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Serum Interleukin-6 in Schizophrenia: Associations with Clinical and Sociodemographic Characteristics

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Интерлейкин-6 сыворотки при шизофрении: ассоциация с клиническими и социодемографическими характеристиками

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Original Research

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ABSTRACT

BACKGROUND: Recently a significant part of schizophrenia studies have been focused on the role of cytokines, especially interleukin-6 (IL-6). Some authors have suggested a pathogenetic role for IL-6 in schizophrenia and concluded that therapy that centers on suppressing IL-6 activity may prove beneficial for certain categories of patients with the disorder. However, many questions about whether the changes in IL-6 levels in schizophrenia are primary, related to symptoms or caused by therapy, are concomitant metabolic disorders, are related to smoking or other secondary factors remain unanswered.

AIM: To assess the level of serum IL-6 in patients with schizophrenia in comparison with healthy controls, as well as to study its association with clinical and socio-demographic characteristics.

METHODS: Some 125 patients with schizophrenia and 95 healthy volunteers were examined. The evaluation of IL-6 was performed by enzyme immunoassay. All patients were assessed using standardized psychometric instruments. Information from patient medical records on the course of the disease and treatment was analyzed.

RESULTS: The level of IL-6 was significantly higher in the patients than in the healthy volunteers (z=2.58; p=0.0099), but among men the difference between the patients and volunteers was not significant. Statistically significant correlations were found between the level of serum IL-6 and the severity of the cognitive impairment of patients: (auditory [ρ=–0.31; p=0.00063] and working memory [ρ=−0.25; p=0.0065], hand-eye coordination [ρ=−0.29; p=0.0011], verbal fluency [ρ=−0.28; p=0.0019] and problem-solving capacity [ρ=−0.22; p=0.013]), total severity of schizophrenia symptoms (PANSS, ρ=0.22; p=0.016), PANSS positive subscale (ρ=0.18; p=0.048), and the age of manifestation (ρ=0.20; p=0.025) and disease duration (ρ=0.18; p=0.043). The level of IL-6 was the lowest in patients treated with third-generation antipsychotics, and the highest in those treated with a first-generation antipsychotics (H=6.36; p=0.042). Moreover, in hospital patients, the level of IL-6 was significantly higher than in outpatients and inpatients hospitals (H=18.59; p=0.0001).

CONCLUSION: The study confirmed that there there are associations between the serum IL-6 level and schizophrenia, the age of the patient, duration of the disease and how late in one's life cycle it began manisfesting itself, as well as a number of clinical characteristics. Considering that IL-6 is associated with a wide range of symptoms that are loosely controlled by antipsychotics, this biochemical marker needs to be studied to look into how closely its level tracks with an unfavorable course of schizophrenia. That would require further prospective studies.

АННОТАЦИЯ

ВВЕДЕНИЕ: В настоящее время при изучении шизофрении большое внимание уделяется роли различных цитокинов, при этом наиболее часто упоминаются изменения уровня интерлейкина-6 (IL-6). Некоторые авторы выдвигали предположения о патогенетической роли IL-6 при шизофрении и целесообразности терапии, направленной на подавление активности IL-6, у определенных категорий пациентов с этим расстройством. Однако до сих пор остается много вопросов о том, являются ли изменения уровня IL-6 при шизофрении первичными, связанными с симптомами, или вызваны терапией, сопутствующими метаболическими нарушениями, курением и другими вторичными факторами.

ЦЕЛЬ: Оценить уровень сывороточного IL-6 у больных шизофренией по сравнению со здоровым контролем, а также изучить его связь с клиническими и социально-демографическими характеристиками.

МЕТОДЫ: Обследовано 125 пациентов с шизофренией и 95 здоровых добровольцев. Оценку IL-6 проводили иммуноферментным анализом. Все пациенты были обследованы с использованием стандартизированных психометрических инструментов. Проанализированы данные медицинских карт о течении заболевания и лечении.

РЕЗУЛЬТАТЫ: Уровень IL-6 был статистически значимо выше у пациентов, чем у здоровых добровольцев (z=2,58; *p*=0,0099), однако среди мужчин разница между пациентами и добровольцами была незначительна. Выявлены статистически значимые корреляции между уровнем сывороточного IL-6 и выраженностью когнитивных нарушений у пациентов: (слуховой [ρ=−0,31; *p*=0,00063] и рабочей памяти [ρ=−0,25; *p*=0,0065], зрительно-моторной координации [ρ=−0,29; *p*=0,0011], беглости речи [ρ=−0,28; *p*=0,0019] и проблемно-решающего поведения [ρ=−0,22; *p*=0,013]), общей тяжестью симптомов шизофрении (PANSS, ρ=0,22; *p*=0,016), подшкалой продуктивных синдромов PANSS (ρ=0,18; *p*=0,048), возрастом манифестации (ρ=0,20; *p*=0,025) и длительности заболевания (ρ=0,18; *p*=0,043). Уровень IL-6 был самым низким у пациентов, получавших антипсихотики 3 поколения, и самым высоким у получавших антипсихотики 1 поколения (H=6,36; *p*=0,042). При этом у пациентов круглосуточного стационара уровень IL-6 был статистически значимо выше, чем у амбулаторных и пациентов дневного стационара (H=18,59; *p*=0,0001).

ЗАКЛЮЧЕНИЕ: Исследование подтвердило ассоциацию уровня IL-6 сыворотки крови с шизофренией, возрастом больных, длительностью заболевания и его более поздним началом, а также рядом клинических характеристик. Учитывая, что IL-6 связан с широким спектром симптомов, плохо контролирующихся антипсихотиками, данный биохимический маркер нуждается в изучении на предмет ассоциации с неблагоприятным течением шизофрении, что требует дальнейших проспективных исследований.

Keywords: *interleukin-6; schizophrenia; cognitive symptoms*
Ключевые слова: *интерлейкин-6; шизофрения; когнитивные симптомы*

INTRODUCTION

Schizophrenia is classified as a chronic mental disorder with a multifactorial etiology, but our understanding of its pathology remains limited [1]. Schizophrenia leads to a decrease in one's ability to function socially and an increase in the likelihood of early disability [1]. The approaches currently used to treat the disease are not pathogenetic. Moreover, they are quite limited in their ability to help shed light on the areas of negative symptoms and cognitive impairment, which are largely responsible for both the

ability of the patient to function daily and to work. Given this the effort to identify the pathological mechanisms of schizophrenia and come up with new therapeutic strategies that can attack the symptoms remains highly relevant.

Currently, much of the attention in the study of the schizophrenia etiopathogenesis centers on the role of cytokines and the immunoinflammatory hypothesis [2]. Changes in the level of interleukin-6 (IL-6), one of the key regulators of inflammatory and immune processes, are the most often mentioned [3–7]. Some authors have suggested a pathogenetic role for IL-6 in schizophrenia and concluded that therapy aimed at suppressing IL-6 activity may be useful to certain categories of patients suffering from the disorder [3, 5].

IL-6 is produced by various types of immune cells and acts as a mediator in the chain of information transmission during the immunoinflammatory response [5]. The level of IL-6 in serum increases rapidly under stressful conditions and modulates immune system activity: hematopoiesis, migration of neutrophils, the synthesis of the C-reactive protein with other elements [5]. Moreover, IL-6 can assume both pro- and anti-inflammatory properties, depending on the context. As a neurotrophic factor, it plays a crucial role in the differentiation of oligodendrocytes and the regeneration of peripheral nerves [8], but under certain conditions it can trigger and mediate various pathological conditions [9]. Despite its active role in the acute inflammatory response, in the long term, this cytokine embodies regenerative and immunosuppressive properties aimed at fighting inflammation [5]. Excess or lack of IL-6 secretion can lead to a disruption of the ratios of certain immune cells (Th17 and Treg) and lead to autoimmune and chronic inflammatory diseases. The functional dichotomy of IL-6 is underlied by its ability to perform signal transmission both through the classical binding to specific cellular receptors and through an alternative pathway via intracellular signaling molecules [9]. There is a hypothesis holding that, under conditions of oxidative stress, the disruption of the lipid-protein balance of the IL-6 receptor is one of the reasons behind the switch in the signal transmission from a classical one to an alternative pathway, which is responsible for a furthering of the pathological process.

A meta-analysis of pro-inflammatory cytokine levels in patients with schizophrenia showed an increase in IL-6 levels, along with changes in a number of other immune-response markers [3]. Miller et al. (2011) in an evaluation of 40 studies in an extensive meta-analysis, found that the levels of IL-1β, IL-6, and TGF-β were increased in the acute phase of the disease (both in patients with a relapse of schizophrenia and in the first psychotic episode, FPE) and decreased with effective treatment [2]. The level of IL-6 correlated with the overall levels of psychopathology in two of the five studies where the severity of the symptoms was assessed [2]. Other authors later also demonstrated that IL-6 is associated with symptom severity in schizophrenia [10]. It has been hypothesized that IL-6 may be a state-dependent marker of inflammation that disappears with a fading of symptoms. But in the other 3 studies included in the meta-analysis by Miller et al. (2011) association between IL-6 and symptom severity was not confirmed [2]. The results by Borovcanin et al. (2012) also failed to confirm an increase in the level of IL-6 either during the FPE or during the relapse of schizophrenia [11]. Therefore, further study of the IL-6 role in schizophrenia is needed. Moreover, elevated levels of IL-6 have been found in subjects at high risk of psychosis. Therefore, according to the authors of that study, cytokine can be used as a marker in the prodromal period [12].

At the same time, several works have reported increased levels of IL-6 in chronic schizophrenia [13]. In some of those studies, the level of IL-6 in peripheral blood showed a significant positive correlation with the duration of schizophrenia [2, 8]. This prompted a hypothesis about the effect of the therapeutic process on the secretion of IL-6. But in the systematic review and meta-analysis of 14 studies by Upthegrove et al. (2014) [14], patients (n=570) who had not been previously treated with antipsychotics (APs) also showed increased IL-6 levels. At the same time, there is evidence of a decreased IL-6 level after therapy in patients with the first episode of schizophrenia [15]. Some researchers, after *in vitro* experiments, have suggested that cytokines (including IL-6) suppress the activity of microglia, which may partially accompany the effects of some APs [16], in particular clozapine, in schizophrenia [17–19]. Khandaker et al. (2014) reported levels of IL-6 (p=0.001) and IL-13 (p=0.004) that were significantly lower after AP treatment than before the treatment in patients [10]. A meta-analysis by Miller et al. (2011) also showed that the elevated level of IL-6 during an exacerbation of psychosis and untreated FPE returns to normal after AP treatment [2]. Finally, another recent meta-analysis confirmed the drop in peripheral IL-6 levels in response to AP treatment [20]. Thus, the idea that the level of IL-6

increases in schizophrenia due to AP treatment remains unconfirmed to date.

Some studies contend that IL-6 may mediate the risk of metabolic syndrome in patients with schizophrenia [6]. Dennison et al. (2012) showed that elevated levels of IL-6, in particular, and the "pro-inflammatory phenotype", in general, in schizophrenia are closely associated with a childhood traumatic experience [21].

A number of recent studies not related to schizophrenia have shown that smoking increases IL-6 levels [22, 23]. But in patients with schizophrenia, this association is unclear. Studies focused on the association between serum IL-6 and smoking have not been published yet, although many publications have suggested that the level of inflammatory cytokines may be associated with stress, smoking, and other lifestyle factors [5]. In a meta-analysis by Goldsmith et al. (2016) [13], where smoking was considered a confounding factor potentially affecting cytokine levels in schizophrenia, the authors concluded that, due to the large heterogeneity of the studies, it was premature to draw conclusions.

The hypotheses we set out to test in this work were as follows: the presence of an association between serum IL-6 levels and different types of schizophrenia symptoms and other clinical characteristics (time of onset, duration of the disorder, etc.); treatment characteristics (generation of APs, potency, and doses); the body mass index (BMI); as well as smoking, childhood trauma, and demographic factors (gender, age).

The aim of this work was to assess the levels of serum IL-6 in patients with schizophrenia in comparison with healthy controls, as well as to study its association with clinical and socio-demographic factors.

METHODS

Study design

This is cross-sectional observational study.

Ethical approval

The study was performed according to the principles of the Helsinki Declaration of the World Medical Association. All study participants provided a written informed consent for participation and data processing. The study protocol and the informed consent were approved by Local Ethics Committee No. 1 of the of the Privolzhsky Research Medical University (the protocol No. 15 of the meeting dated October 26, 2020).

Participants

Inclusion criteria were as follows: confirmed diagnosis of schizophrenia based on the Mini International Neuropsychiatric Interview for Diagnostic and Statistical Manual, Version 5 (M.I.N.I. for DSM-5). The shared inclusion criteria for both groups were as follows: no prior history of chronic somatic and neurological conditions associated with inflammation; voluntary consent to participate in the study; and no history of intake within a month before inclusion of any synthetic vitamins, anti-inflammatory drugs or antioxidants.

Exclusion criteria for the control group were as follows: a prior history of mental illness, having undergone psychiatric consultation during one's lifetime, as well as social maladjustment and substance abuse (except for nicotine). The exclusion criteria for the entire study cohort were a refusal to participate in the study; a history with a severe mental pathology accompanied by altered consciousness or a substance use disorder (except for nicotine use); severe unstable somatic conditions that could affect the study procedures; and chronic somatic diseases and neurological disorders associated with inflammation.

The average time elapsed from the first manifestation of schizophrenia was 93.4 (119.0) months (arithmetic mean and standard deviation, further m[σ]) and 34 (15; 155) months (median and interquartile range, further Me [Q1; Q3]). Overall, 39 patients were recruited from daycare departments; 70 — from the inpatient departments; and 16 — from the outpatient treatment program.

In total, 41 patients received first-generation APs; 51 — second-generation APs; 9 — third-generation APs; 22 — a combination of first- and second-generation APs; and 2 patients did not receive APs at the time of the evaluation.

Setting

For the purposes of the study, 125 patients with schizophrenia and 95 healthy volunteers were randomly selected. All participants were residents of the Nizhny Novgorod region (European Russia). The study participants were recruited from April 2019 to February 2022.

Variables and measurement

Venous blood was drawn in the morning hours, strictly after fasting, from the cubital vein. Serum was used for biochemical studies.

Quantitative determination of IL-6 was performed by ELISA based on a three-stage "sandwich version" using mono- and polyclonal antibodies to IL-6. At the first stage of our analysis, the studied samples were incubated with immobilized monoclonal antibodies. The resulting complex interacts with human IL-6 polyclonal antibodies with biotin. At the third stage, a conjugate with streptavidin was added. The amount of conjugate bound to streptavidin was determined by the intensity of the staining, which is proportional to the content of IL-6 in the sample. The optical density was measured spectrophotometrically at a wavelength of 450 nm, and the reference wavelength was 620 nm (Sunrise, Tecan spectrophotometer, Austria). The calculation of the concentration was performed on the basis of the calibration curve. Laboratory evaluation was performed in the AVK-Med Centralized Laboratory, Nizhny Novgorod, Russia.

Patients underwent a standardized examination with the Positive and Negative Syndrome Scale (PANSS [24]), Calgary Depression Rating Scale for Schizophrenia (CDRS [25]), Snaith-Hamilton Pleasure Scale (SHAPS [26]), Bush-Francis Catatonia Rating Scale (BFCRS [27]), and the Brief Assessment of Cognition in Schizophrenia (BACS [28]). The personal and social functioning level was also assessed using the Personal and Social Performance scale (PSP [29]). The evaluation of the treatment's side effects was performed using the UKU side effect rating scale (version of "The UKUSERS-Clin" [30]) and the extrapyramidal symptoms (EPS) — using a special section "The UKUSERS-Clin", as well as the Simpson-Angus scale (SAS [31]), the Abnormal Involuntary Movement Scale (AIMS [32]), and the Barnes Akathisia Rating Scale (BARS [33]). The Childhood Trauma Questionnaire (CTQ [34]) was used to assess early traumatic experience. Information about the treatment received, the time of disease onset, education, alcohol and nicotine use, and anthropometric data (including BMI) was gathered on the basis of patient self-reporting and the analysis of medical records.

Bias

The laboratory analysis was blind to the study group status and the results of the clinical evaluation of the patients. Patient evaluation was performed by 4 specially trained raters blind to the laboratory results.

Statistical methods

The statistical analysis was performed using Statistica 6.0. According to the Shapiro-Wilk normality test, the distribution of variables deviated from the normal. So nonparametric criteria were used in our statistical analysis: the Mann-Whitney U-test (MWU-test, Z) for comparison of 2 groups, and the Kruskal-Wallis test (H) for comparison of more than 2 groups. The data were presented in the median and interquartile range (Me [Q1; Q3]), and the mean value ± standard deviation (m±σ). The spearman rank coefficient (ρ) was used for the correlation analysis. Qualitative variables were assessed using frequency tables (Chi-square with Yates correction, χ^2). P-values less than 0.05 were considered statistically significant.

RESULTS

The sociodemographic characteristics of the sample are presented in Table 1. As the samples of the patients and healthy volunteers differed statistically in age, that factor was further considered in our statistical calculations.

Table 1. Demographic characteristics of the studied cohort

Variable name	Patients, *n*=125	Healthy volunteers, *n*=95	*p*
Female/Male, abs.	62/63	60/35	χ^2=3.49; *p*=0.062
Age, years Me [Q1; Q3]/ [Min; Max]	33 [26; 43]/[18; 65]	29 [22; 38]/[19; 62]	Z=1.99; *p*=0.046
BMI, kg/m^2 Me [Q1;Q3]	23.85 [20.2; 27.6]	23.5 [21.0; 26.3]	Z=0.23; *p*=0.82
Nicotine use presence/ absence, abs.	51/74	30/65	χ^2=1.97; *p*=0.16

Note: the significance of the difference level was assessed using the Yates-adjusted chi-square test and the Mann-Whitney U-test (Z); Me [Q1; Q3] — median, interquartile range, Min — minimum value, and Max — maximum value.

Table 2. Serum IL-6 (pg/ml) in subgroups of the studied cohort

Variable name	Serum IL-6 levels (pg/ml)		MWU-test; *p*
	Patients, *n*=125	Healthy volunteers, *n*=95	
All participants: m (σ); Me [Q1; Q3]	5.6 (16.6); 1.5 [0.7; 4.9]	2.7 (3.7); 0.8 [0.3; 4.7]	z=2.58; *p*=0.0099
Women: Me [Q1; Q3]	1.73 [0.67; 8.31]	0.74 [0.29; 4.05]	z=2.89; *p*=0.0038
Men: Me [Q1; Q3]	1.41 [0.70; 2.86]	0.92 [0.41; 6.53]	z=0.51; *p*=0.61

Note: m (σ) — mean value (standard deviation); Me [Q1; Q3] — median and interquartile range; and MWU-test — Mann-Whitney U-test. Reference range of the IL-6 serum level — 0–10 pg/ml.

Table 3. Association of IL-6 with the clinical characteristics of patients

Variable name		Me [Q1; Q3]	Spearman, ρ	*P*
Age of disease manifestation, years (*n*=125)		25 [20; 32]	0.20	0.025
Daily dose of antipsychotic, chlorpromazine equivalent (*n*=125)		180 [100; 300]	0.073	0.42
Disease duration, months (*n*=125)		34 [15; 156]	0.18	0.043
Positive symptoms PANSS score (*n*=125)		12 [10; 16]	0.18	0.048
Negative symptoms PANSS score (*n*=125)		19 [15; 24]	0.17	0.07
General psychopathology PANSS score (*n*=125)		37 [31; 43]	0.19	0.038
Total symptom severity PANSS score (*n*=125)		69 [59; 82]	0.22	0.016
Level of personal and social functioning (PSP score) (*n*=125)		57 [45; 67]	−0.13	0.17
Anhedonia (SHAPS score) (*n*=117)		2 [0; 4]	0.056	0.55
Depression (CDSS score) (*n*=122)		3 [1; 7]	0.045	0.62
Adverse effects of therapy, UKU total score (*n*=125)		9 [6; 16]	−0.018	0.84
EPS (UKU-EPS score) (*n*=125)		1 [0; 3]	−0.030	0.74
EPS (SAS score) (*n*=73)		0 [0; 0]	0.15	0.22
Dyskinesia (AIMS score) (*n*=73)		1 [0; 2]	0.055	0.65
Akathisia (BARS score) (*n*=73)		0 [0;0]	0.082	0.49
Catatonia (BFCRS score) (*n*=72)		0 [0; 1]	0.053	0.66
BACS score (*n*=122)	auditory memory	36 [26; 45]	−0.31	0.00063
	working memory	15 [12; 18]	−0.25	0.0065
	motor speed	56 [46; 70]	−0.027	0.77
	verbal fluency	42 [30; 55]	−0.28	0.0019
	hand-eye coordination	36 [24; 50]	−0.29	0.0011
	problem-solving behavior, executive functions	16 [12; 18]	−0.22	0.013
Childhood trauma questionnaire (CTQ score) (*n*=113)	emotional abuse	9 [6; 13]	0.070	0.46
	physical abuse	6 [5; 8]	−0.034	0.72
	sexual abuse	5 [5; 5]	0.088	0.35
	emotional neglect	11 [8; 15]	−0.10	0.29
	physical neglect	8 [6; 10]	0.0089	0.93

Note: IL-6 — interleukin-6; PANSS — Positive and Negative Syndrome Scale; PSP — Personal and Social Performance scale; SHAPS — Snaith-Hamilton Pleasure Scale; CDSS — Calgary Depression Scale for Schizophrenia; UKU — the UKU Side Effect Rating Scale (version "The UKUSERS-Clin"); EPS — extrapyramidal symptoms; SAS — Simpson-Angus scale; AIMS — the Abnormal Involuntary Movement Scale; BARS — Barnes Akathisia Scale; BFCRS — Bush-Francis Catatonia Rating Scale; BACS — Brief Assessment of Cognition in Schizophrenia; Me [Q1; Q3] — median and interquartile range. There was a statistically significant association between the IL-6 levels and several PANSS scores: P2 (conceptual disorganization, ρ=0.31; *p*=0.00044), N5 (difficulty in abstract thinking, ρ=0.29; *p*=0.0011), N6 (lack of spontaneity and flow of conversation, ρ=0.18; *p*=0.047), G8 (uncooperativeness, ρ=0.18; *p*=0.042), G10 (disorientation, ρ=0.33; *p*=0.00019), G11 (poor attention, ρ= 0.20; *p*=0.027), and G12 (lack of judgment and insight, ρ=0.18; *p*=0.044).

Comparative analysis of IL-6 levels in patients and healthy controls

Table 2 shows that the level of IL-6 is almost twice as high in the patients compared to the volunteers. In female patients, the level of IL-6 was significantly higher than that in the healthy women. In men, it was also higher, but not as significantly. The differences in the IL-6 levels between men and women were not significant both across the entire studied sample (Z=−0.056; *p*=0.95) and separately among patients (Z=−1.45; *p*=0.15) and volunteers (Z=0.85; *p*=0.39). The lack of statistically significant differences in men was probably due to the smaller number of observations in a subgroup of healthy volunteers.

In the patients, the levels of IL-6 rather weakly correlated with age (ρ=0.21; *p*=0.016). In the healthy volunteers, however, this pattern was not found (ρ=0.029; *p*=0.78). No association between IL-6 levels and the BMI or weight was found either among the patients (ρ=−0.074; *p*=0.48

Table 4. The serum IL-6 level and daily doses of antipsychotics in patients with different clinical characteristics

Subgroup characteristic		Serum IL-6, pg/ml	H; *p*	Daily dose of APs in CPE	H; *p*	Correlation between serum IL-6 & daily dose, ρ; *p*
ICD-10 diagnosis	Paranoid schizophrenia (*n*=97)	1.55 [0.74; 5.83]	H=5.70; *p*=0.22	200 [100; 300]	H=1.89; *p*=0.76	0.09; 0.38
	Acute polymorphic psychotic disorder with symptoms of schizophrenia (*n*=17)	1.55 [0.42; 1.89]		150 [100; 280]		0.052; 0.84
	Undifferentiated schizophrenia (*n*=8)	0.95 [0.43; 1.42]		138 [68; 264]		−0.095; 0.82
	Simple schizophrenia (*n*=2)	3.36 [0.20; 6.53]		150 [70; 330]		NA
	Hebephrenic schizophrenia (*n*=1)	8.09		140		NA
Type of the disease course	Continuous (*n*=58)	1.54 [0.82; 6.53]	H=1.24; *p*=0.54	240 [135; 380]	H=2.01; *p*=0.37	0.040; 0.77
	Episodic with progressive deficit (*n*=48)	1.34 [0.50; 5.60]		150 [100; 238]		0.094; 0.53
	Course uncertain, period of observation too short (*n*=17)	1.55 [0.42; 1.89]		150 [100; 280]		0.079; 0.76
Disease duration	less than 1 year (*n*=27)	1.55 [0.50; 2.90]	H=4.60; *p*=0.10	150 [75; 250]	H=3.26; *p*=0.20	−0.052; 0.80
	1-5 years (*n*=51)	1.34 [0.67; 2.19]		160 [100; 300]		0.0061; 0.97
	over 5 years (*n*=47)	2.42 [0.74; 9.22]		230 [132; 380]		0.17; 0.25
Age of manifestation	under 30 years old (*n*=87)	1.52 [0.70; 2.86]	H=3.59; *p*=0.058	195 [100; 350]	H=1.12; *p*=0.29	0.16; 0.15
	over 30 years old (*n*=38)	2.29 [0.62; 9.22]		150 [100; 250]		−0.013; 0.94

Note: IL-6 — interleukin-6; IL-6 level displayed in Me [Q1; Q3] — median and interquartile range; H — Kruskal-Wallis test; ρ — Spearman rank coefficient; NA — not applicable; *p* — significance level of differences; AP – antipsychotic; and CPE — chlorpromazine equivalent.

and ρ=−0.11; *p*=0.26, respectively) nor among the healthy volunteers (ρ=0.17; *p*=0.10 and ρ=0.16; *p*=0.12, respectively). Moreover, in the patients treated with second-generation APs (which most significantly affect the metabolic profile), the association of IL-6 levels with BMI tended to have a weak negative correlation: ρ=−0.23; *p*=0.068.

The association of IL-6 with the clinical characteristics of patients is illustrated in Table 3. There was a statistically significant association between the IL-6 levels and several PANSS scores: P2 (conceptual disorganization, ρ=0.31; *p*=0.00044), N5 (difficulty in abstract thinking, ρ=0.29; *p*=0.0011), N6 (lack of spontaneity and flow of conversation, ρ=0.18; *p*=0.047), G8 (uncooperativeness, ρ=0.18; *p*=0.042), G10 (disorientation, ρ=0.33; *p*=0.00019), G11 (poor attention, ρ=0.20; *p*=0.027), and G12 (lack of judgment and insight, ρ=0.18; *p*=0.044).

Comparative analysis of IL-6 levels in subgroups of patients with different clinical and therapeutic characteristics

Table 4 presents a comparative characteristic of the level of serum IL-6 and daily doses of APs in patients from various clinical groups and also shows the correlation of IL-6 with doses in each subgroup. The highest doses of APs were found in the paranoid type, continuous course, and disorder duration of over 5 years (not significant); while the serum IL-6 level was highest in patients with a simple and hebephrenic form, with a disorder duration of over 5 years and onset after 30 years of age (statistically significant only in the case of onset before and after 30 years). None of the clinical subgroups showed a trend towards a correlation between IL-6 and daily doses.

The levels of IL-6 significantly differed amongst patients receiving different generations of APs (Table 5). According to pairwise comparisons, the IL-6 differences between patients treated with first- and third- generation APs were statistically significant (Z=2.12; *p*=0.034); between patients treated with first- and second-generation APs, the differences approached the level of statistical significance (Z=1.87; *p*=0.061); while between patients receiving second- and third-generation APs, they were not significant (Z=1.24; *p*=0.22). The selectivity (potency for D2 receptors)[1] of APs was not associated with the IL-6 levels (Table 5). Patients treated with combinations of APs with different selectivity showed

[1] Haloperidol, risperidone, aripiprazole, cariprazine, zuclopenthixol were included in the group of highly potent APs; olanzapine, trifluoperazine, perphenazine — in the group of medium potent APs; clozapine and quetiapine — in the group of low-potent APs; other APs were not prescribed to patients of the study sample.

Table 5. Serum IL-6 level in patients receiving different types of pharmacotherapies

Variable name		Serum IL-6, pg/ml	H; *p*/Z; *p*
APs' generation	first (*n*=41) second (*n*=51) third (*n*=10) combination of 1 and 2 (*n*=21)	1.89 [1.09; 8.09] 1.34 [0.50; 2.69] 0.86 [0.16; 1.16] 1.60 [1.20; 3.11]	6.36; 0.042
APs' selectivity[1]	highly potent (*n*=47) medium potent (*n*=31) low potent (*n*=15) combination of APs with different selectivity (*n*=30)	1.51 [0.63; 6.53] 1.38 [0.45; 2.03] 1.41 [0.95; 4.90] 1.71 [0.99; 7.00]	1.37; 0.51
Correctors of extrapyramide disorders	absent (*n*=80) present (*n*=45)	1.34 [0.62; 5.25] 1.85 [1.17; 3.87]	0.58; 0.56
not taking APs (*n*=2)		6.11 [0.74; 11.49]	NA

Note: IL-6 — interleukin-6; IL-6 level displayed in Me [Q1; Q3] — median and interquartile range; H — Kruskal-Wallis test (in case of more than 2 groups); Z — Mann-Whitney U-test (in case of 2 groups); *p* — significance level of differences; AP — antipsychotic; NA — not applicable.

Table 6. Comparative characteristics of patients receiving various types of psychiatric care

Variable name	Hospitalized patients (*n*=69)	Patients of daycare departments (*n*=39)	Outpatients (*n*=17)	H; *p*
Serum IL-6, pg/mL	2.15 [1.34; 8.09]	0.88 [0.42; 1.97]	0.91 [0.41; 1.53]	H=18.59; *p*=0.0001
Age, years	33 [26; 46]	33 [24; 40]	34 [26; 39]	H=1.51; *p*=0.47
Onset age, years	26 [20; 32]	25 [19; 31]	26 [22; 33]	H=0.51; *p*=0.77
Disease duration,months	36 [14; 190]	28 [16; 96]	34 [22; 120]	H=1.05; *p*=0.59
Positive symptoms PANSS, score	13 [10; 16]	12 [9; 14]	11.5 [10; 16]	H=2.51; *p*=0.28
Negative symptoms PANSS, score	20 [17; 27]	16 [12; 19]	20 [17; 21.5]	H=17.64; *p*=0.0001
General psychopathology PANSS, score	39 [34; 45]	33 [28; 38]	39.5 [32.5; 48]	H=12.35; *p*=0.0021
Total symptom severity PANSS, score	75 [65; 87]	62 [50; 69]	73 [60.5; 84]	H=14.89; *p*=0.0006
Daily dose of APs, CPE	200 [105; 380]	150 [100; 225]	176 [100; 225]	H=2.44; *p*=0.30
Generation of APs used: 1/2/3/combination of 1–2 (number of patients)	28/25/0/16	11/18/5/4	2/8/5/1	χ^2=25.3; *p*=0.0056
auditory memory (BACS, score)	32 [24; 40]	40 [33; 48]	42 [32.5; 51.5]	H=12.45; *p*=0.0020
working memory (BACS, score)	14 [11; 18]	16 [13; 18]	15.5 [13; 22.5]	H=4.07; *p*=0.13
motor speed (BACS, score)	51 [41; 64]	62 [54; 74]	70.5 [46; 80]	H=13.09; *p*=0.0014
verbal fluency (BACS, score)	36 [28; 47]	49 [37; 59]	51 [41.5; 58.5]	H=13.75; *p*=0.0010
hand-eye coordination (BACS, score)	27 [19; 38]	46 [38; 52]	43.5 [33; 53]	H=29.63; *p*=0.0000
problem-solving behavior (BACS, score)	14.5 [8; 18]	17 [14; 18]	18.5 [15.5; 19.5]	H=11.93; *p*=0.0026

Note: IL-6 — interleukin-6; data displayed in Me [Q1; Q3] — median and interquartile range; H — Kruskal-Wallis test; *p* — significance level of differences; PANSS — Positive and Negative Syndrome Scale; AP — antipsychotic; CPE — chlorpromazine equivalent; BACS — Brief Assessment of Cognition in Schizophrenia; χ^2 — the hi-square criterion for tables.

the highest levels of IL-6. Correctors of extrapyramidal disorders (biperiden, amantadine, trihexyphenidyl) did not affect IL-6 levels.

The comparative characteristics of patients receiving various types of psychiatric care (Table 6) showed that in hospitalized patients IL-6 levels were significantly higher compared to inpatients (Z=4.02; p=0.000057) and outpatients (Z=2.59; p=0.0097), while no significant differences were observed between inpatients and outpatients (Z=0.080; p=0.94).

Hospitalized patients more often were treated with first-generation APs (no one received third-generation APs, and only 25/69 received second-generation APs). Patients treated with third-generation APs were younger than patients treated with first-generation APs (Z=2.02; p=0.044), and those were more often treated on an outpatient basis and in daycare units. Therefore, it is likely that the lower level of IL-6 in patients treated with third-generation APs (n=10) has to do not with the treatment used, but with the younger age and lesser severity of the disease. There were no differences in the IL-6 levels between patients who took first- and second-generation APs in the hospital (Z=0.77; p=0.44). Separately, significant association between age and IL-6 level was confirmed in the subgroup of inpatients (n=69): ρ=0.36; and p=0.0018. However, in the combined subgroup of outpatients (n=17) and inpatients (n=39), there was virtually no correlation between IL-6 levels and age: ρ=−0.066; p=0.63.

Nicotine dependence and IL-6 levels in study participants

In patients with nicotine dependence, IL-6 levels did not differ from those of other patients (Z=0.16; p=0.88), and they did not tend to differ (in nicotine-dependent patients, mean IL-6 levels were lower than those in non-smokers). In the entire studied sample, IL-6 levels also did not differ between individuals with and without nicotine dependence (Z=0.19; p=0.84).

DISCUSSION

Our study showed statistically significant higher levels of serum IL-6 in patients with schizophrenia compared with healthy volunteers. Our results were consistent with previously published data [3–7].

Data on the IL-6 serum level association with the majority of the studied domains of cognitive function, as well as with the PANSS general psychopathology and total scores, appears to indicate that this biochemical marker could be a reflection of the severity of the schizophrenic process, the social maladaptation, as well as disability (due to cognitive impairment). This finding is further supported by the specific profile of PANSS symptoms as they show significant correlation with serum IL-6 levels (N5 — difficulty in abstract thinking, N6 — lack of spontaneity and stilted conversation, P2 — conceptual disorganization, G8 — uncooperativeness, G10 — disorientation, G11 — poor attention, G12 — lack of judgment, and insight). Our data were consistent with previously published research results. In Miller et al. meta-analysis (2011) IL-6 showed correlation with symptom severity in two of five studies [2]. Khandaker et al. (2014) [10] also demonstrated that IL-6 is associated with the severity of schizophrenia symptoms. Thus the study's results are consistent with the hypothesis that IL-6 is a state-dependent marker of inflammation. Moreover, we obtained data on a strong association between the serum IL-6 level and the cognitive functions of patients with schizophrenia. Those findings are consistent with the results of a recently published meta-analysis of the association of pro-inflammatory cytokines (including IL-6) with cognitive decline in schizophrenia [35]. Thus the heterogeneity of the clinical manifestations of schizophrenia may be associated with immunological heterogeneity, which finds indirect confirmation in the correlations identified in our study. This allows us to assign patients with the most severe symptoms of schizophrenia, especially those with severe cognitive impairment, to the category of candidates for targeted diagnostics of immune-inflammatory markers and personalized correction of immune-inflammatory dysfunctions, which requires further investigation through longitudinal studies.

Noteworthy is the weak positive correlation of IL-6 with age only in patients, but not in healthy volunteers. The correlation of cytokine levels with the duration of the disease in patients is consistent with the results of other studies in which the peripheral blood IL-6 level had a significant, positive correlation with the duration of schizophrenia [2, 8]. The association of IL-6 with the duration of the disease may be indication of an increase in the role of the immune response with the course of the disease, which does not exclude a secondary role for this pathogenetic process in relation to the other pathogenetic mechanisms studied in schizophrenia. In addition, patients with a longer duration of the disorder could hypothetically experience an earlier onset of schizophrenia and, thus,

a greater severity of the symptoms. However, this contradicts our data pointing to a direct IL-6 correlation with the age of manifestation of the disease. This discrepancy may have something to do with a later entry date into the psychiatric care system for some patients and a longer duration of untreated psychosis in the subgroup of patients with a later age of manifestation of the disease.

We have not been able to find studies on the association of IL-6 and other immunoinflammatory markers with a later manifestation of schizophrenia. However, some studies showed that late-onset psychoses are often secondary in up to 60% of cases and require a more thorough differential diagnosis and the exclusion of somatogenic causes for the psychosis, also using autoimmune panels [36, 37].

More pronounced differences in the level of IL-6 between patients and volunteers in women compared with men were consistent with data on a higher incidence of autoimmune encephalitis in women [38]. Anti-NMDA receptor encephalitis can phenotypically manifest as a symptomatic psychosis that meets the diagnostic criteria for schizophrenia; according to a systematic review by Al-Diwani et al. (2019) 32% of cases of NMDAR-antibody encephalitis are associated with ovarian teratoma [38, 39]. Thus, the gender differences in immuno-inflammatory disruptions in schizophrenia may be of interest for further study.

The association of serum IL-6 levels with smoking, identified in a pilot study [40], was not confirmed in this work. The association of IL-6 levels with different EPS subtypes obtained in the same pilot study [40] was also not confirmed in this work.

The differences in the IL-6 levels of patients receiving antipsychotics of different generations merit close attention. Patients who received first-generation APs, as well as combinations of APs of different generations, had a significantly higher level of IL-6 (Table 5). However, as shown in Table 6, inpatients received them significantly more often, therefore, they also had more pronounced symptoms that were associated with the level of IL-6. At the same time, within the subgroup of inpatients, there were no differences in the level of IL-6 between patients treated with first- and second-generation APs. In addition, there was no association between IL-6 levels and AP doses in CPE. We can assume that the therapy applied does not have a significant effect on the level of serum IL-6, the latter being more closely associated with the symptoms of the disease and cognitive functions. This is consistent with data obtained earlier by other researchers [2, 10, 14, 15].

Fang et al. (2019) obtained data on the association of IL-6 levels with the metabolic syndrome in patients treated with second-generation AP [6]. According to them, this association may be due to the fact that second-generation APs activate the pro-inflammatory molecular mechanisms involved in the metabolic syndrome pathology. This hypothesis was also not confirmed in our study. There was a tendency to a weak negative correlation between the level of IL-6 and BMI in patients treated with second-generation APs. This may be due to the use of different drugs within the second-generation APs group, which requires additional analysis. Patients in our sample who received the most BMI-affecting drugs (clozapine *n*=11, olanzapine *n*=18) had a lower BMI and IL-6 than other patients (not significantly). That could be due to recent prescription of these drugs (which was not evaluated), as well as to the personalized selection of therapy (considering the initial data on BMI and the exclusion of clozapine and olanzapine use in the risk group with an initially high BMI). Given that IL-6 in patients treated with clozapine was lower than in the other patients in our sample (not significantly), and in alignment with data in the literature [15–17], and considering the data in a large body of studies pointing to a decrease in the level of IL-6 during AP treatment [2, 10], further study into the effects of AP on the immune-inflammatory profile is called for.

Strengths and limitations of the study

Strengths of the study: In-depth phenotyping of patients was conducted using standardized validated psychometric instruments and laboratory studies were blind to the participant group, and clinical examination was blind to laboratory results.

Limitations of the study: A cross-sectional design did not allow one to draw conclusions on any causal relationship between IL-6 and clinical characteristics. The duration of AP intake before inclusion was not analyzed in patients, which may have Interfered with the analysis of the APs effect on the IL-6 levels.

The severity of schizophrenia symptoms, especially cognitive symptoms, a late-onset of the disorder, and the female gender can serve as clues in targeted diagnostics and personalized approach to the mitigation of disruptions caused by immune inflammations. This requires a more thorough differential diagnosis and the exclusion of somatogenic causes of psychosis.

CONCLUSION

Our study highlights an association between serum IL-6 levels and schizophrenia, patient age, duration of the disease and a later onset, various clinical variables in schizophrenia patients (cognitive impairment, severity of the PANSS general psychopathology subscale, as well as the total PANSS score). Considering that IL-6 is associated with a wide range of symptoms that are poorly controlled by APs and affect the daily activities of patients, this biochemical marker needs to be considered for association with an unfavorable course of schizophrenia, which requires further prospective studies. The results obtained here point to the pressing need for further investigation of inflammatory markers among patients with schizophrenia in order to isolate the data with a bearing on their causality in the disease's pathogenesis.

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Efficacy and Safety Profiles of Antipsychotic Drugs as Viewed by Psychiatrists: A Comparative Analysis of Cariprazine and Risperidone

Эффективность и безопасность антипсихотических препаратов с точки зрения психиатров: сравнительный анализ карипразина и рисперидона

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Original research

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ABSTRACT

BACKGROUND: Physicians hold the belief that the treatment outcomes and the treatment strategy they eventually adopt is largely determined by the differences in medications. Despite numerous studies focusing on the decision-making processes of psychiatrists, including the choice of antipsychotics when prescribing pharmacotherapy, the impact of therapeutic drug profiling on physicians' decision-making remains poorly comprehended.

AIM: The aim of this study is to assess the quantitative differences in perceptions of antipsychotics by psychiatrists using cariprazine and risperidone as examples.

METHODS: A total of 79 psychiatrists were interviewed anonymously in St. Petersburg, Russia. The physicians documented the clinical advantages they perceived drugs to possess relative to one another, following a predetermined principle: A >B, A=B, A <B (2-AC protocol). The comparison is based on eleven parameters that assess the effectiveness and safety of cariprazine or risperidone. It has been hypothesized that the pattern of responses (qualitative difference) and the degree of preference for each drug (quantitative difference) may not align with the data in the original meta-analyses.

RESULTS: The perception parameter exhibited a greater difference than anticipated (δ — 0.889), while the threshold for differentiating between the drugs was lower (τ — 1.001). The response pattern only aligned with theory by 44.37%. The dispersion of responses was associated with the length of work experience.

CONCLUSION: The perceived difference between the drugs significantly deviates from the theoretical data, both in terms of strength of perception and pattern (quantitative and qualitative differences).

АННОТАЦИЯ

ВВЕДЕНИЕ: Врачи придерживаются мнения, что результаты лечения и стратегия лечения, которую они в конечном итоге принимают, в значительной степени определяются различиями в лекарственных препаратах. Несмотря на многочисленные исследования, посвященные процессам принятия решений психиатрами, в том

числе выбору антипсихотиков при назначении фармакотерапии, влияние терапевтического профилирования препаратов на принятие решений врачами остается малоизученным.

ЦЕЛЬ: Цель данного исследования — оценить количественные различия в восприятии антипсихотиков психиатрами на примере карипразина и рисперидона.

МЕТОДЫ: Опросили 79 врачей-психиатров в Санкт-Петербурге (Россия) с помощью слепого опросника. Врачи фиксировали клинические преимущества, которыми, по их мнению, обладают препараты по сравнению друг с другом, следуя заранее определенному принципу: A >B, A=B, A <B (протокол 2-AC). Сравнение проводилось по одиннадцати параметрам, оценивающим эффективность и безопасность карипразина или рисперидона. Была выдвинута гипотеза, что паттерн ответов (качественные различия) и степень предпочтения каждого препарата (количественные различия) могут не совпадать с данными оригинальных метаанализов.

РЕЗУЛЬТАТЫ: Параметр восприятия показал большую разницу, чем предполагалось (δ — 0,889), в то время как порог различения препаратов оказался ниже (τ — 1,001). Паттерн ответов соответствовал теоретическому только на 44,37%. Разброс ответов был связан со стажем работы.

ЗАКЛЮЧЕНИЕ: Воспринимаемые различия между препаратами значительно отклоняются от теоретических данных как по силе восприятия, так и по паттерну (количественные и качественные различия).

Keywords: *schizophrenia; decision-making; medication prescribing; Thurstonian model; 2-AC protocol*
Ключевые слова: *шизофрения; принятие решений; назначение препарата; Терстоновская модель; 2-AC протокол*

INTRODUCTION

Schizophrenia is a severe mental disorder, the burden of which is growing worldwide [1]. The prescription of antipsychotic therapy is the primary medical intervention for this disorder [2]. Antipsychotics are traditionally divided into first- and second-generation ones. A unifying feature of first-generation antipsychotics is direct blockage of D2 dopamine receptors [3]. The discovery of clozapine and attempts to replicate its unique receptor profile led to the second generation of antipsychotics [4]. Second-generation antipsychotics have a high affinity for other receptors, such as serotonin 5-HT2A, histamine H1, and others [4–6]. A subgroup of antipsychotics, the main feature of which is partial agonism to D2/D3 receptors (third generation), has been recently separated from second-generation ones [3, 4, 6]. At the time of writing, aripiprazole, brexpiprazole, and cariprazine are recognized to have this property.

The choice of a particular antipsychotic for treatment is a multidimensional undertaking, because not only the manifestations of the disease and comorbidities have to be considered, but the pharmacological profile of the drugs as well [7]. There is a large number of drugs, each of which is characterized by its profile of therapeutic activity and safety [5, 8]. An unambiguous recommendation of a specific name, clozapine, is justified only in the case of resistant forms of schizophrenia [9]. There is also no consensus in the current clinical guidelines on the choice of the generation of antipsychotics [5, 10]. In summary, there are no hard-and-fast rules when it comes to choosing a particular drug for the treatment of schizophrenia [11].

Yet, in practice, physicians regularly make the decision to prescribe a specific drug. That choice is thought to be driven by two main criteria: the probability that the drug will be effective in treating the disease (efficacy), and the probability that side effects will not occur as a result of the use of the drug (safety) [12–14]. Two factors have a direct impact on the decision-making process in the clinical context: “factor one”, which is intuitive, automatic, based on experience and affect, and “factor two”, which is analytical, slow, verbal, and logical [15, 16]. To date, the important role of unconscious factors (“factor one”) in clinical decision-making has been demonstrated [16]. For instance, the “belief” in the efficacy and safety of second-generation antipsychotics is a stronger argument in favor of prescribing a drug than the data rebutting it [13]. The choice of which generation of antipsychotics

to use is influenced by a physician's practice [17, 18], which indirectly confirms the role of experience in the decision-making process. Thus, in addition to efficacy and safety, medical decision-making is influenced by a variety of factors, such as cognitive errors [19].

Despite the large body of existing research, there is still a need for further study into the decision-making process. We could not find any research that assesses the quantitative differences in drug perception, and this has been the reason behind our decision to undertake the present study. We have anticipated that the perceptions of psychiatrists would not align with the reference differences between drugs known from meta-analyses. Preference would, as a matter of course, be given to a drug with a long history of use; i.e., risperidone. To test this hypothesis, statistical theories were formulated: (a) the structure of the responses fully aligns with the structure of initial differences between drugs, and (b) the parameters of a quantitative assessment of perception and the decision-making process match the initial data. The rejection of these statistical hypotheses would be confirmation of our research hypotheses.

METHODS

Target selection

The object of the study is the subjective evaluations of psychiatrists working in the public health care system regarding the choice of antipsychotics. The questionnaires were distributed to psychiatrists of the state system. The requirements for completing the questionnaire are as follows:

1. A valid credential that confers the right to provide medical care in the field of psychiatry;
2. Experience in using cariprazine for the treatment of schizophrenia — more than 5 treated patients;
3. Experience in using risperidone for the treatment of schizophrenia — more than 5 treated patients.

The return of a completed questionnaire has been viewed as confirmation of consent to participate in the study.

Sample

A quota sampling strategy was used to recruit participants to the study. In each state health care center (3 psychiatric hospitals, 2 psychiatric hospitals with an out-patient unit, 10 psychoneurological out-patient clinics), psychiatrists were invited to fill out a blind questionnaire. The place of practice (outpatient clinic, day hospital, 24-hour hospital) was a quota characteristic. An equal number of two versions of the questionnaire was assumed for each quota.

Since the survey did not require any information from the participants, the study did not need an ethics review. The participants were assured that every attempt would be made to ensure that their responses to the questionnaire remained confidential. Administrative coercion was excluded in the sampling process. The return of an anonymized questionnaire was considered to be indicative of informed consent. These considerations are in keeping with the ethical principles set out in the Helsinki Declaration.

Drug comparison model

Where an object's properties can be described using an interval value system, the difference on the measurement scale provides a quantitative measure of the difference. This approach is inappropriate for cases where measurement tools are unavailable or reliant on a value judgment system. Violation of the equidistant principle can result in inaccurate assessment of classical measures such as total score and arithmetic mean and hinder the use of statistical models like linear regression and analysis of variance [20]. For this category of data, ordinal regression is the appropriate approach [21]. The detailed rating model is presented in the Appendix A (in the Supplementary).

The described methodology utilizes classical sensometric protocol of 2-Alternative Forced Choice, with the option of "No difference" (2-AC protocol) [22]. This protocol is commonly employed to determine product preference. In this particular study, we sought to evaluate psychiatrists' perception of a drug's specific attribute severity, based on their individual professional experience.

Variables

The drugs risperidone and cariprazine have been chosen for comparison. Risperidone is the oldest second-generation antipsychotic [4]. At one point, experts regarded it as the drug of choice for the treatment of schizophrenia [23]. Risperidone is the most commonly prescribed medication [13], and this is also true in Saint Petersburg, as shown in the current study [24]. In addition to the recognition and wide popularity of risperidone, that choice has influenced its use as a comparison drug in studies of cariprazine [25–27].

Cariprazine is a new antipsychotic being a partial agonist of D3/D2 dopamine receptors that predominantly effects D3 receptors. The drug was created based on several

assumptions: affinity for the D2 receptor is mandatory, and that partial agonism or antagonism to D3 receptors can improve cognitive functions and reduce the risk of catalepsy. In addition, the drug is believed to have a greater affinity for D3 receptors [28]. Cariprazine is effective against the core symptoms of schizophrenia, including the first psychotic episode, and it has good tolerability [29–31]. There is evidence that Cariprazine is highly effective in patients who display predominantly negative symptoms [25–27, 32].

The meta-analyses by Pillinger et al. [33] and Huhn et al. [8] were used to create a drug comparison model. All network analyses served as a basis: overall change in symptoms, all-cause discontinuation, positive symptoms, negative symptoms, depressive symptoms, weight gain, use of antiparkinsonian drugs, akathisia, increased prolactin levels, QT interval prolongation, sedation, anticholinergic side effects [8], increase in total cholesterol, low-density (LDL) and high-density (HDL) lipoproteins, triglycerides, and glucose [33]. The use of the surface under the cumulative ranking curve allowed us to identify three superiority positions for risperidone, ten comparable positions, and four cariprazine superiority positions (3 – 10 – 4). This distribution of the results is described by the theoretical parameters δ 0.147 and τ 1.167. For identifying the calculated figures, 928 responses are required (power — 80%, confidence probability — 95%).

To simplify our study, we analysed the positions under consideration to determine if any could be excluded. The first excluded characteristic was a general change in symptoms. Usually, the total score is calculated as a sum of subscales. As there are distinct sources of data on the negative and positive symptoms, it becomes unnecessary to incorporate the overall score into the analysis. The exclusion of all-cause discontinuation is related to the inability to conduct an evaluation in clinical practice. The need for antiparkinsonian therapy does not fully reflect the assessment of the occurrence of parkinsonism; so, it has been excluded. Exclusion of two positive characteristics for risperidone and one neutral characteristic resulted in an excessive optimistic difference between the drugs (1 – 9 – 4, δ — 0.636, τ — 1.436, 54 observations).

Furthermore HDL, LDL, and triglycerides have not been included in the experiment for the following reasons: total cholesterol is a composite of lipoproteins and provides the best standardization in laboratory testing compared to other lipids and lipoproteins [34]. Since total cholesterol is a composite of lipoproteins, replacing the indicator to simplify the model is warranted. Replacing several parameters with one common variable is a means to simplify the model. In particular, the exclusion of the laboratory measure of LDL, for which cariprazine is shown to be beneficial, is a way to partially balance out the exclusion of the two positive characteristics of risperidone. Thus, for identifying the difference between the answers in the sequence "Risperidone" — "No difference" — "Cariprazine" (1 – 7 – 3), 79 questionnaires have been required (δ — 0.517, τ — 1.372).

Table 1. The cariprazine and risperidone characteristics used in the study

Parameter	Average value [95% CI]	Advantage per meta-analysis
"+" Positive symptoms (SMD)	-0.30 [-0.46; -0.15]	Risperidone
"+" Negative symptoms (SMD)	-0.04 [-0.17; 0.08]	No difference
"+" Depressive symptoms (SMD)	0.14 [-0.15; 0.43]	No difference
"–" Weight gain (kg)	0.71 [-0.09; 1.51]	No difference
"–" Akathisia (RR)	0.79 [0.50; 1.37]	No difference
"–" Prolactin elevation (ng/ml)	41.17 [34.63; 47.74]	Cariprazine
"–" QT interval prolongation (ms)	6.22 [1.58; 11.01]	Cariprazine
"–" Sedation (RR)	1.79 [1.14; 3.23]	Cariprazine
"–" Anticholinergic effects (RR)	0.91 [0.56; 1.54]	No difference
"–" Cholesterol (SMD)	0.15 [-0.02; 0.31]	No difference
"–" Glucose (SMD)	-0.18 [-0.50; 0.14]	No difference

Note: SMD (Standardized Mean Difference), RR (Relative Risk), and CI (Confidence Interval), "+" is used to indicate that the advantage has been evaluated according to the greater relative severity of the effect, while "–" means the advantage is determined by the smaller relative magnitude of the impact.

In addition to the quantitative differences between the drugs (parameters δ and τ), qualitative differences in perception can captured. Quantitative differences do not reflect the conformity of the responses to the initial therapeutic profile of the drugs. Therefore, the qualitative dimension of the perception is assessed by the proportion of the respondents' answers matching the original perceived advantages. Table 1 presents the number of included parameters and the decisions made for each drug's property in the meta-analyses.

The introductory part of the questionnaire included questions regarding the length of service, place of work (outpatient service, day hospital, 24-hour inpatient hospital), prescription of the drugs, and the number of treated patients. The first question of the main part concerned the immediate choice between cariprazine and risperidone in as uncertain circumstances as possible. The second question asked the respondent to compare in pairs the three factors that are most important in prescribing the drugs: the accessibility and availability of discounted drug coverage, the efficacy of the drug, and the side effect profile. Since these two questions are the subject of a separate analysis, they are not used in this paper.

The third portion of the questionnaire included questions related to the comparison of the drugs based on selected variables from the meta-analysis. The questions began with: "*According to your experience and clinical practice, choose the drug that in your opinion…*". The third portion is divided into three subgroups of parameters reflecting the therapeutic effect, side effects, and changes in objective parameters. Since some of the questions reflect the worst characteristic (for example, weight gain), reverse order for calculations is used, but the evaluated categories remain the same. To counteract the effects of consistency, all questionnaires are divided into two versions. In questions 1 and 3 of the first version, the list of answers began with cariprazine; and in the second — with risperidone. In question 2, the sequence of comparison pairs is mirrored in each of the versions. This approach meets the requirements of the 2-AC protocol [35]. Appendix B (in the Supplementary) provides an example of the questionnaire that is offered for completion.

Statistical analysis

Absolute values and prevalence, n (%), were used to describe categorical variables. Variables with a continuous distribution were described by a mean (M). When necessary, 95% confidence intervals for the calculated parameters (lwr; upr) were provided. The minimum and maximum values (|min;max|) were also calculated.

The planned number of respondents was calculated using the *twoACpwr* function, and the discrimination parameters were calculated using the *twoAC* function[1]. For repeated measures, the number of responses required was equated to the number of questionnaires required. The description of the 2-AC protocol and its technical implementation are provided by the developer of the *sens*R library [22]. Alignment of the response pattern with the results of the meta-analysis has been verified using the *opa* library[2], which was designed to make sure that the observed response structure corresponds to a hypothetical distribution [36]. The percentage of correct classifications (*PCC*) and the coefficient of randomness of the result (*c-value*) were calculated. To determine the relative difference in the responses [37], calculation of a multinomial distribution with a 95% confidence interval using the function *MultinomCI* was employed[3]. The relationship between variables was estimated by ordinal regression[4]. The optimal model was chosen according to the lowest Akaike's criteria (AIC). The strength of association between variables was represented as an odds ratio and a 95% confidence interval (OR [lwr; upr]). All calculations were performed in the Rv4.2.3 programming language[5].

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Table 2. Distribution of answers on the perception of the clinical difference between drugs

Parameter	Risperidone (proportion, [95% CI])	No difference (proportion, [95% CI])	Cariprazine (proportion, [95% CI])	Advantage by meta-analysis	Advantage by survey results
"+" Positive symptoms	0.57 (0.43; 0.72), *n*=45	0.42 (0.28; 0.57), *n*=33	0.01 (0.00; 0.17), *n*=1	Risperidone	Risperidone
"+" Negative symptoms	0.01 (0.00; 0.06), *n*=1	0.05 (0.00; 0.10), *n*=4	0.94 (0.89; 0.99), *n*=74	No difference	Cariprazine
"+" Depressive symptoms	0.04 (0.00; 0.16), *n*=3	0.24 (0.13; 0.36), *n*=19	0.72 (0.61; 0.84), *n*=57	No difference	Cariprazine
"–" Akathisia	0.32 (0.16; 0.48), *n*=25	0.42 (0.27; 0.58), *n*=33	0.27 (0.11; 0.43), *n*=21	No difference	No difference
"–" Anticholinergic symptoms	0.03 (0.00; 0.16), *n*=2	0.70 (0.58; 0.83), *n*=55	0.28 (0.16; 0.41), *n*=22	No difference	No difference
"–" Sedation	0.00 (0.00; 0.11), *n*=0	0.23 (0.13; 0.34), *n*=18	0.77 (0.67; 0.88), *n*=61	Cariprazine	Cariprazine
"–" Weight gain	0.01 (0.00; 0.11), *n*=1	0.16 (0.08; 0.26), *n*=13	0.82 (0.73; 0.92), *n*=65	No difference	Cariprazine
"–" QT extension	0.00 (0.00; 0.09), *n*=0	0.86 (0.78; 0.95), *n*=68	0.14 (0.06; 0.23), *n*=11	Cariprazine	No difference
"–" Increase in prolactin	0.00 (0.00; 0.11), *n*=0	0.23 (0.13; 0.34), *n*=18	0.77 (0.67; 0.88), *n*=61	Cariprazine	Cariprazine
"–" Increase in glucose	0.01 (0.00; 0.13), *n*=1	0.76 (0.66; 0.88), *n*=60	0.23 (0.13; 0.35), *n*=18	No difference	No difference
"–" Increase in cholesterol	0.00 (0.00; 0.10), *n*=0	0.82 (0.73; 0.92), *n*=65	0.18 (0.09; 0.28), *n*=14	No difference	No difference

Note: n — number of observations, CI — confidence interval. "+" — the advantage was evaluated according to the greater relative severity of the effect, "–" — the advantage was evaluated according to the lesser relative severity of the effect.

RESULTS

A total of 79 psychiatrists were interviewed anonymously. The psychiatrists had an average experience of 11.0 (9.4, 12.7) years in the specialty, with a minimum of 2 years; and a maximum of 40 years. Cariprazine was used for a period of 5 to 48 months, whereas risperidone was used for 11 to 264 months. The number of patients treated with cariprazine was subjectively assessed to be 10.5 (8.6, 12.5), while the same figure for risperidone was 360.1 (95.3, 624.9). The distribution of physicians according to their practice setting was as follows: outpatient clinic — 34.1%; day hospital — 32.9%; and 24-hour hospital — 32.9%.

Table 2 displays the distribution of responses regarding the clinical difference between the drugs. When analyzing whether the pattern of respondents' answers matched the hypothesis behind the model, only 44.37% (c <0.001) matched the hypothesis.

Upon analysis of the response profile, it was found that most respondents viewed risperidone (0.57 [0.43; 0.72]) as superior in terms of efficacy towards positive symptoms. However, this did not differ from the proportion of those who reported a comparable antipsychotic effect between the drugs (0.42 [0.28; 0.57]). The advantage of cariprazine was overwhelmingly noted regarding its impact on negative (0.94 [0.89; 0.99]) and depressive (0.72 [0.61; 0.84]) symptoms. Cariprazine was also rated as safer than risperidone as relates to the risk of the following side effects: sedation (0.77 [0.67; 0.88]), weight gain (0.82 [0.73; 0.92]), and increase in prolactin (0.77 [0.67; 0.88]). The risk of anticholinergic side effects (0.70 [0.58; 0.83]), QT interval prolongation (0.86 [0.78; 0.95]), increased glucose (0.76 [0.66; 0.88]), and cholesterolemia (0.82 [0.73; 0.92]) was rated as comparable between the drugs. Most respondents rated the risk of akathisia as comparable (0.42 [0.27; 0.58]), but this was not unlike the proportion of those who considered cariprazine safer (0.27 [0.11; 0.43]).

When calculating the parameters of perception, the results showed that δ was 0.889 (0.774, 1.004) and τ was 1.001. The discrimination index obtained was higher than the calculated one, their confidence intervals not overlapping (the prior value being 0.517 [0.404, 0.630]). The boundary of the "No difference" category was lower than the calculated one (prior τ being 1.372). The results suggest a statistically significant difference between the hypothesis and empirical data.

Figure 1 illustrates the difference between hypothetical and empirical parameters.

In addition, the hypothesis of the impact of the length of service on the perception of the differences between the drugs was tested. Adding age as a covariate improved the model's performance (AIC 1622.97 vs. 1624.94).

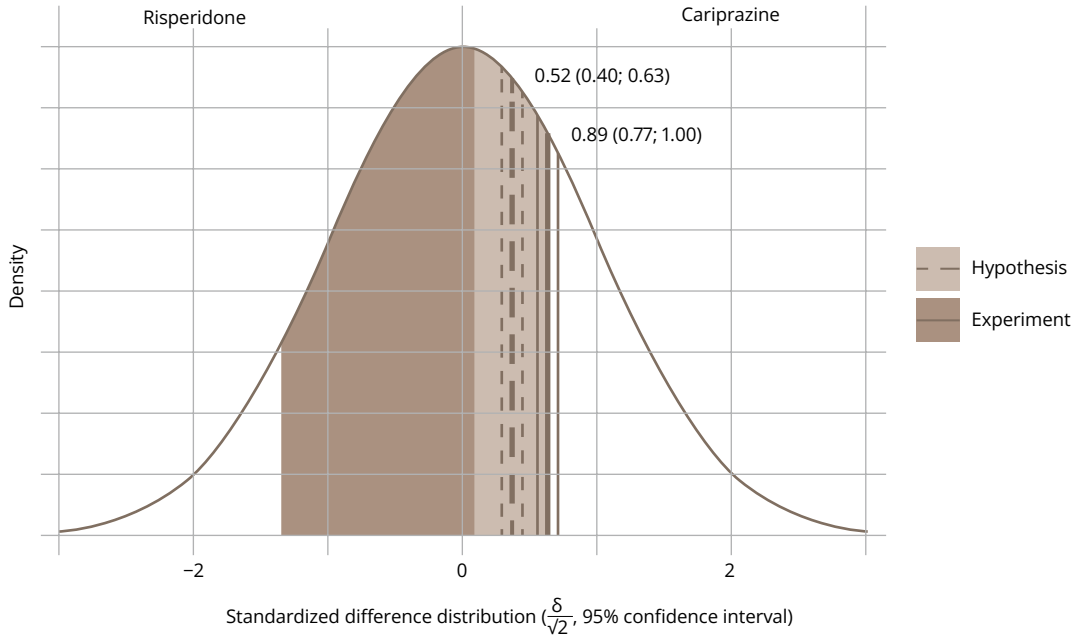

Figure 1. Standardized distribution of the differences between the drugs.

The length of service parameter exceeded the classical threshold of statistical significance (0.01 [0.00; 0.02], *p*=0.047). There was also a correction of the δ parameter towards a slight decrease (0.725). Figure 2 shows that the probability of choosing cariprazine increases with an increase in the length of experience, while the proportion of responses "No difference" and "Risperidone" drops. There was no correlation identified between the correspondence of the hypothetical pattern responses from individual participants and their length of work experience (*p*=0.870).

DISCUSSION

The aim of this study was to assess the quantitative differences in psychiatrists' perceptions of the efficacy and safety of various antipsychotics. The 2-AC protocol was used to quantify the difference in perceptions and compare it with a reference difference. The meta-analyses were used as a reference, and the reference values of the discrimination and decision-making parameters were calculated: δ — 0.517, τ — 1.372. Based on questionnaire data, the parameters had the following values: δ — 0.889, τ — 1.001. The qualitative aspect of the perception was also evaluated. The complete agreement of the response structure with the data from the meta-analyses is equivalent to 100% PCC. The observed value of 44.37% indicates a disagreement between the perception structure of psychiatrists and the objective data. Thus, the first part of the hypothesis of the study was confirmed. Regarding the perception bias in favor of risperidone, the hypothesis was not confirmed.

Every day physicians make decisions, the consequences of which affect the lives of patients and society as a whole [38]. Even in the face of considerable uncertainty, the physician is in a position to anticipate consequences and come up with solutions. The cost of this ability is cognitive distortions and errors that can negatively affect the final result [19]. For this reason, it is necessary to implement decision-support

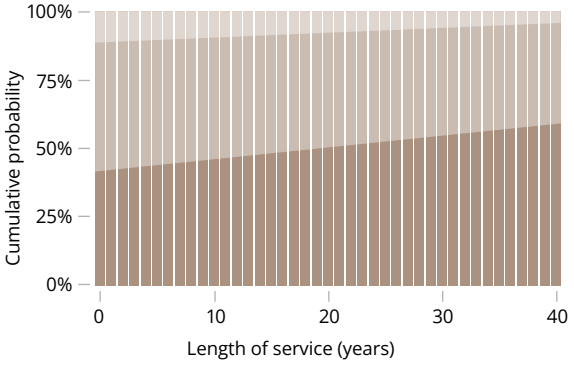

Figure 2. Probability of response depending on the length of service as a psychiatrist.

systems, the task of which is to minimize the number of erroneous decisions [12]. How such a system functions depends on the input information and algorithms provided by the developers. For example, it is easy to implement a drug selection protocol for the treatment of delirium with an extrapolation of the QT interval [39]. It is much harder to objectify the rating of antipsychotics [40].

The creation of the Personal Antipsychotic Choice Index [40] has been one attempt to generate such a ranking system based on therapeutic activity profiles in drug trials by expert evaluation. Direct ranking based on numerical characteristics has been performed only in large meta-analyses [8, 33]. However, these studies do not take into account the perception of therapeutic efficacy from both physicians and patients. Patients have been known to prefer drugs that result in less fatigue and memory problems [41]. The studies also uncovered a difference in the way doctors and patients choose drugs [42], which we believe is related to the perception of the disease itself and one's idea about how to manage it.

The perception of the therapeutic properties of drugs is a specific case of this general problem. Both assumptions and decisions depend on background information. This is illustrated in this case study. The authors of the meta-analysis [8] intentionally have excluded studies on the therapeutic effects on patients with predominant or prominent negative symptoms, since that issue is the subject of a separate study [43]. For this reason, the initial hypothesis assumed no difference between risperidone and cariprazine in terms of effectiveness as relates to negative symptoms. However, a significant difference in the perception of clinicians is obvious as concerns cariprazine and risperidone with respect to their effect on negative symptomatology, since there was no specific subgrouping of patients in practice.

For depressive symptoms, the situation is probably similar. The expected difference between cariprazine and risperidone in terms of their effect on depressive symptoms is insignificant (0.14 [-0.15; 0.43]) [8], although in practice this effect is perceived as strong. The result can be explained by the fact that the overall score is the result of a number of factors. For example, it is difficult to distinguish between negative symptoms and symptoms of depression [44, 45]; so, it cannot be excluded that the antidepressant effect reflected in the physicians' experience might be due to a change in the severity of the negative symptoms. It should be noted that the original data relate only to depressive symptoms within a psychotic episode, whereas depression in schizophrenia is a more complex condition [46].

This may also explain the difference in QT interval estimates and weight gain rather than actual clinical effects. A QT interval shortening of -1.45 (-6.20; 3.20) ms is known to occur regarding cariprazine in comparison with placebo, whereas an increase in the interval by 4.77 (2.68; 6.87) ms has been proven for risperidone [8]. However, these results indicate a statistical difference that may not coincide with the practical significance [47]. In our opinion, if physicians had not noticed the critical complications that accompanied the drugs, they might not have noticed any difference between cariprazine and risperidone (despite the fact that cariprazine is safer as relates to this parameter). Strangely enough, a similar structure of differences regarding weight gain has been perceived differently. On cariprazine, the average increase in body weight is less than one kilogram (0.73 [-0.06; 1.52]), which is comparable to the placebo. Risperidone, as has been shown, can increase body weight by more than a kilogram (1.44 [1.05; 1.83]). It would seem that the conclusion should be identical as when assessing cardiac activity, but weight gain worries patients [41, 42] and they are more likely to insist on this problem in their complaints. On the other hand, physicians are also concerned about the risk of weight gain in patients [42]. This may explain why the statistically insignificant difference between cariprazine and risperidone (0.71 [-0.09; 1.51], kg) is a perception of the superiority of cariprazine.

Finally, an explanation is needed regarding the effect of the length of experience of the physicians on the discrimination index. We anticipate that a lengthier service has to increase the number of "Risperidone" responses. This conviction is based on the preference for first-generation antipsychotics by physicians with more experience [17, 18]. In a similarly way, an "older" drug like risperidone would have been perceived as preferable, but that assumption has not been confirmed. In our opinion, the evaluation of efficacy and safety does not align with the decision about the choice of a drug. Further research is needed to understand how and why the length of experience affects the perception of the differences between drugs.

Limitations

The first limitation relates to the subjective choice of the initial parameters in creating the model. The model was

based on the results of two network meta-analyses and does not include all the therapeutic properties of the drugs. In addition, when simplifying the study model, it proves impossible to evenly exclude the advantages of the drugs. Therefore, the set of tested variables cannot be upheld as perfectly balanced. The second limitation has to do with location. All the physicians in the study have practiced in public institutions in Saint Petersburg, Russia. We believe that in other cities and regions of Russia, the results might be different. Thirdly, the results cannot be considered as a guide to a particular set of actions in clinical practice. Fourth, it would be misguided to judge the therapeutic properties of the drugs from these results, as the aim of the study was to assess the perceptions of mental health practitioners, not to evaluate the drugs as used in clinical practice.

CONCLUSION

To the best of our knowledge, the current study is the first to parameterize safety and efficacy characteristics using the sensometric theory. For the first time, a quantitative difference in the perception of the therapeutic properties of antipsychotics has been uncovered using cariprazine and risperidone as examples. Clinicians routinely perceive differences between drugs, and these differences are starker than expected. The pattern of perceived differences is not fully consistent with the results of clinical trials. This result can be considered when updating clinical guidelines and further developing decision-support systems.

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Supplementary data

Supplementary material to this article can be found in the online version at doi: Appendix A: 10.17816/CP12049-145162 Appendix B: 10.17816/CP12049-115496

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The Effects of Cognitive Impulsivity on the Duration of Remission in Alcohol-Dependent Patients

Влияние когнитивной импульсивности у больных алкогольной зависимостью на продолжительность ремиссии

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Original research

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ABSTRACT

BACKGROUND: Cognitive impulsivity manifesting in impaired inhibitory control and decision-making impulsivity is observed both in alcohol-dependent and substance-dependent individuals and may affect the ability to maintain long-term (persistent) remission.

AIM: To evaluate the effects of cognitive parameters of impulsivity on the duration of remission in alcohol-dependent patients.

METHODS: The study included 83 patients with alcohol dependence and 51 mentally healthy study subjects as the control group. The distribution of patients by duration of remission was based on the DSM-5 criteria. Patients were divided into two groups according to the duration of their most recent remission: patients with early remission (n=48) and patients with sustained remission (n=35). Impulsivity was assessed using the Go/No-Go task, which included a response inhibition component (inhibitory control). Choice impulsivity was assessed using two cognitive tests that encompass its separate components: decision-making under risk (Cambridge Gambling Task, CGT), and decision making under uncertainty (Iowa Gambling Task, IGT).

RESULTS: The study groups (patients and the controls) differed significantly in all domains of impulsivity: decision making under risk [GT: decision making quality (H(2, N=134)=30.233, p <0.001) and decision-making time (H(2, N=134)=18.433, p <0.001)] and decision making under uncertainty [IGT: selecting cards from "losing" decks (H(2, N=134)=9.291, p=0.009)]. The group of patients with sustained alcohol remission was characterized by longer decision times in CGT compared to the group of patients with early remission (z=2.398, p=0.049). Decision quality in CGT (z=0.673, p=0.999) and IGT scores (z=1.202, p=0.687) were not statistically significantly different between the groups of patients with sustained and early remission from alcohol dependence. The assessment of impulsive actions showed that the study groups were significantly different in terms of their ability to suppress their dominant behavioral response when performing the GNG task [false presses when seeing the "No-Go" signal (H(2, N=134)=28.851, p <0.001)]. The group of patients in sustained remission from alcohol dependence was characterized by better suppression of the behavioral response to the "No-Go" signal relative to the patients in early remission [H(2, N=134)=2.743, p=0.044)]. The regression analysis showed that the decision-making quality (t=2.507, p=0.049) and decision-making time (t=3.237, p=0.031) and the number of false presses when seeing the "No-Go" signal in the GNC task had a statistically significant impact on the duration of remission (t=3.091, p=0.043).

CONCLUSION: The results of this study indicate that impaired decision-making processes and the ability to inhibit the dominant behavioral response have a significant impact on the ability of alcohol-dependent patients to maintain long-term remission.

АННОТАЦИЯ

ВВЕДЕНИЕ: Когнитивная импульсивность, проявляющаяся в импульсивности принятия решений и нарушении ингибиторного контроля, отмечается как у лиц, склонных к злоупотреблению алкоголем, так и у больных с зависимостью от алкоголя и других психоактивных веществ, и может влиять на способность поддерживать длительную (стойкую) ремиссию.

ЦЕЛЬ: Оценить влияние когнитивных показателей импульсивности на продолжительность ремиссии больных алкогольной зависимостью.

МЕТОДЫ: В исследовании приняли участие 83 пациента с алкогольной зависимостью и 51 психически здоровый испытуемый в качестве группы контроля. Распределение пациентов по длительности ремиссии было основано на критериях DSM-5. Пациенты были разделены на две группы в зависимости от длительности последней ремиссии: пациенты с неустойчивой ремиссией (n=48) и пациенты с устойчивой ремиссией (n=35). Импульсивное действие оценивалось с помощью задачи Go/No-Go, которая охватывает компонент торможения реакции (ингибиторный контроль). Оценка импульсивности выбора проводилась с помощью двух когнитивных тестов, которые охватывают ее отдельные компоненты: принятие решений в условиях риска (Кембриджская игровая задача, CGT), и принятие решений в условиях неопределенности (игровая задача Айова, IGT).

РЕЗУЛЬТАТЫ: Исследуемые группы (пациенты и контроль) имели значительные различия по всем доменам импульсивного выбора: принятие решений в условиях риска [CGT: качество принятия решений (H(2, N=134)=30,233, p <0,001) и время принятия решений (H(2, N=134)=18,433, p <0,001)] и принятие решений в условиях неопределенности [IGT: выбор карт из «проигрышных» колод (H(2, N=134)=9,291, p=0,009)]. Группа пациентов с устойчивой алкогольной ремиссией характеризовалась большим временем принятия решений в CGT по сравнению с группой пациентов с неустойчивой ремиссией (z=2,398, p=0,049). Качество принятия решений в CGT (z=0,673, p=0,999) и результаты IGT (z=1,202, p=0,687) между группами пациентов с устойчивой и неустойчивой алкогольной ремиссией статистически значимо не различались. При оценке импульсивного действия обнаружено, что исследуемые группы значительно различались по своей способности подавлять доминирующую поведенческую реакцию при выполнении задачи GNG [ложные нажатия при сигнале «No-Go» (H(2, N=134)=28,851, p <0,001)]. Группа пациентов с устойчивой алкогольной ремиссией характеризовалась лучшим подавлением поведенческой реакции на сигнал «No-Go» относительно пациентов с неустойчивой ремиссией [H(2, N=134)=2,743, p=0,044]. Результаты регрессионного анализа показали, что качество принятия решений (t=2,507, p=0,049), время принятия решений (t=3,237, p=0,031) и количество ложных нажатий при появлении сигнала «No-Go» в задаче GNG оказывали статистически значимое влияние на продолжительность ремиссии у пациентов (t=3,091, p=0,043).

ЗАКЛЮЧЕНИЕ: Результаты исследования показывают, что нарушение процессов принятия решений и способности подавлять доминирующую поведенческую реакцию оказывают существенное влияние на способность больных алкоголизмом поддерживать длительную ремиссию.

Key words: *decision making; response inhibition; alcohol dependence; remission*
Ключевые слова: *принятие решений; торможение реакции; алкогольная зависимость; ремиссия*

INTRODUCTION

Alcohol dependence is a chronic, often relapsing psychiatric disorder associated with specific changes in brain function [1, 2]. An imbalance between reward-related decision-making and executive control processes is thought to be the key component of addiction [3]. Impaired inhibitory control, as one of the most important domains of executive functioning, and decision-making impulsivity are observed both in alcohol-dependent and substance-dependent individuals [4–6] and may affect the ability to maintain long-term (persistent) remission [6, 7].

Cognitive impulsivity is a complex and multilevel process that is associated with a willingness to make quick, ill-considered choices and involves a reduced willingness to tolerate delay in satisfying a desire. Cognitive impulsivity implies the presence of difficulties related to self-control in choosing out of two or more alternative options [8]. Thus, a cognitive impulsivity model includes two domains: impulsive choice and impulsive action.

Impulsive choice is driven by impulsive decision-making related to rewards, high risk, and a preference for smaller immediate rewards over larger but delayed rewards [9]. To assess the choice impulsivity, computerized gambling tasks are used, such as the Iowa Gambling Task (IGT) [10], which evaluates decision-making under uncertainty, and the Cambridge Gambling Task (CGT) [11], which evaluates decision-making under risk. Evidence suggests that although impulsive choice tasks measure time-anchored decision-making ability, different tasks include different domains of the cognitive function [12].

Impulsive action is associated with deficits in the inhibition of the rapid response to a stimulus [13]. It is typically measured using Stop-Signal Tasks (SST) [14], which involve the cancellation of an already initiated motor response (i.e., action cancelation), and/or a Go/No-Go (GNG) task [15], which requires the suppression of a dominant behavioral response (i.e., action inhibition). Most of the known studies have used the SST and GNG tasks as interchangeable alternatives that measure the same latent process (i.e., response inhibition).

Impulsive choice and impulsive action are among the most prominent and common cognitive impairments in alcohol-dependent individuals. Multiple studies show that alcohol dependence is characterized by inhibitory control deficits [16, 17] and an impaired decision-making ability [18, 19]. In addition, cognitive impairment is often associated with poor treatment outcomes [6, 17, 20].

Study hypothesis: based on the above, we hypothesize that cognitive impulsivity may hinder the achievement of long-term (persistent) therapeutic remission in patients with alcohol dependence.

The aim of the study is to evaluate the effects of cognitive parameters of impulsivity on the duration of remission in alcohol-dependent patients.

METHODS

Study design

This is an observational cross-sectional naturalistic study.

Ethical approval

The study was conducted in compliance with the principles of the 1964 Declaration of Helsinki as amended between 1975 and 2013 and was approved by the local Bioethics Committee at the Mental Health Research Institute of the Tomsk National Research Medical Center of the Russian Academy of Sciences. All study subjects, as well as individuals from the control group, gave their written informed consent for participation in the study and the processing of their personal data.

Participants

Patients were selected from the 24-hour inpatient clinic of the Mental Health Research Institute of the Tomsk National Research Medical Center of the Russian Academy of Sciences. The study included 83 patients: 66 males and 17 females (median age and interquartile range Me [Q1; Q3]=45 [40; 52] years) with the following clinical diagnosis: mental and behavioral disorders due to the abuse of alcohol and dependence syndrome (F10.2 according to ICD-10 criteria). The study (interviewing) of the patients was conducted on days 3–5 after hospital admission (for the purpose of management of alcohol withdrawal syndrome, psychological interventions, and rehabilitation) after detoxification.

Inclusion criteria: a diagnosis of alcohol dependence according to ICD-10, voluntary consent to participate in the study, and age of 20–60 years.

Exclusion criteria: refusal to participate in the study, dementia, mental retardation, head injuries with loss of consciousness for more than 30 minutes, and use of drugs affecting impulsivity (i.e., antipsychotics, antidepressants, benzodiazepines).

The diagnosis of the current mental state was made by psychiatrists using the clinical method and the ICD-10

diagnostic criteria. In addition, a questionnaire specially designed for this study was used. It included information on the age of the first alcohol try, the age of the beginning of alcohol abuse, the number of hospitalizations in drug addiction facilities, the duration of the disease, and the duration of the last intermission.

Also, the following socio-demographic information was collected: age, gender, and level of education.

Patients were divided into two groups: with a history of sustained and early remission from alcohol dependence prior to the current exacerbation of the disease. The attribution of patients to groups by duration of remission was based on the DSM-5 criteria. In the DSM-5 (2013), there is a "Alcohol use disorder" class that includes early remission, when no evidence of alcohol use is noted for at least 3 months (but less than 12 months) and sustained remission with no evidence of the disorder for 12 months or longer [21].

The control group included 51 mentally healthy subjects (37 males and 14 females aged Me [Q1; Q3]=43 [39; 49] years). Subjects were recruited from among the staff of the Tomsk National Research Medical Center of the RAS (researchers, physicians, nurses, administrative staff, auxiliary personnel).

Inclusion criteria: voluntary consent to participate in the study and age of 20–60 years.

Exclusion criteria: refusal to participate in the study, dementia, mental retardation, head injuries with loss of consciousness for more than 30 minutes, and use of drugs affecting impulsivity (i.e., antipsychotics, antidepressants, benzodiazepines). To assess alcohol use, all participants in the control group were asked to complete the Alcohol Use Disorders Identification Test (AUDIT) scale in the Russian-language adaptation of the scale (RUS-AUDIT) [22]. The sum of AUDIT scores in the control group ranged from 0 to 7, corresponding to a low level of risk for problems due to alcohol use. Additionally, the subjects in the control group were examined by psychiatrists; history of mental illnesses and somatic disorders, as well as socio-demographic data (age, gender, education level), was collected.

All subjects from the patient and control groups were assessed for impulsive actions and impulsive choices.

Methods of impulsive action assessment

Impulsivity was assessed using a neurocognitive GNG task [23], which included a response inhibition component (i.e. automatic inhibition or inhibitory control).

A GNG task is a computer-based assessment of response suppression. In this version of the test, subjects were asked to press a button when a green oval appeared on the screen "Go" and not to press it when a red oval appeared "No-Go". Stimuli (ovals) were presented in random order. The stimulus presentation time was 500 ms, and the inter-stimulus interval was 800 ms. There were 60 stimuli in total: 30 were "Go" and 30 were "No-Go". The output data included the number of errors — false presses when seeing the "No-Go" signal reflecting an incorrect response to a nontarget stimulus as a primary indicator of response disinhibition and impulsive action.

Methods of impulsive choice assessment

Choice impulsivity was assessed using two cognitive tests that encompass its separate components: decision-making under risk and decision-making under uncertainty.

The Cambridge Gambling Task [24] is a computerized test that allows one to evaluate various aspects of the decision-making process under risk. In this version of the test, subjects had to guess whether the token was hidden in the red or blue boxes (there were 10 boxes in total, and the red and blue boxes could be represented in various ratios from 5:5 to 9:1) and then bet (from a set of four predetermined amounts: 5, 25, 50, or 75 points) on the accuracy of their decision. If the guess was correct, the subject was credited with the selected number of points; if incorrect, that number of points was deducted. The subjects had a total of 10 attempts. During the test, the quality of decision-making (percentage of logically correct answers based on the ratio of red and blue boxes) and average decision-making time in seconds were analyzed.

The Iowa Gambling Task [25] is a psychological task aimed at assessing decision making based on emotional learning under uncertainty. In the IGT version used, the participant is asked to choose cards from any deck out of four decks on the screen. Two decks contain high-risk cards. They give high points (100 points each) but also rare large penalties (250 to 500 points), the result is losing in the long run when choosing predominantly these cards. The other two decks give small points (50 points each), but also small penalties (50 points each), resulting in a win in the long term if you choose predominantly these cards. The analysis of the results of performing this task included the number of selected cards from "high" risk ("losing") decks out of 100 possible choices.

Statistical analysis

Statistical analysis was performed using the Statistica 12 software package (StatSoft). The minimum sample size was determined using the method of K.A. Otdelnova [26] for a significance level of p=0.05. The normal distribution of data was verified using the Shapiro-Wilk test. The obtained data were not normally distributed. Qualitative data are presented by frequency parameters in absolute and relative units, *n* (%). Quantitative variables are presented as a median and interquartile range Me [Q1; Q3]. The subjects were divided into three groups for statistical data analysis: a group of patients with alcohol dependence and early remission; a group of patients with alcohol dependence and sustained remission; and a control group. The Kruskall-Wallis (ANOVA) with Dunn's test for *a posteriori* pairwise comparison procedure was used to assess differences between all three groups in terms of sociodemographic parameters and cognitive test scores. The Mann-Whitney test was used to compare clinical data between the two patient groups. The χ^2 test was used to compare frequencies. We also conducted a linear regression analysis to assess the effect of selected quantitative measures of cognitive impulsivity on the remission duration in alcohol-dependent patients. The differences were considered statistically significant at p <0.05.

RESULTS

Sample description

A total of 134 subjects were enrolled in the study. The control group included 51 healthy volunteers. Patients with alcohol dependence were divided into two groups depending on the duration of their last remission (before this hospital admission) according to DSM-5 criteria. The group of patients with early remission (3 to 12 months of abstinence from alcohol) included 48 patients with a duration of remission Me [Q1; Q3]=6 [3; 10] months. The group of patients with sustained remission (more than 12 months of abstinence from alcohol) included 35 patients with a duration of remission Me [Q1; Q3]=30 [18; 60] months. The patient and control groups were well balanced in terms of sociodemographic variables (Table 1). There were no differences that were statistically significant in terms of age [H(2, N=134)=3.717, p=0.155], sex [χ^2(2, N=134)=0.871, p=0.647], or education level [χ^2(4, N=134)=2.972, p=0.562].

The Table 2 shows the analysis of differences in alcohol consumption characteristics between patients with alcohol dependence with early and sustained remission revealed significant intergroup differences only in terms of the duration of remission (U=1861, p <0.001).

Table 1. Sociodemographic characteristics of the sample

Parameter		Control (*n*=51)	Alcohol-dependent patients with early remission (*n*=48)	Alcohol-dependent patients with sustained remission (*n*=35)
Age (years), Me [Q1; Q3]		43 [39; 49]	45 [39; 52]	47 [43; 51]
Sex, *n* (%) male		37 (72.5%)	38 (79.2%)	28 (80%)
Education level, *n* (%)	Higher education	33 (64.7%)	23 (47.9%)	19 (54.3%)
	College education	11 (21.6%)	15 (31.3%)	9 (25.7%)
	High school	7 (13.7%)	10 (20.8%)	7 (20%)

Table 2. Differences in the characteristics of alcohol use among groups of patients with different remission types

Parameter	Alcohol-dependent patients with early remission (*n*=48)	Alcohol-dependent patients with sustained remission (*n*=35)	U	*p*
Age of the first try of alcohol (years)	16 [15; 18]	16 [16; 17]	531	0.984
Age of the start of alcohol abuse (years)	25 [20; 35]	26 [22; 35]	514	0.813
Number of hospitalizations	2 [1; 4]	2 [2; 3]	799	0.999
Duration of the disease (years)	17 [11; 21]	18 [12; 24]	652	0.183
Duration of the last remission (months)	6 [3; 10]	30 [18; 60]	1861	<0.001

Table 3. Intergroup differences in terms of impulsive choice parameters and impulsive actions

Parameter		Control (*n*=51)	Alcohol-dependent patients with early remission (*n*=48)	Alcohol-dependent patients with sustained remission (*n*=35)	H	*p*
Cambridge Gambling Task	Decision-making quality (%)	90 [80; 100]	60 [50; 70]	60 [50; 80]	30.233	<0.001
	Decision-making time (s)	3 [2.8; 3.3]	3.5 [2.8; 4.6]	4.4 [3.6; 5.3]	18.433	<0.001
Selection of cards from "losing" decks in the Iowa Gambling Task (*n*)		48 [40; 55]	53 [51; 61]	55 [52; 63]	9.291	0.009
Go/No-Go task	False presses when seeing the "No-Go" signal (*n*)	0 [0; 1]	3 [2; 4]	2 [1; 3]	28.851	<0.001

Choice impulsivity and impulsive actions in the study group

The statistical data analysis between the patient and control groups in choice impulsivity assessment tasks (CGT, IGT) showed that the study groups differed significantly in all impulsive choice domains (Table 3). An additional *post hoc* analysis (Dunn's test) for pairwise comparisons showed that all study groups compared with each other. It was revealed that the control group, compared with patients with sustained remission, was characterized by better decision-making, both under risk (CGT), quality of decision-making (z=3.882, p <0.001), and decision-making time (z=4.281, p <0.001), and under uncertainty (IGT): choosing cards from "losing" decks (z=2.953, p=0.009). At the same time, when comparing the control group with patients with early remission, statistically significant differences were revealed in the CGT only in terms of decision-making quality (z=5.038, p <0.001) and the IGT [choosing cards from "losing" decks (z=2.085, p=0.018)]. The comparison between the decision-making time in the CGT for the control group and the patients with early remission showed no statistically significant differences (z=1.941, p=0.156).

The group of patients with sustained remission from alcohol dependence was characterized by longer decision-making times in the CGT compared to the group of patients with early remission (z=2.398, p=0.049). The comparison of the decision-making quality in the CGT (z=0.673, p=0.999) and choosing cards from "losing" decks in the IGT (z=1.202, p=0.687) between the groups of patients with sustained and early remission from alcohol dependence showed no statistically significant differences.

The assessment of intergroup differences in the impulsive action task (GNG task) also showed that the study groups were significantly different in terms of their ability to suppress the dominant behavioral response (pressing the button falsely at the "No-Go" signal). A *post hoc* analysis using the Dunn's test showed that the control group had better suppression of their behavioral response to the "No-Go" signal compared with both groups of patients [when compared with the group of patients with sustained remission (z=4.111, p <0.001), and when compared with the group of patients with early remission (z=4.297, p <0.001), respectively].

On the other hand, the group of patients with sustained remission from alcohol dependence displayed better suppression of their behavioral response to the "No-Go" signal relative to the patients in early remission (z=2.743, p=0.044).

Assessment of the effects of different parameters of cognitive impulsivity on the duration of remission in alcohol-dependent patients

To determine the effects of various domains of cognitive impulsivity on the duration of remission in alcohol-dependent patients, a series of separate regressions were performed, where the choice impulsivity parameters were used as independent variables: (1) decision-making under risk (CGT: decision quality, decision time); (2) decision-making under uncertainty (IGT: the number of cards selected from the "high" risk decks) and impulsive action; and (3) the ability to successfully suppress a dominant behavioral response in a GNG task.

The first model obtained based on decision-making under risk (CGT) turned out to be statistically significant [F (2.42)=4.999, p=0.031]. R^2=0.331, indicating that decision-making quality and decision-making time explained approximately 33% of the variability in remission duration. The predictors of remission duration were statistically

significant: both decision-making quality (t=2.507, p=0.049), and decision-making time (t=3.237, p=0.031). The equation is as follows: remission duration = 0.191 × decision-making quality + 6.155 × decision-making time − 10.558.

The second model based on decision-making under uncertainty (IGT) was found to be statistically insignificant [F(1.43)=0.479, p=0.492]. R^2=0.011, which indicates that the number of selected cards from "high" decks in the IGT explains only about 1% of the variability in the duration of remission. The number of cards selected from "high" risk decks in the IGT did not significantly affect the duration of remission (t=0.692, p=0.492). The equation is as follows: duration of remission = 10.858 + 0.202 × number of selected cards from "high" risk decks.

Finally, the third model, which used the ability to successfully inhibit the dominant behavioral response as a predictor, was statistically significant [F(1.81)=4.315, p=0.043]. R^2=0.271, indicating that the number of false presses when seeing the "No-Go" signal in the GNG task was associated with approximately 27% of the variability in remission duration. The number of false presses when seeing the "No-Go" signal in the GNG task had a statistically significant impact on the duration of remission (t=3.091, p=0.043). The equation is as follows: remission duration = 17.491 − 1.285 × number of false presses when seeing the "No-Go" signal.

DISCUSSION

The goal of this study was to evaluate the effects of the cognitive parameters of impulsivity on the duration of remission in alcohol-dependent patients. The study showed that decision-making under risk (decision-making quality and time) and the ability to successfully suppress the dominant behavioral response influenced the duration of remission in alcohol-dependent patients.

The effects of impulsive choice on the duration of remission

The evaluation of choice impulsivity showed that longer remission was associated with better decision-making under risk; however, decision-making under uncertainty did not affect the duration of remission. These results suggest that the tendency to make choices prematurely (decision-making time) and irrationally (decision-making quality) without anticipating possible negative consequences may serve as a factor of disruption in alcohol-dependent patients. The obtained data are consistent with previous studies that reported a similar trend in samples of alcohol-dependent patients with early and long-term remission [27, 28].

The obtained data also showed that both groups of patients with alcohol dependence demonstrated poor decision-making under both risk and uncertainty compared with participants from the control group. These results are consistent with previous studies and support the assumption that the decision-making process is impaired in alcohol dependent patients [6, 29]. In addition, there were intergroup differences in decision-making under risk between patients with sustained and early remission: patients with early remission from alcohol dependence had shorter decision-making time; i.e., they tended to make a choice prematurely.

Thus, the results of the study indicate that there is an association between impulsive choice and the duration of remission in alcohol-dependent patients. This is consistent with the results of neuroimaging tests demonstrating persistent structural and functional abnormalities of the orbitofrontal cortex and function in various types of addiction involved in impulsive choice tasks [30, 31]. These studies also show that long-term toxic exposure to a variety of psychoactive substances (including alcohol) leads to changes in brain functioning that may underlie the maladaptive behaviors and disadvantageous decisions that characterize the daily lives of people with alcohol dependence. However, impaired decision-making can also be seen as a risk factor that may explain the tendency of substance users to continue their behavior despite negative long-term consequences. In this context, the differences in decision-making under risk (decision time) between patients with sustained and early remission from alcohol dependence in this study may reflect the stable premorbid cognitive characteristics of people who are able to successfully maintain long remission. Accordingly, patients who are able to abstain from alcohol for extended periods of time may be characterized by an unchanged or more adaptive decision-making process, which in turn may explain their ability to successfully maintain long-term abstinence.

The effects of impulsive action on the duration of remission

The results obtained in the area of impulsive actions indicate that regardless of the duration of remission, alcohol-dependent patients showed a reduced ability to

inhibit their dominant motor response (i.e., the dominant behavioral response) compared to the control group.

The observed differences in the effectiveness of motor response suppression between members of the control group and alcohol-dependent patients are consistent with other studies [32, 33]. It is also important to note that according to the regression analysis, the ability to suppress the dominant behavioral response is a factor that influences the duration of remission. Thus, the results of the study indicate that there is an association between impulsive choice and the duration of remission in alcohol-dependent patients.

The observed differences in the GNG task success between groups of patients with different durations of remission from alcohol dependence may also reflect premorbid cognitive features underlying their ability to maintain long-term abstinence from alcohol.

Strengths and limitations

The main strength and main practical result of this study is the demonstration of significant relationships between cognitive impulsivity parameters and the duration of remission in alcohol-dependent patients. The study results emphasize the potential impact of impulsive choices and impulsive actions on patients' ability to maintain long-term (persistent) remission. Further study of the cognitive domains of impulsivity in relation to clinical-dynamic variables offers hope for the development of more personalized and person-centered approaches in the psychiatric rehabilitation of individuals with alcohol dependence.

The present study has a number of limitations that need to be considered when interpreting the data. First, the patients' acute condition after heavy drinking could affect the results of cognitive tests. This, in turn, could lead to asthenia, more formal task performance, which could ultimately result in their being different from the control group. Second, this study did not take into account additional cognitive and affective processes that could have influenced or mediated the impulsive choices and impulsive actions in alcohol-dependent patients. Future research should include the assessment of additional cognitive functions such as working memory, attention, and the emotional processes known to affect the performance of tasks involving impulsive choices and impulsive actions. Third, a cross-sectional study design limits our knowledge of the effects of the individual neurocognitive aspects of impulsivity on the duration of remission. In addition, the duration of remission was assessed retrospectively (based on the patient's history). Our results may not reflect the potential changes associated with recovery of the decision-making ability and inhibition of reactions during abstinence, but rather reflect the specific premorbid characteristics of individuals who are able to successfully maintain long-term remission. Fourth, this study did not include a comprehensive assessment of the concomitant psychiatric disorders that often co-occur with alcohol dependence, such as mood disorders, anxiety disorders, and personality disorders. Future studies could assess the impact of other psychiatric disorders on cognitive impulsivity in patients with alcohol dependence more thoroughly. Another limitation of this study is the lack of control for the the different therapeutic interventions effects on cognitive impulsivity parameters. Given that most of the patients enrolled in the study had been treated during previous hospitalizations, these treatment programs may have had some impact on their neurocognitive functioning. Therefore, future studies should further investigate the effects of different pharmacologic and non-pharmacologic interventions on selected domains of cognitive impulsivity in patients with different durations of remission. Finally, the group of patients with sustained remission was very heterogeneous in terms of the duration of abstinence: abstinence periods ranged from 12 months to 5 years. Future studies should collect data in relatively more homogeneous groups of patients abstaining from alcohol that reflect different stages of recovery process (e.g., 1–2 years of abstinence, 2–3 years of abstinence, etc.).

CONCLUSION

Thus, the study showed that impaired decision-making processes and the ability to inhibit the dominant behavioral response had a significant impact on the ability of alcohol-dependent patients to maintain long-term remission. Consistent with previous studies, the current findings highlight the growing need to develop new personalized cognitive rehabilitation programs for alcohol-dependent patients at various stages of remission. The development of personalized therapeutic interventions aimed at correcting impaired cognitive functioning, specifically cognitive impulsivity, may have broad practical implications for the rehabilitation of patients with alcohol dependence and may help to address some of the limitations of traditional therapeutic approaches.

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The Use of Umbilical Cord Blood Nucleated Cells in the Treatment of Regressive Autism: A Case Report

Применение ядросодержащих клеток пуповинной крови в лечении регрессивного аутизма: клинический случай

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Case report

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ABSTRACT

BACKGROUND: Interest in the issue of childhood autism has surged in the recent decades. At the same time, despite the significant progress achieved in understanding the etiological and pathogenetic aspects of the condition, effective ways to treat it have continued to elude us. Stem cell therapy appears to hold great promise in the treatment and rehabilitation of patients with both neurological diseases (cerebral palsy, hydrocephalus) and mental disorders (autism, schizophrenia).

METHODS: This article presents a case report describing the use of nucleated cord blood cells in a patient with regressive autism and resistance to standard therapies. The child's condition was assessed before treatment and 6 and 12 months after.

RESULTS: Clinical observation, psychometric, and instrumental diagnostic methods led to a significant improvement in the child's condition in the form of perception development, reduction of somatosensory disorders, normalization of emotional status, and a development of social and communication skills.

CONCLUSION: We assume that the result obtained may be associated with the normalization of the immunological status of our patient thanks to the cord blood cells therapy and consider it necessary to conduct further studies into the effectiveness of the method, taking the pathogenic mechanisms of autism into account.

АННОТАЦИЯ

ВВЕДЕНИЕ: Последние десятилетия можно отметить усиление интереса к проблеме детского аутизма. При этом, несмотря на значительное продвижение в понимании этиологических и патогенетических аспектов,

до сих пор не удалось найти эффективные способы лечения аутизма. Терапия стволовыми клетками показала большие перспективы в лечении и реабилитации пациентов как с неврологическими заболеваниями (ДЦП, гидроцефалия), так и с психическими расстройствами (аутизм, шизофрения).

МЕТОДЫ: В этой статье приводится клинический случай, описывающий применение ядросодержащих клеток пуповинной крови у пациента с регрессивной формой аутизма и резистентностью к стандартным методам терапии. Состояние ребенка оценивалось до лечения и через 6 и 12 месяцев.

РЕЗУЛЬТАТЫ: Клиническое наблюдение, психометрические и инструментальные методы диагностики позволили выявить выраженную положительную динамику в состоянии ребенка в виде развития восприятия, снижения соматосенсорных нарушений, нормализации эмоционального статуса, развития социализации и коммуникативных способностей.

ЗАКЛЮЧЕНИЕ: Мы предполагаем, что полученный результат может быть связан с нормализацией иммунологического статуса нашего пациента на фоне терапии клетками пуповинной крови и считаем необходимым проведение дальнейших исследований эффективности методики с учетом патогенетических механизмов развития аутизма.

Keywords: *treatment; autism; cell therapy; children disorders; HUCBCs*
Ключевые слова: *лечение; аутизм; клеточная терапия; расстройства у детей; ядросодержащие клетки пуповинной крови*

INTRODUCTION

Autism is a congenital disorder of the central nervous system formation, with variable etiology and pathogenesis, that manifests itself in social and communication skill impairment and repetitive, stereotypical behavior [1]. In most cases, the causes of autism are closely tied to the genes that affect the maturation of synaptic connections in the brain, but the genetic mechanisms of this disease are quite complex [2–4]. Due to the diversity of causes and mechanisms, there is no single established drug therapy. Pharmacotherapy is confined to affecting individual manifestations (aggression, agitation, anxiety) and not the key disorders (communication, social skills, sensory impairment, intelligence, and speech) [5–6]. The effectiveness of the applied methods is quite low, and in most cases patients with autism are unable to work [7].

Due to the lack of effectiveness of standard therapy, the development of new treatments for autism is becoming a priority. One of the most important and promising areas in neurology and psychiatry is the use of cell technologies; namely, methods of treatment using stem cells [8, 9]. One of the most accessible sources of stem cells is cord blood. There have been studies of allogeneic nucleated cord blood cells (CBCs) used in cerebral palsy [10, 11], stroke [12], perinatal encephalopathy [13], Alzheimer's disease [14], schizophrenia [15, 16]. Using nucleated CBCs in patients with autism is of even greater interest [17–19].

This article presents the results of therapy with nucleated CBCs in a patient with autism and intellectual disability. The use of CBCs was prompted by the ineffectiveness of standard therapies on this patient.

CASE REPORT

An 8-year-old male patient came to a psychiatrist with his parents. His mother presented complaints about the child's developmental delay, hyperactivity, episodes of excitement with aggression, motor stereotypies, as well as significant speech and communication disorders. The purpose of the visit was to select therapy and define the contours of the rehabilitation measures.

Medical history

The child had developed normally during the first two years. At the age of two years, after a severe ARVI with hyperthermia of up to 40 degrees, changes in his behavior appeared in the form of aggression and motor disinhibition; the child lost his previously acquired speech skills, stopped responding to treatment, and started manifesting stereotypical behavior.

The parents turned to a psychiatrist for the first time when the child was three years old; he was diagnosed

with atypical autism with mental retardation (F 84.11) in accordance with the ICD-10 criteria. From the time of the diagnosis, the patient has regularly received antipsychotics and antidepressants to treat behavioral disorders, and by the time of the visit he was taking chlorprothixene at a dose of 45 mg/day. Drug therapy produced no significant improvement; significant behavioral disorders persisted, manifesting themselves in the form of aggressive and auto-aggressive reactions, impulsivity, emotional instability, and severe cognitive and speech disorders. At the age of 8, the child underwent magnetic resonance imaging (MRI) of the brain and electroencephalography (EEG). MRI showed no significant changes; electroencephalography indicated the absence of epileptiform activity.

Prior to the start of therapy with CBCs, the child's speech development corresponded to level 1 general speech underdevelopment with a pronounced sensory component and the level of intellectual development corresponded to moderate intellectual disability.

At the time of the patient's request for medical care, the Department of Pediatric Psychiatry at the V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology was conducting a research study titled "Use of nucleated cord blood cell concentrate in children with severe cognitive deficit with a decreased contact level or autistic manifestations" (the study protocol was approved by the LEC of the V.M. Bekhterev NMRC PN on June 22, 2017, and approved at the meeting of the Academic Council on June 28, 2017; the study was conducted from September 2017 to June 2021). Given the low efficacy of standard therapy and the patient's eligibility, his parents were offered participation in this study. After a positive decision, the parents signed a voluntary informed consent to participate in this study, as well as an informed consent to the publication of the case report.

PRODUCT CHARACTERISTICS AND ADMINISTRATION PROCEDURE

CBC samples were taken after cutting the umbilical cord, according to the generally accepted method as part of a gratuitous donation on the basis of a voluntary informed consent signed by pregnant women hospitalized at National Medical Research Center For Obstetrics, Gynecology And Perinatology Named After Academician V.I. Kulakov. Within a maximum of 4 hours after sampling, the samples were delivered to the laboratory, where the CBCs were isolated according to the preparation procedure used in oncological hematology as an alternative to donor bone marrow [20]. The CBC concentrate was poured into cryotubes and stored in liquid nitrogen at -196°C. Blood samples from the mother and cord blood samples were tested for sterility and blood-borne infections by an independent laboratory. The cord blood samples were tested and found negative for human immunodeficiency virus (HIV-1/2, antigen/antibody), hepatitis B (HBs Ag, anti-HBc-total) and C (anti-HCV-total), T-cellular leukemia (anti-HTLV-1/2), herpes simplex viruses type 1 and 2 (anti-HSV IgM), cytomegalovirus (anti-CMV IgM), pathogens of toxoplasmosis (anti-Toxo IgM), syphilis (Syphilis RPR), bacteria, and fungi. The samples were simultaneously characterized in terms of AB0/Rh and the content of CD34 cells [21, 22].

Before clinical use, the CBCs were thawed under aseptic conditions, washed from the cryoprotectant, assessed for viability using the trypan blue test, and placed in an infusion medium. The finished product is a sealed polymer container with 20 ml of a pale pink opalescent liquid containing a suspension of 250±50 million nucleated CBCs in a sterile saline solution, with the addition of rheopolyglucin and human serum albumin. The cells thawed and washed from the cryoprotectant were transported to the department in a thermal container at +1...+4°C (on ice). The time from the moment the concentrate was thawed to the start of administration to the patient did not exceed 2 hours. The patient was administered an intravenous injection of cord blood cell concentrate compatible in terms of blood type and Rh factor at a dose of 250±20 million cells per injection. There was a total of 4 injections with an interval of 14 days. In accordance with the study protocol, the patient had his drug therapy completely discontinued before the start of CBC administration (at the time of admission, the child was receiving chlorprothixene at a dose of 45 mg/day).

METHODS FOR ASSESSING CHANGES IN THE PATIENT'S CONDITION

To assess cognitive functions, separate subtests of the Wechsler method were used before the start of therapy and after 6 and 12 months. To assess the changes in autistic manifestations, the Checklist for autism spectrum disorders (CASD) and Autism treatment evaluation checklist (ATEC) questionnaires were completed before the start of therapy and after 6 months. CASD records the presence or absence of 30 characteristic symptoms to differentiate autism from other developmental disorders. This method detects autism in children with 99.5% accuracy and is intended

for children aged 1 to 16 years [23]. ATEC is a method for evaluating the effectiveness of ongoing treatment in autism. The test questions are divided into 4 groups: speech and communication, socialization, sensory and cognitive abilities, and health and behavior [24].

Among the subtests of the Wechsler scale, the following ones were chosen: "Digit span", "Picture completion", "Kohs blocks", and "Coding". The "Digit span" subtest assessed working memory and active attention; the "Picture completion" subtest was used to assess perceptual abilities, observation, and concentration; the "Kohs blocks" subtest was used to assess analytical and synthetic abilities; while the "Coding" subtest helped assess attention characteristics and development of hand-eye coordination [25].

The instrumental method involves studying brainstem auditory-evoked potentials (BAEPs) of the brain before the start of treatment and after 6 months. The essence of this method is registration of the electrical responses of the brain to auditory stimuli. The method was used to detect abnormal connection between the ears and the brain and helped to assess the functional state of the structures of the pontomedullary and pontomesencephalic levels of the brain [26]. The child also underwent an EEG before the start of treatment and after 6 months.

The safety of intravenous CBC suspension was assessed on the basis of the Common Terminology Criteria for Adverse Events scale (CTCAE)[1]. In accordance with this scale, all adverse events are ranked as mild, moderate, severe, life-threatening, and resulting in death.

THERAPY RESULTS

CBCs at a dose of 250 ± 20 million cells were well tolerated. No adverse events were recorded during therapy.

Changes in the patient's condition according to the psychometric and instrumental assessment

Before CBC administration, due to significant communication disorders and emotional-behavioral characteristics, it was not possible to conduct a complete standard examination using the Wechsler scale. Therefore, we selected separate subtests of the scale to assess the main cognitive functions. The "Digit span" subtest assessed working memory and active attention; the "Picture completion" subtest was used to assess perceptual abilities, observation, and concentration; the "Kohs blocks" subtest was used to assess analytical and synthetic abilities; and the "Coding" subtest helped assess attention characteristics and the development of hand-eye coordination. Test results are presented in Table 1.

As can be seen from the presented table, there is a significant increase in the "Picture completion", "Kohs blocks", and "Coding" subtest scores. It should also be noted that 12 months after the first CBC administration, a full Wechsler test could be conducted with this patient. The verbal indicator of intelligence in formal numerical terms was 42 points, and the non-verbal was 79 points. Due to the large speard of the results it was not possible to obtain an overall Wechsler intelligence score. Testing became possible thanks to significant improvements in the contact, attention, and emotional-volitional control of the patient's behavior.

Analysis of the CASD and ATEK scales also revealed a significant improvement (Tables 2 and 3). The total CASD score decreased from 16 (before the first injection) to 6 (6 months after the first injection), the total ATEC score decreased from 80 (before the first injection) to 16 (6 months after the first injection). The ATEC score decreased from

Table 1. Results of the separate subtests of the Wechsler scale before the start of therapy and after 6 and 12 months

Subtest name	Before the start of therapy	After 6 months	After 12 months
Digit span (attention and memory)	1 (attention — 0, memory — 0 points)	2 (attention — 0, memory — 2 points)	1 (attention — 0, memory — 2 points)
Picture completion (perceptual ability, focus)	0	0	**5**
Kohs blocks (analysis-synthesis with a visual standard)	4	**5**	**8**
Coding (hand-eye coordination, speed of formation of new skills)	2	**4**	**9**

Note: 0 — did not understand the instruction; normal range is above 5.

[1] Common Terminology Criteria for Adverse Events, v.5.0 [Internet]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Table 2. CASD score before and 6 months after the start of therapy

CASD sections	Before the start of therapy	After 6 months
«Social interaction issues»	1	1
«Perseverations»	4	0
«Somatosensory disorders»	2	1
«Deviations in communication and development»	5	4
«Mood disorders»	2	0
«Attention and danger awareness issues»	2	0
Total score	16	6

Table 3. ATEK score before and 6 months after the start of therapy

ATEK sections	Before the start of therapy	After 6 months
Speech/Language/Communication Skills	18	5
Socialization	27	3
Sensory skills/Cognition	12	1
Health/Growth development/Behavior	23	7
Total score	80	16

27 to 3 in the "Socialization section, from 23 to 7 in the "Health/growth development/behavior" section, from 18 to 5 in the "Speech/language/communication skills" section, and from 12 to 1 in the "Sensory skills/cognition" section. The greatest improvement of the CASD score was in the "Obsessive actions (perseveration)" section (a decrease from 4 [out of 5] to 0) and in the "Mood disorders" section (a decrease from 2 [out of 4] to 0).

EEG analysis involved assessing the general functional state of the brain, the level of maturity of the bioelectrical activity, the severity of EEG changes, and clarifying the location of pathological changes; it showed a significant improvement of parameters 6 months after CBC administration (Figures 1, 2). BAEP analysis showed an improvement of auditory signal conduction in the "auditory olivary complex" area on the left 6 months after CBC administration (interval I-III: 2.57 ms before the start of therapy and 2.35 ms after 6 months).

EEG performed 6 months after the start of therapy showed an increase in the number of groups of α-waves, a decrease in the amplitude of the baseline EEG, a decrease in the number of polyphasic potentials in the occipital leads of both hemispheres, and a decrease in slow-wave spectrum waves (θ-waves, single σ-waves). There was also

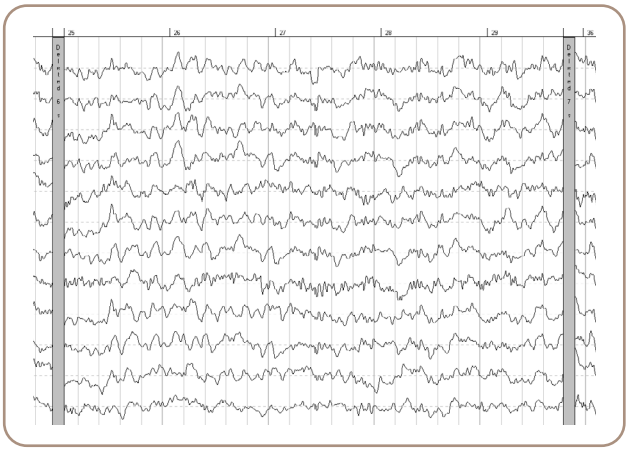

Figure 1. EEG before the start of therapy.

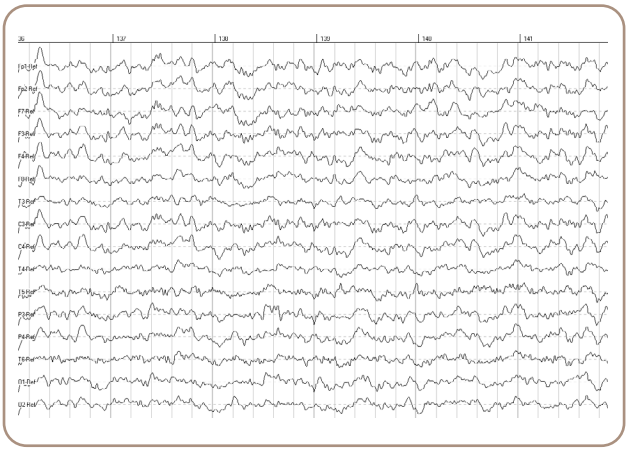

Figure 2. EEG 6 months after the start of therapy.

a significant decrease in amplitude characteristics and zoning in the form of a pronounced increase in amplitude from the frontal cortex to the occipital cortex, which was not observed before the start of therapy. Comparison of the quantitative EEG data with eyes closed shows the following: an increase in the power of α-waves in the parietal and occipital leads of both hemispheres and a decrease in the power of θ-waves in the occipital-parietal leads of both hemispheres. Analysis of the reorganization of the leading electroencephalographic pattern over time indicates a decrease in the severity of functional immaturity of the brain structures in the patient after treatment.

Changes in the patient's condition revealed by clinical evaluation

A few months after the start of the therapy, the child's vocabulary had expanded significantly, a simple phrase had appeared, and speech had begun to be communicative. But the most noticeable result was observed in the emotional dimension and behavior: the child became much calmer, aggression and affective outbursts disappeared, which made it possible to completely discontinue neuroleptics.

The dramatic development of cognitive functions was reflected in the child's drawings (Figures 3, 4). Before therapy, the patient's drawings had been monotonous and non-objective. Thanks to the development of attention, perception, and fine motor skills, the child began to develop reading and writing skills.

DISCUSSION

There has been a significant increase in research into the use of stem cells for the treatment of neurological and psychiatric disorders in recent decades. Among these, there are many case reports in which cell therapy produced a real breakthrough [27–31].

In our opinion, the same can be said about our case. Despite a large number of publications, there has not been a single successful case report of CBC therapy for regressive forms of autism, although there is a sufficient amount of data on the effect of neuroinflammation on the development of regressive autism, as well as on the immunomodulatory function of stem cells. Patients with regressive autism are characterized by immune disorders, increased production of pro-inflammatory cytokines,

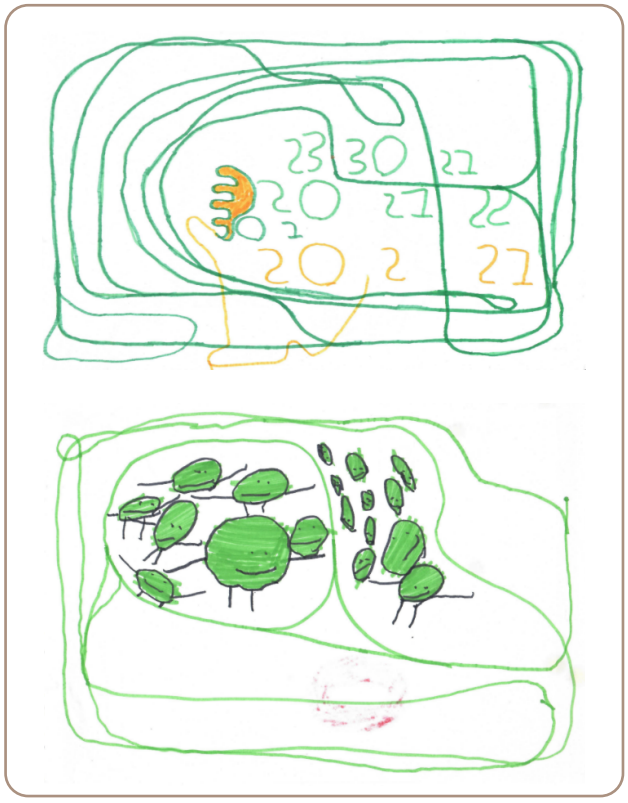

Figure 3. Patient's drawings before the start of treatment.

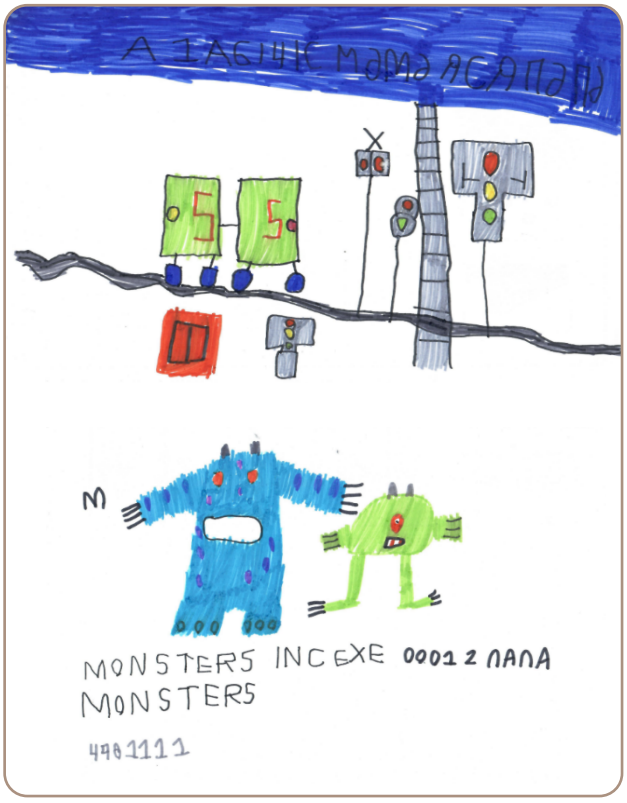

Figure 4. Patient's drawings after 6–9 months.

impaired blood-brain barrier, and subacute inflammation in the brain tissue [32]. Pro-inflammatory cytokines, by penetrating the blood-brain barrier, affect microglia and astroglia, which leads to impaired pruning and synaptic transmission [33]. From the microanatomical perspective, patients with autism have a shorter length of dendrites (especially in the frontal, temporal, and motor cortex), an increased number of cortical columns with a decrease in their volume, and blurred gray-white matter transition [34, 35]. The pro-inflammatory immune status of such patients causes a tendency toward an inadequate response of the immune system to triggers (infections, immunization) and the production of autoantibodies to the body's own tissues, which often leads to a regression of previously acquired skills and an increase in autistic symptoms [36, 37]. This is also confirmed by studies on the successful use of anti-inflammatory therapy for the treatment of regressive autism [38, 39]. Numerous studies have shown that stem cells (SCs) have an immunomodulatory effect, suppressing the activity of innate immunity factors (dendritic cells, natural killer cells, complement) and the functions of cytotoxic T-lymphocytes and T-helper cells. In addition, SCs translate their functions to other cells, in particular, regulatory T-lymphocytes, which determines the effectiveness of cell therapy even after lysis of the injected stem cells [40–42]. The regression and the development of the disease two years after an infection suggest that our patient has a regressive form of autism, which is mostly characterized by immune disorders [32]. This assumption explains the significant improvement in the drug-resistant patient following CBC therapy. However, it should be noted that the described case is currently the only one and that confirmation of the hypothesis requires extended clinical studies on a large sample of patients with regressive forms of autism, as well as immunobiochemical studies confirming the abnormal immune status of their patients.

CONCLUSION

The use of CBCs is associated with good tolerability and the absence of significant adverse events. The use of nucleated CBCs in a patient with regressive autism led to a significant improvement in cognition and a decrease in the severity of their autistic symptoms. There was an improvement in the child's condition in the form of perception development, reduction of somatosensory disorders, normalization of emotional status, and development of socialization and communication skills. The complete discontinuation of neuroleptics is also an important positive result of the treatment. This case provides evidence that the use of CBCs in some forms of autism in children can lead to a significant improvement in their condition.

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The Interdisciplinary Diagnostics of Autism Spectrum Disorder Using DC:0-5™: A Case Report

Междисциплинарная диагностика расстройства аутистического спектра с использованием DC:0-5™: клинический случай

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Case report

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ABSTRACT

BACKGROUND: The Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood (DC:0-5™) is widely used in many Western countries. For Russian specialists, such classification represents a relatively new tool for the comprehensive diagnosis of mental disorders in children from birth to the five-year-old threshold. The purpose for presenting this case study report is to showcase the practical application of the DC:0-5™.

AIM: This study aims to illustrate the diagnostic process according to the DC:0-5™ criteria using the example of a specific clinical case report involving the collaborative efforts of two specialists: a child psychiatrist and a clinical child psychologist.

METHODS: DC:0-5™ consists of five axes. The main axis focuses on clinical diagnosis criteria for mental disorders, considering their age specificity. The remaining four axes allow one to take into account and specify data related to biological, social, and psychological factors, which play a crucial role in understanding the causes and characteristics of a mental disorder in a child.

RESULTS: In the examined case, an analysis of symptoms by means of the Clinical Disorders axis revealed that they were consistent with the diagnostic criteria for autism spectrum disorder. The use of the remaining axes supplemented the clinical diagnosis with specific details about the adverse physical health factors in the child, a high cumulative stress burden, significant developmental delays in the emotional, speech, and social dimensions, as well as dysfunction in the mother-child dyad. Since the parents declined medication for their son, this information proved crucial in developing a support program for both the child and the family.

CONCLUSION: The comprehensive diagnostic approach using the DC:0-5™ axes proved highly effective, not only in psychiatric diagnosis but also in establishing goals and objectives for subsequent intervention. Its application in psychiatric, clinical psychology, and corrective educational practices has the potential to make support for children in their early years a more personalized and family-oriented undertaking.

АННОТАЦИЯ

ВВЕДЕНИЕ: Распространенная во многих западных странах Диагностическая классификация нарушений психического здоровья и развития в младенчестве и раннем детстве (Diagnostic classification of mental health and

developmental disorders of infancy and early childhood, DC:0-5™) является для российских специалистов достаточно новым инструментом комплексной диагностики психических расстройств у детей от рождения до пяти лет. Представление клинического случая имело целью проиллюстрировать применение DC:0-5™ на практике.

ЦЕЛЬ: Продемонстрировать проведение диагностики по критериям DC:0-5™ на примере конкретного клинического случая при совместном участии двух специалистов — детского психиатра и детского клинического психолога.

МЕТОДЫ: DC:0-5™ состоит из пяти осей. Основная ось клинического диагноза содержит критерии психических расстройств с учетом их возрастной специфики. Четыре дополнительные оси позволяют учесть и конкретизировать данные о влиянии биологических, социальных и психологических факторов, играющих важную роль в понимании причин и особенностей психического расстройства у ребенка.

РЕЗУЛЬТАТЫ: В рассматриваемом случае анализ симптоматики по оси клинических расстройств показал ее соответствие диагностическим критериям расстройства аутистического спектра. Использование остальных осей дополнило клинический диагноз конкретизированной информацией о неблагоприятных факторах физического здоровья ребенка, высоком уровне кумулятивной стрессовой нагрузки на него, выраженном отставании в развитии в эмоциональной, речевой и социальной сферах, нарушениях функционирования материнско-детской диады. С учетом отказа родителей от медикаментозного лечения сына эти данные оказались важными для разработки программы помощи ребенку и семье.

ЗАКЛЮЧЕНИЕ: Комплексная диагностика с применением осей DC:0-5™ показывает свою высокую эффективность, как в плане постановки психиатрического диагноза, так и в плане определения целей и задач последующего вмешательства. Использование ее в коррекционно-педагогической, клинико-психологической и психиатрической практике способно сделать помощь детям первых лет жизни более персонализированной и семейно-ориентированной.

Keywords: *DC:0-5™; autism spectrum disorder; case report*
Ключевые слова: *DC:0-5™; расстройство аутистического спектра; клинический случай*

INTRODUCTION

A significant milestone in the interdisciplinary diagnosis of early mental health disorders is the development and implementation of DC:0-5™ (Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood) [1]. Created by leading global experts for ages spanning from infancy to five years, this classification has now been translated and published in numerous foreign countries. In Russia, the translated version was published in 2022 [2] and it has already found application in domestic psychological and psychiatric practice [3, 4]. DC:0-5™ includes cross-references to ICD-10 and DSM-5, allowing it to serve as a complementary diagnostic tool.

Diagnosis using DC:0-5™ involves an evaluation across five axes [5]. In addition to the primary axis addressing clinical disorders, it includes four supplementary axes that consider various factors crucial for understanding the development of mental disorders in young children. These factors include aspects of family dynamics, the cumulative stress burden on the child and family, and indicators of the child's biological health and maturity for his age. The interdisciplinary data gathered contribute to the provision of more adequate and comprehensive care in each specific case [6].

The aim of this article is to illustrate the diagnostic process as outlined based on DC:0-5™ criteria using the example of a specific clinical case report involving the collaborative efforts of two specialists: a child psychiatrist and a clinical child psychologist.

CASE REPORT

Patient

The boy, Pavel (name changed), was 3 years and 1 month old at the time of the first visit. His parents, both 44 years old, have college degrees. The mother, before Pavel's birth, was the owner of a small business. Currently, she is

a housewife. The father, an engineer by training, is involved in that field. There are no other children in the family. The family is well-off and resides in the suburbs of the Moscow region in good housing conditions.

Parents complaints at the initial visit: speech delay, stubbornness, disobedience, refusal to communicate, as well as the presence of fear and stereotypical behaviors.

Medical history

The family had endured a tragic experience in the year leading up to the pregnancy and throughout, involving the disappearance, extended search, and eventually news of the death of their eldest teenage son. The pregnancy itself was unplanned, and the mother, in part, made the decision to carry it to term as an emotional attempt to cope with the loss of her eldest child.

The delivery occurred spontaneously at 34 weeks, with a birth weight of 5,84lb and an Apgar score of 6–7 points. The infant was fed on formula milk, and both the boy and his mother spent the first month post-birth in a hospital. The child was discharged with a diagnosis of cerebral ischemia and CNS (central nervous system) oppression syndrome and subsequently put on outpatient neurologist follow-up.

During the first 10–11 months, the parents raised no concerns about the child's development. The baby was calm, he ate and slept well, smiled frequently, could laugh, displayed no fear of loud noises, and enjoyed watching apartment renovation work. According to his mother, he made her happy. The child achieved milestones such as sitting independently at 9 months, crawling at 10 months, standing without support at 11 months, and walking at 11,5 months. He started babbling around 8 months. Due to delayed motor development, at 9 months, a neurologist recommended intensive outpatient treatment, including injections (the parents could not tell the specific drugs) and massage, during which the boy became very agitated and cried often.

After 11 months, Pavel started experiencing problems with sleep, accompanied by the emergence of a significant timidity level. At 12 months, he began rocking in his crib. Throughout his second and third years, the boy remained highly agitated, reacting intensely to every sound. He could cry for hours due to noise from the neighboring apartment and required prolonged rocking to fall asleep until the age of three. Pavel developed a fear of strangers, crying and hiding from them. He had intense fear of his grandfather, who accompanied him to medical procedures; Pavel vomited in the car. A few months after it first appeared, the rocking behavior occurred whenever the child was dissatisfied and later extended to include stereotypical behavior such as falling to his knees and banging his head on the floor or against the wall. The parents also noted Pavel's persistent urge to play with running water, spending extended periods pretending to wash dishes, watching the washing machine for hours, or standing on the windowsill to observe the movement of tree branches. He resisted any attempt to wash his hair and started biting his nails to the point of causing skin damage. He became highly irritable when faced with restrictions, often shouting and attempting to hit. He did not produce his first words by the age of 12–15 months. On a neurologist's prescription at a children clinic, Pavel underwent treatment with stimulant and sedative medications, including periciazine, which resulted in uncontrollable vomiting, leading to the discontinuation of the drug. At 18 months, Pavel underwent outpatient removal of a superficial hemangioma on his scalp without his mother's presence. This sudden, albeit brief, separation, along with the medical procedure, induced extreme fear in the child. Shortly afterward, Pavel was attacked by a dog, causing a terrible fright and involuntary defecation. First word-like sounds appeared briefly around the age of 2, used during play but not in communication. At 2.5 years, Pavel inserted a cherry pit into his nose, leading to choking and requiring a medical intervention. Following the incident, speech in play disappeared.

Over the last two years, relations in the family have been marked by the mother's deep concerns primarily for her son's physical health, her frequent irritation in response to Pavel's "abnormal" behavior and the instances of anger outbursts directed at both her husband and son. Concurrently, Pavel consistently exhibited protest behavior, manifesting as screaming, crying, attempts to hide, and hitting an adult or banging his head in response to requests from his mother. Notably, the child did not engage in communication with his peers or adults beyond the immediate family circle and displayed no interest in interacting with other children.

Status: The child underwent an examination during a home visit with the presence of both parents, conducted by two specialists — a child psychiatrist and a clinical child psychologist.

Physical development was age-appropriate. He had no external stigmas of dysembryogenesis. Establishing contact with the child proved challenging due to his

reluctance to communicate and desire to hide, which lasted more than half an hour. Through the application of techniques to establish contact, the boy became more cooperative, agreeing to stay in the same room with the adults. However, he kept his distance, avoided eye contact, and did not engage in communication. Simultaneously, he attentively listened to his parents' narrative about him. Unfazed by their son's presence, the parents provided a detailed account of his illness and gave their opinion about his condition. Pavel communicated with his parents using gestures and some syllables, but he seemed to understand their speech well. When his parents tried to interact with him, he mostly refused to comply with their requests, expressing dissatisfaction through yelling before retreating to another room. There, he turned on children songs at high volume while rocking his body. According to his mother the boy exhibits this behaviour with consistency. A brief episode was organized where Pavel played with his father. The child's game actions involved repetitive combinations of construction kit parts, accompanied by a hushed, unaddressed mooing sound. Despite his father's persistent attempts to provide guidance in the game, Pavel remained unresponsive, ignoring his efforts. Upon his father's request, Pavel effortlessly and accurately identified objects, animals, and letters in pictures, showcasing his recent accomplishment of learning the entire alphabet in just five days, as reported by his father.

A conversation with the parents and observation of the manner of interaction in the family revealed several distinctive features. Throughout the discussion, the mother appeared predominantly anxious, expressing concerns for her son and seeking ways to help him. However, many of her proposed solutions had little to do with Pavel's current condition, such as deliberations on the ideal age for school enrollment or strategies for future university admission. She communicated readily with specialists and was talkative. Her interactions with her son mainly comprised comments, reprimands, or criticism, seemingly ignored by Pavel. Although Pavel occasionally attempted to attract his mother's attention through sounds or gestures, none of them were noticed by her. The mother confessed to frequently yelling at the child, persistent irritability, and occasional outbursts of rage, leading to physical punishment with a belt. In contrast, the father's interactions with his son looked gentle and calm. The father's attitude was characterized by his desire to explain in detail to his 3-year-old son the consequences of various dangers, such as touching electrical outlets or disregarding traffic rules, etc. The parents exhibited a seemingly well-grounded relationship with each other. Both expressed reservations about resorting to drug treatment for Pavel, fearing potential allergic reactions, and consequently opted against it.

PRELIMINARY STAGE OF INTERVENTION

The child's mother received a recommendation to consult a psychiatrist, leading to a diagnosis of Recurrent depressive disorder, current episode moderate (F33.1). The attending physician noted the chronic nature of depression, emphasizing its polymorphic manifestation with symptoms including anxiety, apathy, and suicidal thoughts. A prolonged course of antidepressants was prescribed, and she adhered to the medication regimen diligently. Furthermore, psychoeducational discussions were conducted with both parents and separately with the mother, focusing on the parent-child relationship.

Upon reevaluation three months later, improvements were noted in both the mother's and the child's conditions, primarily having to do with emotional stabilization. The mother reported a cessation of her anger attacks, while the child displayed increased calmness, with improved interaction with other relatives. Notably, the child began imitating sounds and producing the first words in his speech. While Pavel's inclination towards negativism persisted, he ceased banging his head in a sign of protest. Overall, the intensity of stereotypical actions diminished, although they surged again as anxiety heightened. Increased sensitivity to sounds persisted.

QUALIFICATION OF THE CASE USING DC:0-5™ DIAGNOSTIC CRITERIA

The qualification process for the clinical case comprised several stages: 1) evaluation of the child's medical history and qualification of his mental state; 2) assessment of the stress level for the child and family, the developmental milestones the child achieved and family relationship context, using standard tabular DC:0-5™ forms; and 3) discussion of the results and collaborative development of recommendations for therapeutic intervention. The first stage was performed by a child psychiatrist; the second, by a clinical psychologist, with both contributing to the third stage. To present the data, the recommended sequence of axis evaluation from DC:0-5™ was followed: starting with axis III, followed by axes IV, V, II, and finally, axis I.

Axis III: Physical Health Conditions and Considerations

The analysis of the case revealed influences on the health status of factors such as prematurity, low birth weight, and hypoxic brain injury during childbirth. These factors led to the child being hospitalized in the first month of life with a diagnosis of cerebral ischemia and central nervous system oppression syndrome. Additionally, there was a high likelihood of perinatal encephalopathy with a minor delay in motor development, supported by long-term outpatient follow-up and neurological prescriptions (the parents were unable to provide details of the neurological diagnosis made at the polyclinic). The child's good general physical condition and satisfactory development until 10–11 months suggested a mild form of perinatal encephalopathy. The removal of a superficial infantile hemangioma from the scalp at 18 months did not directly affect the child's health.

Table 1. Psychosocial and environmental stressor checklist

Stressors	Age of onset	Comments, including duration and severity
Presence of psychological trauma in a significant adult	Before birth	Ongoing, high-intensity stress for the entire family
Mental illness in a family member (maternal depression)	Before birth	Throughout pregnancy and until present time
Exposure to stressors due to psychological trauma in mother during pregnancy	Before birth	Throughout pregnancy, high-intensity stress for the mother
Painful or frightening medical procedures	9 months	For two months, high-intensity stress for the child
Physical violence against a child (punishment)	12 months	Until now
Separation of the child from his mother (during a medical procedure) and the procedure itself	18 months	Short-term, sudden, high-intensity stress
Animal attack	18 months	Short-term, sudden, high-intensity stress

Table 2. Competency domain rating summary table

Competency Domain Rating	Emotional	Social-Relational	Language-Social Communication	Cognitive	Movement and Physical
Exceeds developmental expectations	-	-	-	-	-
Functions at age-appropriate level	-	-	-	-	V
Competencies are inconsistently present or emerging	-	-	V	V	-
Not meeting developmental expectations (delay or deviance)	V	V	-	-	-

Table 3. Dimensions of Caregiving (mother)

Dimensions of Caregiving	Contribution to Relationship Quality		
	Strength	Not a concern	Concern
Ensuring physical safety	V	-	-
Providing for basic needs (e.g., food, hygiene, clothing, housing, health care)	V	-	-
Conveying psychological commitment to and emotional investment in the infant/young child	-	-	V
Establishing structure and routines	V	-	-
Recognizing and responding to the infant's/young child's emotional needs and signals	-	-	V
Providing comfort for distress	-	-	V
Teaching and social stimulation	-	-	V
Socializing	-	-	V
Disciplining	-	V	-
Engaging in play and enjoyable activities	-	-	V
Showing interest in the infant's/young child's individual experiences and perspectives	-	-	V
Demonstrating reflective capacity regarding the infant's/young child's developmental trajectory	-	-	V
Tolerating ambivalent feelings in the caregiver–infant/young child relationship	-	-	V

Axis IV: Psychosocial and Environmental Stressors

The axis contains a detailed list of stressors that may be associated with the child's mental state. Each identified stress factor was assessed for its duration, severity, and suddenness. The specialist is asked to fill out the relevant form from the manual (Table 1).

Axis V: Developmental Competence

DC:0-5™ involves the evaluation of a child's development across 5 domains (Table 2). Data can be gathered through diverse channels, including discussions with parents, observations of the child during interactions and play, developmental charts, and standardized tests.

Axis II: Relational Context

The specialist is asked to fill out the standard tabular form "Dimensions of Caregiving" (Table 3) and draw a conclusion about the level of adaptive functioning in each dyad, as well as the need for intervention.

The adaptive functioning of the mother-child dyad was classified as the third level, encompassing relationships that ranged "from being at risk to being disturbed". This level suggests that the existing relationship may have a negative impact on the child's condition and development; therefore, therapeutic intervention is indicated.

The length of this article does not allow for a detailed assessment of Pavel's relationship with his father. It is worth noting, however, that the functioning of the father-child dyad was categorized at a relatively more favorable but still somewhat problematic second level, characterized by a relationship "from tense to concerning". Consequently, ongoing observation is recommended in this case, not excluding intervention.

Axis I: Clinical Disorders

Analysis of the child's symptoms on Axis I resulted in a diagnosis of autism spectrum disorder (ASD), meeting all the necessary diagnostic criteria outlined in DC:0-5™ for this condition. Specifically, within the domain of social communication (the first diagnostic category), the child exhibits at least four symptoms out of the required three for diagnosis: atypical social approach, limited ability to initiate joint attention, atypical use of eye contact, and lack of interest in peers. In the second diagnostic category, restrictive and repetitive behavior is represented by three symptoms out of the required two: stereotyped motor movements and use of objects and toys, atypical fixation on item or topic of interest, and atypical responsivity to sensory inputs. These identified symptoms have a significant impact on both the child and family functioning, meeting another essential criterion for the disorder. Among the associated features that support a diagnosis according to DC:0-5™ criteria, developmental and speech delays, prematurity, and low birth weight may be noted. Furthermore, this case aligns with the point of view outlined in ICD-10 and reflected in DC:0-5™ regarding the frequent co-occurrence of ASD with anxiety and phobic disorders.

RECOMMENDATIONS FOR THERAPEUTIC INTERVENTION

Considering the parents' rejection of medication therapy for their son, a care program was recommended. This program involves ongoing observation of the child and mother by a psychiatrist, implementation of measures to enhance mother-child interaction, sensory integration courses, incorporation of the Floortime approach, and corrective pedagogical strategies. The Floortime approach consists of daily, brief episodes of non-directive play between a parent and a child, including techniques to promote social-emotional interaction. These techniques are imparted to the parent by a specialist [7]. Specific targets for clinical and psychological intervention were identified through a comprehensive diagnosis across the DC:0-5™ axes.

DISCUSSION

The use of DC:0-5™ Axis I, which contains clear criteria for 42 early psychopathological syndromes, has shown its usefulness as a tool for diagnostic clinicians in assessing young children. However, the development of therapeutic interventions solely based on Axis I can pose challenges for child psychiatrists. This difficulty may arise primarily due to age-related constraints on drug treatment and/or, as observed in the analyzed case, the parents' decision to reject it. Furthermore, a clinical diagnosis *per se* does not provide insights into the pathogenesis of a specific condition of the patient.

This information is gleaned through a meticulous look into the history (Axis III and IV) and analysis of supplementary examination findings (Axis V and II). In the discussed case, Axis III unveiled unfavorable biological factors affecting the child's physical health, though these factors did not have a direct impact on the onset and course of the primary mental disorder. Simultaneously, Axis IV identified

numerous stressors that could indirectly influence the emergence and progression of ASD symptoms. Some stressors demonstrated a clear temporal relation to the initial and subsequent phases of ASD symptoms. For instance, a notable decline in the child's mental state at 10–11 months of age appeared to be associated with intensive, painful, and fright-inducing medical procedures. Axis V data indicated a significant delay in emotional development, as well as social and interpersonal relationships. The results of the Axis II examination revealed notable disruptions in the functioning of the mother-child dyad. The structured and tabular presentation of indicators on this axis facilitates the identification of areas that could be used to optimize the maternal behavior.

The persistent depression experienced by the mother, detected in an additional psychiatric assessment, may be a contributing factor encumbering her interaction with the child. The prescription of an antidepressant treatment, coupled with psychoeducational interventions, resulted in a noticeable improvement in mother-child interaction and a degree of progress in the child's development. It is crucial to highlight that these improvements occurred without any specific therapy targeting the child himself. This once again underscores the significance of the close connection between a young child and his/her mother, to the extent that his/her mental health can improve merely through the stabilization of the mother-child relationship [8].

On the further development of corrective actions, it is useful to consider a factor still relatively overlooked in Russian infant psychiatry. We are referring to an ASD criterion used in Axis I, also present in the DSM-5™, known as atypical responsivity to sensory inputs. This aspect is evident in the described case, involving sensory changes in the auditory, tactile, and potentially vestibular and proprioceptive domains. The pathogenetic role of sensory changes in the clinical presentation of ASD and their correction is being actively investigated both abroad [7, 9, 10] and in Russia [11, 12].

Transitioning from this specific case discussion to the potential wider implementation of DC:0-5™ in Russian practice, several noteworthy considerations emerge. Primarily, there is a notable absence of organizational capacity to conduct interdisciplinary assessments during routine outpatient visits. Typically, child psychiatrists and clinical psychologists perform assessments separately, posing a challenge for any subsequent collaborative evaluation and reducing objectivity. To address this issue, a potential solution could be to integrate the methodologies of both specialists and leverage modern technologies, such as widely available video recording. Moreover, when employing DC:0-5™, it becomes essential to take into consideration the disparities in established diagnostic approaches between Western and Russian psychiatric, psychological, and correctional pedagogical schools. However, for psychiatrists, this challenge is somewhat alleviated by the inclusion in the DC:0-5™ clinical axis of references for each diagnosis to its counterpart in ICD-10. For instance, the diagnosis of "autism spectrum disorder" according to DC:0-5™ aligns with the diagnosis of "Childhood autism" (F84.0) in ICD-10, although the criteria for this disorder in early age are not comprehensively covered in the latter.

CONCLUSION

In the examined case, an analysis of symptoms by means of the Clinical Disorders axis revealed that they were consistent with the diagnostic criteria for autism spectrum disorder, specifically, the presence of prerequisite symptoms in the categories of social communication and restrictive and repetitive behaviors. Employing a comprehensive diagnostic approach with the use of the remaining axes supplemented the clinical diagnosis with specific details about the adverse physical health factors in the child, a high cumulative stress burden, significant developmental delays in the emotional, speech, and social domains, as well as dysfunction in the mother-child dyad. The diagnosis conducted across the DC:0-5™ axes facilitated the development of a care program for the child and family. This program is grounded in ongoing observation of the family by a psychiatrist, corrective and pedagogical measures, sensory integration courses, and optimization of mother-child interactions.

In essence, the application of a comprehensive diagnosis using the DC:0-5™ axes has demonstrated its utility, both in establishing a psychiatric diagnosis and in delineating the goals and objectives for subsequent intervention. Its application in psychiatric, clinical psychology, and corrective educational practices undoubtedly has the potential to make support for children in their early years more personalized and family-oriented undertaking.

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Recurrent Psychotic Episodes Induced by Synthetic Cathinones in a Monozygotic Twin with Drug Addiction: A Case Report

Рекуррентные психотические эпизоды вследствие употребления синтетических катинонов: клинический случай монозиготных близнецов

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Case report

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ABSTRACT

We have described a clinical case of psychotic disorder induced by synthetic cathinones in one drug-addicted monozygotic twin. This clinical case is unique, because it offers the opportunity to observe many features of the singularity of the dependence syndrome in twin brothers: drug choice; motivation to use drugs; and the development of multiple, long-lasting psychoses in one of the brothers. We pursued a twelve-month follow-up of this case. The case substantiates the paucity of a fundamental understanding of mental disorders and highlights the importance of further research into the clinical features of drug-induced psychoses, especially those induced by novel psychoactive substances such as synthetic cathinones.

АННОТАЦИЯ

В статье описан случай развития психотического расстройства у одного из монозиготных близнецов, оба из которых имеют сформированный синдром зависимости от нескольких психоактивных веществ. Этот случай предоставляет редкую возможность наблюдать индивидуальные особенности в процессе параллельного формирования синдрома зависимости у близнецов (наркотик выбора, мотивация к употреблению) и дальнейшее развитие двух затяжных психозов только у одного из братьев. В статье описаны и проанализированы результаты 12-месячного наблюдения. Данный случай демонстрирует нехватку фундаментального понимания механизмов развития психических расстройств и подчеркивает важность дальнейшего изучения психозов, связанных с употреблением психоактивных веществ, в частности синтетических катинонов.

Keywords: *synthetic cathinones; "bath salts"; psychotic disorders; twins; case report*

Ключевые слова: *синтетические катиноны; «соли для ванн»; психотические расстройства; близнецы; история болезни*

INTRODUCTION

Synthetic cathinones (Scaths) are modern psychoactive substances which are synthetic analogues of cathinone. Cathinone is an alkaloid found in the leaves of *Catha edulis* (Khat). Scaths have psychostimulant, euphorigenic, and empathogenic action. The actions spectrum is similar to that of "traditional" drugs, such as methamphetamine, amphetamine, and methylenedioxymethamphetamine [1–3]. In Russia, α-pyrrolidinopentiophenone (α-PVP) and 4-methylenemethcathinone (mephedrone) are the most prevalent Scaths [4, 5]. In comparison with traditional stimulants, they (a) cause a stronger reinforcement system activation, which leads to severe craving and higher overdose risk, and (b) are capable of inducing psychoses, including those with schizophreniform clinical presentation.

Accordingly, Scath-induced psychoses are often hard to diagnose, as they are similar to schizophrenia manifestations and sometimes may trigger mental disorders. In the case of comorbidity between dependence syndrome and schizophrenia both disorders have an altered clinical picture. Clinical presentation and the course of the disease in comorbid schizophrenia with modern psychoactive substances addiction are currently the object of rigorous research [6–9].

Schizophrenia is known to show an inheritance rate of up to 50%; in monozygotic twins, the heritability rate of schizophrenia can attain 79% [10]. A meta-analysis by Murrie et al. (2020) arrived at a 25% rate of schizophrenia development (CI 18%–35%) during a four-year follow-up period after drug-associated psychosis manifestation [11]. The study found that the highest risk of schizophrenia development was associated with cannabinoid-associated psychoses (34%; CI 25%–46%), while hallucinogens and amphetamine constitute a slightly lower risk, 26% (CI 14%–43%) and 22% (CI 14%–34%), respectively [11]. Thus, schizophrenia and drug-induced psychoses can no longer be considered antithetical conditions. Today, their concepts are frequently seen as overlapping, providing opportunities for research into the etiology and pathophysiology of mental disorders. Not with standing the aforesaid differential diagnosis of psychoses in psychoactive substance users remains relevant for us.

We present a clinical case of a psychotic disorder induced by synthetic cathinones in a drug-addicted monozygotic twin. This clinical case is unique, because it offers the opportunity to observe many of the features that constitute the singularity of the dependence syndrome in twin brothers, from the first experience to the development of multiple, long-lasting psychoses in one of the brothers that we followed-up for 12 months.

Written informed consent was obtained from both brothers after a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Ethics Committee of the I.M. Sechenov First Moscow State Medical University (Sechenovskiy University).

PATIENT INFORMATION AND CLINICAL FINDINGS

Patient M, 26 years old, presented himself at the private addiction clinic in Moscow accompanied by his parents and brother B.

Patient M and his monozygotic brother B had used alpha-PVP and mephedrone for 4 months without interruption before the admission of M. Ten days before admission, M became aloof and irritable, professed to be "tired of drugs", and stopped using them. On the admission date, he started scrutinizing cars for special signs on license plates and "realized" that he had to depart for the USA in order to become a senator. He was found in such a condition in front of the roof door at his office building, where he was trying to "catch a helicopter to reach the USA".

During the interview, M was well oriented in time, place, and his own personality, although alert, strained, suspicious, and taciturn. According to the information from his relatives, during the day M behaved excitedly, was talkative, and claimed to have special abilities for which he could be persecuted. M did not argue with his parents when they reported on his condition, but he seemed tense and upset. The patient himself answered questions in a monosyllabic manner, sitting with his fists clenched. He kept his ruminations secret and said nothing about his supposed persecutors. Despite the apparent psychic tension, M easily agreed to stay in the hospital. He was admitted with the primary diagnosis F15.5 "Mental and behavioral disorders due to use of other stimulants, including caffeine: psychotic disorder".

Meanwhile B seemed anxious during the entirety of M's interview. At first B declined to answer when asked about his worries, but shortly afterwards he confessed to having consumed the same drugs as M in the last months and was now afraid to develop psychosis too. At that moment, B had been abstinent for a week and displayed no signs of developing psychosis. Therefore, B agreed with his parents

to submit to blood testing for drugs weekly for the next month and that if he tested positive, he would be placed in the rehabilitation center.

Life history

Family history was related by both brothers during two parallel interviews. The paternal grandmother and paternal grandfather of the patient had suffered from alcohol use and the second female cousin had an opioid dependence. The parents did not suffer from any psychiatric disorders or substance misuse. There is no family history of mental disorders.

Since childhood, M and B had lived together and been always active and physical. The brothers were brought up by their grandparents on the mother's side, while the parents were busy with their jobs. The development of M and B was simultaneous and in line with their age. At the age of five, the brothers started to show a divergence in character: while M started to turn into a shy and introverted individual, B began to develop sociability and gregariousness. In 2000, at the age of seven, the brothers began school. At school, M kept his distance from peers and stuck to his brother; M made efforts in his studies. On the contrary, B became livelier and leaned towards copying off from M rather than studying himself. At the age of 13, the brothers' behavior changed. M became more aggressive, having turned into a frequent participant in school fights. Although B's behavior was far from perfect, B got into trouble less frequently because he was more careful and slyer.

At the age of 13, the brothers tried beer and cannabinoids (bulk weed) for the first time. The effect of cannabinoid use did not appeal to the brothers: hence, they never again used these substances until their first year at university. Alcohol intake did not appeal to the brothers after the first try either. However, their attitude changed later. By the age of 14, the brothers were systematic alcohol consumers. Both drank up to 0.5 liter of hard liquor (vodka) every week. Both brothers graduated from school (full 11-grade course) with poor marks, but M having higher marks than B, and entered university having chosen the same major. On the first university year, M and B got closer to rich peers and began to attend parties at which substance use was common. In this company, the brothers felt embarrassed of their inferior financial status. To blend into the group, the brothers started consuming drugs as well. Accordingly, from the age of 18, M has complemented alcohol with hashish and, by graduation from university, amphetamine. B, however, chose stimulants initially. M liked the feeling of being aloof, indifferent, and relaxed, while B gained the feeling of his own might, overcame his fear and shyness in social interactions, and found it easier to complete academic and work tasks under the influence of amphetamine.

After a year of drug use, the brothers found out that it became harder to stay sober even for a few days. During the sober days, they experienced deep melancholy, mixed with anxiety or agitation and a desperate need for drugs. To avoid feeling that way, the brothers began taking drugs daily. Three years later, at the age of 21, patient M's tolerance for cannabinoids had increased by up to 4–5 grams of hashish and 2 grams of amphetamine per day. Meanwhile B preferred to use amphetamine only, and his tolerance stayed at a similar level of 2 grams per day. M became more aloof, spending time in solitary reading and playing guitar. At the age of 23 (in 2017), the brothers tried Scath (mephedrone) for the first time. The effect of mephedrone highly appealed to M; he experienced euphoria that was stronger than that caused by amphetamine. During the following year, M's drug use turned severe, his craving for mephedrone became irresistible: the patient sniffed mephedrone every 30 minutes and began to experience difficulties with nasal breathing, which led to M's transition to smoking. B traveled a similar course, with acute craving, and constant mephedrone consumption at high doses, but he quit amphetamines. During this period, the brothers kept smoking cannabinoids a few days a week to "slowdown" after stimulants use.

At the age of 24 (in 2019), M's mental condition changed dramatically. He became taciturn and detached and was telling his brother about his constant fear of persecution by special services and criminal organizations. M was also complaining of racing thoughts and difficulties thinking. Despite such a dramatic turn in his condition, M continued his substance use (either did B). Three months later, M developed visual, tactile, and verbal hallucinations: he could visualize his former teachers demanding that he confess to having committed a murder. Concurrently, M started hearing threatening voices that were "dropping into his head directly". Experiencing extreme fear, M began to bang his head against the wall, which led to the loss of consciousness. M was found unconscious by his girlfriend, who lived with him. He was taken to the neurology unit of a city hospital by ambulance. In the city hospital, M did not tell the doctors about his fears. After having been

discharged from the city hospital, M was sent by his parents to the rehabilitation center for patients with addictive disorders. One week later, M escaped from the center, having taken no warm clothing despite the winter weather. After having wandered in the city for several hours, M froze up and came back to the rehabilitation center. Upon coming back, M stated that he had seen a "dream" in which "the real owners of the drugs that he had lost had come to him and explained everything that had been going on". He described that condition as a journey to the parallel universe, where he had been shown "the truth". M told the staff of the rehabilitation center that he was "the chosen one" as he had "special" blood flowing in his veins. According to the patient, "anything" could be made of his "special" blood. He also talked about his fear of being killed by unknown powers and feeling that someone is manipulating his thoughts. M claimed to see around him special signs that were passing him messages. Seeing that, M's parents committed him to a psychiatrist, who initiated a treatment with second-generation antipsychotics. Upon treatment, M's condition improved and psychosis retreated. M adhered to maintenance therapy and abstained from recreational drugs. During the same period, B also ceased drug use without professional assistance. On the third month of sobriety M found a job as a sales manager in an airline company, lived alone in a rental apartment, and was socially active. After seven months of maintenance therapy M decided to give up treatment, as he "felt fine and got overweight because of therapy". Afterwards, M experienced intense craving for Scaths and during the New Year's holidays (in 2020) resumed consumption. B did as well. The brothers had been using Scaths four months straight before M's admission. They reported that daily consumption was approaching upward of 10 grams of mephedrone or 7 grams of alpha-PVP. Table 1 provides a summarized timeline of events.

DIAGNOSTIC ASSESSMENT

During neurological examination hands tremor was observed, and during physical examination tachycardia (96 beats per minute) was discovered.

A series of routine tests were administered upon the patient's admission: in blood tests, ECG and EEG were normal. Toxicological blood test (gas chromatography-mass spectrometry) did not show the presence of any substances (since it had been 10 days since the last drug intake according to patient report).

In terms of psychiatric assessment, we performed a psychopathological differentiation between substance-induced psychosis and schizophrenia spectrum disorder using the facts from the patients` history and their present mental state.

Based on our clinical judgment, the psychotic episodes had delusional manifestation, with a trend towards increasing complexity: hallucinations combined with pseudohallucinations and psychic automatism (thought broadcasting and insertion) and oneiroid syndrome (dream-like statement at the peak of the first psychotic episode) were observed. Furthermore, during the first psychotic episode M believed in his own might, special possibilities, and adopted risky behavior, which can be considered as mania symptoms. The first psychotic episode lasted around six months; such duration is atypical for substance-induced psychosis, as novel psychoactive drugs usually

Table 1. Timeline summary of patients events

Age (year)	Event
13 years old (2006)	First alcohol and cannabinoids intake (M and B).
from 14 to 18 years old (2007–2010)	Regular alcohol consumption (M and B).
from 18 to 23 years old (2010–2016)	M is using cannabinoids and amphetamine regularly. B is using amphetamine regularly.
23 years old (2017)	First mephedrone intake (M and B).
24 years old (2018)	M and B are using Scath regularly. M has developed a first episode of psychosis. Treatment in the rehabilitation center for addictions, then outpatient psychiatric treatment with antipsychotics during 7 months that patient discontinued himself.
the New Year holidays (2019–2020)	M and B resumed consumption of Scaths at the same day. After this point they continued using Scaths for 4 months.
26 years old (2020)	M's second psychosis and current admission. B quits drugs without professional help.

cause psychotic episodes that last 5–7 days. Nevertheless, by the time the psychotic episode ended, M had fully recovered, got a job, and showed no signs of negative symptoms for seven months.

In the absence of negative symptoms, such a condition could be interpreted as schizoaffective disorder. But a few counter-arguments exist:

a. there was no signs of affective disorders (neither mania, nor depression) beyond the peak of the first psychotic episode;
b. on the current admission, delusion with self-aggrandizing ideas was also observed, but euphoria, elevated or irritable mood, psychomotor agitation and impulsivity were not present;
c. the patient kept formal insight into his condition and was able to conceal his condition, which is not typical for severe affective disorders; and
d. a large dose of substances and long period of their consumption led to the development of psychosis, whereas exacerbation of a primary psychiatric disorder usually happens after a moderate substance consumption.

The current episode began approximately 10 days after the last Scath intake and cannot be explained by intoxication or withdrawal syndrome. Therefore, the patient meets ICD-10 diagnostic criteria for F15.5 "Mental and behavioral disorders due to use of other stimulants, including caffeine: psychotic disorder".

THERAPEUTIC INTERVENTION

The patient received the following round of therapy in the addiction treatment unit of the psychiatric hospital: fluid therapy up to 1 liter per day, haloperidol up to 20 mg/day, and valproic acid up to 1200 mg/day. During the treatment course, M remained taciturn and aloof, spending most of the day in bed with closed eyes. Nevertheless, the patient would easily wake up and join a conversation with a doctor. From the first days of the therapy, M denied having psychotic symptoms, including fear of persecution, referring to the therapy effects. However, he remained detached and distrustful, tried to limit any kind of verbal contact, and all his answers were monosyllabic. So doctors concluded that M is still experiencing psychosis. A felt burdened by staying in hospital, was curious about discharge date, and often asked for a call to his parents.

Fluid therapy lasted for 3 days in order to prevent possible electrolytic and rheological disorders. Antipsychotics and anticonvulsants were used throughout the period of the stay in the addiction treatment unit. Psychosis was in retreat by the second week of treatment, M's condition improved. He became more communicative and active and reported no complaints. On the third week of therapy, M was referred to the rehabilitation unit.

TWELVE-MONTH FOLLOW-UP

M remained under the supervision of the psychiatrist. In general, therapy with haloperidol and valproic acid was well tolerated. However, the patient was sedated and after three weeks of treatment developed akathisia. His therapy was modified: haloperidol and valproic acid were discontinued, carbamazepine 600 mg/day and olanzapine 15 mg/day were prescribed. This course remained unchanged until the end of the follow-up period. The patient endured blood testing every month and a physical examination every week to monitor adverse effects. No side-effects were noticed.

M was active and coopereative from the first day in the rehabilitation unit. Psychotherapy consisted of a twelve-step program and individual therapy with a gestalt therapist. Concurrently, B stayed sober. He started individual sessions with a therapist in the cognitive-behavioral approach and joined the Narcotics Anonymous community.

During his first month in the rehabilitation unit, M did not reveal his worries. Instead, M was telling his psychiatrist that he felt well and was willing to recover. However, his speech consisted of clichéd "right" phrases. After three months in the rehabilitation unit, M's condition improved. He became less guarded and confessed that his recent condition was almost identical to his first psychosis: M reported seeing signs that imparted him various pieces of information, to have thought of others speaking of him in secret, and to have thought to have "special" blood coursing through his veins.

Upon improvement, M became an active participant in every event, started asking staff for help, and was amicable and genuinely interested in advice given by the psychiatrist and the psychologist.

Despite noticeable improvement, the possibility of a schizophrenia spectrum disorder could not be excluded. On the 11th month of the follow-up, a cognitive evaluation by psychologist was performed. M's thinking was concrete. Abstraction and generalization were somewhat impaired. There were isolated generalization distortions and derailments. M's emotional status was remarkable for its

vivid emotionality and immaturity of emotional reactions. Short-term and long-term memory were intact. Working efficiency, warming-up extent, and mental stability were normal. Attention span was normal, but attention fluctuations were observed. Thus, no signs of organic-type or schizophrenic-type disorders were detected in M.

The psychiatrist did not detect any negative symptoms during the year of follow-up. No specific thought or emotional-volitional disorders (power potential decrease, blunted affect, and schizophrenia-type thought disorder) were observed during the psychological examination. Therefore, the diagnosis of schizophrenia was excluded.

After a year of follow-up, M was discharged from the rehabilitation unit of the private clinic with an ICD-10 diagnosis F19.202 "Dependence syndrome due to multiple drug use, currently in remission, stage 2" based on the main criteria for the dependence syndrome: presence of craving, lack of control over consumption, high tolerability for a drug, and withdrawal syndrome.

Concurrently, B remained sober and has landed a job as a manager. B now rarely experiences a craving for drugs and the craving is easy to overcome. In addition, he attends open city groups of the Narcotics Anonymous community. B never experienced psychotic symptoms.

DISCUSSION

This case demonstrates the paucity of a fundamental understanding of mental disorders and highlights the importance of further research into the clinical features of psychoactive drug-induced psychoses, especially those induced by novel psychoactive drugs such as Scaths.

The case is unique for several of its development features and the course of the dependence syndrome in the twin brothers: the choice of a recreational drug, motivation for consumption, and, undoubtedly remarkably, psychosis development. Genetic predisposition would be suggested not only by the hereditary load, but also by a concurrent development of addiction syndrome in the brothers. The age of drug abuse onset, consumption frequency, the development of regular consumption, and the progressive disorder course are identical in both brothers. Following in the steps of the community, in which it was customary to use psychoactive drugs, consequent expansion of the consumed psychoactive drugs range and fast development of regular use generally reflect the effects of the environmental factor. The different motivation for psychoactive drug use is remarkable: while M wanted to stand out in a crowd and isolate himself from society, B desired to overcome his shyness and fear to achieve a higher social status. Hence, personality traits have determined in this case the vector of psychoactive drug choice. M, having schizoid personality traits, preferred alcohol and cannabinoids at the initial stage of his addiction and started using Scath only after full development of the addiction, when his tolerance level had risen and there was a need for a stronger effect. B, being more inclined towards hysteroid personality traits, chose stimulants initially. Remarkably, B did not develop any psychotic episode throughout the whole observation period despite the severity of his dependence and his drug consumption being as intense as that M himself. Another remarkable aspect of our case is the so-called "twin telepathy": B's periods of not professionally assisted sobriety were concurrent with M's periods of abstinence, as well as B's relapses.

The case has some key findings. Firstly, there are several factors that affect the risk of psychosis development, and that risk is not identical even for monozygotic twins. Secondly, schizophrenia-like psychosis induced by novel substances have to be differentiated from schizophrenia spectrum disorders even when repetitive psychotic episodes are being observed. And thirdly, prolonged supervision under a qualified psychiatrist is necessary for patients with substance-induced psychoses.

The challenge that comes with differentiating a diagnosis of substance-induced psychotic disorder (SIPD) from that of schizophrenia spectrum disorders (SSD) is significant. The Diagnostic and Statistical Manual (DSM-5) emphasizes that patients with SIPD demonstrate different social and demographic features compared to patients with schizophrenia [12]. The risk of developing schizophrenia is higher in families with a history of any psychotic disorders [13]. Yang et al. (2020) found that the methamphetamine use initiation age correlates negatively with the Brief Psychiatric Rating Scale total score and the Activation subscale score, and that the duration of methamphetamine use correlates positively with the duration of psychosis [14]. Despite the fact that the positive symptoms of stimulant-induced psychoses (SIP) and SSD are generally similar, research confirms the absence of negative symptoms in SIP. [15]. On the other hand, there is evidence of a global and domain-specific cognitive dysfunction in SIP with a similar magnitude as schizophrenia compared to healthy controls [16]. We consider it safe to state that our case corresponds to the mentioned features as well: a family history of an

addictive disease with no psychiatric history; a socially active and well-adapted patient despite the reality of severe addiction; no signs of primary psychiatric disorder before the psychosis; long-lasting psychosis after a long episode of consumption; and severe, positive symptoms with no negative symptoms. Nevertheless, based on current data, stimulant-induced psychosis morphs into schizophrenia in approximately 20% of cases during a five-year period and patients with repetitive prolonged psychosis face the highest risk of schizophrenia [9, 11].

Our case has practical value for the treatment of comorbid psychotic and addictive disorders. We obtained a sufficiently result of the therapeutic combinations in multiple ways: (a) a parallel approach to psychosis and addiction treatment was performed, which appeared the best in this situation; (b) a combination of individual and group therapy for addiction was performed; (c) and a combination of psychotherapy and pharmacotherapy was utilized. This combined, comprehensive approach to the treatment of comorbid disorders appears optimal due to the need to develop strong motivation for sobriety and compliance with medical professionals to prevent further deterioration of a patient's condition.

Limitations

This case report has limitations that should be acknowledged. Unfortunately, this case description is based primarily on the patients' retelling of their life history and other information obtained from their relatives, which mostly could not be verified by any medical documentation. That makes disputable the equality of the consumed amounts of drugs and the periods of sobriety stated by the brothers during the interview, as well as the accuracy of the description of the first psychotic episode. Moreover, negative symptoms of schizophrenia may appear minor at this stage or concealed by antipsychotics.

PATIENT PERSPECTIVE

After a year of treatment, the brothers have developed a strong motivation for sobriety based on their own internal values. M said the following during the interview: "Rehab showed me that I really have a choice, but on the other hand I met people who fell deeper in this abyss and don't have a chance to return. I'm about to live a fulfilling life and I've realized how lucky I am for not being disabled forever or forever hallucinating." Nevertheless, he had a controversial view on medication: "I agree that it's necessary to take pills, but I'd like to stop it someday. I don't have some serious side effects like I've had before with my first psychiatrist, such as weight gain, but I would like to be more active and feel less sleepy".

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Endoxifen in Treatment of Individuals with Borderline Personality Disorder with Predominant Impulsivity: A Case Series

Применение эндоксифена при пограничном расстройстве личности с выраженной импульсивностью: серия клинических случаев

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Case report

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ABSTRACT

Endoxifen, a protein kinase C inhibitor, has been approved for use in manic episodes in India. One of the symptom traits that it predominantly targets is impulsivity. Impulsivity can also be a symptom dimension of other mental health conditions, one of which is Borderline Personality Disorder (BPD). Management of BPD is challenging, with limited pharmacological options that are symptom-directed and psychotherapy sessions that are fraught with early dropouts and lack of compliance. Impulsive behaviors represent a major reason for seeking help in BPD, especially with regard to non-suicidal self-injury, substance abuse, high-risk sexual behavior, aggression, etc. Here, we present a case series comprising five individuals with a diagnosis of BPD whose treatment regimens were changed and endoxifen added at a dose of 8 mg once daily. Clinical improvement was monitored using the Borderline Evaluation of Severity Over Time (BEST). All the subjects improved in the impulsivity domains as well as with regard to attention deficits, mood fluctuations, and overall functioning. Endoxifen is thus potential promising in terms of the management of BPD, but needs more extensive study to fully substantiate its clinical benefits.

АННОТАЦИЯ

Эндоксифен, ингибитор протеинкиназы С, был одобрен в Индии для применения при маниакальных эпизодах. Импульсивность — один из симптомов, на который преимущественно направлено действие данного вещества. Импульсивность присуща различным психическим расстройствам, одним из которых является пограничное расстройство личности (ПРЛ). Лечение ПРЛ является сложной задачей, поскольку фармакологические средства, направленные на устранение симптомов, ограничены, а сеансы психотерапии могут спровоцировать прекращение лечения на ранней стадии и несоблюдение режима терапии. При ПРЛ импульсивное поведение зачастую является первопричиной обращения за помощью, особенно при несуицидальном самоповреждающем поведении, злоупотреблением психоактивных веществ, рискованным сексуальным поведением, агрессией и т.д. В данной статье представлена серия из пяти клинических случаев пациентов с диагностированным ПРЛ, которым в схему лечения был добавлен эндоксифен в дозе 8 мг один раз в день. Клиническая динамика отслеживалось с помощью опросника Динамической оценки тяжести проявлений пограничного расстройства личности (Borderline Evaluation of Severity Over Time, BEST). У всех испытуемых улучшились показатели в отношении импульсивности, дефицита внимания, колебаний настроения и общего функционирования. Таким образом,

эндоксифен является потенциально перспективным препаратом для лечения ПРЛ, но для полного подтверждения его клинических преимуществ необходимы более обширные исследования.

Keywords: *borderline personality disorder; impulsivity; protein kinase C; endoxifen; case series*
Ключевые слова: *пограничное расстройство личности; импульсивность; протеинкиназа С; эндоксифен; серия клинических случаев*

INTRODUCTION

Borderline personality disorder (BPD) is a complex clinical disorder, with symptoms ranging from identity diffusion to impulsive behaviors, self-injury, inappropriate intense anger, suicidal/self-harm behaviors, instability of interpersonal relationships, and affective instability [1, 2]. This disabling mental health condition leads to impaired function, and usually appears during youth, though it impacts patients throughout their lifespans [1]. Among the general adolescent population, the prevalence of BPD is 3% [2], whilst the lifetime prevalence of BPD is 1.4% [1, 2]. Among adolescents attending an outpatient clinic, the prevalence of BPD is 11%, while among suicidal adolescents attending an emergency department, the prevalence is a staggering 78%. The treatment approach to BPD includes evidence-based pharmacotherapy along with supportive psychotherapy, dialectic behavioral therapy, etc. [3, 4]. A combination of pharmacotherapy and psychotherapy is more effective than a single therapeutic approach for the management of BPD [2–4], though retention in treatment and insight facilitation are practical challenges.

There is currently no approved molecule for the BPD pharmacotherapy. Endoxifen, a protein kinase C (PKC) inhibitor, has antimanic properties and has been approved for manic episodes with or without mixed features of bipolar I disorder [5]. There are also reports of its effectiveness in patients with impulsivity and substance abuse. A common thread among these is PKC overactivity, and therefore endoxifen could be evaluated for these indications [6].

Evidence on endoxifen is accumulating and would serve to increase our understanding of the value of this molecule. This case series describes the utility of endoxifen in the management of patients with BPD who displayed traits of impulsivity such as non-suicidal self-injury (NSSI), easy anger outbursts, and inappropriate sexual behavior (ISB). All cases involved individuals who had been diagnosed with BPD prior to the current presentation (for a period of over three years) and who had been treated with various drugs during that time. Treatment with endoxifen was effective and well-tolerated, signifying the importance of this drug in the management of BPD. Informed consent for endoxifen treatment and publication of data was obtained from all patients in their own languages.

CASE DETAILS

The individual case demographics, medications on which they presented, the treatment changes and improvement observed are presented in Table 1. The symptom dimensions of the patients are highlighted below. Clinical diagnosis was made as per DSM-5. We used the Borderline Evaluation of Severity Over Time (BEST) scale to objectively record the improvement with treatment. The BEST scale rates the behaviors, emotions, and thought patterns typical of BPD. The scale is sensitive to clinical change as early as four weeks into interventions and the score correlates positively with symptom severity [7]. This scale is a 15 items rated on a Likert scale. The BEST scale composed of 3 subscales: subscale A (thoughts and feelings), which includes eight items each with a maximum score of 5 (maximum score for subscale A is 40); subscale B (behaviors-negative), which includes three items each with a maximum score of 5 (maximum score for subscale B is 15); and subscale C (behaviors-positive), which includes 3 items each with a maximum score of 5 (maximum score for subscale C is 15).

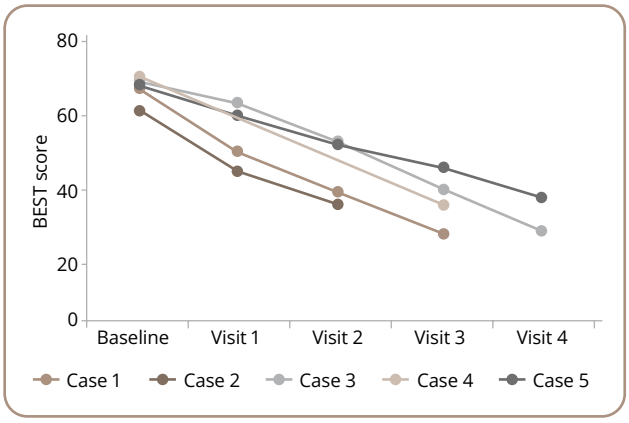

Figure 1. Improvement in BEST score for the individual patients after the introduction of endoxifen treatment.

Note: Each visit is at a monthly interval.

Table 1. Summary of the treatment details of the reported patients

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Patient age	21	19	28	25	29
Patient gender	F	F	M	F	M
Comorbid diagnosis	No comorbidities	Adult ADHD	BPAD (?)	Adult ADHD	Nil
Initial treatment	Fluoxetine 40 mg, aripiprazole 10 mg, oxcarbazepine 900 mg	Lamotrigine 100 mg, lithium 450 mg, risperidone 1 mg, clonazepam 1 mg, atomoxetine 36 mg	Carbamazepine 600 mg, clonazepam 1.5 mg, escitalopram 10 mg, risperidone 4 mg + trihexyphenidyl 2 mg, multivitamins	Lithium 1200 mg, haloperidol 5 mg, amisulpride 100 mg	Amisulpride 100 mg, vortioxetine 20 mg, divalproex 1 g
Change in treatment	Endoxifen 8 mg, lamotrigine 300 mg, oxcarbazepine 900 mg (for three months) then 600 mg; aripiprazole was tapered and stopped	Endoxifen 8 mg, escitalopram 15 mg, lamotrigine 200 mg, atomoxetine 36 mg; risperidone 2 mg (for one month) then tapered and stopped; clonazepam and lithium were tapered and stopped	Endoxifen 8 mg, carbamazepine 600 mg, clonazepam 1 mg, risperidone 2 mg; escitalopram was tapered and stopped	Endoxifen 8 mg (for 1 month) then 16 mg, lithium 1200 mg, haloperidol 5 mg, methylphenidate; amisulpride was tapered and stopped	Endoxifen 8 mg, divalproex 750 mg, vortioxetine 20 mg
Duration of endoxifen treatment	Three months	Two months	Four months	Three months	Four months
No. of reviews after first visit	3	2	4	2	4
BEST score at baseline	67	61	69	70	68
BEST score at last visit	28	36	29	36	38
Improvement observed with endoxifen	Reduced consumption of alcohol and tobacco; markedly reduced impulsivity; more composed and functional in relationships; no instances of harming others and herself	Improvement in mood and focus; symptoms of ADHD were alleviated; able to actively engage with family members; no further instances of self-harm or violence	No classical mood episodes; reduction in mood fluctuations and irritability; improvement at the workplace (fewer altercations and better attendance)	Reduction in impulsivity, grandiosity, anger outbursts, and ADHD symptoms; improvement in overall biological functions	Reduced suicidal tendency; fewer episodes of violence and anger outbursts; improvement in depressive symptoms; improved work performance (more days of perceived productive work, more flexibility with shifts, more alert)
Laboratory investigations during treatment with endoxifen	Hemoglobin: 10.2 g/dL, total leukocytes: 6600/μL with normal differential count, fasting blood sugar: 108 mg/dL, thyroid stimulating hormone: 1.2 mIU/L, vitamin B12: 457 pg/mL	Hemogram, fasting blood sugar, thyroid profile, vitamin B12, and vitamin D levels — normal	Hemogram, vitamin B12 levels, liver function tests, and serum electrolytes — normal	Hemogram, thyroid profile, fasting lipid profile, and liver function test — normal	Hemogram, liver function test, gamma-glutamyl transferase, fasting blood sugar, and thyroid profile — normal
Present status	Sustains improvement (last seen — one month previously)	Sustains improvement (last seen — two months previously)	Sustains improvement (last seen — one week previously)	Relapsed (after drug default)	Lost to follow-up

Note: ADHD — Attention-deficit Hyperactivity Disorder, BEST — Borderline Evaluation of Severity over Time; BPAD — Bipolar affective disorder.

Box 1. Borderline Evaluation of Severity over Time (BEST) scale

Instructions: For the first 12 items, the highest rating (5) means that the item caused extreme distress, severe difficulties with relationships, and/or prevents getting things done; the lowest rating (1) means the item caused little or no problems. Rate items 13–15 (positive behaviors) according to frequency.

A. THOUGHTS AND FEELINGS

1. Worrying that someone important in your life is tired of you or is planning to leave you.
2. Major shifts in your opinions about others such as switching from believing someone is a loyal friend or partner to believing the person is untrustworthy and hurtful.
3. Extreme changes in how you see yourself. Shifting from feeling confident about who you are to feeling like you are evil or that you don't even exist.
4. Severe mood swings several times a day. Minor events cause major shifts in mood.
5. Feeling paranoid or like you are losing touch with reality.
6. Feeling angry.
7. Feelings of emptiness.
8. Feeling suicidal.

B. BEHAVIORS (NEGATIVE)

9. Going to extremes to try to keep someone from leaving you.
10. Purposefully doing something to injure yourself or attempting suicide.
11. Problems with impulsive behavior (not counting suicide attempts or injuring yourself on purpose). Examples include: overspending, risky sexual behavior, substance abuse, reckless driving, binge eating, other _____ (circle those that apply).
12. Temper outbursts or problems with anger leading to relationship problems, physical fights, or destruction of property.

C. BEHAVIORS (POSITIVE)

13. Choosing to use a positive activity in circumstances where you felt tempted to do something destructive or self-defeating.
14. Noticing ahead of time that something could cause you emotional difficulties and taking reasonable steps to avoid/prevent the problem.
15. Following through with therapy plans to which you agreed (e.g., talk therapy, homework assignments, coming to appointments, medications, etc.).

The composite score is calculated as 15 + A + B – C. A higher score indicates greater symptom severity in individuals with BPD and a greater degree of functional impairment [7]. The BEST scale is detailed in Box 1 [7].

Two individuals were followed up for four months, two patients for three months, and the remaining one for two months. Reviews were conducted at monthly intervals.

Case 1: A 21-year-old female student with a documented history of BPD spanning four years presented to the psychiatry clinic for a routine follow-up. The patient reported significant impulsive buying, poor distress tolerance, self-harm attempts, as well as problems at the workplace and with family (a severe anger outburst that resulted in harm to herself and her brother). The patient was unrepentant about the anger outbursts. The patient was experiencing reduced concentration and an erratic sleep-wake schedule, along with pronounced mood fluctuations. The patient had a dependence on tobacco and engaged in harmful alcohol use. The BEST score was 67. Previous treatment included lamotrigine 200 mg (for three months), lithium 600 mg (for one month), oxcarbazepine 1200 mg (for two months), risperidone 4 mg (for six months), fluoxetine 60 mg (for two years), and aripiprazole 15 mg (for nine months).

At the time of the visit, the patient was undergoing treatment with fluoxetine 40 mg, aripiprazole 10 mg, and oxcarbazepine 900 mg. The patient reported experiencing gastrointestinal disturbances (attributed to lithium), extrapyramidal side effects (EPS), and galactorrhea (attributed to risperidone), and syndrome of inappropriate antidiuretic hormone secretion (SIADH) due to oxcarbazepine. Endoxifen 8 mg once-daily and lamotrigine 300 mg once-daily were initiated, while aripiprazole was tapered and stopped due to akathisia; oxcarbazepine was continued for 3 months, after which the dose was reduced to 600 mg once-daily. Fluoxetine was stopped after a month due to gastric side effects. There was a gradual improvement in BEST score (Figure 1, Table 1), with reduced consumption of alcohol and tobacco usage. Due to sleeplessness experienced with endoxifen, the patient discontinued endoxifen for two weeks, leading to a relapse of mood dysregulation, anger dyscontrol, and

agitation within 21 days. Endoxifen was restarted at the same dose. After four months of treatment, the patient showed markedly reduced impulsivity.

Case 2: A 19-year-old female student diagnosed with BPD (for the last three years) and moderate depression with somatic syndrome (for the last year) presented for review. Over the course of her illness, the patient had been prescribed escitalopram 20 mg (for one year), olanzapine 10 mg (for six months), valproate 500 mg (for one year), and risperidone 2 mg (for eight months). At the time of presentation, the patient and her family expressed a desire to reduce the number of medications, which consisted of lamotrigine 100 mg, lithium 450 mg, risperidone 1 mg, clonazepam 1 mg, and atomoxetine 36 mg. The patient exhibited significant impulsivity, which involved NSSI, as well as mood fluctuations, irritability, and occasional episodes of unprovoked violence and high-risk ISB. The patient also displayed symptoms suggestive of attention-deficit hyperactivity disorder (ADHD). Childhood history was unclear. There was no history of substance abuse. The BEST score at presentation was 61.

The patient's treatment plan was altered to include once-daily endoxifen 8 mg and escitalopram 15 mg daily, while clonazepam and lithium were tapered and discontinued. The dose of risperidone was initially increased to 2 mg for a month, then tapered and stopped, while lamotrigine was increased to 200 mg. The patient experienced gastric irritation, nausea, and reduced sleep, possibly due to the timing of the late afternoon dosing. The patient reported an improvement in mood and focus. There were no further instances of self-harm or violence. Additionally, endoxifen demonstrated efficacy in alleviating symptoms of ADHD. BEST scores showed improvement (Table 1, Figure 1). The dose of lamotrigine was tapered down. She could engage in psychotherapy sessions after two months of treatment.

Case 3: A 28-year-old obese male working as an information technology (IT) professional was diagnosed with BPD 10 years ago. The patient presented with symptoms of severe impulsivity, including gambling, excessive spending, feeling deceived, mood episodes resembling mania, overspending, increased familiarity, grandiosity, and heightened libido. The duration of these episodes was typically several hours. The patient also experienced occupational dysfunction, frequent absenteeism, and fights and verbal altercations with co-workers. There was a history of changing jobs, incomplete assignments, and periods of heightened productivity. The episodes were too brief to consider a syndromal diagnosis of bipolar disorder. The patient had a cannabis dependence and a history of alcohol consumption. The baseline BEST score was 69.

The patient's prescribed treatment regimen included carbamazepine 600 mg, clonazepam 1.5 mg, escitalopram 10 mg, risperidone 4 mg, and trihexyphenidyl 2 mg, in addition to multivitamins. Since the patient experienced mood fluctuations resembling those seen in bipolar disorder, a diagnosis of bipolar spectrum was made. Endoxifen 8 mg once-daily was initiated, and escitalopram was tapered and stopped. Carbamazepine 600 mg was continued along with clonazepam 1 mg, and risperidone 2 mg. After two months, the dose of endoxifen was increased to 16 mg once-daily. There was progressive reduction in the BEST score (Figure 1). The patient demonstrated a significant decrease in alcohol consumption, and laboratory investigations were normal. The patient did not exhibit any classical mood episodes, and there was improvement at the workplace functioning (Table 1). No adverse effects were reported following the addition of endoxifen to the treatment regimen. Clonazepam was tapered and stopped.

Case 4: A 25-year-old female had received a diagnosis of BPD at the age of 18. She had previously tried multiple medications without significant benefits. Her drug history included lithium 1500 mg, valproate 1 g, risperidone 8 mg, haloperidol 10 mg, and amisulpride 600 mg. She was currently taking lithium 1200 mg, haloperidol 5 mg, and amisulpride 100 mg. The patient appeared to be in a manic/euphoric state at the time of assessment and reported increased sleep. Recent symptoms included impulsivity, frequent mood fluctuations, fluctuant energy levels, pervasive patterns of problems in interpersonal issues (not amounting to bipolar affective disorder), and thoughts of self-harm and suicidality. The patient experienced non-specific paranoia, reduced self-esteem, easy anger outbursts, and low distress tolerance. The patient was not employed, and was living apart from her husband. The BEST score was 70, and the Young Mania Rating Scale (YMRS) score was 18. A high BEST score shows the greater intensity and frequency of symptoms associated with borderline personality, whereas the YMRS score indicates the presence of clinical mania. A diagnosis of bipolar affective disorder (BPAD) was considered, with possible adult ADHD.

Endoxifen 8 mg once-daily was added to the treatment regimen, while amisulpride was tapered and discontinued after 1 month. Endoxifen was increased to a twice-daily dose. Even after the YMRS reduced to 4, which indicated clinical remission of the manic episode, impulsivity and NSSI persisted. Significant attention deficits were noted, and atomoxetine was added up to 36 mg daily.

The patient reported rashes during the first few days of treatment, followed by headaches and insomnia. Benzodiazepines were prescribed to manage insomnia. There was no intermittent review for this individual and they consulted only after three months. At this review, the patient's family reported a reduction in impulsivity, grandiosity, anger outbursts, and ADHD symptoms. There was an improvement in overall biological functions. Retrospectively, they reported the improvement in agitation, mood, sleep and impulsive behavior to have started within three weeks of starting endoxifen. The BEST score at follow-up had reduced to 36 and the YMRS score was 2. Due to financial constraints, the family could not continue with endoxifen and stopped it after a total four months of treatment. Three weeks after stopping medications, the patient experienced outbursts of anger, agitation, and NSSI wishes, although these were not as severe as before starting treatment.

Case 5: A 29-year-old male, employed as a police constable, had received a diagnosis of BPD at the age of 19. He had a history of stuttering and recurrent depressive disorder, was dependent on tobacco, and consumed alcohol. His illness exhibited a fluctuating course, and he was inconsistent with his medication regimen. The patient had a history of unprovoked severe aggression followed by a subsequent calm period. He lacked remorse following these outbursts but experienced feelings of depression. Mood instability negatively affected his relationships, and the patient was unable to report to work. A complaint had been lodged against him for undue altercations with members of the public, and being authoritative and argumentative. The patient mentioned that anxiety made him irritable, and that he had reduced appetite. The patient had subjective memory deficits. The BEST score was 68, which increased to 70 after one week. Childhood history indicated oppositional behavior and difficult temperament.

The patient was undergoing treatment with amisulpride 100 mg, vortioxetine 20 mg, and divalproex 1 g daily. Endoxifen 8 mg once-daily was added to the regimen, whilst amisulpride and vortioxetine were discontinued, and the dose of divalproex was reduced to 750 mg daily. Laboratory investigations undertaken during treatment showed normal results. There was a progressive decrease in the BEST score (Figure 1). Symptom assessments revealed fewer episodes of violence and anger outbursts, improvement in depressive symptoms, and improved work performance (Table 1).

However, upon discontinuation of the medication (due to sleeplessness with endoxifen), the patient experienced a relapse of easy irritability, impulsivity, and alcohol abuse. A revisit has been planned.

The authors would also like to present narratives from two individuals in this case series who were treated with endoxifen. Informed consent has been obtained from same. These narratives are from the final visit (Case 1: after 3 months and Case 2: after 2 months).

They were asked: *"How different do you feel after you received the treatment? Can you please detail it?"*

"I was always under fire. Every single time I was irritated it felt like I could break the world. It was very difficult to interact and work. After treatment, I feel better. I can talk to my friends and colleagues without the fear of turning aggressive. My sudden decision making has reduced and I am able to give it a thought before I decide on turning rash towards myself or others. I wish it stays the same".

Case 1

"My mood was almost never steady. I myself didn't know when I would get sad, frustrated or furious! Besides, if I didn't break things or hurt myself — I didn't feel that I could get through things. I cannot explain — there is this intense desire to just burst out on everyone and everything. I was doubtful about the treatment, but it helped me. The medicines calm me down and I can engage with my counselling sessions. I am not that much at unrest anymore but I wish to improve further".

Case 2

Such narratives have a subjective bias but nevertheless give us a living experiential account of how the individuals must have felt with the treatment change.

It is also worthwhile noting that in four individuals (all with the exception of Case 4), the frequency of positive behaviors (items 13–15 BEST scale, Box 1) also increased, starting from the first monthly review, after endoxifen was started. Increases in these positive coping behaviors

has been shown to reduce distress, improve mood dysregulation, and reduce dysfunction in individuals with BPD [2, 7].

DISCUSSION

To the best of our knowledge, this is the first case series or report to be published on the use of endoxifen in management of BPD. In this case series, all patients displayed traits of impulsivity and were not satisfactorily treated with various medications at the time of presentation. These patients had received diagnoses of BPD over three years prior and were treated with various medications over that time. Endoxifen was prescribed due to the lack of effectiveness or poor tolerability of various other drugs. Treatment with endoxifen was well-tolerated and resulted in improvements in BEST scores and clinical improvement in symptom domains [8]. Endoxifen was beneficial in managing BPD with a soft bipolar phenotype characterized by significant impulsivity, irritability, and mood fluctuations.

Impulsivity is a core feature of BPD that is precipitated by emotional stress, and can lead to suicidal and risky behavior [9]. Impulsivity is also a core feature of bipolar disorder, and both BPD and bipolar disorder lead to emotional dysregulation involving an inability to refrain from reacting to provocative stimuli. Debates on the overlap of these two conditions suggest that they either lie on a spectrum or that they are separate entities that can be comorbid [10]. In fact, the presence of borderline personality traits has been shown to adversely influence the clinical outcome of BPAD with increases in cycling, severity of episodes, and risk of substance abuse [11]. Targeting impulsivity, a core BPD trait, may hence have a favorable outcome in BPAD patients with comorbid Cluster B personality, and also those with the "soft bipolar" phenotype.

The current treatment approach for impulsive-behavioral dyscontrol symptoms involves selective serotonin reuptake inhibitors (SSRIs), and can be supplemented with an anti-psychitic, antidepressant, lithium, carbamazepine, or valproate. However, antidepressants have not displayed efficacy for impulsivity while evidence on antipsychotics for impulsivity is inconclusive. First-generation antipsychotics and antidepressants have limited benefit, and the long-term use of drugs has not been studied [12]. Pharmacotherapy for BPD is primarily adjunctive, with the aim of targeting impulsive behavioral dyscontrol [13–15], and it can be expected that symptomatic relief would positively impact treatment outcomes through better response to psychotherapy. Two individuals (Case 1 and 2) proved to be more amenable to psychotherapy after treatment with endoxifen, which is an interesting benefit.

The effect of endoxifen on impulsivity can be explained by the fact that impulses are regulated by the prefrontal cortex [16], and deficits in this region are associated with altered PKC intracellular signaling. PKC impairs cognitive functioning of the prefrontal cortex. Endoxifen is a PKC inhibitor utilized for the management of bipolar disorder that also exhibits impulsive behavior as a core symptom. Endoxifen has a four-fold stronger inhibitory effect on PKC compared to its parent molecule (tamoxifen), achieves steady-state concentration within two weeks of administration, and has a favorable safety profile [5, 17].

Specific data on use of endoxifen in young women is lacking. The risk of adverse effects of endoxifen are dependent on the dose and duration of treatment [18]. Studies on endoxifen for the treatment of breast cancer prescribe doses up to 160 mg for anti-estrogen activity [19]. Taking into account the dose and duration of treatment in this study (low-dose endoxifen [8 mg daily] for a short duration of four months or less), the risk of side effects was considered to be low. Furthermore, studies on the use of case reports demonstrate the safety and efficacy of endoxifen in women treated for four months and one year [20, 21].

In this case series, treatment with endoxifen led to a reduction in symptoms in people with BPD (predominant impulsivity traits), and in a few patients who discontinued endoxifen treatment a relapse of symptoms was noted. The patients in this case series included those who had had a BPD diagnosis for over three years and were either non-responsive to, or did not tolerate, other medications. Endoxifen was thus prescribed due to its action on PKC, which has been implicated in impulsivity, substance abuse, and mania. In this specific subset of patients, there was an improvement in BEST scores, along with reduced substance abuse, impulsivity, and NSSI, as well as improved interpersonal relationships and work productivity. There were also fewer episodes of violence/self-harm and anger. Side-effects were few but included nausea, sleeplessness, and anxiety. However, the high cost of the medication can be a potential constraint. Further large-scale studies are necessary to establish the efficacy and long-term safety of endoxifen as a potential therapeutic tool in the challenging management of BPD.

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Biological Reductionism as an Obstacle to the Advancement of the Biopsychosocial Concept of Mental Disorders

Биологический редукционизм как препятствие для дальнейшего развития биопсихосоциальной концепции психических расстройств

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Opinion

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ABSTRACT

The substantial progress in neurobiological technologies has narrowed the horizons of many psychiatrists, ultimately leading them to focus exclusively on biomedical research, primarily aimed at studying the biological basis of mental illnesses. This has led to an unjustified dominance of the biomedical paradigm in understanding the nature of mental disorders, while virtually ignoring the study of other components of the disease related to the psychosocial maladjustment of patients. This trend, largely associated with advancements in neuroscience employing neuroimaging techniques to study the brain's activity as a biophysical object, has contributed to the development of such innovative field as evidence-based medicine. The methods of evidence-based medicine are seen as adequate in terms of determining the effectiveness of therapy for predominantly biologically determined components of mental illness (including the selection of medications) and only partially for psychological interventions. However, it seems that the predominant use of evidence-based medicine principles is insufficient for a holistic diagnostic approach, which includes a multilevel (diversified) representation of the criteria of effectiveness for pharmacological and psychological interventions. In this regard, it is promising to establish a scientifically and clinically productive combination of, on the one hand, the evidence-based concept of effectiveness assessments based on high-quality randomized scientific studies, and on the other, expert opinions of highly qualified scientific specialists, as well as practicing physicians with their personal professional experience in individualized therapy. This makes it reasonable to develop a personality-oriented personalized psychiatry, based on a biopsychosocial understanding of the nature of mental disorders, their holistic assessment, and the development of comprehensive therapeutic measures.

АННОТАЦИЯ

Масштабные успехи нейробиологических технологий «сузили оптику» многих психиатров. В итоге специалисты сосредоточились на проведении исключительно биомедицинских исследований, направленных в первую очередь на изучение биологических основ психических заболеваний. Это ведет к неоправданному доминированию биомедицинской парадигмы понимания природы психических расстройств при фактическом игнорировании

изучения других компонентов заболевания, связанных с психосоциальной дезадаптированностью пациентов. Указанная тенденция, в значительной степени связанная с достижениями в области наук, изучающих с помощью соответствующих нейровизуализационных техник деятельность головного мозга как биофизического объекта, способствовала развитию такого инновационного направления, как доказательная медицина. Методы доказательной медицины видятся адекватными в плане определения эффективности терапии преимущественно биологически обусловленных компонентов психического страдания (включая выбор медикаментов) и лишь отчасти — психологических интервенций. Однако представляется, что доминирующее использование принципов доказательной медицины является недостаточным для холистического диагностического подхода, включающего полифоническое (многовекторное) представление о критериях эффективности фармакологических и психологических интервенций. В связи с этим перспективно скорейшее налаживание научно и клинически продуктивного соединения с одной стороны — доказательной концепции оценок эффективности, основанной на результатах высококачественных рандомизированных научных исследованиях, а с другой стороны — экспертных мнений высококвалифицированных научных специалистов, а также врачей-практиков с их личным профессиональным опытом индивидуализированной терапии. Это делает обоснованным развитие личностно ориентированной персонализированной психиатрии, основанной на биопсихосоциальном понимании природы психических расстройств, холистической их оценке и разработке комплексных терапевтических мероприятий.

Keywords: *biological reductionism; biopsychosocial approach; evidence-based medicine; person-centered psychiatry*
Ключевые слова: *биологический редукционизм; биопсихососциальный подход; доказательная медицина; личностно-персонализированная психиатрия*

INTRODUCTION

Over the past 20 years, many advanced technologies have emerged that have significantly expanded our knowledge of the brain and the neurobiology of mental disorders. At the same time, a lack of new biology-centered knowledge precludes a real breakthrough in applied neuroscience [1].

Moreover, against the background of rapid progress of medical technology, psychiatry has demonstrated, over the past two decades, an apparent conceptual diagnostic and therapeutic crisis due to the loss of the vector for further development of both theoretical research and clinical practices, which are a natural extension of the theory [2–8]. The fact is that the considerable advances in neurobiological technologies have narrowed the view of many psychiatrists, who eventually focused on conducting exclusively biomedical research aimed primarily at studying the biological basis of psychiatric diseases. As a result, the concept of mental illness as a disorder affecting the entire psychophysical system, which was established in psychiatric science during the 19th and 20th centuries, is being reduced. This complex picture is being transformed to a simplified view of "brain diseases" [9, 10]. Prioritizing genetic, as well as neuroimaging and cognitive research, proponents of this approach essentially postulate a *neurobiological paradigm* of psychiatric disorders (in which the understanding of their nature borders on Democritus' atomistic-materialistic conception), ignoring the *dualistic organization of the human psyche* (first mentioned by Aristotle), which in modern times is viewed according to the framework of *psychophysical parallelism* (using the terminology of Gottfried Wilhelm Leibniz).

The most obvious manifestation of the crisis in psychiatry at the beginning of the 21st century, as a result of its pronounced "biologizing bias", was the fact that the theoretical and practical potential of the categorical principle in the diagnosis of psychiatric disorders had been largely exhausted by the end of the 20th century [11, 12]. As a result, the strict demarcation of exogenous-endogenous relationships was abandoned in favor of conceptions of the spectra of mental disorders. At the same time, even with this "updated" approach, psychiatric terminology, in fact, remained disconnected from the actual person suffering from the particular mental illness.

As a result, psychiatry as a science in which the natural scientific and humanitarian components are in an unbreakable unity (which corresponds to the unity of man as an indissoluble psychophysical phenomenon) is being transformed into a purely technocratic science focusing on certain clinical manifestations, rather than on the person. In turn, the subject-subject relationship that underlies the medical care delivered by the physician to

the patient turns out to be an exclusively subject-object one. In other words, psychiatry as a science becomes a technology, which leads to its *dehumanization*.

Emphasis here must be placed on the following. Once the development of psychiatry, which led to the emergence of concepts of "spectra" of psychiatric disorders and their *dimensional (quantitative) assessment* allowing in many cases the determination of the severity grade of a particular psychopathological domain. On the other hand, in isolation from the further development of the categorical approach, this quantitative assessment is far from helping to a achieve tangible breakthrough in the current clinical and diagnostic crisis and turns out to be one of the its aspect.

The fact is that dimensional diagnostic constructs are ineffective in the absence of a fully updated theoretical basis. They do not allow for a comprehensive theoretical approach, because they are based on an arbitrary conventional and simplified eclectic approach that describes psychiatric disorders without taking into account individual features and the psychological history of the individual.

With this approach used in practice, especially in the treatment of mental disorders that not associated with stress, it is limited to the use of psychotropic drugs, which destroys both the comprehensiveness of therapeutic efforts and the system for evaluating its effectiveness. Moreover, last mentioned is reduced only to documenting a decrease in the severity of certain full-blown psychiatric syndroms. In turn, this means that the treatment efficacy assessment suffers from an extremely wide and uncontested use of evidence-based criteria obtained solely on the basis of randomized scientific studies of psychopharmacological medicines.

Today, study designs are focused on symptomatic improvement methods implemented through randomized controlled trials (RCTs). At the same time, the significance of the efficacy indicators proposed based on RCTs is not ranked or at least clearly defined [13].

A simple review of the literature can easily detect a significant quantitative prevalence of randomized clinical trials investigating the efficacy of pharmacological interventions over studies of non-pharmacological interventions [14].

The question is, should we rely solely on statistical analysis of numerical data, as is the case with randomized controlled clinical trials [15]? Is it possible to increase the proportion of psychosocial systematic empirical studies relevant to clinical practice, in which psychological interventions are used along with drug therapy [16, 17]?

DISCUSSION

The main criticisms of the results obtained in psychiatry through the use of RCTs and other evidence-based methods concern its three main drawbacks:

1. Excessive dependence on experimental biological (genetic, pharmacological, etc.) empiricism [18], which reflects a rather superficial level of relationships in contrast to theoretical approaches that reveal essential connections of reality;
2. An erroneous t understanding of the very term "evidence" [19];
3. Doubtfulness of the idea that the basic provisions of evidence-based medicine are the only ones that can be correct [20].

It should be noted that Russian psychiatrists, who have taken the path of evidence-based medicine, are often extremely narrow and rigid in their interpretation of the approach based solely on high-quality RCTs, while at the same time maintaining that this is the only possible approach. According to this approach, identified general patterns observed in a small cohort of specially selected patients are declared axiomatic for a whole spectrum of psychiatric disorders, without taking into account individual characteristics of patients. As a result, the main methods in the evidence-based medicine system are statistical methods [21], despite the fact that establishing a statistically average probability is a scientific-statistical, but not a scientific-systematic approach [22], and that improving statistical procedures is unlikely, first, to advance the understanding of psychiatric disorders and, second (no less important), to improve the outcome for a particular patient [23].

In addition, ardent proponents of the evidence-based approach essentially deny the value of author expertise as an important source of relevant knowledge. This means that both expert opinion (based on clinical thinking and the personal professional experience of the physician) and the specifics of the individual adaptive and compensatory potential of a particular patient are left out. In particular, descriptive reviews reflecting the personal positions of the authors of a publication on a particular problem are assessed by evidence-based medicine practitioners as "low-grade", contrasting them with systematic reviews as the result of serious scientific research [24]. It is easy to see that this is nothing more than a very vulgar

and far from scientific attempt to "rank" completely different types of scientific research, each of which has its own set of "limits" inherent in the research algorithm itself.

As a result, many doctors (not only psychiatrists) are simply made to believe that truly scientific and trustworthy evidence can only be based on experimental material and, moreover, it must be thickly, layer-by-layer embalmed with mathematical formulae that probably guarantee such evidence eternal value and immortality. This kind of idea has also become popular with Russian specialists in the field of psychiatric and behavioral disorders, although the relevant section of the current classification ICD-10 is not a product of evidence-based medicine, but a compromise convention) [25].

It must be underlined that the principle of *Cochrane evidence*[1] is interpreted more broadly in the West than by the majority of its Russian adherents. Many Western proponents of RCT (EBM) consider evidence-based medicine to be centered on the patient's personality as a whole, rather than on fragmentary symptom-related indicators tested in biological experiments. From this point of view, evidence-based medicine appears to be a process of providing medical care that involves the accumulation, interpretation, and integration of reliable, important, and reasonably applicable evidence that serves to improve the quality of clinical decisions regarding the treatment of a particular patient [26].

A number of Western, as well as "moderate" Russian, supporters of *Cochrane evidence* harbor the idea that both RCTs and the analytical processing of their data always require the consideration of a number of factors *known to limit* the relevance of evidence-based medicine methods and necessitate additional control and retesting of results obtained through RCTs (EBM). These factors are:

1. The efficacy-effectiveness gap, which remains the Achilles heel of evidence-based academic approaches [27]. There are differences between the benefits of a drug intervention in a simulated setting (RCTs) and in real-world practice [22]. This situation calls into question the absolute validity of the results of RCTs that have demonstrated the efficacy of certain drugs [28].
2. Lack of a universal approach to demonstrating a direct relationship between the individual approach and median RCT data [22]. This results in limited utility of reliable RCT results for individual patients [29], as these studies do not take into account the fact that "statistical results obtained in randomized controlled trials (RCTs), systematic reviews and meta-analyses are of little use for decision-making regarding individual clinical cases, as they provide only a probabilistic answer to the questions and do not take into account individual patient characteristics" [30]. Even setting aside the question of potential diagnostic errors in RCTs, it seems quite clear that RCTs, which use average group values, do not provide answers to questions about the treatment of individual patients [29]. The existing tools for therapeutic choice involving RCT data (assessment of sample size, benefit-risk profile, characteristics of adverse outcomes in the test and control groups, etc.) do not allow for prediction with a high probability of any actual impact of the treatment on an individual patient, who is not a hypothetical "average person". In other words, general patterns identified in randomized trials (the effectiveness of a particular drug in certain psychiatric conditions) cannot be taken as axiomatic for an individual case (individual patient). It is natural then that evidence-based medicine is suggested as a variant of species survival strategy, whereas clinical practice is suggested as an individual survival strategy [31]. It is also important to emphasize that the failure to take into account the *conditionality* of conventional diagnostic distinctions in the assessment of RCT results leads to unjustified absolutization and excessive generalization of conclusions regarding the efficacy of particular therapeutic interventions in a wide range of psychiatric disorders. Finally, RCTs study "ideal patients" whose proportion in the population does not exceed 5–10%. At the same time, study results obtained in a small, clinically refined group of conditions are subsequently extrapolated to all patients and serve to justify standardized treatment

[1] Cochrane Collaboration is a registered not-for-profit organization involved in the development of World Health Organization guidelines. The name of the organization comes from the last name of its founder, the Scottish medical scientist Archibald Cochrane (Archibald Leman Cochrane, 1909–1988), who advocated evidence-based medicine and clinical trials and wrote the book *Effectiveness and Efficiency: Random Reflections on Health Services* (Cochrane Archie, 1972).

for a large group of conditions, and without taking into account the individual features of the patient. Yet averaged efficacy and tolerability indicators obtained in the course of evidence-based studies may prove useful, useless or even harmful in the treatment of a particular patient.

3. Methodological impossibility of conflict-free (impartial) use of the evidence-based doctrine in psychiatric practice [8, 32, 33]. This factor has to be placed here, because it is impossible to completely exclude its role due to the influence of pharmaceutical companies on the results of clinical trials, despite all the measures taken to counter this impact [34]. It is common practice for practitioners — who are under the direct influence of pharmaceutical companies — to ignore evidence supporting the efficacy of older treatments while actively encouraging the use of new, more expensive therapies [14]. According to Every-Palmer and Howick [28], it is often the case that opinion leaders advocating the value of trial evidence are also paid specialists of the marketing departments of pharmaceutical companies. The obvious conflict of interest means that their conclusions cannot be perceived as scientifically objective. Furthermore, even clinical recommendations based on the individual authority of investigators, who are directly or indirectly associated with pharmaceutical companies, cannot be free from suspicion of bias. Pharmaceutical companies are also known to use many indirect ways to influence choice of treatment. There is still no satisfactory solution to these issues of the qualitative analysis of study results.
4. In medical practice, including "evidence-based" studies, complete elimination of the role of the physician's personality ("charisma") accumulating their individual education and medical experience, empathy, and intuitive judgments is unlikely (and in reality impossible).

As noted by Zobin and Ustinova [22], these factors complicate the unification of therapeutic choices if it is based solely on the data obtained during RCTs. This does not mean, however, that the relationship between evidence-based medicine and psychiatric practice cannot be discussed in terms of the dialectical interaction of the general and particular.

It appears that the total and dominant use of evidence-based medicine principles is insufficient in the context of a biopsychosocial diagnostic approach, which includes a multi-dimensional (multi-vector) view of treatment efficacy criteria. It involves a differentiated examination of the patient's clinical, psychological and social status. The "refined" postulates of so-called evidence-based medicine cannot always be used as a means to determine the most effective option of therapeutic intervention [2]. Evidence-based medicine should also be used very carefully in the evaluation of psychosocial and "client-centered" interventions, where existential factors that can by no means be described by RCTs must always be considered as very important.

In addition, attempts to determine the strength of evidence for various psychotherapy methods also appear unsuccessful. Where evidence-based medicine methods — despite both scientific and simple common sense — are still considered as the only method appropriate to the determination of the efficacy of non-drug (in particular, psychotherapeutic and sociotherapeutic) interventions and organizational rehabilitation measures, these methods often turn out to be not just useless, but even harmful. It should be repeated here that the founders of the evidence-based concept never declared that their method was unique or indispensable in all diagnostic and therapeutic scenarios without exception.

That said, evidence-based medicine does have its own strengths, and initially it was not meant to do away with the traditional paradigm (a "cuckoo chick" pushing out competitors out of the nest), but was instead intended to be a means of universal assistance in expanding clinical experience and making informed therapeutic decisions [35], that is, decisions stemming, firstly, from the physician's individual experience and, secondly, from data obtained through the analysis of large bodies of diverse clinical evidence. Evidence-based medicine methods appear to be effective primarily in choosing the appropriate treatment for biologically determined components of mental illness (including the choice of medication). It is these aspects of the nature and purpose of evidence-based medicine that meet "clinicians' desire to obtain more detailed information for the choice of treatment options in real-world clinical practice" [30].

In addition, it should be emphasized that the alternative to evidence-based medicine, i.e., the *subjective expert* (individual physician-centered) approach is also vulnerable and should by no means be viewed as the only effective tool. The weaknesses of this approach are as follows:

1. There is still no satisfactory solution to the problem of inclusion of subjective characteristics (based on the clinician's perception of external data and personal wishes of patients) in a formalized clinical decision-making protocol.
2. A clinician's assessment of the efficacy of various treatments is largely determined by their analytical abilities, depth of understanding of the methodologies of different study designs, and knowledge of basic statistical procedures. That is, it depends on many subjective factors that collectively contribute to the physician's art, which, ideally, is a properly calibrated body of evidence, expert conclusions, and clinical experience [36].
3. The patient's needs are also difficult to systematize, as they are determined by their personal preferences, individual psychosocial characteristics, and specifics of the therapeutic alliance [23]. Additionally, the declared need to take into account the patient's preferences and values when choosing a treatment in psychiatry is limited by the potential inability of the patient to adequately assess their condition due to the nature of the disease itself. It should be added that the mentioned right of the patient is limited not only by their competence, but also by objective factors related to the complexity of interpretation of the evidence.

And yet, despite the mentioned limitations of the subjective expert (individual physician-centered) method, it is the physician who remains the integrator and guide in the search for optimal clinical solutions and therapeutic choice. As a result, it is still firmly believed that the search for the most effective therapeutic intervention in psychiatry should be guided not by a formal protocol, as recommended by the strict rules of evidence-based medicine, but by an expert consensus that should be in agreement with the protocol. The absence of such agreement only increases the risk of the basic provisions of the evidence-based approach being compromised [23]. In these cases, therapy is sometimes reduced to strict compliance with the prescribed pharmacologically focused "standards", that is, in most cases, reduced to a routine prescription of the required drugs "legalized by classifications" as the only adequate means of treating specific clinical forms of the disease. Thus, the treatment of the condition becomes disconnected from the integrated nature of the mental disorder, that is, only the patient's disease is treated rather than the patient themselves.

All of the above — at a new level of understanding — brings us back to the statement at the beginning of the article of the crisis state psychiatry is now in due to the conflict of the purely *biomedical model* supported by pharmaceutical companies and still prevailing in practical medicine and the *biopsychosocial model,* which, in reality, is maintained only by some scientists and practitioners.

As follows from the facts and generalizations discussed above, this conflict is more subjective than objective and should be resolved as soon as possible and completely. The point is that *biologizing* approaches are fundamentally insufficient to achieve the final goal of providing the most effective comprehensive therapy for mentally ill patients and achieving their functional recovery, if the humanistic approaches are completely ignored. Similarly, humanitarian approaches are insufficient if they are completely "disconnected" from the neurobiological basis and operational criteria. At the same time, the *biologizing* and *humanistic* approaches (based on the biopsychosocial paradigm) appear to be in unequal conditions. The former, receiving financial and lobbying support from pharmaceutical companies, are actively being implemented. The latter, due to the lack of lobbying, are being increasingly isolated from current psychiatric practice, which appears to be almost entirely focused on psychopathological diagnosis and the introduction of purely psychopharmacological treatments.

As an interim summary, it should be emphasized that the two strategies being discussed cannot be "reconciled" or combined. Furthermore, they do not follow from each other and do not form a hierarchy. They are always parallel and complementary. It is only necessary to be aware of their purpose and make sure that one of these approaches does not destroy the other in order to facilitate vulgar ideological simplifications covered by references (often incorrect) to "authorities" or promote the commercial interests of pharmaceutical companies.

A particular patient combines features of both the general (species) and the single (individual). Since there are no absolutely identical or completely different patients, opposing evidence-based approaches on the one hand and clinical practice on the other makes no sense [23]. Nor do the attempts to declare "monopolism" of any of them.

These considerations elucidate increasingly clearly that evidence in medicine must — in order to be purely beneficial — include 3 mandatory intersecting components (Figure 1).

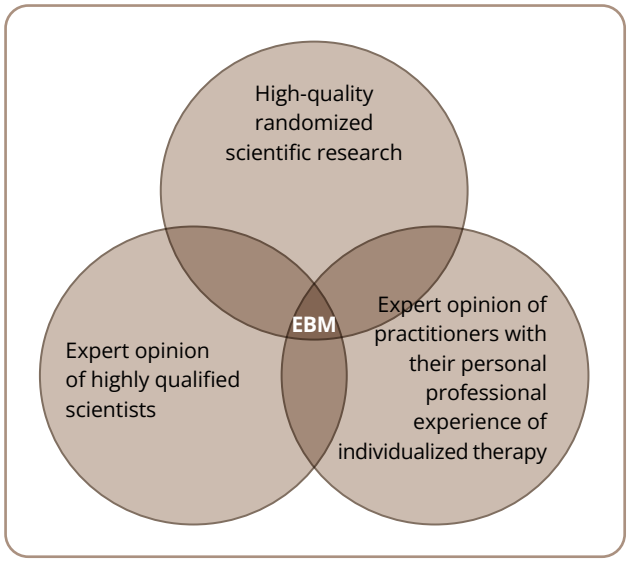

Figure 1. Scheme representing the evidence-based medicine (EBM) "triad".

As can be seen, to be justified, evidence-based medicine must take into account the following data:

a. high-quality randomized scientific research,
b. expert opinion of highly qualified scientists (it should be noted here that the methodological error of the strictly understood *Cochrane evidence* principle is in the fact that the competencies and expertise of particular specialists are subtly excluded from the "evidence-based medicine" system itself),
c. expert opinion of practitioners whose experience allows for the discovery of the individual adaptive and compensatory potential of patients and take it into account during treatment.

In this regard, a promising type of study would be one that involves a mutually beneficial "cooperation" of these three components of evidence, which can form the basis for the development of a biopsychosocial understanding of the nature of psychiatric disorders, their holistic diagnostic assessment, and the development of comprehensive therapeutic options, as such studies would not be limited to the consideration of the biological mechanisms of the disease.

CONCLUSION

Modern medicine, as we have already pointed out earlier [37], seeks to approach the exact sciences in many ways, but will still never become one of them. The fact is that the expert judgment of a physician (be it a scientist or a practitioner) based on their individual experience and their personality, as well as their knowledge of the features of the patient, has always been and will be important for effective treatment, which, in turn, is the main goal of medicine both as a science and as a practical activity. It should be further emphasized here that in the field of psychiatry, the evidence-based medicine principles positioned to turn out to be the farthest (compared with other medical specialties) from the complex nature of the disorders being studied and, therefore, from the right to be considered a monopoly approach to treatment effectiveness assessment.

Evidence-based medicine in the strict sense is not equivalent to medical evidence. Currently, there is a clear polarity of views about the use of RCT results in healthcare practice. The bias towards the evidence-based medicine principles takes on another negative aspect in our current situation, when pretext of the absolute value of "evidence" is used to "optimize" treatment and healthcare. This leads not only to a decrease in the availability of a wide range of specialized medical care, including psychiatric care, but also to a deterioration in its quality (due to the practical reduction of therapy to the use of psychopharmacological drugs only). As a matter of fact, psychiatry is losing clinical ground.

We need a constructive convergence of the two points of view. On the one hand, it must be admitted that a clinician who does not use RCT data is like a traveler without a compass and a map. On the other, however, it is also clear that a physician who blindly follows the "evidence-based" standards and does not have their own clinical experience, not taking into account the individual features of the patient, is like a traveler, although with a compass, but in an area of magnetic anomaly. Because of this, both physicians relying only on their personal experience and common sense (expert opinion) and physicians treating exclusively "according to what is written" in meta-analytical reviews (high-quality research studies) are equally alarming: even if you regularly read the most up-to-date systematic reviews (which are an *ultimo ratio* from the point of view of *evidence proponents*), it is the physician who, as Trisha Greenhalgh correctly observes [38], "must decide how this quantitative result, significant or non-significant, will affect the treatment of this patient". And although the methods of *evidence-based medicine,* when used to assess the efficacy of psychotherapy, require an extremely complicated RCT protocol (and, it seems, completely rule out the use of the double-blind design due to ethical and pragmatic considerations), they do not cancel out the

"universal evidence-based" concept itself, which is aimed at the "absolute" reproducibility of results.

We would like to conclude this discussion of the prospects of "removing" the basically artificial opposition and conflict of the evidence-based paradigm in the assessment of the effectiveness of diagnostic and treatment options, on the one hand, and the expert-oriented paradigm, on the other, as well as of the urgent need for the establishment of their mutually beneficial "cooperation", with a philosophical generalization of Yu.A. Aleksandrovskiy [39], which reveals the mutually complementary "solidarism" of all living beings, including the scientific description and understanding of these living beings: "The evolutionary, multi-century association of living cells and the formation of the simplest, and then complex, animal and human organisms are vital to the interaction process, despite temporary situational confrontations. With this in mind, we can think of the need to create a unified general theory of integration and development for both biology and sociology". What has been said seems extremely topical and focuses our attention on the need to develop, as soon as possible, a full-fledged theory of evolutionary psychiatry and integrative methodology in order to synthesize biological psychiatry (as a natural science) and psychosocial psychiatry (as a largely humanitarian science), as comprehensive therapeutic efforts cannot be successful without this. In this case, the evidence-based approach, with a moderately critical attitude to it, can become valid for all types of research studies.

In connection with the above, we have to agree with the D.A. Zateyshchikov [40] that, since variability is the law of life and there are no two identical organisms or two people with identical diseases, we should proceed from evidence-based medicine to individualized medicine, since evidence-based medicine "treats not the patient, but the population, i.e., it decreases the incidence rate in the population as a whole". Especially dramatic in this context is the issue of technological depersonalization and objectivist neglect of the mental patient's psychological identity in the current system of "evidence-based digital" psychiatry [41]. This negative trend makes the important, although non-specific, aspects of treatment (such as the patient-perceived quality of the treatment alliance) secondary, while the culture and meanings of this alliance are often key to how the characteristics of the patient's mental state change over time [42]. Therefore, the focus on the person-centered (individualized) approach to the patient is becoming particularly important.

Thus, the future lies in the targeted development and evidence-based consideration of the effects of therapeutic interventions on the mechanisms of pathogenesis of psychiatric disorders, including the study of cause-effect relationships between their constituent biopsychosocial domains. The choice of therapeutic intervention, as well as the assessment of its quality, should be based on a person-centered, individualized approach to the patient that should be in agreement with the biopsychosocial views on the development of psychiatric disorders. This approach implies that the patient is treated not only as an object (even if only a single object), but also as a subject with a complex inner world. It goes without saying that the role of the "humanistic component", in addition to natural science and biology, is extremely significant for certain fields, such as psychology and psychiatry — the latter having a rehabilitative function that clearly requires the use of psychological and social therapy in addition to psychopharmacology.

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