Clinical and Biochemical Correlations of Aggression in Young Patients with Mental Disorders

LAVINIA DUICA[1,2], ELISABETA ANTONESCU[1,3]*, MIHAIL PIRLOG[4], TRAIAN PURNICHI[5], JULIANNA SZAKACS[6], MARIA TOTAN[1,7], BOGDAN IOAN VINTILA[3], MIHAELA CERNUSCA MITARIU[1,3], SEBASTIAN IOAN CERNUSCA MITARIU[1,3], ANDREEA STETIU[1,3], GABRIELA BOTA[1,3], ALINA BEREANU[1,3], MARINELA MINODORA MANEA[8]

[1] Lucian Blaga University of Sibiu, Faculty of Medicine, 2A Lucian Blaga Str., 550169, Sibiu, Romania

[2] Psychiatric Hospital Doctor Gheorghe Preda Sibiu, 12 Doctor Dumitru Bagdazar Str., 550082, Sibiu, Romania

[3] Sibiu County Emergency Clinical Hospital, Romania, Sibiu, 2-4 Corneliu Coposu Blvd., 550245, Sibiu, Romania

[4]University of Medicine and Pharmacy of Craiova, Faculty of Medicine, 2 Petru Rares Str., 200349, Craiova

[5]Hospital of Psychiatry, Prof. Dr. Al. Obregia, 10 Berceni Road, 041914, Bucharest

[6]University of Medicine and Pharmacy Tirgu Mures, Faculty of Medicine, 38 Ghe. Marinescu Str, 540139, Tirgu Mures, Romania

[7] Clinical Pediatric Hospital of Sibiu, 1-3 Gheorge Baritiu Str,550178, Sibiu, Romania

[8] Iuliu Hatieganu, University of Medicine and Pharmacy, 8 Victor Babes Str, 400012, Cluj Napoca, Romania

Hyperdopaminergia has been identified at impulsive or psychotic patients, the polymorphism of COMT or other enzymes that metabolize dopamine could be involved. The deficiencies of the serotoninergic system in suicidal behaviour has been mentioned by many studies that indicate the reduction of 5-HT, 5-HIAA in CSF or 5-HTT polymorphism. Young patients with psychotic or depression symptoms manifest, frequently, aggressive and self-harm behaviour. Besides the association between the young age and the aggressivity of the patients with serious mental disorders, our study shows gender differences and this matter is sustained by hormonal factors. The study was conducted at the Gheorghe Preda Psychiatric Hospital in Sibiu. The study comprises 52 patients aged between 18 and 35 who were diagnosed with the diagnosis of Schizophrenia, Bipolar Affective Disorder, Depressive Episode and Major depressive disorder according to the DSM-5 criteria. Evaluation of the severity of psychiatric and depressive symptomathology were assessed with Brief Psychiatric Rating Scale and Beck Depression Inventory; aggression and self-aggression in the patients with Schizophrenia, respectively with Bipolar disorder, depressive episode and Major depression disorder were assessed with Buss Perry Aggression Questionnaire and Suicide Intent Scale. Regarding the severity of aggression in the young patients from our study (Buss Perry scale score), male gender is higher than female gender: higher percentages in males (35% and 10%) than in females (16 and 0%). Determining aggression in schizophrenia is possible due to COMT polymorphism that lead to impulsivity or psychotic symptoms. The study show a significant positive correlation between the severity of symptoms of schizophrenia and aggression. From the analysis of the severity of depression in young patients (SIS score) it is noted that its severity is higher in the female gender. Women had higher scores of moderate depression (58%) and severe (26%) than men (37 and 25%, respectively). This relationships could be possible due to the polymorphism of the gene encoding the 5-HTT serotonin transporter related with serotonin deficiency.The study do not show a significant positive correlation between the severity of the depressive symptomatology and the degree of the suicide intent.

Keywords: aggression, depression, young patients, biological marker, mental disorders

The vast majority of people with mental disorders (about 90%) are non-violent [1], however, statistics show an increased risk of violence among individuals with a mental disorder compared to the general population [2]. A comprehensive retrospective of a total of 20 studies has shown that general aggression in psychosis and, in particular, in schizophrenia is found to be 4-5 times higher than in the general population, and the homicide rate was 14- 25 times higher [3]. Moreover, most violent behaviours occurred during the first episode of psychosis [4], that is, on the onset of schizophrenia, which usually takes place in the first years of youth. A proportion of 20-40% of young patients showed aggressive behaviours before being presented in mental health services. The aggressivity is one of the main feature at young patients, in comparison with elderly patients whose the core feature is the cognitive deficit, the most important predictor of the social functioning [5].

One way to classify the aggressive behaviours is a dual-model category as: premeditated and impulsive aggression [6]. Impulsive aggression is generated by multiple brain systems and is highly associated with the comorbidity with many disorders [7] like drug abuse, schizophrenia and bipolar disorder [8]. In contrast, instrumental aggression refers to harm another, using social cues [9] and is mainly seen in psychopathy [10]. Instrumental aggression is related to cortical structures, while impulsive aggression is mediated at the level of the hypothalamus and limbic system [11].

Aggressive behaviour in patients with schizophrenia or other mental disorders implies high costs for the patients themselves, for the family, the healthcare staff and for society in general. For the patient, the aggressive behaviour is associated with prolonged hospitalization, with difficulty of integrating the patient in community, in safety conditions and with a negative prognosis of the disease [12]. Otherwise, aggressive behaviour can cause physical injuries to medical staff [13] and decreased work satisfaction, thus bringing additional costs to society [14].

* email: elisabeta.antonescu@ulbsibiu.ro; Phone: 0723610900 *All authors had equal scientific contribution in publishing this material*

Aggressive behaviour in schizophrenia

Psychopathologically, aggressive behaviour in schizophrenia can be explained by the presence of psychotic symptoms, substance abuse, cognitive symptoms, but some distinct neurobiological mechanisms also play an important part [15].

In schizophrenia, both psychotic and impulsive aggression can occur. This is due to the structural and functional abnormalities in the frontal and temporal cotex and to the connectivity between them because a disbalance is created between cortical inhibitor control and instinctual impulses [16].

Several studies have shown that aggression is to some extent transmitted genetically. However, the contribution of certain sociodemographic factors, stress, the presence of psychotic symptoms, the use of psychoactive substances, the current treatment - a network intersecting and giving rise to violence in schizophrenia is well known [17].

The genetic contribution of COMT polymorphism has been highlighted in a variety of studies. The homozygous form of the Met/Met allele was found to be significantly elevated in children aged 7 to 11 years with behavioral disorder when exposed to maternal intranatal stress [18]. Patients with psychotic disorders presenting the Met/Met homozygote gene exhibited a greater psychotic symptomatology and a higher stress response than the Val/Val homozygous form or the Val/Met heterozygote [19]. The role of genetic factors has also been demonstrated by violent crimes in patients with schizophrenia whose parents who have committed crimes [20].

Biologically, genes associated with *novelty seeking* personality trait, impulsivity, or attention deficit hyperactivity disorder (ADHD) [21] have been studied. Polymorphism of the gene that synthesizes COMT, one of the enzymes involved in genes of these traits, is involved. The polymorphism of this gene consists of replacing Val with Met at the level of codon 158 located on chromosome 22q11.1-q11.2 [22]. Since the Val allele is associated with higher enzyme activity than the Met allele, this leads to a reduced metabolic activity of the COMT enzyme by 3-4 times, along with dopamine increase.

Other candidate candidates relevant for the study of aggression in schizophrenia are the MAO-A, involved in the dopamine and serotonin metabolism and dopamine receptor D4 (DR_4) gene associated with exploratory temperament [23]. If some studies have shown that in the case of MAO-A, the frequency of an allele with 3.5 and 4 repetitions (high-activity variants) was identified [24], others did not find this association [25].

Suicide in depression

Suicide ranks first among young people worldwide (WHO), with nearly 1 million young people committing suicide each year [26].

The involvement of the *serotoninergic* system in depression and suicide has been mentioned for a long time, the first research indicated the reduction of 5-HT, 5-HIAA metabolite levels in CSF [27]. Serotonin decreases by a reduced signalling of the serotoninergic system (receptors, serotonin transporters, enzymes) is associated with suicidal behaviour. Suicidal patients have been found to have an increased number of $5\text{-}HT_{1A}$ postsynaptic receptors in the prefrontal cortex [28]. Depression and suicidality have also been associated with an increase in the activity and number of $5\text{-}HT_{2A}$ receptors in the prefrontal cortex and hippocampus [29].

Mention must be made of the biochemical studies that highlight in CSF: reduced levels of serotonin (5-HT) and *5-Hydroxyindoleacetic* acid (5-HIAA) especially in repeated suicide attempts [30]. Post-mortem studies show a decrease of the number of serotonin transporter sites in brainstem, prefrontal cortex, hypothalamus, the method characterized by an increased validity as against the decrease of the amount of 5-HT and 5-HIAA in the brainstem, as the rate of metabolism of these products after death is not known [31].

Remarkable alterations of cellular signalling systems - phosphatidyl-inositol and AMP_c-adenyl cyclase in the prefrontal cortex of suicidal victims [32], decrease of phosphokinase C activity, decrease of phosphokinase A activity and low protein G activity. Autoradiographic studies reveal the increase in density and the ability to bind $5\text{-}HT_{1A}$ and $5\text{-}HT_{2A}$ receptors in the ventromedial prefrontal cortex [33], as a mechanism to compensate for the decrease in serotonergic transmission or, in the case of $5\text{-}HT_2$, to increase gene expression as well as the decrease in the binding capacity of serotonin transporter receptors 5-HTT in the prefrontal cortex [34].

Enzymatic research has also revealed a low immunogenicity of TPH (tryptophan-hydroxylase) enzyme in the cerebral cortex [35] or increased [36], as a compensatory mechanism, so that molecular genetics studies to point to the polymorphism of the TPH gene [37], the SERT gene [38], the $5\text{-}HT_{1A}$ gene [39], the MAO-A gene in suicidal depressive patients [40].

The polymorphism of the gene encoding the serotonin transporter in neuronal 5-HTT leads to 2 variants of alleles having a different activity and size: a long (L) allele with 16 repetitions and one short (S) with 14. The S allele reduces the activity of the transporter along with the decrease of mRNA and 5-HTT expression. The SS variant of the allele produces a decrease in serotonin transporter transcription, which was associated with an increased risk for affective disorders [41].

Experimental part

Materials and methods

The research was conducted at the *Gheorghe Preda* Psychiatric Hospital in Sibiu. 52 patients aged between 18 and 35 were included in the study and who were diagnosed with the diagnosis of *Schizophrenia*, *Bipolar Affective Disorder* and *Major depressive disorder* according to the DSM-5 criteria [42].

To measure the severity of psychiatric symptoms, symptoms of schizophrenia and depressive symptoms, the following instruments were used: Brief Psychiatric Rating Scale (BPRS), developed by Overall and Gorham (1963) [43]; a score between 0-9 - no syndrome,10-20 - minor syndrome, +21 - major syndrome.

The Beck Depression Inventory was developed by Aaron T. Beck [44], containing 21 items; the score can range from 0 to 63 and indicates: 0-9 - normal patient, 10-15 - mild depression, 16-23 - moderate depression, 24-63 - severe depression.

Evaluation of aggression in the patients included in the study - heterogression in patients with Schizophrenia and autoaggression in patients with *Bipolar Affective Disorder, Depressive Episode* and *Major Depressive Disorder* - was achieved with the following scales: 25-50 - rather a peaceful person; 50-70 - sometimes reacts violently; 76-100 - there are enough occasions when he/she reacts violently; 101-125- he/she very hard controls the aggressive behaviour.

The aggression of patients diagnosed with schizophrenia was assessed using the questionnaire of Arnold Buss and Mark Perry (1992) [45].

Suicide Intent Scale (SIS) was invented by Aaron T. Beck to be used in patients who have had suicidal attempts but survived; the total score of the scale ranges from 15 to 45 and indicates: 15-19 low intent; 20-28 moderate intent; 29+ increased intent [46].

Results and discussions

The socio-demographic analysis of the group of young patients included in the study showed the following configuration: 56% are males and 44% females, 52% are from rural areas, 48% from urban areas; according to educational level, 71% have middle education, 23% are employed, 75% are unmarried, 17% are married, 8% live in concubinage.

Regarding the severity of aggression in the study patients (Buss Perry scale), male gender is higher than female gender: higher percentages in males (35 and 10%) than in females (16% and 0%) in the range 76-100 and 101-125, respectively (fig. 1).

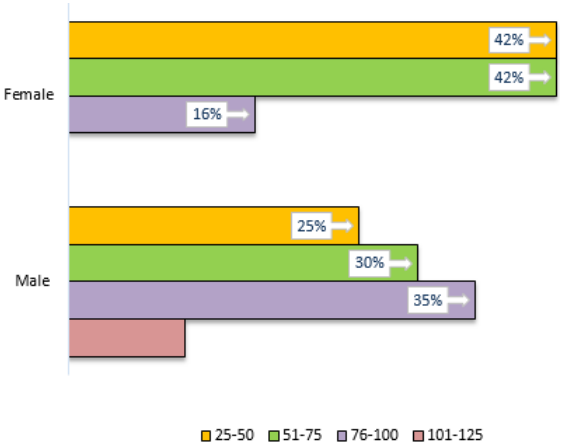

Fig. 1. The severity of aggression in the study patients

These data are in line with the study conducted by Heinz Hafner: the manifestations of schizophrenia do not essentially differ between men and women. In contrast, there are major differences in young age. Men do not have the protective effect of estrogen, which reduces sensitivity at D2 receptors level, with therapeutic effects on both negative and positive symptoms. As a result, men have a greater potential for aggressive behaviour [47].

A study of 90 boys aged 9 years has shown that high levels of androgens are a biological marker in relation to individual differences in aggressive behavior [48]. For a proper diagnostic it is important to have the values of these hormones correctly determined.[49, 50] Testosterone alters neuronal activity, in the sense of increasing dopamine

During adolescence, testosterone modulates dopaminergic tone in the black substance by increasing the level of enzymes regulating the synthesis and metabolism of dopamine, which shows an increase in dopamine use and turnover in this area. A study conducted on male mice at adolescence revealed the regulation of TPH, COMT, MAO-A, MAO-B through estrogenic nuclear receptors. In several studies, substitution with testosterone increased COMT activity in both cortex and striatum [52].

Although most patients with schizophrenia are not violent, although there is an increased risk of aggression in them. There is a significant positive correlation between BPRS values (severity of psychiatric symptomatology) and Buss Perry scale (aggression) ($r = 0.302$, $p < 0.05$) (table 1).

From a neurochemical point of view, these anomalies also have as a substrate an imbalance of dopamine and serotonin. In the prefrontal cortex of aggressive patients, serotonin is low while dopamine is elevated. Dopamine is involved in the initiation and manifestation of aggression, and elevated levels of dopamine have been identified in impulsive and psychotic patients; hyperdopaminergia is able to decrease the capacity of inhibitory circuits, thus appearing aggression [53].

There is a multitude of pharmacological evidences that associate dopamine and impulsivity. Thus, dopaminergic agonists increase motoric impulsivity [54], certain drugs of abuse increase the extracellular levels of dopamine and, consecutively, increase the impulsive behavior [55], while hyperdopaminergic disposition in mania and other psychoses are manifested by impulsivity symptoms that respond to antipsychotic medication [56].

Serotonin modulates prefrontal cortex activity; aggressive behavior was correlated with the decrease in 5-HIAA level in the CSF, a serotonin metabolite [57]. Decreased serotonin in the prefrontal cortex and anterior cingulate lobe in impulsive patients leads to low cortical control [58]. During an aggressive confrontation, serotonin decreases in the prefrontal cortex up to 80% [59]. The $5HT_{2A}$ receptor may be involved in aggressive behavior, the availability of the $5HT_{2A}$ receptor is higher in aggressive patients than in non-aggressive or control cases [60].

In a study of 132 patients with schizophrenia and 80 control subjects, there was not registered a high degree of aggression in COMT carriers with low-activity allele, but also in those who exhibited psychotic symptoms and important cognitive deficits [61]. Hence, aggression in schizophrenia is associated with increased tonic dopaminergic activity and cognitive inflexibility. The same author also conducted other studies that investigated the relevance of the 5-HTTPR serotonin transporter in terms of aggression in schizophrenia, but COMT polymorphism remains the most plausible clinical hypothesis since it is

		BPRS	Buss_Perry
BPRS	Pearson Correlation	1	0.302*
	Sig. (1-tailed)		0.046
	N	32	32
Buss_Perry	Pearson Correlation	0.302*	1
	Sig. (1-tailed)	0.046	
	N	32	32

Table 1
CORRELATION BETWEEN BPRS VALUES AND BUSS PERRY SCALE

associated with the increase of the psychotic symptoms of these patients [62].

From the analysis of the severity of depression in patients with *Major depressive disorder* and *Bipolar affective disorder, depressive episode* it is noted that its severity is higher in the female gender. Figure 2 shows that women had higher scores of moderate depression (58%) and severe (26%) than men (37% and 25%, respectively).

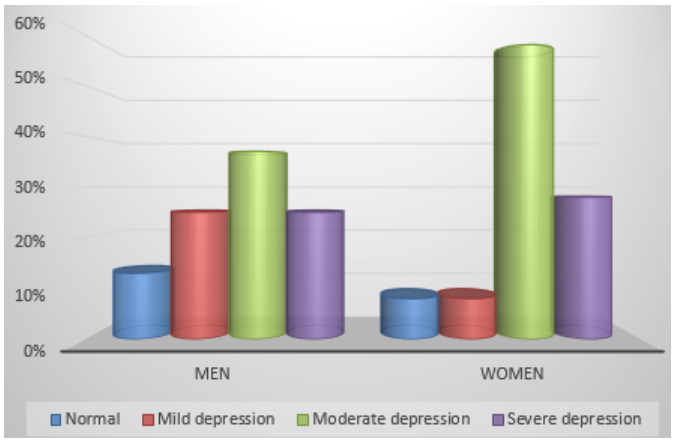

Fig. 2 The severity of depression in patients

The study by Parker G. recorded marginal and insignificant results with regard to the severity of depression symptoms which are higher in women than in men. Thus, there was only a greater prevalence of depressive symptoms in the female patients diagnosed with bipolar disorder [63].

The prevalence of major depressive disorder is higher in women than in men; in 2010, the annual prevalence was 5.5% for women and 3.2% for men, which means an incidence 1.7 times higher in women. The ratio between prevalence rates of depression in both genders is similar in the developed countries, and globally it results that this difference is due to gender biology characteristics, and less due to race, culture, diet, socio-economic factors [64].

Moreover, depression is twice as prevalent in young women than in men aged 14-25 years, this ratio decreasing with age, thus pleading even more for gender differences [65]. The results of the studies indicate that the sudden or sustained decrease in estrogen, as well as the fluctuating levels of estrogen correlate with affectivity disorders [66].

Both estrogen and progesterone have been shown to alter the serotonin response to SSRIs. Experiments on Macaccus Rhesus have shown that sex hormones interact with 5-HTT functional polymorphism by influencing the response to SSRI [67]. In human studies, an association was found between the functional polymorphism of the serotonin transporter gene 5-HTTLPR and the antidepressant efficacy in postmenopausal women [68].

Regarding suicide intent measured by the SIS scale, the following results were observed: men have a moderate suicide intent of 50%, increased by 12%, while women have a moderate suicide intent of 33% and increased by 17%.

It has not been shown that there is a significant positive correlation between the severity of the depressive symptomatology and the degree of the suicide intent (table 2).

Many studies reported that more than two-thirds of those who committed suicide (complete suicide or attempted suicide) experienced depressive episodes at the time of the dead [69]. The suicidal ideation, which is the key point

Table 2

CORRELATION BETWEEN THE SEVERITY OF THE DEPRESSIVE SYMPTOMATOLOGY AND THE DEGREE OF THE SUICIDE INTENT

		Beck	SIS
Beck	Pearson Correlation	1	-0.161
	Sig. (1-tailed)		0.249
	N	20	20
SIS	Pearson Correlation	-0.161	1
	Sig. (1-tailed)	0.249	
	N	20	20

of severe depression also correlated with suicidal behaviour [70].

In a study conducted in 2004 in Sibiu on 47 patients presenting *Non-fatal self-harm acts,* there was a significant negative correlation between age and the score of the subscale *Fear of Social Disapproval* ($r = -0.422$, $p<0.01$), one subscale of *Reasons for life Inventory* [71]. This negative correlation could express a decrease of social disapproval at young people, maybe a prove of self-confidence in front of the society expectancies [72]. This fact may facilitate the suicidal behaviour at youth.

The fact that our study does not demonstrate the correlation between the severity of depression and suicide intent may be based on the impulsivity in these patients; studies have shown that psychiatric symptoms are less severe in patients performing impulsive suicidal attempts [73]. In addition, impulsivity is the basic feature of suicide attempts specific to younger age [74].

Conclusions

This study found that aggression is higher in young male patients with schizophrenia. Aggression in males is associated with the presence of testosterone, and in patients with schizophrenia, it is potentiated by psychotic symptoms and impulsivity, which are based on increased dopaminergic transmission in the mesolimbic pathway and serotonin decrease in the prefrontal cortex. Determining aggression in schizophrenia is possible due to COMT polymorphism by replacing Val with Met at the level of codon 158 located on chromosome 22.

This association is demonstrated by the significant positive correlation between the severity of symptoms of schizophrenia (BPRS score) and aggression (Buss Perry score). This correlation can also be explained by the fact that psychotic episodes, and especially those with severe intensity, can be accompanied by aggression, mainly occurring in youth.

In young depressed patients, there was registered a higher intensity of depression in females. This result is consistent with numerous studies conducted on depressed patients of any age, where the prevalence of depression in women was primarily associated with hormonal factors and to some extent with race, ethnicity, or socio-economic factors. In many studies, the polymorphism of the gene encoding the 5-HTT serotonin transporter is incriminated, with the creation of two allele variants, the SS variant decreases the transcription of this transporter.

Correlation of depression intensity in young patients (Beck score) with suicidal intent (SIS score) and expressing

self-aggression did not show a statistically significant relationship between the two dimensions. The suicidal behaviour has a complex determinism, biochemical factors may influence the occurrence of self-aggression, but this is modulated by a complex constellation of psycho-socio-cultural factors.

Abreviations

COMT - catechol-O- methyl-transferase
Met - methionine
Val - valine
MAO-A - Monoamine oxydase A
MAO-B - Monoamine oxydase B
DR_4 gene - dopamine 4 receptor gene
CSF - cerebrospinal fluid
5-HT - 5-hydroxytryptamine
5-HIAA-5-hydroxyindoleacetic acid
AMPc - adenozin monofosfat ciclic
$5\text{-}HT_{2A}$ receptor - serotonin 2A receptor
$5\text{-}HT_{1A}$ receptor - serotonin 1A receptor
5-HTT - serotonin transporter gene
SERT gene - serotonin transporter gene
TPH - tryptophan-tyroxilase
5-HTTPR - serotonin transporter promoter region
SSRI - selective serotonin reuptake inhibitor

References

1.*** EARLY PSYCHOSIS GUIDELINES WRITING GROUP. Australian Clinical Guidelines for Early Psychosis, 2nd edition: A Brief Summary for Practitioners. Orygen Youth Health, Melbourne, 2010.
2.CITROME, L.L. Aggression: Overview, epidemiology, assessment and differential diagnosis. Ed. Bienenfeld D, 2015.
3.FAZEL, S., GULATI, G., LINSELL, L ET AL., PLoS Med, 2009; 6,
4.NIELSSEN, O., LARGE, M., Schizophr Bull, 36, 2010, p. 702-712.
5.MUTICA, M., CIUBARA, A., DUICA, L., ALEXANDRU, D., CONDRATOVICI PLESEA, C., PIRLOG, M., CARA, M. Elderly schizophrenic patients - clinical and social correlations 2016; 26(Supplement 2): S512.
6.NEW, A.S., HAZLETT, E.A., BUCHSBAUM, M.S., GOODMAN, M., REYNOLDS, D., MITROPOULOU, V., SPRUNG, L., SHAW JR., R.B., KOENIGSBERG, H., PLATHOLI, J., SILVERMAN, J., SIEVER, L.J., Archives of General Psychiatry, 59, 2002, p. 621–629.
7.SEO, D., PATRICK, C.J., KENNEALY, P.J., Aggress Violent Behav, 13(5), 2008, p.383-395.
8.VORAVKA, J., Psychiatria Danubina, 25(1), 2013, p. 24-33.
9.VAILLANCOURT, T., SUNDERANI, S., Brain and Cognition, 77, 2011, p. 170-175.
10.VON BORRIES, A.K.L., VOLMAN, I., DE BRUJIN E.R.A., BULTEN, B. H., VERKES R.J., ROELOFS, K, Psychiatr Research, 2012, p. 761-766.
11.VAN GOOZEN, S.H., FAIRCHILD, G., SNOEK, H., HAROLD, G.T., Psychol. Bull., 2007, p. 133-149.
12.STAHL, S.M., MORRISSETTE, D.A. Stahl's Illustrated: Violence: Neural Circuits, Genetics and Treatment. Cambridge, UK, Cambridge University Press, 2014.
13.ANDERSON, A., WEST, S.G., Innov Clin Nerosci, 8(3), 2011, p. 34-39.
14.QUANBECK, C., MCDERMOTT, B., LAM, J., EISENSTARK, H., SOKOLOV, G., & SKOTT, C., 58(4), 2007, p. 521–528.
15.FAZEL, S., GRANN, M., CARLSTROM, E., LICHTENSTEIN, P., LANGSTRÖOM N. J Clin Psychiatry, 70, 2009, p. 362–369.
16.COMAI, S., TAU, M., PAVLOVIC, Z., GOBBI, G., J. Clin. Psychopharmacol., 32 (2), 2012, p. 237-260.
17.VOLAVKA J, CITROME L., Schizophr Bull, 37, 2011, p. 921–929.
18.THOMPSON, J.M., SONUGA-BARKE, E.J., MORGAN, A.R., CORNFORTH, CM., TURIC, D., ET AL., Dev Med Child Neurol, 54, 2012, p. 148–154.
19.COLLIP, D., VAN, W.R., PEERBOOMS, O., LATASTER, T., THEWISSEN, V., ET AL., CNS Neurosci Ther, 17, 2011, p. 612–619.
20.FAZEL, S., GRANN, M., Am J Psychiatry, 63, 2006, p. 1397-1403.
21.KOTLER, M., BARAK, P., COHEN, H., AVERBUCH, I.E., GRINSHPOON, A., GRITSENKO, I., NEMANOV, L., EBSTEIN, R.P. Am J Med Genet., 88(6), 1999, p. 628-33.
22.LACHMAN, H.M., PAPOLOS, D.F., SAITO, T., YU, Y.M., SZUMLANSKI, C.L., WEINSHILBOUM, R.M., Pharmacogenetics., 6, 1996, p. 243–250.
23.FRESAN, A., CAMARENA, B., APIQUIAN, R., AGUILAR, A., URRACA, N., NICOLINI, H., Neuropsychobiology., 55, 2007, p.171–175.
24.MANUCK, S.B., FLORY, J.D., FERRELL, R.E., MANN, J.J., MULDOON, M.F., Psychiatry Res., 95, 2000, p. 9-23.
25.STROUS, R.D., NOLAN, K.A., LAPIDUS, R., DIAZ, L., SAITO, T., LACHMAN, H.M., Am J Med Genet B Neuropsychiatr Genet., 120B, 2003, p. 29–34.
26.*** WORLD HEALTH ORGANIZATION. Investing In Mental Health, WHO, 2003.
27.ROY, A., NIELSEN, D., RYLANDER, G., SARCHIAPONE, M., AND SEGAL, N., J. Clin. Psychiatry, 60. 1999, p. 12–17.
28.ARANGO, V., UNDERWOOD, M.D., BOLDRINI, M., TAMIR, H., KASSIR, S.A., HSIUNG, S., CHEN, J.J., AND MANN, Neuropsychopharmacol., 25, 2001, p. 892-903.
29.PANDEY, G.N., DWIVEDI, Y., RIZAVI, H.S., REN, X., PANDEY, S. C., PESOLD, C., ROBERTS, R.C., CONLEY, R.R., TAMMINGA, C.A., Am. J. Psychiatry, 159, 2002, p. 419-429.
30.PLACIDI, G.P., OQUENDO, M.A., MALONE, K.M., HUANG, Y.Y., ELLIS, S.P., MANN, J.J., Biol Psychiatry, 50, 2001, p. 783-791.
31.CARLBORG, A., JOKINEN, J., NORDROSTROM, A., JONSSON, E., NORDSTROM, P., Schizophrenia research, 112(1-3), 2009, p. 80-85.
32.DWIVEDI, Y., ET AL., Neuropsychopharmacology, 27, 2002, p. 499-517.
33.MANN, J.J., ARANGO, V. Suicide: An unnecessary death, Ed. Wasserman D, 2001, p. 29-34
34.AUSTIN, M.C., WHITEHEAD, R.E., EDGAR, C.L., JANOSKY, J.E., LEWIS, D.A., Neuroscience, 114, 2002, p.807-815.
35.WALTHER, D.J. ET AL., Science, 299(5603), 2003, p. 76.
36.ONO, H., ET AL., Mol Psychiatry, 7, 2006, p. 127-1132.
37.BACH-MIZRACHI, H., UNDERWOOD, M.D., KASSIR, S.A. ET AL., Neuropsychopharmacology, 31, 2006, p. 814-824.
38.CURRIER, D., MANN, J.J., Psychiatr Clin North Am, 31, 2008, p. 247-269.
39.LEMONDE, S., TURECKI, G., BAKISH, D. ET AL, J Neurosci 23(25), 2003, p. 8788-8799.
40.LEWITZKA, U., MULLER-OERLINGHAUSEN, B., BRUNNER, J., HAWELLEK, B., RUJESCU, D., ISING, M., LAUTERBACH, E., BROOCKS, A., BONDY, B., RAO, M., FRAHNERT, C., FELBER, W., HEUSER, I., HOHAGEN, F., MAIER, W., BRONISCH, T., Acta Psychiatr Scand, 117(1), 2008, p. 41-49.
41.HAENISCH, B., HERMS, S., MATTHEISEN, M., STEFFENS, M., BREUER, R., STROHMAIER, J., ET AL., J Affect Disord. 146, 2013, p.438-440
42.*** AMERICAN PSYCHIATRIC ASSOCIATION. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
43.OVERALL, J.E., GORHAM, D.R. The Brief Psychiatric Rating Scale (BPRS), Psychol Rep, 10, 1962, p. 799-812.
44.BECK, A.T., STEER, R.A., BROWN, G.K. BDI-II: Beck Depression Inventory Manual. Psychological Corporation. 1996.
45.BUSS, A.H., PERRY, M. The aggression questionnaire. Journal of personality and social psychology, 63(3), 1992, p. 452.
46.BECK, A.T., SCHUYLER D., HERMAN, I. Development of suicidal intent scales. In: Beck AT, Resnik HLP, Lettieri DJ, eds. The Prediction of Suicide. Bowie, Md: Charles Press, 1974.
47.HAFNER, H. , Rev. psiquiatr. clín., 29(6), 2002, p. 267-292.
48.SANCHEZ-MARTIN, J.R., AZURMENDI, A., PASCUAL-SAGASTIZABAL, E., CARDAS, J., BRAZA, F., BRAZA, P., MUÑOZ, J.M., Psychoneuro-endocrinology, 36 (5), 2011, p. 750-760.
49.ANTONESCU, E., TOTAN, M, BOITOR, G.C., SZAKACS, J, SILISTEANU, S.C., FLEACA, S.R., CERNUSCA MITARIU, S.I., SERB B.H., Rev. CHIM (Bucharest), **68**, no. 2, 2017, p 243
50.ANTONESCU E, SZAKACS J, TOTAN M, Revista Romana de Medicina de Laborator, 24(3), 2017, p 347-350

51.KRAKOWSKI, M., Journal of Neuropsychiatry and Clinical Neurosciences, 15(3), 2003, p. 294-305.
52.MEYERS, B., D'AGOSTINO, A., WALKER, J., KRITZER, M.F., Neuroscience., 165 (3), 2010, p. 850-862.
53.SIEVER, L.J., Am J Psychiatry., 165(4), 2008, p. 429-442.
54.DANG, D., CUNNINGTON, D., SWIECA, J, Clin Neuropharmacol, 34, 2011, p. 66-70.
55.PALOYELIS, Y., ASHERSON, P., MEHTA, M.A., FARAONE, S.V., KUNTSI, J., Neuropsychopharmacology, 35, 2010, p. 2414-2426.
56.NOLAN, K.A., D'ANGELO, D., HOPTMAN, M.J., Psychiatry Res 2011, 187, p. 301-303.
57.MORRISSETTE, D.A STAHL, S.M., MORRISSETTE, D.A., CNS Spectr , 19(5), 2010, p. 438-448.
58.COCCARO, E.F., SRIPADA, C.S., YANOWITCH, R.N., PHAN, K.L., Biol Psychiatry, 69(12), 2011, p. 1153–1159.
59.COMAI, S., TAU, M., PAVLOVIC, Z., GOBBI, G., J. Clin. Psychopharmacol., 32 (2), 2012, p. 237-260.
60.ROSELL, D.R., THOMPSON, J.L., SLIFSTEIN, M., ET AL., Biol Psychiatry. 67(12), 2010, p. 1154-1162.
61.HAN, D.H., KEE, B.S., MIN, K.J, ET AL., Neuroreport, 17, 2006, p.95–99.
62.HAN, D.H., PARK, D.B., NA, C., KEE, B.S., LEE, Y.S., Psychiatry Res. 129, 2004, p.29–37.
63.PARKER, G., FLETCHER, K., PATERSON, A., ANDERSON, J., HONG, M. , J Affect Disord., 167, 2014, p.351-357.
64.RAI, D., ZITKO, P., JONES, K., ET AL., Br J Psychiatry, 202, 2013, p. 195-203.
65.PATTEN, S.B., WANG, J.L., WILLIAMS, J.V., ET AL, Can J Psychiatry, 51, 2006, p.84-90.
66.DOUMA, S.L., HUSBAND, C., O'DONNELL, M.E., BARWIN, B.N., WOODEND, A.K., Advances in Nursing Science 28 (4), 2005, p. 364-75.
67.MICHOPOULOS V, BERGA SL, WILSON ME., Exp Clin Psychopharmacol. 19(6), p. 2011, 401-8.
68.GRESSIER, F., VERSTUYFT, C., HARDY, P., BECQUEMONT, L., CORRUBLE, E., Arch. Womens Ment. Health. 17, p. 569-573.
69.POMPILI, M., INNAMORATI, M, RAJA M, FALCONE I, DUCCI G, ET AL., Neuropsychiatr Dis Trat , 4, 2007, p. 247-255.
70.ZHU, Y., ZHANG, H., SHI, S., GAO, J., LI, Y., ET AL. Suicidal risk factors of recurrent major depression in Han Chinese women, PLoS One. 2013;8: e80030.
71.LINEHAN, M.M., GOODSTEIN J.L., NIELSEN, S.L., CHILES, J.A., Journal of Consulting and Clinical Psychology, 51(2), 1983, 276- 286.
72.DUICA, L., CHIRITA, R., TALAU, G., CHIRITA, V., Bulletin of Integrative Psychiatry, 4(43), 2009, p 32-37.
73.WEI, S., LIU, L., BI, B., LI, H., HOU, J., CHEN, W., ET AL., Gen Hosp Psychiatry., 35, 2013, p.186–191.
74.WILLIAMS, C.L., DAVIDSON, J.A., MONTGOMERY, I., Journal of Clinical Psychology., 36(1), 1980, p. 90-94.

Manuscript received: 21.01.2018