Personalized Psychiatry and Neurology

Case Report

Predictive Pharmacogenetic Testing in Psychiatry: Pros and Cons

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Abstract: Pharmacogenetic testing (PGx) is an important diagnostic tool for achieving an optimal balance between the effectiveness and safety of psychotropic drugs, especially those requiring long-term use. The most prescribed medications in psychiatric practice are antipsychotics (APs). Despite the long period of use of APs, their safety profile remains insufficiently high. Due to the high incidence of adverse drug reactions (ADRs), from the central nervous system (CNS) and other organs and tissues of the human body. Therapeutic drug monitoring can help predict and diagnose AP-induced ADRs only if the patient is receiving APs. PGx helps to individually select an AP, its dose and clarify the risk of ADRs before prescribing an AP, or at the start of therapy. This explains the importance of PGx in psychiatrist practice. However, to date, most practicing psychiatrists rarely use predictive PGx or do not use this method. PGx is more often prescribed in the case of a long history of unsuccessful AP-therapy, or in the case of the development of serious ADRs, the risk of which could be significantly reduced if predictive PGx was used. This case report of PGx in a 56-year-old woman with severe bipolar disorder demonstrates that the trajectory of ADRs and socialization could be significantly improved if this method was prescribed before the initiation of APs, rather than in the event of the development of serious ADRs.

Keywords: *bipolar affective disorder; pharmacogenetic testing; treatment; safety*

1. Introduction

Pharmacogenetic testing (PGx) is the identification of specific genotypes associated with changes in pharmacological response. These tests are based on polymerase chain reaction (PCR). One of the most important areas of application of PGx is clinical psychiatry [2]. According to various data, only 60%-70% of patients with mental disorders respond to therapy with psychotropic drugs [5; 8; 9]. Conducting PGx can contribute to the personalization of psychotropic therapy, the correct choice of a drug, selection of an individual dose, makes it possible to predict the drug response, and reduce the range of unwanted drug reactions (ADRs) [7]. However, at the present stage of development of

psychopharmacotherapy, prescribing of PGx has not become widespread. On the one hand, this is due to the insufficient level of evidence of the studied genetic markers, including their ethnic heterogeneity, insufficient clarity of the mechanism of action of some groups of psychotropic drugs, the low level of training in the field of psychopharmacogenetics among psychiatrists and the insufficient number of clinical pharmacologists in the psychiatric treatment network, the low rate of intensification of new diagnostic methods in psychiatry, and the seeming economic inexpediency of PGx. On the other hand, data from various studies indicate the clinical and cost-effectiveness of PGx [3; 13].

The needing for PGx is explained by the use of psychotropic drugs with a wide range and severity of ADRs, long-term use of psychotropic drugs, the use of psychotropic drugs with a narrow therapeutic corridor, and the high risk of developing ADRs (when using expensive psychotropic drugs) [6; 12].

There is now convincing scientific evidence in favor of predictive PGx before the development of ADRs [1; 8].

The purpose of this case report is to present the experience of using PGx in a 56-year-old woman with a treatment-resistant depressive episode of bipolar affective disorder.

2. Materials and Methods

2.1. Procedure

The PGx screening panel was used to clarify the pharmacogenetic profile of a patient with a mental disorder, including the identification of homo- or heterozygous carriage of risk alleles (low-functioning and non-functional single nucleotide variants (SNVs) of the *CYP1A2, CYP2C9, CYP3A4, CYP3A5, CYP2D6* genes encoding isoenzymes liver cytochrome P450 involved in metabolism of psychotropic drugs. PGx was performed using a microarray. We assessed the cumulative risk of developing psychotropic drugs-induced ADRs. Blood was taken from a peripheral vein in a volume of 5 ml.

2.2. Criteria for Prescribing Pharmacogenetic Testing

A psychiatrist used the following criteria to select patients for PGx: signed voluntary informed consent; age over 18 years; established diagnosis F31.53 (bipolar affective disorder, depression with congruent delusions); taking psychotropic drugs for more than 6 months; presence of psychotropic drugs-induced ADRs. Predictive PGx was not used in this case report.

2.3. Laboratory Research

To assess the functioning of organs and systems during long-term use of psychotropic drugs, the patient underwent other research methods including: clinical blood test and biochemistry tests. The scope of diagnosis was determined by the standard of care for patients with bipolar disorder [4]

2.4 Ethical Considerations

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

The course of the disease has become non-remission in nature with a continuous change of poles and with pictures of mixed states over the past 3 years. The use of any of the main normotimic drugs was impossible due to contraindications or low tolerability. Recently, the patient has been experiencing repeated sudden attacks of severe anxiety, accompanied by involuntary urges to move, restlessness, psychosensory disorders, psychedelic experiences, misrecognition of others and the environment. Confusion often develops at the height of an attack. The anxiety attacks lasted on average about two hours. The patient's state of health between attacks was satisfactory. However, increased fatigue and mild akathisia persisted.

At the 2nd visit, a clinical pharmacologist was consulted, and therapy was adjusted taking into account the PGx results (Table 1). The clinical pharmacologist recommended: discontinue quetiapine; prescribe cariprazine at a dose of 3-4.5 mg/day.

Table 1. Previously taken psychotropic medications

Drugs	**Maximum dose (mg/day)**	**Duration of admission (days)**	**Effect**	**Applications**
		Mood stabilizers		
Lithium carbonate	60	11	Hypothyroidism (100 mcg/day decompensation of hypothyroidism)	
Carbamazepine	1000	53	No effect	
		Antidepressants		
Trazodone	250	30	No effect	
Duloxetine	60	23	Phase inversion	
Paroxetine	40	110	No effect	
Venlafaxine	300	70		
		Antipsychotics		
Quetiapine	800	53	No effect	
Clozapine	225	55	No effect	
Chlorprothixene	250	23	No effect	

Zuclopenthixol-acufase	100		Extrapyramidal syndrome
Zuclopenthixol	20	60	Phase inversion
Aripiprazole	30	30	No effect
Haloperidol	5	5	Extrapyramidal syndrome
Trifluoperazine	5	1	Extrapyramidal syndrome
		Benzodiazepines	
Bromodihydrochlorophenyl benzodiazepine	3	5	No effect

3.2. Laboratory Results

Instrumental and laboratory studies were carried out:

Biochemistry tests: ALT 30.1 U/l, AST 21.0 U/l, GLU 5.37 mmol/l, total BIL 8.56 μmol/l, creatinine: 59.7 μmol/l.

Clinical blood test dated 08/08/2023: WBC 3.44 10`9/l, RBC 4.07 10`12/l, HGB 117 g/l, HCT 34.0%, MCV 83.7 fl., PLT 182 10`9/l , ESR 12 mm/h.

Analysis: TSH – 4.440 μIU/ml, T4 – 1.34 ng/dl, T3 - 2.58 pg/ml.

Urinalysis: no clinically significant abnormalities.

3.3. Instrumental Studies Results

ECG: moderate sinus tachycardia with heart rate 94 beats/min.

FLG: chest organs within the limits of age-related changes.

Ultrasound of the kidneys: Ultrasound signs of a cyst in the right kidney.

Ultrasound of the pelvic organs: no formations or infiltrative changes were detected.

MRI of the brain: MRI picture of focal changes in the white matter, probably of a vascular nature; the forming “empty” sella turcica.

3.4. Pharmacogenetic Testing Results

The results of the performed PGx are presented in Table 2.

Table 2. Results of pharmacogenetic testing in a patient with treatment-resistant bipolar affective disorder (clinically significant abnormalities shown).

Name/Indicator	**Single nucleotide variant (NCBI SNP, allelic variant)**	**Genotype**	Evaluation
Analysis of common genetic variants in the *CYP2C19* gene	rs1799853(C430T, Cys144Arg) rs1057910 (Ile359Leu,A1075C)	C/C A/A	Normal, pharmacogenetic profile EM (extensive metabolizer)
Analysis of common genetic variants in the *CYP2C19* gene	rs4244285 (CYP2C19*2) rs4986893 (CYP2C19*3) rs28399504 (CYP2C19*4)	**G/A!** G/G A/A	Heterozygous carrier of the non-functional allele A, pharmacogenetic profile IM (intermediate metabolizer)
Analysis of common genetic variants in the *CYP2D6* gene	rs4986774 (CYP2D6*3A) rs1065852 (CYP2D6*10) rs3892097 (CYP2D6*4)	A/A C/C G/G	Normal, pharmacogenetic profile EM (extensive metabolizer)
Analysis of common genetic variants in the *CYP3A4* gene	rs4987161 (CYP3A4*17) rs28371759 (CYP3A4*18) rs2740574 (CYP3A4*1B)	T/T T/T A/A	Normal, pharmacogenetic profile EM (extensive metabolizer)
Analysis of common genetic variants in the *CYP1A2* gene	rs2069522	**T/T!**	Homozygous carrier of the non-functional T allele, pharmacogenetic profile PM (poor metabolizer)
Analysis of common genetic variants in the *MDR1* gene	rs1045642 (C3435T)	C/C	Normal, pharmacogenetic profile EM (extensive metabolizer)

Note: abnormal PGx indicators are highlighted in bold with an exclamation mark.

The patient's pharmacogenetic profile is a poor metabolizer.

The cumulative risk of developing ADRs in the setting of taking psychotropic drugs with hepatic and predominantly hepatic metabolism with the participation of isoenzymes 2C19 and 1A2 of cytochrome P450 was assessed by a clinical pharmacologist as high.

In screening PGx with detection of the most common low-functional and non-functional SNVs of the *CYP2C9, CYP2C19, CYP1A2, CYP3A4* and *CYP2D6* genes, encoding the activity of isoenzymes 2C9, 2C19, 1A2, 3A4 and 2D6 of the liver cytochrome P450, and the *MDR1* gene, encoding the transport protein P-gp (P-glycoprotein), heterozygous carriage of the non-functional allelic variant A rs4244285 of the *CYP2C19* gene and homozygous carriage of the non-functional allelic variant T rs2069522 of the *CYP1A2* gene were revealed, which are the most common among non-functional SNVs of these genes in the European population.

The identified genetic markers are associated with a moderate decrease in the functional activity of the 2C19 isoenzyme and a pronounced decrease in the functional activity

of the 1A2 isoenzyme of the liver cytochrome P450, which leads to a slower utilization of drugs with hepatic metabolism and an increased risk of ADRs, including neurotoxic ones.

Psychotropic drugs metabolized in the liver with the participation of the *CYP1C19* isoenzyme are:

1. antidepressants (citalopram, escitalopram, fluoxetine, sertraline, levomilnacipran, agomelatine, venlafaxine);

2. antipsychotics (haloperidol, quetiapine, clozapine, perphenazine, pipothiazine, promazine, risperidone, thioridazine);

3. anticonvulsants (carbamazepine, valproic acid, phenytoin, phenobarbital, topiramate, felbamate, primidone).

Psychotropic drugs metabolized in the liver with the participation of the *CYP1A2* isoenzyme are:

1. antidepressants (agomelatine, duloxetine, mirtazapine, tricyclic antidepressants, paroxetine, fluvoxamine, citalopram, escitalopram);

2. antipsychotics (azenapine, haloperidol, zotepine, quetiapine, clozapine, loxapine, lumateperone, olanzapine, perphenazine, pimozide, promazine, thioridazine, thiothixene, trifluperazine, flupenthixol, chlorpromazine);

3. anticonvulsants (carbamazepine).

3.5. Recommendations from a Clinical Pharmacologist

1. It is recommended to use with caution drugs that are metabolized with the participation of the 2C19 isoenzyme, encoded by the *CYP2C19* gene (taking into account the identified pharmacogenetic profile of IM in the patient). It is recommended to reduce starting and target doses by 20-25% of the average therapeutic dose (according to the instructions for this drug) in monotherapy and by 50% in polytherapy (in particular, when taken simultaneously with drugs with similar metabolism).

2. It is recommended not to use or use with great caution drugs that are metabolized with the participation of the 1A2 isoenzyme, encoded by the *CYP1A2* gene (taking into account the identified pharmacogenetic profile of PM in the patient). It is recommended to reduce starting and target doses by 50% from the non-therapeutic average (according to the instructions for this drug) in monotherapy and by 75% or not to use in polytherapy (in particular, when taken simultaneously with drugs with similar metabolism).

3. Monitor the development of possible ADRs, when taking any drugs, primarily those registered and indicated in the instructions for use.

4. Strictly follow the instructions for use of drugs, including recommendations for use in connection with meals and drug-drug interactions.

5. Do not include grapefruit juice or pomelo in your diet, as the components of these products change the rate of metabolic reactions in the liver. Other citrus juices are allowed.

6. Do not take medications with milk (unless specifically instructed), jelly, or tea. It is preferable to drink it with water.

7. It is recommended to conduct extended pharmacogenetic testing, as well as DNA profiling to exclude Gilbert-Lebrouillet syndrome, due to the development of ADRs and the risk of therapeutic resistance when using drugs indicated by the patient that are

not metabolized by cytochrome P450 isoenzymes and are not transported with the participation of the transporter protein presented in this screening panel.

8. Taking into account the history of the development of antipsychotic-induced extrapyramidal syndrome in the setting of taking a wide range of antipsychotics, the patient is recommended to undergo genetic testing of risk alleles of genes encoding dopamine receptors and key enzymes of dopamine metabolism, as well as to exclude genetic predisposition and/or family history of Parkinson's disease.

4.1. Discussion

The presented clinical case report indicates a late prescription of PGx after 10 years the start of psychotropic therapy. And about the refusal of practicing psychiatrists observing this patient to use predictive PGx.

Although, there is great clinical interest in studying the role of the psychotropic drugs metabolism in predicting their safety effectiveness. Most typical and atypical antipsychotics and antidepressants for the treatment of bipolar disorder have hepatic or predominantly hepatic metabolism. Hepatic metabolism of psychotropic drugs can be carried out by oxidation, glucuronidation, N-deamination, acetylation, etc. P-oxidation is the leading mechanism of hepatic metabolism of most psychotropic drugs and is carried out with the participation of liver cytochrome P450 isoenzymes [10]. 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. The set of cytochrome P450 isoenzymes in the endoplasmic reticulum and on the inner membrane of mitochondria differs due to genetic characteristics in different people [4]

5. Conclusion

In modern psychiatry, the most pressing issue is the problem of ADRs and the lack of effect from the therapy taken. Such ADRs as extrapyramidal symptoms, neurological disorders, somatic, vegetative and endocrine effects and complications significantly reduce the quality of life of patients and create secondary psychological problems, as well as problems of social and labor adaptation, which in turn reduce compliance, and in some cases, it is the reason for refusing treatment. Against this background, the possibility of PGx at the initial stages of therapy is of particular importance; this will allow the psychiatrist to achieve better and longer-lasting remission and significantly improve the quality of life of patients. It is also advisable to talk about the cost-effectiveness of PGx, since patients with resistance spend many years taking expensive drugs that do not achieve the desired result.

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References

1. Bochanova, E.N. Pharmacogenetics of antiepileptic drugs (literature review). *Kachestvennaya Klinicheskaya Praktika*. 2017;(1), 51-55.
2. Nasyrova, R.F.; Neznanov, N.G. Clinical psychopharmacogenetics. SPb: DEAN Publishing Center. **2020**;408. ISBN 978-5-6043573-7-8
3. Ivanov, S.V.; Voronova, E.I. Depression therapy for somatic diseases. *S.S. Korsakov Journal of Neurology and Psychiatry*. **2021**;121(5):106–112. DOI:10.17116/jnevro2021121052106
4. 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. DOI:10.52667/2712-9179-2022-2-2-90-96.
5. Kohlrausch, F.B.; Gama, C.S.; Lobato, M.I. Naturalistic pharmacogenetic study of treatment resistance to typical neuroleptics in European-Brazilian schizophrenics. *Pharmacogenet. Genomics*. **2008**;18(7):599–609. DOI:10.1097/FPC.0b013e328301a763
6. Mackenzie, B.; Souza, R.; Likhodi, O.; Tiwari, A.; Zai, C.; Sturgess, J.; Müller, D. Pharmacogenetics of antipsychotic treatment response and side effects. *Therapy*. **2010**;7(2):191-198. DOI:10.2217/thy.10.3.
7. Mazo, G.E.; Neznanov, N.G. Treatment-resistant depression. SPb.: Ladoga. **2013**;372.
8. Nasyrova, R.F.; Schnaider, 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(4):88-93. DOI:10.14412/2074-2711-2018-4-88-93
9. Novitsky, M.A.; De Suosa, A.; Asadullin, A.R.; Gavrilyuk, O.A.; Petrov, A.V.; Nasyrova, R.F. Possibilities and limitations of antidepressant use to correct depressive and negative symptoms in schizophrenia. *Personalized Psychiatry and Neurology*. **2021**;1(2):21-45. DOI:10.52667/2712-9179-2021-1-2-21-45
10. Shnayder, N.A.; Abdyrakhmanova, A.K.; Nasyrova, R.F. Oxidation of Antipsychotics. *Encyclopedia*. **2022**;2: 974-989. DOI:10.3390/encyclopedia2020064

11. Syunyakov, T.S. Molecular genetics and pharmacogenetics of bipolar affective disorder: a review of the proceedings of the 26th Congress of the European College of Neuropsychopharmacology. Barcelona, October 5-9, 2013. *Psychiatry.* **2014**;3:25–35.
12. Verbenko, V.; Dvirsky, A. The SSRI antidepressants: clinical aspects, new side effects and mechanisms of actions. *Psikhiatriya*. **2018**;1(77):123-133. DOI:2618-6667-2018-77-123-133.
13. Yagudina R.I.; Serpik, V.G.; Babiy, V.V.; Ugrekhelidze D.T. Criteria of efficiency in pharmacoeconomic analysis. *Pharmacoeconomics. Theory and practice*. **2017**;5(3):5-10. DOI:10.30809/phe.3.2017.7