

Review

Pharmacogenetic Factors of Clozapine-Induced Metabolic Syndrome

Aiperi K. Khasanova

Russian Medical Academy of Continuous Professional Education, 125993, Moscow, Russia

Citation: Khasanova, A.A.

Pharmacogenetic Factors of Clozapine-Induced Metabolic Syndrome. *Personalized Psychiatry and Neurology* 2023, 3 (2): 38-47. <https://doi.org/10.52667/2712-9179-2023-3-2-38-47>

Chief Editor: Nikolaj G. Neznanov,
D Med Sci, Professor

Received: 02 November 2023
Accepted: 07 November 2023
Published: 15 November 2023

Publisher's Note: V.M. Bekhterev NMRC PN stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2023 by the authors.

*Correspondence: e-mail: abdyrahmanova_peri@mail.ru; Tel.: +79122760968 (K.A.K.)

Abstract: (1) Introduction: Despite modern therapies, approximately 20-30% of patients with schizophrenia remain resistant to psychopharmacotherapy. Clozapine is the only antipsychotic with proven efficacy for treatment resistance in schizophrenia (TRS). The most common adverse drug reaction (ADR) during clozapine administration are metabolic disturbances, particularly metabolic syndrome (MS). Because MS leads to a twofold increase in mortality from cardiovascular disease and a 1.5-fold increase in mortality from all causes, and clozapine is often the only treatment option for TRS, it is critical to monitor and management metabolic abnormalities. The high interindividual differences in the development of clozapine-induced MS suggest that genetic factors may play an important role. (2) Purpose: The aim of this study was to identify relevant single nucleotide polymorphisms (SNPs) of candidate genes for clozapine-induced MS, because based on these data, a genetic risk panel can be constructed to assess the likelihood of developing clozapine-induced MS in patients with schizophrenia. (3) Materials and Methods: We searched for full-text publications in PubMed, Web of Science, Springer, Google Scholar, and electronic libraries in English and Russian, available from inception to 30 October 2023. Keywords were the following: metabolic disturbances, clozapine, metabolic syndrome, schizophrenia, genes, adverse drug reactions, antipsychotics, pharmacogenetics, genetic biomarker, single nucleotide variant, polymorphism, association, variation, and metabolic syndrome genes. (4) Results: we included 6 naturalistic cross-sectional open-label trials, included patients with schizophrenia, schizoaffective, schizophreniform disorder or psychotic disorder, who were treated with first and second generations antipsychotics, among which there was also clozapine and 1 meta-analysis which reviewed association between *HTR2C* gene polymorphisms and antipsychotic-induced MS in schizophrenia patients. According to the results of our scoping review the carriage of SNPs in the studied candidate genes associated with clozapine-induced MS are the following: 1) *CYP1A2* gene: genotype AA of rs762551 (NG_008431.2:g.32035C>A); 2) *CYP2C19* gene: CYP2C19*2 polymorphism; 3) *HTR2C* gene: genotype CC of rs518147 (NM_000868.2:c.-697G>C), minor allele C of rs1414334 (NG_012082.3:g.324497C>G), genotype CC of rs518147 (NM_000868.2:c.-697G>C), genotype GG of rs12836771 (NG_012082.3:g.71829A>G); 4) *LEP* gene: genotypes AG and GG of rs7799039 (NG_044977.1:g.475G>A); 5) *LEPR* gene: genotypes AG and GG of rs1137101 (NG_015831.2:g.177266A>G). (4) Conclusions: Uncovering the genetic biomarkers of clozapine-induced MS may provide a key to developing a strategy for the personalized prevention and treatment of this ADRs of clozapine in patients with schizophrenia spectrum disorders in real clinical practice.

Keywords: metabolic disturbances; clozapine; metabolic syndrome; schizophrenia; genes; adverse drug reactions; antipsychotics; pharmacogenetics; genetic biomarker; single nucleotide variant; polymorphism; association; variation; and metabolic syndrome genes.

Introduction

Schizophrenia is a severe mental illness with a mortality rate 2-3 times higher than the general population [1]. The main causes of increased risk of mortality in schizophrenia are unhealthy lifestyles and somatic diseases, particularly cardiovascular disease [2].

Despite modern therapies, approximately 20-30% of patients with schizophrenia remain resistant to psychopharmacotherapy. Clozapine is the only antipsychotic with proven efficacy for treatment resistance in schizophrenia (TRS) [3].

This is attributed to its unique mechanism of action based on its complex pharmacology [4]. In addition to its proven efficacy in TRS, clozapine also reduces aggressive behavior in patients with schizophrenia [5], has a proven antisuicidal effect and is associated with the lowest all-cause mortality rate among all antipsychotics [6,7].

However, it is estimated that only 10-20% of eligible patients in the United States are prescribed clozapine due to a number of factors, including a wide range of adverse drug reactions (ADRs), including metabolic abnormalities, cardiovascular complications, neutropenia/agranulocytosis, myocarditis/cardiomyopathy, tachycardia, sialorrhea, orthostatic hypotension, constipation, obsessive-compulsive symptoms, etc. [8]. The most common ADRs during clozapine administration are metabolic disturbances [9], particularly metabolic syndrome (MS). MS is a combination of clinical and laboratory abnormalities, including abdominal obesity, insulin resistance, hypertension, low high-density lipoprotein (HDL), high cholesterol and high triglycerides, which are a combination of metabolic risk factors for cardiovascular disease and type 2 diabetes mellitus. MS leads to a twofold increase in mortality from cardiovascular disease and a 1.5-fold increase in mortality from all causes [10].

Among all antipsychotics, clozapine is the most dangerous in terms of metabolic disturbances, as it is the most frequently leads to this ADRs [11]. For example, an observational study of outpatients taking clozapine found that 80% were overweight and 58% met criteria for MS [12]. Another retrospective study also confirmed that 45% of patients taking clozapine met the criteria for MS [13]. Because premature death in schizophrenia is primarily caused by cardiometabolic abnormalities [14], and clozapine is often the only treatment option for TRS, it is critical to monitor and management metabolic abnormalities.

The mechanism behind the metabolic abnormalities when treated with clozapine is not entirely clear. Current evidence shows that risk factors for metabolic abnormalities during clozapine administration in patients with schizophrenia are: genetic predisposition, psychiatric disorder itself, poor diet, lack of exercise, cigarette smoking and stress, hypothalamic-pituitary-adrenal system disorders, clozapine treatment, etc. [15].

The high interindividual differences in the development of clozapine-induced MS suggest that genetic factors may play an important role [16].

Genetic predisposition to MS development involves carrying single nucleotide polymorphisms (SNPs) of genes. The role of SNPs in the mechanism of clozapine-induced MS has been evaluated for the last 10 years, and the number of publications revealing the significance of SNPs/candidate gene polymorphisms in the pathogenesis of clozapine-induced MS continues to increase [17-23]. Thus, the study of SNPs of other candidate genes associated with clozapine-induced MS in patients with schizophrenia is relevant.

Objective

The aim of this study was to identify relevant SNPs/candidate gene polymorphisms for clozapine-induced MS, because based on these data, a genetic risk panel can be constructed to assess the likelihood of developing clozapine-induced MS in patients with schizophrenia.

Materials and Methods

Search Strategy

We searched for full-text publications in PubMed, Web of Science, Springer, Google Scholar, and electronic libraries in English and Russian, available from inception to 30 October 2023. Keywords were as follows: metabolic disturbances, clozapine, metabolic syn-drome, schizophrenia, genes, adverse drug reactions, antipsychotics, pharmacogenetics, genetic biomarker, single nucleotide variant, polymorphism, association, variation, and metabolic syndrome genes.

Eligibility Criteria

We included reviews that met the criteria:

- 1) describing the positive association of SNPs/candidate gene polymorphisms with clozapine-induced MS in patients with schizophrenia, schizoaffective or schizophreniform disorder or psychotic disorder;
- 2) peer-reviewed articles;
- 3) availability of the full text of the article;
- 4) the studies could be of any design (besides preclinical) and could include any comparator intervention or control or a lack thereof.

These criteria are purposefully inclusive because the evidence base on pharmacogenetic factors in clozapine-induced MS is limited. We were therefore also inclusive in terms of publication date (any).

We excluded articles in which data were not statistically significant; SNPs data did not match international nomenclature databases; and associations with specific alleles/polymorphisms were not indicated in the articles.

Review Strategy

Data were presented as text and categorized by gene. The data are summarized in Table 1, 2, and 3, considering genes, SNPs, association with clozapine-induced MS, p-value, sample size and biogeographical group.

Data Synthesis

A formal critical appraisal of study risk of bias or quality was not undertaken, as is standard for scoping reviews, particularly when studies vary in design, participants, and outcomes. A narrative synthesis was planned to summarize the extracted data and observe emerging patterns.

Results

Characteristics of Included Studies

6 studies were naturalistic cross-sectional open-label trials, included patients with schizophrenia, schizoaffective, schizophreniform disorder or psychotic disorder, who were treated with first and second generations antipsychotics, among which there was also clozapine [17-22]. 1 study was a meta-analysis which reviewed association between *HTR2C* gene polymorphisms and antipsychotic-induced MS in schizophrenia patients [23].

Based on the results of this scoping review the following SNPs of genes that encode proteins/enzymes involved in the clozapine-induced MS have been studied:

- 1) Pharmacogenetic pharmacokinetic factors of clozapine-induced MS (Table 1): genes coding isoenzymes of cytochrome P450 (*CYP1A2*, *CYP2C19*);

- 2) Pharmacogenetic pharmacodynamic factors of clozapine-induced MS (Table 2): gene of serotonin receptor isoform (*HTR2C*);
- 3) Pharmacogenetic hormone factors of clozapine-induced MS (Table 3): genes of leptin hormonal system (*LEPR*, *LEP*).

Pharmacogenetic pharmacokinetic factors of clozapine-induced MS

CYP1A2 gene

Clozapine is almost completely metabolized prior to excretion, and only trace amounts of unchanged drug are detected in the urine and feces. Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP2D6, CYP3A4 and CYP2C19. Clozapine is metabolized to clozapine N-oxide and N-desmethyl clozapine (norclozapine) via the cytochrome system. The pharmacodynamic effects of norclozapine are reported to be 50% to 70% of those of the original. CYP1A2 is the main cytochrome P450 isozyme in clozapine metabolism [24].

CYP1A2 gene is located on 15q24.1 chromosome and encodes CYP1A2 cytochrome P450 isozymes [25]. Vasudev K. et al. conducted cross-sectional study in 2017. Among 59 European patients with schizophrenia spectrum disorders 18 patients received clozapine for at least 6 months. A significant interaction was observed between smoking and CYP1A2*1F A/A (rs762551) carrier status ($P = 0.028$) and MS. It was suggested that clozapine-treated smokers with the CYP1A2*1F A/A genotype have 4.6 times higher odds for clozapine-induced MS, whereas nonsmokers with CYP1A2*1F A/A have an about 92% lower odds compared to CYP1A2 C/C carriers. Importantly, clozapine blood level was significantly associated with a higher risk for MS, with an 11% increase in the odds per 100 ng/mL. Clozapine blood levels in patients with MS were about 1.5 times higher compared to those without MS (1886.0 ± 894.5 vs. 1282.9 ± 984.7 , $P = 0.0097$) [17].

CYP2C19 gene

CYP2C19 also involves, albeit to a lesser extent than CYP1A2, in clozapine metabolism [24].

Table 1. Pharmacogenetic pharmacokinetic factors of clozapine-induced MS

Gene (OMIM * Number)	SNP (Location)	Association with AIA	Study type	p-Value	Sample	Reference
CYP1A2 (124060)	rs762551 (NG_008431.2: g.32035C>A)	Genotype AA is associated with increased likelihood of antipsychotic-induced MS compared to genotypes AC and CC in patients with tobacco use disorder	Cross-sectional	0.0213	59 (MS cases = 30; non-MS cases = 20); biogeographical group: European; 18 patients received clozapine	Vasudev K. et al., 2017 [17]
CYP2C19 (124020)	CYP2C19*2	CYP2C19*2 polymorphism is associated with increased likelihood of antipsychotic-induced MS compared to CYP2C19 *1/*1		0.033		

Note: MS – metabolic syndrome.

CYP2C19 gene is located on 10q23.33 chromosome and encodes CYP2C19 cytochrome P450 isozymes [25]. In Vasudev's K. et al. cross-sectional study, which was mentioned above, patients with 2 CYP2C19*2 alleles (poor metabolizer phenotype) showed a trend to higher dose-normalized clozapine concentration ($P = 0.1056$) and a significantly increased clozapine to norclozapine ratio ($P = 0.0237$), suggesting enhanced systemic

exposure due to impaired clozapine metabolism. They found that clozapine blood level significantly predicted a higher risk for MS, and the presence of at least 1 CYP2C19*2 allele ($P = 0.033$) is associated with MS [17].

Pharmacogenetic pharmacodynamic factors of clozapine-induced MS

HTR2C gene

Current studies have reported that the serotonin (HT) system is important in food and body weight regulation. In addition, serotonin subtype 2C (HT2C) agonists can decrease appetite, while HT2C antagonists have the opposite effect. A recent animal model demonstrated that 5-HT2C receptor (*HTR2C*)-knockout mice display chronic hyperphagia leading to obesity. The *HTR2C* gene contains several polymorphisms that are associated with the presence of MS. In humans, it was suggested that *HTR2C* expressed within the brain is associated with second-generation antipsychotic-induced MS [26]. The second-generation antipsychotics make a disbalance into the central mechanisms of food regulation behavior due to interaction with *HTR2C* and *H1* receptors [27]. *HTR2C* gene is located on Xq23 chromosome and encodes *HTR2C* [25]. This is an x-linked gene, male subjects have only one copy of the allele (C or G) whereas female subjects can have CC, CG or GG genotype.

Mulder et al. [18] in 2007 conducted cross-sectional study, in which among 112 European patients with schizophrenia spectrum disorders 41 patients received clozapine. *HTR2C* gene polymorphisms are associated with an increased risk for the MS in carriers of the variant alleles rs518147 (−697) C (OR, 2.62; 95% CI, 1.00–6.85; $P = 0.049$) and rs1414334 C (OR, 4.09; 95% CI, 1.41–11.89; $P = 0.01$). It is notable that combined genotype with carriers of the *HTR2C*: c.1–142948(GT)n 13 repeat allele, the common allele rs3813929 (−759) C, the variant alleles rs518147 (−697) C and rs1414334 C, which was present in 18% of the patients, is associated with an increased risk (44% vs. 17%) of the MS (OR, 4.69; 95% CI, 1.34–16.45; $P = 0.016$) compared with the combined genotype with the common alleles.

Mulder et al. [19] continued research in this direction and in 2009 in the sample of 164 European with schizophrenia spectrum disorders, among which 37 patients received clozapine, found that the variant rs1414334 C allele was strongly associated with the clozapine-induced MS (OR, 9.20; 95% CI, 1.95–43.45; $P < 0.05$). Carriers of a combined genotype, including the *HTR2C*: c.1j142948(GT)n 13R allele, the common C allele of rs3813929, the variant C allele of rs518147, and the C allele of rs1414334, had a strongly increased risk for the MS in the pooled analysis with the results of 2007 year study (OR, 3.08; 95% CI, 1.40–6.78), similar to the findings in the original sample.

Risselada et al. [20] in 2010 studied MS in 186 European patients, 31 patients received clozapine. Risselada et al. revealed that carriership of the *HTR2C* gene rs1414334 C allele is significantly associated with an increased risk for the MS (OR 3.73; 95% CI 1.29–10.79, $P = 0.015$). Further analysis showed a significant association for carriership of the variant rs1414334 C allele and elevated triglyceride concentrations (2.4 vs 1.7 mmolL^{−1}, $P = 0.014$), but no association with high-density lipoprotein (HDL) concentrations was found (1.32 vs 1.28 mmolL^{−1}, $P = 0.72$).

Later Puangpetch et al. [21] in 2018 in 200 patients with psychotic disorders sample, among which 50 had a monotherapy of clozapine, determined that *HTR2C* rs518147 CC and rs12836771 GG associated with the presence of MS after adjusting for the combination of second-generation antipsychotic therapy in multivariate logistic regression. Participants that carried the *HTR2C* rs518147 CC or rs12836771 GG had a greater chance to present with MS that was 2.44 times (95% CI = 1.01–5.93; $P = 0.048$) and 2.65 times (95% CI = 1.04–6.79; $P = 0.042$), respectively, that observed in participants carrying the homozygous wild type (rs518147GG, rs12836771AA) or heterozygous genotype (rs518147GC, rs12836771AG).

The results of the above studies confirm a meta-analysis from 2016 of *HTR2C* gene polymorphisms and olanzapine/clozapine/risperidone-induced MS, 10 studies were

included in this meta-analysis. Among them, 3 studies consider the association of *HTR2C* -697G/C polymorphism and olanzapine/clozapine/risperidone-induced MS, 3 studies consider the association *HTR2C* gene rs1414334:C>G polymorphism and olanzapine/clozapine/risperidone-induced MS. The pooled population included 843 patients with schizophrenia spectrum disorders. rs1414334 C allele had a significantly positive association with olanzapine/clozapine/risperidone-induced MS (OR = 2.44; 95% CI = 1.48, 4.00; $P = 0.0004$; $I^2 = 0$) using the random-effect model. Further, since there was no between-study heterogeneity ($I^2 = 0$), a fixed-effect model was also used to perform the analysis which generated the same result as the random-effect model (OR = 2.42; 95% CI = 1.48, 3.96; $P = 0.0004$; $I^2 = 0$) [23].

Table 2. Pharmacogenetic pharmacodynamic factors of clozapine-induced MS

Gene (OMIM * Number)	SNP (Location)	Association with AIA	Study type	P-Value	Sample	Reference
<i>HTR2C</i> (312861)	rs518147 (NM_000868.2: c.-697G>C)	Genotype CC is associated with increased likelihood of antipsychotic-induced MS compared to genotypes CG and GG	Cross-sectional	0.049	112 (MS cases = 28; non-MS cases = 84); biogeographical group: European; 41 patients received clozapine	Mulder H. et al., 2007 [18]
				0.01		
				$P < 0,05$	164 (MS cases = 60; non-MS cases = 104); biogeographical group: European; 37 patients received clozapine	
	rs1414334 (NG_012082.3: g.324497C>G)	Minor Allele C is associated with increased likelihood of antipsychotic-induced MS compared to allele G	Meta-analysis	0,015	186 (MS cases = 56; non-MS cases = 130); biogeographical group: European; 31 patients received clozapine	Risselada A. J. et al., 2012 [20]
				0.0004	843; (MS cases = ND; non-MS cases = ND); biogeographical group: European; number of patients received clozapine - ND	
	rs518147 (NM_000868.2: c.-697G>C)	Genotype CC is associated with increased likelihood of antipsychotic-induced MS compared to genotypes CG and GG	Cross-sectional	0.048	200 (MS cases=64; non-MS cases=136); biogeographical group: East Asian; 50 patients received clozapine	Puangpetch A. et al., 2018 [21]
	rs12836771 (NG_012082.3: g.71829A>G)	Genotype GG is associated with increased likelihood of antipsychotic-induced MS compared to genotypes AA and AG		0.042		

Note: MS – metabolic syndrome; ND – no data.

LEP gene

There is evidence of an interaction between the serotonergic system and leptin. It has been shown that mice knocked out of the *5-HT2C* gene, show hyperleptinemia and leptin insensitivity. Leptin is secreted mainly by white adipose tissue adipocytes, reducing food intake and increasing energy expenditure through central control of appetite and peripheral regulation of metabolic activity [28], and is encoded by the *LEP* gene, which is located on 7q32.1 chromosome [25].

Stimulation of leptin receptors in hypothalamic nuclei decreases the effects of appetite-stimulating hormones such as melanin-concentrating hormone and neuropeptide Y, while increasing the activity of appetite-suppressing hormones such as α -melanocyte-stimulating hormone (α -MSH) and corticotropin-releasing factor. Evidence for the metabolic activity of leptin has been demonstrated in mice that have a genetic inability leptin production is phenotypically manifested as overeating and, as a result, obesity. People carrying mutations in both copies of the *LEP* gene are obese and respond to exogenous leptin, whereas in heterozygotes this effect is less pronounced. Leptin levels are positively correlated with the amount of adipose tissue, but the fact that obese individuals may have chronically elevated leptin levels suggests some level of leptin insensitivity. The level of circulating leptin has been shown to be positively correlated with body mass index. Leptin has multiple effects on energy homeostasis through activation of key hypothalamic nuclei and energy balance regulator peptides such as neuropeptide Y, proopiomelanocortin (POMC) and its product, α -melanocyte-stimulating hormone [27,28]

Yevtushenko et al. [22] in cross-sectional study from 2008 year in 120 European patients with schizophrenia spectrum disorders, and 21 patients received clozapine, revealed that the effect of leptin genotypes AG and GG (rs7799039) on presence of MS, when grouped on the basis of presence or absence of the G allele, was significant ($P = 0.032$).

LEPR gene

The leptin receptor (LEP-R) is a protein that in humans is encoded by the *LEPR* gene, which is located on 1p31.3 chromosome [25]. Modifications in the leptin receptor are responsible for obesity [28]. Vasudev et al [17] in 2017 in cross-sectional study of 59 European patients with schizophrenia spectrum disorders, 18 patients received clozapine, found that genotypes AG ($P = 0.0252$) and GG ($P = 0.0204$) of rs1137101 are associated with increased likelihood of antipsychotic-induced MS compared to genotype AA.

Table 3. Pharmacogenetic hormone factors of clozapine-induced MS

Gene (OMIM * Number)	SNP (Location)	Association with AIA	Study type	p-Value	Sample	Reference
<i>LEP</i> (16416)	rs7799039 (NG_044977.1: g.475G>A)	Genotypes AG and GG are associated with increased likelihood of antipsychotic-induced MS compared to genotype AA	Cross-sectional	0.032	120 (MS cases = 46; non-MS cases = 74); biogeographical group: European; 21 patients received clozapine	Yevtushenko O.O. et al., 2008 [22]
<i>LEPR</i> (601007)	rs1137101 (NG_015831.2: g.177266A>G)	Genotypes AG and GG are associated with increased likelihood of antipsychotic-induced MS compared to genotype AA		0.0252	59 (MS cases = 30; non-MS cases = 20); biogeographical group: European; 18 patients received clozapine	Vasudev K. et al., 2017 [17]

Note: MS – metabolic syndrome; ND – no data.

Discussion

Our review of the potential genetic biomarkers of clozapine induced-MS made it possible to systematize the results of previous associative genetic studies. The greatest interests for researchers concerning the genetic biomarkers of clozapine induced-MS, including the candidate genes: *CYP1A2*, *CYP2C19*, *HTR2C*, *LEP* and *LEPR*. According to the results of our scoping review, only 7 studies could be included that confirmed the carriage of SNPs in the studied candidate genes:

- 1) *CYP1A2* gene: genotype AA of rs762551 (NG_008431.2: g.32035C>A);
- 2) *CYP2C19* gene: CYP2C19*2 polymorphism;
- 3) *HTR2C* gene: genotype CC of rs518147 (NM_000868.2: c.-697G>C), allele C of rs1414334 (NG_012082.3: g.324497C>G), genotype CC of rs518147 (NM_000868.2: c.-697G>C), genotype GG of rs12836771 (NG_012082.3: g.71829A>G);
- 4) *LEP* gene: genotypes AG and GG of rs7799039 (NG_044977.1: g.475G>A);
- 5) *LEPR* gene: genotypes AG and GG of rs1137101 (NG_015831.2: g.177266A>G).

The limitations of this scoping review are the following:

- 1) Most studies have a cross-sectional design, the limitation of this design is that there is no data on the metabolic parameters of patients at the time of initiation of antipsychotic treatment. Therefore, it is not possible to analyze the data for changes in these parameters over time due to clozapine use.
- 2) The relatively small sample size made it difficult to analyze sex differences or the effects of rarer genotypes.
- 3) Although we conducted a comprehensive search of frequently used databases and search terms, it cannot be ruled out that some recent publications may have been overlooked.
- 4) Not investigated pharmacogenetic factors of clozapine-induced MS in TRS patients, at least the articles don't mention it. Also, in Russia no genetic studies of clozapine-induced MS have been found.
- 5) The main limitation of this review is the absence of a systematic review with meta-analysis, which we did not conduct for the following reason: considering the purpose of the review, the inclusion criteria are intentionally inclusive and broad for a more complete understanding and extensive analysis. Because of the heterogeneity of both the candidate genes themselves and the SNPs associated with clozapine induced-MS, as well as the presence of single studies for each SNP (except for a few studies for rs1414334, for which a meta-analysis has already been written), it is inexpediently to make a systematic review with meta-analysis.

Clozapine interacts with a very wide range of receptors, which accounts for the diversity of its clinical effects. Clozapine has a high affinity for dopamine, histamine, M-cholinergic, and $\alpha 1$ and B-adrenergic receptors, which determines its specific clinical and pharmacological properties, genes of which may have variability and influence the clozapine induced-MS. It would also be interesting to determine possible increased risk of MS when carrying several SNPs associated with clozapine-induced MS.

Clinical manifestations of clozapine induced-MS lead to a significant decrease in the quality of life of patients with schizophrenia and a decrease in their compliance with psychopharmacotherapy [29]. This explains the need for further research aimed at searching for the genetic biomarkers of clozapine induced-MS in various racial and ethnic groups of

psychiatric patients. The planning of large single-center and multicenter studies adopting a standardized design seems to be required. Furthermore, future studies should concentrate on including ethnically and racially heterogeneous populations of Russia and other countries.

Conclusions

It should be recognized that there is no final or single decision on the leading role of any SNPs/polymorphisms of candidate genes in the development of clozapine-induced MS. Uncovering the genetic predictors of clozapine-induced MS (as the most common ADRs in the treatment by clozapine) may provide a key to developing a strategy for the personalized prevention and treatment of clozapine-induced MS in patients with TRS in real clinical practice. However, to confirm this theory, there is a need for larger multicenter studies with different racial and ethnic groups of patients. Of course, currently, there are publications of studies of candidate genes leading to the development of clozapine-induced MS, but at the same time, clear genetic biomarkers are not known.

Funding: This research received no external funding.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Auquier, P.; Lancon, C.; Rouillon, F.; et al. Mortality in schizophrenia. *Pharmacoepidemiol Drug Saf* **2006**, *15*(12), 873–879.
2. De Hert, M.; Correll, C.U.; Bobes J.; et al. Physical illness in patients with severe mental disorders: prevalence, impact of medications and disparities in health care. *World Psychiatry* **2011**, *10*(1), 52–77.
3. Sosin, D.N.; Zhuperin, A.A.; Moshevitin, S.Yu.; et al. New prospects for getting over treatment resistant schizophrenia using drugs with adrenergic mechanism of action. *Sovrem. ter. psih. rasstrojstv* [Current Therapy of Mental Disorders] **2023**, *1*, 23–30.
4. Yin, J.; Barr, A.M.; Ramos-Miguel, A.; et al. Antipsychotic Induced Dopamine Supersensitivity Psychosis: A Comprehensive Review. *Curr Neuropharmacol* **2017**, *15*(1), 174–83.
5. Frogley, C.; Taylor, D.; Dickens, G.; et al. A systematic review of the evidence of clozapine's anti-aggressive effects. *Int J Neuropsychopharmacol* **2012**, *15*(9), 1351–71.
6. Vera, I.; Rezende, L.; Molina, V.; et al. Clozapine as treatment of first choice in first psychotic episodes. What do we know? *Actas Esp Psiquiatr* **2012**, *40*(5), 281–9.
7. Tiihonen, J.; Lonnqvist, J.; Wahlbeck, K.; et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* **2009**, *374*(9690), 620–7.
8. Yuen, J.W.Y.; Kim, D.D.; Procyshyn, R.M.; et al. A Focused Review of the Metabolic Side-Effects of Clozapine. *Front Endocrinol* **2021**, *12*, 609240.
9. Kim, D.D.; Barr, A.M.; Fredrikson, D.H.; et al. Association between Serum Lipids and Antipsychotic Response in Schizophrenia. *Curr Neuropharmacol* **2019**, *17*(9), 852–60.
10. Mottillo, S.; Filion, K.B.; Genest, J.; et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol* **2010**, *56*, 1113–32.
11. Henderson, D.C. Weight gain with atypical antipsychotics: evidence and insights. *J Clin Psychiatry* **2007**, *12*, 18–26.
12. Lappin, J.M.; Wijaya, M.; Watkins, A.; et al. Cardio-metabolic risk and its management in a cohort of clozapine-treated outpatients. *Schizophr Res* **2018**, *199*, 367–73.
13. Tso, G.; Kumar, P.; Jayasooriya, T.; et al. Metabolic monitoring and management among clozapine users. *Australas Psychiatry* **2017**, *25*(1), 48–52.
14. Henderson, D.C.; Nguyen, D.D.; Copeland, P.M.; et al. Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: results of a 10-year naturalistic study. *J Clin Psychiatry* **2005**, *66*(9), 1116–21.
15. Hurley, K.; O'Brien, S.; Halleran, C.; et al. Metabolic Syndrome in Adults Receiving Clozapine; The Need for Pharmacist Support. *Pharmacy* **2023**, *11*, 23.
16. Mulder, H.; Cohen, D.; Scheffer, H.; et al. HTR2C gene polymorphisms and the metabolic syndrome in patients with schizophrenia: a replication study. *J Clin Psychopharmacol* **2009**, *29*(1), 16–20.
17. Vasudev, K.; Choi, Y-H, Norman, R, et al. Genetic Determinants of Clozapine-Induced Metabolic Side Effects. *The Canadian Journal of Psychiatry* **2017**, *62*(2), 138–149.
18. Mulder, H.; Franke, B.; Beek van der, A.A.; et al. The Association Between HTR2C Gene Polymorphisms and the Metabolic Syndrome in Patients With Schizophrenia. *Journal of Clinical Psychopharmacology* **2007**, *27*(4), 338–343.

19. Mulder, H.; Cohen, D.; Scheffer, H.; et al. HTR2C Gene Polymorphisms and the Metabolic Syndrome in Patients With Schizophrenia. *Journal of Clinical Psychopharmacology* **2009**, *29*(1), 16–20.
20. Risselada, A.J.; Vehof, J.; Bruggeman, R.; et al. Association between HTR2C gene polymorphisms and the metabolic syndrome in patients using antipsychotics: a replication study. *The Pharmacogenomics Journal* **2010**, *12*(1), 62–67.
21. Puangpetch, A.; Unaharassamee, W.; Jiratjintana, N.; et al. Genetic polymorphisms of HTR2C, LEP and LEPR on metabolic syndromes in patients treated with atypical antipsychotic drugs. *J Pharm Pharmacol* **2018**, *70*(4), 536–542.
22. Yevtushenko, O.O.; Cooper, S.J.; O'Neill, R.; et al. Influence of 5-HT2C receptor and leptin gene polymorphisms, smoking and drug treatment on metabolic disturbances in patients with schizophrenia. *Br J Psychiatry* **2008**, *192*(6), 424–8.
23. Ma, X.; Maimaitirexiati, T.; Zhang, R.; et al. HTR2C polymorphisms, olanzapine-induced weight gain and antipsychotic-induced metabolic syndrome in schizophrenia patients: a meta-analysis. *Int J Psychiatry Clin Pract* **2014**, *18*(4), 229–42.
24. Drugbank.com. Available online: <https://go.drugbank.com/drugs/DB00363> (accessed on 25 October 2023).
25. Genecards.org. Available online: <https://www.genecards.org/> (accessed on 25 October 2023).
26. Reynolds, G.P.; Templeman, L.A.; Zhang, Z.J. The role of 5-HT2C receptor polymorphisms in the pharmacogenetics of antipsychotic drug treatment. *Prog Neuropsychopharmacol Biol Psychiatry* **2005**, *29*, 1021–1028.
27. Dobrodeeva, V.S.; Shnayder, N.A.; Mironov, K.O.; et al. Pharmacogenetic markers of antipsychotic-induced weight gain: leptin and neuroepitide Y. *V.M. Bekhterev review of psychiatry and medical psychology* **2021**, *55*(1), 3–10. (In Russ.)
28. Dobrodeeva, V.S.; Abdyrahmanova, A.K.; Nasyrova, R.F. Personalized approach to antipsychotic-induced weight gain prognosis. *Personalized Psychiatry and Neurology* **2021**, *1*(1), 3–10.
29. Krivoy, A.; Malka, L.; Fischel, T.; et al. Predictors of clozapine discontinuation in patients with schizophrenia. *Int Clin Psychopharmacol* **2011**, *26*(6), 311–5.