УДК 616.895.8-07-08-02:616.89-008.45/.48
https://doi.org: 10.20538/1682-0363-2020-3-36-43

Influence of clinical and therapeutic indicators on the severity of neurocognitive deficits in patients with schizophrenia

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ABSTRACT

Aim. To assess the association of clinical and therapeutic parameters with the severity of the neurocognitive deficits in patients with schizophrenia.

Materials and methods. We examined 118 patients with schizophrenia, aged 34 [29; 41] years, and with a disease duration of 10 [4; 16] years. 33 patients (28%) received conventional antipsychotic drugs (CAD), and 85 (72%) patients received atypical antipsychotic drugs (AAD). As concomitant therapy, 58 people (49.1%) took trihexyphenidyl, 60 people did not take it (50.9%). Assessment of cognitive functions was carried out for all patients using the Brief Assessment of Cognition in Schizophrenia (BACS), and clinical psychopathological symptomatology was evaluated using the Positive and Negative Syndrome Scale (PANSS). Statistical analysis of the data was performed using the Kruskal – Wallis test ANOVA with the multiple comparison procedure, the Pearson's chi-squared test, and K-means cluster analysis.

Results. Neurocognitive deficits formed three clusters of disturbances that differ in clinical severity: 1) mild, 2) moderate, 3) severe. According to the subscale of positive PANSS symptoms, patients with mild neurocognitive deficits had a lower average total score compared to patients with severe neurocognitive deficits ($p = 0.011$), who, in turn, received significantly longer antipsychotic therapy compared with patients with moderate ($p = 0.014$) and mild ($p = 0.01$) neurocognitive deficits. Herewith, the duration of CAD treatment did not differ between clusters; consequently, the obtained results on antipsychotics as a whole were obtained due to AAD ($p = 0.005$ and $p = 0.001$, respectively). Trihexyphenidyl did not affect the severity of neurocognitive deficits.

Conclusion. The severity of positive symptoms of schizophrenia was lower in patients with mild neurocognitive deficits. The most pronounced neurocognitive deficits are observed in patients receiving AAD.

Key words: schizophrenia, neurocognitive deficits, antipsychotics, trihexyphenidyl.

Conflict of interests The authors declare no obvious or potential conflict of interest related to the publication of this article.

Source of financing. The study was conducted with the support from the grant of RFBR 18-315-20019 "New approaches to the genetics of clinical polymorphism and neurocognitive deficits in schizophrenia".

Conformity with the principles of ethics. All the people included in the study gave their written informed consent. The study was approved by the ethics committee of Mental Health Research Institute of Tomsk National Research Medical Center (Protocol No. 99 of 17.04.2017).

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For citation: Kornetova E.G., Goncharova A.A., Dmitrieva E.G., Arzhanik A.A., Kornetov A.N., Semke A.V. Influence of clinical and therapeutic indicators on the severity of neurocognitive deficits in patients with schizophrenia. *Bulletin of Siberian Medicine.* 2020; 19 (3): 36–43. https://doi.org: 10.20538/1682-0363-2020-3-36-43.

Влияние клинических и терапевтических показателей на выраженность нейрокогнитивного дефицита у пациентов с шизофренией

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РЕЗЮМЕ

Цель. Оценить связь клинических и терапевтических показателей с выраженностью нейрокогнитивного дефицита у пациентов с шизофренией.

Материалы и методы. Были обследованы 118 пациентов с шизофренией в возрасте 34 [29; 41] лет, с длительностью заболевания – 10 [4; 16] лет. Конвенциональные антипсихотические препараты (КАП) получали 33 пациента (28%), атипичные антипсихотическое препараты (ААП) – 85 (72%) пациентов. В качестве сопутствующей терапии 58 человек (49,1%) принимали тригексифенидил, не принимали его 60 человек (50,9%). Оценка когнитивных функций проведена всем пациентам по шкале краткой оценки когнитивных функций у пациентов с шизофренией (Brief Assessment of Cognition in Schizophrenia, BACS), клинико-психопатологической симптоматики – с использованием шкалы позитивных и негативных синдромов (Positive and Negative Syndrome Scale, PANSS). Статистический анализ полученных данных выполнен с использованием критерия Краскела – Уоллиса ANOVA с процедурой множественного сравнения, критерия $\chi 2$ Пирсона и кластерного анализа методом *K*-средних.

Результаты. Нейрокогнитивный дефицит образовал три кластера нарушений, отличающихся между собой клинической выраженностью: 1) легкий, 2) умеренно выраженный, 3) выраженный. По субшкале позитивных симптомов PANSS пациенты с легким нейрокогнитивным дефицитом имели меньший средний суммарный балл по сравнению с больными с выраженным нейрокогнитивным дефицитом ($p = 0{,}011$), которые, в свою очередь, значимо дольше получали антипсихотическую терапию по сравнению с пациентами с умеренным ($p = 0{,}014$) и легким ($p = 0{,}01$) нейрокогнитивным дефицитом. При этом длительность приема КАП не различалась между кластерами, следовательно, имеющиеся результаты по антипсихотикам в целом получены за счет ААП ($p = 0{,}005$ и $p = 0{,}001$ соответственно). Тригексифенидил не оказал влияния на выраженность нейрокогнитивного дефицита.

Заключение. Выраженность позитивных симптомов шизофрении была ниже у пациентов с легким нейрокогнитивным дефицитом. Наиболее выраженные нейрокогнитивные нарушения отмечаются у пациентов, получающих ААП.

Ключевые слова: шизофрения, нейрокогнитивный дефицит, антипсихотики, тригексифенидил.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование выполнено при поддержке гранта РФФИ 18-315-20019 «Новые подходы к генетике клинического полиморфизма и нейрокогнитивного дефицита при шизофрении».

Соответствие принципам этики. Все лица, вошедшие в исследование, подписали письменное информи-

рованное согласие. Исследование одобрено этическим комитетом НИИ психического здоровья, Томского НИМЦа (протокол № 99 от 17.04.2017).

Для цитирования: Корнетова Е.Г., Гончарова А.А., Дмитриева Е.Г., Аржаник А.А., Корнетов А.Н., Семке А.В. Влияние клинических и терапевтических показателей на выраженность нейрокогнитивного дефицита у пациентов с шизофренией. *Бюллетень сибирской медицины.* 2020; 19 (3): 36–43. https://doi.org: 10.20538/1682-0363-2020-3-36-43.

INTRODUCTION

Contemporary antipsychotics are primarily antagonists of second type dopamine receptors and can induce extrapyramidal adverse events [1]. Anticholinergics are widely used for their relief in psychiatric practice. However, anticholinergic agents precipitate different peripheral side effects like dry mouth, urination disturbances, and constipation; as well as central side effects: cognitive deficits, worsening of tardive dyskinesia and emergence of delirium [2]. Cognitive deficits occur at the earliest stages of schizophrenia process and account for the main part of functional problems related to the disorder. Likely, the long-term combined use of antipsychotics and anticholinergics intensifies the basic cognitive deficits in patients with schizophrenia, which eventually affects their quality of life [3]. Thus, modern guidelines for the treatment of schizophrenia do not normally recommend preventive and long-term use of anticholinergic agents. Nevertheless, the widespread long-term use of anticholinergics in the combination with antipsychotics has taken place in several countries [3–5]. The results of the study of this problem are debatable. The number of surveys of the previous decade shows the positive effect of anticholinergic agents on cognitive functions in patients with schizophrenia [4, 6, 7]. An earlier study dedicated to the possible effect of anticholinergics on residual symptoms of schizophrenia showed that antipsychotics and trihexyphenidyl in combination have a positive effect on the memory and attention of patients [8].

However, modern studies contain more data indicating the adverse effect of anticholinergics on the cognitive functions of patients with schizophrenia, or the absence of such an effect [5, 9, 10]. Thus, S. Ogino et al. [3] defined that cancellation of long-term use of anticholinergics can improve objective indicators of cognitive functions and subjective characteristics of the quality of life for patients with chronic schizophrenia.

S. Eum et al. [10] investigated the influence of the total anticholinergic burden arising from the combined use of anticholinergic and antipsychotic drugs on the cognitive functions of patients with psychotic disorders and schizophrenia. According to their data, the common anticholinergic burden was inversely proportional to the level of cognitive activity; especially, it affected the impairment of verbal memory. Despite the similar cumulative anticholinergic burden in groups with various psychotic disorders, increased cognitive susceptibility to anticholinergic agents was revealed in patients with schizophrenia.

A number of studies have shown improvement in cognitive functions of varying degrees with the use of second-generation antipsychotics in the treatment of long-term schizophrenia or the first psychotic episode. The positive effects of clozapine, risperidone, olanzapine, quetiapine, sertindole, and aripiprazole on various cognitive functions were noted. At the same time, some authors have the opinion that there is currently no convincing evidence of the greater effectiveness of second-generation antipsychotics compared to first-generation antipsychotics for cognitive impairment [4, 6].

In routine clinical psychiatric practice in various countries, psychiatrists continue to widely use a combination of antipsychotics and anticholinergics for the treatment of schizophrenia. In this connection, there is a necessity to further study the effects of prolonged combined use of antipsychotics and anticholinergic agents for the treatment of schizophrenia.

The aim of the study was to assess the association of clinical and therapeutic parameters with the severity of neurocognitive deficits in patients with schizophrenia.

MATERIALS AND METHODS

The study included inpatients of the hospital of Mental Health Research Institute of Tomsk National Research Medical Center of the Russian Academy of Sciences and Tomsk Clinical Psychiatric Hospital. The criteria of inclusion in the study were age from 18 to 60 years, verified diagnosis of schizophrenia

according to the ICD-10 Classification of Mental and Behavioral Disorders – Diagnostic Criteria for Research [11], and the ability to write informed consent. The criteria for non-inclusion were the presence of organic mental disorders, brain and severe somatic disorders leading to organ failure, and refusal to take part in the study.

Thus, we examined 118 patients with schizophrenia, aged 34 [29; 41] years, and with a disease duration of 10 [4; 16] years and the average age of onset of 23 [20; 29] years. All patients included in the study received antipsychotics as basic therapy in therapeutic dosages approved by the Russian Ministry of Health.

Based on the receptors profile of basic antipsychotic therapy patients were divided into two groups: 33 patients (28%) received conventional antipsychotic drugs (CAD), and 85 (72%) patients received atypical antipsychotic drugs (AAD). All dosages of various antipsychotics were brought to uniformity in the equivalent of chlorpromazine (CPZeq) [12], common antipsychotic burden was 320 [160; 598.5]; for CAD – 416.9 [160; 1000], for AAD – 300 [199.9; 428.1].

As concomitant therapy, 58 people (49.1%) took trihexyphenidyl and 60 people did not (50.9%). The duration of receiving trihexyphenidyl was 2 [0.5; 4] years. In this study, due to its observational nature, the reasons and purpose of trihexyphenidil prescription in the course of treatment of patients were not taken into account, but the fact of prescribing an anticholinergic drug was assessed as likely to have an effect on cognitive deficit in patients with schizophrenia.

Assessment of cognitive functions was carried out for all patients on the Brief Assessment of Cognition in Schizophrenia (BACS) [13], in the adapted Russian version [14]. A set of tasks on this scale ("List learning", "Digit sequencing task", "Token motor task", "Verbal fluency", "Symbol coding", "Tower of London") allows us to evaluate the parameters according to the sequence of the list: verbal memory, working memory, motor speed, processing speed, attention and processing speed, executive functions.

The psychopathological assessment was carried out using a Positive and Negative Syndrome Scale (PANSS) [15] in the adapted Russian version – SCI-PANSS [16].

The obtained data were tested for normal distribution with the SPSS Kolmogorov – Smirnov Test for Normality (with the Lilliefors significance correction) and the Shapiro – Wilk Test. Data with a normal type of distribution are presented as mean and standard deviation ($M \pm SD$), in the absence of a normal distribution; the data are presented as the median and quartiles (Me [Q_1; Q_3]). Qualitative data are presented by frequency indicators (n (%)). Comparing several independent samples of quantitative data having a non-normal distribution, we used the Kruskal – Wallis ANOVA test with the multiple comparison procedure. To compare frequencies, the Pearson's chi-squared criterion was used. To reveal the variants for the severity of neurocognitive deficits (NCD), K-means clustering was used. Statistical analysis was performed using the software Statistica for Windows (V. 12.0). The threshold value of the achieved significance level of p was taken equal to 0.05.

RESULTS

Neurocognitive deficits are formed by three clusters of impairment registered in accordance with all BACS subscales, which differ in clinical severity: 1) mild, 2) moderate, 3) severe. Consequently, patients were stratified according to the level of severity as follows (Fig., Table 1): cluster 1 (37 (31.4%)), cluster 2 (51 (43.2%)) and cluster 3 (30 (25.4%)). The results of the analysis of variance for all clusters represent the good quality of clustering (< 0.0001).

Then, the assessment of the connection between the severity of NCD and clinical and therapeutic indicators was made in the selected clusters.

The average age of schizophrenia onset and the duration of the disorder had no differences between the clusters; however, the average age of the patients in the study had significant differences (Table 2) between cluster 2 and cluster 3 ($p = 0.024$).

An assessment of the effect of the actual mental state on the severity of NCD (Table 3) showed that according to the subscale of positive symptoms PANSS patients with mild NCD had a lower average total score of positive symptoms compared with patients with severe NCD, who had a more pronounced predominance of the positive symptom complex ($p = 0.011$).

For assessing the effect of trihexyphenidyl on the severity of NCD, the Pearson's chi-squared criterion was used; statistically significant differences were not established. The duration of receiving trihexyphenidyl was evaluated in 58 patients; the evaluation was based on interviews and medical records including medical histories. The duration of receiving was presented in years. Differences between the clusters were not revealed. Also, the clusters of the severity of NCD had

no differences depending on the type of basic antipsychotic therapy: patients receiving CAP or patients receiving AAP. Assessment of the total antipsychotic burden revealed that CPZeq had no differences in all clusters as well as in groups receiving CAP and AAP.

The duration of antipsychotic therapy had differences (Table 4) between cluster 1 and cluster 3 ($p = 0.01$), as well as between cluster 2 and cluster 3 ($p = 0.014$). These results suggest that patients receiving long-term antipsychotic therapy have more severe NCD.

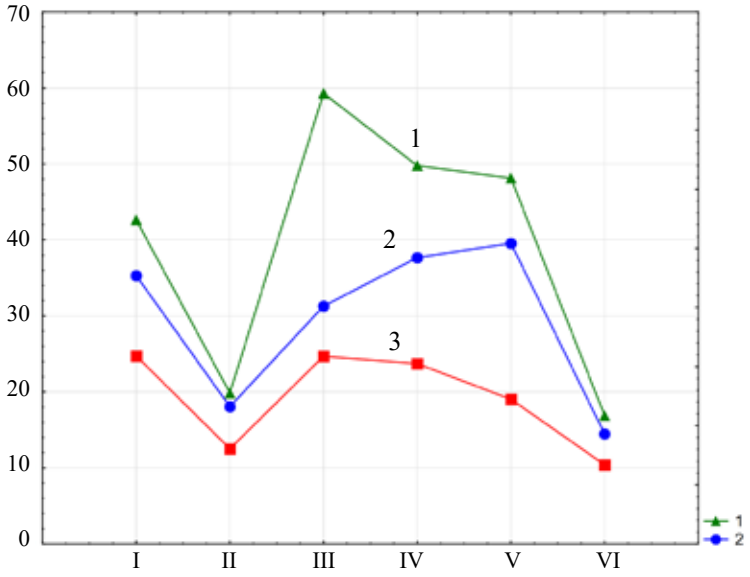

Figure. "Cognitive profile" of the selected variants of the severity of neurocognitive deficits according to BACS in the group of patients with schizophrenia: I – List Learning Test; II – Digit Sequencing Task; III – Token Motor Task; IV – Verbal Fluency; V – Symbol Coding; VI – Tower of London Test; 1 – cluster 1; 2 – cluster 2; 3 – cluster 3.

Table 1

Descriptive statistics for identified clusters in accordance with BACS, *M* ± *SD*

Tasks of BACS	Cluster 1 $n = 37$ (31.4%)	Cluster 2 $n = 51$ (43.2%)	Cluster 3 $n = 30$ (25.4%)
List learning	42.6 ± 11.4	35.3 ± 9.5	24.7 ± 9.1
Digit sequencing task	19.8 ± 3.8	18.1 ± 4.7	12.5 ± 4.8
Token motor task	59.2 ± 11.6	31.3 ± 13.3	24.6 ± 11.6
Verbal fluency	49.7 ± 11.5	37.6 ± 9.7	23.7 ± 8.1
Symbol coding	48.1 ± 12.4	39.6 ± 9.7	19.0 ± 8.9
Tower of London	16.8 ± 2.3	14.5 ± 4.7	10.4 ± 5.8

Table 2

Clinical indicators depending on the severity of NCD according to BACS, *Me* [Q_1; Q_3]

Clinical indicators	Cluster 1 $n = 37$ (31.4%)	Cluster 2 $n = 51$ (43.2%)	Cluster 3 $n = 30$ (25.4%)	p (1–2; 1–3; 2–3)
Age, years	35 [29; 39]	32 [28; 38]	37.5 [33; 53]	1.0; 0.167; 0.024
Age of onset, years	26 [20; 29]	22 [19; 27]	23.5 [20; 29]	0.588; 1.0; 1.0
Duration of the disorder, years	10 [4; 14]	8 [2; 16]	13.5 [5; 22]	1.0; 0.118; 0.073

Table 3

PANSS scores depending on the severity of the NCD according to BACS, *Me* [Q_1; Q_3]

PANSS subscales	Cluster 1 $n = 37$ (31.4%)	Cluster 2 $n = 51$ (43.2%)	Cluster 3 $n = 30$ (25.4%)	p (1–2; 1–3; 2–3)
Positive symptom subscale score	19 [16; 22]	21 [15; 25]	23 [20; 27]	0.626; 0.011; 0.166
Negative symptom subscale score	25 [23; 28]	25 [21; 28]	26.5 [22; 30]	1.0; 1.0; 0.485
General psychopathology subscale score	54 [48; 60]	54 [48; 58]	55.5 [49; 61]	1.0; 1.0; 0.807
Total score	100 [92; 107]	100 [86; 109]	107.5 [94; 114]	1.0; 0.227; 0.199

Table 4

Duration of basic antipsychotic therapy depending on the severity of NCD according to BACS, *Me* [Q_1; Q_3]

Parameter	Cluster 1 *n* = 37 (31.4%)	Cluster 2 *n* = 51 (43.2%)	Cluster 3 *n* = 30 (25.4%)	*p* (1–2; 1–3; 2–3)
Duration of antipsychotic therapy	3 [0.5; 5]	3 [1; 5]	7 [3; 17]	1.0; 0.01; 0.014

The duration of CAP administration had no differences in the clusters of the severity of NCD, it means that the available results on antipsychotics were obtained due to AAP generally: 1–3 clusters – $p = 0.001$; 2–3 clusters – $p = 0.005$ (Table 5).

Table 5

Severity of NCD according to BACS depending on the duration of the therapy with the use of conventional and atypic antipsychotics, *Me* [Q_1; Q_3]

Duration of antipsychotic therapy	Cluster 1 *n* = 37 (31.4%)	Cluster 2 *n* = 51 (43.2%)	Cluster 3 *n* = 30 (25.4%)	*p* (1–2; 1–3; 2–3)
Duration of receiving CAP	5.5 [2.5; 10.5]	3 [1; 8]	8.5 [0.3; 20]	1.0; 1.0; 1.0
Duration of receiving AAP	3 [0.3; 4]	3 [0.8; 5]	7 [4; 13.5]	1.0; 0.001; 0.005

DISCUSSION

At present, in addition to the existing dichotomic theory of schizophrenia dividing positive and negative syndromes, the cognitive symptom complex is considered as the third component of the disorder [2], while cognitive functioning of patients is increasingly in view of the researchers, not only in the field of clinical and biological psychiatry [17, 18] but also in the sphere of somatic medicine [19].

The use of anticholinergic agents in the treatment of adverse movement phenomena of antipsychotic therapy has a negative effect on cognitive functions in patients with schizophrenia [9, 20], just like the general index of anticholinergic burden [10]. Attention to this issue should be strengthened with consideration of the physical status of the patients and the potential influence of anticholinergics in combination with other agents used in psychiatry on the cardiovascular system [21], as cardio-vascular diseases themselves induce cognitive impairment. The obtained results did not show the influence of the use of trihexyphenidyl on the intensity of NCD in patients with schizophrenia. The attained results have some limitations, as the influence of a particular medication was assessed, but not the total cholinergic burden. The use of somatic drug groups with similar effect was not taken into consideration either. Nevertheless, in contemporary literature, this issue has hardly been discussed and the studies on the influence of the combination of antipsychotics and anticholinergic agents have been few [3, 6, 22].

The existing assumption on the influence of antipsychotics on the cognitive functions in patients with schizophrenia took root in the psychiatric community; for example, the use of CAP is thought of being connected with the negative influence on the cognitive functions, while the use of AAP is thought to be connected with their improvement [7, 23], although this fact is controversial [4]. In our study, we have not observed differences in the intensity of NCD in patients who received CAP and AAP as basic therapy.

Meta-study of A.L. Mishara, T.E. Goldberg [24] demonstrated that CAP, in general, has a moderately positive effect on cognitive functions, while the dosage of the medicine does not have any effect on cognitive functions, which was also observed in the course of our study. The use of agents of the third generation is connected with multiple advantages, including their positive effect on cognitive functions [25].

It was revealed that the longer the patient receives antipsychotic therapy, the higher the intensity of NCD; although the length of the disorder, which is closely linked to the duration of receiving supporting therapy, in our sampling did not have such significant influence. The length of use of AAP is also linked to the higher intensity of NCD, which was not found in patients receiving CAP, although they were used for a longer period. The revealed data on the higher intensity of NCD in view of increasing the length of the basic antipsychotic therapy in patients receiving AAP precisely appears interesting, as the long-term treatment observation of patients with schizophrenia showed that after 8 weeks of treatment there did not appear to be any dissimilarities in cognitive indicators in patients with schizophrenia receiving CAP and AAP [26].

The existence of negative symptoms and neurocognitive deficits in clinical evidence of schizophrenia has a relatively constant character, unlike the positive symptoms which can fluctuate in the course of the disorder. Lowering of the score according to the subscales of negative and positive symptoms PANSS was connected with the improvement in BACS task performance in patients with schizophrenia [27]. It should be emphasized that the surveyed patients were in the active phase of the disorder, so the PANSS

scores must be cross-referenced with the results of similar studies conducted in the period of remission [28]. The received dissimilarities in the higher score according to the PANSS subscale of positive symptoms in patients with significant NCD in comparison with the patients with mild NCD correspond with the data referring to the length of use of basic antipsychotic therapy, as the choice of AAP was possibly made taking into account the grave mental condition and the predominance of delusions and hallucinations.

CONCLUSION

The influence of trihexyphenidyl and atypical antipsychotics of the second generation on cognitive indicants in patients with schizophrenia remain an open question and warrant further investigation and examination of the issue taking into account the combined drug burden. As expected, patients performed the BACS tasks better against the background of AAP usage, although long-term use of agents of this group was connected with the higher level of NCD in patients with schizophrenia.

REFERENCES

1. Servonnet A., Samaha A.N. Antipsychotic-evoked dopamine supersensitivity. *Neuropharmacology*. 2020; 163: 107630. DOI: 10.1016/j.neuropharm.2019.05.007.
2. Stępnicki P., Kondej M., Kaczor A. A. Current Concepts and Treatments of Schizophrenia. *Molecules*. 2018; 23(8): E2087. DOI: 10.3390/molecules23082087.
3. Ogino S., Miyamoto S., Tenjin T., Kitajima R., Ojima K., Miyake N. Effects of discontinuation of long-term biperiden use on cognitive function and quality of life in schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2011; 35: 78–83. DOI: 10.1016/j.pnpbp.2010.08.030.
4. Keefe R.S.E., Harvey P.D. Cognitive impairment in schizophrenia. *Handbook of Experimantal Pharmacology*. 2012; Novel Antischizophrenia Tratments: 11–37.
5. Wojtalik J.A., Eack S.M., Pollock B.G., Keshavan M.S. Prefrontal gray matter morphology mediates the association between serum anticholinergicity and cognitive functioning in early course schizophrenia. *Psychiatry Research*. 2012; 204 (2-3): 61–67. DOI: 10.1016/j.pscychresns.2012.04.014.
6. Desmarais J.E., Beauclair L., Annable L., Belanger M.C., Kolivakis T.T., Margolese H.C. Effects of discontinuing anticholinergic treatment on movement disorders, cognition and psychopathology in patients with schizophrenia. *Therapeutic Advances in Psychopharmacology*. 2014; 4(6): 257-67. DOI: 10.1177/2045125314553611.
7. Jann M.W. Implications for atypical antipsychotics in the treatment of schizophrenia: neurocognition effects and a neuroprotective hypothesis. *Pharmacotherapy*. 2004; 24: 1759–83. DOI: 10.1592/phco.24.17.1759.52346.
8. Tandon R., Greden J.F., Silk K.R. Treatment of negative schizophrenic symptoms with trihexyphenidyl. *Journal of Clinical Psychopharmacology*. 1988; 8(3): 212-215. DOI: 10.1097/00004714-198806000-00012.
9. Baitz H.A., Thornton A.E., Procyshyn R.M., Smith G.N., MacEwan G.W., Kopala L.C., Barr A.M., Lang D.J., Honer W.G. Antipsychotic medications: linking receptor antagonism to neuropsychological functioning in first episode psychosis. *Journal of the International Neuropsychological Society*. 2012; 18: 717–727. DOI: 10.1017/S1355617712000343.
10. Eum S., Hill S.K., Rubin L.H., Carnahan R.M., Reilly J.L., Ivleva E.I., Keedy S.K., Tamminga C.A., Pearlson G.D., Clementz B.A., Gershon E.S., Keshavan M.S., Keefe R.S.E., Sweeney J.A., Bishop J.R. Cognitive burden of anticholinergic medications in psychotic disorders. *Schizophrenia Research*. 2017; 190: 129–135. DOI: 10.1016/j.schres.2017.03.034.
11. World Health Organization: The ICD-10 Classification of Mental and Behavioural Disorders – Diagnostic Criteria for Research. Geneva: WHO, 1993.
12. Andreasen N.C., Pressler M., Nopoulos P., Miller D., Ho B.C. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. *Biological Psychiatry*. 2010; 67: 255–262. DOI: 10.1016/j.biopsych.2009.08.040.
13. Keefe R.S., Harvey P.D., Goldberg T.E. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). *Schizophrenia Research*. 2008; 102 (1–3): 108–115. DOI: 10.1016/j.schres.2008.03.024.
14. Sarkisyan G.R., Gurovich I.Ya., Keefe R.S. Normative data for the Russian population and standardization of the brief assessment of cognition in schizophrenia (BACS) scale. *Social and Clinical Psychiatry*. 2010; 20 (3): 13–19 (in Russ.).
15. Kay S.R., Fiszbein A., Opler L.A. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*. 1987; 13 (2): 261–76. DOI: 10.1093/schbul/13.2.261.
16. Mosolov S.N. Psychometric rating scales of symptoms of schizophrenia and concept of cognitive and negative disorders. Moscow, 2001: 238 (in Russ.).
17. Mel'nikov M.Y., Bezmaternykh D.D., Petrovskiy E.D., Kozlova L.I., Shtark M.B., Savelov A.A., Shubina O.S., Natarova K.A. The response time to emotional stimuli (including facial expressions photos) during the fMRI scanning in affective disorders: mild and moderate depression and dysthymic disorder. *Bulletin of Siberian Medicine*. 2018; 17 (1): 130–138 (in Russ.). DOI: 10.20538/1682-0363-2018-1-130-138.
18. Polyakov V.M., Rychkova L.V., Belogorova T.A., Mikhnovich V.I., Bugun O.V., Berdina O.N., Prokhorova Z.V., Teterina T.A., Lebedeva L.N., Lebedeva L.I. Influence of L-tryptophan use on the dynamics of cognitive functions in the complex therapy of delayed psycho-speech development in children. *Bulletin of Siberian Medicine*. 2018; 17 (2): 71–79 (in Russ.). DOI: 10.20538/1682-0363-2018-2-71-79.
19. Lebedeva E.V., Gorokhov A.S., Schastnyy E.D., Repin A.N., Simutkin G.G., Shishneva E.V., Perchatkin V.A., Surovtseva A.K., Winter S., Karpov R.S., Bokhan N.A. Time course of cognitive dysfunction and biochemical marker of CNS lesions S100ß in coronary artery bypass graft. *Bulletin of Siberian Medicine*. 2018; 17 (4): 72–84 (in Russ.). DOI: 10.20538/1682-0363-2018-4-72-84.

20. Brébion G., Bressan R.A., Amador X., Malaspina D., Gorman J.M. Medications and verbal memory impairment in schizophrenia: the role of anticholinergic drugs. *Psychological Medicine*. 2004; 34(2): 369-374. DOI: 10.1017/s0033291703008900.
21. Ostanko V.L., Kalacheva T.P., Kalyuzhina E.V., Livshits I.K., Shalovay A.A., Chernogoryuk G.E., Bespalova I.D., Yunusov R.S., Lukashova L.V., Pomogaeva A.P., Teplyakov A.T., Kalyuzhin V.V. Biological markers in risk stratification and progression of cardiovascular disease: present and future. *Bulletin of Siberian Medicine*. 2018; 17 (4): 264–280 (in Russ.). DOI: 10.20538/1682-0363-2018-4-264-280.
22. Lupu A.M., Clinebell K., Gannon J.M., Ellison J.C., Chengappa K.N.R. Reducing anticholinergic medication burden in patients with psychotic or bipolar disorders. *The Journal of Clinical Psychiatry.* 2017; 78(9): e1270–e1275. DOI: 10.4088/JCP.16m11269.
23. Harvey P.D. Cognitive and functional effects of atypical antipsychotic medications. *The Journal of Clinical Psychiatry*. 2006; 67: e13. DOI: 10.4088/JCP.1006e13.
24. Mishara A.L., Goldberg T.E. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. *Biological Psychiatry*. 2004; 55: 1013–1022. DOI: 10.1016/j.biopsych.2004.01.027.
25. Mariyan K. Topolov M.K., Getova D.P. Cognitive impairment in schizophrenia, neurotransmitters and the new atypical antipsychotic aripiprazole. *Folia Medica.* 2016; 58(1): 12–18. DOI: 10.1515/folmed-2016-0002.
26. Nielsen R.E., Levander S., Kjaersdam T.G., Jensen S.O., Ostergaard Ch.T., Leucht S. Second-generation antipsychotic effect on cognition in patients with schizophrenia – A meta-analysis of randomized clinical trials. *Acta Psychiatrica Scandinavica*. 2015; 131: 185. DOI: 96. 10.1111/acps.12374.
27. Keefe R.S.E., Harvey P.D., Khan A., Saoud J.B., Staner C., Davidson M., Luthringer R. Cognitive Effects of MIN-101 in Patients with Schizophrenia and Negative Symptoms: Results from a Randomized Controlled Trial. *Journal of Clinical Psychiatry*. 2018; 79 (3). DOI: 10.4088/JCP.17m11753.
28. Shmukler A.B., Semenkova E.A. Age-related characteristics of neurocognitive deficit at early stages of schizophrenia and schizophrenia spectrum disorders. *Social and Clinical Psychiatry.* 2010; 23 (4): 19–23 (in Russ.).

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Kornetova E.G. – conception and design of the study, drafting of the article, critical revision for important intellectual content. Goncharova A.A. – clinical-psychopathological and psychometric examination of the sampling, processing of statistical data, analysis of literature on the research topic, drafting of the article. Dmitrieva E.G. – psychometric examination of the sampling, drafting of the article, analysis of literature on the research topic. Arzhanik A.A. – processing of statistical data. Kornetov A. N. – critical revision for important intellectual content. Semke A.V. – final approval of the manuscript for publication.

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Received 16.01.2020
Accepted 16.06.2020