

# Genetic variability of CYP2D6, CYP2C19, and CYP1A2 in patients with treatment resistance to antipsychotics and antidepressants

Tatiana A. Zhiganova<sup>1</sup>, Evgenia A. Radkova<sup>2</sup>

<sup>1</sup> Dynasty Medical Centers, Saint Petersburg, Russia

<sup>2</sup> OST-RUS, Saint Petersburg, Russia

**Corresponding author:** Tatiana A. Zhiganova, Dynasty Medical Centers, 5B Lenin St., 197101 Saint Petersburg, Russia; Email: askclinpharm@yandex.ru

**Received:** 12 February 2025 ♦ **Accepted:** 24 April 2025 ♦ **Published:** 29 August 2025

**Citation:** Zhiganova TA, Radkova EA. Genetic variability of CYP2D6, CYP2C19, and CYP1A2 in patients with treatment resistance to antipsychotics and antidepressants. *Folia Med (Plovdiv)* 2025;67(4):e149527. doi: 10.3897/folmed.67.e149527.

## Abstract

**Aim:** The study objective was to assess the frequency of gene alleles responsible for the metabolism and elimination of drugs in treatment-resistant patients to antipsychotics and/or antidepressants.

**Materials and methods:** The frequency of CYP2D6, CYP2C19, and CYP1A2 gene alleles was studied in 133 patients aged 18–70 years in comparison with a healthy population.

**Results:** Patients with treatment resistance to antipsychotics and/or antidepressants demonstrated the increased allele frequency of CYP2D6 \*3 (4.5% vs. 1.0%, OR 4.5,  $p=0.003$ ), CYP2C19 \*17 (24.4% vs. 15.4%, OR 1.78,  $p=0.027$ ), CYP1A2 \*1A (68.5% vs. 41.4%, OR 3.03,  $p<0.001$ ), decreased allele frequency of CYP2C19 \*1 (61.3% vs. 88.3%, OR 0.21,  $p<0.001$ ) and CYP1A2 \*1F (30.4% vs. 58.6%,  $p<0.001$ ). The frequency of CYP2D6 \*5 allele was higher in females (3.8% vs. 0% in males, OR 11.6,  $p=0.029$ ). No age difference was found in CYP2D6, CYP2C19, and CYP1A2 alleles frequencies in the subgroups of patients aged 18–30 years versus 31–70 years.

**Conclusion:** The observed difference in the genotype prevalence of CYP2D6, CYP2C19, and CYP1A2 in patients with antipsychotic and/or antidepressant resistance allows us to recommend pharmacogenetic testing for routine clinical practice in order to select the most effective and safe treatment for patients with antipsychotic and antidepressant resistance.

## Keywords

allele polymorphism, cytochrome, pharmacogenetic testing

## Introduction

The pharmacotherapy of neuropsychiatric disorders is distinguished by significant inter-individual variability in drug response as well as the emergence of side effects that prevent further dose increases to achieve a clinical effect.<sup>[1]</sup> Treatment resistance (TR) to antipsychotics (AP) and antidepressants (AD) is defined as a failure to achieve a full or sustained remission of the symptoms after the treatment with at least two different drugs used in the appropriate doses for 6–8 weeks.<sup>[2]</sup>

TR to AP is diagnosed in 30%–60% of patients<sup>[3]</sup>, while TR to AD is found in 33%–55% of patients<sup>[4,5]</sup>. TR is one of the main reasons for increasing the cost of treatment for psychiatric patients.<sup>[6]</sup>

One of the primary factors contributing to TR is a genetic variation in the proteins involved in drug metabolism, particularly cytochromes such as CYP2D6, CYP2C19, and CYP1A2, which play a key role in metabolizing most APs and ADs.<sup>[7,8]</sup>

Different polymorphisms in CYP2D6, CYP2C19, and CYP1A2 cause the production of proteins with varying lev-

els of enzyme activity. As a result, individuals can be classified as extensive (normal) metabolizers (EM), poor metabolizers (PM), intermediate metabolizers (IM), or ultrarapid metabolizers (UM).<sup>[7,9]</sup> Slow drug metabolism in PMs leads to high plasma drug concentration and puts patients at high risk for side effect development. Therefore, a lower dosing regimen is preferred for such patients. Increased CYP activity in UMs causes rapid drug metabolism and low drug plasma levels. Such patients will require higher drug doses to achieve the therapeutic effect.<sup>[8,10]</sup>

## CYP2D6

CYP2D6 EMs bear \*1 allele variants associated with the normal enzymatic function, whereas the alleles CYP2D6 \*3, \*4, \*5, and \*6 code proteins with no function.<sup>[7]</sup> CYP2D6 PMs are at increased risk of side effects, such as the development of suicidal ideation or AD-induced mania during the treatment.<sup>[11]</sup> The FDA issued a black box warning for selective serotonin reuptake inhibitors (SSRIs)<sup>[12]</sup>, requiring caution and close monitoring at the start of treatment, while CYP2D6 UMs demonstrated better response to venlafaxine treatment and remission in patients with major depressive disorder<sup>[13]</sup>.

## CYP2C19

The CYP2C19 \*1 allele variant codes an enzyme with a normal function; the CYP2C19 \*17 allele increases CYP2C19 activity, the alleles CYP2C19 \*2 and \*3 are responsible for the loss of protein function.<sup>[7]</sup> CYP2C19 metabolizes escitalopram, citalopram, and sertraline.<sup>[7,14]</sup> CYP2C19 PMs are at higher risk of the side effects developing during the treatment with escitalopram, leading to the treatment discontinuation, while low efficacy occurs in UMs.<sup>[15]</sup>

## CYP1A2

The CYP1A2 enzyme is encoded by the CYP1A2 gene and is responsible for the metabolism of agomelatine, duloxetine, mirtazapine, olanzapine, and clozapine.<sup>[16]</sup> CYP1A2 \*1A allele codes protein with normal function; \*1C variant is associated with a decreased enzyme activity.<sup>[7]</sup> The CYP1A2 \*1F variant codes a protein with decreased function, it is highly inducible by tobacco smoke and cruciferous vegetables, leading to increased enzyme activity.<sup>[17,18]</sup>

## Aim

The current study sought to investigate the allele frequency of CYP2D6, CYP2C19, and CYP1A2 in TR psychiatric patients, comparing them to the general healthy population, as well as by age and sex subgroups.

## Materials and methods

This was a retrospective observational study by design that used pharmacogenetic (PG) test data from 133 TR patients who received AP or/and AD as outpatients in Saint Petersburg, Russia.

Treatment resistance is defined as the presence of any of the following criteria: (1) frequent hospitalizations– at least twice a year–during treatment with AP and/or AD; (2) persistent symptoms after two or more attempts at treatment with two drugs at adequate doses with an assessment of efficacy after at least 6 weeks of treatment; (3) side effects during treatment that prevent dose escalation to achieve a response.

PG testing was performed in the MedLab laboratory (Saint Petersburg, Russia). Cytochrome CYP2D6 (alleles \*1, \*3, \*4, \*5, \*6), CYP2C19 (alleles \*1, \*2, \*3, \*17), and CYP1A2 (alleles \*1A, \*1F, \*1C) polymorphisms were assessed. CYP2D6 and CYP2C19 testing was performed in 133 patients (266 alleles), and CYP1A2 testing was performed in 130 patients (260 alleles).

The retrospective nature of the study precluded the acquisition of patients' informed consent. However, prior to real-world routine medical procedures, patients' rights and privacy were protected in accordance with applicable local regulations. Written consent was obtained from each patient before admission to the outpatient hospital for blood collection at the medical laboratory. Personal data were processed and stored in compliance with the Russian Federation law N 152-FZ, Personal Data, to follow confidentiality standards. To ensure patient privacy, all patient data used in this study were anonymized.

The findings were compared with previously published data from a healthy population in Central and Northwestern Russia. An additional comparison was carried out between subgroups of different sexes and ages: women versus men, and patients aged 31 to 70 versus patients aged 18 to 30.

Statistical analysis was performed with Python 3.11. Odds Ratios with 95% confidence intervals were calculated, Pearson  $\chi^2$ , and Fisher criteria tests were used for comparison of proportions.

## Results

In total, data of 133 patients were included in the analysis, 67 males (50.4%) and 66 females (49.6%) aged 18 to 70 years (mean: 32.7; median: 31; [Q1; Q3] interquartile range: 24; 38).

Schizophrenia, schizotypal, and delusional disorders (F20-F29) were diagnosed in 92 patients (69.2%); affective disorders (F30-F39) and neurotic, stress-related, and somatoform disorders (F40-48) in 28 (21.0%) patients; organic, including symptomatic mental disorders (F00-09) and disorders of personality and behavior in adults (F60-61), were identified in 13 patients (9.8%). Sex and age subgroups did not differ in median age, sex, and diagnoses distribution.

**Table 1** demonstrates the frequency of CYP2D6 alleles in TR patients in comparison with the healthy population. An increased frequency of the slow \*3 allele was found in TR patients as compared to the control group (4.5% vs. 1.0%, OR 4.5,  $p=0.003$ ). All TR patients bearing the slow \*5 allele were females, allele frequency made up 3.8% vs. 0% in males, OR 11.6,  $p=0.029$ ; no difference was found in the age subgroups, with a trend to increased frequency of \*5 allele in patients aged 18–30 years (3.1% vs. 0.7%). A trend towards a decreased frequency of the non-functional allele \*6 (0.4% vs. 1.2%) and increased frequency of gain-function \*1NUM allele of CYP2D6 was revealed (1.7% vs. 3.0%).

**Table 2** shows the frequency of CYP2C19 alleles in TR patients. The wild allele (\*1) of CYP2C19 in the TR group made up 61.3% and was lower than in the control group (88.3%, OR 0.21,  $p<0.001$ ) with the simultaneous increase in the frequency of the ultrarapid allele \*17 (24.4% vs. 15.4%, OR 1.78,  $p=0.027$ ) with no sex and age differences between subgroups. A slight trend to the increased \*17 allele frequency occurred in patients of the 31-70-year age subgroup in comparison to the 18-30-year age subgroup (28.3% vs. 20.3%).

**Table 3** shows the frequency of CYP1A2 wild allele \*1A in TR patients was 68.5% versus 41.4% in the control group

(OR 3.03,  $p<0.001$ ), with the simultaneous decrease in the frequency of allele \*F (30.4% vs. 58.6%, OR 0.31,  $p<0.001$ ). No sex and age differences were found.

In addition, we calculated the number of patients bearing at least one combination of gain-function allele (CYP2D6 \*1NUM, CYP2C19 \*17, and CYP1A2 \*1F in smoking patients) and non-functional allele (CYP2D6 \*3 and \*4, CYP2C19 \*2 and \*3, CYP1A2 \*1F (in non-smokers) and \*1C. A prevalence of patients bearing combinations of such alleles made up 19.5% (26 of 133 patients) of the total TR population.

## Discussion

Although pharmacogenetic testing is currently available in medical laboratories, it is not widely used in routine psychiatric practice. Traditionally, choosing the optimal anti-psychotic (AP) or antidepressant (AD) is done through a trial-and-error process, which can be very time-consuming, as the treatment response to APs and ADs should be assessed after 4–8 weeks of drug intake.

This study demonstrated that the patients with TR to AP and/or AD differ from the healthy population by the

**Table 1.** Frequency of CYP2D6 alleles in TR patients (TR group) in comparison with the healthy Russian population (Control<sup>[19]</sup>)

| CYP2D6 allele      | Control<br>N=580<br>n (%) | TR group<br>N=266<br>n (%) | TR subgroups by sex     |                           | TR subgroups by age (years) |                         |
|--------------------|---------------------------|----------------------------|-------------------------|---------------------------|-----------------------------|-------------------------|
|                    |                           |                            | Males<br>N=134<br>n (%) | Females<br>N=132<br>n (%) | 18–30<br>N=128<br>n (%)     | 31–70<br>N=138<br>n (%) |
| <b>*1 allele</b>   | 411 (70.9%)               | 201 (75.6%)                | 103 (76.9%)             | 98 (74.2%)                | 96 (75.0%)                  | 105 (76.1%)             |
| OR [95% CI]        | 1.26 [0.9, 1.75]          |                            | 0.87 [0.5, 1.52]        |                           | 1.06 [0.61, 1.85]           |                         |
| <i>p</i>           | 0.156                     |                            | 0.619                   |                           | 0.837                       |                         |
| <b>*3 allele</b>   | 6 (1.0%)                  | 12 (4.5%)                  | 6 (4.5%)                | 6 (4.5%)                  | 6 (4.7%)                    | 6 (4.3%)                |
| OR [95% CI]        | 4.5 [1.7, 12.5]           |                            | 1.02 [0.32, 3.25]       |                           | 0.92 [0.29, 2.93]           |                         |
| <i>p</i>           | 0.003                     |                            | 0.999                   |                           | 0.999                       |                         |
| <b>*4 allele</b>   | 105 (18.1%)               | 39 (14.7%)                 | 22 (16.4%)              | 17 (12.9%)                | 17 (13.3%)                  | 22 (15.9%)              |
| OR [95% CI]        | 0.77 [0.5, 1.1]           |                            | 0.75 [0.38, 1.49]       |                           | 1.24 [0.63, 2.46]           |                         |
| <i>p</i>           | 0.216                     |                            | 0.415                   |                           | 0.540                       |                         |
| <b>*5 allele</b>   | 14 (2.4%)                 | 5 (1.9%)                   | 0 (0.0%)                | 5 (3.8%)                  | 4 (3.1%)                    | 1 (0.7%)                |
| OR [95% CI]        | 0.77 [0.27, 2.17]         |                            | 11.6 [0.63, 211.9]      |                           | 0.23 [0.03, 2.09]           |                         |
| <i>p</i>           | 0.804                     |                            | 0.029                   |                           | 0.199                       |                         |
| <b>*6 allele</b>   | 7 (1.2%)                  | 1 (0.4%)                   | 0 (0.0%)                | 1 (0.8%)                  | 0                           | 1 (0.7%)                |
| OR [95% CI]        | 0.31 [0.04, 2.5]          |                            | 3.07 [0.12, 76.05]      |                           | 2.8 [0.11, 69.36]           |                         |
| <i>p</i>           | 0.447                     |                            | 0.496                   |                           | 0.999                       |                         |
| <b>*3+*4+*5+*6</b> | 132 (22.8%)               | 57 (21.4%)                 | 28 (20.9%)              | 28 (22.0%)                | 27 (21.1%)                  | 30 (21.7%)              |
| OR [95% CI]        | 0.92 [0.65, 1.32]         |                            | 1.07 [0.60, 1.92]       |                           | 1.04 [0.58, 1.87]           |                         |
| <i>p</i>           | 0.666                     |                            | 0.831                   |                           | 0.898                       |                         |
| <b>*1NUM</b>       | 10 (1.7%)                 | 8 (3.0%)                   | 3 (2.2%)                | 5 (3.8%)                  | 5 (3.9%)                    | 3 (2.2%)                |
| OR [95% CI]        | 1.75 [0.68, 4.55]         |                            | 1.72 [0.40, 7.35]       |                           | 0.55 [0.13, 2.35]           |                         |
| <i>p</i>           | 0.303                     |                            | 0.499                   |                           | 0.487                       |                         |

**Table 2.** Frequency of CYP2C19 alleles in TR patients (TR group) in comparison with the healthy Russian population (Control<sup>[19,20]</sup>)

| CYP2C19 allele      | Control<br>N=580<br>n (%) | TR group<br>N=266<br>n (%) | TR subgroups by sex     |                           | TR subgroups by age (years) |                         |
|---------------------|---------------------------|----------------------------|-------------------------|---------------------------|-----------------------------|-------------------------|
|                     |                           |                            | Males<br>N=134<br>n (%) | Females<br>N=132<br>n (%) | 18–30<br>N=128<br>n (%)     | 31–70<br>N=138<br>n (%) |
| <b>*1 allele</b>    | 512 (88.3%)               | 163 (61.3%)                | 82 (61.2%)              | 81 (61.4%)                | 79 (61.7%)                  | 84 (60.9%)              |
| OR [95% CI]         | 0.21 [0.14, 0.30]         |                            | 1.01 [0.62, 1.65]       |                           | 0.96 [0.59, 1.57]           |                         |
| <i>p</i>            | <0.001                    |                            | 0.977                   |                           | 0.887                       |                         |
| <b>*2 allele</b>    | 65 (11.2%)                | 37 (13.9%)                 | 17 (12.7%)              | 20 (15.2%)                | 22 (17.2%)                  | 15 (10.9%)              |
| OR [95% CI]         | 1.28 [0.83, 1.96]         |                            | 1.23 [0.61, 2.47]       |                           | 0.59 [0.29, 1.2]            |                         |
| <i>p</i>            | 0.262                     |                            | 0.561                   |                           | 0.137                       |                         |
| <b>*3 allele</b>    | 2 (0.3%)                  | 1 (0.4%)                   | 0 (0.0%)                | 1 (0.8%)                  | 1 (0.8%)                    | 0 (0.0%)                |
| OR [95% CI]         | 1.08 [0.1, 12.5]          |                            | 3.07 [0.12, 76.05]      |                           | 0.31 [0.01, 7.68]           |                         |
| <i>p</i>            | 0.999                     |                            | 0.496                   |                           | 0.481                       |                         |
| <b>*2+*3 allele</b> | 67 (11.6%)                | 38 (14.3%)                 | 17 (12.7%)              | 21 (15.9%)                | 23 (18.0%)                  | 15 (10.9%)              |
| OR [95% CI]         | 1.28 [0.83, 1.96]         |                            | 1.30 [0.65, 2.59]       |                           | 0.56 [0.28, 1.13]           |                         |
| <i>p</i>            | 0.263                     |                            | 0.453                   |                           | 0.098                       |                         |
| <b>*17 allele</b>   | 25 (15.4%)*               | 65 (24.4%)                 | 35 (26.1%)              | 30 (22.7%)                | 26 (20.3%)                  | 39 (28.3%)              |
| OR [95% CI]         | 1.78 [1.07, 2.94]         |                            | 0.83 [0.47, 1.45]       |                           | 1.55 [0.88, 2.74]           |                         |
| <i>p</i>            | 0.027                     |                            | 0.520                   |                           | 0.132                       |                         |

\*Data are presented for N=162.

**Table 3.** Frequency of CYP1A2 alleles in TR patients (TR group) in comparison with the healthy Russian population (Control<sup>[21,22]</sup>)

| CYP1A2 allele     | Control<br>N=608<br>n (%) | TR group<br>N=260<br>n (%) | TR subgroups by sex     |                           | TR subgroups by age (years) |                         |
|-------------------|---------------------------|----------------------------|-------------------------|---------------------------|-----------------------------|-------------------------|
|                   |                           |                            | Males<br>N=132<br>n (%) | Females<br>N=128<br>n (%) | 18–30<br>N=126<br>n (%)     | 31–70<br>N=134<br>n (%) |
| <b>*1A allele</b> | 252 (41.4%)               | 178 (68.5%)                | 91 (67.9%)              | 87 (67.4%)                | 87 (68.0%)                  | 91 (67.4%)              |
| OR [95% CI]       | 3.03 [2.22, 4.16]         |                            | 0.98 [0.58, 1.64]       |                           | 0.97 [0.58, 1.63]           |                         |
| <i>p</i>          | <0.001                    |                            | 0.935                   |                           | 0.922                       |                         |
| <b>*1F allele</b> | 356 (58.6%)               | 79 (30.4%)                 | 40 (29.9%)              | 39 (30.2%)                | 38 (29.7%)                  | 41 (30.4%)              |
| OR [95% CI]       | 0.31 [0.23, 0.42]         |                            | 1.02 [0.60, 1.73]       |                           | 1.03 [0.61, 1.75]           |                         |
| <i>p</i>          | <0.001                    |                            | 0.946                   |                           | 0.904                       |                         |
| <b>*1C allele</b> | 2 (1.3%)*                 | 3 (1.2%)                   | 1 (2.2%)                | 2 (2.3%)                  | 1 (2.3%)                    | 4 (2.2%)                |
| OR [95% CI]       | 1.10 [0.18, 6.65]         |                            | 1.04 [0.21, 5.25]       |                           | 0.95 [0.19, 4.8]            |                         |
| <i>p</i>          | 0.999                     |                            | 0.999                   |                           | 0.999                       |                         |

\*Data are presented for N=158.

increased frequency of the non-functional CYP2D6 \*3 allele, ultrarapid (gain-function) CYP2C19 \*17 allele with the concomitant decrease of the wild allele \*1; and the increased frequency of the CYP1A2 \*1A wild allele with a concomitant decrease in \*1F allele frequency.

All patients bearing the CYP2D6 \*5 allele were females; the allele frequency made up 3.8% vs. 0% in males (OR 11.6,  $p=0.029$ ). That was the only sex difference found.

No difference was found in the age subgroups. Our previous study demonstrated both age and sex difference in

MDR1 C3435T genotype frequency in TR patients to AP and AD.<sup>[23]</sup>

During the literature review, we identified just one study that found no difference in CYP2D6 and CYP2C19 allele variants between Bulgarian psychiatric patients and general European population<sup>[24]</sup>; thus, we would cautiously suggest that the TR patient population differs from the general population of psychiatric patients.

It should be pointed out that the study results demonstrated the heterogeneity of the TR patient population: a

combination of both non-functional and gain-function alleles that includes the patients with side effects as well as patients with no treatment effect despite high doses of AP and AD. A calculated number of patients with combinations of non-functional and gain-function alleles in TR patients made up 20%, which supports the idea of using the personalized approach of PG testing for the choice of the safest and most effective drug in the population of TR patients.

The study results allow us to suggest that the most effective drugs in TR patients for AP and AD will be substrates of CYP1A2, such as olanzapine, clozapine, mirtazapine, and duloxetine<sup>[25]</sup>, as their effects would be predictable due to the high prevalence of the wild (normal function) 1A allele and decreased frequency of allele 1F.

The presence of the non-functional CYP2D6 \*3 allele will require the use of CYP2D6 substrates (risperidone, zuclopenthixol, fluvoxamine, imipramine, paroxetine, etc.) in decreased doses to prevent side effects from developing. The use of venlafaxine in patients with a decreased activity of CYP2D6 will be less effective as the formation of the active metabolite desvenlafaxine, potent inhibitor of nor-epinephrine reuptake, will be decreased.<sup>[26]</sup> The presence of the CYP2C19 \*17 ultrarapid allele may decrease the efficacy of escitalopram, citalopram, sertraline, and haloperidol (partially).

It should be noted that AP and AD drugs are usually metabolized by several metabolic pathways with the involvement of cytochromes, which makes the choice of the proper drug for TR patients challenging. The use of PG testing in the psychiatric practice leads in 48.5% reduction of treatment costs in the PG-guided arm in comparison to the standard trial-and-error approach.<sup>[27]</sup>

However, despite the established cost-effectiveness of PG testing, its integration into routine clinical practice remains limited. This is partly due to insufficient awareness among psychiatrists regarding its benefits, even with the availability of relevant guidelines developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and PharmGKB. Additionally, selecting the optimal medication for individual patients requires an in-depth understanding of drug metabolism and gene-drug interactions specific to APs and ADs. To address this gap, collaboration with a trained clinical pharmacologist could improve decision-making by interpreting PG results within the context of patient-specific factors.

To complement physician and clinical pharmacologist education in PG testing implementation, we propose the development of a therapeutic algorithm or clinical decision support system. Such tools could integrate patient-specific PG data, age, and sex to guide tailored treatment strategies. The findings from this study could be used for the development of such algorithms.

Implementing PG-guided medication selection could enhance treatment response rates for ADs and APs, reduce the likelihood of adverse effects, and improve patient compliance. PG testing thus represents a valuable tool for

optimizing therapeutic efficacy, fostering treatment compliance, and improving patients' quality of life.

The primary limitation of this study is its relatively small sample size. Furthermore, the generalizability of the findings is constrained by the fact that most participants were recruited from a single city (Saint Petersburg), which may not fully represent the broader population of western Russia.]

## Conclusions

Our study demonstrated the difference in the frequency of CYP2D6, CYP2C19, and CYP1A2 polymorphisms, as well as sex difference in CYP2D6 polymorphism distribution in patients with TR to AP and/or AD in comparison to the healthy population.

The identified difference allows us to recommend PG testing of CYP2D6, CYP2C19, and CYP1A2 to personalize treatment selection for patients. It may improve patient compliance, quality of medical care, and reduce the treatment cost for the healthcare system.

Thus, PG-guided treatment choice may be helpful in a psychiatric practice and favorable for the healthcare system as it is cost-effective.

## Funding

The authors have no funding to report.

## Competing interests

The authors have declared that no competing interests exist.

## Acknowledgements

The authors acknowledge Elena V. Schepkina (Russian Presidential Academy of National Economy and Public Administration, Research and Practical Clinical Center for Diagnostics and Telemedical Technologies, Moscow, Russia).

## References

1. Leichsenring F, Steinert C, Rabung S, et al. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: An umbrella review and meta-analytic evaluation of recent meta-analyses. *World Psychiatry* 2022; 21:133–45.
2. Howes OD, Thase ME, Pillinger T. Treatment resistance in psychiatry: state of the art and new directions. *Mol Psychiatry* 2022; 27(1):58–72.
3. Kane JM. Treatment of schizophrenia. *Schizophr Bull* 1987; 13:133–56.
4. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 2001; 178(3):234–41.

5. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR\*D: implications for clinical practice. *Am J Psychiatry* 2006; 163(1):28–40.
6. Thomas L, Kessler D, Campbell J, et al. Prevalence of treatment-resistant depression in primary care: cross-sectional data. *Br J Gen Pract* 2013; 63(617):e852–58.
7. Mrazek DA. *Psychiatric Pharmacogenomics*. New York: Oxford University Press; 2010; 280.
8. Lane H-Y, Tsai GE, Lin E. Assessing gene-gene interactions in pharmacogenomics. *Mol Diagn Ther* 2012; 16:15–27.
9. Durham D, Thirumaran R. *Psychiatric Pharmacogenetics: From concepts to cases*. New York: Fortis Caliga Academic Press; 2017; 147.
10. Skokou M, Karamperis K, Koufaki MI, et al. Clinical implementation of preemptive pharmacogenomics in psychiatry. *EBioMedicine* 2024; 101:105009.
11. Lucire Y, Crotty C. Antidepressant-induced akathisia-related homicides associated with diminishing mutations in metabolizing genes of the CYP450 family. *Pharmacogenomics Pers Med* 2011; 4:65–81.
12. Fornaro M, Anastasia A, Valchera A, et al. The FDA “Black Box” warning on antidepressant suicide risk in young adults: more harm than benefits? *Front Psychiatry* 2019; 10:294.
13. Ahmed AT, Biernacka JM, Jenkins G, et al. Pharmacokinetic-pharmacodynamic interaction associated with venlafaxine-XR remission in patients with major depressive disorder with history of citalopram/escitalopram treatment failure. *J Affect Disord* 2019; 246:62–8.
14. Van Westrhenen R, Aitchison KJ, Ingelman-Sundberg M, et al. Pharmacogenomics of antidepressant and antipsychotic treatment: how far have we got and where are we going? *Front Psychiatry* 2020; 11:94.
15. PharmGKB. Escitalopram. Available from: <https://www.pharmgkb.org/genotype> (accessed 16 July 2024).
16. Alchakee A, Ahmed M, Eldohaji L, et al. Pharmacogenomics in psychiatry practice: the value and the challenges. *Int J Mol Sci* 2022; 23(21):13485.
17. Eum S, Lee AM, Bishop JR. Pharmacogenetic tests for antipsychotic medications: clinical implications and considerations. *Dialogues Clin Neurosci* 2016; 18(3):323–37.
18. Howes OD, Thase ME, Pillinger T. Treatment resistance in psychiatry: state of the art and new directions. *Mol Psychiatry* 2022; 27(1):58–72.
19. Gaikovitch EA, Cascorbi I, Mrozikiewicz PM, et al. Polymorphisms of drug-metabolizing enzymes CYP2C9, CYP2C19, CYP2D6, CYP1A1, NAT2 and of P-glycoprotein in a Russian population. *Eur J Clin Pharmacol* 2003; 59(4):303–12.
20. Mirzaev KB, Zelenskaya EM, Barbarash OL, et al. CYP2C19 polymorphism frequency in Russian patients in Central Russia and Siberia with acute coronary syndrome. *Pharmacogenomics Pers Med* 2017; 10:107–14.
21. Korytina G, Kochetova O, Akhmadishina L, et al. Polymorphisms of cytochrome P450 genes in three ethnic groups from Russia. *Balkan Med J* 2012; 29(3):252–60.
22. Cabaleiro T, López-Rodríguez R, Román M, et al. Pharmacogenetics of quetiapine in healthy volunteers: association with pharmacokinetics, pharmacodynamics, and adverse effects. *Int Clin Psychopharmacol* 2015; 30(2):82–8.
23. Zhiganova T, Shkadova, S, Sergeeva T, et al. Genotyping of CYP2D6, CYP2C19, CYP1A2 and p-glycoprotein MDR1 (C3435T) in patients with treatment resistance to antipsychotics and antidepressants: step to implementation of personalized approach into clinical practice. *Russ J Exp Clin Pharmacol* 2024, 87(11):13–9.
24. Ivanov HY, Grigorova D, Lauschke VM, et al. CYP2C19 and CYP2D6 genotypes and metabolizer status distribution in a Bulgarian psychiatric cohort. *J Pers Med* 2022; 12(7):1187.
25. U.S. Food & Drug Administration. Healthcare professionals: FDA’s examples of drugs that interact with CYP enzymes and transporter systems. Available from: <https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems> (accessed 12 December 2024).
26. PharmGKB. Genotype information. Available from: <https://www.pharmgkb.org/genotype> (accessed 12 December 2024).
27. Skokou M, Karamperis K, Koufaki MI, et al. Clinical implementation of preemptive pharmacogenomics in psychiatry. *EBioMedicine* 2024; 101:105009