PPN

Personalized Psychiatry and Neurology

Case Report

Pharmacogenetic Testing of Cytochrome P450 System Enzymes in the Therapy of Bipolar Affective Disorder

Aiperi K. Khasanova[1]*, Regina F. Nasyrova[2,3]

[1] Russian Medical Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation;
[2] V. M. Bekhterev National Medical Research Centre for Psychiatry and Neurology, 192019 Saint Petersburg, Russia;
[3] Samara State Medical University, 443099 Samara, Russia;

* Correspondence: abdyrahmanova_peri@mail.ru (A.K.K.).

Citation: Khasanova, A.K.; Nasyrova, R.F. Pharmacogenetic Testing of Cytochrome P450 System Enzymes in the Therapy of Bipolar Affective Disorder. *Personalized Psychiatry and Neurology* **2022**, *2 (2)*: 90-96. https://doi.org/10.52667/2712-9179-2022-2-2-90-96

Chief Editor: Nikolaj G. Neznanov, D Med Sci, Professor

Received: 21 August 2022
Accepted: 31 October 2022
Published: 15 November 2022

Publisher's Note: V.M. Bekhterev NMRC PN stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Bipolar affective disorder (BPS) is a common and socially significant mental disorder that requires long-term use of psychotropic drugs (PDs). Long-term use of PDs increases the risk of developing adverse drug reactions (ADRs) and/or therapeutic resistance in some patients. This may be due to a genetically determined impairment of PDs metabolism by cytochrome P450 enzymes. Pharmacogenetic testing (PGx) is a method to identify a group of patients with a high risk of developing PDs -induced ADRs. Our experience of using PGx to search for low-functional and non-functional single nucleotide variants (SNVs) / polymorphisms of the *CYP1A2*, *CYP2C8*, *CYP3A4*, *CYP3A5* and *CYP2D6* genes encoding cytochrome P450 enzymes involved in PDs metabolism demonstrates the importance of this new personalized approach to the choice of PDs and its dosing in patients with pharmacogenetic profile poor metabolizer. The main purpose of the case report is to present the experience of using PGx in the therapy of dipolar affective disorder.

Keywords: *dipolar affective disorder; therapeutic resistance; unwanted reaction; psychotropic drugs; pharmacogenetic testing*

Introduction

Bipolar disorder (BPs) is one of the most serious and socially significant mental disorders, the prevalence of which reaches millions of cases worldwide. For the treatment of mental disorders, including BPs, psychotropic drugs (PDs) are usually used, in particular, antipsychotics (APs) and drugs with normothymic action [1]. The problem of PD-induced adverse drug reactions (ADRs) has not been solved yet, and the accumulated experience in targeted prevention of PD-induced ADRs suggests that most of them can be prevented or their consequences can be significantly reduced [2-5].

This problem causes: a decrease in the quality of patients' life; reducing the adherence of patients with mental disorders to chronic PD therapy; development of pseudoresistance of mental disorders to PDs; disease progression [4]. The study of the PD - induced ADRs mechanisms is based on the change in their metabolism and transport, which depends on the following risk factors: modifiable factors (choice of PD, its dose, dosing regimen, consideration of comorbid conditions, etc.); non-modifiable factors (gender, age of patients, genetic predisposition).

The study of genetic predisposition to the development of PD-induced ADRs is based on associative genetic studies and genome-wide studies of single nucleotide

variants (SNVs) and polymorphisms of the candidate genes involved in the metabolism, transport, cumulation, excretion of PDs and their active metabolites [6-8].

Objective

The aim of the case report is to present the experience of using pharmacogenetic testing (PGx) in a 26-year-old patient with bipolar affective disorder and a medical history of PD-induced ADRs.

Materials and Methods

Procedure

PGx was used based on the pharmacogenetic profile of patients with mental disorders (homo- and heterozygous carriers of risk alleles of low-functional and non-functional SNVs of the *CYP1A2, CYP2C8, CYP3A4, CYP3A5, CYP2D6* genes encoding cytochrome P450 enzymes involved in PDs metabolism. PGx was carried out using microchips, while the cumulative risk of developing PD-induced ADRs was assessed due to impaired 1th, 2nd and 3rd generations APs and drugs with normothymic action metabolism by cytochrome P450 enzymes: CYP1A2, CYP2C8, CYP3A4, CYP3A5, CYP2D6.

The features of the genotype and phenotype of patients, information of genetically determined PDs metabolism was determined. Patients were divided into three phenotypes (poor metabolizers, intermediate metabolizers, extensive metabolizers, ultra-rapid metabolizers) by testing 17 low-functional and non-functional SNVs of the *CYP1A2, CYP2C8, CYP3A4, CYP3A5, CYP2D6* genes.

As a result of testing, a list of APs and drugs with normothymic action was obtained, divided into four categories: "use as directed" in case of homozygous carriage of fully functional allelic variants of SNVs in these genes in a patient; "use with caution" in case of heterozygous carriage of low-functional allelic variants; "use with increased caution and with more frequent monitoring" in case of homozygous carriage of low-functional allelic variants; "do not use" in case of homozygous carriage of non-functional allelic variants.

Inclusion and Exclusion Criteria

The following inclusion criteria were used in selecting patients: signed voluntary informed consent; age over 18 years; established diagnosis of bipolar affective disorder (F31.x); taking PDs for more than 6 months; the presence of PD-induced ADRs.

Patient Observation

At visit 1, biological material (venous blood) was collected from the patient. Then the genetic analysis of the sample was carried out by PGx. PGx revealed SNVs of the candidate genes (*CYP1A2, CYP2C8, CYP3A4, CYP3A5, CYP2D6*), and assessed the cumulative risk of PD-induced ADRs.

At visit 2, correction of the therapy was carried out taking into account the results of PGx.

Ethical Aspects

The study was performed in accordance with the standards of good clinical practice and the principles of the Declaration of Helsinki. The clinical approbation was carried out within the framework of the state order. The participant signed a voluntary informed consent. The patient did not receive any remuneration for participating in the clinical trial. Researchers did not receive any remuneration for conducting clinical trials.

Results

4.1. Medical History

Patient K., 26 y.o., has been suffering from bipolar affective disorder since the age of 21. He was admitted to the clinic due to the lack of a therapeutic response to PDs for several years after the onset of the disease. There was an increase in affective fluctuations, as well as the development of PD-induced ADRs in the treatment of various PDs in monotherapy and polytherapy.

4.2. Pharmacogenetic Testing

The results of the PGx performed are presented in Table 1.

Table 1. Results of pharmacogenetic testing in a patient with treatment-resistant schizophrenia (clinically significant deviations are shown).

Gene	Protein	Rs	Normal	Result
CYP1A2	CYP1A2	rs2069514	GG	AG
		rs56276455	GG	AG
CYP2C8	CYP2C8	rs11572080	CC	TT
CYP3A4	CYP3A4	rs4986910	TT	CC
		rs56324128	CC	TT
		rs12721634	TT	CC

Thus, the patient showed that the functional activity of the CYP1A2 enzyme (responsible for the metabolism of the following PDs: clozapine, olanzapine, trifluoperazine, chlorpromazine, haloperidol, quetiapine, thioridazine) was reduced. Found: heterozygous carriage of the low-functional allele A of the rs2069514 variant (3860 G>A) and heterozygous carriage of the low-functional allele A of the rs56276455 variant (2385 G>A) of the *CYP1A2* gene encoding the activity of the CYP1A2 enzyme.

The functional activity of the CYP2C8 enzyme (responsible for the metabolism of the following PDs: clozapine, perospirone, perphenazine, lumateperone, carbamazepine) was significantly reduced. Found: homozygous carriage of the low-functional allele T of the rs11572080 (95067273 C>T) variant of the *CYP2C8* gene encoding the activity of the CYP2C8 enzyme.

The functional activity of the CYP3A4 enzyme (responsible for the metabolism of the following PDs: carbamazepine, clozapine, lurasidone, quetiapine, risperidone, haloperidol, cariprazine, ziprasidone, zuclopenthixol, asenapine, paliperidone, chlorpromazine) was significantly reduced. Found: homozygous carriage of the low-functional allele C of the rs4986910 variant (28285 T>C), homozygous carriage of the low-functional allele T of the rs56324128 variant (99778079 C>T) and homozygous carriage of the low-functional allele C of the rs12721634 variant (5148 T>C) of the *CYP3A4* gene encoding the activity of the CYP3A4 enzyme.

Thus, the use of PGx to assess the functional activity of cytochrome P450 enzymes made it possible to explain the development of PD-induced ADRs and pseudoresistance to previously used PDs in this patient. The cumulative pharmacogenetic risk of reducing the metabolism of PDs, including APs and drugs with normothymic action, with the participation of cytochrome P450 enzymes CYP1A2, CYP2C8, CYP3A4 in the patient is regarded as high. Given that the functional activity of three out of the five studied cytochrome P450 enzymes, which provide the metabolism of psychotropic drugs of a wide range of PDs, was significantly reduced, the phenotype of this patient was assessed as a "poor metabolizer".

4.3. Recommendations for the Patient

We recommended the patient use the following APs with increased caution and more frequent therapeutic drug monitoring: olanzapine, trifluoperazine, thioridazine,

perospirone, perphenazine, lumateperone. The starting and target dose of these APs should be reduced by an average of 50% compared to the average therapeutic dose (according to the instructions for these drugs).

We advised the patient to do not use the following PDs: carbamazepine, clozapine, lurasidone, quetiapine, risperidone, haloperidol, cariprazine, ziprasidone, chlorpromazine, zuclopenthixol, asenapine, paliperidone.

We advised to avoid prescribing inhibitors of 3A4, 2C8, 1A2 cytochrome P450 enzymes (promazine, lurasidone, haloperidol, olanzapine).

The normotimic of choice for this patient was valproic acid (CYP2A6, CYP2B6, CYP2C19, CYP2C9, CYP2E1). The APs of choice for this patient was zuclopenthixol (CYP2D6, to a lesser extent CYP3A4), whose metabolism does not involve the mentioned low-functional enzymes of the CYP 450.

There was a positive clinical effect after the correction of psychopharmacotherapy in the form of a reduction in affective symptoms and a reduction in the patient's previously PD-induced ADRs.

Discussion

Of great clinical interest is the study of the role of hepatic metabolism of PDs, since most of them used in real clinical practice have a hepatic or predominantly hepatic metabolism. Hepatic metabolism of PDs can be carried out in various ways, including oxidation, glucuronization, N-deamination, etc. Oxidation is the leading mechanism of hepatic metabolism of most PDs used in clinical practice and is carried out with the participation of liver cytochrome P450 isoenzymes.

Cytochrome P450 (cytochrome P450-dependent monooxygenase) is the common name for enzymes of the P450 family, which are part of the class of hemoproteins and belong to type b cytochromes.

In different people, the set of the cytochrome P450 isoenzymes in the endoplasmic reticulum (ER) and on the inner mitochondrial membrane differs due to genetic characteristics. In this regard, the study of genetically determined changes in the expression of the functional activity of CYP family isoenzymes is of great clinical importance in psychiatry and clinical pharmacology [2-10].

In humans, 57 genes and more than 59 pseudogenes encoding CYP isoenzymes have been identified. These isozymes are divided into 18 families and 43 subfamilies. The following enzymes are mainly involved in the metabolism of PDs through the oxidation process: CYP1A2, CYP2C8, CYP2D6, CYP3A4, CYP3A5 [2].

Cytochrome P450 enzyme 1A2 is an enzyme encoded in humans by the *CYP1A2* gene. The CYP1A2 enzyme is expressed in the liver (Figure 1) [11]. The CYP1A2 enzyme is localized in the ER and its expression is induced by several polycyclic aromatic hydrocarbons (PAHs), some of which are found in cigarette smoke. The endogenous substrate of the enzyme is unknown. However, it is able to metabolize some PAHs to carcinogenic intermediates. Other xenobiotic substrates for this enzyme include caffeine, aflatoxin B1, and paracetamol. The CYP1A2 enzyme is associated with 72 reactions in 10 different subsystems: cytosol, extracellular, mitochondria, nucleus, peroxisome. The CYP1A2 enzyme is involved in the metabolism of a wide range of drugs, including PDs [2].

Cytochrome P450 enzyme 2C8 (CYP2C8) is an enzyme that in humans is encoded by the *CYP2C8* gene. The CYP2C8 isoenzyme is predominantly expressed in the liver (Figure 2) [11]. Cytochrome CYP2C8 also has epoxygenase activity, it metabolizes long chain polyunsaturated fatty acids such as arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid and linoleic acid to their biologically active epoxides. CYP2C8 also has epoxygenase activity: it is one of the main enzymes responsible for attacking various long chain polyunsaturated fatty acids on their double (alkene) bonds to form epoxide products that act as signaling agents. It metabolizes: arachidonic acid to various epoxyeicosatrienoic acids (also called EET); linoleic acid to 9,10-epoxyoctadecaenoic acid (also called vernolinic acid, linoleic acid 9:10-oxide, or leukotoxin) and 12,13-epoxyoctadecaenoic acid (also called

coronary acid, 12,13-oxide linoleic acid, or isoleucotoxin); docosahexaenoic acid to various epoxydocosapentaenoic acids (also called EDPs); and eicosapentaenoic acid to various epoxyeicosatetraenoic acids (also called EEQ). The CYP1A2 enzyme is involved in the metabolism of a wide range of drugs, including PDs [12].

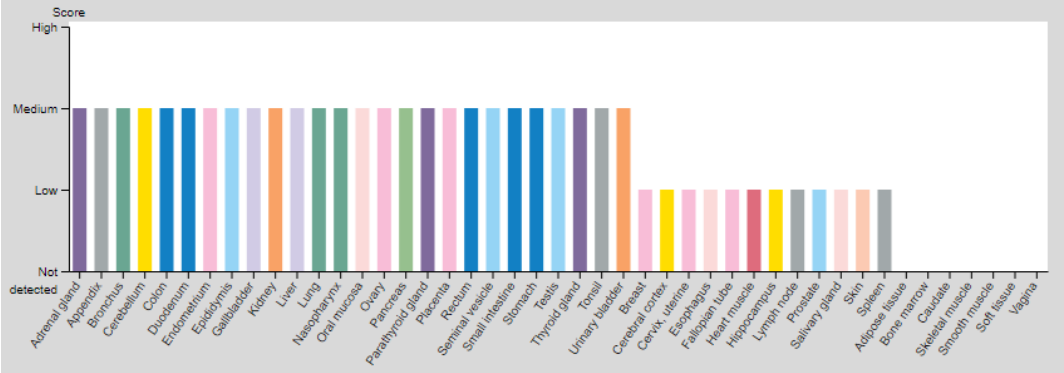

Figure 1. Expression level of CYP1A2 in human organs and systems

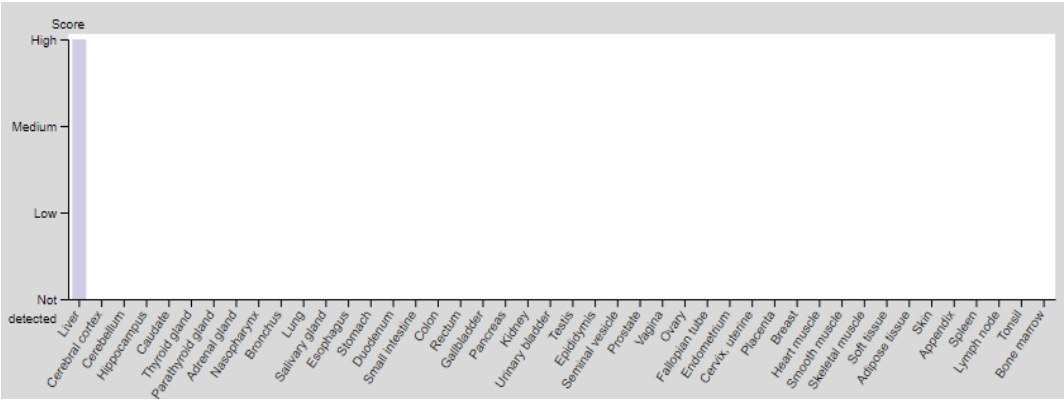

Figure 2. Expression level of CYP2C8 in human organs and systems.

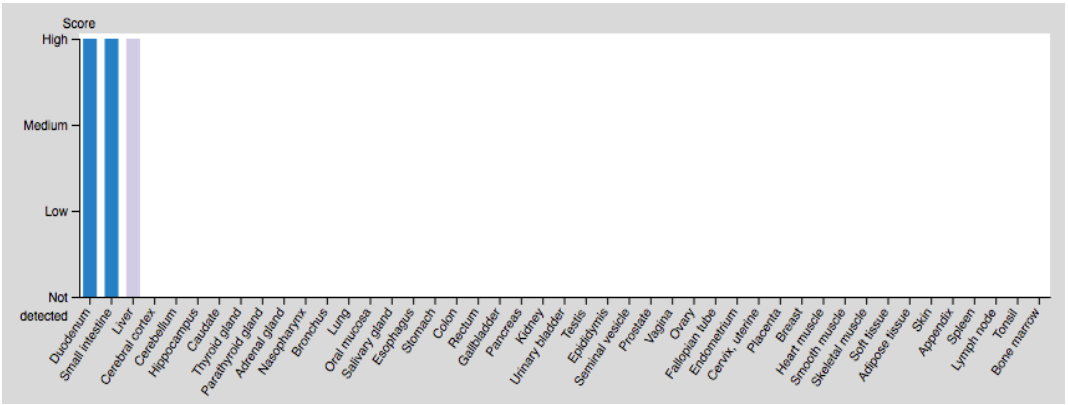

Figure 3. Expression level of CYP3A4 in human organs and systems.

Cytochrome P450 enzyme 3A4 (CYP3A4) is an enzyme that in humans is encoded by the *CYP3A4* gene. The CYP3A4 enzyme is expressed predominantly in the liver, duodenum, and small intestine (Figure 3) [11]. This is one of the most important enzymes involved in the metabolism of xenobiotics and drugs in the human body. Its purpose is to oxidize small foreign organic molecules such as toxins or drugs so that they can be removed from the body. CYP3A4 is one of a large group of the cytochrome P450 enzymes.

This protein is localized in the ER of hepatocytes, and its expression is induced by glucocorticoids and some other drugs. The CYP3A4 enzyme is involved in the metabolism of a wide range of drugs, including PDs [13].

Thus, the use of PGx to assess genetically determined changes in the functional activity and expression of these cytochrome P450 enzymes in patients with mental disorders is promising and justified. Bipolar affective disorder is a common and socially significant mental disorder that requires long-term use of PDs. Long-term use of PDs increases the risk of developing ADRs and/or therapeutic resistance in some patients. This may be due to a genetically determined disorder of PDs metabolism in the liver and other organs and systems. PGx is a method that allows to identify a group of patients with a high risk of developing PD-induced ADRs.

Foreign panels GeneSight Psychotropic test (GeneSight) [14] and Genecept Assay (Genecept) [15] for PGx do not include many significant non-functional variants of the genes encoding enzymes of the CYP family. When using the GeneSight test, analysis is performed on 59 allelic variants of 8 genes - *CYP1A2*, *CYP2C9*, *CYP2C19*, *CYP3A4*, *CYP2B6*, *CYP2D6*, *HTR2A* and *SLC6A4*. The attending physician is provided with information already analyzed by the program based on the results of the patient's genotyping. The conclusion contains a list of antipsychotics and antidepressants divided into 3 categories: "use as directed", "use with caution", and "use with increased caution and more frequent monitoring".

The Genecept Assay was developed in the USA. The study is carried out on allelic variants in 20 genes, including 5HT2C, MC4R, DRD2, COMT and genes of the cytochrome P450 system. The conclusion is provided in the form of a detailed table with recommendations for prescribing medicines for a particular patient Our experience of using PGx to search for low-functional and non-functional SNVs/polymorphisms of five genes (*CYP1A2*, *CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*) encoding enzymes that are centrally involved in PDs metabolism demonstrates the importance of this new personalized approach to the choice of PDs and its dosing in patients with a pharmacogenetic profile, a poor metabolizer.

Conclusion

Our experience of the PGx use based on the pharmacogenetic profile of cytochrome P450 enzymes metabolizing PDs in patients with mental disorders and the presented clinical case demonstrate the promise of its use in adult patients not only in the case of ADRs development, but also before the start of therapy. This is important for improving the personalized strategy for choosing PDs, their dosing regimen, the rate of dose increase, and the possibility of combination with other APs if polytherapy of mental disorders is required.

Author Contributions: Conceptualization, R.N.F..; methodology, R.F.N.; software, A.K.K.; validation, A.K.K. and R.F.N.; formal analysis, A.K.K.; investigation, A.K.K.; resources, A.K.K.; data curation, A.K.K.; writing—original draft preparation, .A.S. and A.K.K.; writing—review and editing, R.F.N.; visualization, A.K.K.; supervision, R.N.F.; project administration, R.F.N. All authors have read and agreed to the published version of the manuscript.
Funding: This research received no external funding.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient to publish this paper.
Acknowledgments: Not applicable.
Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kato, T. Current understanding of bipolar disorder: toward integration of biological basis and treatment strategies. *Psy Clin Neurosciences* **2019**, *73*, 526–540. https://doi.org/10.1111/pcn.12852
2. Shnayder, N.A.; Abdyrakhmanova A.K.; Nasyrova R.F. Phase I of antipsychotics metabolism and its pharmacogenetic testing. *Personalized Psychiatry and Neurology* **2022**, *2*, 4-21. https://doi.org/10.52667/2712-9179-2022-2-1-4-21
3. Abdyrakhmanova, A.K.; Shnayder, N.A.; Nasyrova, R.F. A clinical case of late pharmacogenetic diagnosis of adverse reactions during psychopharmacotherapy in a patient with recurrent depressive disorder. *Pharmacogenetics and Pharmacogenomics* **2021**, *2*, 21-23. (In Russ.). https://doi.org/10.37489/2588-0527-2021-2-21-23
4. Dobrodeeva, V.S.; Abdyrahmanova, A.K.; Nasyrova R.F. Personalized approach to antipsychotic-induced weight gain prognosis. *Personalized Psychiatry and Neurology* **2021**, *1*, 3-10. https://doi.org/10.52667/2712-9179-2021-1-1-3-10
5. Abdyrakhmanova, A.K.; Shnayder, N.A.; Neznanov, N.G.; Nasyrova R.F. Pharmacogenetics of quetiapine. *Personalized Psychiatry and Neurlogyo* **2021**, *1*, 73-83. https://doi.org/10.52667/2712-9179-2021-1-1-73-83
6. Abdyrakhmanova, A.K.; Nasyrova R.F. Pharmacogenetic testing of cytochrome p450 metabolizing enzymes in 28-year-old man with treatment-resistant schizophrenia. *Personalized Psychiatry and Neurology* **2022**, *2*, 81-88. https://doi.org/10.52667/2712-9179-2022-2-1-81-88
7. Nasyrova, R.F.; Shnayder, N.A.; Mironov, K.O.; Shipulin, G.A.; Dribnokhodova, O.P.; Golosov, E.A.; Tolmachev, M.Yu; Andreev, B.V.; Kurylev, A.A.; Akhmetova, L.Sh.; Limankin, O.V.; Neznanov, N.G. Pharmacogenetics of schizophrenia in real clinical practice: a clinical case. *Neurology, Neuropsychiatry, Psychosomatics* **2018**, *10*, 88–93. https://elibrary.ru/item.asp?id=36547318
8. Shnayder, N. A.; Abdyrakhmanova, A. K.; Nasyrova, R. F. Oxidation of antipsychotics. *Encyclopedia* **2022**, *2*, 974–989. https://doi.org/10.3390/encyclopedia2020064
9. Zhuravlev, N.M.; Shnayder, N.A.; Vaiman, E.E.; Abdyrakhmanova, A.K.; Petrova, M.M.; Bochanova, E.N.; Romanova, I.V.; Gavrilyuk, O.A.; Lareva, N.V.; Nasyrova R.F. Interindividual variability of anticonvulsant-induced qt prolongation risk. *Personalized Psychiatry and Neurology* **2022**, *2*, 22-45. https://doi.org/10.52667/2712-9179-2022-2-1-23-45
10. Nasyrova, R.F.; Dobrodeeva, V.S.; Scopin, S.D.; Shnayder, N.A.; Neznanov, N.G. Problems and prospects for the implementation of pharmacogenetic testing in real clinical practice in the Russian Federation. *Bulletine of Psychiatry, Neurology and Neurosurgery* **2020**, *3*, 6-8. (In Russ.). https://doi.org/10.33920/med-01-2003-01.
11. The Human Protein Atlas. Available online: https://www.proteinatlas.org (accessed on 14 February 2022).
12. Backman, J.T.; Filppula, A.M.; Niemi, M.; Neuvonen, P.J. Role of cytochrome P450 2C8 in drug metabolism and interactions. *Pharmacol Rev* **2016**, *68*, 168–241. https://doi.org/10.1124/pr.115.011411
13. Zhou, S.F. Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. *Curr Drug Metab* **2008,** *9(4)*, 310-22. doi: 10.2174/138920008784220664.
14. Genesight. Available online: https://genesight.com/product/ (accessed on 11 October 2022).
15. Genecept Assay. Available online: https://ncbi.nlm.nih.gov/gtr/tests/523653.4/ (accessed on 11 October 2022).