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**ASOCIAȚIA ROMÂNĂ
DE PSIHIATRIE ȘI PSIHOTERAPIE**

www.romjpsychiat.ro

ROMANIAN JOURNAL OF PSYCHIATRY

Vol XIX

Nr. 4

December 2017

QUARTERLY

CNCSIS B+

p-ISSN: 1454-7848


e-ISSN: 2068-7176

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Revista Română de Psihiatrie este indexată de Consiliul Național al Cercetării Științifice din Învățământul Superior la categoria **B+**. Apare trimestrial.

Colegiul Medicilor din România acordă abonaților la această publicație **5 credite EMC/an**. Articolele științifice publicate în revistă sunt creditate cu **80 credite EMC/articol**.

Revista Română de Psihiatrie este editată de *Asociația Română de Psihiatrie și Psihoterapie și Asociația Medicală Română*

MULTIDIMENSIONAL MACHIAVELLIANISM CONCEPTUALIZATION

*Ionela A. Bota*¹, *Monica A. Bilca*², *Istvan Z. Szasz*³, *Alexandra A. Bota*⁴, *Aurel Nireştean*⁵

Abstract: *The different variants of manipulation of social behavior have always awakened the interest of psychiatrists, psychologists and sociologists. For the contemporary psychology, the term Machiavellianism refers to a facet of the interpersonal behavior defined by a person's tendency to manipulate the attitude of others to achieve their own interests. These are associated with a cynical view of the human nature in which the expectations and needs of people in the social environment are ignored in a selfish and egocentric way. From a particular personal perspective, Machiavellianism is considered to belong to a "black triad" of the personality together with*

narcissism and psychopathy, having evil effects on social life. Despite the pejorative meanings that can be attributed to the term Machiavellian, they can represent a way of deeper knowledge of human psychology. It integrates a variant of maladaptive functioning of personality in social life and has a genetic, neurobiological and clinical expression. We aim to comment on the legitimacy of considering Machiavellianism as one of the personality disorders using the diagnostic criteria related to them.

Key words: *Machiavellianism, personality, disorder, black triad, alexithymia*

Personality disorders represent a particular sector in the psychiatric nosology and nosography due to their persistent structural conditions of abnormality, clinically manifested by a discontinuous adaptive behavioral deficit, often masked by the tolerance of the others, by special spiritual qualities or by an intellectual level that substantiates a particular versatility within the interpersonal relationships. Within them, the egocentrism of pathological personalities is nourished and promoted also by the deficit in structuring the super-ego, the moral « posture » towards self coexisting with the immoral one towards the others.

The origin of the term « Machiavellianism » is in the work « The Prince » by Niccolò Machiavelli, the Florentine philosopher, historian and diplomat, a work that represents a tribute to Lorenzo de Medici and which is meant to be a guide for conquering and maintaining the power using certain means opposed to the traditional ones (1). However, the use of this term in order to define a psychological structure started only in 1970 and we owe it to Richard Christie and Florence L. Geis.

The psychological traits that characterize an unscrupulous leader, in Niccolò Machiavelli's view, subsequently have been considered characteristic symptoms of a homonymic personality dominated by the lack of trust in the human nature and the tendency to manipulate in interpersonal relationships, the selfish pursue of one's own interests based on the motto « the end justify the means ». This concept has certainly gained more and more interest in relation to the study of personality and its disorders. From the social psychology perspective, the Machiavellian traits are a version to adjust to the pressure, exercised by the social life's dynamics on the individual. They are not considered be able to be correlated to the social class, to

different ideologies, nor to the level of intelligence or different versions of success in life.

The Machiavellianism clinical side includes a cynical, suspicious, treacherous and manipulative behavior in the interpersonal relationships, maintained by a selfish detachment from the community norms and values to which are associated anxiety and emotional instability (2). The Machiavellian style can be charming and attractive, but at the same time shallow and obviously interested in competing, in material values and power. It is in a reverse correlation with the faith in the human being and with his moral values or virtues as empathy, honesty, modesty and gratitude, being animated only by selfish motivations. The first attribute, that allows a person with Machiavellian traits to always successfully adapt to the dynamic and roles of life is flexibility, fostered also by the Machiavellian person's capacity to anticipate the intentions of the persons with which he interacts, a phenomenon known as « theory of mind » (3).

Recent studies plead for the existence of two facets of empathy, a cognitive one, respectively an affective one. The first would correspond to the theory of mind in the meaning of anticipatory understanding and use of emotional experiences and reasoning and judgment of the other, and the second one, by the capacity to experience and share emotions to the other persons (4). Cognitive empathy is also simultaneously an attribute of subclinical psychopathy, subsequently described by Emil Kraepelin as a psychopathic personality. In the same context, Cleckley describes in psychopaths a « semantic aphasia » to which corresponds the incapacity to grant an affective meaning to life's events and experiences, so they know only the words, but not the music (5). This trait seems to be also common to psychopathy and personalities with

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Received May 8, 2017, Revised June 24, 2017, Accepted July 19, 2017.

Machiavellian traits.

The dominant attributes of Machiavellianism suggest – from a personological perspective – the need of a dimensional approach in the event of which the most indicated is the model of five factors - the Big Five – which has been applied to significant populational groups in all the cultures. The five dimensions are Extraversion, Agreeableness, Conscientiousness, Neuroticism and Openness to experience. Assessing the Machiavellian behavior through these dimensions, it has been determined a negative correlation with Agreeableness and Conscientiousness, as well as with Openness to experience (6). There is no positive correlation with Extraversion either, very probably due to its polarization around emotional stability. Extraversion associated with emotional instability, therefore with a high Neuroticism, is characteristic to Machiavellianism, and explains the incisiveness and domination tendencies on those around them. The low values of Neuroticism in this association do not characterize Machiavellianism because they mean affective stability, self-confidence, self-determination, hedonic and relaxation abilities. Consequently, Neuroticism is a dimensional attribute specific to Machiavellianism.

Recent studies add to the Machiavellian traits also alexithymia, that is the individual's incapacity to express through words emotions and feelings (8). In addition, there are encountered difficulties also in understanding one's own emotions, low creativity and lack of introspection abilities. Those with Machiavellian traits, being incapable to develop emotional relationships, are leading their existence by establishing two patterns of interpersonal relationships, going from one extreme to the other, either dependence and instability in time, or absolute social isolation. The "Emotional Inability" of the Machiavellian person explains partly the ways in which relates to the others. The association with alexithymia has influenced the introduction of the concept of "volitional Machiavellianism", which explains also the lack of empathy.

Indeed, as it has been illustrated in the previous paragraphs, the concept of Machiavellian personality is dominated by Emotional detachment from others and lack of interpersonal warmth, a close description of alexithymic individuals. A second emotional attribute, which may be considered as a defining one for Machiavellianism, is Anhedonia. This term, defined as the incapacity to feel pleasure, means also a diminished sensitivity to events that are considered aversive. Anhedonia can also be considered a vulnerability factor or a defence mechanism and it is positively correlated with the lack of empathy.

It is considered to exist a primary Machiavellianism with early manifestations and related to the structure of the personality, and a secondary one which can be regarded as a defence mechanism and may characterize the behavior of depressed patients and of those with schizophrenia. They are not capable to interpret the intentions and emotions of others around them or they change their significance.

Paulhus includes Machiavellianism in a black triad of personality, next to narcissism and subclinical psychopathy, and the joint element which confers them malefic influences on others around them, being the

manipulation, lacking any kind of regret or remorse.

Narcissism and psychopathy are assigned today to personality disorders dominated by selfishness and egocentrism, exploitative and hostile style in interpersonal relationships, emotional detachment from one's peers, poorly structured super-ego which do not allow be aware of one's own defects and cultivate a false and vulnerable image and self-esteem. Conceptually, Machiavellianism is associated to two types of pathological personalities, but there are differences from a dimensional perspective that must be commented upon. Thus, psychopathic personalities, the narcissistic ones and those with Machiavellian traits, are encountered on the territory of affective detachment and lack of affective resonance in the relationships with others. From the perspective of the Big Five model, the low level of Agreeableness is characteristic to all the three structural versions, and those with Machiavellian traits and the psychopaths have in common also a low level of Conscientiousness. While Machiavellianism means also a high level of Neuroticism, its level is minimum in psychopaths, in their case the lack of anxiety and charm confers them an antisocial position of first rank in the reference triad. On the other hand, the high levels of Extraversion and Openness to experience may partially dim the maladaptive traits of the narcissistic and of the psychopath (7).

Therefore we may define as fundamental traits of Machiavellianism the lack of empathy, the high level of alexithymia, dysphoria and anhedonia, cognitive and affective negative empathy, traits assembled around interpersonal duplicity, cynical vision of the surrounding world and lack of morality.

So, there is a double orientation in defining Machiavellianism. On one hand, there are the authors who sustain the independence of Machiavellianism in relation to the other personality disorders and the need to classify it as a distinct entity in the international classifications. On the other hand, other authors are oriented towards the integration of Machiavellianism in the known personality disorders, especially those included in the Black Triad of Personality, Machiavellianism being just another facet of them.

As the term assigned to it suggests, Machiavellianism represents a psychological and personological entity of which conceptualization remains further to be desired.

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ANXIETY, DEPRESSION AND COGNITIVE IMPAIRMENT IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Mihaela R. Dumitrescu¹, Mihai Bran², Andra E. Morasan³, Maria Ladea⁴

Abstract: Depression, anxiety and cognitive impairments are common among patients with chronic obstructive pulmonary disease and these psychological aspects are associated with poor treatment adherence and worse outcomes. Identifying the psychological symptoms and developing appropriate treatment strategies are very

important for this category of patients. This paper tries to synthesize the current understanding of patients with chronic obstructive pulmonary disease and comorbid psychological symptoms.

Keywords: depression, comorbidities, pulmonary disease.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide (1) and it is a leading and growing cause of the global burden of disease (2). Defined by the presence of chronic airflow limitation, exertional dyspnea and recurrent respiratory infections, COPD is now considered a complex, heterogeneous and multicomponent condition. The presence of other comorbidities, such as cardiovascular disease, depression, anxiety, osteoporosis, diabetes, substantially contributes to the severity of the disease.

DEPRESSION AND ANXIETY IN COPD PATIENTS

Mood disorders like major depression and dysthymia, and anxiety disorders (generalized anxiety disorder, phobias and panic disorders) are common in patients with COPD (3) and earlier diagnosis and treatment would be very beneficial (4). Prevalence vary widely, due in part to the use of varied measurement tools and to the different degrees of illness severity across studies. The global prevalence of depression and anxiety is much higher in patients with COPD compared with general population. It is reported that depressive disorders or depressive symptoms can vary between 40% and 74% of patients with COPD (5, 6, 7, 8). Nonetheless, precise data on depression rates in patients with COPD are lacking and further research are needed. Moreover, a recent systematic review and meta-analysis of 25 studies with long-term follow-up revealed that the relationship between COPD and depression is likely bi-directional, as depression may be both a cause and a consequence of COPD (9).

A cross-sectional study reported that COPD patients are 85% more likely to develop anxiety disorders compared to healthy, matched controls (10). In addition, the prevalence of clinical anxiety in COPD outpatients ranges between 13% and 46% (11). Patients with anxiety or depressive disorders and COPD are twice as likely to experience functional limitations, poorer exercise tolerance and higher frequency of acute exacerbations

compared to those without anxious or depressive symptoms. Anxiety disorders seems to be more disabling and, unless adequately treated, have the potential to become chronic, to lower patient's self-esteem, to predispose to suicidal ideation, and to increase the risk of hospitalization (9, 11).

Comorbid depression which is often associated with feeling of hopelessness, social isolation, decreased energy and fatigue can lead to poor self-care behaviors like unwillingness to engage in pulmonary rehabilitation, decreased physical activity, failure to quit smoking, poor eating habits and poor medication adherence (12, 13, 9). The goal of pulmonary rehabilitation is to change patient health behaviors especially by increasing physical activity. Comorbid psychological symptoms like depression and anxiety have an important role in this behavior change.

A large study (ECLIPSE study) examined the prevalence of depression in COPD patients compared with smokers and nonsmokers without COPD. The prevalence of depression was 26%, 12%, and 7% of COPD, smokers, and nonsmokers, respectively. In subjects with COPD, higher depression prevalence was seen in females, current smokers, and those with severe disease. Its findings indicate that clinical and biologic markers were less important determinants of depression in COPD than disease symptoms and quality of life (14).

It is known that depressive symptoms are associated with dysfunction of HPA axis and inflammatory factors. It is also known that COPD is characterized by a systemic inflammatory response involving increased pro-inflammatory cytokines such as IL-1, IL-6 and TNF-alfa (15). Recent studies suggest that low-grade chronic inflammation mediates in part the association of depressive symptoms with pulmonary function in COPD (16). Systemic inflammation has been suggested as an etiologic factor in the development of multiple comorbidities in COPD patients, but its role remains to be elucidated in the future. A causal relationship between low-grade systemic inflammation

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Received May 7, 2017, Revised June 23, 2017, Accepted July 17, 2017.

and comorbidities in COPD has not yet been proved. The current findings also show that the possible interactions between biomarkers of systemic inflammation and comorbidities in patients with COPD are very complex (17).

COGNITIVE IMPAIRMENT IN COPD PATIENTS

In recent years, cognitive impairment was often referred as a comorbidity in patients with COPD. The risk of dementia is naturally higher in older COPD patients, and dementia speeds up the progression of COPD. The increased risk of neuronal injury in COPD may be due to hypoxemia, systemic inflammation or as a result of other comorbidities such as vascular disease or smoking. However, the studies suggest an association rather than a causal link (18). When present, impaired cognitive function is associated with reduced quality in life, poor compliance with both medication and oxygen therapy (19), and poor compliance increases the risk of acute exacerbation, and may be predictive of increased morbidity and mortality in COPD patients (20). The most widely-used tests which cover multiple cognitive domains are the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Clock Drawing Test (CDT). These tests have good diagnostic accuracy and can provide healthcare professionals with a prompt overview of patients' cognitive status when cognitive impairment is suspected.

TREATMENT AND INTERVENTIONS OPTIONS

Untreated comorbid anxiety and depression in patients with COPD may have major consequences on the course of illness. There are several barriers for detection of and treatment of anxiety and depression in patients with COPD (21). Patient barriers include lack of knowledge about the possibility of anxiety or depression as well as their treatment options, stigma regarding mental illness, self-blame for their disease. Physician barriers include lack of standardized diagnostic approach for anxiety and depression, short consultation time, lack of time for educating patients about depression and counseling. System issues include poor communication between primary care and mental health care and lack of adequate resources for mental health treatment.

Patients with COPD should be screened for depression and anxiety on presentation and whenever their clinical, economic, or psychosocial status changes. A variety of validated, easily administered, or self-administered depression and anxiety screening tools are available. Common screening tools for anxiety and depression in patients with COPD are The Hospital Anxiety Depression Scale and the Beck Depression and Anxiety Inventory Scale. Clinicians should be aware of the somatic overlap between anxiety and/or depression and COPD. Patients who screen positive should undergo a clinical interview for further assessment.

Evidence for the efficacy of antidepressant therapy in COPD associated with depressive or anxiety symptoms is limited. Many patients suffer transitory mood symptoms during respiratory exacerbations and there is no evidence that these time-limited symptoms require specific treatment. The National Institute for Health and Care Excellence (NICE) has published clinical guidelines for the use of stepped approaches to psychological and/or pharmacological treatment of

depression in people with long-term conditions (22). NICE guidelines advise that antidepressants should not be routinely prescribed for physically ill patients with subthreshold symptoms of depression or mild-to-moderate depression. Pharmacological therapy must be considered when major depression is diagnosed to avoid its long-term effects on overall disability. Selective Serotonin Reuptake Inhibitors SSRIs may be considered a more safe choice with little or no effect on ventilator drive. On the contrary, benzodiazepines may cause respiratory depression and should be avoided in COPD patients

Concerning anxiety, several studies have investigated the effectiveness of specific medications (23) with contradictory results for buspirone (24) and inconclusive results for SSRIs, even though they are better tolerated and can relieve symptoms of panic (25, 26), but compliance may be poor.

Patients prefer nonpharmacological treatments and clinical guidelines (27, 22) promote both individual and group therapy psychosocial interventions in COPD patients. NICE guidelines recommend cognitive behavioral therapy (CBT) to COPD patients with mental health difficulties, because of the time-limited and action-oriented nature of the intervention. A recent study demonstrated how cognitive behavior therapy may be an effective option for rapid symptom relief for COPD patients with anxiety and depressive symptoms while suggesting that the mental health care should be integrated into the overall medical regimen for COPD (28).

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NEW PSYCHOTHERAPY APPROACH IN GENERALIZED ANXIETY DISORDERS

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Abstract: Generalized Anxiety Disorder (GAD) is a challenge in terms of diagnostic identification because of the high comorbidity that occurs with this disorder. Due to long-term implications on patient function, treatment methods range from psychopharmacological therapy to cognitive-behavioral therapy or a combination of both.

The present article he proposes to present the latest psychotherapeutic methods, specific to “the third wave” of CBT, in the generalized anxiety disorder.

Keywords: „the third wave” of cbt, cognitive-behavioral therapy, metacognitive therapy, personality dimensions, dysfunctional cognitive schemas.

INTRODUCTION

Generalized Anxiety Disorder (GAD) is described in the DSM-5 through excessive anxiety and anticipated anxiety, and it is difficult for the patient to control these feelings so that for the diagnosis, these symptoms should be present for a longer period than six months, and the social, professional, and family roles of the patient be affected by these symptoms. More precisely, GAD is associated with three or more of the following six symptoms: (1) patients are feeling restless or feeling keyed up or on edge; (2) He/she becomes easily fatigued, with difficulty concentrating; (3) Irritability characterizes mood mood; (4) muscle tension; (5) sleep disorder (difficulty falling or staying asleep, or restlessness, unsatisfactory sleep) (1). Mental health surveys data indicate that anxiety disorders affect up to 33.7% of population during their lifetime. The lifetime prevalence of GAD varies between 2.8 % and 6.2 %, and the presence of GAD for a 12-month period is 2.8% and 2.9 % (2).

GAD occurs mainly in young adults and the average age at onset is 31 years (3). However, approximately 25% of GAD cases debut around the age of 20 years, and 50% of onsets occur between 20 and 47 years (4). Also, there is a high likelihood of chronic anxiety to associate over time with an organic comorbidity. In the case of GAD, over time, there is an increase of comorbidity between Irritable Bowel Syndrome (IBS) and chronic pain. For this reason, it is recommended that these patients undergo periodic medical investigation in order to prevent medical complications (5).

From an economic point of view, a French study revealed that the costs of psychiatric treatment for GAD (with no comorbidity) and additional medical consultations (internal medicine, radiology, etc.) carried out in order to exclude organic pathologies could reach \$733/month. Additionally, in the case of co-occurrence of GAD with another physical disease, the cost could reach \$1,208/month for a single patient. The study also showed that the adjacent costs, resulting from inability to work, was \$233/month in GAD patients with no comorbidities,

and \$416/month in comorbidity with another psychiatric diagnosis (6). Thus, it is important to identify causes, determinants, or new treatment methods designed to decrease treatment costs and discomfort, and to increase quality of life for these patients. Even though the GAD diagnosis has been widely disputed over time, the unanimously accepted conclusion is that this disorder becomes chronic in some patients over time which directly influences the quality of patients' lives (7).

PERSONALITY DIMENSION AND GAD

At the same time, there is a combination of TAG with personality dimensions, following The Big Five (FFM). These five big factors are biologically determined, being at the same time inborn and genetically transmissible features (8). Additionally, behavioral models of shyness or shame can be explained by a factorial combination of low *Emotional Stability* and low *Extraversion* (9). From a genetic point of view, certain risk factors also exist in association with various psychiatric conditions. A genome-wide single-nucleotide polymorphism (SNP) assessment shows 6% to 12% of phenotypical variation in the case of low *Extraversion* and *Emotional Stability*. These results are identical with the estimations in the Cloninger temperament scale (10) (11), as well as the Risk Avoidance and Novelty Seeking scales (12). We note that TAG etiopathogenesis (as many other psychopathological spectra) has a bio-psycho-social determinant.

MALADAPTIVE/DYSFUNCTIONAL COGNITIVE SCHEMAS (MCS)

From a psychological point of view, for optimal development children have certain basic needs that must be satisfied. First and foremost, children have the need for safety, stability, and acceptance, with attachment figures responding to these needs by building close relationships with the children. At the same time, in order to experience healthy development, children have the need for autonomy to acquire skills and discover their own identities. Thus, children's freedom to express

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Received May 27, 2017, Revised June 29, 2017, Accepted July 13, 2017

feelings and emotions, to engage in spontaneity and playful activities while also having appropriate limits and self-control, contribute to their emotional and mental health in adulthood (13) (14) (15). Furthermore, there is an association between early parental styles (e.g., rigid parenting) and developing Maladaptive / Dysfunctional Cognitive Schemes (MCS), which could determine the onset of certain symptoms particular to personality disorders, or chronic anxiety and / or depressive disorders (16). Once the Maladaptive / Dysfunctional Cognitive Schemes (MCS) are triggered by a negative life event, this process will be accompanied by intense negative emotions that generate major discomfort in patients. These MCS are considered to be absolute truths even though individuals are not consciously aware of the great impact they have on their perception of life's events. Despite causing distress, these schemata are considered to be "correct" by the individuals (17) (18).

Therefore, from the point of view of developmental psychology, GAD could be explained by using an interpersonal perspective whereas if early childhood needs (e.g., need for safety, trust, or affection) are not met this could facilitate the onset of feelings of fear and worry. Consequently, these dysfunctional schemas are developed over time and effect the individual's thought processes during future interpersonal relationships. With regard to the relationship between MCS and GAD, for instance in the case of patients with psychoactive substance addictions, there is an association between the symptoms of generalized anxiety and the autonomy and performance fields specific to MCS (19). Additionally, referring to anxiety disorders, common schemas exist which occur in social phobia and social anxiety, but which are different from the specific EMS occurring in panic attacks (20).

"THE THIRD WAVE" APPROACH IN GAD

By determining these specific patterns with the profile of this disorder, practitioners from the mental health system could improve psychological treatments for GAD. Treatment consists of anti-depressant and anxiolytic medication and/or Cognitive Behavior Therapy (CBT). It is known that therapy consisting of the combination of CBT and antidepressant medication is not superior to monotherapy (21). However, regarding anxiety disorders (e.g., GAD), CBT is considered a viable and efficient therapeutic choice, whether or not associated with medication (22).

Furthermore, the Metacognitive Model (MCM) shows that two types of worries occur in association within GAD. Type I worries are responsible for the distorted informational processing that cause the anxiety. Type II worries refer to 'worrying about worrying' and they are responsible for the occurrence of inefficient avoidance strategies, thought suppression, or focusing on emotion in situations which patients regard as dangerous (23) (24) (25) (26) (27). Approaching GAD through Metacognitive Therapy (MCT), with a particular focus on Type II worries (3-12 sessions), resulted in a significant reduction of worry-related symptomatology as well as an enduring effect seen in follow-up sessions demonstrating the efficiency of MCT in treating this disorder (28) (29).

By applying TCC specific techniques, maladaptive cognitive schemes are modified in particular by assimilation by the patient of new information through

cognitive restructuring. The induction of positive emotions in the psychotherapeutic process contributes to the processing of information as a whole, the easier accumulation of new information and the development of a type of thinking characterized by flexibility by the patient with TAG. Thus, the induction of positive emotions in TAG psychotherapy can prevent restoration of anxiety after the completion of behavioral exposure techniques (30).

Acceptance and commitment therapy (ACT) it is another CBT orientation specific of "the Third Wave". ACT is a therapy characterized as belonging to the post-Skinnerian behavioral orientation, and is based on the relational framework theory, represented by the relational context frame (RTF) and functional context (FC): (1) From the RTF perspective psychopathology occurs because the patient makes the confusion between the content of thought and the product of thought. (2) Functional context, is a derived branch of pragmatic psychology and radical behaviorism. As such, in relation with this approach past experiences are responsible for our present behavior. (31) (32) (33). In summary, from the perspective of ACT, for patients with GAD the map becomes the same as the territory. Thoughts are linked / generate specific emotions, manifest behaviors, respectively, correlated with the first situation in which they occurred (33) (34). ACT is a therapy in which patients are not taught to fight with their thoughts and discomfort, but paradoxically, they are encouraged to accept their anxiety and states, the focus being on the behavioral changes of the patient. Progress in therapy is achieved when the patient has no more existential avoidance, acts responsibly and in relation to his or her life values and acquires new adaptive behaviors by which he/ she manages to cope with anxiety (35). ACT is a new approach that attempts to alter maladaptive behaviors in anxiety by reference to values, present and action. This does not mean that ACT excludes CBT or that the two are not complementary. CBT tries instead to modify the patient's negative thoughts, dysfunctional cognitive schemes, targeting the emotional discomfort caused by anxiety. The two approaches seem different, giving them a common denominator: the behavioral techniques that are used successfully in both interventions (36). Also, a recent study investigated the effectiveness of Metacognitive Therapy (MCT) versus Cognitive-Behavioral Therapy in Treatment-Anxiety Disorders. The results indicated that MCT had a faster effect on anxiety symptom reduction, but after completion of treatment, the clinical effect was similar, with no major difference in clinical efficacy in treating anxiety between the two psychotherapeutic approaches (37).

CBT APPROACHES FOR GAD

According to Beck's cognitive model on anxiety and depression, there are three levels of information processing. The first, which is the most profound, corresponds to the disadaptive cognitive care schemes embodying central beliefs such as "I'm unlovable; I have no value; I am unnecessary". The peculiarities of these systems consist of their absolute rigidity and their absolute and definite character being related to the experience of life once you activate, distort the information and produce, through the mechanism of inference, negative thoughts that make anxiety contribute to selective processing

related to danger and helplessness (38). GAD treatment through CBT requires a multimodal and integrative perspective. Combining CBT with progressive relaxation techniques and desensitization leads to a significant improvement in the symptoms of anxiety and depression in TAG. It is supposed that adding an interpersonal component to CBT psychotherapeutic treatment would increase therapeutic effectiveness and reduce the post-therapy recovery rate and increase the quality of life for these patients (39).

From the neurophysiological point of view, there is pre-treatment CBT of sub-activation of the anterior cingulate and the island. After the treatment, there is a greater connection in the amygdalo-insular area, and a sub-activation of amygdalar and subgenual anterior cingulate in patients with GAD. The intervention of CBT is associated inclusive with a change in cingulo-amygdalar reactivity (40).

CONCLUSIONS

However, the comparison of CBT standard with "third wave" therapy approaches, shows that there are no significant differences between the two types of guidelines for effective anxiety treatment. Nevertheless, in terms of efficacy proven over time, CBT standard remains the "gold standard" in psychotherapeutic interventions in GAD.

ABBREVIATIONS:

ACT = Acceptance and Commitment Therapy

FFM = The Big Five

MCS = Cognitive Maladaptive Schemes

MCT = Metacognitive Therapy

GAD = Generalized Anxiety Disorder

CBT = Cognitive-Behavioral Therapy

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PATHOLOGICAL MECHANISMS OF THE PSYCHIATRIC COMPLICATIONS ASSOCIATED WITH RADIOTHERAPY FOR BRAIN TUMORS

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Abstract

The neoplasms of the central nervous system represent a frequent and heterogeneous disease group, with treatment implying a combination of surgical intervention with both chemotherapy and radiotherapy. Cerebral radiotherapy affects not only the tumor tissue but also the viable brain tissue, causing direct lesions to both the white matter and the gray matter and so leading to cognitive impairments, depressive and anxiety syndromes. The pathogenesis of psychiatric syndromes induced by radiotherapy is complex and not yet fully understood and the current review tries to summarize some of the possible pathogenic ways involved. Key words: radiotherapy, cognitive impairment, depressive syndrome

Rezumat

Neoplazmele sistemului nervos central reprezinta un grup frecvent si heterogen de afectiuni al caror tratament implica de obicei combinarea tehnicilor chirurgicale cu chimioterapia sau radioterapia. Radioterapia cerebrala nu afecteaza numai tesutul tumoral ci si tesutul cerebral viabil, determinand leziuni directe atat asupra substantei albe cat si cenușii si producand astfel deficite cognitive sau sindroame depresive sau anxioase. Mecanismul patogenetic al sindroamelor psihiatrice induse de radioterapie este unul complex si inca neinteleș pe deplin iar acest articol incearca sa summarizeze cateva din posibilele cai patologice implicate. Cuvinte cheie: radioterapie, deficit cognitiv, sindrom depresiv

The neoplasms of the central nervous system make up a heterogeneous disease group, the treatment of which generally implies combining a surgical intervention with both chemotherapy and radiotherapy. Whole Brain Radiotherapy (WBRT) has been used as the primary non-surgical therapeutic modality for the treatment of brain tumors (1) and was due, in part, to the limited other chemotherapeutic options demonstrated to be efficacious. Many patients in whom control of brain disease is achieved with WBRT are surviving to experience the considerable neurocognitive sequelae and declines in quality of life that are associated with this treatment (2, 3, 4, 5). Despite the technological progress, cerebral radiotherapy also affects the viable tissue, causing direct lesions to both the white matter and the gray matter through inflammation, angiogenesis and cellular death. Depending on which healthy cerebral areas are irradiated (structures belonging to the limbic system and the cerebral system, the frontal lobes and the temporal lobes), the patients with cerebral tumors will frequently display cognitive disorders (functions like attention, short term memory, processing speed, learning, visual orientation and speech being the most frequently affected) (6, 7). Meyers et al (8) reported in a study including patients that had received radiotherapy 20 months to 20 years prior, that 80% of the patients displayed memory disorders, approximately 33% of them also presenting executive dysfunctions. Some studies have failed to identify

cognitive disorders resulted from cerebral radiotherapy probably due to the specificity of the assessments (9) but other data from literature suggests an incidence of between 0 and 80%. The degree of neurocognitive decline in patients with brain tumors receiving radiotherapy can be confounded by the effects of tumor at presentation and other therapeutic interventions (like chemotherapy) on cognitive function (10).

The risk factors of developing cognitive dysfunctions induced by radiotherapy include: ages older than 60, higher dose than 2Gy/fraction, higher total dose, larger cerebral volume being irradiated, shorter treatment period, simultaneous chemotherapy, the presence of comorbid factors for cardiovascular risk, like diabetes (11, 12). Other frequent complications of cerebral irradiation consist of the occurrence of depressive and anxious syndromes (13, 14, 15). The clinical reactions of irradiated healthy cerebral tissue can be classified as acute, subacute and tardive. The acute effects occur within the first 48 hours to the first week and imply dizziness, headaches and nausea. The subacute effects appear after 6 to 10 weeks and consist of fatigue and sleepiness, symptoms that are generally reversible. The tardive effects of radiation on cerebral tissue include a vague decline of cerebral function, the easiest of which to notice being cognitive disorders (16). Neurological symptoms like seizures and an increase of intracranial pressure may also be observed (17, 18). All these

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Received April 27, 2017, Revised May 28, 2017, Accepted June 19, 2017

psychiatric and neurological effects may lead to a poor quality of life as some studies may suggest (19, 20).

When the cells and stromal cells or the central nervous system are exposed to ionizing radiations, the neurons, neuroglia and blood vessels respond in a similar way to the cells and stromal cells other organs. Post-irradiation lesions are similar to the rest of the body and changes in function are comparable. Higher dosage of radiation can lead to immediate death of neurons, the activation of astrocytes and production of reactive gliosis (similar to the post irradiation peritoneal fibrosis). The irradiation of the oligodendrocytes affects the formation and maintenance of the myelin sheath, that can lead to demyelination and affect the transmission of the nerve impulse. The blood-brain barrier can be affected and can lead to the occurrence of cerebral edema, the consequences of which can be disastrous (comparable to the emergence of pulmonary hyaline membrane disease in lungs priory exposed to ionizing irradiation). Both large blood vessels and the capillaries are affected by lesions similar to the rest of the body but given the lower resistance to ischemia of the cerebral tissue the toxic effects are of greater importance.

Consequential to the action of ionizing radiation on a cerebral level several types of lesions can be observed: demyelination, proliferative and degenerative glial reactions, loss of endothelial cells and occlusion of the capillaries. All these changes are as a result to complex alterations that took place in different cerebral functional compartments: damage to vascular structures, the disappearance of the precursors of mature astrocytes and oligodendrocytes, the disappearance of the neural stem cells from the hippocampus, cerebellum and cortex, generalized alterations to the expression of the cytokines. To sum up the facts, there are 3 targets for the radiations on the cerebral level: the neurons, the glial cells and the vascularization, but the distinction is somewhat arbitrary given that there is significant interaction in between these components.

Effects on the neurons

Certain studies prove the fact that radiation can induce the apoptosis of neurons in the case of newly born animals (21) although in the case of adult animals the observed effects weren't similar (22), confirming the fact that the neurotoxicity of radiation does not have direct damage to neurons as an underlying factor.

Vascular toxicity

Vascular alteration is important in the development of post-irradiation complications and structural alterations at the cerebral level (23). The first effects of the radiation on a capillary level are the detachment of the endothelium, cytoplasmic vacuolization, increases in nuclear volume, changes that determine the development of the initial edema. The endothelial cells become hypertrophied causing a reorganization of the f-actin filaments. Eissner and collaborators show that endothelial apoptosis can be achieved by generating intracellular ceramides or the adhesion of the irradiated leukocytes that can trigger the apoptosis thought TNF (24). The endothelium is progressively damaged for weeks to months, which leads continuously to the aggregation of irradiated platelets and the formation of blood clots, until the vessels become partially or fully thrombosed which in turn leads to the hypoperfusion of cerebral tissue. At the same time an abnormal proliferation of the endothelium as well as the

thickening of the basement membrane and the replacement of the lumen with collagen deposits can be observed (?). The cellular mechanisms involved in the pathogenesis of vascular toxicity induced by radiation include and increase in the production or various adhesion molecules that mediates the aggregation of leukocytes on the vascular walls, like E-selectin and ICAM-1 (25). Endothelial cells display a decrease in enzymatic activity: alkaline phosphatase, the enzyme responsible for the conversion of angiotensin. The increase of permeability for different molecules, hyper coagulation and increased aggregation of thrombocytes because of the increase in the production of the von Willebrand factor and a decrease of the plasminogen activators, consequent in an inefficient fibrinolysis, can be observed. Endothelial cells, of course, have defense mechanisms against the effects of radiation, they consist of reactive oxygen species like glutathione or superoxide dismutase (26).

In a in vitro study was observed that the lethal dose or radiation for the endothelial cells ranges between 100 and 200 cGy (27). The in vivo doses what would have a similar effect are much higher. Sub-lethal doses of radiation affect the morphology and different functions of the endothelial cells.

Glial cells and demyelination

Many of the effects radiation has on the central nervous system can be explained by disorders in the transmission of nerve impulse which originate from demyelination. Oligodendrocytes play a key role in the demyelination produced by radiation. Both oligodendrocytes, that play a role in the formation of the myelin sheath and astrocytes, that contribute to the transmission of electric potential through the nodes of Ranvier have a common precursor, namely the O2A cells (type 2 oligodendrocyte-astrocyte precursor). Radiation can affect the O2A cells directly, thus decreasing their numbers and reducing the possibility of regeneration for both the oligodendrocytes and astrocytes. The radiation also has negative effects on adult oligodendrocytes, reducing their number and thus creating the need for additional production of new ones from the O2A cells. Oligodendrocytes can be affected by cytokines like TNF alpha, the production of which can be simulated by radiation (28). The theory behind the involvement of oligodendrocytes and O2A cells in the occurrence of post-irradiation demyelination lesions is not completely explained, but there is sufficient proof from animal studies (29, 30, 31).

An important cerebral area that is affected after radiation is the hippocampus which remains mitotically active in adults. Studies have shown that the cells from this area are capable of differentiating between neuron and neuroglia and and of migrating long distances in order to contribute to the reparatory processes after the radiation therapy (32). It is demonstrated the hippocampus involvement in the pathogenesis of depressive disorder and cognitive impairment, and radiotherapy techniques sparing this region could improve the post treatment status of patients receiving brain radiotherapy.

Radiation induced apoptosis and gene expression

The induction of apoptosis in the case of different cerebral cellular compartments is the basis of the toxicity of radiation. Two major mechanisms to induce apoptosis on a cerebral level:

- the first mechanism consists of the activation of

apoptosis by the ligand family of TNF alpha, CD95-L and TRAIL-R1 and TRAIL-R2 via caspase 8

•the second apoptotic mechanism concerns direct toxicity for DNA, especially the mitochondrial DNA which determines the activation of the caspase system (33)

Simultaneous to the induction of apoptosis, the activation of certain gene expression seems to play a major role in the cerebral toxicity induced by ionizing radiation. Among the genes with an increased expression because of the radiation the most important ones seem to be pro inflammatory cytokines (TNF alpha, INF gamma) and the adhesion molecules (ICAM).

Radiation therapy has an important role in the management of brain tumors and could be considered a targeted therapy as it remains the 'go to' modality for the treatment of most brain tumors, particularly at the time of initial diagnosis. However, these interventions are responsible for well recognized and substantial adverse events in some cases (34). Neurotoxicity that arises from cancer treatment and especially from radiotherapy has been widely recognized and could limit the course of treatment (35). Common adverse effects of cancer treatment include cognitive dysfunction, depressive and anxiety syndromes which result from direct damage to the nervous cells and their surrounding microenvironment. The complete pathogenesis of psychiatric syndromes induced by radiotherapy is complex and not yet fully understood and effective strategies to minimize these problems would be of great advantage to the patients with brain tumors.

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HYPOTHESIS OF NEUROINFLAMMATION IN DEPRESSION

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Abstract:

Numerous clinical and experimental studies show that neuroinflammation hypothesis became a foundation pillar in the etiopathogenesis of depression alongside the monoamine hypothesis, given the fact that the existence of a pro-inflammatory status was repeatedly proven both in human subjects and laboratory animals. Depression induced by cytokine treatment in cancer and by interferon treatment in viral chronic hepatitis became a frequent therapeutic entity in the later years, on the opposite pole being important proofs of amelioration in psychic and neurovegetative depressive symptoms with anti-cytokine and anti-inflammatory treatment.

Key words: pro-inflammatory cytokines, neurodevelopment, neuro-inflammation, depression.

Rezumat:

Numeroase studii clinice și experimentale arată că ipoteza neuroinflamației a devenit alături de ipoteza monoaminică un pilon de bază în etiopatogenia depresiei dat fiind că existența unui status proinflamator a fost dovedită repetat atât la subiecți umani cât și la animalele de laborator. Depresia indusă de tratamentul cu citokine în cancer și interferon în hepatite virale cronice a devenit în ultimii ani o entitate terapeutică frecvent întâlnită, la polul opus aflându-se dovezi importante ale ameliorării simptomatologiei psihice și neurovegetative asociate depresiei la tratamentul anticitokinic și antiinflamator. Prin urmare noi studii sunt necesare pentru a atesta necesitatea adăugării terapiei antiinflamatoare la terapia antidepresivă și pentru a determina factorii de rezistență la tratamentul antidepresiv.

Cuvinte cheie: citokine pro-inflamatorii, neurodezvoltare, neuroinflamație, depresie.

BACKGROUND

Pro-inflammatory cytokines play an important role in the etiopathogenesis of depression, fact sustained by many experimental data and clinical trials. Experimental data show that an increased prenatal and early age level of pro-inflammatory cytokines favors the apparition of neurodevelopmental abnormalities which determine symptoms similar to depression in lab rats: social withdrawal, cognitive dysfunctions, anhedonia, increased hypothalamic-pituitary-adrenal axis activity, psychomotor retardation, sleep disturbances and the alteration of neural transmission. There are numerous clinical proofs regarding the risk of depression in patients who receive recombinant cytokines in the treatment of cancer and viral infections. The apparition of depression in these patients was linked with a decreased tryptophan level due to the induction of indoleamine 2-3 dioxygenase, the enzyme that metabolizes this amino acid. The degradation of tryptophan by this enzyme and the proliferation of T-lymphocytes is induced by interferon and other inflammatory cytokines. (1) For a long time it was thought that depression was associated with immunosuppression, but this theory was subsequently infirmed, being considered that the etiopathogenic factor was not immunosuppression, but a lack of balance in the immune system functioning, with the activation of monocyte and macrophage activity, associated with the diminishing lymphocyte activity. (2)

The antidepressants that exist now on the market have the target of increasing in monoamine transmission, the

monoamine theory of depression being the main etiopathogenic theory studied. (3,4) Nevertheless, there are many non-responsive patients, which suggests that the etiopathogenesis of depression is much more complex, as there are more factors that have not been considered regarding the therapeutic alternatives. Numerous studies suggest that depression, especially the major type, is associated with a deregulation of the immune system and the production of pro-inflammatory cytokines, the most frequently encountered being (IL)-1 β , IL-2, IL-6, interferon γ (IFN γ), tumor necrosis factor α (TNF α), the soluble receptor for IL-6 (IL-6R), and the antagonist of IL-1 receptor (IL-1RA). Many studies have also reported a low level of anti-inflammatory cytokines in depression (IL-4 and IL-10) (5,6)

SHORT HISTORY

The first information regarding the possible involvement of cytokines in depression was taken from gastroenterology and oncology. The oncologic patients and those with hepatitis B and C with cytokine treatment for immune system stimulation presented psychosis and/or major depressive symptoms a few weeks after the treatment was initiated. (7) Then Smith's macrophage theory of depression appeared in 1991, stating that a high level of interleukine-1 associated with the presence of macrophage degradation products produces cerebral abnormalities that are the base of depression pathogenesis. It was further experimentally demonstrated that pro-inflammatory cytokines determine the activation of hypothalamic-pituitary axis, fact associated with major depressive symptoms in laboratory animals. It was initially considered that patients with major depression

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Received April 24, 2017, Revised May 29, 2017, Accepted August 19, 2017

are immunosuppressed due to low activity of natural killer cells and lymphocyte proliferation. It was further demonstrated that depression is not associated with immunosuppression, but with a malfunction and a lack of balance in the immune system functioning. This was associated with monocyte and macrophage hyperactivity, which activates the apoptosis and leads to apparition of toxic cerebral degradation products. In 1995, Maes was the one who showed increased pro-inflammatory cytokines and acute phase proteins in the plasma of patients with major depression. (8) In 1996 Yirmiya demonstrated that antidepressant treatment administered for a long time in laboratory mice ameliorates anhedonia and social withdrawal, confirming the theory stating that anti-cytokine treatment and antidepressants decrease cytokine production and diminish depression symptoms. (9) Numerous clinical studies were performed later, but they didn't show such a pronounced lack of equilibrium in the immune system as experimental data showed. But new data appeared, and according to these, a high level of pro-inflammatory cytokines and the activation of hypothalamic- pituitary system are not only etiopathogenic factors in depression but also in schizophrenia, and the increased level of pro-inflammatory cytokines and acute phase proteins in a first psychotic episode is positively correlated with a low response to treatment in subsequent episodes.

CLINICAL AND EXPERIMENTAL STUDIES

In 1999, Levine et al. developed a clinical trial that included 23 patients, 13 with non-treated major depression and 10 controls, in order to confirm Smith's macrophage theory of depression. It was shown that the level of pro-inflammatory IL-1 β in the cerebrospinal fluid and serum was higher in hospitalized patients with major depression compared to controls, being positively correlated with the severity of depression. In spite of this, IL-6 and TNF α levels were not significantly modified in patients versus controls. (10) Also in 1999, Hack et al. tried to include risk factors for depression like advanced age, smoking, increased BMI and personal history of infection into a similar study. The results were disappointing, as no evidence of alteration in serum interleukins and pro-inflammatory proteins for 361 depressed patients versus 61 controls was shown. (11) This study was contradicted later in the same year when Anisman demonstrated an increased interleukin-1 β level in dysthymia and unipolar depression, statistically correlated with onset and disease duration. (12) But in 2001, a study on patients with melancholic depression didn't show an increased production of IL-1 β compared to healthy controls, the only pro-inflammatory increased cytokine being the α -2-macroglobulin with a high monocyte level, but in patients with depression without melancholic features. (13) Experimental studies were much more prolific regarding the confirmation of macrophage and neuroinflammatory theory in depression. It was observed that antidepressant treatment, regardless of pharmacologic class, determines the amelioration of behavioral characteristics and neuroendocrine effects associated to immune activation. A better response was obtained for tricyclic antidepressants and tianeptine compared to selective serotonin reuptake inhibitors. (14) Antidepressants also ameliorate the lack of equilibrium between the lymphocyte arm and the macrophage arm of

the immune system, and between the secretion of anti-inflammatory and pro-inflammatory cytokines in the brain. (15) In spite of this, clinical studies didn't show such good results regarding the decrease of pro-inflammatory cytokine level during antidepressant treatment compared to experimental studies, further investigations being necessary. Animal models for depression were created, a modification of the cytokine equilibrium in the brain being proved. In mice, medium intensity chronic stress was associated with the increased production of IL-1 and 2 and the decreasing activity of natural killer cells. (16) Connor et al demonstrated an attenuated cytokine pro-inflammatory response to lipopolysaccharides in bulbectomized rats, effect accentuated during chronic treatment with desipramine. (17) Schmidt et al. showed that exposure to IL-1 induced the increased sensitivity of adrenocorticotrophic hormone secretion through increasing the number of secreting neurons in the paraventricular nucleus of hypothalamus, which determines the activation of hypothalamic- pituitary axis. This process causes the persistence of hormonal stress response in the organism for many weeks after the stressor factors disappeared. (18) In conclusion, the hypothalamic- pituitary feedback system is also affected in depression.

NEUROINFLAMMATORY HYPOTHESIS OF DEPRESSION

Exogenous administration of pro-inflammatory cytokines in laboratory animals determines a disease-modified behavior (neurovegetative basis): asthenia, fatigability, muscle weakness, malaise, food refusal and somnolence, associated with depression symptoms like anhedonia and social withdrawal. Neurovegetative symptoms predominate, leading to disease modified behavior (19) while administration of IL-1 in human subjects leads to similar symptoms, the ones that are common both clinically and experimentally being food refusal and nyctohemeral rhythm alteration. (20) All of these symptoms are due to excess activation of some branches in the immune system, which leads to a lack of immune equilibrium in the organism. Administration of α -interferon in patients with chronic hepatitis leads to fatigability as the main symptom. Fatigability was also associated with increased pro-inflammatory markers in patients with ischemic heart disease. (1) In animals, anhedonia is only induced by administration of IL-2, no results being obtained for IL-6 and IL-1 β . (21) So, a new type of depression needs to be added as diagnostic formulation: the one induced by cytokine treatment, which is more obvious in treatment for cancer, chronic hepatitis and autoimmune diseases. Pro-inflammatory cytokines do not only induce somatic and psychiatric symptoms characteristic to depression, but also cognitive disturbances. This fact was demonstrated in patients treated with IL-2 and α -interferon in cancer, nyctohemeral rhythm alteration being added to the lack of concentration capacity and decreasing memory. The chronology of symptom apparition differs according to treatment modality, but cognitive and neurovegetative symptoms appear very early (generally from the first week) for IL-2 treatment and later, after 4-8 weeks for interferon treatment. Delaying of symptom apparition during interferon treatment led to a promising study:

administration of paroxetine for depression prophylaxis in patients treated with α -interferon prevented the apparition of depressive symptoms. In spite of this, paroxetine wasn't efficient in the amelioration of neurovegetative symptoms, the most persistent being fatigability. (22) Alongside IL-2 and 2, IL-6 is a very well studied cytokine, as it represents a predictor factor for cardiovascular diseases and osteoporosis, its level being also high in depressed patients. Secretion of IL-6 is activated by the sympathetic neurovegetative system through β -adrenergic receptors, which makes it an important activator for the sympathetic vegetative system but also for the hypothalamic- pituitary axis. This cytokine is also a stimulator of the acute phase hepatic inflammatory response, increasing the pro-coagulating factors and platelets expression and endothelial cells activation, which makes it an important cardiovascular risk factor. IL-6 and IL-1 β are activators of modified disease behavior (lack of motivation, social withdrawal, somnolence, fatigability an diffuse somatic manifestations- muscle and articular pains, headache). The peak of IL-6 secretion is between 1 and 5 am, the lowest secretory activity being registered also in the morning, between 8 and 10 am. (1,2) Alesci et al. show that the pattern of IL-6 secretion is modified in depressive patients, a new peak appearing in the afternoon, with persistent increased IL-6 levels during the day. Also, the morning level of IL-6 was increased in depressive patients compared to controls, while no circadian cortisol rhythms modifications were registered. The peak of IL-6 secretion in depressive patients was detected in the morning, with the lowest level during sleep hours, this pattern being completely different from the normal secretion pattern of this interleukin. The same modifications were demonstrated for chronic insomnia and sleep deprived healthy individuals. The morning secretion peak of IL-6 in depressive patients predisposes them to a 2-3 fold higher risk of cardiovascular premature pathology, compared to the non-depressive patients because it maintains an inflammatory pro-thrombotic status in the organism. (26) The most extensive and cited meta-analysis was published in 2010 and it included 24 clinical trials, studies that measured the following markers in both serum of patients and controls: TNF- α (n=13 studies), IL-1 β (n=9), IL-6 (n=16), anti-inflammatory IL-4 (n=5), IL-2 (n=5), IL-8 (n=4), anti-inflammatory IL-10 (n=6), IFN- γ (n=4). High levels of TNF- α and IL-6 were obtained. For the other markers, no significant high values or differences were recorded compared to controls, neither for IL-1 β , a very high studied cytokine in experimental trials, with major increases in laboratory mice with similar symptoms to major depression. (27) TNF- α and IL-6 are acute phase proteins which are secreted when the organism is confronted with an immunological aggression, their high level outside an inflammatory status, infectious or traumatic being considered abnormal. (28) IL-6 is secreted in the periphery by macrophages and natural killer cells and it stimulates the macrophages' pro-inflammatory cytokines and prostaglandin release. (27) It is stated that an increasing of pro-inflammatory cytokines has pathologic effects on the brain, affecting the neurogenesis, fact observed in laboratory animals not only in depression but also in schizophrenia. The most affected structure in depression is the hippocampus, whose volume is reduced, being proved that an increased IL-6 at this level

activates the microglial cells, which promote an anti-neurogenic signal. (29) An anti-proliferation activity upon progenitor neuronal cells was also proved for TNF- α and it's activity on the TNF 1 receptor. (30) Therapeutically, it was demonstrated that selective reuptake serotonin inhibitors might have a neurogenic effect by increasing the expression of BDNF, which maintains the proliferation and survival of progenitor neuronal cells. (31) IFN- γ , TNF- α and IL-6 determine the increased expression of indoleamine 2-3 dioxygenase (IDO), both in the central and peripheral nervous system. This enzyme degrades tryptophan, a precursor of synthesis for serotonin and melatonin, which can lead to depressive symptoms and circadian rhythm alterations. Kynurenin, a metabolite of tryptophan, and quinolinic acid, a metabolite of kynurenin, also have a negative effect upon hippocampal neurogenesis. Quinolinic acid is a NMDA receptor agonist, which perturbs the glutamate neurotransmission, increasing excitotoxicity in hippocampal neurons, which leads to apoptosis and decrease of hippocampal volume, leading in the end to major depression. (33) Given the numerous proofs of neuroinflammation in depression, more studies were made regarding the effect of anti-inflammatory agents in depression, preliminary studies having good results for patients treated with rofecoxib. (34) Another double blind, placebo-controlled randomized study, made on major depressive patients treated with reboxetine and celecoxib obtained a more important amelioration of symptoms compared to patients treated only with reboxetine. (35)

MECHANISMS OF CYTOKINE- INDUCED DEPRESSION

The fact that the apparition of depressive and neurovegetative symptoms differs according to the type of cytokine administered and also the fact that some symptoms respond to antidepressants while others don't, suggest that the action mechanisms of pro-inflammatory cytokines are different according to the type of cytokine but also to the cerebral structure vulnerability and personality of the individual. A first hypothesis for depressive symptoms is linked to hypothalamic- pituitary axis modulation by pro-inflammatory cytokines. These cytokines lead to the increased activation of this axis and suppression of negative feedback for glucocorticoids with decreasing of cortisol-releasing hormone (CRH) secretion. (18) It is proven that IL-1 affects translocation on glucocorticoids receptor, which leads to increased resistance for this hormone in some cells. (23) This process affects organism's response to stressor factors by inadequate glucocorticoid secretion, mechanism also involved in neuroinflammation hypothesis in schizophrenia. A second neuroinflammation hypothesis of depression is linked to the chemical neurotransmission in the brain, as it is considered that pro-inflammatory cytokines lead to symptoms similar to depression by decreasing serotonin synthesis. Psychomotor retardation and anhedonia were associated with a perturbed function of basal ganglia due to dopamine synthesis alteration. The decrease in serotonin synthesis is due to it's precursor alteration, tryptophan, it's metabolism being modified by the induction of an enzyme named indoleamine- 2,3-dioxygenase which degrades tryptophan to kynurenine and quinolinic acid, in detriment of serotonin synthesis. (24) Tryptophan metabolism, according to the activity of

the enzymes involved, can take place in two directions: serotonin synthesis or active metabolites synthesis (quinolinic acid and kynurenic acid). Alteration of tryptophan metabolism with increased kynurenic acid synthesis in detriment of serotonin synthesis is considered a critical element in depression etiopathogeny. The equilibrium between serotonin synthesis and kynurenin synthesis from the same element, tryptophan, is controlled by three enzymes: indoleamine-2,3-dioxygenase 1, indoleamine-2,3-dioxygenase 2 (IDO 1 and IDO 2) and tryptophan-2,3-dioxygenase (TDO2). The expression of these three enzymes is regulated by the innate immune system. (42) Alteration in tryptophan metabolism with production of kynurenins in detriment of serotonin was demonstrated both cerebral and peripheral, on laboratory animals treated with cytokines. (24)

This theory was confirmed by studies made on cancer patients on cytokine treatment, these presenting low serum tryptophan levels, correlated with the severity of depressive symptoms and behavior disturbances. The same results were obtained on patients with chronic hepatitis C in treatment with interferon. (25,7) In conclusion, we consider that future clinical studies for neuroinflammation in depression must consider numerous factors like somatic comorbidities and external stressors, both having a major influence upon the immune system but also upon cerebral synthesis of neurotransmitters. Inflammation has to be viewed globally, as it is a pathological state associated with numerous somatic and neurovegetative symptoms (cachexia, muscle weakness, fatigability), representing an important risk factor for cardiovascular diseases.

METABOLIC SYNDROME AND DEPRESSION

Metabolic syndrome is an affection that has a high pro-inflammatory status, associated with a very high risk for cardiovascular diseases. This disease caught the attention of researchers given that 12-36% of patients with depression present an associated metabolic syndrome. Depression influences glucose metabolism and the risk for metabolic syndrome and diabetes in patients with abdominal adiposity, first hypothesis in this direction being launched by Capuron et al. in 2008. (40) Depressive patients present alterations in vegetative system function, which lead to increased pulse, decreased cardiac adaptation to effort and stress, modification in circadian secretion of glucocorticoids and pro-inflammatory cytokines, and hypothalamic-pituitary axis hyperactivity. All these factors prepare the organism for insulin resistance and abdominal obesity, which favor the development of metabolic syndrome. Many pro-inflammatory markers associated with the metabolic syndrome (C reactive protein, TNF- α , IL-6, fibrinogen, leptin, resistin and adiponectin) are increased in patients with major depression (mostly TNF- α and IL-6). A study published in 2010 shows that adiponectin had low levels in patients with depression and metabolic syndrome. A high increase of IL-6 was demonstrated for patients with metabolic syndrome, similar to patients with depression. Increased acute phase proteins were observed in patients with metabolic syndrome but positive variations of C-reactive protein and fibrinogen appeared in depressed patients. (41) So patients associating depression and metabolic syndrome have an important pro-inflammatory

status and a high risk for cardiovascular disease. This study comes to confirm the neuroinflammatory hypothesis in depression, showing that a similar inflammatory status is found in depression and a somatic disease, the metabolic syndrome.

THERAPEUTIC CONSIDERATIONS

In 2009, Yoshimura et al published a study that followed the IL-6, TNF- α and BDNF in patients with major depression treated with SSRI (one group) and SNRI (a second group), versus a control group, giving the fact that SSRI and SNRI are the reference antidepressant classes in depression treatment. The starting hypothesis was that patient's response to treatment could be predicted according to the plasmatic level of pro-inflammatory cytokines. The study included 51 patients with major depression and 30 controls. SSRI group received paroxetine (n=16), sertraline (n=15) and fluvoxamine (n=10). SNRI group received milnacipran (n=10). Treatment for both groups was administered for 8 weeks, pro-inflammatory cytokine dosing being made before and after treatment. High plasma levels were shown for IL-6 and TNF- α in patients with depression, compared to control group and treated group, associated with low BDNF level in depressive patients. IL-6 levels dropped during treatment, TNF- α dropping being less significant than that of IL-6. In patients that did not respond to treatment (regardless the pharmacologic class), IL-6 level was more increased than in the responsive ones, with TNF- α level remaining constant. No difference in BDNF level was observed in patients treated with SSRI versus SNRI. A positive correlation was found between plasmatic IL-6 level and HAM-D score. No correlation between HAM-D and TNF- α was found. IL-6 level was maintained low after 8 weeks of treatment in both treated groups, TNF- α level remaining unmodified. A temporary conclusion would be that plasma IL-6 level could be a predictor for resistance to antidepressant treatment and could reflect the severity of depression. (36) Anti-inflammatory therapy represents an important starting point, numerous studies stating it's efficiency in amelioration of depressive symptoms and fatigability in treated patients. Etanercept and infliximab, both TNF- α inhibitors, had a positive effect upon depressive symptoms in patients treated with monoclonal antibodies for Crohn disease and psoriasis. (37) At this moment there are many studies that follow their efficacy in subjects without autoimmune diseases, but suffering from major depression resistant to treatment. Association of cyclooxygenase inhibitors to antidepressant treatment increases the symptom response, while promising results were obtained with aspirin associated with antidepressants in patients nonresponsive to SSRI. (38) There are also some studies that show other therapies benefits (psychotherapy and physical exercise therapy) in decreasing inflammatory markers. (39)

CONCLUSIONS

Numerous clinical and experimental studies show that neuroinflammation hypothesis became a foundation pillar in the etiopathogenesis of depression alongside the monoamine hypothesis, given the fact that the existence of a pro-inflammatory status was repeatedly proven both in human subjects and laboratory animals. Depression induced by cytokine treatment in cancer and by interferon

treatment in viral chronic hepatitis became a frequent therapeutic entity in the later years, on the opposite pole being important proofs of amelioration in psychic and neurovegetative depressive symptoms with anti-cytokine and anti-inflammatory treatment.

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CASE REPORT - SERTRALINE INDUCED PSYCHOSIS

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Abstract

Mrs. P, was an 18-year-old female adolescent who met the DSM-V criteria for an episode of major depression without psychotic symptoms. The main complaints were depressed mood, loss of interest, irritability, decreased concentration, loss of appetite and weight. She was treated with sertraline 50mg per day and after 2 weeks she developed psychotic symptoms. The patient appeared to

have no known predisposition to psychosis. After discontinuation of sertraline, psychotic symptoms resolved. The emergence of psychotic symptoms, in patients with non-psychotic mood disorders can have future implications for their prognosis.

Key words: depressive disorder; sertraline, induced psychosis

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are the most prescribed anti-depressants and among SSRIs, sertraline is one of most commonly prescribed. Sertraline is a potent inhibitor of neuronal serotonin reuptake, but it also can weakly inhibit the reuptake of dopamine, particularly at high dosages (1, 2). For this reason, sertraline has sometimes been described as a —serotonin-dopamine reuptake inhibitor (SDRI) (3). But, significant inhibition of dopamine reuptake by sertraline at clinical dosages is controversial by experts (4). The clinical implications and significance of this combine serotonin and dopamine increase is not yet clarified.

Sertraline also have a relatively favorable side effect profile which includes nausea, diarrhea, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, and decreased libido. But occasional cases of sertraline induced psychotic symptoms have been reported over the time (5, 6). We report a case of sertraline induced psychosis to a female adolescent patient.

CASE REPORT

Mrs. P, 18-year-old female adolescent came with her mother to an outpatient psychiatric clinic accusing that she cannot maintain her attention at school as she used to do and her grades were much lower than usual. She cannot eat anymore and lost weight (5 kilograms over the last month). She is always irritated and admits that she does not get along with his family anymore and everything seems pointless and cannot find pleasure in anything. During the last two month she didn't socialized as she used to do, argued with her friends and spend a lot of time in house “doing nothing”. She thought about suicide, but she had been too afraid about that.

She had no previous history of psychiatric treatment, suicide attempt, mania or psychosis. She reported an occasionally alcohol use in the last year and no drug use. There was no family history of psychosis or depression. Hematological and metabolic screening revealed no significant abnormalities. Thyroid functions were within normal limits. Any other medical condition was not identified.

Psychiatric examination revealed depressed

mood, anhedonia, loss of appetite and weight, decreased concentration, fatigue and loss of energy, feeling of worthlessness, mild anxiety, symptoms which have been present for at least two month before presenting to the clinic. The symptoms had a significant impact on her overall functioning and were not better explained by physiological effects of a substance or another medical condition. She met the DSM-V criteria for major depressive episode without psychotic symptoms (7).

She was treated in an outpatient psychiatric clinic with sertraline 25mg per day for the first 4 days and then 50mg per day. On the next evaluation after 4 weeks, there was no significant reductions in her depressive symptoms, but she reported auditory hallucinations over the last 2 weeks. She was anxious, agitated and reported difficulties in concentration due to the “voices who threatened her”. Her psychiatric exam revealed also delusional ideas of reference (strangers were watching her and talking about her) and she became more reluctant to attend school. No manic symptoms were observed.

The sertraline was discontinued and olanzapine 5mg per day was introduced. After one week her psychotic symptoms gradually decreased and at the next evaluation, after one month until olanzapine was introduced, psychotic symptoms were completely resolved, but depressive symptoms had no significant improvement. Olanzapine was gradually stopped over the next week and escitalopram 10mg per day was started. Over the next 3 months, Mrs. P depressive symptoms improved significantly. No psychotic symptoms reappeared.

DISCUSSIONS

The appearance of psychotic symptoms after the administration of an antidepressant may have different causes and implications in the future prognosis of the patient.

In some cases, psychosis can be a natural progression of an underlying psychotic disorder (schizoaffective disorder or schizophrenia). Mrs. P has no family history of psychosis or depression but she must be followed up for as much as possible throughout the course of her affective

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Received April 24, 2017, Revised May 30, 2017, Accepted July 19, 2017

disorder.

Bipolar disorder often presents initially with one or more episodes of major depression with or without psychotic symptoms and the first episode of mania or hypomania may appear during treatment with an antidepressant. Mania can easily resemble psychosis in some cases. DSM-5 now consider that elevated mood induced by antidepressant can justify the diagnosis of bipolar disorder. This switching is particularly common among juvenile and young adults exposed to treatment with an antidepressant (8). However, clinical presentation of our patient was not suggestive for a manic episode, but follow up is necessary to exclude the emergence of mania at a future date and consequentially a change of diagnosis.

Psychotic symptoms following administration of an antidepressant may be due to an underlying medical condition, which was not yet identified or didn't express itself. Withdrawal from a psychoactive substance or use of a psychoactive substance may be implicated. Our patient denied any psychoactive substance use and any other medical condition was not identified.

Another possible cause of psychosis in a patient receiving antidepressant medication is pharmacokinetic interaction with other drugs the patient is taking. The possible interaction can be extensive. In our case, the patient only received the antidepressant.

In our patient the appearance of psychotic symptoms following administration of sertraline and their immediate disappearance after its discontinuation may suggest that sertraline induce the psychotic symptoms. No psychotic symptoms reappeared over the next 3 months.

However, sertraline was not reintroduced to patient and escitalopram was administrated for the following months. Follow-up of the patient for an extended period of time will be necessary in this case.

The mechanism by which antidepressants (in our case sertraline) may lead to psychosis is still unknown and future investigations will determine their role. A caution approach may be necessary in starting antidepressant in a new patient with depression if one or more of the above clinical factors are present.

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THE XTH NATIONAL CONFERENCE OF BIOLOGICAL PSYCHIATRY AND PSYCHOPHARMACOLOGY. CRAIOVA, MARCH 22-25, 2017

Abstracts

ORAL PRESENTATIONS

ROLE OF NEUROPROTECTION IN THE PRESERVATION OF THE COGNITIVE RESERVE IN ALZHEIMER'S DISEASE

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The pathogenesis of Alzheimer's Disease assumes two models. The first involves the genetic spectrum and is characterized by early onset and rapid cognitive decline. The second relies on a pluri-factorial vulnerability, where the role of genetic factors is emphasized by vascular and metabolic dysfunction and the collapse of the neurobiochemical transmission. Clinically, the latter is characterized by the late onset, while cognitive impairment depends on the preservation of cognitive reserve, which, in turn, is tightly interdependent with the vulnerability factors mentioned above.

Unquestionably, the progression of dyscognitive and deteriorative elements is enhanced by the interference of dysprotective evolutionary moments and consequently, the cognitive structures and brain functioning lose the capability of defense against the neurodegeneration.

In this context, the premorbid psychiatric disorders involving a multi-systemic pathogenic model, especially elderly depression, have a particular dimension.

Keywords: neurodegenerative model, multifactorial vulnerability, vascular dysfunction.

SCHIZOPHRENIA AS A DISORDER OF THE SELF

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Schizophrenia has ever been an ill-defined concept, a hardly categorized mental disorder in a certain nosological group. In both clinical practice and in the research area we have been used an operational definition of schizophrenia that includes descriptive and a theoretical criteria from Diagnostic and Statistical Mental Disorder (DSM), actually DSM-5.

However, extensive studies in the area of schizophrenia highlighted “self-disordered” anomalies, more precisely one of “self” categories, the “minimal self”. Loosening the self-unity leads to different bizarre feelings relating to body functions, temporality, “not being in the world” and

the Schneider's “first rank” symptoms.

The “self” structures that have been emphasized by the cranial nuclear magnetic resonance (cranial NMR) at healthy subjects contain fronto-temporo-parietal neural circuits. These studies showed cortical structures implicated in “sense of self” elaboration as ventral medial and dorsal medial prefrontal cortex, anterior and posterior cingulate cortex, superior temporal sulcus, inferior parietal cortex.

In schizophrenia, in a resting state NMR studies demonstrated an aberrant functional connectivity in the prefrontal cortex and between the medial prefrontal cortex and posterior cingulate cortex. Although, in the recent years, in schizophrenia have been many evidences of neural circuits alterations in spite of unclear mechanisms relating to psychosis and other anomalies.

Keywords: schizophrenia, self, minimal self.

NEUROVASCULAR LANDMARKS IN THE EVALUATION OF THE ORGANIC LESIONS OF THE DENTATE GYRUS AT THE PATIENTS WITH SUICIDAL BEHAVIOR

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In this paper, we try to follow the neuro-vascular correlation from gyrus dentatum (the dorsal extension of hippocampus), in cases of death by mechanic asphyxiation after hanging.

After autopsy we have taken hippocampus fragments from people between 16 and 85 years old. The fragments were processed by hematoxylin and eosin technique.

Besides neurovascular changes related to age, particularly atherosclerotic changes, we found also perivascular neurolysis in dentate gyrus.

The role of paleocortex in affective and emotional behavior and also in memory is well known. From paleocortical structures, the hippocampal complex has a different structural and functional dynamics in ontogenesis. According to this information, we consider that these associated lesions are not random.

In conclusion, the study of the hippocampus is a first step for a new research of the pathogenesis of neuropsychiatric symptoms.

Keywords: dentate gyrus, hippocampus, hanging, vascular genesis.

THE ROLE OF THE PSYCHIATRIST IN THE PSYCHIATRIC FORENSIC EXPERTISE

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In Romania, the forensic expertise is institutionalized, forensic institutions being the sole provider of medical evidence for justice. Given that expertise offers fundamentals for establishing criminal or civil liability, this activity is carried out only in boards of expertise. Both forensic doctors and psychiatrists have the status of official experts when appointed to perform forensic work. Tasks of the members of the forensic psychiatry board are distinct, both individual and common ones. Irrespective of the individual responsibilities thus not only the one who drafted the report, the legal responsibility is individual for each board member. By signing the report by all its members, it acquires legal force of evidence, subject to all legal provisions in this regard.

Keywords: forensic expertise, expert, board, responsibility, competence.

PTSD – VICTIM SYNDROME – COMPLEX POST TRAUMATIC STRESS SYNDROME – SPECIAL PSYCHOTRAUMATOLOGY – VICTIMOLOGY. PSYCHIATRIC FORENSIC PARTICULARITIES

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Introduction: European Commission recommends precise attention to all causes involving psychotraumatology's and victimology's particulars. This report shows a meta-analysis that can be applied in many psychiatric-forensic issues by offering an important contribution in solving lots of cases about granted privileges and not only.

Discussions: The report starts from the limited experience on this subject in our country that leads to many wrong ways of medical approaching and legally approaching also.

The authors specify/mark the necessary notions about a forensic expertise and its subject – the victim: psychotraumatology, victimology, psychotrauma/psychotraumatic experiences, reaction, forensic reactions, psychotraumatic process, post-trauma status, predisposition, biological substrate, primary victim, secondary victim, direct/indirect consequences, short/ long consequences.

Through criteriological delimitation of Posttraumatic Stress Syndrome from Complex Posttraumatic Stress Syndrome are outlined forensic expertises' dilemmas.

Conclusions: In our current socio-historical context, psychotraumatology and victimology's particularities require certain attention and commitment to the way of training the young specialists in psychiatry and forensic medicine.

Keywords: psychotraumatology, primary victim, secondary victim.

NEW PHARMACOLOGICAL APPROACHES IN OBESITY

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Background: Obesity is a frequent comorbidity in psychiatric patients and stands as a major public health problem in many countries. Obesity is associated with higher mortality and lower quality of life, but it also reduces therapeutic adherence and increases the risk for organic complications. Pharmacological substrate of weight gain is related to known mechanisms- like H1 and 5HT2C receptors antagonism of several psychotropics, but also to other, largely unknown, biological variables.

Methods: We searched medical databases (MEDLINE, PubMed, Cochrane, EMBASE) for guidelines and expert consensus focused on the pharmacological treatment of obesity issued between 2000 and 2017.

Results: Naltrexone plus bupropion, liraglutidine, lorcaserin, orlistat, phentermine plus topiramate are the current pharmacologic options for the treatment of obesity. According to American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for patients with obesity (2016) potential benefits of these treatments outweigh the risks for the chronic treatment of the disease. The above-mentioned drugs cover a large area of pharmacodynamic properties, from 5HT2C antagonism (lorcaserin), glucagon-like peptide-1 receptor agonist (liraglutide), combination of norepinephrine and dopamine reuptake inhibitor and opioid antagonist (bupropion plus naltrexone), lipase inhibitor (orlistat), to a combination of sympathomimetic amine and a very complex anticonvulsant (phentermine/topiramate).

Conclusions: There are several well-documented options for the pharmacologic treatment of obesity, with various pharmacodynamic mechanisms. These agents should be integrated, according to the guidelines in a life-style therapy and not administered by themselves. Caution should be mentioned regarding specific adverse events and contraindications of each of these pharmacological agents.

Keywords: obesity, endocrinology, H1 and 5HT2C antagonist, glucagon-like peptide-1 agonist, lipase inhibitor, inhibitor of norepinephrine and dopamine reuptake, opioid antagonist.

ALZHEIMER'S DISEASE – MOLECULAR BIOLOGY AND NEUROPATHOLOGY

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Alzheimer's disease is the most common and most important degenerative disease of the central nervous system, harboring a huge social impact. Approximately 50% of all people aged over 70 years suffer from this disease. If mild and insidious impairment of cognitive

function is usually the most common form of disease onset, ultimately it evolves towards a generalized collapse of the brain function.

From the moment when Alois Alzheimer, a Bavarian psychiatrist presented for the first time the clinical and neuropathological features of the presenile dementia in a patient of 51 years old, describing in 1906 senile plaques and neurofibrillary tangles, it began the controversy that continues to persist even today in the study of the pathophysiology of Alzheimer's disease. Recently, there were developed transgenic animals expressing the mutations that cause the disease in humans and these animals also develop a resembling neuropathology. The disease is characterized by the presence of suggestive morphological abnormalities and of a variety of associated pathologies. This spectrum of changes is dominated by the presence of the amorphous material called "amyloid" stored almost anywhere in the parenchyma and neurofibrillary tangles, made of microtubule-associated tau protein aggregations in the neuronal bodies and neuronal extensions.

Although A β peptide has been identified as the main component of amyloid plaques, the conditions responsible for their aggregation in the brains of the patients are not yet fully understood.

This presentation aims to review the main morphopathological data, molecular biology and genetics of Alzheimer's disease.

Keywords: Alzheimer's disease, amyloid plaques, morphopathology.

PULMONARY THROMBOEMBOLISM IN A PATIENT RECEIVING PALIPERIDONE - A CASE REPORT

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Antipsychotic treatment, both typical and atypical, has been linked to higher risk of venous thromboembolism, including PTE, which is potentially fatal cardiovascular disease. Clozapine was associated with the highest risk of VTE, followed by ziprasidone, olanzapine and risperidone [3], while aripiprazole and quetiapine were not found to increase the risk.

Experimental studies have shown that paliperidone led to changes in the serum levels of coagulation factors VIII and IX in rats. Therefore, paliperidone may be causing thromboembolism in a dose-independent manner.

We would like to report the case of a 44-year-old woman, sound editor, single, who was admitted to our hospital for a first episode psychotic disorder. Treatment with paliperidone (6 mg/d) was initiated, and the dose was increased after 3 days to 12 mg/d, leading to partial resolution of the psychotic symptoms. The patient had a history of total hysterectomy due to endometriosis 6 years ago and consumed 25 cigarettes per day, but had interrupted smoking when admitted to out hospital. After 3 weeks of treatment, the patient was referred to the department of cardiology with complaints of thoracic pain and hemoptysis. Based on the results of computed

tomographic thoracic angiography and plasma D-dimers level, the diagnosis of PTE was established. Standard anticoagulant treatment was started and the patient recovered immediately. Her paliperidone treatment was discontinued and changed to aripiprazole up to 20 mg/d, but her evolution was not satisfactory. The patient was recently readmitted for a suicide attempt, in the context of acute psychotic symptoms.

This case report suggests that clinicians should consider antipsychotic drugs, including paliperidone, as a potential risk factor for PTE. In our patient, this also led to limited therapeutic options for her recurrent psychotic symptoms. Controlled studies are needed to further elucidate this adverse effect and to determine the possible predisposing factors and the biological mechanism involved.

Keywords: pulmonary thromboembolism, antipsychotics, side effects.

MEDICAL ASSISTANCE IN DYING: SPECIAL ISSUES FOR PATIENT WITH MENTAL ILLNESS

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Background: Medical Assistance in Dying (MAID) is now legal in many jurisdictions for competent adults who have intolerable suffering and/or have a terminal illness with a short prognosis. Mental illness can be a source of suffering of these individuals, but it can also affect their capacity to make medical decisions. Clinicians and psychiatrists in particular, need to understand how to assess patients with mental illness who are requesting MAID, to determine the impact of their mental illness on the MAID request.

Methods: Psychiatric disorders can be a primary indication for MAID in parts of Europe, and recent published case series from Belgium and the Netherlands have generated strong responses from the psychiatric community. Patients dying of terminal illness who request MAID often have symptoms of depression or anxiety, but psychiatrists are rarely involved in their care. Medical Assistance in Dying is now legal or will like soon be legal in many jurisdictions around the world. Psychiatric illness can impact a MAID request in many ways: psychiatric illness can be a cause of suffering in patients dying of a physical illness; psychiatric illness may compromise decisional capacity for a patient who is requesting MAID; and in some jurisdictions, psychiatric illness itself can be a primary indication for MAID. Psychiatrist are often not consulted for patients who request MAID, legal or professional guidelines often mandate a psychiatric assessment wherever mental illness is present or suspected in a patient who requests MAID.

Results: There is a currently no "gold standard" method for psychiatrists to assess and document decisional capacity in patients with mental illness who request MAID. The psychiatric community would benefit from clear professional standards in this area, and educational initiatives to help practitioners achieve this standard.

Conclusions: Psychiatrists may be helpful in assessing decision capacity, but documentation of capacity

assessment could be improved. There is a broad need to develop educational resources to train current and future physicians about MAID.

MAID represents an ethical and clinical challenge for psychiatrists in a variety of ways. As more jurisdictions legalize MAID, the psychiatric community will need to be prepared to meet these challenges with robust clinical standards and educational programs to ensure the highest standards of care of patients.

Keywords: active, assisted, euthanasia, mental competency, psychiatry, suicide, voluntary.

NEUROBIOLOGICAL CORRELATES OF SEVERE ANTISOCIAL ACTS IN THE EVOLUTION OF SCHIZOPHRENIA

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The incidence of severe antisocial acts (murder, attempted murder, violence) is correlated by the biological models with the existence of dysconnectivity between frontotemporal and temporal-amygdala structures. Dysconnectivity may be linked to neurodevelopmental abnormalities, or secondary to the inadequate psychotropic therapies, in which the dopamine deficit induced by first generation antipsychotic enhances the glutamatergic activations, determining structural alterations of neurons and astrocytes in the frontal cortex, their dysconnectivity with dopamine controlled amygdala structure.

Early diagnosis and appropriate therapy could be important factors for the prevention of forensic accidents in the evolution of schizophrenia, which would diminish the negative social impacts and mitigation stigma for these patients.

Keywords: dysconnectivity, hyper-glutamatergy, early diagnosis and treatment.

QUALITY OF LIFE AND SOCIAL REINTEGRATION IN SCHIZOPHRENIA

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The concept of quality of life (defined by the World Health Organisation as people's perception of their position in life compared to their goals and system of values, which have accepted and assimilated in terms of the decisions they have to take) and the necessity to quantify it have been as well introduced in the assessment of those diagnosed with major psychiatric disorders.

Constant evaluation of the patient's quality of life has become extremely necessary for the assessment of physical, psychological and social effects of the state of illness, the subjective perception of this state, the effects of the therapeutic process upon everyday life and also for determining the patient's needs concerning psychological and social support during the evolution of this disease.

The tools for assessing and quantifying patients' quality of life and their systematic use helps healthcare providers to

offer the best therapeutic options, to maintain a proper communication with the patient in order to provide better information regarding the possible side effects of the various medical procedures, to monitor the evolution of the disease therefore, efficient healthcare packages can be provided, based on gathered data.

From the point of view of ensuring the quality of life for patients, several studies have shown that one of the targets of the therapeutic management is represented by the social reintegration of the mentally ill patient after an acute episode of illness, frequent or long term hospitalizations having a negative influence upon their decision-making capacity and self-control ability in social context.

Social reintegration has become a major goal in the therapeutic process, being perceived as the time spent by the schizophrenia affected person in the midst of the community, time during which he can ensure his primary needs by himself and especially fulfil his social goal seen as a sum of the social function, here including social activity and conduct, drafted and imposed by society and conditioned by the place the individual occupies among the social relations system.

Keywords: schizophrenia, quality of life, reintegration.

ASSESSING VULNERABILITY TO STRESS

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Vulnerability to stress is the increased sensitivity to psychogenic stress agents, characteristic to certain individuals who react excessively, by developing reactions to stress.

Vulnerability to stress is an important premise for the emergence of neuroses, reactive psychoses and psychosomatic diseases.

The objective of the study: the impact of social, biological factors, and psychological types upon the vulnerability to stress.

Material and method: A cross-section study was conducted on a sample of 216 people (112 women and 104 men) aged between 18 and 60 years. These were selected by simple random sampling method on a voluntary basis, freely expressed consent and minimum inclusion and exclusion criteria. The cases were evaluated during the January to March 2016 period, using as independent variables: age, sex, educational level, marital and socio-professional status.

The parameters analyzed were: psychological types (introvert-extrovert); social factors: behavioral factors (smoking, excessive alcohol consumption, energy drinks), lifestyle, social support, income, faith and biological factors (health, weight).

Instruments used: Miller and Smith stress vulnerability scale.

Results: Data were statistically analyzed and the following were found:

1. Depending of the independent variables, vulnerability to stress is higher in women, in people aged between 35 to 49 years and 50 to 60 years, in people with low educational

and socio-professional status; in terms of family status singles are more vulnerable to stress.

2. In terms of the analyzed parameters, introverts with an unbalanced lifestyle, sedentary, without social support, overweight and in poor health are most vulnerable to stress.

Conclusion: An understanding of the concept of stress and knowledge of individual vulnerability to stress may lead to the acquisition of skills for managing stress by changing attitude and lifestyle.

Keywords: vulnerability to stress, psychological types, social factors, behavioral factors and biological factors.

MOBBING. TRAUMATIC POTENTIAL. PSYCHIATRIC FORENSIC STATEMENTS

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Introduction: *Mobbing* concept defines, in mass-media's point of view, psychological harassment at work. From a psychiatric point of view, it exemplifies a specific behavior with a psychologically traumatic effect on a certain person, chosen as victim. Epistemological studies are very few, in our country, practically, missing.

Discussions: *Mobbing's* pathogenic mechanism is a debated problem for getting a particular result of blaming the victim ("blaming-the-victim-solution") and also the consequences of psychotrauma process. Pathogenic mechanisms, pre-clinical and clinical symptoms and medical methods of preventing long-term consequences are demonstrated by meta-analytical studies and reported through the author's clinical cases in her own medical practice. Psychiatric forensic connections (related to law) are the most harmful consequences of 'mobbing'. Without knowing very well the meaning of the concept, there are many unclear conclusions about the main targets of the expertise and their answers, ignoring the psychotrauma.

Conclusions: Till finding the best way of managing the civil cases where jurisprudence is involved regarding psychotraumatology, in general, and 'mobbing', in particular, the author recommends: certain attention and commitment in training the young specialists and a complete analyze of each case, in every forensic report.

Keywords: mobbing, psychiatric forensic expertise.

THE ROLE OF THE HERPES ZOSTER INFECTION IN PRECIPITATING THE COGNITIVE DETERIORATION OF ALZHEIMER'S DISEASE

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Herpes infection has a significantly increased frequency with age, occurring in the elderly amid decreasing of the immune defense capacity. Vulnerability to Zoster infection and its occurrence is considered by some authors as a trigger that for neurodegeneration in Alzheimer's disease within different pathological conditions, and for rapid transition from Syndrome Mild Cognitive Impairment (MCI) to cognitive impairment itself.

Memantine has efficacy on Zoster virus and its neuroprotective and antiapoptotic type mechanisms

suggests a prophylactic possibility on the onset of Alzheimer's disease pathology, by addressing concomitant therapy with memantine and antiviral medication in such patients.

Keywords: viral infection, memantine, anti-apoptotic action.

QUALITY OF LIFE ASSESSMENT DURING PHARMACOLOGICAL TREATMENT IN PATIENTS WITH SCHIZOPHRENIA

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Background: Monitoring of the quality of life in patients with schizophrenia is a very important dimension when social functioning and professional reinsertion are considered as targets of the treatment. Therefore, controlling of positive, negative, behavioral, affective and cognitive symptoms of schizophrenia, defined as main objectives of the current pharmacological treatment in this pathology, should be corroborated with the reflection of these dimensions in the patients' quality of life, as a specific variable.

Methods: Literature research focused upon the psychological instruments created for quantifying quality of life in patients with schizophrenia during pharmacological treatment.

Results: The Short Form 36 items version and the EuroQOL (EQ-5D) are the most widely used instruments in patients with psychiatric disorders, although these instruments were not specifically designed for patients with schizophrenia. These questionnaires have good psychometric properties and their use is supported by large number of clinical trials. Lehman Interview for Quality of Life (QoLI) was developed in 1983 for the evaluation of specific needs and prognosis in chronic disorders in patients who are institutionalized. Therefore, QoLI was studied in patients with schizophrenia and other psychotic disorders, and this instrument is considered to be able to monitor patient' satisfaction in daily life activities, social relationships, relaxation activities, work, financial safety, legal and health problems.

Conclusions: A number of psychological instruments are used for monitoring changes in the quality of life in patients diagnosed with schizophrenia. While some scales are not specific for this population, QoLI is a well-designed, semi-structured, self-administered questionnaire adequate for patients with schizophrenia and sensitive to changes during pharmacological treatment.

Keywords: quality of life, schizophrenia, EuroQoL (EQ-5D) QoLI, specific needs, prognosis.

RECOMMENDATIONS FOR LONG ACTING INJECTABLE ATYPICAL ANTIPSYCHOTICS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Long acting injectable atypical antipsychotics are useful therapeutic instruments in clinical settings, but differences between them are not well-documented in terms of efficacy and tolerability, due to a significant lack of head-to-head randomized clinical trials. No clear-cut recommendations are included in the latest guidelines that could favor one long acting injectable atypical antipsychotic instead of other.

Methods: We search through the available electronic databases for differences between the existing long acting injectable atypical antipsychotics, at pharmacodynamic and pharmacokinetic level, in order to verify if specific recommendations could be formulated for each drug.

Results: Pharmacological properties of risperidone microspheres, paliperidone palmitate 1-month and paliperidone palmitate 3-month administered formulations, olanzapine pamoate, aripiprazole monohydrate and aripiprazole lauroxil were analyzed and specific properties were underlined. There are a number of pharmacological properties of these drugs that should be taken into consideration when specific variables are considered, like special populations (d.e. renal or hepatic failure), comorbidities (d.e. obesity, metabolic syndrome), individual sensibility to extrapyramidal adverse events, life-style impact (sedation, weight gain, sexual dysfunctions etc). Of course, therapeutic adherence is the main argument for these formulations, but no study has yet demonstrated that longer action (d.e. 12 weeks or 6 weeks interval between doses compared to only 2 to 4 weeks) of some of the above mentioned formulations are associated with higher adherence.

Conclusions: A relatively wide range of long acting injectable atypical antipsychotics is available, or for some formulations will be soon available, therefore choosing between them in clinical practice should be based on a careful analysis of drugs' specific pharmacological properties and target population characteristics.

Keywords: schizophrenia, long-acting injectable atypical antipsychotic, therapeutic adherence, specific pharmacological properties.

PHARMACOLOGICALLY-INDUCED PSYCHIATRIC COMPLICATIONS IN PARKINSON'S DISEASE

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Parkinson's disease - complex degenerative, multilesional medical condition - frequently includes psychiatric phenomena in the clinical picture, besides the motor symptomatology. The presence of emotional, cognitive and psychotic changes determining the impact on the quality of life, as well as a poor therapeutic response specific to Parkinson. Given the inter-relationship between Parkinson's disease epidemiology, of risk factors, comorbidities, complex neurophysiologic elements, it is difficult to set the optimal pharmacological management of Parkinson. There are several psychiatric manifestations

induced by the very antiparkinsonian treatment, among which depression, delirium, obsessive behavior. Even if antidepressants, antipsychotics or even medication for the cognitive improvement of the patient, the results are not as desired.

The anticholinergic medication may determine confusion syndrome upon the sudden discontinuation of treatment in emergency or surgical medical situations. Classical antipsychotics (phenothiazines, butyrophenones) decrease the efficacy of levodopa, since they are antagonists of dopaminergic receptors, generally non-selective or with some selectivity on the D2 receptors. From the atypical antipsychotics, olanzapine and risperidone may worsen the parkinsonian symptomatology, while clozapine and quetiapine proved their usefulness in Parkinson patients, with important antipsychotic effects without worsening Parkinsonian symptomatology.

The wearing-off phenomenon of the levodopa treatment may be confused with side effects of antipsychotic medication. The dopaminergic medication may induce several psychiatric symptoms included in the Parkinsonian psychosis. This is more frequent in elderly patients, with more advanced stages of the disease. Anticholinergics and amantadine are among the antiparkinsonian agents that can induce psychotic phenomena after levodopa therapy, but also dopaminergic agonists and selegiline. Management of Parkinsonian psychosis consists of reducing or eliminating the antiparkinsonian medication in the following order: anticholinergics, amantadine, MAO-B inhibitors, dopaminergic agonists and COMT inhibitors. Levodopa will remain the last, its dosage to be reduced to the minimum ensuring the motility of the antipsychotic treatment. The treatment can be done with clozapine which has a multi-receptor action mechanism, with an efficient minimum dose of 25 mg/day, in one administration. Quetiapine can also be administered, which is less effective than clozapine, but it lacks major side effects. Benzodiazepines can be used also for short periods in acute episodes.

Keywords: antipsychotics, Parkinson's disease, psychiatric complications.

DEPRESSIVE DISORDER IN MULTIPLE SCLEROSIS

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Multiple sclerosis is a neurodegenerative disease that associate multiple psychiatric comorbidities, the most frequent being depressive disorder in its prodrome and cognitive impairment in the late stages of the evolution.

Studying the relationship between depression and multiple sclerosis is bidirectional, depression could be prodromal, and through its pathogenic cellular mechanisms emphasizes the progression of specific type elements (plates of demyelination due to the rise of the pro-inflammatory phenomena type and of the cytokine-type aggression) or depression subsequently to cortisonic medication in high doses, phenomenon that favors hippocampal atrophy and the onset of the deteriorative type elements. Anticholinergic antidepressants may

enhance cholinergic blockade on the cognitive circuits, enhancing the neurodegenerative mechanisms. Depression may take an organic type in the moment when the development of demyelinating plaques in the frontal cortex is excessive, by setting up an apathy-aboulia form with intense anhedonia, indistinguishable to decrease of cognitive processes. Therapeutic resistance of depression in multiple sclerosis can be a clinical marker for poor evolution with multiple plaques and frontal-hippocampal dysconnectivity.

Early diagnosis of depressive disorder and the use of neuroprotective medication along with cortisone therapy can ameliorate the evolution of the neurodegenerative process, increasing the patient's quality of life and improving the functional evolution of the disease.

Keywords: frontal-hippocampal dysconnectivity, hypercortisolemia, cognitive impairment, anhedonia.

MOTIVES AND METHODS FOR SUICIDAL ACTIONS IN CHILDHOOD AND EARLY ADOLESCENCE

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Aim: Presentation of data on suicide attempts and completed suicides among children in Bulgaria for a seven-year period 2009-2015.

Methodological approaches: Our study adopted the standard approach to suicide registration in Bulgaria: information for each case of proven suicide is entered into two specially designated documents developed and approved by the Ministry of Healthcare – “Suicidal act notification” and “Suicidal act chart”. All collected notifications and charts are processed by the regional inspectorates of the Ministry of Healthcare and by the “Mental Health” department of the National Center for Public Health and Analyses. The results are then entered into a software product allowing detection and removal of duplicate data.

Main results: Leading methods of suicide are self-poisoning and cut with stab within girls and among boys self-poisoning and hanging. Leading reasons for self-destructive actions are conflicts with parents and unrequited love.

Conclusion: Suicide remains the most important issue in public and mental health with strong cultural, ethnic and socio-economic determinants. Each of the age groups is characterized by features that allow specific preventive measures in this area.

Keywords: attempts, suicide, children, motives, methods.

CARDIOVASCULAR PATHOLOGY IN MAJOR PSYCHIATRIC DISORDERS - MYTH OR REALITY?

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The relative high incidence of sudden death occurred during antipsychotics or antidepressants therapy suggests an important component of acute cardiac pathology

(myocardial infarction, severe rhythm disorders) whose reality is questionable, with two points of view:

▪The existence of cardiac diseases as side-effects of psychotropic therapies - cardio-metabolic syndrome, diabetes and obesity, with the causal relationship between cardiovascular and psychiatric disorders conditioned by the dysmetabolic vulnerability induced through D2 or H1 type receptors blockade. In this first assessment, it becomes important to select the patients and to individualize the pharmacological therapies, based on the pharmaco-genomic predictive factors highlighted by their family history, and strictly monitoring of these patients.

▪The second variant is linked to abnormal neurodevelopment (prenatal dysmetabolic or infection type pathologies, obstetrical trauma with asphyxia and hypoxic hyperglutamatergic encephalopathy) and it is constantly associating vulnerabilities in the coronary vessels (abnormal neurodevelopment of them), with an evident predisposition in various myocardial pathologies, or association with genetic spectrum of the DiGeorge syndrome (22q11.2 deletion), in which the schizophreniform type pathology is associated with congenital heart abnormalities.

Neurodevelopmental abnormalities, according to the precocity of installation of prenatal aggressive factors, can lead to congenital defects, some severe, evident from birth, others less expressed, unknown and ignored, such as Botallo foramen or myocardial fiber changes and junction with the specific excitation system represented by ion channels.

Keywords: abnormal neurodevelopment, 22q11.2 deletion syndrome, hypoxic hyperglutamatergic encephalopathy.

PERSONALIZED MEDICINE AND PSYCHOPHARMACOGENOMICS

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Background: Although not a very new concept worldwide, pharmacogenomics seems quite far away from clinical psychiatric practice in our country. Determinations for CYP450 genotype, specific receptors and transporters genetic variants, but also for specific genetic diseases that could impact recommendation of some psychotropics could be useful in clinical settings, in order to increase the response rate and to reduce the risk of adverse events.

Methods: Literature analysis for detecting possible applications of pharmacogenomics in clinical psychiatric setting.

Results: Laboratory kits for CYP2D6 and 2C9/2C19 genotyping were found, and trials that correlated these genetic variants with clinical response were detected. Analysis of serotonin transporter gene is also correlated with clinical response to serotonergic antidepressants, although the available results are contradictory. 5HT2A and 2C receptors were correlated with various adverse events and clinical effects, therefore further studies for clarifying their genetic variants in relation to drug reactions and psychopathology are needed. Determination

of mitochondrial disorders caused by DNA polymerase Y gene (POLG) is important for prevention of valproate induced liver failure and death.

Conclusions: The path to a personalized psychiatry is still far from being clear, but several milestones are identified, and some important steps could be made in the near future. Pharmacogenetics could offer the key to identify the population at risk for non-response (due to lower blood concentration through metabolic enzymes hyperactivity), toxic reactions (based on higher concentrations, secondary to lower acting CYP enzymes) and other types of adverse events.

Keywords: genomic pharmacology, transporters, pharmacogenetics, CYP2D6, CYP2C9, CYP2C19.

AUGMENTING SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN CASE OF PARTIAL RESPONSE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Background: Partial therapeutic response to selective serotonin reuptake inhibitors (SSRI) is, unfortunately, quite often detected in clinical practice. Faced with the dilemma “switch or augment”, the clinician should analyze all possible causes of partial response, like low therapeutic adherence, multiple psychiatric diagnosis, organic or toxic interferences, metabolizer genotype status, pharmacokinetic and pharmacodynamic negative interactions, environmental factors, sufficient time for an adequate trial etc.

Methods: Analysis of available data in the literature regarding the efficacy of augmenting strategies in cases of SSRI-partial responders.

Results: Using of buspirone, thyroid hormones, lithium, other antidepressant with a different mechanism of action (like agomelatine, mirtazapine, trazodone, bupropion or venlafaxine), atypical antipsychotic (aripiprazole, olanzapine and quetiapine are the most well studied variants), mood-stabilizer (valproate, lamotrigine or carbamazepine), and benzodiazepine drugs could be tried if patients diagnosed with major depressive disorder have a partial response after 4-6 weeks of maximum tolerated dose of a SSRI agent. Monitoring the adverse events and efficacy is strongly recommended, especially if multiple drugs are concomitantly used, and the duration of the combined treatment should be reduced to minimum.

Conclusions: Multiple options for patients with major depressive disorder partial responders to SSRI are available, and choosing between them is dependent of specific biological and clinical peculiarities, after a careful analysis of factors that could hinder therapeutic response. A close monitoring using psychometric scales is recommended, beside regular clinical observation and structured interview.

Keywords: selective serotonin reuptake inhibitors, therapeutic partial response, major depressive disorder.

INTRANASAL OXYTOCIN AS A MODERN TREATMENT FOR SOME PSYCHIATRIC DISORDERS

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Oxytocin is a nonapeptide hormone which is synthesized in the hypothalamus and is directly projected into other brain areas, where it acts as a neurotransmitter. Recently, several data have suggested that besides the classical roles in parturition and milk letdown, oxytocin could play an important part in the pathophysiology of some psychiatric disorders mainly characterized by impairments in the social functioning. In addition, our group is also lately interested in understanding the role of the oxidative stress in the complex effects mediated by oxytocin at the central level in the aforementioned neuropsychiatric disorders.

Keywords: Oxytocin, neuropsychiatric disorders, oxidative stress.

RISK OF DEMENTIA IN PERITONEAL DIALYSIS PATIENTS COMPARED WITH HEMODIALYSIS PATIENTS

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Cognitive disorders are common in dialysis patients and are associated with significant morbidity. The frequency of these disturbances grows and continues to affect various areas of patient care, such as adherence to treatment and quality of life. The most frequently affected is executive function, essential for planning and carrying out tasks. The impaired executive function is associated with increased mortality.

Although it is known that chronic kidney disease causes dementia, there is also evidence that hemodialysis may accelerate cognitive decline.

The cohort studies that use the data from the US medical database system, report that people with chronic kidney disease stage 5 using hemodialysis have the highest prevalence of dementia and the incidence of dementia for people undergoing hemodialysis is 3 times higher compared with general population.

Studies on cognitive decline for people with peritoneal dialysis are fewer and suggest that the occurrence of dementia is lower for these patients compared to those on hemodialysis.

Initiating treatment for chronic kidney disease stage 5 with hemodialysis with switching from peritoneal dialysis to hemodialysis increases the risk of dementia, in both short and long-term. Patients switching from hemodialysis to peritoneal dialysis have a much lower risk of dementia than those who remain on hemodialysis. These provisions are consistent with the hypothesis that the lack of hemodynamic fluctuations may reduce the risk of dementia in the long term.

Studies conducted on patients with dementia and chronic renal disease highlights the need for clinicians to regularly evaluate cognitive functions on people with dialysis, early

recognition of dementia helping physicians to adapt the treatment to patients' cognitive abilities. Such prospective studies would be required to include the initial MMSE value and cognitive repeated assessments on dialyzed population to confirm that the hemodialysis affects cognition. A standardized measurement of cognitive status could be included on the registration form of chronic kidney disease stage 5 patients providing a measure of cognitive function base for future analysis.

Keywords: chronic kidney disease, dementia, dialysis.

CORTISOL: A CLINICAL AND PARACLINICAL MARKER OF CHRONIC STRESS, DEPRESSION AND ANXIETY

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Anxiety - depressive disorders are often seen as the most common psychiatric condition related to chronic stress. Chronic stress can induce depression and anxiety through alterations of the HPA axis and immune system. The HPA axis and the immune system are related. Regarding the fact, that usually, HPA axis transmitted impulses, would calm the inflammatory reactions, prolonged hyperreactivity of this way would induce abnormal immune responses with the consequences of anxiety and depression.

Is depression leading to inflammation, or is inflammation leading to depression? We can't tell for sure.

The linked mechanism of these two is still unknown, though we can say it can be through a positive - feedback pathway. Depression symptoms can trigger an easily respondent inflammatory reaction, through hormonal changes in HPA axis, resulting in a high sensitivity to infections.

The hormonal response is related to the nature of the chronic stress and with the coping mechanisms of the individual.

Considering the fact that HPA axis is the final way for the most depressive symptoms transmission, new hypothesis are researched regarding the biological aspect of depression. The cytokines response in inflammation is considered. A 24 meta-analysis study of the measured value of seric cytokines, revealed a high level of TNF alpha and IL-6 in depression

Basal cortisol level - is a crude response parameter, in the evaluation of stress reactions. A correlation between plasmatic cortisol levels and psychiatric history exists in the study of stress reactions. Low level cortisol correlated with psychiatric history, resulted in an introverted personality. Whereas low level cortisol with a psychiatric history, lead to an expanded personality, after stress.

Keywords: hypothalamic-pituitary-adrenal axis (HPA axis), cortisol, depression, anxiety, chronic stress.

DEPRESSION AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC KIDNEY DISEASE WHICH ARE IN PROGRAM OF SUBSTITUTE RENAL FUNCTION BY DIALYSIS

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Depression is one of the most common diagnoses in psychiatric practice, having a major impact on patient functionality. The symptoms include: depressed mood for most of the day, fatigue, diminished interest or pleasure, insomnia or hypersomnia every day, decreased appetite and weight loss, diminished ability to concentrate, guilt and devaluation feelings, recurrent thoughts of death, recurrent suicidal ideation without a specific plan or a suicide attempt or a specific plan for committing suicide. In the general population, the prevalence of depression is 10-25% for women and 5-12% for men, which means that some patients entering chronic dialysis have already suffered a history of depression. For these patients, the risk of suffering from depression, after initiation of dialysis, is much higher. Other risk factors for depression in patients undergoing hemodialysis are: female gender, dialysis time, lack of employment and lack of supportive family environment.

It is estimated that about 20% of dialysis patients voluntarily choose to discontinue therapy of end stage renal disease. Age, medical complications and life failures are usually associated with the decision to discontinue dialysis. A recent study has shown that depression is a factor of interrupted dialysis.

Alcohol addiction, frequent hospitalization for substance abuse and the presence of mental disorders were strongly associated with suicide among dialysis patients.

Hemodialysis patients use various strategies to cope with stress factors, related to their disease and treatment procedures. Type coping strategy that uses it also depends on personal experiences, social support system, personal beliefs and resource availability.

Reduced kidney function is associated with reduced levels of business activity. A significant number of subjects folds in work when the program alternates, are initiated renal function. Giving up work is often associated with depression and anxiety, also having a significant impact on the financial support, which becomes extremely limited.

Keywords: depression, chronic kidney disease, hemodialysis.

OBESITY AND IMPULSIVITY IN PSYCHIATRIC DISORDERS: THERAPEUTICAL PERSPECTIVES

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Impulsivity is found in a wide range of psychiatric disorders and is characterized by the inability to resist the urge to engage in harmful behaviors directed towards the self and/or the others.

In addition to that, the most recent studies involving psychiatric patients have not only shown an increased prevalence of obesity among them, but also a neurobiological relationship between metabolic disorders, weight gain and impulsive behavior.

Monoamines and acetylcholine play a key role in the development of mental disorders, but they also modulate

the activity of hunger and satiety centers in the hypothalamus. Moreover, it's been shown that imbalance in the metabolism of ghrelin, leptin and adiponectin is associated with pathological impulsivity and other conditions, such as ADHD, personality disorders and affective disorders. Psychotropic treatments regulate the activity of neurotransmitters in the central nervous system, improving the mental state of the patients, but they may also induce weight gain and metabolic imbalances, the importance of which is often undermined until late stages, when the chances of a successful therapy are also reduced.

Given that obesity and metabolic disorders are associated with elevated morbidity and mortality in psychiatric patients, there is an urgency for prevention and/or rapid initialization of treatments. Furthermore, studies have shown that concomitantly approaching the metabolic and the psychiatric disorders of a patient, using both psychotropic substances and a dietary regimen promise better results than addressing these conditions separately.

Keywords: impulsive behavior, metabolic disorders, weight gain, monoamines, acetylcholine, ghrelin, leptin, adiponectin.

PERSONALITY DISORDERS AND PATHOLOGICAL GAMBLING

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Background: To approach recent developments in the field of personality disorders and their association with pathological gambling or gambling disorder.

Methods: This study covers literature published from 2015 to present time to offer you the possibility of understanding the prevalence rates of common personality disorders among pathological gamblers.

Frequently observed personality disorders in pathological or problem gamblers represent Cluster B disorders. There are reports indicating prevalence of Clusters A and C personality disorders as well. The rates of personality disorders among pathological gamblers reported in these studies align with Hill's guide lines - Strengths, Specificity and Temporality. Biological gradient, plausibility and replicability indicate a strong association between pathological gambling and personality disorders. Studies are predominantly cross-sectional and consistently show that the presence of a personality disorder is associated with gambling severity and early age of onset pathological gambling.

Results: Research on pathological gambling should advance beyond estimating rates of personality disorders and focus on longitudinal research to understand the pathways between personality disorders and onset and severity of pathological gambling. Current research shows consistently high rates of personality disorders among pathological gamblers. There is a need for consistency across studies in the assessment of pathological gamblers and comorbid personality disorders especially in light of changes in the classification of pathological gambling to gambling

disorder in DSM-5.

Conclusions: Pathological gambling is addictive disorder not impulse control any longer. These developments in our understanding of the disorder will generate more ideas for prevention and interventions for the consequences as well as the exposures to this disorder. Research should move beyond estimating prevalence of personality disorders among persons with gambling problems to delineate the interaction of personality disorders and problem gambling resulting in other adverse outcomes.

Keywords: addiction, comorbidity, gambling disorder, pathological gambling, personality disorders.

THERAPEUTIC RESISTANCE IN THE PHARMACOLOGICAL THERAPY OF DEPRESSION

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The existence of a discrepancy between the wide range of pharmacological means of intervention in the therapy of depression and the high rate of incomplete remissions (75%) represents the point of emergence for therapeutic resistance type mechanisms.

Primary therapeutic resistance is associated in most cases with an erroneous diagnosis, being often represented by the traumatic, toxic, infectious, or neoplastic damages of the frontal pole. A particular form of this component is represented by closed head injuries with relatively low intensity, but common in terms of domestic violence. This injury associated cerebral axonal dysfunction.

Within avoided potential diagnosis in therapeutic resistance are blood dyscrasias, liver and kidney function alterations. Also, a particular place is occupied by silent strokes and blood-brain barrier dysfunction. The capacity of therapeutic resistance is directly related to the conservation of neurogenesis in the granular subventricular zone and in the CA1 - dentate gyrus hippocampal area.

Excessive use of antipsychotics associated with antidepressant medication practically destroys the neurogenesis, and the existence of prolactin may be a predictive marker of potential therapeutic resistance.

Keywords: neurogenesis, axonal dysfunction, blood dyscrasias.

CLINICAL AND FORENSIC IMPLICATIONS OF MENTAL ILLNESS IN VIOLENT BEHAVIOR DETERMINATION

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Linking up violent behavior and mental illness has been certified by numerous authors over time. In 1857 dr. John Gray described 49 cases of homicide committed by patients diagnosed with major mental illness. In 1919 Kraepelin presented in his monograph about schizophrenia that in certain circumstances the impulsive actions of the patients may become extraordinarily dangerous. However, there are studies who claim there is no real connection between mentally ill patients and violent behavior and those individuals with serious mental illness are no more dangerous than members of the general

population. Link showed in one of his studies that from 1500 subjects questioned 61% answered that psychiatric patients are more likely to commit violent acts due to their condition. For the past several years a large number of studies in the field of forensic psychiatry confirmed a close relationship between violent offenders a comorbid substance abuse. Recent studies showed causal relationship between mentally ill patients, alcohol abuse and criminal actions such as: physical assault, rape, attempted murder and homicide. This observational study analyses the causal linkage between major mental illness and its type, abusive alcohol consumption or drug usage, and criminal acts considering the following criteria: onset debut, gender, socioeconomic status and clinical risk factors. Today the main objective of forensic psychiatry treatment services is the management of the violent offenders with psychiatric comorbidity which requires a multilevel, clinical evidence based approach to the patient. Psychotherapy, psychopharmacology and occupational therapy are absolutely necessary for obtaining an optimal rehabilitation, prevention of recidivism and stability in social functioning of the patient inside the community.

Keywords: forensic psychiatry, alcoholism, violent behavior, homicide, mental illness.

PHARMACOLOGICAL MANAGEMENT OF DEPRESSION IN ALZHEIMER'S DISEASE

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An important aspect related to the non-cognitive treatment of Alzheimer disease is the management of depression, aimed to alleviate the clinical symptomatology of depression, but also to improve or maintain the patient's life quality. Selective serotonin reuptake inhibitors (SSRIs) are first-line antidepressants, out of which citalopram and sertraline demonstrated significant impact both on psychosis as well as depression, suggesting that these agents might have antipsychotic potential in Alzheimer patients. Improvements were also recorded for aggressiveness, anxiety and excitement.

As second line treatment recommendations go to dual antidepressants such as mirtazapine, venlafaxine or trazodone, while tricyclic and tetracyclic antidepressants (amitriptyline, doxepin, imipramine) should be avoided due to the anticholinergic effects. Trazodone, a serotonergic antagonist and reuptake inhibitor (SARI), is still recommended as first choice in patients with Alzheimer and depression, where symptomatology includes also insomnia or aggressiveness. The treatment of depressive relapses should be done with mood stabilizers, while delirious depression requires lithium salts. Given the Alzheimer specificity, clinical manifestations may appear generated by treatment discontinuation or interruption. Personality or behavioral changes may lead to confusions as for their real cause. It is difficult to state whether this clinical picture is pharmacologically induced or is a relapse.

SSRIs are considered the best alternative in the treatment of depression in Alzheimer, due to the increase of serotonergic neurotransmission by serotonin reuptake

inhibition. Additionally, the safety and side effects profile is highly superior compared with that of tricyclic ones or monoamine oxidase inhibitors. The advantages of not being anticholinergic and not producing orthostatic hypotension recommend these therapeutic agents for a wider use on elderly patients.

It is essential that every patient diagnosed with Alzheimer associated with depressive symptomatology is permanently monitored in order to adequately evaluate the therapeutic benefits, as well as potential side effects or tolerance issues. Treatment discontinuation should be considered in patients with symptomatology decline.

Keywords: antidepressants, Alzheimer, depression.

PHARMACOLOGICAL PRECAUTIONS IN THE THERAPY OF BEHAVIORAL SYMPTOMS IN ALZHEIMER'S DISEASE

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Behavioral and psychological symptoms associated with dementia (BPSD) lead to a poor quality of life and increase of care costs, involving multifactor etiology, with neurobiologic, psychological and social factors. The medication that targets the specific symptoms in the BPSD spectrum should be limited to the situations where other physical causes were identified and treated yet the symptomatology is disturbing the patient and the family, especially after the patient was unsuccessful in applying non-biological strategies (behavioral therapy, environmental adjustment and change, music therapy, improvement of sleep hygiene). Most issues created by antipsychotic therapy were related to cardiovascular or infectious pathology, walking disorders and extrapyramidal effects.

The general principles for pharmacologic management of behavioral and psychological symptoms in Alzheimer's disease are:

1. Clear specification and quantification of target symptoms with issues to allow objective evaluation of medication efficacy; monitoring behavioral symptoms before and after medication.
2. Selection of the therapeutic agent most adequate to the treatment class of a certain symptom of a defined psychiatric syndrome, based on its efficacy for those relevant symptoms and minimum potential of side effects.
3. Initiate administration with small dosage (between 1/3 and 1/2 from the usual initial dose for adults, for example risperidone 0,25 mg twice per day, or 2,5 mg olanzapine per day).
4. Dosage adjustment is done gradually depending on the monitored therapeutic effects and the presence of adverse reactions.
5. In the absence of desired clinical effects, medication is discontinued and another therapeutic method is required.
6. Association of agents, multidrug therapy should be avoided due to interactions between medication. Monitoring of potential drug interactions in terms of pharmacokinetic and pharmacodynamic.
7. Re-evaluation of the therapeutic regimen, both pharmacological and non-pharmacological strategies,

done every three months.

8. Identifying and monitoring comorbid medical diseases, and their therapies.

Keywords: pharmacological management, Alzheimer disease, behavioral symptoms.

ATYPICAL ANTIPSYCHOTICS TREATMENT FOR PATIENTS WITH DEPRESSION

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The research regarding depressive disorder is growing, given the scale of the phenomenon and its consequences socially and financially. It is anticipated that maintaining the current pace of growth in the next century, depression will rank second in the general classification of diseases, the first being located to cardiovascular diseases.

The use of antipsychotics to treat depression has a long history, with many controlled studies that demonstrate the effectiveness. Initial investigations have verified the hypothesis that conventionally phenothiazine antipsychotics have antidepressant activity, either alone or administered in combination with a tricyclic antidepressant. Using this combination lost popularity when registering occurrence of extrapyramidal side effects and the risk of important tardive dyskinesia to a significant percentage of patients. However, remained a first-line indication for patients with psychotic depression where are present hallucinatory or delusional phenomena. The introduction of atypical antipsychotics increased interest in this direction, attitude encouraged by the low incidence of secondary parkinsonism, decreased risk of tardive dyskinesia and reduced impact on cognitive function. Current clinical guidelines recommend that first-line approach combining a classic antidepressant atypical antipsychotic treatment. Atypical antipsychotics can augment the action of antidepressants by blocking 5HT_{2A} receptor. Alpha 2 antagonists have an additional effect and increase the release of noradrenaline.

Psychopharmacology studies suggest that next-generation neuroleptics can have a mood stabilizer activity. There are cases in the literature and studies presented which suggests that risperidone, quetiapine, clozapine and olanzapine may be useful for some patients with affective disorders.

Keywords: depression, atypical antipsychotics, treatment.

COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

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Parkinson's disease is a neurodegenerative disorder that affects over 10 million people, in Romania 70.000 people being diagnosed with this malady. Given the aging of the population and the age prevalence of illness occurrence, early recognition of symptoms associated represents an important aspect of disease management. Although Parkinson's is regarded as a motor system disorder, non-

motor symptoms are common, can occur at any stage of the disease and can affect function and quality of life equally with motor symptoms.

In this category, they are commonly found: sleep disorders, autonomic (gastrointestinal, sexual dysfunction, salivation), sensory symptoms (paraesthesia), neuropsychiatric symptoms (depression, apathy, anxiety, attention deficit disorder).

Cognitive dysfunction is present in 50% of patients with Parkinson's disease, which may present impaired executive function, impaired working memory, attention or language deficiency. Mild cognitive impairment can be present since the early stages of the disease, but being a neurodegenerative disease, it shows progression over time. Dementia is late associated with Parkinson's, with a prevalence of 20-40% and it shows different clinical and neuroimaging aspects from the Alzheimer's dementia. The lack of clear diagnostic criteria and assessment tools make it difficult to identify and treat cognitive impairment.

Keywords: Parkinson's disease, neuropsychiatric symptoms, cognitive impairment, dementia, Alzheimer.

BIO-CHEMICAL AND PSYCHOLOGICAL VULNERABILITY IN SUICIDAL ATTEMPTS

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Trans temporal and transcultural character of suicidal phenomenon raises the question of a possible "irreducible rate" of suicide among humans and etiological suicide dilemma seen as "the price of civilization or of life." In general, medical practice, suicide is often correlated with the anxiety caused by chronic debilitating and incurable or masked depression. To properly assess the patient with suicidal risk, bear in mind the context and polymorphic multifactorial etiology, including both psyche and soma how and socio-cultural dimension.

Suicide is considered to be a rational act, executed by moral reasons, social, religious, philosophical or personal reasons or, conversely, a pathological act that occurs during the evolution of mental illness. The presence in the structure of personality of manifestations explosive impulsive, frequent depressive relapses and low adaptation in family and matrimony facilitates suicidal risk. Suicidal behavior must be addressed and considered in terms of danger. This causes danger vital prognosis and whatever the motivation or underlying pathological structure, material circumstances remain important act of self-harm. All these findings confirm our assumptions that the suicide attempt takes place amid vulnerabilities individual elevated in all fields (bio-genetic, bio-chemical, psychological, cognitive and social), to which can be added a number of contextual factors predisposing. To avoid suicidal behavior is particularly important an early detection of any sign, risk factors for suicide as competent and appropriate psychotherapeutic approach to psychiatric consultation and transfer to a specialized unit.

Keywords: suicidal attempt, vulnerability, risk factors, psyche and soma and socio-cultural dimension.

INFLAMMATION, OBESITY AND DEPRESSION

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The term neuro-inflammation is generally used to describe the immune-related processes that took place in the central nervous system (CNS). The acute neuro-inflammation process that takes place in the CNS are usually in a context dependent situation. The transient inflammatory response is in general protective for the CNS. On the other hand, the chronic inflammation exposure is associated with neurodegenerative disease, affective disorders and possible cognitive degradation. When astrocytes are activated, it increases the IL-1 β , CCL2, PGE2, TNF α , the reactive oxygen species (ROS) and modulates the glutamate level (they can indirectly increase it or take the excess of glutamate from the synapse level and converts it to glutamine that is send back to the neuron), so it acts also on neuromodulation and Blood-Brain-Barrier stability. So, by many intrinsic mechanisms the inflammation acts on neuromediators level, neurogenesis, endocrine factors and obesity and all of these precipitates or aggravates the depression. From the clinical point of view the treatment of depression should take into consideration as add-on therapies the reduction of the chronic inflammation, obesity and endocrine dysfunction.

Keywords: inflammation, endocrine factors, obesity.

POSTER PRESENTATIONS

ORAL HEALTH CARE IN A SAMPLE OF PATIENTS WITH PSYCHIATRIC DISORDERS

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General and oral health are closely connected, with oral health being a part of the general health. There is a large number of somatic diseases such as chronic infections, diabetes mellitus, cardiovascular diseases that can contribute to an impairment of the oral health. Some dietary behaviors such as consuming sparkling beverages, but also smoking and alcohol consumption have a negative influence upon oral health. Other situations associated with impairment of oral health in psychiatric patients are related to the type, the severity and the stage of the disorder, the side effects of the medication, the mood, the motivation and self-esteem, the lifestyle, patient's habits, the lack of information, the social, economical and cultural status. The attitude and knowledge regarding psychiatric disorder that medical team of dental care has, but also the inability and sometimes even the lack of willingness to care for psychiatric patients can influence the providing and the access to oral care services. In this context, we present data concerning caring habits for oral health from a research study on 40 patients with psychiatric disorder sample. Research results are showing that only in 16.7% of the cases the assessed patients presented to a dentist for routine consult, while in almost half of the cases (48.5%) they have presented for dental pain. The data regarding the caring methods used by these patients show that most patients in the research sample are using daily dental brushing, but they are not using

additional caring methods.

Keywords: psychiatric disorders, oral health, dental brushing.

PREDICTIVE FACTORS FOR DEPRESSION IN INFLAMMATORY BOWEL DISEASES

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Background: Inflammatory bowel diseases - ulcerative colitis (UC) and Crohn's Disease (CD) - represents a real problem for public health and impairs the quality of life.

Aim: We aimed to study the frequency of depression in patients with inflammatory bowel diseases.

Methods: The study was performed on 60 patients (28 women and 32 men), with the average age of 46.7 years, diagnosed with inflammatory bowel diseases (21 patients with CD and 39 patients with UC).

Clinical and laboratory data were collected using standardized forms (anamnesis, biological assay - hemogram, inflammatory tests, colonoscopy with biopsy, magnetic resonance enterography for intestinal Crohn disease, etc.) and psychological/psychiatric evaluation.

Patients diagnosed with inflammatory bowel diseases underwent a psychiatric exam consisting in a clinical psychiatric interview and the Hamilton Rating Scale for Depression (HAMD). Then, using multivariate analysis, we identified demographic, biochemical, and endoscopic factors associated with the presence of depression.

Results: The HAMD scores were indicative of depression in 26 patients (43.3%): 2 cases (3.33%) major depression (HAMD>18), 10 cases (16.66%) moderate depression (HAMD = 12-18) and 14 cases (23.33%) mild depression (HAMD = 8-12).

Patients fears have been linked to the risk of job loss or tensions in their families and less to the risk of malignancy in inflammatory bowel disease.

Depressive symptoms were correlated with the severity of diarrhea and the presence of rectal bleeding.

Diarrhea was present in 88.33 % of the patients (95% CI 85–90). In 18.33 % of the patients (95% CI 15–19) diarrhea was severe (more than 10 stools/day), impairing activity.

In multivariate analyses, depressive mood was associated with the following risk factors: age over 50 years, rectal bleeding, severity of diarrhea and a past history of depressive disorder. Other variables such as gender, level of education, luminal extension of endoscopic lesions or the level of inflammatory syndrome - were not predictive factors.

Conclusions: Depression is a common expression in inflammatory bowel disease, significantly impairing quality of life and is correlated with presence and severity of diarrhea and rectal bleeding.

Keywords: inflammatory bowel disease, depression, predictive factors.

THE RELATIONSHIP BETWEEN THE MICROBIOME AND THE BRAIN: MENTAL HEALTH IMPLICATIONS

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Recent international specialty literature and clinical studies have shown that there is a close link between the gut and the brain.

The gut microbiome is composed, mainly, of bacteria, fungi, archaea, viruses and protozoa, and their number could reach as high as 400 trillion. The microbiome mediates a part of the hypothalamic–pituitary–adrenal axis and it is an important component of the immune system.

The communication between the gut and the brain is bidirectional, direct and indirect, occurring through the enteric and central nervous systems, the vagus nerve, the endocrine and immunoinflammatory systems and through

the modulation of neurotransmitters.

The microbiome communicates with the brain through three ways – hormonally, immune system and direct mechanisms. Some of the gut microorganisms can transmit signals to the brain via the vagus nerve by realizing neurotransmitters.

Animal studies have shown that microbiome alterations can produce behaviors related to anxiety or depression. If we take into consideration the theory that depression may be an inflammatory disorder, then the gut could be an important mediator of this disorder. Also, the amount of serotonin in the gut and the microbiome influence on tryptophan, the serotonin precursor, seem to play an important role in mental health.

The relationship between the microbiome and the brain isn't fully understood, but the possibility of being able to alleviate psychiatric disorders through lifestyle changes, like a specific type of diet and exercise, is to be taken into consideration.

Key words: microbiome, brain, gut, depression, neurotransmitters.

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- all financial and material support for this research and work are clearly identified in the manuscript.
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Romanian Journal of Psychiatry and Psychotherapy is recognized in Romanian National Council for Scientific Research in Higher Education, starting with January 2010, at **B+** category

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Romanian Journal of Psychiatry and Psychotherapy is indexed in the international data base **Index Copernicus – Journal Master List**, starting with 2009.

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