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Review | Обзор

Pharmacogenetic Biomarkers of Clozapine-Induced Sialorrhoea: A Systematic Review

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ABSTRACT

INTRODUCTION. Despite the proven clozapine effectiveness in patients with treatment resistant schizophrenia, its use can cause adverse drug reactions, including clozapine-induced sialorrhoea (CIS). Data on CIS pathogenesis are limited. Identifying CIS pharmacogenetic predictors will make it possible to both predict adverse drug reactions prior to therapy and specify individual pathogenetic elements.

AIM. This review aimed to identify CIS predictors using systematic analysis of literature data.

DISCUSSION. Research was conducted independently by two co-authors using PubMed, Google Scholar, GeneCards, and PharmGKB databases. A total of six (6) studies were selected that examined 17 candidate genes. The *ADRA2A* and *DRD4* genes were associated with CIS. The rs1800544 polymorphism of *ADRA2A* gene regulates the expression of alpha-2A adrenergic receptor (ADRA2A). Alpha-2-adrenoreceptors regulate salivation, thus clozapine antagonistic effect causes CIS. The 120-bp polymorphism of *DRD4* will reduce expression of type 4 dopamine receptor (DRD4). In turn, this may result in CIS as clozapine increases the receptor blockade. However, the results contradicted other studies, presumably due to assessment of different polymorphisms in the above studies. Moreover, the analysed studies had a number of methodological limitations.

CONCLUSIONS. The performed systematic review made it possible to identify CIS pharmacogenetic predictors. However, large multicenter studies using a strong prospective design and considering these limitations are required in order to verify the identified associations and develop a pharmacogenetic panel with high predictive accuracy for CIS.

REGISTRATION. Systematic review protocol is included in the international systematic review register (PROSPERO), Registry No. CRD420251089235.

Keywords: pharmacogenetics; clozapine; schizophrenia; treatment resistant schizophrenia; sialorrhea; adverse drug reaction; genetic polymorphisms; pharmacogenomic testing; systematic review

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Фармакогенетические биомаркеры сиалореи, вызванной приемом клозапина: систематический обзор

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РЕЗЮМЕ

ВВЕДЕНИЕ. Клозапин эффективен при лечении пациентов с терапевтической резистентностью при шизофрении, но его применение может сопровождаться развитием нежелательных реакций, в частности клозапин-индуцированной сиалореей (КИС). Данные о механизме развития КИС ограничены. Выделение фармакогенетических предикторов КИС позволит оценить вероятность возникновения осложнений до назначения терапии, а также уточнить отдельные звенья патогенетического механизма данной нежелательной реакции.

ЦЕЛЬ. Выявление фармакогенетических предикторов клозапин-индуцированной сиалореи при помощи систематического анализа данных литературы.

ОБСУЖДЕНИЕ. Поиск исследований проводили независимо два соавтора по базам PubMed, Google Scholar, GeneCards, PharmGKB. В общей сложности было найдено 6 исследований, в которых рассматривалось 17 генов-кандидатов. Ассоциация с КИС была выявлена для генов *ADRA2A*, *DRD4*. Полиморфизм rs1800544 гена *ADRA2A* регулирует экспрессию адренорецептора альфа 2A типа (ADRA2A). При этом α2-адренорецепторы участвуют в регуляции секреции слюны, а антагонистическое действие клозапина на них приводит к возникновению КИС. Носительство полиморфизма 120-bp *DRD4* приводит к снижению уровня экспрессии дофаминового рецептора 4 типа (DRD4). Это, в свою очередь, может вызвать развитие КИС за счет повышения степени блокады рецептора клозапином. Однако полученные данные противоречат результатам ряда других исследований. Возможным объяснением данного несоответствия является анализ различных полиморфизмов в указанных работах. Кроме того, проанализированные исследования имели ряд методологических ограничений.

ВЫВОДЫ. Проведенный систематический обзор литературы позволил определить фармакогенетические предикторы КИС. Но для уточнения полученных ассоциаций и разработки фармакогенетической панели с высокой прогностической точностью в отношении КИС необходимо проведение крупных мультицентровых исследований, использующих строгий проспективный дизайн с учетом выявленных ограничений.

РЕГИСТРАЦИЯ. Протокол систематического обзора зарегистрирован в международном проспективном реестре систематических обзоров (PROSPERO), регистрационный номер CRD420251089235.

Ключевые слова: фармакогенетика; клозапин; антипсихотики; шизофрения; терапевтическая резистентность при шизофрении; сиалорея; нежелательные реакции; полиморфизмы генов; фармакогенетическое тестирование; систематический обзор

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Финансирование. Данная работа выполнена при финансовой поддержке Министерства здравоохранения Российской Федерации, тематика государственного задания «Разработка фармакогенетической тест-системы для повышения эффективности и безопасности фармакотерапии пациентов кардиологического и психиатрического профилей» (ЕГИСУ НИОКТР № 124021200054-3).

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INTRODUCTION

Schizophrenia affects approximately 1% of the global population [1]. Advances in modern psychopharmacotherapy have taken the treatment of this disorder to a new level: in addition to managing positive symptoms (such as delusions, hallucinations, etc.), it has become possible to improve negative symptoms (for example, emotional-volitional deficits), while safety profile of psychopharmaceuticals has significantly improved [2]. However, approximately 30% of patients do not respond to antipsychotic treatment, meaning they have treatment-resistant schizophrenia (TRS) [3, 4]. Clozapine is the only antipsychotic effective in TRS [3, 5]. It improves positive schizophrenia symptoms, reduces suicide risk, and its long-term use is associated with improved outcomes in TRS patients [6–9]. However, clozapine is associated with a broad range of adverse drug reactions (ADRs), the most significant being agranulocytosis, myocarditis/cardiomyopathies, seizures, metabolic disturbances, constipation, sedation, and sialorrhoea [10, 11].

Sialorrhoea is one of the most frequently reported ADRs associated with clozapine use [12, 13]; it induces excessive salivation significantly more often than other antipsychotics [14, 15]. Pharmacoepidemiological data indicate that clozapine-induced sialorrhoea (CIS) occurs to some degree in 91.8% of patients [14], more commonly in the early stages of treatment, and may persist for a long time. Sialorrhoea significantly increases the risk of aspiration pneumonia [16, 17], a leading cause of death among patients treated with clozapine [18].

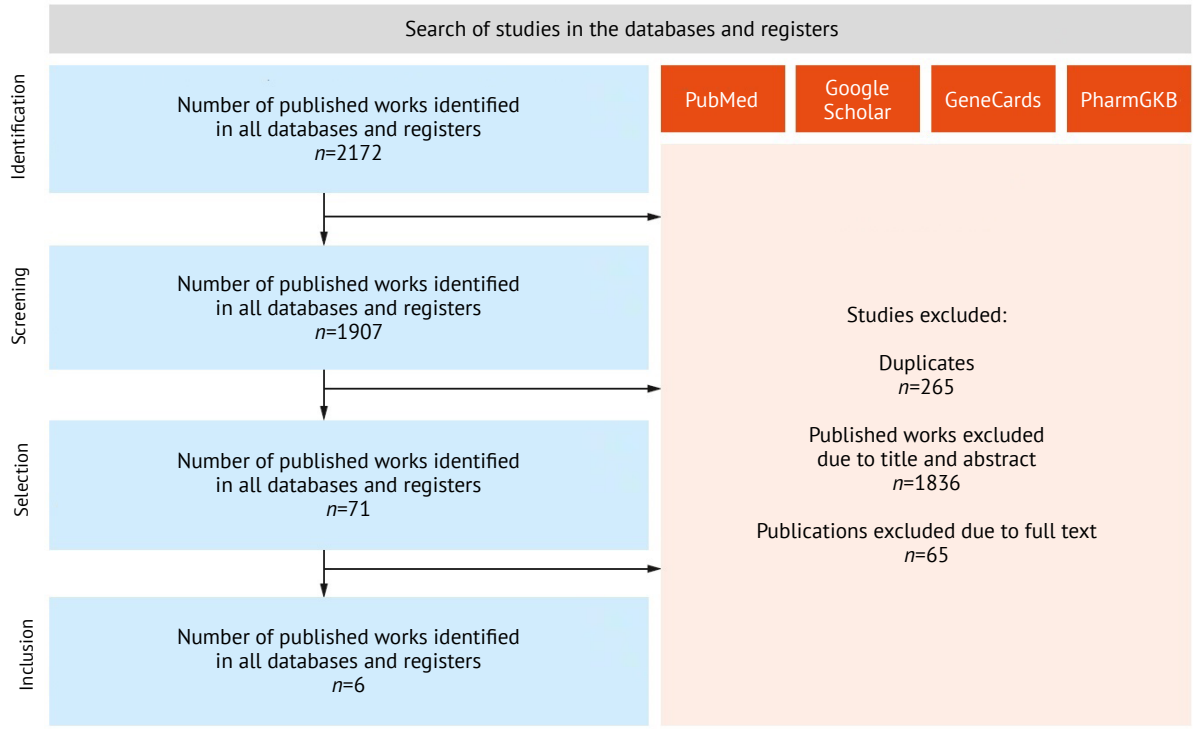
The exact underlying mechanism remains unclear. The primary hypothesis is clozapine selectively stimulating muscarinic receptors in the salivary glands [19, 20]. Salivary gland cells express M_1 and M_3 muscarinic receptors, with the M_3 receptor being primarily responsible for regulating salivation [21]. Clozapine and its metabolite, N-desmethylclozapine, are known as partial agonists of muscarinic receptors [22]. A 2020 study demonstrated that high serum concentrations of N-desmethylclozapine are associated with the risk of developing CIS [23]. *In vitro* studies show that, unlike clozapine, N-desmethylclozapine modifies calcium flux in salivary gland cells, while atropine inhibits this effect [23].

Currently, active pharmacogenetic research is being conducted to enhance the safety and efficacy of pharmacotherapy based on patient genome analysis [24]. Significant progress has been made in general medicine and cardiology. In psychiatry, data remain limited; current guidelines recommend pharmacogenetic testing for complex patient groups, including those with treatment resistance in psychiatric disorders [25, 26]. Clozapine is a promising candidate for pharmacogenetic testing since it is effective in treatment-resistant schizophrenia; however, its use is limited by the risk of serious ADRs [27]. Identification and subsequent systematisation of research findings aimed at discovering CIS pharmacogenetic biomarkers by separate scientific groups will help clarify the mechanism of this ADR, allowing for earlier intervention and management.

The aim of this study was to identify pharmacogenetic predictors of clozapine-induced sialorrhoea by conducting a systematic analysis of the literature data.

The review was prepared according to the PRISMA guidelines[1] *(Figure 1)*. The systematic review protocol was registered in the international prospective register of systematic reviews (PROSPERO[2]), Registry No. CRD420251089235, and

[1] https://www.prisma-statement.org/prisma-2020
[2] https://www.crd.york.ac.uk/PROSPERO/home



The figure is prepared by the authors / Рисунок подготовлен авторами

Figure 1. Flowchart of publication search for inclusion in a literature review

is publicly available. Two authors independently performed the literature search (Yu.S. Bellevich, A.G. Kirova). When selecting publications, any controversies were resolved through discussion until a consensus was reached. If the authors could not reach an agreement, they consulted the other co-authors (D.N. Sosin, S.N. Mosolov, D.A. Sychev).

Search queries for the scientific databases included: 1) PubMed — "(clozapine OR sialorrhoea) AND (schizophrenia OR pharmacogenetics) AND (polymorphism OR gene)"; Google Scholar — "clozapine", "sialorrhoea", "schizophrenia", "pharmacogenetics", "polymorphism", "gene". Furthermore, a search was performed in specialised pharmacogenetic and genetic databases: GeneCards[3] and PharmGKB[4]. Candidate genes were selected using the keyword "clozapine". All genes identified by this query were thoroughly examined for their potential role in CIS development. No timeframe was applied to the search.

Studies meeting the following criteria were included in this literature review: 1) study population: patients receiving clozapine as their primary therapy; 2) patients aged 18 to 65 years; 3) detecting association between genes and/or their polymorphisms and CIS; 4) works published in Russian or English. Conference materials, reports, abstracts, and results of preclinical studies were excluded.

At the literature screening stage, after removing duplicates, publication abstracts were analysed to select works meeting the inclusion criteria. Subsequently, the full texts were analysed. Furthermore, the authors examined reference lists of these works to identify publications potentially eligible for inclusion in this review (snowball method).

The following data were extracted from the selected publications: study aim and design, sample description, diagnosis, therapy, CIS specifics, studied gene polymorphisms, and statistical significance of the obtained associations (p-values). A critical assessment of the risk of systematic errors and bias, as well as a meta-analysis, was not performed due to the limited number of available studies. The analysed data were grouped under individual studies due to the small number of included works.

RESULTS

This literature review included six publications *(Table 1)*.

[3] https://www.genecards.org/ (authorised access)
[4] https://www.pharmgkb.org/ (authorised access)

Table 1. Research of CIS pharmacogenetic biomarkers

Source	Country	Study design (sample size)	Nosology	Selection of treatment resistant schizophrenia	Monotherapy with clozapine	Clozapine dosage, mg/day	Gene and its polymorphism	Association with sialorrhoea	Method for sialorrhoea assessment
Tsai S, et al., 2000 [28]	Taiwan	Prospective case–control (n=35, control=48)	Schizophrenic disorders (DSM-IV)	*Yes*	Yes (adjusted)	276±104	Biallelic polymorphism in the *ADRA2A* promoter region (C–1291G, rs1800544)	Not associated	Udvald for Kliniske Undersogelser Scale (UKU)
Rajkumar A, et al., 2012 [30]	India	Cross-sectional, case-control (n=101)	Schizophrenia (DSM IV-TR)	*Yes*	Not mentioned	340.84±119.04	*HTR3A* rs1062613, rs2276302	Not associated	Clinically (patient complaints and/or reports from relatives, medical records)
Rajkumar A, et al., 2013 [31]	India	Cross-sectional, case–control (n=101)	Schizophrenia (DSM IV-TR)	*Yes*	Not mentioned	340.84±119.04	*CYP1A2* rs2069514, rs35694136, rs2069526, rs762551	Not associated	Clinically (patient and/or relative complaints, medical records)
Rajagopal V, et al., 2014 [32]	India	Cross-sectional (n=95)	Schizophrenia (DSM IV-TR)	*Yes*	Not mentioned	358.8±110.28	*DRD4* 120-bp tandem duplication in the gene promoter region	Associated (OR 2.95, 95% CI: 1.51–5.75); p=0.0006)	Clinically (patient and/or relative complaints)
Solismaa A, et al., 2014 [33]	Finland	Cross-sectional (n=237)	Schizophrenia, schizoaffective disorder and other non-organic non-affective psychoses (ICD-10)	No	Yes, in a subset of the sample (n=155)	403±152	*CHRM1* rs2507821, rs542269, rs2075748	Not associated	Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS)
							CHRM3 rs4620530, rs6429157, rs6690809	Not associated	
							CLOCK rs1801260, rs3749474, rs4580704, rs6850524	Not associated	
							ADRA2A rs1800544	Associated (OR 2.13, 95% CI: 1.17–3.88; p=0.029)	

Table 1. Continued

Source	Country	Study design (sample size)	Nosology	Selection of treatment resistant schizophrenia	Monotherapy with clozapine	Clozapine dosage, mg/day	Gene and its polymorphism	Association with sialorrhoea	Method for sialorrhoea assessment
Puloakka H, et al., 2024 [34]	Finland	Cross-sectional (*n*=237)	Schizophrenia, schizoaffective disorder, and other non-organic non-affective psychoses (ICD-10)	No	Yes, in a subset of the sample (*n*=155)	403±152	*VIP*, *ERBB1, ERBB2, ERBB4*, *GRK2, GRK5, CHRM1, CHRM3, CHRM4*, *IP3*, *NK1*, *NTS*, *ADRA2A, DRD4*	Not associated	Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS)

The table is prepared by the authors

Note. DSM-IV, Diagnostic and statistical manual of mental disorders IV (1994–2000); DSM-IV-TR, Diagnostic and statistical manual of mental disorders IV (2000); OR, odds ratio; CI, confidence interval; ICD-10, International Classification of Diseases, 10th revision.

S. Tsai et al. [28] conducted a 2001 study in a Han Chinese population (*n*=97), with a prospective patient observation period of at least eight (mean 51.3±39.5) weeks. The study enrolled TRS patients switched to clozapine therapy. A certain limitation is the fact that the authors did not specify the criteria for classifying TRS patients. In addition to sialorrhoea, the authors assessed clozapine efficacy and association of the *ADRA2A* gene polymorphism rs1800544 with schizophrenia (the study included a comparison group of healthy volunteers).

Clozapine dose ranged from 50 to 700 mg/day (mean dose 276±104 mg/day). The authors did not explicitly state that clozapine was used as a monotherapy. However, the article lacks data on concomitant therapy, suggesting that patients were likely to receive only clozapine during the study. The presence of sialorrhoea was assessed using the UKU scale (Udvalg for Kliniske Undersogelser Scale) with only "hypersalivation" sub-item. As a result, CIS developed in 35 patients, while 48 did not have sialorrhoea.

The researchers investigated the association of a biallelic polymorphism in the *ADRA2A* promoter region (alpha-2A adrenergic receptor gene). Since modern nomenclatures, specifically dbSNP (database of Single Nucleotide Polymorphisms), were not introduced at the time of the study, the authors designated gene regions according to S. Lario et al. (1997) [29]. Based on our analysis, we determined that the authors studied association of the *C-1291G* polymorphism (rs1800544) with CIS. This study did not confirm an association between rs1800544 and CIS.

A. Rajkumar et al. conducted two studies in 2012 and 2013 [30, 31] in a population of Indian patients (*n*=101). Both publications present identical patient data, indirectly indicating that the studies were performed on the same clinical sample. The design in both cases was a cross-sectional case-control study. The subjects were patients with schizophrenia confirmed by the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM IV-TR) and taking clozapine for at least 12 weeks. Clozapine was prescribed in patients meeting TRS criteria. The authors do not explicitly state that patients received clozapine as a monotherapy; however, the publications lack data on concomitant therapy, indirectly suggesting monotherapy. The mean dose was 340.84±119.04 mg/day (dose range 100 to 650 mg/day).

Safety assessment was performed clinically: the authors collected complaints from patients and their relatives, and also retrospectively evaluated medical records. Besides sialorrhoea, other safety and efficacy parameters of clozapine were assessed, which are not considered within the scope of this literature review.

The 2012 study [30] analysed two polymorphisms of the *HTR3A* gene (serotonin receptor type 3A), rs1062613, and rs2276302, while the 2013 study [31] examined four polymorphisms of the *CYP1A2* gene (cytochrome P450 1A2): rs2069514, rs35694136, rs2069526, and rs762551. No association was found between the studied polymorphisms and CIS.

The study by V. Rajagopal et al. (2014) [32] was also conducted in a South Indian population of patients (*n*=95). The key patient characteristics coincide with those of the two previously described studies [30, 31]. Accordingly, the design, clozapine prescribing regimen, duration of its use, and safety assessment methods are also identical to the previous studies. However, the authors focused solely on CIS, without considering other safety parameters or the efficacy of clozapine. Out of the total number of patients (101 individuals), only 95 were included in the analysis due to insufficient genetic material for 6 patients. Due to the reduced number of patients, the mean daily clozapine dose changed: it was 358.8 ±110.28 mg/day in the group of sialorrhoea patients and 334.5±124.32 mg/day in the control group (*p*=0.025).

This study explored the correlation of 120-bp polymorphism of the *DRD4* gene (dopamine receptor D4 gene) with CIS. This polymorphism is a tandem duplication in the promoter region of *DRD4*. It was found that one long allele in the patient's genome (DRD4 120/240bp genotype) was associated with a 2.95-fold increased risk of developing CIS (odds ratio OR=2.95; 95% confidence interval (CI): 1.51–5.75; significance level *p*=0.0006), and the presence of two long alleles (240/240bp genotype) increased the risk 8.7-fold.

The study by A. Solismaa et al. (2014) [33] was performed in European patients (*n*=237). The authors designed a cross-sectional observational study with partial retrospective analysis. Patients diagnosed with schizophrenia, schizoaffective disorder, or other non-organic and non-affective psychoses were included (according to the International Classification of Diseases, 10th Revision (ICD-10)). All patients were receiving clozapine treatment for at least three months prior to inclusion in the study, with a mean dose of 403±152 mg/day. The authors

did not identify TRS patients separately. Clozapine was an antipsychotic monotherapy in 155 (65.4%) patients; the remaining 82 (34.6%) patients received it in combination with other antipsychotics. Thirty-two patients receiving only clozapine were also prescribed a tricyclic antidepressant (amitriptyline or doxepin). The authors classified these patients in the CIS group, as these drugs can be used to manage CIS. Based on the study description, it cannot be concluded that clozapine was taken as a monotherapy (without psychopharmaceuticals from other groups).

LUNSERS (Liverpool University Neuroleptic Side Effect Rating Scale) was used to assess CIS. The authors evaluated role of the following gene polymorphisms in the occurrence of CIS: *CHRM1* (cholinergic receptor muscarinic 1 gene) rs2507821, rs542269, rs2075748; *CHRM3* (cholinergic receptor muscarinic 3 gene) rs4620530, rs6429157, rs6690809; *CLOCK* (clock circadian regulator gene) rs1801260, rs3749474, rs4580704, rs6850524; *ADRA2A* (adrenergic receptor alpha 2A gene) rs1800544.

As a result, a role for the *ADRA2A* gene polymorphism rs1800544 was demonstrated: carriers of the CC genotype were twice as likely to develop CIS compared to carriers of the CG and GG genotypes (OR=2.13, 95% CI: 1.17–3.88, p=0.013). This correlation obtained in the overall sample persisted in the subset of patients taking only clozapine (n=155, p=0.044), but was not confirmed in patients taking other antipsychotics together with clozapine (n=82, p=0.11).

This team of authors published the results of another study [34] conducted in 2024 in the same patient sample (with identical clinical parameters), although analysing other pharmacogenetic endpoints. The study employed a genotyping method using microarrays, analysing 531,983 single nucleotide polymorphisms (SNPs). However, the authors selected 14 genes that could potentially be associated with CIS or dry mouth during clozapine treatment and investigated 9,039 polymorphisms of these genes (the complete list of studied polymorphisms was not presented in the work). Polymorphisms of the following genes were studied: *VIP* (vasoactive intestinal peptide gene), *ERBB1* (epidermal growth factor receptor gene), *ERBB2* (erb-b2 receptor tyrosine kinase 2 gene), *ERBB4* (erb-b2 receptor tyrosine kinase 4 gene), *GRK2* (G protein-coupled receptor kinase 2 gene), *GRK5* (G protein-coupled receptor kinase 5 gene), *CHRM1, CHRM3, CHRM4* (cholinergic receptor muscarinic 4 gene), *IP3*[5], *NK1* (NK1 homeobox transcription factor gene), *NTS* (neurotensin gene), *ADRA2A*, and *DRD4*. None of the studied SNPs showed an association with CIS.

DISCUSSION

Clozapine stands out among other atypical antipsychotics due to its efficacy in TRS; however, its use in clinical practice is limited by the potential development of serious ADRs [35, 36]. Sialorrhoea is reported four times more frequently with clozapine than with other antipsychotics [32]. The mechanism underlying CIS is quite complex and remains incompletely understood to date [12].

As a result of the conducted systematic literature review, we have identified a relatively small number of published studies. Of the six published works, three studies were performed for the same patient sample [30–32]; another two were also conducted on a single sample [33, 34]. It is important to note that in all studies, the authors investigated genetic panels related to the pathways of clozapine mechanism of action (either pharmacokinetic or pharmacodynamic). In total, 17 genes were analysed across all publications for an association with CIS. *ADRA2A* was the most frequently studied gene evaluated in three publications, with two of these studies conducted on the same sample. Notably, these studies yielded conflicting results (whereas the work by H. Puolakka et al., 2024 [34], does not specify the particular polymorphisms assessed by the authors).

The *DRD4* gene was included in two studies, also with the opposing results [32, 34]. This is quite plausible, as the authors evaluated the association of different single nucleotide polymorphisms with CIS.

The *CHRM1* and *CHRM3* genes were also studied in two works conducted in the same patient sample [33, 34]. The remaining genes were examined only once in the above studies.

Consequently, an association with CIS was demonstrated only for two genes: *ADRA2A* and *DRD4*. In the first case, the authors studied the rs1800544 polymorphism associated with an increased CIS risk. This polymorphism represents cytosine to guanine transversion at position –1291 in the promoter region of the *ADRA2A* gene [37]. Given its location in an intergenic region, this polymorphism does not affect the protein structure; however, it may hypothetically regulate the expression of the alpha-2A adrenergic receptor (ADRA2A) [29,

[5] Inositol-1,4,5-trisphosphate is a signaling molecule. This system includes a large number of different genes; we could not determine exactly what genes the authors studied in their work [34], therefore we provide the description unchanged.

37]. The adrenergic system exerts a modulatory effect on saliva production in the human body, leading to an increased protein content therein [38]; α2-adrenoreceptors, among others, regulate saliva secretion, and the antagonistic action of clozapine on these receptors leads to CIS [39, 40].

The next gene associated with CIS is *DRD4*. An association was established between a 120-bp tandem duplication in the promoter region of this gene and the risk of developing CIS. This mutation is known to be of functional significance, influencing the *DRD4* gene expression [41]. Lower transcriptional activity associated with the long allele of this polymorphism causes reduced expression levels of the dopamine D4 receptor (DRD4) [41]. The authors hypothesise that due to the decreased density of these receptors in carriers of the long allele, these individuals might experience a higher degree of receptor blockade by clozapine (compared to carriers of short alleles), which, in turn, could lead to CIS [32].

The studies included in this literature review have several significant limitations. Primarily, this concerns the sizes of the patient samples. The number of patients in the studies ranged from 83 to 237, a relatively small sample size for pharmacogenetic research. Furthermore, only one out of the six studies employed a prospective design; the rest were cross-sectional, which also somewhat increases the likelihood of systematic error.

Another substantial limitation is the inclusion of patients taking clozapine in combination with psychotropic drug classes. Other psychotropic medications are known either to enhance CIS manifestations (e.g., paliperidone) or reduce them (e.g., amisulpride), which undoubtedly negatively affects the experiment integrity and the risk of systematic error [42–44].

A further limitation is the inclusion of patients from nosological groups other than schizophrenia. Specifically, not all studies separately identified patients with TRS. This is an important aspect, as TRS patients may have different underlying biology, which, in turn, could influence the risk of CIS [45–47].

Moreover, the studies utilised different assessment methods of sialorrhoea severity. In three studies [28, 33, 34], researchers used specialised rating scales, while in the remaining three works (conducted on the same patient sample) [30–32], a clinical method was used to determine ADRs. This method involved analysing clinical manifestations based on patient self-reports, reports from close relatives, and medical records. Besides the inherent lack of objectivity associated with the clinical approach to a considerable degree, the use of different assessment methodologies leads to difficulties in comparing results across studies during analysis.

CONCLUSION

The data obtained from this systematic review indicate the involvement of the *ADRA2A* and *DRD4* genes in developing CIS. In both cases, hypotheses regarding the underlying genetic mechanisms have been proposed. Despite certain limitations in the studies included in this review, the results are of significant scientific value and can serve to develop an algorithm for the personalised clozapine prescription.

Carriers of the CC genotype (rs1800544 of the *ADRA2A* gene) and of the long *DRD4* allele are found to be at an increased risk of CIS. Identifying such patients prior to prescribing clozapine allows for planning management tactics in clinical practice. This could include, among others, increasing the frequency of CIS assessment, implementing a slower dose titration of clozapine (compared to patients without this risk factor) or dose reduction, and timely CIS management.

Large multicenter studies employing a strict prospective design considering the above limitations are required to further identify CIS pharmacogenetic predictors. The results of such studies could form the basis for developing a pharmacogenetic panel with high predictive accuracy of CIS.

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