at patients who have been on antipsychotic medication for at least a year to treat symptoms of schizophrenia or psychosis, in order to determine the rates of monitoring in primary care.

METHODS

The populations of three general practices were searched on practice computers using SystemOne for patients meeting the audit search criteria.

Search criteria

'Antipsychotic medication' for over 1 year AND 'Psychotic disorder' or 'Schizophrenia'.

This search was conducted in March 2019 in yielding 19, 8 and 30 patients at practice 1, 2 and 3 respectively, with a total of 57 patients.

Once this cohort of 57 patients had been identified, their patient notes were manually searched for evidence of physical health monitoring in the last 12 months, as specified by NICE guidelines. This evidence included recordings of full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs), blood lipids, glucose measurements (including HbA1c and fasting blood glucose), and prolactin. In addition to these measurements, the patient notes were searched for measurements of weight, waist circumference, blood pressure and pulse, as well as for records of lifestyle advice given to the patient.

RESULTS

The results demonstrate heterogeneity in monitoring across all three practices. For example, practice 2 achieved a 75% rate of recording lifestyle advice given to patients, while practices 1 and 3 recorded a much lower percentage of patients to whom lifestyle advice had been given in any context. Fasting blood glucose was only monitored in 5.3% of patients in practice 1, whereas practice 2 and 3 achieved monitoring of 62.5% and 40% of their patients' fasting blood glucose respectively (Table 1, Figure 1).

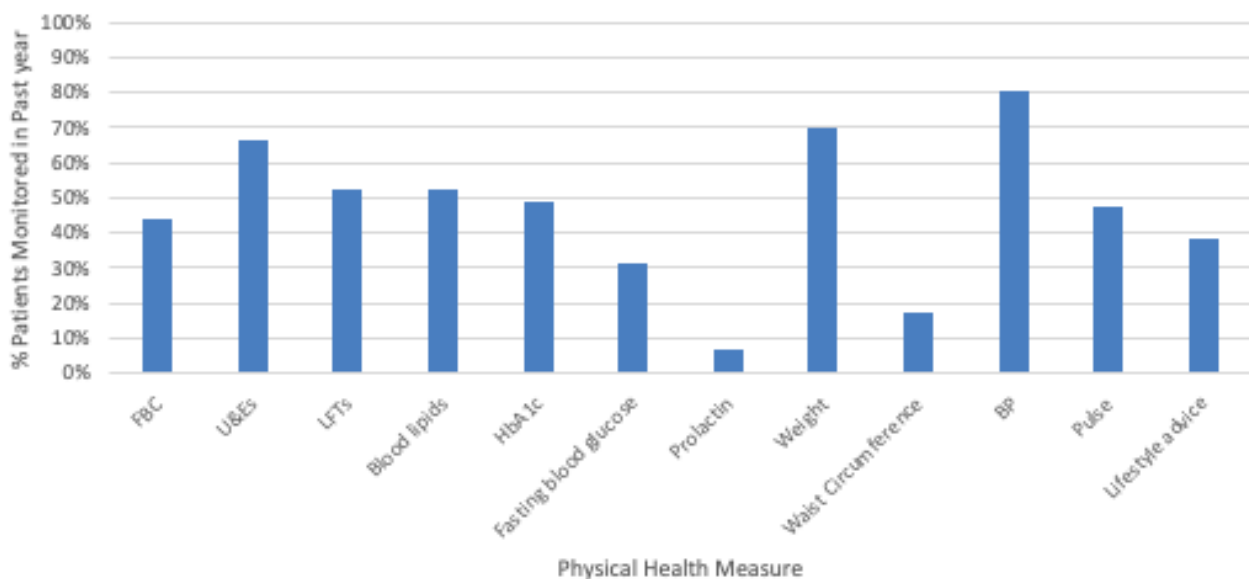


Figure 1. Physical Health Monitoring of Patients on Antipsychotic over the Past Year

Table 1. Physical Health Monitoring

Physical Health Measure	FBC	U&Es	LFTs	Blood lipids	HbA1c	Fasting blood glucose	Prolactin	Weight	Waist Circumference	BP	Pulse	Lifestyle advice
Practice 1	47.40%	57.90%	52.60%	31.60%	47.40%	5.30%	10.50%	73.70%	15.80%	94.70%	42.10%	31.60%
Practice 2	62.50%	62.50%	75.00%	62.50%	37.50%	62.50%	0.00%	75.00%	62.50%	75.00%	50.00%	75.00%
Practice 3	36.70%	66.70%	46.70%	63.30%	53.30%	40.00%	6.70%	66.70%	6.70%	73.30%	50.00%	33.30%
Total	43.90%	66.70%	52.60%	52.60%	49.10%	31.60%	7.00%	70.20%	17.50%	80.70%	47.30%	38.60%

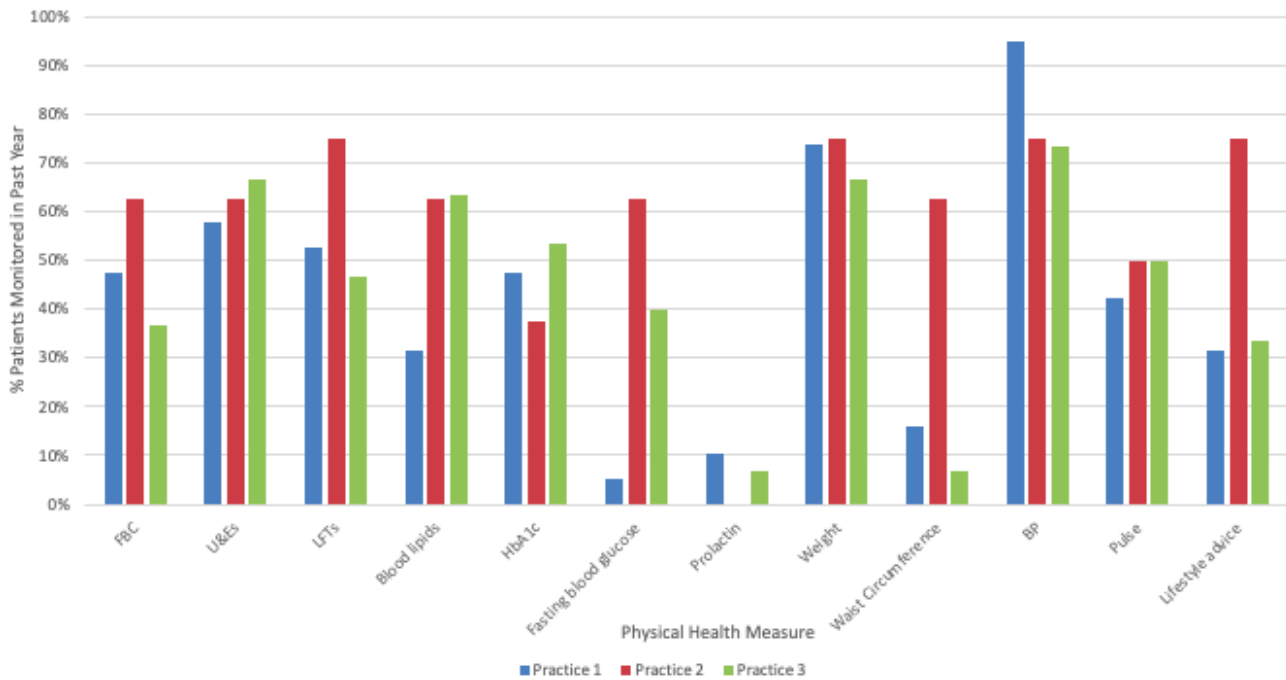


Figure 1. Physical Health Monitoring of Patients on Antipsychotic over the Past Year - 3 practices

The overall rate of physical health monitoring of the 57 patients from the 3 practices on antipsychotic medication for psychotic symptoms or schizophrenia is extremely low, with no single physical health measure being monitored in 100% of patients in the past year. Across all three practices, the most well recorded measure was blood pressure, while the least well recorded measure was prolactin (Figure 2).

The variation demonstrated in these results, both across physical health measures and across practices, highlights the need for a more uniform and regimented approach to monitoring in this cohort of patients.

DISCUSSION

This audit found that, across three different GP practices, patients on antipsychotics were not being adequately monitored for physical health changes as recommended by NICE guidelines. Although it is recommended that patients are monitored annually, this audit found that none of the physical health measures were being monitored in 100% of the patients and, furthermore, that the rates of monitoring the different measures varied from practice to practice.

The results demonstrate low rates of monitoring, despite the adverse health outcomes and high rates of mortality experienced by patients suffering from schizophrenia (Andor et al. 2019). Schizophrenia is associated with a greater cardiovascular risk, which could be secondary to both the disease as well as the high level of cardiovascular risk factors associated with that patient population. The life expectancy is approximately 13-30 years shorter amongst patients with schizophrenia (Andor et al. 2019). This difference in mortality is assumed to be due to other comorbidities, such as cardiovascular disease, diabetes, and poor monitoring of other risk factors. Thus monitoring of modifiable risk factors and regular follow ups and lifestyle advice with such patients could prevent this disparity in life expectancy (Eich & Nick 2008).

Furthermore, schizophrenic patients have a greater chance of dyslipidaemia (Mhalla et al. 2018), yet 52.6% of the total patients were sent for blood lipid tests within the last year, with Practice 1 having the lowest percentage of checks at 31.6%.

Enforcing regular blood lipid checks is important in preventing future cardiovascular events. Lifestyle measures such as smoking cessation advice should furthermore be offered (Wilson et al. 2019).

Blood pressure and weight monitoring were more adequately monitored than the other measures across all three practices. This is perhaps partially because these measures were often recorded in GP attendances pertaining to other conditions and comorbidities, such as cardiovascular disease or diabetes. For instance, both blood pressure and weight monitoring are included in NICE Quality Outcomes Framework indicators. This encourages general practitioners to establish and maintain a register of patients aged 18 or over with a BMI >25 in the preceding 12 months (NICE id code: NM128), and to keep a record of patients' blood pressure for other disease monitoring and primary prevention.

Across all three practices, prolactin levels were systematically under-measured, with practices 1 and 3 monitoring under 10% of their patients, and practice 2 having no records of prolactin measurements in any of the cohort of patients. This is particularly concerning, as there are many studies linking the use of antipsychotics to high levels of prolactin, and this has been a recognised common adverse effect of antipsychotic medication since the 1970s (Peuskens et al. 2014). In order to prevent or identify the potential consequences of hyperprolactinaemia, which includes gynaecomastia, galactorrhoea, infertility and amenorrhoea, as well as osteoporosis, adequate monitoring of prolactin in these groups is crucial.

Recommendations

In order to address the heterogeneity in monitoring, and to increase overall rates of monitoring, we suggest creating and implementing a template on SystmOne to increase adherence, including all of these measures:

- FBC, U&Es, LFTs;
- Blood lipids;
- HbA1c;
- Fasting blood glucose;
- Weight;
- Waist circumference;
- Blood pressure;
- Pulse;
- Prolactin.

Overall physical health assessment, including comment on diet, exercise levels and overall function.

We recommend that practitioners should review patients and consider for psychiatric referral for altering of medication if the HbA1c rises above 42mmol/mol (6.0%), or fasting glucose above 5.5mmol/L, both which are indicators of pre-diabetes. This would help improve rates of primary prevention of metabolic syndrome which, as discussed above, has been found to be associated with antipsychotic use. In addition, lifestyle advice (including advice to stop drinking or smoking, and to control diet), and consideration of review should be given if one carries clinical suspicion of metabolic syndrome or risk of cardiovascular disease. For example, this might be considered after observing a

significant increase in weight or blood lipid levels within a year. If the antipsychotic medication is found to be causing features of metabolic syndrome, the patient should be referred back to psychiatry to consider a change of medication. If it is decided that medication cannot be changed, then other modifiable risk factors for metabolic syndrome, such as cholesterol and hypertension, must be managed.

Furthermore, it may be beneficial to educate GPs and other primary healthcare professionals on the side effects of antipsychotic medication so that they better understand the reasons for which schizophrenic patients must be so closely monitored. This would improve adherence to the implementation of a regimented physical monitoring template, and thus improve patient outcomes.

CONCLUSION

Much of the literature has corroborated the importance of primary prevention across many states of ill health, particularly cardiovascular disease, but further research is required concerning the importance of preventing this increased rate of mortality in patients receiving antipsychotic medication. However, the consensus seems to be that increased monitoring of physical health measures should be a priority for primary healthcare practitioners (Osborn et al. 2007).

This audit has identified particularly low levels of monitoring of prolactin in this cohort, and more consistent monitoring of blood pressure and weight. Therefore, there is scope for improvement of monitoring, which may be achieved through implementation of a template including all the required physical health measures. These changes will hopefully lead to primary prevention of causes of increased morbidity and mortality among this cohort of psychiatric patients, including reduced risk of cardiovascular disease and type 2 diabetes mellitus.

The results of this audit may be limited by the fact that the three practices were located in a similar geographical area, which may influence the results, reflecting local differences in practice. Additionally, several patients were noted to have not arrived for scheduled appointments, or to have refused blood testing. This limits the frequency of monitoring of these patients, and may explain, in part, why the results showed a discrepancy in rates of monitoring of different physical health measures, with simple testing that can be performed in the same appointment tending to have been carried out across a larger proportion of the cohort, compared with tests requiring a second appointment to be booked. In order to address these limitations, further auditing could be undertaken across a wider geographical range, and the rates of non-attendance for different types of appointment in this cohort of patients could be investigated.

The results demonstrate that rates of monitoring in patients receiving antipsychotic medication across three general practices were low across all measures. As

previously discussed, such poor levels of monitoring of physical health in this cohort may have detrimental effects, stemming from a fundamental lack of identification of patients at risk of metabolic and other disease. The result is the advent of adverse health outcomes in what is already a disadvantaged group.

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Contribution of individual authors:

Gloria Lau developed the Audit Standards.

Gloria Lau, Juliette Murphy & Natasha Chaudhury carried out the audit.

Mark Agius supervised the analysis and writing up of the project.

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THE WIDER EFFECTS OF PATERNAL POST NATAL DEPRESSION: AN OVERVIEW

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SUMMARY

Paternal Post Natal Depression (PPND), although becoming more prevalent, is still poorly recognised. Unfortunately, its effects and negative outcomes have not been as widely researched as that of maternal postnatal depression. PPND can affect the fathers parenting style and lead to a negative effect on their child's behaviour and social development. Furthermore, depressed fathers may feel unsupported and this can lead to problems with the marital relationship and be associated with concurrent maternal postnatal depression. Moreover, support services and interventional therapy come at a cost to the health service and therefore treating PPND can impact the economy. Identifying the effects PPND has is important as implementing reliable screening measures and better education may prevent negative outcomes.

Key words: *Paternal Postnatal Depression – postpartum – depression - Edinburgh Post Natal Depression Scale - marital relationship*

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INTRODUCTION

It is estimated that paternal postnatal depression (PPND) occurs in 4% to 25% of new fathers during the first postpartum year (Stadtlander 2015). However because PPND is poorly researched and recognised, its true prevalence may be under reported. There are no available definitions of PPND and no clear set of diagnostic criteria in aiding clinicians to assess for it. Nevertheless PPND is receiving more attention as its prevalence and negative outcomes are becoming better understood. Apart from the obvious effect on the father, PPND has been linked with poor child development, increased healthcare costs and can have a damaging effect on the relationship with the mother.

AIMS

The two main aims of this review are:

- To review the available literature on paternal postnatal depression;
- To identify the wider effects PPND can have on the mother, the child and to evaluate its cost to healthcare.

METHOD

The literature review was undertaken by a comprehensive search of PubMed and Cochrane Library databases. I searched for the terms paternal, postnatal, depression, child and relationships within titles and abstracts in different combinations. The search was limited to studies posted before November 2018 (last search: 20 November 2018). The search elicited 114 results from PubMed and 7 results from the Cochrane Library. Additional studies were also identified by reviewing the reference lists of all retrieved studies.

The inclusion criteria for the article selection was that they were written in English and provided data on the impact of paternal postnatal depression.

RESULTS

PPND in fathers can present in a multitude of ways. Symptoms include indecisiveness, withdrawal, frustration, partner violence, negative parenting behaviours and alcohol and substance misuse. In turn these can have effects on the family dynamic which will be reviewed.

Effect on the Mother

Approximately half of all fathers with PPND have partners with maternal postnatal depression (Goodman 2004). It is difficult to elicit whether the paternal depression influenced the mental health of the mother or whether it was the other way around. Low marital relationship satisfaction is significantly correlated with the onset of PPND (Nishimura 2015). Furthermore, a correlational study with 54 fathers diagnosed with depression and 99 fathers without depression reported that the depressed group reported higher levels of criticism and lower levels of affection from their partners (Kumar 2018). Overall this led them to be less confident in the future success of their relationship. This highlights that clinicians need to be aware of changes in the marital relationship when screening for PPND and to explore them further. Furthermore it suggests that interventions such as couples therapy may be important in treating PPND and minimising its effects on the relationship.

Effect on Child

Paternal postnatal depression can negatively affect the child's social, behavioural and cognitive development. A large population-based study showed that PPND was

associated with adverse emotional and behaviour outcomes in children aged 3.5 years, and increased risk of conduct problems in boys (Ramchandani 2005). This result remained even after controlling for maternal and postnatal depression and later paternal depression. This may lead to children having difficulties in school and potentially participating in antisocial behaviour later on in life. Another study identified that fathers who were distressed during the postnatal period, and had high levels of hostile parenting styles, which led to behavioural challenges in children between the ages of 4 and 5 years old (Kumar 2017). This may be a causal mechanism for the changes in behaviour and so therapies focusing on parenting style may help in treating the fathers with PPND.

Effect on Healthcare Costs

PPND, like maternal postnatal depression is associated with an increased cost to the NHS (Edoka 2011). The mean cost for the depressed father-child dyad was £1103.51 compared with £945 for those without depression. The difference in cost can be attributed to more contact time with the GP and psychologists in the depressed father cohort. There is an increased demand for these services as postnatal depression is becoming more prevalent, and so will result in future increased costs. Nonetheless this study had a low response rate during recruitment and a small sample size, which has contributed to a lack of statistical significance when analysing the economic data. There is a need to further research the effect of PPND on the economy and the cost-effectiveness of its prevention and treatment measures.

CONCLUSION

PPND has only recently been recognised as an important issue in today's society and it is very much under researched compared with maternal postnatal depression.

Considering the number of effects PPND has on the marriage, child's behaviour and economy, there is need to implement screening and intervention programmes to reduce the effects taking place. Currently healthcare services do not provide screening questionnaires to identify postnatal depression in fathers. However the Edinburgh Post Natal Depression Scale used to identify maternal postnatal depression, is a suitable screening tool for fathers in the postpartum period, but with a different cut off criteria (Matthey 2011). The cut off to detect distress is 7/8 in mothers but a lower cut off of 5/6 has been recommended in screening for depressed fathers postpartum. Since the whole family is affected by a father suffering from PND, it makes sense to offer this screening questionnaire at the same time that the mother is

assessed, for example during the 6 week baby check. Postnatal depression awareness campaigns may also allow men to disclose their symptoms to their GP because both patient and GP would then be more aware of PPND as a condition and the patient would therefore feel supported. This holistic perspective would also enable intervention measures to consider both parents, helping them to improve their interactions with each other and their offspring in order to minimise negative effects. To enable this, clinicians need to be educated on the presentation of PPND and be able to detect it in the postnatal period.

Hopefully with the right screening tools and suitable interventional therapy, PPND can be identified early to reduce the undesirable effects on the surrounding family relationships and child's developmental outcome.

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Contribution of individual authors:

Ciara Mahon devised the literature search and developed the paper.

Mark Agius supervised the paper.

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THE EFFECTS OF EATING DISORDERS IN PREGNANCY ON MOTHER AND BABY: A REVIEW

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SUMMARY

The psychological and physiological interaction between anorexia and the pregnant state has a large intrapartum and postpartum impact on mother and baby. Current research has attempted to discern the short and long term effects of eating disorders (EDs) on pregnancy as well as mother and baby-related sequelae; however little is understood about which management strategies are likely to prove most successful in mitigating these risks. The incidence and effect of low pre-pregnancy body mass index (BMI) on obstetric outcomes, and possible health complications in the future child, has attracted widespread attention. Especially concerning is the fact that it has long been known that the incidence of EDs in women of childbearing age is not only the highest out of all age categories but also is on an increasing trajectory.

This paper aims to highlight the recent evidence underpinning the management of pregnant women with EDs in the light of the discussed short and long term effects of the disorders on mother and baby. We shall focus on those women who have a previous diagnosis of an ED prior to being pregnant.

Particular attention will be paid to those studies considering anorexia nervosa. We argue for the use of early intervention strategies for the management of pregnant women with eating disorders, and for the use of a multidisciplinary approach in the treatment of these patients with complex problems.

Key words: Eating Disorder – pregnancy - anorexia nervosa

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INTRODUCTION

The psychological and physiological interaction between anorexia and the pregnant state has considerable intrapartum and postpartum effects on mother and baby. Current research has attempted to discern the short and long term effects of eating disorders (EDs) on pregnancy as well as mother and baby-related sequelae; little however is understood about which management strategies are most likely to prove to be most successful in mitigating these risks. The incidence and effect of low pre-pregnancy body mass index (BMI) on obstetric outcomes, as well as possible health complications in the future child, have attracted widespread attention. Especially concerning is the fact that while it has long been known that the incidence of EDs in women of childbearing age is not only the highest out of all age categories but also is on an increasing trajectory.

This paper aims to highlight the recent evidence underpinning the management of pregnant women with EDs in the light of the discussed short and long term effects of the disorders on mother and baby. We shall focus on those women who have a previous diagnosis of an ED prior to being pregnant.

CURRENT PREVALENCE

Anorexia nervosa is present in 0.3-1% of the population and subthreshold disease is estimated to be present in 5-7% of the population, with increased incidence

in women of childbearing age. Pregnancy itself has been found to increase risk of EDs in some, including a 22% relapse rate (Koubaa 2005). In addition, according to Lowes et al. (2012) there is a sixfold increase in perinatal mortality associated with eating disorders. This highlights the significance of the issue and the importance of successful management to mitigate these risks.

EFFECTS ON MOTHER AND BABY

Before pregnancy, women with Eating Disorders may present with menstrual dysfunction, low bone density and sexual dysfunction (Andersen 2009). Once pregnant, these women are predisposed to obstetric complications such as miscarriage, preterm delivery, or low birth weight in offspring (Andersen 2009). Eating disorders may complicate pregnancy both in a direct and consequential manner (Paslakis 2019). Here we shall focus on those women who have a previous diagnosis of an eating disorder (ED) prior to being pregnant.

Thus those women with Eating Disorders presenting for the first time during pregnancy will not be discussed.

ADVERSE OBSTETRIC EFFECTS ON MOTHER

Current research shows that having an active eating disorder in pregnancy predisposes a multitude of unfavourable obstetric outcomes (Eik-Nes 2018). Linna has shown that patients with eating disorders were more

likely to be childless than controls (odds ratio (OR) 1.86; 95% confidence interval (CI) 1.62-2.13, $p < 0.001$) (Linna 2013). Pregnancy and childbirth rates have been shown to be lower among patients with eating disorders than among controls (Linna 2013). Linna has also shown that Bulimia Nervosa is associated with an increased risk of induced abortion compared to controls (OR 1.85; 95% CI 1.43-2.38, $p < 0.001$), whereas, by contrast, Binge Eating Disorder is associated with an elevated risk of miscarriage (OR 3.18; 95% CI 1.52-6.66, $p = 0.002$) (Linna 2013).

A recent study by Eik-Nes et al. (2018), solidifies this association and in particular pays attention to preeclampsia, preterm birth, perinatal deaths, small for gestational age (SGA) and large for gestational age (LGA) outcomes. The study confirmed an association between EDs and all of the above, with particular attention to the perceived increased incidence of SGA, Caesarian sections and low Apgar score at 5 minutes. However, not all research has demonstrated this effect, and in contrast to these results, Bulik et al. (2009) found no association between maternal self-reported Anorexia Nervosa and SGA in a large Norwegian study population (Bulik 2007).

Despite many studies opting to consider Eating Disorders as a general compilation, some studies have considered the interaction of specific types of eating disorder in pregnancy. Most of these choose to survey the interaction of anorexia nervosa and adverse obstetric outcomes. Dinas (2008) reports that patients with Anorexia Nervosa experience hypertension, miscarriage, difficult labour, and premature delivery.

Bulik (1999) analysed personal interview data from 66 women who had anorexia during pregnancy and met the diagnostic criteria. Those in the Eating Disorder (Anorexia) group were more likely to need a Caesarian section than those without any history of an Eating Disorder. Caesarian sections increased the risk of operative complications such as infection, postpartum haemorrhage, thrombus formation and anaesthetic complications. Furthermore Koubaa (2005) showed that women with a past or current eating disorder reported more hyperemesis gravidarum during the pregnancy. However, the confound of co-occurring bulimic tendencies cannot be ruled out in such a report, and future research needs to disentangle the effects of Eating Disorders on true hyperemesis gravidarum using reliable controls. Binge Eating Disorder, on the other hand, was associated positively with maternal hypertension and long duration of the first and second stage of labour (Linna 2014).

ADVERSE PSYCHOLOGICAL EFFECTS ON THE MOTHER

A prospective community based cohort study (Micali 2007) classified women into cohorts of recent or past Eating Disorder, obesity before pregnancy and a

general population group. The study showed that the women with a recent Eating Disorder reported more concerns regarding weight gain and body shape during pregnancy compared with the control groups. These women also dieted more, had an increased use of laxatives and participated in self-induced vomiting behaviours more than the control groups during pregnancy (Micali 2007) They also had an increased risk of hyperemesis ($P < 0.01$) (Koubaa 2005). Although not as prevalent, those women with a past Eating Disorder still showed similar Eating Disorder symptoms and behaviours during their pregnancy. This further highlights the need to identify and screen for increased Eating Disorder symptoms in patients with a history of current or active Eating Disorders during pregnancy.

ADVERSE EFFECTS ON THE BABY

With regards to the effect of eating disorders on the baby, several adverse outcomes have been observed. Kuobaa et al. (2005) list several complications associated with Eating Disorder in pregnancy as compared to controls such as: low birth weight ($P < 0.01$) (Koubaa 2005), smaller head circumference ($P < 0.001$) (Koubaa 2005), increased risk of microcephaly ($P < 0.05$) (Koubaa 2005) and infants being born small for gestational age (SGA) ($P < 0.05$) (Koubaa 2005). Linna et al. (2014) observed similar outcomes with the addition of anaemia, premature birth and perinatal death and other groups (Linna 2014, Eagles 2012, Dinas 2008) have also seen higher rates of Intra Uterine Growth Restriction.

Eagles (2012) reported that while Mothers with Anorexia Nervosa delivered lighter babies, this difference did not persist after adjusting for maternal body mass index (BMI) in early pregnancy. Standardized birthweight (SBW) scores suggested that the mothers with Anorexia Nervosa were more likely to produce babies with intrauterine growth restriction (relative risk (RR) 1.54, 95% confidence interval (CI) 1.11-2.13) (Eagles 2012). Eagles also noted that mothers with Anorexia Nervosa were more likely to experience ante-partum haemorrhage (RR 1.70, 95% CI 1.09-2.65) (Eagles 2012).

It is useful to compare outcomes of pregnant patients with Anorexia Nervosa with those with other eating disorders such as Bulimia Nervosa and Binge Eating Disorder.

According to Linna (2014) Women with Anorexia Nervosa and Bulimia Nervosa gave birth to babies with lower birthweight compared with unexposed women, but the opposite was observed in women with Binge Eating Disorder. Maternal Anorexia Nervosa was related to anaemia, slow fetal growth, premature contractions, short duration of the first stage of labour, very premature birth, small for gestational age, low birthweight, and perinatal death. Increased odds of premature contractions, resuscitation of the neonate, and very low Apgar score at 1 minute were observed in mothers

with Bulimia Nervosa. Binge Eating Disorder was associated positively with birth of large-for-gestational-age infants (Linna 2014).

Infants born with a low birth weight are more likely to develop insulin resistance, type 2 diabetes mellitus and hypertension in later life (Triunfo 2015), thus the long term effects on the child of an anorexic mother are both substantial and deleterious. A large study of over 50,000 women also concluded the effects of eating disorders in pregnancy are negative (Watson 2017). Thus, Watson found anorexia nervosa immediately prior to pregnancy was associated with smaller birth length (relative risk = 1.62; 95% CI (1.20, 2.14)), bulimia nervosa with induced labour (relative risk = 1.21; 95% CI (1.07, 1.36)), and binge-eating disorder with several delivery complications, larger birth length (relative risk = 1.25; 95% CI (1.17, 1.34)), and large-for-gestational-age (relative risk = 1.04; 95% CI (1.01, 1.06)). Maternal pregravid body mass index and gestational weight mediated most associations (Watson 2017).

CYCLE OF RISK

Despite the wealth of adverse outcomes relating directly to the mother and pregnancy, the effects of active maternal eating disorders are not limited to the pregnant period. Mothers with a lower pre-pregnancy BMI and poor nutritional intake during pregnancy have an increased risk of preterm birth which in itself predisposes anorexia nervosa in the unborn child (Bulik 2005). Bulik (2005) outlines this in his 'cycle of risk' algorithm, demonstrating the susceptibility for offspring to develop anorexia nervosa in their own development following their mother's own diagnosis. In order to break this perpetuating cycle, there is a need to implement measures that ensure adequate nutrition and support for women with Eating Disorders (especially anorexia nervosa) prior to and during pregnancy.

INTERVENTION STRATEGIES

The clinical and psychological effects of anorexia on mother, baby, and the pregnancy have important implications for resource allocation such as the need for mental health professionals, dieticians, and education of wider healthcare teams alike. The management of pregnant women who suffer from eating disorders requires the cooperation of a perinatologist, internist, nutritional therapist, psychiatrist or psychologist, with their ancillary staff. Therefore a multidisciplinary approach would most likely improve outcome (Kníže 2018), although more evidence is needed as to MDT effectiveness for maternal and fetal outcomes.

It is universally acknowledged that specialized mental health providers who treat women with ED should work together with obstetrical providers, as well as general practitioners to improve the care for women with Eating Disorder (Eik-Nes 2018). Earlier identi-

cation and treatment may be advised and as Linna et al. (2013) suggest reproductive counselling for those affected may be beneficial.

Additionally, Schmidt et al. (2017) performed several randomised controlled trials comparing the effectiveness of different intervention strategies in women with anorexia nervosa. In particular, it was found that psychological therapy improved outcomes in those treated as outpatients with Anorexia Nervosa and an email guided relapse prevention programme increased BMI and lowered distress at 12 months following discharge. We propose that such preventive interventions may be beneficial in pregnancy alongside the multidisciplinary approach.

CONCLUSION

Overall, evidence suggests that eating disorders in pregnancy are dangerous for the health of the mother and baby. Not only does this pose a risk to short term to the baby, but Eating Disorders affect the child's future health and the likelihood of developing an eating disorder themselves. Women with a recent or a history of Eating Disorder tend to continue to have some Eating Disorder symptoms in pregnancy, although usually they have fewer symptoms than before pregnancy (Micali 2007). Therefore, screening for Eating Disorder symptoms during pregnancy may provide a useful opportunity for engagement in treatment and to reduce behaviours that may be detrimental to the foetus (Micali 2007). Dinas (2008) points out that management of pregnancy complicated by anorexia nervosa, requires involvement of a multidisciplinary team and hospitalization in severe cases, given the complexity of the possible complications. Based on the reviewed articles, a multidisciplinary approach, aimed at early intervention in pregnancy is advisable for maintenance of psychological and physiological health for those with eating disorders in pregnancy.

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Contribution of individual authors:

Charlotte Arnold, Hayley Johnson & Ciara Mahon are joint first authors; they jointly carried out the search and drafted the paper.

Mark Agius supervised the project and improved the text.

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DEPRESSION AND DRY EYE DISEASE: A NEED FOR AN INTERDISCIPLINARY APPROACH?

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SUMMARY

A recent meta-analysis including data from 22 studies including 2.9 million patients found that anxiety and depression are more prevalent in patients with dry eye disease (DED) than in controls. DED is a common disorder of the tear film which can cause ocular irritation, foreign body sensation and visual disturbance. However there is often a great discrepancy between signs and symptoms of DED, which the symptoms often being more associated with non-ocular disorders such as depression and PTSD than to tear film parameters. In this way it could be considered as more of a psychiatric than ophthalmic complaint. DED and depression feedback on one another in a synergistic manner. Severity of DED is associated with symptoms of anxiety and depression. Treatment of DED could help reduce depression symptoms, but also effective management of depression could help alleviate symptoms of DED. Complicating this however is the evidence that SSRIs can exacerbate DED. This makes the management of these comorbidities more difficult, however there are putative therapeutic targets which may be a source of future treatments for DED-associated depression.

In conclusion, it is clear that DED and depression are closely linked and influence one another in ways that drastically affect patients' lives. Collaboration between psychiatrists and ophthalmologists could be beneficial in the management of those with DED.

Key words: depression - dry eye disease - multidisciplinary care

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Introduction

Dry eye disease (DED) is a common disorder of the tear film which can cause ocular irritation, foreign body sensation and visual disturbance. It has numerous causes including ageing, medications, Lasik refractive surgery and inflammatory conditions such as Sjögren's syndrome. A recent meta-analysis including data from 22 studies including 2.9 million patients found that anxiety and depression are more prevalent in patients with DED than in controls with an odds ratio of 2.92 (Wan et al. 2019). It has a significant effect on quality of life with patients with moderate to severe disease reporting an effect on their quality of life comparable to that of a disabling hip fracture (Buchholz et al. 2016). However there is often a great discrepancy between signs and symptoms of DED, which the symptoms more associated with non-ocular disorders such as depression and PTSD than to tear film parameters (Galor et al. 2015). In this way it could be considered as much a psychiatric as an ophthalmic complaint. In this narrative review, we will argue that patients with DED would benefit from shared management between psychiatrists and ophthalmologists to optimise both their ocular and mental health.

Dry eye disease and depression are linked

There is an established link between dry eye disease and psychiatric conditions such as depression. A study conducted in 2018 reported that severity of both DED and depression both rose and fell in tandem but it is worth noting that the link between DED and anxiety

did not reach statistical significance (Bitar et al. 2019). Importantly, Kaiser et al. found that subjective well-being did not correlate well with features of DED but with regards to depressive symptoms their findings were more in line with other studies (Kaiser et al. 2015). A retrospective case-control study conducted in North Carolina reviewed 7,000 patients between 2008 and 2013 with DED and reported the odds ratio for DED and depression to be 2.8. While this significant correlation suggests this link is not just present in a niche subset of the population, the authors acknowledge that confounding from the use of antidepressants may be influencing results (van der Vaart et al. 2015). The association is seen across multiple age groups with Asiedu et al. demonstrating that DED symptoms impacted depressive symptoms to a greater extent when compared to other psychosomatic symptoms in a young population (Asiedu et al. 2018).

Dry eye symptoms correlate more to psychiatric comorbidities than to ocular signs

In a study conducted by Gonzales et al, patients with dry-eye symptoms were 1.82 times more likely to have depressive symptoms. In addition, even non-specific ocular symptoms, such as burning, also coincided with much higher likelihood of expressing depressive symptoms (Gonzales et al. 2018). Symptoms of DED actually correlated more reliably with depression and post-traumatic stress disorder (PTSD) opposed to tear film criteria, such as ocular surface disease index (OSDI), Schirmer's test and corneal fluorescein staining

(Han et al. 2015). Thus the consequences of failing to treat DED are that depressive symptoms may worsen and the knock-on effect of this may lead to depression-associated sleep disorders (Ayaki et al. 2018).

Sleep disorders

Sleep disorders are common in DED, affecting around half of patients. These can be debilitating with sleep being impaired on a number of measures including long sleep latency, short duration and poor subjective quality (Ayaki et al. 2018). There are a number of possible mechanisms underlying disturbed sleep. Primary Sjögren's syndrome itself is associated with sleep disorders. Pain from nocturnal eye exposure could also be contributing. Depression is a significant contributing factor, and the poor sleep that can often be found in depression may be further exacerbated by the other factors in DED, and there could therefore be reciprocal effects thereby further worsening both the DED and depression. The authors of a recent review on this topic endorsed the involvement of liaison psychiatry as well as ocular interventions in the management of sleep problems in these patients (Ayaki et al. 2018).

Mechanism of link

DED and depression have been shown to have common risk factors including age and female sex, the latter suggesting there could be a hormonal component (Hallack 2005). The prevalence increases from 3.9% (aged 50–54) to 7.67% (aged above 80) and 5.7% (aged under 50) to 9.8% (aged over 75) in the US male and female population respectively (Han et al. 2017). However, the precise biological mechanism by which they are correlated is still equivocal as is the order in which they occur. Theories have been put forward suggesting that DED negatively impacts quality of life and this psychological burden complicates patients' emotional state thus contributing to depressive symptoms (Hallack 2005). However, biologically the link may relate to a central nervous system sensitisation in the hypothalamo-pituitary-adrenal axis as seen in conditions like PTSD and fibromyalgia; two other psychiatric conditions that share a link with dry eye disease (Bitar et al. 2019).

A population based cross-sectional study of risk factors for DED in British women found the strongest associations with chronic pain syndromes including irritable bowel syndrome, pelvic pain and fibromyalgia (Vehof et al. 2014). The authors postulated that this may represent a common aetiology involving somatisation or chronic pain predisposition. A multivariate twin study by the same investigators indicated there may be shared genetic factors underlying both DED and chronic pain syndromes (Mcintosh et al. 2016).

In addition to this there may also be more mechanistic links. Reduced tear break up time, a finding indicating dry eye, can be found in patients with fibromyalgia without any rheumatological disease such as Sjögren's syndrome (Türkyilmaz et al. 2013). DED

patients with incongruous features were found to have a decreased density of the corneal nerve further evidencing the theory that there may be a neurological dysfunction underlying this condition (Han et al. 2015).

Suicidal ideation

Both depression and chronic disease are both significant risk factors for suicidal ideation and suicide attempts, particularly chronic pain conditions (Ro et al. 2015, Ratcliffe et al. 2008). Dry eye symptoms are associated with an increased risk of suicidal ideation in Korean adults. The generalisability of this study is arguably limited by the high background suicide rate in the study population of South Korea. This effect remains after adjusting for confounders such as occupation, income, age and sex. The presence of sleep disorders, a common feature of DED, are a potential confounder. When sleep length is controlled for the effect remains, but long sleep latency, poor subjective quality and other features of sleep can also be perturbed in DED and weren't controlled for in this analysis (Um et al. 2018).

Age-related Macular Degeneration and psychological interventions

Given DED is associated with depression, some investigators have asked whether there are any other ocular disorders which also increase a patient's risk of depression. An analysis of the Korea National Health and Nutrition Examination Survey (KNHANES) found that depressive symptoms were more prevalent in patients with Age-related Macular Degeneration (AMD) (Ryu et al. 2017). However a later analysis of depression in the Beijing Eye Study found that dry eye was the only common ophthalmic complaint associated with an increased depression score and that AMD was not significantly linked (Jonas et al. 2018). However a comparatively low prevalence of depression (2%) in the study population calls into question the generalisability of these results. Despite the currently unclear literature surrounding depression in AMD, a systematic review last year found that psychological interventions combined with low vision rehabilitation reduced the rates of depression in those with AMD, but cautioned that more evidence is required to tailor these further to AMD patients (Senra et al. 2019).

Antidepressants

As well as DED and depression often coexisting, the treatment of one impacts on the management of the other. Antidepressants can cause and exacerbate dry eyes. This was particularly prominent with the anticholinergic effects of tricyclic antidepressants, but also occurs with SNRIs and SSRIs without known anticholinergic effects (Koçer et al. 2015).

The mechanisms underlying this link may involve NF-KB and potentially could lead to therapeutics specifically targeting depression associated dry eye

(Zhang et al. 2019). Due to the complexities surrounding the management of depression in patients with DED, and how common this comorbidity is, an integrated approach to treatment decisions has been proposed (Han et al. 2017).

Conclusion

DED and depression are intertwined conditions: perhaps linked in their aetiology, commonly comorbid, with mutually antagonistic effects, and complexly interacting management. Treatment of DED could help reduce depression symptoms, but effective management of depression could also help alleviate symptoms of DED (Kitazawa et al. 2018). However the use of antidepressant medication can exacerbate DED which in turn then could worsen the depression. The evidence for psychological interventions for prevention of depression in other ocular disorders is strong however, and so this may be a fruitful approach (Senra et al. 2019). Involvement of psychiatrists has been proposed before in managing associated sleep disorders and antidepressant use contributing to dry eye (Ayaki et al. 2018, Han et al. 2017). We would go further and propose that shared care of these patients between ophthalmologists and psychiatrists may produce the best management of both their ocular and mental health.

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Thomas Weatherby - conceiving of project idea, literature review, drafting manuscript.

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Mark Agius - reviewing manuscript, editorial input.

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THE ROLE OF CARE COORDINATORS VERSUS DOCTORS IN THE MANAGEMENT OF CHRONIC MENTAL ILLNESS IN THE COMMUNITY

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SUMMARY

Doctors play an important role in a multidisciplinary team, however therapeutic relationships are not limited to between a doctor and a patient. In Community Mental Health Teams, patients are allocated a care coordinator - usually a community psychiatric nurse or a social worker - and they usually become the healthcare provider the patient is most regularly in contact with. Similarly, a practice nurse in General Practice may be the healthcare professional a patient is most familiar with. In these instances, the patient-provider relationship may be stronger than the doctor-patient relationship. Non-doctor and patient relationships play an increasingly important role in improving the patient experience and contributing to information gathering, shared-decision making, and establishment and adherence to treatment plans. Care coordinators may be in a more superior position than doctors to accurately recognise the ongoing and changing needs of a person with mental illness. Patients value continuity of care, compassion, and mutual trust and respect: these qualities can potentially all be provided by any trained healthcare professional. In this paper, we will review the literature on the emerging role of the care coordinator and other healthcare professionals in the management of chronic mental illness in the community.

Key words: care coordinator - case manager - mental illness - therapeutic relationship

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Introduction

Mental illness in the community describes people with severe mental illnesses that are managed outside of a hospital setting and living within the community, as well as people with milder conditions that are managed in a primary care setting. Historically, doctors have played a key role in a patient's psychiatric treatment and an emphasis placed on the importance of the doctor-patient relationship in this setting. The doctor-patient relationship is built on mutual participation, respect, shared decision making, and trust (Fugelli 2001, Kaba & Sooria-kumaran 2007). Especially with a trusting relationship, patients may feel more obliged to seek care, comfortable in sharing sensitive information, adhere to treatment and improve outcome (Hall 2002). A review of the literature has shown that the quality of the therapeutic relationship in the treatment of severe mental illness is a reliable predictor of patient outcome in mainstream psychiatric care (McCabe & Priebe 2004). However, therapeutic relationships are not limited to between a doctor and a patient. Patients value warmth, empathy and expertise (Lambert 2001, Johansson & Eklund 2003), and therefore, other adequately trained healthcare professionals may all engage with patients in a meaningful way (Cameron 2005, Scanlon 2006, Sudbery 2002). Furthermore, in a system where patients with mental illness in the community may only see their doctor on a monthly to yearly basis, patients may in fact, build a stronger therapeutic relationship with healthcare professionals other than doctors that are involved in their care and whom they see more frequently.

The community mental health team (CMHT) is a multidisciplinary team formed of many different healthcare professionals, including psychiatrists, nurses, psychologists, occupational therapists and social workers. Key aims of the CMHT are to keep patients in the community for as long as possible and reduce the number of hospital admissions and length of stay. Patients may also have a Care Programme Approach (CPA) plan in place with a care coordinator as their key healthcare professional worker, usually a community psychiatric nurse or social worker (Burns 2007). The CPA, a form of case management, was first introduced in 1991 to improve the delivery of healthcare for serious mental illness in the community (Department of Health 1990). It has since been revised and refocused, although the fundamentals remain the same: each patient must have a written care plan, and an allocated care coordinator (Department of Health 1998, The Kings's Fund 2008). The role of a care coordinator is to ensure regular contact with the patient, coordinate care with mental health specialists, monitor any changes in the patient's condition and adherence to treatment, initiate change when treatment is not effective and offer psychosocial support (Katon 2001, Von Korff & Goldberg 2001). Due to care coordinators being in regular contact with their patients, they will often form a strong therapeutic relationship with the patient. Likewise, in primary care, a practice nurse may be more familiar with a patient than the patient's usual doctor (Laurant 2018). In these instances, the patient-provider relationship may be stronger than the doctor-patient relationship. Therefore, other healthcare professionals may be in a superior position to

doctors to more accurately recognise the ongoing and changing needs of the person with mental illness in the community, and reduce hospital admissions.

The Importance of the Care-Coordinator-Patient Relationship

In the modern era, non-doctor and patient relationships play an increasingly important role in improving the patient experience and contributing to information gathering, shared-decision making, and the establishment and adherence of treatment plans (Girard 2017). The importance of such relationships should not be underestimated, with evidence suggesting that building and maintaining a strong patient-provider relationship can be a catalyst for change in itself and lead to positive treatment outcomes (Leach 2005, Leichsenring 2002). Continuity of care also benefits the service user, with greater adherence to medical advice, better take-up of health promotion, and greater trust developed between the patient and the healthcare provider (Mainous 2001). With greater trust, patients are more honest and more likely to disclose sensitive information. Case coordinators are able to provide continuity of care and form long-term relationships with their patients, maintaining contact with them both during crises and periods of stability. Through this, care coordinators are equipped with the knowledge to be able to recognise the patient's 'relapse signature' and arrange for appropriate interventions at an early stage, thus preventing a more detrimental crisis from occurring (Watkins 2001, p115). Relationship building is important for mental illness healthcare where lack of patient engagement can be a significant barrier to treatment (Dixon 2016). Care coordinators are in an ideal position to foster and nurture these important relationships.

Not only do care coordinators have a risk-assessment role to establish when a patient's condition may be deteriorating, but they can also play a role in enhancing treatment. Research has shown that patients view their relationships with their care coordinator as central to their recovery, and some patients feel that their care coordinator in fact provides most of their healthcare (Simpson 2016). The importance of the care coordinator role has been numerously described as crucial to the future of chronic mental illness (Burns & Santos 1995, Faulkner 2017, Goodwin & Lawton Smith 2010). The primary goal of people living with chronic mental illness has been reported to involve service users feeling empowered to sustain and take control of their own mental health (Kaj & Crosland 2001). The smaller case-loads that care coordinators have also allows them to be more proactive and less reactive in the management of their patients (Simpson 2003). Care coordinators also often come from a more empathetic background (Fields 2004) with a greater propensity for a holistic approach to healthcare (Laurant 2008). Hence, care coordinators may be more equipped than psychiatrists to support patients to achieve their aim. There is limited literature

regarding the importance of the care coordinator role and we recommend more research to be done to explore the power of this therapeutic relationship and its effect on patient outcome.

From the Community Mental Health Team to Primary Care Services

It is not only for severe mental illness where nurses and other healthcare providers may be taking over the role of a doctor in the formation of effective therapeutic relationships. In an ageing population, chronic disease is becoming more prevalent. The link between chronic disease and common chronic mental illness such as depression and anxiety is well recognised and people with one or more chronic diseases are at increased risk of mental illness (Chapman 2005, Katon & Schulberg 1992, Moussavi 2007, Noël 2004, Scott 2007). While 90% of people with mental health problems are cared for entirely within primary care (England 2017), general practice has been criticized for inadequately recognizing and managing depression. Therefore, there has been an increasing push for primary care to implement chronic illness management and collaborative care models to better manage depression (Von Korff & Goldberg 2001). Practice nurses are increasingly involved in the care and follow-up of patients with chronic disease, and therefore effectively placed to form therapeutic relationships with this at-risk group of patients (Waterworth 2015). Depression and anxiety may often present atypically in elderly patients (Hodkinson 1973) and a healthcare professional who knows the patient well may be better equipped to spot the first changes which may indicate that a patient is beginning to suffer from a mental illness. With the appropriate support, primary care nurses may also be able to screen for common mental illnesses using standardised tools and providing psychosocial support and lifestyle advice (McKinlay 2011).

Nurses may be utilised not only in the detection of mental health illnesses but also in their treatment. Studies where primary care nurses become care managers for the treatment of patients with both chronic disease and depression have shown an improvement in depressive symptoms and an increase in patient satisfaction (Ekers 2013). Similar to a care coordinator role, a case manager makes regular contact with the patient, monitors the progress of the patient's condition and adherence to treatment, initiates changes when treatment is unsuccessful, offers psychosocial support and coordinates the care with the primary care provider with or without mental health specialist support (Gilbody 2003, Katon 2001, Von Korff & Goldberg 2001). This form of collaborative care has been shown to be effective in primary care (Archer 2012). Within general practice, there is an indication of decline in physician-led continuity of care (Baird 2016). Studies have shown that nurses can make suitable substitutes for doctors in diverse areas of primary care, including diabetes management and blood pressure monitoring (Jackson 2018,

Laurant 2018). Perhaps in the future, we will be seeing nurses replacing doctors in the management of chronic mental conditions too, and also become increasingly reliant on nurses to form therapeutic relationships that are so central to effective mental healthcare.

Conclusion

Although a therapeutic role was not originally designed or portrayed to be a central feature of the CPA care coordinator's remit, over the past quarter of a century, it is clear that the care coordinator role has evolved to have therapeutic potential. Doctors are a necessary part of the multi-disciplinary mental health team to diagnose mental illness, prescribe medication and ultimately recommend treatment. Care coordinators and care managers must be able to work collaboratively with doctors to appropriately escalate interventions to match a patient's needs. Overall, psychiatrists and general practitioners may still build strong doctor-patient relationships with service users but the trust and in-depth knowledge which can be built between the patient and care coordinator/care manager is invaluable to the success of mental healthcare in the community.

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Contribution of individual authors:

Xingyue Maria Wang conducted the literature search and drafted the paper.

Mark Agius supervised the project.

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ATTITUDES TOWARDS A BORDERLINE PERSONALITY DISORDER UNIT - A SMALL-SCALE QUALITATIVE SURVEY

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SUMMARY

Background: Springbank Ward, Fulbourn Hospital, Cambridgeshire and Peterborough NHS Foundation Trust, is a Borderline Personality Disorder (BPD) unit employing positive risk-taking, allowing for relevant psychological therapies to be carried out.

The aim of this survey was to identify staff and patient attitudes to Springbank Ward. Previous research has not addressed the question of patient and staff perception of these therapeutic approaches.

Subjects and methods: We used a qualitative open-ended semi-structured survey of staff and patients (n=2+4, respectively). We gathered information on the perception of the unit, staff, safety and the positive and negative aspects of the ward. Interview transcripts and participation notes were coded and categorised for emerging themes.

Results: The four main themes were: views on the unit: 'safe space', 'opportunity', 'community'; views on the programme: 'successful', 'skills-based', involving patients in their own recovery; views on staff: important part of the therapeutic process by delivering elements of dialectical behaviour therapy (DBT); views on safety: patients and staff feel safe in the context of positive risk-taking.

Conclusions: The long-term therapeutic programme offered at Springbank is perceived positively by both patients and staff. Involving patients actively in their recovery remains a powerful tool. The delivery of DBT by nursing staff contributes significantly to the positive perception of the unit. Positive risk-taking is perceived to be a good and safe strategy.

Key words: Borderline Personality Disorder - surveys and questionnaires - therapeutic community

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INTRODUCTION

Borderline personality disorder (BPD) is a common condition, affecting around 0.4% of adults in the UK, and its cost to society reaches thousands of pounds per person (McManus et al. 2007, van Asselt et al. 2007). Yet, there is a lack of consensus about the cost-effectiveness of various BPD treatments, contributing to the high cost of the condition to society (Brettschneider et al. 2014). According to the most recent National Institute for Health and Care Excellence (2009) (NICE) guidelines, long-term management should focus on risk assessment, risk management and psychological treatment that is comprehensive and prolonged. Furthermore, NICE recommends dialectical behaviour therapy (DBT) programme in the community for women with BPD for whom reducing recurrent self-harm is a priority and to consider pharmacological treatment should be considered for treating comorbid conditions. Therapeutic relationships are very important – patients should be encouraged to take on the responsibility for their recovery and engagement with services (National Institute for Health and Care Excellence 2009, Birch et al. 2011).

One of the challenges in the management of patients with BPD is the risk of self-harm and suicidality. The traditional approach to acute self-harm and suicide is a vigorous intervention, aimed at monitoring and managing a patient's safety (National Institute for Health and Care Excellence 2004). However, for many patients

with BPD who exhibit chronic suicidality this approach is harmful, traumatic and contributes to the prevention of emotional expression and distress communication, which became established over long periods of time (Krawitz et al. 2004; Birch et al. 2011). Instead, a harm minimisation strategy is proposed, consisting of a rapid non-judgmental response, aimed at exploring causes of distress, emphasising alternative coping strategies and the provision of clean materials that can be used in self-harm (Krawitz et al. 2004; National Institute for Health and Care Excellence 2004). The therapeutic community approach has also been shown to significantly reduce the incidence of self-harm (Birch et al. 2011). In that setting self-harm is seen as a form of emotional expression that transgresses a relationship boundary and an act of self-discharge from the community that can only be reversed by showing regret and intention to learn from the experience (Birch et al. 2011). All of these strategies can be seen as elements of positive risk-taking – the idea that in the management of chronically suicidal and self-harming patients the risk can never be eliminated, but professionally-indicated, short-term risk-taking ultimately results in a profound reduction in the long-term risk of suicide (Krawitz et al. 2004).

Springbank Ward in Fulbourn Hospital, Cambridgeshire and Peterborough NHS Foundation Trust, 'is a 12-bed in-patient recovery unit for women with a diagnosis of borderline personality disorder (BPD) who are struggling to cope with the demands of life outside of

hospital, despite the input from community psychiatric services' (Cambridgeshire and Peterborough NHS Foundation Trust 2018b). Admission criteria include: 'women between the ages of 18 and 65 who: have a primary diagnosis of emotionally unstable personality disorder (ICD-10 F60.3); are under the care of a psychiatric community team with an identified care coordinator and a responsible clinician (the responsible clinician may not be the care co-ordinator) (...); have tried but failed to benefit from general acute and community psychiatric services; are willing to be assessed for admission by the staff at Springbank ward; have a permanent place of residence; are able to identify goals they would like to work on whilst being an in-patient' (Cambridgeshire and Peterborough NHS Foundation Trust 2018a). Patients who pose a significant risk of harm to others, require management in a low or medium secure unit and/or are unwilling to engage with the therapeutic programme cannot be accommodated (Cambridgeshire and Peterborough NHS Foundation Trust 2018a). The therapeutic programme offered is usually 12 months long and is based on therapeutic activities and evidence-based interventions, which include DBT, arts and crafts, cooking and others (Cambridgeshire and Peterborough NHS Foundation Trust 2018c). The ideas of a therapeutic community and positive risk-taking are endorsed.

The aim of this qualitative survey was to identify staff and patient attitudes to Springbank Ward as an example of a BPD unit employing the principles of a therapeutic community and positive risk-taking.

SUBJECTS AND METHODS

Direct observation

Direct observation of staff and patients was undertaken over the period of 6 weeks in May and June 2018 as part of a medical student placement at the unit. It included participating in daily ward activities, including group therapy sessions, activity groups, meals, and free time.

Subjects

The goal of the study was to interview staff members and patients from the Springbank ward, Fulbourn Hospital, Cambridge, UK. The participants were not randomly sampled, as only consenting participants were interviewed. All of the patients and staff members, however, were included in the direct observation.

Interview procedure

4 patients (out of 6) and 2 staff members were interviewed. 2 patients who were admitted at the time of the survey were not available for participation. The patients interviewed had been inpatients for between 2 and 11 months. The staff members interviewed had worked there for between 3 and 5 years. The interviews took up

to 20 minutes and were all conducted on the ward, in a quiet and private area. The participants were told that they were being interviewed for a service evaluation of psychiatric care and that the interviews are anonymous. The interviews were conducted in the last two weeks of the interviewer's six-week-long placement, so all interviewees knew the interviewer well and were aware that he was leaving the environment soon.

The questions were designed as unbiased, open-ended and unambiguous. Staff and patients were asked demographic questions, how they would describe Springbank to someone who did not know what it was, what works well, what could be improved, what the staff were like, how the ward compared to other mental health units, and how safe the ward was. Staff and patients were asked the same questions. New questions were added as the interview process progressed. Interviews were continued until a point at which no new themes were emerging.

Analysis

The content of the interviews was handwritten verbatim, during the interview by the interviewer. These interview transcripts and observation notes were then transcribed digitally. Transcripts and notes were then coded for relevant aspects. Codes were grouped together to form the main themes emerging from the survey. The relationships between the themes were examined.

RESULTS

The four main themes that emerged from this survey were: approaches to the unit itself, to the recovery programme, to the staff who work there, and to safety on the ward. All of these themes influence each other and merge to become the perception of what Springbank is and how it works. They all, however, address a subtly different aspect of the life in the unit and offer insights into how each of these parts individually contribute to the final product.

Attitudes to Springbank

It is clearly noticeable that all staff and patients are very proud of where they work or are being treated. The ward is being spoken of in superlatives, set as an example to others, and a hugely beneficial environment. It is described as a 'safe space' and an 'opportunity', where the patients can 'build a life worth living', a life 'without pain or suffering'.

The most frequently mentioned advantages of Springbank are patient involvement and working together. During daily activities on the ward patients, especially those who have been on the ward longer than others, help those who are struggling. In those touching displays of peer support one can see real non-patronising care for each other. The patients themselves recognise that one comes to Springbank to 'build your own reco-

very' in a community where 'everyone works together'. This seems exceptional, considering the difficulties faced by patients who are unwell enough to be referred to specialist units. The patients find it pleasantly surprising that the staff 'encourage [them] to make decisions about your own care'. Some explained that, initially, they found it difficult to settle in and make friends, but emphasised that support was offered for them to stick to their values in the face of adversity, which helped resolve these issues.

Springbank is universally recognised for the uniqueness of psychiatric care it offers in terms of the use of dialectical behaviour therapy (DBT) and positive risk-taking. 'You can come and go as you please, if you have a risk assessment. Sections are very rare. Everyone who is here wants to be here. You're never here against your will.' It was truly emotional to see the gratefulness in one patient's eyes when, for the first time in years, she was not detained under a section of the Mental Health Act, merely days after arriving at Springbank. The patients praise the 'willingness to try new things and approaches to recovery'. Many are surprised that 'there are so many people out there who are struggling and don't even know there is this amazing therapy that works so well'.

Staff members universally disclose that prior to May 2015 'it was very different to what it is now'. 'We had to be one-to-one all the time, [the patients] were self-harming all the time'. 'There were not enough staff (...), it was horrendous'. The transformation of the recovery programme, undertaken as part of a huge team effort and a change in the leadership of the ward, was the turning point. The ward was changed 'into a therapy-based ward', 'it started to get better'.

Nowadays, staff and patients alike consider Springbank 'the best mental health ward in the f...ing world' and voice these opinions in informal conversations. They appreciate that it is the uniqueness of the community that allows them to openly bring up these views in communal areas.

Attitudes to the recovery program

One of the main factors contributing to what everyone describes as a successful ward is Springbank's unique program. It includes DBT, praised for the skills it teaches patients, which 'can be used in real life'. All patients follow a busy timetable, with many activity groups, such as sensory group, creative group, goal-setting group, cooking, and many others. Together they 'teach you to express emotions in creative ways, (...) and work towards achieving goals in every aspect of your life'. In addition to that, there are a multitude of activities outside of the ward, including camping, trips to festivals, open mic nights at local cafes, etc. All this means that 'the patients are not sitting festering in their own problems'. One staff member, who works at a different unit on the same site, said 'Whenever I have a shift at [the other unit] I think to myself – can we not

drag [the patients] out of their rooms? Make them do something? [The other approach] clearly doesn't work, so why do we keep doing it?'. Those who have been taking part in the program for a long time appreciate how well thought out it is. They say that 'everything on the program has a purpose' and even though sometimes one needs to force themselves to participate, 'everything gives you a real sense of achievement when you look back'.

Some patients confess how challenging the program is initially. 'Having to change myself, how I think, my habits – it's difficult'. During my time at Springbank I could see how the program is also constantly developing to match the patient's needs. 'The only thing [that could be improved] (...) – my partner could be more involved. It's gotten better whilst I've been here and he knows that he can call and ask questions. We had a consultation together recently, but it's still something that's not explicitly offered as part of my program', said one patient. Within a week from this conversation an evening carer support group at Springbank was set-up as a result of this feedback.

It is a universal conviction at Springbank that the program is incredibly successful. Those who have recently started their time at the ward 'hear about patients who were previously here (...) and were acutely unwell [at the beginning] who had BPD removed from their list of current diagnoses [after completing the program]'. Others, who have been there for a while appreciate that 'it's shaped [them], it saved [their] life'. Some of the patients get volunteering jobs, start college courses and jobs whilst at Springbank – 'I never thought I would manage to do that', confesses one lady. These are not temporary successes – previous patients visit the ward often and act as a positive example for the current Springbank residents. Patients who leave are convinced they 'will not ever be going back to the hospital', they say it is the 'start of a new life. A happy life'.

Attitudes to staff

One of the main advantages of the staff who work at Springbank that is brought up by patients is that the mental health nurses are involved in DBT. According to one staff member, this helps encourage the patients to participate in various nurse-led groups, which are considered much more of an integral part of the recovery process than before. The additional benefit is that the skills taught in DBT become much more woven into the daily life on the ward. 'All the staff are trained in skills, so all day, every day, you have access to DBT', says one patient.

At the same time, it is very easy for the patients to bond with the team, because 'everybody is themselves (...). They feel like they can bring a part of themselves to work (...) They can be human'. Another person adds that the staff 'work with patients on the same level, rather than as figures of significant authority' and that the patients are equal 'even with the doctors'.

In her thank-you letter to the team that she read out on being discharged, one patient said, ‘When my mum and I were looking at this ward’s website and I saw there are over a dozen nurses and another dozen healthcare assistants, I thought you’d all suck, 90% of you will be shit, and I’d only get on with a handful of you - how wrong I was!’. Indeed, the staff at Springbank are much loved by everyone. Any disagreements between staff and patients, which are bound to happen in any community, are dealt with very sensitively and with continued support for the staff.

Attitudes to safety

The perception of safety at Springbank is of particular interest, given the risk-taking approach. In their interviews everyone said that they feel completely safe at the ward. ‘Sometimes I even forget that I’m in a hospital and that I do need to be careful’, says one staff member. Paradoxically, this feeling of security seems to have come with increased freedom for the patients and the trust that is currently placed in them. ‘I feel very confident, because I know [the patients] well and they feel very safe as well’.

The patients do indeed all report feeling safe, both from themselves and external factors. One patient describes it as: ‘Safety [at Springbank] is the patient’s responsibility. So although there are some things in place to prevent serious harm, like no sharps and stuff, it’s mostly – or entirely – the patient’s responsibility to keep themselves safe’. It is recognised to be hugely beneficial, as the patients ‘work towards reducing self-harming and self-destructive behaviour by choosing not to self-harm even when you have the opportunity to’. In other settings, ‘if [the responsibility] is taken away from you, you never learn to look after yourself’. Some staff members nevertheless think that they are overly protective, but that is not the perception of the patients, who recognise that they need the safe environment to recover. ‘Not only will I be safe, but I will be saved [at Springbank]’, says one of the patients.

DISCUSSION

It has been suggested for a long time that brief patient-initiated admissions to hospital may be superior to prolonged stays in this group of patients (Nehls 1994). Such treatment plans play an important role in crisis management, as well as in the breaking of cycle of repeated hospitalisations, but have been criticised, due to the lack of permanent effect on the difficulties that patients experience on discharge in community (Nehls 1994). The gold standard is currently to bridge that gap with dialectical behaviour therapy delivered outside of hospital (National Institute for Health and Care Excellence 2009). While DBT is a very expensive therapy to deliver – the cost of each individual session is about two times higher than that of a visit to a psychiatrist and the sessions need to be delivered very

often – it is very effective at reducing the total cost to society due to BPD (Wagner et al. 2014).

At Springbank patients are subject to a prolonged voluntary admission to a therapeutic community, whose purpose is to equip them with tools to deal with their difficulties in function in society. The financial burden of DBT delivery is partially reduced by providing training in this type of therapy to the nursing staff, who support the psychologist in delivering it to patients. This model of care, where nursing staff routinely offer psychosocial interventions, is not at all new and has been suggested as the key to improving patient outcomes, but remains a rare occurrence (McCann & Bowers 2005. Mullen 2009).

The benefits of this approach are not only the delivery of very effective psychotherapy at a reduced cost, but also substantial benefits to the staff-patient relations. Understanding DBT increases staff empathy and facilitates a more optimistic therapeutic outlook, which are suggested to be the key to improving staff participation in the recovery programme (Hazelton et al. 2006). This is particularly important, as even staff who work with patients with BPD have been shown to have limited understanding of the aims and process of recovery (Dean et al. 2018) and both historically and currently, borderline personality disorder remains one of the most stigmatised diagnoses, also among healthcare professionals (Gallop et al. 1989, Sheehan et al. 2016). Finally, psychotherapy training for staff members significantly benefits the staff themselves – it has been shown to reduce stress, anxiety and burnout rates, which are very common in those working with patients who are difficult to treat (Caruso et al. 2013).

It is in this environment where staff members empathise with and understand patients, that the positive risk-taking approach to chronic suicidality is being implemented. Despite being proven to reduce self-harm and suicidality (Birch et al. 2011), this approach is still not widespread. Krawitz et al. (2004) in a relatively recent paper explored why that is the case and found that clinicians agree that risk-taking is in the patients’ best interest, but fail to implement it in their practice. The authors identify that the predominant reason is the fear of medicolegal repercussion in the case of patient injury or death, but the patients themselves express overwhelming support for this strategy.

Limitations

Despite this survey providing useful insight, it is not without limitations. Firstly, it was conducted on a very small sample of patients and staff. Secondly, since the questions were open and qualitative, no quantitative data could be obtained and no statistical analysis was conducted. Thirdly, since the interviewer was a temporary member of the clinical team, the interviewees may have had reservations in disclosing some information – although they were instructed that the survey was confidential and the interviewer would cease to be part

of the team at the end of the study. Moreover, the participants do not constitute a representative sample, as they have all worked or participated in the recovery programme at Springbank and the results of this survey can only be extended to a wider population to a certain extent.

CONCLUSIONS

The findings of this study highlight a number of interesting points about staff and patient attitudes to Springbank Ward. Firstly, although not formally recognised as an evidence-based treatment, the long-term therapeutic programme offered at Springbank is thought to be effective in women with BPD who have failed to benefit from acute and community psychiatric treatment. Secondly, the delegation of part of the responsibility for recovery to the patient increases their engagement and satisfaction with the service, even if in the short term it may increase anxiety. Part of that ownership of the process of recovery is positive risk-taking with relation to chronic self-harm and suicidality, which in fact increases the feeling of safety. Thirdly, the bilateral positive relationship that the patients enjoy with members of staff is both psychotherapeutic and personal.

Most importantly, however, this work outlines the importance of further study of successful strategies to manage patients with BPD. Little is known about how best to deliver DBT – in community, as an inpatient in a therapeutic community, by psychologists or multiple professionals – although it appears that training staff in this type of therapy is beneficial. In addition, educating clinical staff about the benefits of professionally-indicated risk-taking in the management of BPD and ethico-legal advice related to it is needed. Additional research is required on the indications for long-term inpatient therapeutic interventions, such as the one offered at Springbank, and how they fit into the current framework of short hospital stays for patients with BPD.

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Contribution of individual authors:

Jakub Nagrodzki – design of the study, data collection, data analysis and interpretation, manuscript writing.

Jorge Zimbron – design of the study, manuscript review.

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GENDER DIFFERENCES IN THE PORTRAYALS OF DEPRESSIVE ILLNESS IN POPULAR CULTURE: A COMPARISON OF LITERARY TEXTS

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SUMMARY

Gender differences in the prevalence, experiences and presentations of mental illnesses are well-known and are reflected in research findings, clinical practice, society and popular culture. This paper will compare and contrast the role that gender and other factors play in the portrayals of depressive illness in two acclaimed texts, 'The Bell Jar' by Sylvia Plath and, 'Darkness Visible' by William Styron.

Key words: depression - memoir - literature - gender differences

* * * * *

Introduction

A plethora of historical texts such as the Psalms of King David and the biography of the prophet Mohammed (PBUH) contain poignant descriptions of pathos, melancholia and despair. Indeed, descriptions of melancholia can be traced as far back as ancient Greece in the teachings of Hippocrates.

More recently, 'mental illness memoirs' have become increasingly popular both as a means of escapism and as a tool for self-help. Take, for example, the excerpt below about British novelist Matthew Haig's Sunday-Times best-selling book, 'Reasons to Stay Alive' that eloquently describes Haig's valiant battle with depressive illness and how his struggles informed his prose:

"Like nearly one in five people, Matt Haig suffers from depression. Reasons to Stay Alive is Matt's inspiring account of how, minute by minute and day by day, he overcame the disease with the help of reading, writing, and the love of his parents and his girlfriend (and now-wife), Andrea. And eventually, he learned to appreciate life all the more for it..."

(<https://www.goodreads.com/book/show/25733573-reasons-to-stay-alive>)

...Matt's frankness about his experiences is both inspiring to those who feel daunted by depression and illuminating to those who are mystified by it. Above all, his humour and encouragement never let us lose sight of hope. Speaking as his present self to his former self in the depths of depression, Matt is adamant that the oldest cliché is the truest - there is light at the end of the tunnel. He teaches us to celebrate the small joys and moments of peace that life brings, and reminds us that there are always reasons to stay alive..."

(<https://www.goodreads.com/book/show/25733573-reasons-to-stay-alive>)

Indeed, it is with the immediacy and authenticity of the first-person narrative that the mental illness memoir creates a vivid picture of human existence in the "kingdom of the sick" (Sontag 1978). Moreover, autobiographical narratives of mental illness have an established tradition of lending themselves to the psychiatric field. For example, Jaspers, in his *General Psychopathology* (Jaspers 1913), based his constructs of delusions and other mental illness phenomena on *Schreber's Memoirs of My Nervous Illness* (Scherber 1903).

In this paper, we compare the portrayal of depressive illness in two acclaimed literary works, 'The Bell Jar' written in 1961 by Sylvia Plath and, 'Darkness Visible' composed by William Styron in 1989. Through critical analysis of the aforementioned texts, and with reference to other supporting material, we will be looking more specifically at some of the differences and similarities that manifest in a male's experience of depression, compared to that of a female.

It is important to note that at first glance, 'The Bell Jar' and 'Darkness Visible' appear similar in many aspects - both seem to chronicle an experience of clinical unipolar depression. Both authors struggled with depression and these experiences informed their writing. Both books also document breakdowns and recoveries. However, throughout this paper it is essential to bear in mind that, 'The Bell Jar' was 'mostly' fictional (we say mostly because it is widely considered to be partly autobiographical) and was intended to be a potboiler, whereas 'Darkness Visible' is autobiographical, and was intended to be educational since it was first given, in abbreviated form, as a lecture addressed to a medical audience. The two texts hence differ in their purpose and tone.

Additionally, the lessons gleaned from the two should not be taken as representative of an entire gender's

experience of depression. Moreover, a limitation of the two texts is that they were both composed before the recognition that there are people in society who now identify themselves as non-binary in terms of their gender.

Factors that contribute to gender differences in depressive illness

The male to female ratio of depressive illness has consistently been reported as 2:1 (Nolen-Hoeksema 1987). A large amount of evidence exists which documents differences and similarities between men and women diagnosed with unipolar depression. By examining the language and style in the two texts, we aim to identify the factors that trigger the onset of depressive illness, how it manifests (including suicidal and self-harm behaviours) and how it is managed.

Rates of depressive illness vary across racial and ethnic groups and how depression is experienced (and indeed how it is expressed i.e. the so-called 'idioms of distress') can differ considerably between and within groups. Multiple hypotheses have been postulated to account for the differential rate of depressive illness in men and women and studies have looked specifically at hormonal differences and genetic variations. Below, we have selected factors that contribute to gender differences in depressive illness that are most relevant for the aims of this paper.

The Sex Role Theory

The sex-role theory states that the elevated levels of stress and reduced sense of fulfilment in the female role compared to the male role leads to the former being predisposed to depressive disorder (Barnett et al. 1987). This is certainly evident in 'The Bell Jar'. Esther, the protagonist, feels pressurized by 1950's societal expectations to be a domestic woman while simultaneously exploring options beyond the sphere of the home. Smith suggests that this ties in strongly with Esther's sense of self, and so when her options start narrowing down, her sense of self also begins to disintegrate (Smith 2010). Esther "saw her life branching out" with wonderful options for her future "beckon(ing)... like a fat purple fig". She "wanted each and every one", but was "unable to decide", and ultimately all "the figs began to wrinkle and go bad". Plath uses the sensuous fig, a symbol of female fecundity, as a metaphor for Esther's options, which suggests that all of her options have to relate back to her sense of womanhood and are also defined and limited by her gender. Jack proposes that the internalized societal expectations of feminine goodness shape women's behaviour in relationships and therefore precipitate depression (Jack 1991).

The Rumination Theory

The rumination theory suggests that women tend to dwell, brood and ruminate (more than men) over their

depression, thinking about its causes and consequences, resulting in a lengthier depressive episode (Nolen-Hoeksema 1990). Several studies suggest the rumination theory can account for some of the gender difference. Furthermore, rumination may not only directly lead to depression, but may also contribute by preventing women from actively trying to conquer stressors in their lives (Nolen-Hoeksema 2001).

Alcohol and depressive illness

Conversely, it is known that a risk factor that affects men more than women is alcoholism. Rates of alcohol abuse are higher amongst men than women (Fowler et al. 1986). Alcoholism has a significantly higher prevalence rate for comorbidity with depression in men than women (Brady & Randall 1999). Interestingly, Styron says that alcohol, "a known depressant", had instead "shield(ed) against anxiety". Styron describes how he lost "the great ally which for so long had kept (his) demons at bay" leaving him "emotionally naked".

The signs and symptoms of depression appear more similar in both genders. Depression can come on gradually and insidiously, and it is difficult to say just when Esther and Styron's depressive mood disorders became apparent. What is evident is that it starts off with a persistently low mood, which can slowly lead to a loss of identity and isolation.

The portrayal of depressive illness in, 'The Bell Jar' and, 'Darkness Visible': A comparison

Esther's sense of self begins to fragment as the metaphorical figs fall away. She ascribes responsibility of decisions (that only isolate her further) to a "zombie voice", and the use of "listened" suggests an almost physical detachment from herself. She feels like someone else is speaking for her, unable to relate how she truly feels, as connoted by her "hollow voice". Indeed, it is not uncommon for people with depressive illness to experience depersonalization, derealization and dissociation and the passivity phenomenon that Esther experiences would be in keeping with a depressive disorder with psychotic symptoms.

Similarly, Styron had a "faint, wheezy" voice. Their voices also represent their ability to communicate with the world and the gradual weakening reveals their increasing isolation. Esther is also no longer able to write, and as a writer this ability is integral to her identity and sense of self-worth. Styron, who is also a fervent writer, feverishly journals but decides to discard his precious notebook before attempting suicide – showing that the core of his identity is most shaken at the very depths of depression.

Another symptom of depression is the loss of appetite, which is extremely marked in Esther, who goes from excessive, decadent eating "I covered the chicken slices with caviar thickly as if I were spreading peanut-

butter on a slice of bread” to covertly “bury(ing) (my hotdog) in the sand”. While Styron’s appetite remained “relatively normal”, he found it “utterly without savour”. These two examples also illustrate how symptoms of depression are inextricably linked – the overall anhedonia could be the cause of withdrawing from society, or perhaps the withdrawing from society could be causing the loss of pleasure. Whichever it is, it is certain that depression causes isolation in its victims, and the stigma of depression causes society to isolate them further. Indeed, there are many narratives from people with lived and living experience of depressive illness who report that debilitating though the symptoms of depressive illness are, the stigma of depression is far worse.

They also both experience insomnia, a hallmark symptom of depression (nhs.uk 2019), with Esther being unable to sleep soundly “for a solid month”. Styron’s sleep disturbance goes beyond that, waking up “at three or four in the morning... wondering and writhing at the devastation taking place in (his) mind”. Early morning waking is also a biological feature of depressive illness that is well documented in the literature.

The two texts comment on the nihilistic thoughts and feelings of depressive illness, namely the hopelessness and helplessness that permeates the minds of those who suffer from this mood disorder. As Styron puts it, “in depression this faith in deliverance, in ultimate restoration, is absent. The pain is unrelenting, and what makes the condition intolerable is the foreknowledge that no remedy will come”. This is startlingly similar to Plath’s writing: “I could see day after day glaring ahead of me like a white, broad, infinitely desolate avenue.” When conducting a mental state examination, mental health professionals often ask patients how they feel about the future; the above extracts typify the responses that are often provided namely a sense of pessimism and a lack of hope.

In their encounters with the disease, Esther and Styron use similar language, particularly that pertaining to the weather, to describe their sufferings. Styron criticizes the word “depression”, preferring instead (the already taken) “brainstorm”, which would more accurately express the “veritable howling tempest” inside his mind. This internal storm also leads to a negative perception of the surroundings and the weather – as shown by the “fading evening light” lacking “its familiar autumnal loveliness”, but instead “ensnar(ing) (him) in a suffocating gloom”. Styron is no longer able to enjoy what he once did. The pathetic fallacy employed by Styron illustrates the very physical manifestation of the malady; much like the weather, depression cannot be controlled by its sufferer.

William Styron eloquently describes the perils of reductionism in, ‘Darkness Visible’, by elaborating on the usage of the term depression and how it came to replace the more apt term melancholia. Styron’s account

commands the attention of all those who stake a claim in wanting to better understand the subjective experience of a psychiatric illness:

“When I was first aware that I had been laid low by the disease, I felt the need, among other things, to register a strong protest against the word “depression”. Depression, most people know, used to be termed “melancholia,” a word which... crops up more than once in Chaucer, who in his usage seemed to be aware of its pathological nuances. “Melancholia” would still appear to be a far more apt and evocative word for the blacker forms of the disorder, but it was usurped by a noun with blank tonality and lacking any magisterial presence, used indifferently to describe an economic decline or a rut in the ground, a true wimp of a word for such a major illness. It may be that the scientist generally held responsible for its currency in modern times, a John Hopkins Medical School faculty member justly venerated - the Swiss born psychiatrist Adolf Meyer - had a tin ear for the finer rhythms of English...As one who has suffered from the malady in extremis yet returned to tell the tale, I would lobby for a truly arresting designation... Told that someone has evolved a storm - a veritable howling tempest in the brain, which is indeed what clinical depression resembles like nothing else - even the uniformed layman might display sympathy rather than the standard reaction that “depression” evokes something akin to “So what” or “You’ll pull out of it” or “We all have had bad days””

When Esther visits her father’s graveyard, “a fine drizzle” appeared from “a grey sky”, and “(she) grew very depressed”. Plath intentionally links the point about the rain to the fact that Esther grew depressed to create an atmosphere of hopelessness and despair. She does this again when Joan, another character in ‘The Bell Jar’, hangs herself; Joan is discovered “in the woods, by the frozen pond.” The image of the frozen pond suggests stasis and death – the once life-giving substance now harsh, cold and solid.

In other depictions of their illness, Esther and Styron both describe depression as a constant presence. The eponymous bell jar in Plath’s novel would follow her wherever she went: “wherever (she) sat”, she “would be sitting under the same glass bell jar, stewing in (her) own sour air.” Even when she improves after electro convulsive therapy, the bell jar still “hung, suspended”, suggesting that the relief was only temporary. Styron says, “one does not abandon, even briefly, one’s bed of nails”. This hopelessness “crushes the soul” “even more than pain”. The harsh image of a bed of nails conveys the crude brutality of depression, and the subversion of the comforting bed to a metal one emphasises how debilitating and without respite a disease depression can be. All these may eventually be too much for its victim, and depression “kills in many instances because its anguish can no longer be borne”.

Plath's 1961 poem "I am Vertical" – written when she was battling depression - opens with "But I would rather be horizontal", concisely conveying to the reader the speaker's wishes. Sadly, an estimated 5,821 people died by intentional self-harm in the United Kingdom in 2017 (Office for National Statistics 2017). The poem describes dying as an ideal, with much reference to beautiful nature and becoming a part of the earth. "Dying/Is an art, like everything else. /I do it exceptionally well." This excerpt from Plath's poem *Lady Lazarus* could as easily have been something written by Esther. The isolation of "dying" draws the readers' eye to it; elevating it to a position of reverence.

Factors that contribute to the differential rates of self-harm and suicide in men and women

For many years, the suicide rate has been approximately four times higher among men than among women. In 2017, adult females in the United States reported a suicide attempt 1.4 times more often than male counterparts (AFSP 2019). Lastly, the highest suicide rate in the UK for 2017 was among men aged 40 to 44, at 24.8 deaths for every 100,000 people (Ons.gov.uk 2019).

Why do more women than men attempt suicide? Why are men more successful? The overrepresentation of women in suicidal behaviour and the larger number of men in completed suicide is known as the gender paradox of suicidal behaviour. A common theory explaining the gender paradox proposes that females are more likely to have internalising disorders, while males are more likely to have externalising behaviour such as violence, behavioural problems and substance abuse. Hence, women are more likely to attempt suicide, while men have a higher rate of completed suicides due to their more determined and impulsive behaviour (Beautrais 2002). This theory is supported by the texts. Esther extensively planned her suicide, from testing out her ability to cut herself, to attempting suicide multiple times via different methods. On the other hand, Styron makes the decision more impulsively, beginning with "stuffing" his notebook "deep down within the garbage can".

Looking at the methods of suicide may enlighten us further on the higher rates of completed suicide by men - hanging (accounting for 58% of male suicides and 42% of female suicides) and poisoning (accounting for 38% of female suicides and 18% of male suicides) are named as the most common methods of suicide (Ons.gov.uk 2019). Males are more likely to attempt to end their life using a high mortality method, while females are more likely to overdose on drugs (Schrijvers et al. 2012). Plath writes "it was just like a man to do it (suicide) with a gun". In 'Darkness Visible', Styron mentions Jean Seberg, who died by suicide by taking "an overdose of pills". Additionally, Romain Gary "put a bullet through his brain". Poiso-

ning or drug overdoses are less immediate in their effects, and hence medical attention is more likely to be given before it is too late. Esther's first suicide attempt was by overdosing on pills, and then lying in a crawl space for a few days – strikingly similar to Plath's own (Brown & Taylor 2004).

In 'The Bell Jar' Plath writes that Esther thought slitting her wrists "would be easy, lying in the tub and watching redness flower from (her) wrists." The use of "flower" lends this romantic, poetic sense to what is in actual fact a violent act. This supports the theory that ideation of suicide is more likely to occur in women. Styron describes in great detail, his decision to end his life, and the "sense of melodrama" as he went about preparing for his "departure", which was "as inescapable as nightfall". However, he ultimately does not attempt suicide, and fortunately, approaches his wife for help.

Esther and Styron get help for their depression in entirely different ways. Esther gets referred to a psychiatrist after telling her doctor that she needed more sleeping tablets. After her suicide attempt, she is hospitalized. While less information is given in the timeline of Styron's clinical presentation, he does inform readers that he "began to visit (Dr. Gold) immediately after (his) return from Paris". He did not think it probable that "conversation with another mortal, even one with professional expertise in mood disorders, could alleviate (his) distress." As aforementioned, women present with depression at a rate of about two times the number of men. A study by Williams et al. found that women are also more likely than men to take antidepressant medication at each and every severity stage of depression (Williams et al. 1995). 'The Bell Jar' does not reveal very much on medication, instead exploring Esther's treatment of electro convulsive therapy and insulin shock therapy. Being written at a very different time, where electric shock and insulin shock therapy were considered less effective than medication, 'Darkness Visible' understandably focuses a lot more on medication. Murphy suggests that men place a higher emphasis on independence and decisiveness, and they regard asking for help as weakness and will try to avoid it (Murphy 1998).

"Depression is much too complex in its cause, its symptoms and its treatment for unqualified conclusions to be drawn from the experience of a single individual." This quote from 'Darkness Visible'. Indeed, there are many possible reasons people develop depression. As stated above, beyond biological gender differences, societal and environmental factors play a large role.

It is evident that Styron and Esther are both creative people; could that be a reason why they both suffered from depression? Not all novelists have experienced psychopathology. Conversely, not all those who have experienced psychopathology become novelists. The notion, nonetheless, of there being an association between 'craziness' and creativity, contentious though it may be, remains a seductive one. A study found that writers were more likely to suffer from unipolar

depression, anxiety disorders, substance abuse and suicide, amongst other mental disorders (Kyaga et al. 2013). Might it be that creative people, especially writers, are more likely to ruminate?

Conclusion

Autobiographical narratives of mental illness are precious sources of information. They provide a 'window' into the nature of psychiatric disorders in a way that is not possible from standard psychiatric texts. They allow psychiatrists, other mental health service providers, relatives of people with mental illness and the general public a rare qualitative insight into the richness of psychopathology as experienced first-hand rather than as drawn out and described by psychiatrists (Hankir et al. 2013).

'The Bell Jar' and 'Darkness Visible' are two different texts which both shed light on how dangerous a disease depression is. As Styron writes, "the pain of severe depression is quite unimaginable to those who have not suffered it... the prevention of many suicides will continue to be hindered until there is general awareness of the nature of this pain." Given the intense stigma that comes with severe depression, we believe these two texts are important as they bring depression out into the open, making it less of a taboo subject, whilst also providing a first-hand account of this mood disorder. Additionally, studies have shown that reading fiction can foster greater empathy (Bal & Veltkamp 2013). For a reader who feels depressed, there is great power in the sense of being known as they identify with characters in books. 'As a species, we derive solace from shared experience...'

This paper has explored some of the gender differences of depression. Whilst these differences are well known, gender-specific treatment and policies incorporating the putative risk factors for gender-specific assessment are lacking. Further exploration is needed, including empirical studies, to try and identify the reasons behind these differences. Only this way, can we help more people, as Styron evocatively wrote, emerge out of "depression's dark wood", to "return from the abyss", to be "restored to the capacity for serenity and joy", and to once again behold the stars in the canopy of the night sky...

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Contribution of individual authors:

Rui-Ernn Natassia Chin conceived the idea for the paper, contributed to the literature review and completed the comparative analysis between the two texts.

Ahmed Hankir & Rashid Zaman contributed to the literature review and revised the manuscript.

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