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Article

Frequency of "Poor Transporter" Phenotype Among Patients with Mental Disorders: Pilot Study

Irina R. Boyko[1], Natalia A. Shnayder [1,2*], Violetta V. Grechkina[1,3], Olga E. Savelieva[1]

[1] V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology, 192019 Saint Petersburg, Russia;
[2] V.F. Voino-Yasenetsky Krasnoyarsk State Medical University of Russia, 660022 Krasnoyarsk, Russia;
[3] City Psychiatric Hospital №6, 191167, St. Petersburg, Russia
*Correspondence: naschnaider@yandex.ru (N.A.S.); Tel.: +7-(812)-620-02-22 (N.A.S.)

Abstract: The problem of psychopharmacotherapy safety is actively studied, but remains unresolved, despite the development of new generations of psychotropic drugs (PDs). Neurotoxic adverse drug reactions (ADRs) are one of the leading causes of pseudo-resistance of mental disorders and patient disability. The development of neurotoxic ADRs is genetically determined, and caused by a slowdown in the efflux of PDs from the brain into the blood through the blood-brain barrier. Of the three transport proteins involved in the efflux of PDs, the most clinically significant and studied is glycoprotein P, encoded by the *MDR1* (*ABCB1*) gene. This transport protein is involved in the efflux of a large number of PDs used in real clinical practice of a psychiatrist. **Objective**: To study the frequency of the non-functional allele 3435T of the single-nucleotide variant rs1045642 of the *MDR1* (*ABCB1*) gene in patients with mental disorders living in the Northwestern region of the Russia. **Methods**: The study included 71 Caucasians patients with mental disorders (34 male and 37 female). Mean age of the study participants was 35.1±16 years). Real-time polymerase chain reaction used for pharmacogenetic testing. **Results**: The frequency of the nonfunctional homozygous genotype *3435TT* (phenotype "poor transporter") was 19.7%, and the frequency of the low-functional heterozygous genotype *3435CT* (phenotype "intermediate transporter") was 57.7%. The allelic frequency of T rs1045642 of the *MDR1* (*ABCB1*) gene in Caucasians patients with mental disorders living in the Northwestern region of the Russia was 97.1%. **Conclusions:** The frequency the nonfunctional allele 3435T of the *MDR1 (ABCB1)* gene associated with a slowdown in PDs efflux through BBB in patients with mental disorders living in the Northwestern region of the Russia is high, which explains the need for a wider introduction of this method of personalized medicine into real psychiatric practice.

Keywords: *efflux of psychotropic drugs; pharmacogenetic testing; neurotoxicity; adverse drug reactions; prognosis; Caucasians.*

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1. INTRODUCTION

Mental disorders are a pressing health issue worldwide, and different approaches are used to treat them [**1**]. For the treatment of mental disorders, various pharmacological groups of psychotropic drugs (PDs) are used, including antipsychotics, antidepressants, mood stabilizers, anxiolytics, anticonvulsants, etc. However, despite the development of new generations of PDs, the optimal balance between their effectiveness and safety is not achieved in more than 30% of cases. The current problem is a low therapeutic response (therapeutic resistance or pseudoresistance) and adverse drug reactions (ADRs), among which neurotoxic ADRs (worsening of the course of a mental disorder, extrapyramidal disorders, cognitive disorders, sleep disorders, etc.) are of particular importance. Therapeutic resistance, which must be verified with pseudoresistance, and neurotoxicity of PDs

depend on modifiable (PD, dosage, consideration of compensation for other diseases, etc.) and non-modifiable (sex, age, genetic predisposition) risk factors **[2, 3].**

Genetic predisposition to the development of neurotoxic ADRs includes genetically determined poor liver metabolism and transport through the blood-brain barrier (BBB) of a wide range of PDs. At the same time, the most studied type of transport is efflux, the mechanism of which consists in the active transfer of PDs from neurons of the brain into the blood by means of a protein pump [**4**].

Among all the transport proteins that provide the efflux of PDs, the most clinically significant and studied is glycoprotein P (P-gp), encoded by the *MDR1* gene (according to the new nomenclature *ABCB1*), OMIM: 171050 [**5**].

Substrates for P-gp are the drugs presented in **Table 1**, and inhibitors are drugs presented in **Table 2**, in addition, inhibit the functional activity of P-gp [**6**] can some nutrients, including green tea, coffee, citrus fruits, cocoa, etc., as well as preparations based on plant raw materials (herbal medicines) [**7**].

Table 1. Drugs transported with the participation of the P-glycoprotein (substrates)

Pharmacological group	Psychotropic drugs
Anticonvulsants	Carbamazepine, oxcarbazepine, phenytoin, vigabatrin, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, phenobarbital, tiagabine, topiramate, zonisamide
Antidepressants	Amitriptyline, citalopram, desipramine, doxepin, fluoxetine, fluvoxamine, imipramine, nortriptyline, sertraline, paroxetine, trimipramine, venlafaxine, citalopram, escitalopram
Antipsychotics	Amisulpride, sulpiride, aripiprazole, chlorpromazine, trifluoperazine, clozapine, olanzapine, quetiapine, risperidone, paliperidone
Anxiolytics	Hydroxyzine
Antiretroviral drugs	Amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir
Steroids	Aldosterone, dexamethasone, hydrocortisone
Cardioactive drugs	Amiodarone, digoxin, diltiazem, quinidine, verapamil
Antihistamines	Cetirizine, desloratadine, fexofenadine

Table 2. Examples of classical P-glycoprotein inhibitors by first and new generation **[7]**.

First Generation	Second Generation	Third Generation
Verapamil	(R)-Verapamil	Tariquidar
Cyclosporine A	Dexniguldipine	Zosuquidar
Vincristine	Elacridar	Laniquidar
Reserpine	Biricodar	ONT-093
Quinidine	Dofequidar	Mitotane
Tamoxifen	Trifluoperazine	Annamycin
Trifluoperazine	Valspodar	

This explains the importance of an integrated approach to assessing primary and secondary inhibition or blockade of the efflux of PD sthrough the BBB in a particular patient and for a specific PD prescribed in mono- or polytherapy. Polytherapy with PDs also requires assessment of drug-drug interactions, which can significantly affect the rate of efflux of PDs taken from various pharmacological groups through the BBB, increasing or decreasing the risk and severity of neurotoxic ADRs and pseudoresistance **[2, 6**].

Thus, recently the problem of pseudoresistance to PDs in patients with mental disorders has been of great interest, which may be associated not only with the low affinity of PDs to the targets of their action in the central nervous system (CNS) [**8**] and/or metabolic impairment in the liver, but also with neurotoxic ADRs caused by slowing down the efflux of PDs through the BBB. Violation of efflux leads to the accumulation of PDs in the CNS with an increase in its concentration to a toxic level and aggravation of symptoms of

mental disorders (for example, hallucinations, psychosis, suicide, etc.). Primary (genetically determined) inhibition or blockade of the efflux of PDs with the participation of P-gp is caused by the carriage of variable (low-functional and non-functional, respectively) alleles of the *MDR1* (*ABCB1*) gene (**Fig. 1**). Single nucleotide variant (SNV) rs1045642C>T of the *MDR1* (*ABCB1*) gene or *3435C>T* (also known as rs1045642A>G) is one of the more studied SNVs in this gene [**9**].

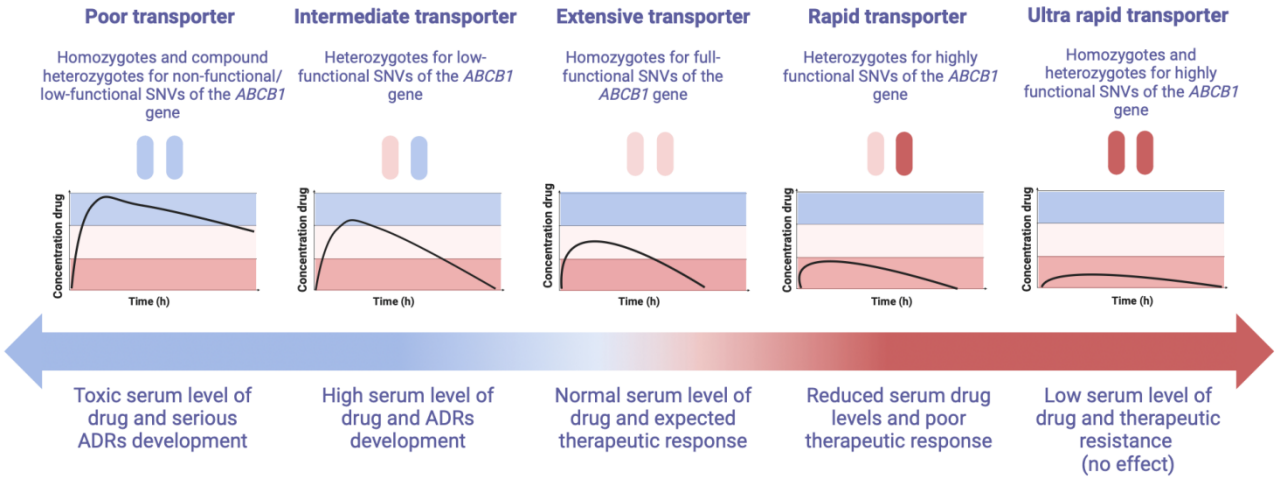

Figure 1. Type of pharmacological profile in patients with mental disorders.

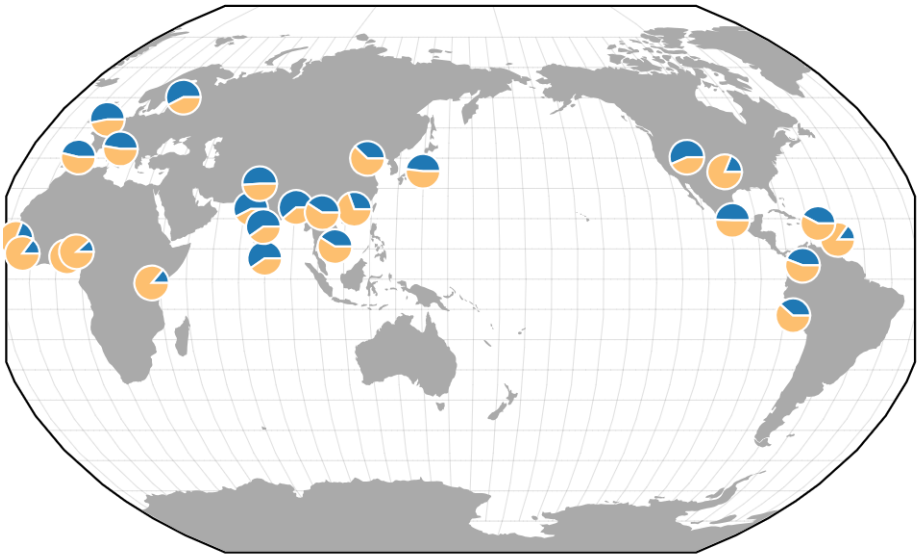

Figure 2. Geography of single nucleotide variant 3435T rs1045642 of *MDR1* (*ABCB1*) gene in the world [**11**].
Note: orange – common (major) allele C, blue – variable allele T (minor).

The *MDR1* (*ABCB1*) gene is expressed in various tissues to protect them from the ADRs of xenobiotics, including PDs. Although this gene is a well-conserved gene, association genetic studies of recent years convincingly demonstrate that some of its SNVs can significantly affect substrate specificity [**10**]. It was previously shown that the frequency

of the synonymous SNV rs1045642 *C>T3435* is the highest in populations of different countries of the world, but may depend on the ethnicity of patients (**Fig. 2**). For example, the allele frequency of the non-functional 3435T allele in the Northern European countries, geographically close to the North-West region of the Russia, exceeds 50% of cases (the allele frequency is 0.575757575758) [**11**]. This explains our choice of this SNV as a priority for inclusion in the pharmacogenetic testing (PGx) screening panel in this region of the Russia. PGx can help practicing psychiatrists understand why patients with mental disorders respond differently to PDs and make more informed decisions about the choice of psychopharmacotherapy. This understanding can shift the medical paradigm in psychiatry towards highly personalized therapeutic strategies [**9, 11**].

2. OBJECTIVE

To study the frequency of the non-functional allele 3435T of SNV rs1045642 of the *MDR1* (*ABCB1*) gene in patients with mental disorders living in the Northwestern region of the Russia.

3. MATERIAL AND METHODS

The study included 71 Caucasians living in the Northwestern Federal District of the Russian Federation. Patients with an established mental illness were recruited for genotyping of the rs1045642 (3435C>T) SNV of *MDR1* (*ABCB1*) gene using real-time PCR at the Laboratory of Molecular Genetic Diagnostics of the Institute of Personalized Psychiatry and Neurology of Bekhterev National Medical Research Center for Psychiatry and Neurology of the Ministry of Health of the Russian Federation in the period from 2021 to 2024. Previously, patients received therapy with PDs, against the background of which symptoms of neurotoxicity developed (cognitive impairment, extrapyramidal disorders, sleep disorders, etc.) or the therapeutic effect was not achieved.

The study materials were samples the peripheral blood of patients collected in VACU-ETTE® vacuum tubes (Greiner Bio-One, Kremsmünster, Austria). A standard method of DNA extraction was used. Genomic DNA was isolated from the nuclei of peripheral blood leukocytes using the DNA-Extran-1 kit (Syntol, Moscow, Russia). All PCRs were performed with negative control. The amplicon containing rs1045642 was amplified from genomic DNA using the following primers: CCACC-GTCTGCCCACTCTGC (forward) and GGCCATCTATC-CACCTATCTAA (reverse). The primers were designed using PrimerSelect 4.05©1993–2000 DNASTAR Inc. software and synthesized by Syntol. Carriage of ABCB1 rs1045642 was determined by real-time PCR with the SNP-Screen kit from ZAO Syntol. The program included preliminary denaturation at 95°C lasting 3 minutes, 40 cycles of denaturation at 95°C for 15 seconds per cycle, and then annealing at 60°C for 40 seconds using Real-Time CFX96 Touch (Bio-Rad Laboratories Inc., Hercules, CA, USA).

4. RESULTS

The study included 71 participants, including: male– 34 (47.9%), female - 37 (52.1%). The average age of the participants in the total sample was 35.1±16 years (**Table 4, Fig. 3**). Distribution of study participants by age: 15 (21.1%) children and adolescents (age ranged from 7 to 20 years, average age 12.6±5 years); 56 (78.9%) adults (age ranged from 21 to 74, average age –40.9±13.04 years).

Table 4. Characteristics of patients by sex and age

Characteristic	Quantity, n	Minimum, years	Maximum, years	M (SE), years	Me (P25; P75), years
Male	34	7	74	33.9±15.71	34.0 (25.0; 40.0)
Female	37	8	72	36.4±17.53	34.0 (27.0; 53.0)

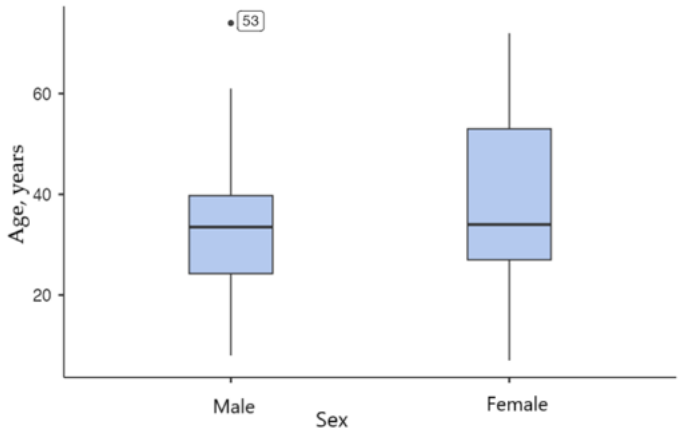

Figure 3. Characteristics of patients by sex and age

We have analyzed the reasons for referring patients with mental disorders to PGx of PDs. As a result, it has been demonstrated that pro-reactive (before the development of ADRs) PGx was prescribed in 22 (31.0%) cases versus 49 (69.0%) cases of reactive (after the development of ADRs) PGx (**Fig. 4**). The adherence of practicing psychiatrists to reactive PGx was 2.2 times higher compared to pro-reactive PGx (p-value < 0.01).

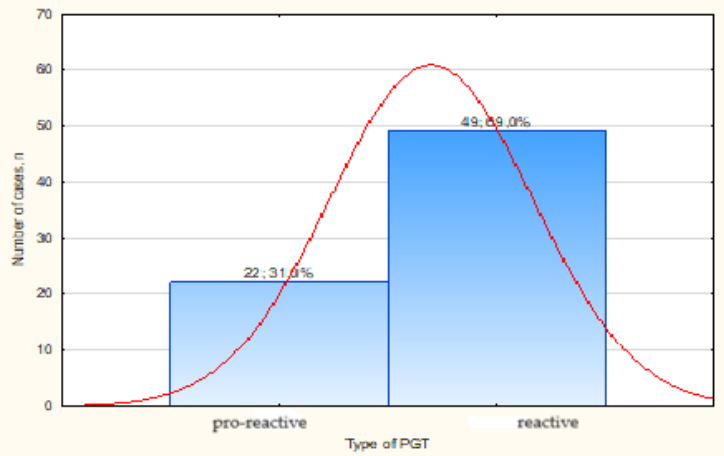

Figure 4. Types of pharmacogenetic testing.

The patients with mental disorders were significantly more likely to be referred to PGx to exclude poor transport of PDs through the BBB after prolonged psychotropic therapy and a long pharmacological history of neurotoxic ADRs and/or resistance to PDs. This finding of our study is an alarming fact, since the possibility of avoiding the development of neurotoxicity and/or therapeutic resistance to PDs by detecting the carrier of the non-functional allele 3435TT of the *MDR1* (*ABCB1*) gene in patients with mental disorders living in the Northwestern region of the Russia is used less often than this it is necessary in real clinical practice. It is important to note that the availability of this method of genetic diagnosis in St. Petersburg and the Leningrad region is quite high, since such studies can be performed in many laboratories in this region. However, it should be recognized that PGx for the identification of patients with unfavorable pharmacogenetic profiles "poor transporter" and "intermediate transporter" is not yet included in the program of state guarantees and can be performed at the

expense of the budget of psychiatric institutions only in severe cases of a mental disorder with a low profile of safety and effectiveness of psychopharmacotherapy. Such difficult clinical cases must be verified and confirmed by experts of the medical commission of a psychiatric medical institution with the participation of a clinical pharmacologist. This explains the high incidence of reactive PGx in our study. Probably, when solving organizational issues in this region and increasing the availability of pro-reactive PGx (as a method for predicting and preventing neurotoxic ADRs and/or therapeutic resistance to PDs) for patients with mental disorders, this diagnostic method could be prescribed more often in the future.

The positive finding of this study is that the number of cases of PGx for children and adolescents with mental disorders is quite high and accounts for about 1/5 of all the cases analyzed by us (21.1%). This is very important, since in such patients the development of neurotoxic ADRs and/or resistance can significantly worsen cognitive functions, socialization and the course of mental disorder, including an increase in the number of cases of antisocial and aggressive behavior. Another positive finding of this study is that the frequency of prescribing pro-reactive PGx in children and adolescents was 1.4 times higher than in adult patients (40.0% in children and adolescents versus 28.6% in adults, p-value < 0.05).

The frequency of the non-functional allele 3435T rs1045642 of the *MDR1* (*ABCB1*) gene in Caucasians patients with mental disorders living in North-Western Russia was high and amounted to 97.2%. Among males with mental disorders, the frequency of this allele was 39.7%, and among females – 56.8%. The frequency of carrying the non-functional allele 3435T in female was 1.4 times higher than among male (p-value < 0.05).

The frequency of the non-functional homozygous genotype 3435TT of the *MDR1* (*ABCB1*) gene associated with the "poor transporter" phenotype in the total sample was 19.7%, and the frequency of the low-functional heterozygous genotype 3435CT associated with the "intermediate transporter" phenotype was 57.7%. The intergroup differences in the frequency of the heterozygous genotype 3435CT, depending on the sex of patients, were significant (55.9% in males versus 59.5% in females, p-value> 0.05). However, the frequency of nonfunctional homozygous genotype 3435TT in female patients was 2.3 times higher than in male patients (11.8% in male versus 27.0% in female, p-value < 0.01).

The results of PGx demonstrated a high incidence of an unfavorable pharmacogenetic profile of the "poor transporter" in both female (predominantly) and male patients. This explains the need to increase the commitment of practicing psychiatrists to the use of PGx (as an objective diagnostic method for predicting and preventing the development of neurotoxic ADRs) and/or resistance to PDs used in adult and pediatric psychiatric practice.

In addition, these results can help in the treatment of middle-aged and elderly patients suffering from mental disorders and having concomitant diseases, including neurodegenerative diseases, cardiovascular diseases, etc., which require additional administration of drugs with a similar efflux pathway. Undoubtedly, such patients need an interdisciplinary approach with the participation of a clinical pharmacologist with practical experience and special training in the field of pharmacogenetics. A polymorbid patient with mental disorders is a serious challenge for practicing psychiatrists, because medications prescribed for concomitant diseases can significantly affect the effectiveness and safety of psychotropic therapy and, accordingly, the course of mental disorder and its outcome.

Table 5. Frequency of alleles and genotypes of the single nucleotide variant rs1045642 of the *MDR1 (ABCB1)* gene in the study groups.

Allele/genotype	Male	Female	p-value
C	41 (60.3%)	32 (43.2%)	p = 0.004
T	27 (39.7%)	42 (56.8%)	X^2 = 11.2
C/C	11 (32.1%)	5 (13.5%)	p = 0.012
C/T	19 (55.9%)	22 (59.5%)	X^2 = 12.9
T/T	4 (11.8%)	10 (27.0%)	

5. DISCUSSION

Our study showed that the frequency of the non-functional allele 3435T of the *MDR1 (ABCB1)* gene in patients with mental disorders living in the Northwestern region of Russia is high and amounts to 97.1%, which exceeds the population frequency of this allele in neighboring regions of the world, including the countries of Northern Europe (**Fig. 2**) [**11**].

6. CONCLUSIONS

On the one hand, our study demonstrated for the first time that the commitment of practicing psychiatrists in the Northwestern region of Russia to the use of reactive PGx is higher compared to proactive PGx. This makes it difficult to identify patients with mental disorders with unfavorable pharmacogenetic profiles of "slow transporter" and "intermediate transporter" before the appointment of PDs or at the stage of titration of their dose. On the other hand, we have demonstrated a high commitment of child and adolescent psychiatrists to the use of proactive (predictive) PGx in this region.

The frequency the non-functional allele 3435T of the *MDR1* (*ABCB1*) gene associated with a slowdown in PDs efflux through BBB in patients with mental disorders living in the Northwestern region of the Russia is high, which explains the need for a wider introduction of this method of personalized medicine into real psychiatric practice.

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Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

1. Neznanov, N.G. A paradigm shift to treat psychoneurological disorders. *Personalized Psychiatry and Neurology* 2021, 1(1): 1-2.

2. Nasyrova, R.F.; Neznanov, N.G. Clinical psychopharmacogenetics. SPb.: DEAN, **2019**, 405 (InRuss.), ISBN 978-5-6043573-7-8.
3. Nasyrova, R.F.; Ivanov, M.V.; Neznanov, N.G. Introduction to psychopharmacogenetics. SPb.: Izdatel'skii tsentr SPb NIPNI im. V. M. Bekhtereva, **2015**, 272 (In Russ.), ISBN 978-5-7452-0020-5.
4. Gorbachev, V.I.; Bragina, N.V. Blood-brain barrier from the point of view of anesthesiologist. Review. Part 1. *Ann. Crit. Care* **2020**, 3:35–45
5. Available online: https://omim.org/entry/171050 (accessed on 11 April 2023).
6. Nasyrova, R.F.; Shnayder, N.A.; Osipova, S.M.; Khasanova, A.K.; Efremov, I.S.; Al-Zamil, M.; Petrova, M.M.; Narodova, E.A.; Garganeeva, N.P.; Shipulin, G.A. Genetic Predictors of Antipsychotic Efflux Impairment via Blood-Brain Barrier: Role of Transport Proteins. *Genes* **2023**, 14:1085. doi:10.3390/genes14051085
7. Dewanjee, S.; Dua, T. K.; Bhattacharjee, N.; Das, A.; Gangopadhyay, M.; Khanra, R.; Joardar, S.; Riaz, M.; Feo, V.; Zia-Ul-Haq, M. Natural Products as Alternative Choices for P-Glycoprotein (P-gp) Inhibition. *Molecules (Basel, Switzerland)* **2017**. *22*(6):871. doi:10.3390/molecules22060871
8. Shnayder N.A.; Vaiman E.E.; Nasyrova R.F. Antipsychotic-induced parkinsonism: A Risk Assessment Scale and Personalised Diagnosis Algorithm. *Safety and Risk of Pharmacotherapy* **2024**. doi:10.30895/2312-7821-2024-418
9. Sychev, D.; Shikh, N.; Morozova, T.; Grishina, E.; Ryzhikova, K.; Malova, E. Effects of *ABCB1 rs1045642* polymorphisms on the efficacy and safety of amlodipine therapy in Caucasian patients with stage I-II hypertension. *Pharmacogenomics and Personalized Medicine* **2018**, 11:157–165. doi:10.2147/PGPM.S158401
10. Fung, K. L.; Gottesman, M. M. A synonymous polymorphism in a common MDR1 (ABCB1) haplotype shapes protein function. *Biochimica et Biophysica Acta* **2009**, *1794*(5):860–871. doi:10.1016/j.bbapap.2009.02.014
11. Available online: https://popgen.uchicago.edu/ggv/?data=%221000genomes%22&chr=7&pos=87138645 (accessed on 21 November 2016).
12. Negay, N.A. Welcome to personalized psychiatry and neurology. *Personalized Psychiatry and Neurology* **2023**, 3(1):1-2. doi:10.52667/2712-9179-2023-3-1-1-2