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Review

The Role of Pharmacogenetic Testing in Optimizing Antipsychotic Therapy

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Abstract: Antipsychotic therapy in psychiatric practice can last from several months to many years, which requires the selection of drugs with the greatest effectiveness and the lowest risk of adverse drug reactions for the patient. According to experts, about a quarter of the total variability in response to antipsychotics is of genetic origin. This review analyzes and summarizes the results of domestic and foreign studies of the role of hereditary risk factors that cause a decrease in hepatic metabolism and efflux of antipsychotics due to polymorphism of genes encoding cytochrome P450 isoenzymes and transporter proteins. The key enzymes of antipsychotic metabolism registered for use in Russia and abroad are presented. The prospects of various options for pharmacogenetic testing in reducing the risk of potentially fatal complications in the selection of antipsychotic therapy in clinical practice are assessed.

Keywords: *pharmacogenetic testing; antipsychotic; classification; pharmacokinetics; cytochrome; transporter; p-glycoprotein; psychopharmacotherapy*

1. INTRODUCTION

The life expectancy of patients with chronic mental disorders is lower than in the general population by more than 20 years [1]. Prevention of fatal outcomes depends on timely, adequately selected therapy and achieving a high level of patient compliance [2]. Since therapy for chronic mental disorders continues for a long time, most often throughout the patient's life, a psychiatrist must evaluate not only the effectiveness, but also the safety of psychopharmacotherapy and even the patient's subjective comfort when taking medications [3, 4].

Antipsychotics are drugs with a psycholeptic (calming) effect, which are able, first of all, to reduce psychotic symptoms and psychomotor agitation [5]. They are widely used in psychiatric practice [6]. But despite the emergence of new generations of antipsychotics, the problem of insufficient effectiveness of antipsychotic therapy and adverse drug reactions (ADRs) with it remains unresolved [7 - 10]. According to various data, only 60-70% of patients with mental disorders respond to antipsychotic therapy [11]. The accumulated experience of preventing ADRs indicates that most of them can be prevented or their frequency and severity of symptoms can be significantly reduced [12]. For this purpose, it is advisable to assess the initial risk of ADRs when selecting drugs, their doses and duration of administration [13]. However, in most cases, practicing

doctors prescribe antipsychotics according to the instructions for use in standard doses without taking into account the patient's characteristics.

In general, differences between people in response to antipsychotics can be caused by environmental, physiological, psychological factors, as well as comorbidities and genetic variability [14, 15]. According to experts, approximately a quarter of the total variability in response to antipsychotics is of genetic origin [16]. Of course, all factors affecting the state of the body are important, but it is genetic analysis that is considered the most promising technology for personalized medicine.

Purpose of the study is to determine the role of pharmacogenetic testing in optimizing antipsychotic therapy.

2. MATERIALS AND METHODS

The search for articles was conducted in the PubMed, eLIBRARY.RU, Google Scholar databases using the keywords: antipsychotic, pharmacogenetic testing, cytochrome, transporter and their combinations. 38 publications were analyzed that most accurately met the objectives of this article.

3. RESULTS

Pharmacogenetics and pharmacogenomics are new areas of clinical medicine that are actively developing in Russia and around the world and are being actively introduced into psychiatric practice [17]. These are scientific and practical areas, the purpose of which is to study and implement data on how genetic information determines the efficacy and safety of drugs, in order to develop personalized methods of therapy. The accumulated data made it possible to create a list of genes for some drugs that participate in the processes of pharmacokinetics (by changing the absorption, distribution, metabolism and elimination of the drug) and pharmacodynamics (by changing the target or signaling pathways that determine sensitivity to the drug) [18 - 23].

Determination of individual characteristics of a patient's genotype is possible using pharmacogenetic testing (PGx) [16]. PGx is the identification of specific genotypes based on the polymerase chain reaction [17]. PGx can facilitate personalization of antipsychotic therapy, selection of the most suitable drug, and selection of the most optimal individual dose. PGx helps a psychiatrist predict drug response and the spectrum of ADRs [7]. Currently, PGx is widely used in various fields of medicine - 37% of prescriptions are for oncology, 12% for infectious diseases. Psychiatry is in third place, accounting for 9% of PGx prescriptions ($p < 0.00001$) [24]. The role of PGx in modern psychiatric practice is becoming increasingly clinically important due to the development and increased availability of screening and expanded PGx panels [25].

Currently, the effectiveness of pharmacodynamic genotyping is still questionable due to the high evolutionary conservation of genes encoding target receptors [26]. In contrast to pharmacokinetic genotyping, which is gaining popularity, since genes encoding drug metabolism enzymes have a significant impact on the efficacy and safety of antipsychotics [27].

Depending on the time of PGx, two variants are possible: predictive (pro-reactive, preliminary) and reactive [28]. Predictive is performed before prescribing antipsychotics. Reactive is used in patients with a long history of ADRs or therapeutic resistance.

Most antipsychotics have hepatic or predominantly hepatic metabolism. Hepatic metabolism of psychotropic drugs can be carried out by oxidation, glucuronidation, N-deamination, acetylation, etc. [29]. P-oxidation is the leading mechanism of hepatic metabolism of most antipsychotics and is carried out with the participation of liver

cytochrome P450 isoenzymes [30] (**Table 1**). Cytochrome P450 (cytochrome P450-dependent monooxygenase) is the general name for enzymes of the P450 family, which are part of the hemoprotein class and belong to the cytochromes type B [17]. The superfamily is a class of proteins that are localized primarily in the liver and are the main enzymes responsible for phase I oxidative reactions of most drugs [30]. More than 50 enzymes are known, the most significant of which are CYP2D6, CYP2C9, CYP2C19, CYP1A2 and CYP3A4 [31]. Approximately 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6 and 23% of CYP3A4 [32, 33].

Tabel 1. Pathway and key enzymes of antipsychotic metabolism [13].

Antipsychotic	Metabolic pathway	Key cytochrome P450 isoenzymes	References
A. First generation antipsychotics			
1. Antipsychotics with incisive action			
Benperidol*	ND	ND	
Haloperidol	Hepatic	3A4, 3A5, 2D6, partially: 1A1, 1A2, 2C9, 2C19, 3A7	[29]
Droperidol	ND	ND	
Zuclopenthixol	Hepatic	Partially: 2D6, 3A4	[29]
Penfluridol*	Hepatic	3A4	[34]
Perphenazine	Hepatic	3A4, 2D6, partially: 1A2, 2C8, 2C9, 2C18, 2C19	[29]
Prochlorperazine*	Hepatic	2D6	[34]
Pimozide*	Hepatic	3A4, 3A5, 3A7, 1A2	[34]
Pipothiazine*	Hepatic	2C19, 2D6, 3A4	[34]
Thiothixene*	Hepatic	2D6, 1A2	[34]
Trifluoperazine	Hepatic	1A2, partially: 2D6	[29]
Flupenthixol	Hepatic	Partially: 2D6	[29]
Fluphenazine	Hepatic	2D6	[29]
2. Antipsychotics with predominantly sedative action			
Levomepromazine	Hepatic	3A4, partially: 2D6, 1A2	[29, 31]
Mesoridazine*	Hepatic	2D6	[34]
Melperone*	Hepatic	2D6	[34]
Pericyazine	Hepatic	2D6	[35]
Pipamperone*	ND	ND	
Promazine	Hepatic	Partially: 1A2, 2D6, 2C9, 2C19, 3A4	[29]
Tiapride	Minimal metabolism	Do not participate in metabolism	[34]
Thioridazine	Hepatic	2D6, partially: 2C19	[29]
Chlorpromazine	Hepatic	2D6, partially: 1A2, 3A4	[29]
Chlorprothixene	Hepatic	2D6, 3A4	[34]
Cyamemazine*	ND	ND	
B. Second generation antipsychotics			
1. Antipsychotics with predominantly disinhibitory action			
Amisulpride	Minimal metabolism	Do not participate in metabolism	[31]
Sulpiride	95% is not metabolized	Do not participate in metabolism	[34]
2. Multireceptor blockers (antagonists of 5-HT2A, D2, M1, H1 receptors)			
Asenapine*	Hepatic	1A2, 2D6, 3A4	[34]
Zotepine*	Hepatic	1A2, 3A4	[34]
Quetiapine	Hepatic	3A4, partially: 2C19, 2D6, 3A5, 3A7	[29]
Clotiapine*	ND	ND	
Clozapine	Hepatic	1A2, 3A4, partially: 3A5, 2D6, 2C8, 2C9, 2C19, 2A6	[29, 36]

Loxapine*	Hepatic	1A2, 3A4, 2D6, partially: 2C19, 2C8	[37]
Olanzapine	Hepatic	1A2, 3A5, partially: 1A1, 2D6, 2C9	[29]
3. Selective antagonists of D2 and 5-HT2A receptors			
Blonanserin*	Hepatic	3A4	[34]
Ziprasidone	Hepatic	1/3 dose 3A4	[29]
Iloperidone*	Hepatic	3A4, 2D6	[34]
Lurasidone	Hepatic	3A4	[29]
Paliperidone	Predominantly renal	Partially: 3A4, 2D6	[29]
Perospirone*	Hepatic	3A4, 2D6, 2C8, 1A1	[34]
Risperidone	Hepatic	2D6, partially: 3A4	[29]
Sertindole	Hepatic	Partially: 2D6, 3A4	[29]
C. Third generation antipsychotics			
1. Partial agonists of D2 and 5-HT1A receptors and antagonists of 5-HT2A receptors			
Aripiprazole	Hepatic	3A4, 3A5, 2D6, partially: 3A7	[29, 36, 38]
Brexpiprazole	Hepatic	3A4, 2D6	[29, 36]
Lumateperone*	Hepatic	3A4, 2C8, 1A2, 1A1, 1A4, 2B15	[34]
Cariprazine	Hepatic	3A4, partially: 2D6	[29, 36]
2. Selective serotonin reuptake agonist and 5-HT2A receptor antagonist			
Pimavanserin*	Hepatic	3A4, 3A5, 2D6, 2J2	[34]

Note: *Paliperidone is an active metabolite of risperidone. Although in vitro studies suggest a role for isoenzymes 2D6 and 3A4 in paliperidone metabolism, in vivo results indicate that they contribute to the elimination of no more than 10% of the paliperidone dose; * - antipsychotic not registered in Russia; ND – no data; D2 - dopamine receptors; 5-HT1A - serotonin receptors; 5-HT2A - serotonin receptors; M1 - acetylcholine muscarinic receptor, H1 - histamine receptors*

The metabolic activity of cytochrome P450 enzymes is genetically determined. Of the three cytochrome subfamilies, the second shows the highest level of genetic diversity [39]. Single nucleotide variants (SNV) in genes can result in enzymes with higher, lower, or no activity [39].

Each antipsychotic may have a different metabolism pattern depending on the genotype. The prevalence of different genotypes varies markedly depending on the ethnicity of the patients [39]. Up to 30% of Caucasians have the poor and intermediate metabolizer phenotype [40, 41]. It follows that empirical prescription of antipsychotics without taking into account the patient's pharmacogenetic profile may expose some patients with poor metabolism to an increased risk of ADRs [16].

An equally important factor in ensuring an optimal balance between the effectiveness and safety of antipsychotic therapy is the work of transport proteins that provide efflux (transport in the direction of the brain - blood) of antipsychotics, and the timely detection of its genetically determined impairment [42].

Multidrug resistance proteins P-glycoprotein 1 (ABCB1 or formerly MDR1), protein 4 (MDR4), breast cancer resistance protein 2 (ABCG2), ABCC1 protein, and other transporters located on endothelial cells lining the cerebral vasculature play an important role in limiting the transport of substances into the brain and enhancing their efflux from the brain [43]. Transporters also interact with metabolic enzymes, eliminating drug metabolites [44].

P-glycoprotein is a membrane transport protein with a wide range of endogenous and exogenous substrates. P-gp is localized in hepatocytes, enterocytes, epithelial cells of the proximal renal tubules, neurons and endothelial cells of the histohematic barriers, including the blood-brain barrier [42]. Increased activity of P-glycoprotein is associated

with the development of drug-resistant forms of mental disorders, and decreased activity causes a delay in the efflux of antipsychotics and increases the risk of ADRs [45]. P-glycoprotein is encoded by the highly polymorphic *ABCB1* gene [46]. About 100 single nucleotide variants identified in different regions are mentioned in the literature [47]. However, only a few of them lead to clinically significant changes in the transport of antipsychotics. The identification of non-functional SNV/polymorphisms of the *ABCB1* gene is of clinical interest, since it is associated with an increased risk of developing antipsychotic-induced ADRs and a decrease in the safety of psychopharmacotherapy for schizophrenia [45].

Depending on the metabolic rate (efflux), five pharmacogenetic phenotypes are distinguished [17]:

- slow metabolizers (transporters) — enzyme activity is low or completely absent, which leads to an increased risk of developing ADRs due to the accumulation of drugs in the body;
- intermediate metabolizers (transporters) — enzyme activity is lower than normal, but higher than that of slow metabolizers (transporters), which leads to an increase in the concentration of antipsychotics in the blood by 1.5 times compared to extensive metabolizers (transporters);
- extensive metabolizers (normal, common) (transporters) — the majority of patients for whom the average therapeutic doses regulated by the instructions for the drug are applicable;
- rapid metabolizers (transporters) — patients with increased enzymatic activity, which leads to rapid elimination of the active substance and the absence of the expected effect;
- ultra-rapid metabolizers (transporters) — patients in whom the drug may have no effect due to abnormally high enzyme activity.

4. DISCUSSION

Currently, the use of PGx has not yet become widespread [16]. On the one hand, this is due to the insufficient level of evidence for the genetic markers studied, including their ethnic heterogeneity, insufficient clarity of the mechanism of action of some antipsychotics, low level of training in psychopharmacogenetics among psychiatrists and an insufficient number of clinical pharmacologists in the psychiatric treatment network, low rates of intensification of new diagnostic methods in psychiatry, and the apparent economic inexpediency of conducting PGx [48, 49]. On the other hand, the results of modern studies appearing in large numbers indicate the clinical and economic effectiveness of PGx [50, 51].

The need to use PGx is explained by the need for long-term use of antipsychotics with a wide spectrum of action, with a narrow therapeutic corridor and the severity of possible ADRs [52]. PGx can help to determine individual genetic features of the metabolism and efflux of antipsychotics, allows to determine the carriage of high-, low- and non-functional single-nucleotide variants of genes encoding key enzymes of the metabolism and transport of the antipsychotic, associated with an increase or decrease in the rate of its metabolism and efflux, respectively, and to predict the effectiveness and safety of the use of an antipsychotic in a particular patient [53].

Of course, predictive PGx is more economically and clinically feasible, since it allows to reduce the costs of drug provision for patients, this is the initial selection of optimal therapy, and a reduction in the dose of the drug, and the absence of prescriptions for drugs to correct ADRs, and predictive PGx helps to achieve a therapeutic response faster, which allows to reduce the duration of hospitalization, and all this, in general, increases patient compliance, reduces the risk of repeated exacerbations and contributes to the

formation of long-term stable remission. Taking into account the comparable cost, reactive PGx is deprived of these advantages of predictive [54].

Although PGx is increasingly being introduced into psychiatric practice due to the development and increased availability of screening and expanded PGx panels [55], predictive PGx is still not widely used. Most psychiatrists continue to titrate antipsychotics empirically or use reactive PGx in patients with a long history of ADRs or therapeutic resistance.

5. CONCLUSION

In modern psychiatry, the most pressing problem is ADRs and lack of effect from the therapy. ADRs such as extrapyramidal symptoms, neurological disorders, somatic, vegetative and endocrine 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 reduces compliance, and in some cases is the reason for refusing treatment. Against this background, the possibility of conducting PGx at the initial stages of therapy is of particular importance, since a wider introduction of predictive PGx and a personalized approach to psychopharmacotherapy in real clinical practice can help to significantly increase the effectiveness and safety of antipsychotic therapy and improve the formation of satisfactory compliance in a patient with a mental disorder, which in general will contribute to an increase in his social functioning and quality of life.

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