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*Personalized Psychiatry and Neurology*

*Review*

# Pharmacogenetics of chlorpromazine and its role in the development of antipsychotic-induced parkinsonism

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**Abstract**

Antipsychotics (AP) is a group of psychotropic drugs for the treatment of mental disorders, in particular schizophrenia. In the mid-1950s, the first AP was synthesized (known as chlorpromazine (CPZ)). This drug has revolutionized the treatment of psychotic disorders. This drug, in addition to the antipsychotic effect, caused severe adverse drug reactions in patients, in particular from the neurological system, such as AP-induced extrapyramidal syndrome (EPS) — chlorpromazine-induced parkinsonism (CPZ-IP). CPZ-IP characterized by the occurrence of motor disorders. CPZ-IP is as a result of damage to the basal ganglia and subcortical-thalamic connections. Drug-induced EPS is subdivided into primary and secondary. Among the primary EPS, drug-IP is the most common (the leading form of secondary parkinsonism). Pharmacogenetic markers of CPZ safety are being actively studied. Some pharmacogenetic markers of therapy safety have been established: single nucleotide variants/polymorphisms of candidate genes for dopaminergic receptors D2 and D3 (*DRD2* (rs1799732 (-141C Ins/Del)), *DRD3* (rs6280 (Ser9Gly)), laforine phosphatase (*EPM2A* (rs1415744 (C/T)).

***Keywords:*** *chlorpromazine, antipsychotic-induced parkinsonism, drug-induced parkinsonism, genes, pharmacogenetics, DRD2, DRD2, EPM2A.*

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## Introduction

Antipsychotics (AP) is a group of psychotropic drugs for the treatment of mental disorders, in particular schizophrenia. In the mid-1950s, the first AP was synthesized (known as chlorpromazine (CPZ)). This drug has revolutionized the treatment of psychotic disorders. Studies of the properties of CPZ contributed to the widespread use of the drug in psychiatric practice. According to Edward Shorter, "CPZ initiated a revolution in psychiatry comparable to the introduction of penicillin in general medicine." [1,2]. The use of phenothiazine compounds as AP was the result of research by Henri-Marie Laborit, a French army surgeon who was looking for a pharmacological method to prevent surgical shock [3]. That's why CPZ has a weak anticholinergic and strong sympatholytic effect, it was originally used as an antihistamine drug. Since 1958, other APs began to appear, such as haloperidol, thioproperazine, trifluoperazine, and others. All these drugs, in addition to the antipsychotic effect, caused severe adverse drug reactions (ADRs) in patients, in particular from the neurological system, such as AP-induced extrapyramidal syndrome (EPS). Thus, this group of drugs was called "antipsychotics". It was believed that the severity and incidence of EPS are directly proportional to the therapeutic effect of AP. However, later other drugs began to appear, such as clozapine, olanzapine, risperidone, quetiapine, aripiprazole, amisulpride, ziprasidone, etc. They caused AP-induced EPS to a lesser extent, and the antipsychotic effect was more pronounced. Thus, the term "neuroleptics" was called into question and now days more correct term is «antipsychotics». Also, due to the differences in drugs in the form of the severity of the antipsychotic effect and the manifestation of AP-induced EPS, they were

divided into two groups: 1st and 2nd generation APs. Thus, CPZ belongs to the 1st generation APs or typical APs [4].

CPZ is currently used in patients with schizophrenia in Russia. However, in the countries of the European Union (EU), its use has been de facto discontinued since the mid-nineties of the XX century due to high neurotoxicity and a huge number of ADRs.

**Objective**

The aim of this study is to review of pharmacogenetics studies of CPZ-induced parkinsonism (CPZ-IP).

**Methods**

A search was carried out for full-text publications in Russian and English in the databases of the RINC, PubMed, Web of Science, Springer by keywords and their combinations (chlorpromazine, antipsychotic, antipsychotic- induced parkinsonism, drug- induced parkinsonism, pharmacogenetics, single nucleotide variant) over the last 10 years. In addition, the review includes earlier publications of historical interest. Despite extensive searches of these commonly used databases and search terms, it cannot be ruled out that some publications may have been missed.

**Results**

CPZ (2-chloro-10- [3- (dimethylamino) propyl] phenothiazine hydrochloride, C17H19ClN2S) is a phenothiazine derivative that is an antiparasitic agent (Figure 1) [5]. CPZ has antipsychotic, sedative, antiemetic effect. The drug weakens or completely eliminates delusions and hallucinations, relieves psychomotor agitation, reduces anxiety. CPZ is used to treat both psychotic disorders, including schizophrenia and manic bipolar disorder, and amphetamine-induced psychotic disorders. The drug is recognized as the standard by which other APs are assessed [6]. CPZ has antiemetic and hypothermic action, enhances the action of barbiturates, alcohol and anesthetics [5].

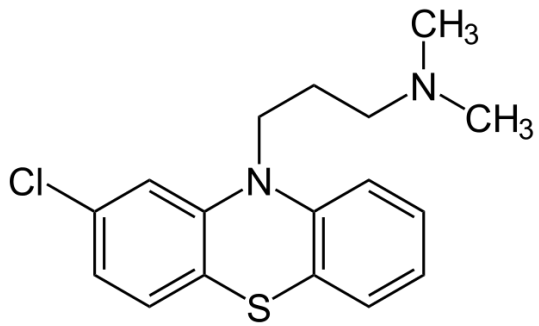


**Figure 1.** 2-chloro-10- [3- (dimethylamino) propyl] phenothiazine - chlorpromazine hydrochloride formula

The mechanism of the antipsychotic action of CPZ is associated with the blockade of postsynaptic dopaminergic receptors in the brain mesolimbic structures. The high-affinity antagonism of CPZ to dopaminergic D2 receptors determines not only the therapeutic effect, but also the development of EPS [7,8]. It also has anticholinergic and antihistaminergic effects: dry mouth; blurred vision; retention of urine; anxiety; tremor; weight gain; lowering blood pressure; dizziness [9]; hyperprolactinemia [10]. It causes a hypotensive effect, disrupt the intracardiac impulse conduction, lengthening the QT interval as

adrenergic antagonist [11]. CPZ at low threshold doses (2.5 mg / kg) increases the concentration of dopamine and norepinephrine metabolites [12-16]. A correlation has been established between the IC50 values (concentration of half-maximal inhibition) for AP and their clinical activity: the higher the affinity for dopaminergic receptors, the higher the clinical AP efficacy. [17]. In addition to the blockade of dopaminergic receptors in the mesolimbic structures of the brain, CPZ has a blocking effect on $\alpha$ adrenergic receptors [18], capable of binding to cholinergic receptors [19].

CPZ is produced in the form of tablets or pills of 25 mg, 50 mg, 100 mg, in the form of ampoules of 1, 2 and 5 ml of a 2.5% solution and 5 ml of a 0.5% solution. Also there are tablets 10 mg for children [20]. CPZ is produced under various trade names, most often used are: "Aminazine", " Chlorpromazine ", " Chlorpromazine hydrochloride". Dosage regimen: small doses - up to 100 mg / day, average therapeutic doses - 200-300 mg / day, large doses - up to 500 mg / day.

The bioavailability of CPZ after single oral doses compared with single intramuscular doses ranges from 10% to 69%. CPZ binds to plasma proteins (95–98%) [21].

CPZ is metabolized in the liver, with the formation of a number of active and inactive metabolites [22]. Metabolic pathways of the drug include hydroxylation, conjugation with glucuronic acid, N-oxidation, oxidation of sulfur atoms, dealkylation. The main metabolites are CPZ N-oxide (CPZNO), CPZ sulfoxide (CPZSO), and free and bound 7-hydroxy CPZ (7-HOCPZ) [23]. Plasma sulfoxide and plasma sulfoxide to CPZ ratios are higher in Non-Responder patients than in Responders [24]. Serum level of CPZ N-oxide in patients taking the drug for a long time is about half of the level of the drug at the beginning of therapy [25]. A decrease in the level of unchanged CPZ in blood plasma is recorded 2 weeks after oral administration [26], which is due to the activation of microsomal oxidizing enzymes of the liver and intestines [27,28]. CPZ is almost completely metabolized in the body and less than 1% is excreted in the form of an unchanged drug in the urine [29]. Different ratios of conjugated and unconjugated metabolites in urine are observed after intramuscular and oral doses of CPZ [29], what can explain the effect of "first pass" in the liver after oral administration of the drug [30].

**Table 1**. Trade names of chlorpromazine and form of release

| International designation name (IDN) | Trade name | Release form |
|---|---|---|
| Chlorpromazine | Aminazine | Dragee 50 mg and 100 mg |
| | | Tablets 25 mg, 50 mg, 100 mg |
| | | Solution 2.5% 1 ml, 2 ml, 5 ml, 10 ml |
| | Aminazin-Ferein | Solution 2.5% 1 ml, 2 ml, 5 ml, 10 ml |
| | Ampliaktil | Tablets 25 mg, 50 mg, 100 mg |
| | Chlorazine | Tablets 25 mg, 50 mg, 100 mg |
| | Contomin | Tablets 25 mg, 50 mg, 100 mg |
| | Chlorpromazine | Tablets 25 mg, 50 mg, 100 mg |
| | Chlorpromazine Canon | Tablets 50 mg, 100 mg |
| | Chlorpromazine hydrochloride | Solution 2.5% 2 ml |
| | Chlorpromazine Organic | Tablets 25 mg, 50 mg, 100 mg |
| | | Solution 2.5% 5 ml, 10 ml |
| | Largactil | Tablets 25 mg, 50 mg, 100 mg |
| | Plegomazin | Tablets 25 mg, 50 mg, 100 mg |
| | Propafenin | Tablets 25 mg, 50 mg, 100 mg |
| | Phenactyl | Tablets 25 mg, 50 mg, 100 mg |
| | Thorazine | Tablets 25 mg, 50 mg, 100 mg |

CPZ metabolism is mediated by enzymes of the cytochrome P450 family (CYP). It was found that CPZ is a competitive inhibitor of the enzyme of cytochrome CYP2D6, to a lesser extent CYP1A2 [31].

The half-life varies from 2 to 31 hours, but in 80% of cases it is 6 hours or less [32]. CPZ penetrates the blood-brain barrier (BBB), while the concentration in the brain is higher than in the plasma [33].

CPZ-IP characterized by the occurrence of motor disorders. CPZ-IP is as a result of damage to the basal ganglia and subcortical-thalamic connections. Drug-induced EPS is subdivided into primary and secondary. Among the primary EPS, drug-IP is the most common (the leading form of secondary parkinsonism) [34].

Pharmacogenetic markers of CPZ safety are being actively studied. Some pharmacogenetic markers of therapy safety have been established: single nucleotide variants (SNV) of candidate genes for dopaminergic receptors D2 and D3 (*DRD2, DRD3*), laforine phosphatase (*EPM2A*) (Table 2) [34].

*DRD2 gene*

An association has been established between the carriage of –141C Ins / Del and the risk of schizophrenia [35]. This variant affects the density of dopamine D2 receptors, the carriage of the Del allele leads to a higher density of D2 receptors [36]. In carriers of this polymorphism low efficiency of AP therapy was established [37]. An in-vitro study shows that the Del of the –141CIns / Del variant is directly associated with the level of DRD2 expression [38]. However, there are reports of opposite results [39].

*DRD3 gene*

The dopamine D3 receptor is predominantly expressed in areas of the limbic and basal ganglia associated with cognitive, emotional, and motor functions. The missense variant in exon 1 of the DRD3 gene leads to the substitution of serine for glycine (rs6280, Ser9Gly) in the N-terminal extracellular domain of the receptor protein, which leads to a change in the affinity for dopamine. The replacement Gly can increase the density of D3 receptors in some areas of the brain. Patients with a heterozygous Ser / Gly genotype respond better to CPZ therapy. Carriage of the Gly increases the risk of EPS, including AIP, and reduces the effectiveness of CPZ therapy [40].

*EPM2A gene*

The EPM2A gene encodes laforin phosphatase, a protein involved in the regulation of glycogen metabolism in brain [41]. Andrade D. and Singh S. put forward a hypothesis about the possible role of impaired glycogen metabolism in the development of schizophrenia and the response to AP [38,39]. Patients with the TT genotype (rs1415744) of EPM2A gene showed a low efficacy of CPZ therapy compared with patients with CC and CT genotypes [42].

**Table 2**. Pharmacogenetic markers of CPZ safety [34]

| Gene | Protein | SNV / polymorphism | Effect |
|---|---|---|---|
| *DRD2* | Dopamine receptor D2 | rs1799732 (-141C Ins/Del) | Carriage of Del1 polymorphism is associated with 1) low effectiveness of therapy, 2) more delayed response to therapy |
| *DRD3* | Dopamine receptor D3 | rs6280 (Ser9Gly) | The carriage of the amino acid Gly is associated with a low efficacy of therapy and an increased risk of developing CPZ-IP |
| *EPM2A* | Laforin Phosphatase | rs1415744 (C/T) | Patients with the CC genotype with schizophrenia have an increased response to CPZ compared to patients with the CT and TT genotypes. |

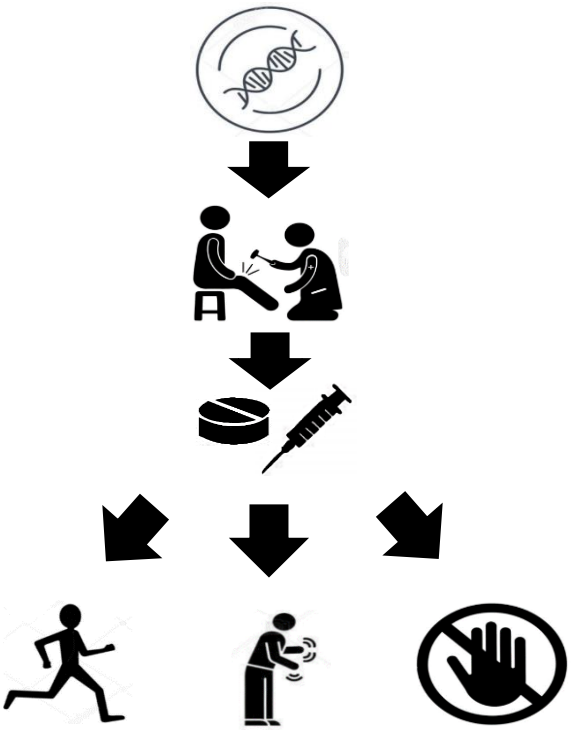

**Figure 2**. Options for the development of adverse reactions in patients with schizophrenia during chlorpromazine therapy

## Discussion

So, CPZ-IP is a genetically determined neurological ADR to AP therapy for schizophrenia. To date, the most studied candidate genes predisposing the development of CPZ-IP are *DRD2, DRD3, EPM2A*. However, the genetics and mechanism of development of CPZ-IP continue to be actively studied. This is important for the development of personalized psychophysiological therapy strategies for schizophrenia and preventive pharmacogenetic testing panels (Figure 2).

In patients of the 1st group (A) (low risk of developing CPZ-IP), CPD should be initiated at moderate therapeutic dosages. In patients of the 2nd group (B) (medium risk of developing CPZ-IP) CPZ can be prescribed in low doses, and in patients of the 3rd group (C) (high risk of developing CPZ-IP) CPZ is contraindicated.

## Conclusions

Disclosure of genetic predictors of CPZ-IP, as the most common neurological ADR in the treatment of patients with schizophrenia and other psychiatric disorders, may provide a key to developing a strategy for its personalized prevention and therapy in real clinical practice. Taking into account the carriage of SNV / polymorphisms of the studied candidate *DRD2, DRD3, EPM2A* genes associated with a high risk of developing CPZ-IP, therapeutic strategies can be individually changed in each specific clinical case. However, it should be recognized that the question of the genetics of AIP is far from being resolved.

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## References


1. Lehmann, H.E., Hanrahan, G.E. Chlorpromazine: New inhibiting agent for psychomotor excitement and manic states. *Archives of Neurology and Psychiatry* **1954**, *71*, 227–237. doi:10.1001/archneurpsyc.1954.023203800
2. Shorter, E. A History of Psychiatry. In: From the Era of Asylum to the Age of Prozac. New York: John Wiley & Sons, Inc. **1997**
3. Lopez-Munoz, F., Alamo, C., Cuenca, E., Shen, W., Clervoy, P., Rubio, G. History of the Discovery and Clinical Introduction of chlorpromazine. Annats of Clinical Psychiatry **2005**, *17(3),* 113-135. doi:10.1080/10401230591002002
4. Mosolov, C.H. Modern antipsychotic pharmacotherapy for schizophrenia. *Russian medical journal* **2004**, *12(10)*, 646–652. (In Russ)]
5. Rees, L. Chlorpromazine and allied phenotihazine derivatives. *Ban Medical Journal Drug Treatment of Disease* **1960**, *522-525*. doi:10.1136/bmj.2.5197.522
6. Adams, C.E., Awad, G.A., Rathbone, J., Thornley, B., Soares-Weiser, K. Chlorpromazine versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews 2014*; doi:10.1002/14651858.cd000284.pub3
7. Ayd, F. J. Survey of Drug-Induced Extrapyramidal Reactions. *JAMA* **1961**, *175*, 1054-1060
8. Rifkin A. Extrapyramidal side effects: a historical perspective // The Journal of Clinical Psychiatry.1987; 48(1): 3-6. PMID 2887555
9. Mi, H., Thomas, P.D., Ring, H.Z., Jiang, R., Sangkuhl, K., Klein, T.E., Altman, R.B. PharmGKB summary. *Pharmacogenetics and Genomics* **2011**, *21(6),* 350–356. doi:10.1097/ FPC.0b013e32833ee605
10. Meites, J. Clemens, J.A. Hypothalamic control of prolactin secretion. *Vitamins and Hormones* **1972**, 165-221. doi:10.1016/s0083-6729(08)60796-7
11. Gokhale, S., Gulati, O., Parikh, H. An investigation of the adrenergic blocking action of chlorpromazine. *British Journal of Pharmacology and Chemotherapy* **1964,** *23(3),* 508–520. doi:10.1111/j.1476-5381.1964.tb01606.x
12. Carlsson, A., Lindqvist, M. Effect of chlorpromazine or haloperidol on formation of 3- methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacologica et Toxicologica* **1963,** *20(2),* 140–144. doi:10.1111/j.1600-0773.1963.tb01730.x
13. Andén, N., Roos, B., Werdinius, B. Effects of chlorpromazine, haloperidol, and reserpine on the levels of phenolic acids in rabbit corpus striatum. *Life Sciences* 1964, 3(2), 149–158. doi:10.1016/0024-3205(64)90196-1
14. Prada, M., Pletscher, A. Acceleration of cerebral dopamine turnover by chlorpromazine. Experientia **1966**, *22(7),* 465–466. doi:10.1007/bf01900988
15. Gey, K.F., Pletscher, A. Acceleration of turnover of 14C-catecholamines in rat brain by chlorpromazine. *Experientia* **1968**, *24*, 335–336. doi:10.1007/bf02140804
16. Nybäck, H., Sedvall, G. Effect of chlorpromazine on accumulation and disappearance of catecholamines formed from tyrosine-C14 in brain. *Journal of Pharmacology and Experimental Therapeutics* **1968**, *162*, 294–301.PMID 5666984
17. Seeman, P., Lee, T., Chau-Wong, M., Wong, K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* **1976**, 261, 717–719. doi:10.1038/261717a0
18. Courvoisier, S., Fournal, J., Ducrot, R., Kolsky, Koetchet P. Propriétés pharmacodynamiques du chlorhydrate de chloro-3 (diméthylamino-3' propyl) – 10 phénothiazine (4.560 R.P.). *Archive of International Pharmacodynamics* **1953**, *92*, 305–361
19. Mailman, R., Murthy, V. Third generation antipsychotic drugs: partial agonism or receptor functional selectivity? *Current Pharmaceutical Design* **2010**, *16(5),* 488– 501. doi:10.2174/138161210790361461
20. Mashkovsky M. D. Medicines. - 16th edition. - M .: Novaya Volna, 2005 .-- S. 52, 763 .-- 1200 p. (In Russ.)
21. Dahl, S.G., Strandjord, R.E. Pharmacokinetics of chlorpromazine after single and chronic dosage. *Clinical Pharmacology & Therapeutics* 1977, 21(4), 437–448. doi:10.1002/cpt1977214437
22. Usdin, E. The assay of ehlorpromazine and metabolites in blood, urine, and other tissues. *CRC Critical Reviews in Clinical Laboratory Sciences* **1971**, *2(3),* 347– 391. doi:10.3109/10408367109151312
23. Yeung, P.K.F., Hubbard, J.W., Korchinski, E.D., Midha, K.K. Pharmacokinetics of chlorpromazine and key metabolites. *European Journal of Clinical Pharmacology* **1993**, *45(6),* 563–569. doi:10.1007/bf00315316
24. Mackay, A.V.P., Healey, A.F., Baker, J. The relationship of plasma chlorpromazine to its 7-hydroxy and sulphoxide metabolites in a large population of ehroniesehizophrenics. *British Journal of Clinical Pharmacology* **1974**, *1(5),* 425–430. doi:10.1111/j.1365-2125.1974.tb00281.x
25. Davidson, J.D., Terry, L.L., Sjoerdsma, A. Action and metabolism of chlorpromazine sulfoxide in man. *The Journal of Pharmacology and Experimental Therapeutics* **1957**, *121(1),* 8-12. PMID 13481822
26. Sakalis, G., Curry, S.H., Mould, G.P., Lader, M.H. Physiologie and clinieal effeets of chlorpromazine and their relationship to plasma level. *Clinical Pharmacology & Therapeutics* **1972**, *13(6),* 931–946. doi:10.1002/ cpt1972136931
27. Dahl, S.G., Strandjord, R.E. Pharmacokinetics of chlorpromazine after single and chronic dosage. *Clinical Pharmacology & Therapeutics* **1977**, *21(4),* 437–448. doi:10.1002/cpt1977214437

28. Hill, M.J., Reynolds, G.P. 5-HT2C receptor gene polymorphisms associated with antipsychotic drug actionalterpromoteractivity. *Brain Research* **2007**, *1149*, 14–17. doi:10.1016/j.brainres.2007.02.038
29. Hollister, L.E., Curry, S.H. Urinary exeretion of ehlorpromazine metabolites following single doses and in steady-state conditions. *Research Communications in Chemical Pathology and Pharmacology* **1971**, *2(3),* 330- 338. PMID 4948435
30. Gibaldi, M., Feldman, S. Route of administration and drug metabolism. *European Journal of Pharmacology* **1972**, *19(3),* 323–329. doi:10.1016/0014- 2999(72)90098-2
31. Yoshii, K., Kobayashi, K., Tsumuji, M., Tani, M., Shimada, N., Chiba, K. Identification of human cytochrome P450 isoforms involved in the 7-hydroxylation of chlorpromazine by human liver microsomes. *Life Sciences* **2000**, *67(2),* 175–184. doi:10.1016/s0024- 3205(00)00613-5
32. Curry, S.H. Chlorpromazine: Concentrations in Plasma, Excretion in Urine and Duration of Effect. *Proc R Soc Med* **1971**, *64(3),* 285–289. PMID 5551485
33. Jaworski, T.J., Hawes, E.M., McKay, G., Midha, K.K. The Metabolism of chlorpromazine N-Oxide in the Rat. *Xenobiotica* 1988, *18(12*), 1439– 1447. doi:10.3109/00498258809042266
34. Clinical psychopharmacogenetics, ed. Nasyrova, R.F., Neznanov, N.G.. - SPb: DEAN Publishing House, 2019. — 405 p. (In Russ.)
35. Arinami, T. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. *Human Molecular Genetics* **1997**, *6(4),* 577–582. doi:10.1093/hmg/6.4.577
36. Ray, W.A., Meredith, S., Thapa, P.B., Meador, K.G., Hall, K., Murray, K.T. Antipsychotics and the risk of sudden cardiac death. *Archives General Psychiatry* **2001**, *58(12),* 1161– 1167. doi:10.1001/archpsyc.58.12.116
37. Wu, S., Xing, Q., Gao, R., Li, X., Gu, N., Feng, G., He, L. Response to chlorpromazine treatment may be associated with polymorphisms of the DRD2 gene in Chinese schizophrenic patients. *Neuroscience Letters* **2005**, *376(1*), 1–4. doi:10.1016/j.neulet.2004.11.014
38. Jönsson, E.G., Nöthen, M.M., Grünhage, F., Farde, L., Nakashima, Y., Propping, P., Sedvall, G.C. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Molecular Psychiatry* **1999**, *4(3),* 290–296. doi:10.1038/ sj.mp.4000532
39. Mihara, K., Kondo, T., Suzuki, A., Yasui, N., Ono, S., Otani, K., Kaneko, S. No relationship between −141C Ins/ Del polymorphism in the promoter region of dopamine D2 receptor and extrapyramidal adverse effects of selective dopamine D2 antagonists in schizophrenic patients: a preliminary study. *Psychiatry Research* **2001**, 101(1), 33– 38. doi:10.1016/s0165-1781(00)00247-x
40. Reynolds, G.P., Yao, Z., Zhang, X., Sun, J., Zhang, Z. Pharmacogenetics of treatment in first-episode schizophrenia: D3 and 5-HT2C receptor polymorphisms separately associate with positive and negative symptom response. *European Neuropsychopharmacology* **2005**, *15(2),* 143–151. doi:10.1016/j.euroneuro.2004.07.001
41. Andrade D.M., Turnbull J., Minassian B.A.Lafora disease, seizures and sugars // Acta Myol. 2007; 26: 83–86. PMID: 17915579
42. Porcelli, S., Balzarro, B., Lee, S.-J., Han, C., Patkar, A.A., Pae, C.U., Serretti, A. PDE7B, NMBR and EPM2A Variants and Schizophrenia: A Case-Control and Pharmacogenetics Study. *Neuropsychobiology* **2016**, *73(3),* 160–168. doi:10.1159/000445295