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The Influence of Genetic Variations in CYP1A2 Associated with Clozapine Metabolism in Schizophrenia Patients

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Abstract

*Schizophrenia is a severe mental disorder that affects how a person thinks, feels, and behaves. Antipsychotic drugs are the treatment of choice for patients with schizophrenia. Clozapine is an atypical antipsychotic with unique efficacy in treatment-resistant schizophrenia. However, genetic variations in CYP1A2 can influence the differences in the activity of this enzyme, which in turn can affect the metabolism of clozapine and the response to treatment. This review aims to examine the impact of CYP1A2 genetic variations on clozapine metabolism in patients with schizophrenia. This review is prepared using the narrative literature review method, literature search was conducted through PubMed over the past ten years (2014-2024) using relevant keywords. The findings indicate that CYP1A2 genetic variations *1F is an ultrarapid metabolizer whose activity is strengthened by the presence of cigarettes, while *1C and *1D shows a decrease in CYP1A2 enzyme metabolism. This review underscores the importance of considering genetic factors, particularly CYP1A2, in tailoring treatment plans for schizophrenia patients*

Keywords: *Clozapine; CYP1A2; Polymorphism; Schizophrenia*

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INTRODUCTION

Schizophrenia is a serious mental illness that affects the way a person thinks, feels, and behaves Individuals with schizophrenia may appear to have lost touch with reality, which can be distressing for them, their families, and their friends Symptoms of schizophrenia can make it difficult for sufferers to carry out daily activities (Hany et al., 2024). Schizophrenia symptoms are divided into three major domains in terms of perceived symptoms First, positive symptoms such as hallucinations, perceptual disturbances, delusional phenomena, and formal thought disorders Second, cognitive dysfunction, which includes deficits in motivation and executive function

And third, negative symptoms, including flat affect, impaired speech, lack of will, and inappropriate emotional responses (Quednow et al., 2020).

Schizophrenia affects about 24 million people or 1 in 300 people (0.32%) worldwide. This figure is 1 in 222 people (0.45 %) among adults (WHO, 2022). The onset is most common in late adolescence and twenties, and onset tends to occur earlier in men than women (Hollis & Rapoport, 2010; McGrath et al., 2008). Schizophrenia is a common factor in poor diet, weight gain, smoking, and drug use. This results in the life expectancy of people with schizophrenia of only about 13 to 15 years. As much as 5 to 10% of the risk of suicide occurs in people with schizophrenia (Hany et al., 2024). In Indonesia, it is recorded that 6.7% of 1000 households have a prevalence of schizophrenia, this number is significantly higher than the global data (Kemenkes RI, 2019).

Schizophrenia is caused by various factors, including genetic, environmental, and neurobiological factors. Research indicates that almost 80% of schizophrenia cases are caused by genetic factors (Hilker et al., 2018), specifically the presence of a rare mutation resulting in the deletion of chromosome 22q112. Although such genetic mutations are generally unlikely to occur genome-wide association studies have identified 130 genes known to increase the risk of schizophrenia nearly 30% of these genes are involved in the function of pre-and postsynaptic elements in glutamatergic synapses, affecting the transmission of N-methyl-D-aspartate (NMDA) receptors environmental factors, in conjunction with genetics, can also influence the likelihood of developing schizophrenia heavy marijuana users have a 6-fold greater risk of receiving a schizophrenia diagnosis compared to non-users.

Schizophrenia is neurobiologically associated with dysfunction of neurotransmitters in the dopamine, serotonin, and glutamate systems (Britannica, 2024; Patel et al., 2014). Neurotransmitters are chemical compounds that act as carriers of impulses from nerve cells (pre synapses) to target cells (post synapses) through chemical synaptic transmission in the synaptic cleft, thereby regulating bodily responses (Sheffler et al., 2024). Hyperactive dopamine transmission leads to positive symptoms of schizophrenia, such as hallucinations and delusions, due to excessive dopamine activity at D2 receptors Conversely, negative symptoms like anhedonia, apathy, and cognitive impairment occur due to deficient dopamine activity in the mesocortical prefrontal cortex pathway, particularly at D1 receptors (Brisch et al., 2014).

Currently, the majority of schizophrenia patients worldwide do not receive mental health services. Approximately 50 % of individuals in psychiatric hospitals have a diagnosis of schizophrenia. Only 31.3 % of psychosis patients receive specialized mental health care (Jaeschke et al., 2021). Out of the total schizophrenia cases in Indonesia, 84.9 % have utilized treatment (Cipta & Saputra, 2022). One of the treatment options for schizophrenia patients is medication. Antipsychotic drugs are a choice for these patients. These drugs help restore neurotransmitter levels to a balanced state. Antipsychotics are divided into two types: typical (first generation) and atypical (second generation). First and second-generation antipsychotic medications have comparable clinical efficacy, except for clozapine (Jibson, 2023). Clozapine is included in atypical with a unique efficacy in treatment-resistant schizophrenia, i.e., for those for whom at least two typical or atypical antipsychotics are ineffective

(Silva et al., 2020; Sriretnakumar et al., 2015; Thorn et al., 2018). Clozapine is also the most widely chosen regimen to be given to schizophrenia patients.

Clozapine has a better affinity for dopamine receptors and blocks 5-HT 2A receptors, decreases the hyperactivity of the mesolimbic dopaminergic pathway, and increases the activity of D1 receptors in the prefrontal cortex (Brisch et al., 2014). Clozapine is metabolized in the liver by the cytochrome P450 (CYP450) enzyme superfamily. CYP1A2 enzyme is the main CYP enzyme involved in clozapine metabolism, and CYP1A2 activity is a potential determinant of clozapine dosage requirements, CYP1A2 is mainly responsible for the formation of N-desmethylclozapine (Silva et al., 2020). Other CYP enzymes involved in clozapine metabolism include CYP2D6, CYP3A4, and CYP2C19 (Dean & Kane, 2012). Clozapine undergoes extensive liver metabolism with the main demethylation pathway to N-desmethylclozapine and oxidation to clozapine N-oxide (Thorn et al., 2018). N-desmethylclozapine is an active metabolite capable of exerting effects through dopamine receptors D2 and D3 (Mendoza & Lindenmayer, 2009). Clozapine N-oxide is considered inactive and can be metabolized back into clozapine (Thorn et al., 2018).

Numerous research has demonstrated that clozapine has a range of effects on cognition, from positive to neutral to detrimental (Islam et al., 2021). Antipsychotic medications only work for one-third of people with schizophrenia (Lesche et al., 2020). Genetic differences in CYP1A2 can impact the enzyme's activity, which in turn can impact the metabolism of clozapine and the response to treatment (Ammar et al., 2021). For example, people with genetic polymorphisms that enhance CYP1A2 activity might have a faster metabolism of clozapine, which could affect the dosage needed to achieve the desired therapeutic benefits. This review looks at how genetic differences in CYP1A2 affect the medication Clozapine in people with schizophrenia.

METHOD

This review is prepared using the narrative literature review method. A narrative literature review is a type of qualitative research that focuses on recounting human life through experiences, interviews, photography, biographies, and other methods of human experience narratives (Ford, 2020). In this method, there is no statistics are involved, and no formal analysis is carried out on the data (Nahdiyin, 2023). In composing this writing, a literature search method was employed regarding discussions in the PubMed database relevan to the topic at hand using the keywords "Clozapine," "CYP1A2," "Schizophrenia," "polymorphism," and "gene." Journal articles were selected based on criteria as primary literature, published within the last 10 years (2014-2024), reporting on the genetic variations of CYP1A2 in schizophrenia patients undergoing Clozapine treatment. Exclusion is from the results of publication reviews, systematic reviews, and meta-analyses of articles that are not considered original research. The data obtained is presented as a descriptive narrative related to the discussion being studied.

The review was obtained from 10 articles with patient populations from different countries with the same variable, namely schizophrenia patients taking Clozapine. Schizophrenia is a chronic and severe psychiatric disorder that exhibits variability in response to many antipsychotic medications. Factors such as ethnicity, co-medicine, age, gender, diet, as well as genetic variability for cellular receptors and drug metabolism, have been shown to influence Clozapine (Silva et al., 2020). Changes in CYP1A2 function can affect the metabolism of Clozapine. Clozapine is mostly metabolized by CYP1A2, which is 70% (Caetano & Piatkov, 2015).

RESULT AND DISCUSSION

It is known that there is a linear relationship between the dose (D) of Clozapine (mg/day) and the concentration (C) (ng/mL), or it can be said that the ratio of concentration to dose (C/D). This C/D ratio is a measure of drug elimination that is influenced by genetics, individuals and environment. A low C/D ratio of Clozapine indicates the presence of an ultra rapid metabolizer (UM) phenotype, while a high C/D ratio indicates the presence of a poor metabolizer (PM) phenotype (Ruan et al., 2019). There are about 25 CYP1A2 allele variants that have been reported, some of which affect the activity of the CYP1A2 enzyme. For example, some alleles whose enzyme activity has been known such as the *1C allele are associated with reduced enzyme activity, while the *1F allele is associated with increased enzyme activity (Dean & Kane, 2012).

Table 1. Research Results Discussing CYP1A2 Gene Variations in Clozapine-treated Schizophrenia Patients

Researcher	Country	Gene	Conclusion
Caetano & Piatkov (2015)	Australia (n= not reported)	*1C, *1F, *1D	Patients with CYP1A2*1C and *1D polymorphisms showed higher serum Clozapine concentrations and an increased risk of increased serum insulin lipids and insulin resistance.
Caetano & Piatkov (2016)	Australia (n= not reported)	*1D, *1F	Polymorphism homozygous CYP1A2*1D (rs35694136) in smokers is associated with decreased activity and higher concentrations of Clozapine in patients who have alleles *1C and *1D.
Huang et al., (2016)	Taiwan (n=143)	*1F	The Clozapine levels in patients with the *1F (-163A>C) allele who smoke and do not smoke appear significant.

Researcher	Country	Gene	Conclusion
Vasudev et al., (2017)	Canada (n= 60)	*1F, *1C, *1D	The genetic factor CYP1A2*1F A/A and smoking lifestyle can simultaneously affect the metabolic syndrome of patients consuming Clozapine.
Ruan et al., (2019)	China, Taiwan, Korea, India (n=429)	*7	The Phenotype PM ranges from 2-13%, with 5 individuals being associated with extreme obesity, while the Phenotype UM ranges from 0-16%, affecting one individual in India, with metabolism induction related to excessive coffee consumption.
Lesche et al., (2020)	Australia (n= 66)	*1A, *1F	Other factors such as smoking and the use of other drugs like esomeprazole affect the activity of the CYP1A2 enzyme on clozapine levels in the blood.
Smith et al., (2020)	Norwegian (n= 484)	NFIB (rs28379954)	The habit of smoking is associated with a significant decrease in serum clozapine concentration, specifically an estimated 37,6% reduction in serum clozapine concentration adjusted for dosage, in carriers of the heterozygous minor allele rs28379954 C compared to homozygous wild-type carriers (rs28379954 TT).
Ammar et al., (2021)	Tunisia (n=51)	*1C, *1F	The CYP1A2*1F rs762551 (-163C>A) polymorphism affects clozapine metabolism in the body.
Islam et al., (2021)	Canada (n=30)	*1, *1F	CYP1A2 *1F/*1F has a much higher concentration of Clozapine compared to *1/*1 and *1/*1F.
Pfeifervan et al., (2022)	Several countries (n=804)	CYP2C19	High PRS (polygenic risk score) and high CYP2C19 enzyme activity are associated with milder symptoms.

The Allele CYP1A2*1F rs762551 (-163C>A) is associated with higher mRNA expression, leading to increased enzyme activity and a higher dose requirement for Clozapine Conversely, the Alel CYP1A2*1C rs2069514 (-3860G>A) is linked to limited mRNA expression, resulting in decreased enzyme activity and a lower

Clozapine requirement (Ammar et al., 2021). The Allele CYP1A2*1F is predicted to be an ultra-rapid metabolizer (Lesche et al., 2020).

Table 2. Enzyme Activity Based on Allele Variations of CYP1A2

Enzym activity	CYP1A2 allele haplotypes
Normal Function (NF)	*1, *1A
Decreased Function (DF)	*1C, *1K, *3, *4, *6, *7, *8, *11, *15, *16
No Function	*6
Increased Function (IF)	*1F

Source: (Dean & Kane, 2012; PharmVar, 2017; SNPedia, 2018)

It is reported Lesche et al., (2020) that the CYP1A2 enzyme that metabolizes clozapine may be affected by cigarette use. Two gene variations (polymorphism) concern how cigarettes can affect CYP1A2. This aligns with the polymorphism *1F is associated with increased enzyme activity in smokers (Ros et al., 2005). In CYP1A2*1F patients who received clozapine, it was associated with unresponsiveness to treatment requiring higher doses. Smoking CYP1A2*1F (rs762551), homozygotes had lower plasma clozapine levels, higher metabolite concentrations, and faster elimination than non-smoking ones. Patients with low-expression alleles of CYP1A2 are more likely to experience side effects related to increased plasma clozapine levels, decreased metabolites, and decreased elimination (Thorn et al., 2018).

Smoking can increase the activity of the enzyme CYP1A2, thus necessitating an increase in the dosage of Clozapine (Lesche et al., 2020). This is consistent with findings of Vasudev et al., (2017) that show patients with a smoking lifestyle have lower concentrations of Clozapine compared to non-smoking patients. This indicates the induction of CYP1A2 metabolism by cigarettes.

The research conducted by Smith et al., (2020) found that smoking habits in the CYP1A2 gene can lead to more severe symptoms and lower clozapine concentration in the blood The reduced clozapine concentration is due to a more active metabolic process, resulting in faster elimination of clozapine The *1D allele in the CYP1A2 gene, especially in smoking patients, indicates decreased enzyme activity (Caetano & Piatkov, 2016). This decreased enzyme activity means that the enzyme does not function efficiently.

The research findings of Caetano & Piatkov (2015) revealed that the genotype of patients with heterozygous polymorphism CYP1A2 rs35694136 is associated with decreased enzyme activity, resulting in higher serum levels of Clozapine and Clozapine/Norclozapine ratio than expected for the given dosage It is known that the therapeutic range for Clozapine serum levels is 350-420 µg/L (de Leon et al., 2022).

Patients with a smoking lifestyle and a CYP1A2*1F A/A genotypes have a 46 times higher risk of metabolic syndrome compared to those with a CYP1A2 C/C genotype. Meanwhile, non-smoking patients with the same genotype, CYP1A2*1F A/A, have a 92 % lower chance of metabolic syndrome compared to those with the CYP1A2 C/C genotype (Vasudev et al., 2017).

The Asian population (from Pakistan to Japan) or Native Americans have lower CYP1A2 activity and require a lower dose of clozapine to achieve a concentration of 350 ng/mL (de Leon et al., 2022). However, the Dutch Pharmacogenetics Working Group (D.P.W.G.) further states that there is no gene-drug interaction between CYP1A2 and clozapine due to the limited effect of known genetic variants on CYP1A2 function As a result, both the F.D.A. and D.P.W.G. do not recommend dose adjustments based on CYP1A2 genotype There are no coding sequence variants of CYP1A2 associated with clozapine metabolism, possibly due to their shallow frequency in most populations (Thorn et al., 2018).

Table 3. Summary of PK gene variants and associated phenotypes (Thorn et al., 2018)

Gene Variants	Allele/Genotype	Association
CYP1A2 rs762551 (*1F)	A A	Decreased likelihood of Metabolic Syndrome in non-smokers
CYP1A2 rs762551 (*1F)	A A	Increased likelihood of Metabolic Syndrome in smokers
CYP1A2 rs762551 (*1F)	A A	Not responsive
CYP1A2 rs35694136 / rs2069514 (*1C)	DEL/A	increased likelihood of insulin levels
CYP1A2 *1F	*1F/*1F	increased risk of seizures
CYP1A2 *1C	*1C	increased severity of Confusion, Drug Toxicity, Headache, Muscle Stiffness, sedation, and Tachycardia
CYP2C19	*17/*17	higher serum N-desmethyl clozapine levels, lower prevalence of diabetes, improvement of Schizophrenia symptoms
CYP2C19	*2/*2	higher serum clozapine levels
CYP2C19	*2	Increased likelihood of metabolic syndrome

CONCLUSION

Knowing the polymorphism of the CYP1A2 gene, which is considered to affect clozapine metabolism, that essential information for the personalization of treatment and the adjustment of different drug doses allows it necessary to achieve optimal therapeutic effects without causing side effects, but further studies and in-depth knowledge regarding the impact of genetic variants on the CYP1A2 gene are needed. In addition, the use of cigarettes also affects the activity of the CYP1A2 gene enzyme, so the smoking status in patients needs to be known for the adjustment of the dose of Clozapine given. Variations in the CYP1A2 gene for Clozapine metabolism are known to be closely related to smoking lifestyles. However, the shortcomings in this review

need to address how the mechanism of cigarettes may affect how the enzymes produced by CYP1A2 work.

REFERENCES

Ammar, H., Chadli, Z., Mhalla, A., Khouadja, S., Hannachi, I., Alshaikheid, M., Slama, A., Ben Fredj, N., Ben Fadhel, N., Ben Romdhane, H., Chaabane, A., Boughattas, N. A., Gaha, L., Zarrouk, L., & Aouam, K. (2021). Clinical and genetic influencing factors on clozapine pharmacokinetics in Tunisian schizophrenic patients. *Pharmacogenomics Journal*, *21*(5), 551–558. https://doi.org/10.1038/s41397-021-00231-x

Brisch, R., Saniotis, A., Wolf, R., Bielau, H., Bernstein, H.-G., Steiner, J., Bogerts, B., Braun, A. K., Jankowski, Z., Kumaritlake, J., Henneberg, M., & Gos, T. (2014). The Role of Dopamine in Schizophrenia from a Neurobiological and Evolutionary Perspective: Old Fashioned, but Still in Vogue. *Frontiers in Psychiatry*, *5*. https://doi.org/10.3389/fpsyt.2014.00047

Britannica, T. E. of E. (2024). *neurotransmitter*. Encyclopedia Britannica. https://www.britannica.com/science/neurotransmitter. Accessed on 17Th July 2024

Caetano, D., & Piatkov, I. (2015). Higher than expected clozapine serum level and clozapine/norclozapine ratio due to CYP450 gene polymorphisms. *Personalized Medicine*, *12*(6), 555–558. https://doi.org/10.2217/pme.15.33

Caetano, D., & Piatkov, I. (2016). Ultrarapid clozapine metabolism and CYP2D6 gene duplication in a patient with schizophrenia. *Personalized Medicine*, *13*(2), 113–117. https://doi.org/10.2217/pme.15.56

Cipta, D. A., & Saputra, A. (2022). Changing Landscape of Mental Health from Early Career Psychiatrists' Perspective in Indonesia. *JoGHNP*. Published online August 5, 2022:e2022011 https://doi.org/doi:10.52872/001c.37413

de Leon, J., Schoretsanitis, G., Smith, R. L., Molden, E., Solismaa, A., Seppälä, N., Kopeček, M., Švancer, P., Olmos, I., Ricciardi, C., Iglesias-Garcia, C., Iglesias-Alonso, A., Spina, E., Ruan, C.-J., Wang, C.-Y., Wang, G., Tang, Y.-L., Lin, S.-K., Lane, H.-Y., … Müller, D. J. (2022). An International Adult Guideline for Making Clozapine Titration Safer by Using Six Ancestry-Based Personalized Dosing Titrations, CRP, and Clozapine Levels. *Pharmacopsychiatry*, *55*(2), 73–86. https://doi.org/10.1055/a-1625-6388

Dean, L., & Kane, M. (2012). Clozapine Therapy and CYP Genotype. In *Medical Genetics Summaries*. National Center for Biotechnology Information (US). http://www.ncbi.nlm.nih.gov/pubmed/26364648.

Ford, E. (2020). Tell me your story: Narrative inquiry in LIS research. *College & Research Libraries*, *81*(2), 235–247. https://doi.org/https://doi.org/10.5860/crl.81.2.235

Hany, M., Baryiah, R., Rizvi, A., & Chapman, J. (2024). *Schizophrenia*. StatPearls.

https://www.ncbi.nlm.nih.gov/books/NBK539864/

Hilker, R., Heleniusd, D., Fagerlund, B., Skytthef, A., Christensenf, K., Werge, T. M., Nordentoft, M., & Glenthøj, B. (2018). Heritability of Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register. *Biological Psychiatry*, *83*(6), 492–498.

Hollis, C., & Rapoport, J. (2010). Child and adolescent schizophrenia. In Weinberger, D.R., & Harrison, P.J. *Schizophrenia,* 24–46. Wiley. https://doi.org/https://doi.org/10.1002/9781444327298.ch3

Huang, H. C., Lua, A. C., Wu, L. S. H., Wu, B. J., Lee, S. M., & Liu, C. Z. (2016). Cigarette smoking has a differential effect on the plasma level of clozapine in Taiwanese schizophrenic patients associated with the CYP1A2 gene 163AC single nucleotide polymorphism. *Psychiatric Genetics*, *26*(4), 172–177. https://doi.org/10.1097/YPG.0000000000000139

Islam, F., Maciukiewicz, M., Freeman, N., Huang, E., Tiwari, A., Mulsant, B. H., Pollock, B. G., Remington, G., Kennedy, J. L., Müller, D. J., & Rajji, T. K. (2021). Contributions of cholinergic receptor muscarinic 1 and CYP1A2 gene variants on the effects of plasma ratio of clozapine/N-desmethylclozapine on working memory in schizophrenia. In *Journal of Psychopharmacology,* 35(1), 31–39. https://doi.org/10.1177/0269881120946288

Jaeschke, K., Hanna, F., Ali, S., Chowdhary, N., Dua, T., & Charlson, F. (2021). Global estimates of service coverage for severe mental disorders: findings from the WHO Mental Health Atlas 2017. *Global Ment Health (Camb)*, *8*(e27). https://doi.org/https://doi.org/10.1017/gmh.2021.19

Jibson, M. D. (2023). *Second-generation antipsychotic medications: Pharmacology, administration, and side effects*. Www.Uptodate.Com ©. https://www.uptodate.com/contents/second-generation-antipsychotic-medications-pharmacology-administration-and-side-effects/print. Accessed on 17Th July 2024

Kemenkes RI. (2019). *Laporan Riskesdas 2018 Nasional*. https://repository.badankebijakan.kemkes.go.id/3514/1/Laporan Riskesdas 2018 Nasional.pdf. Accessed on 17Th July 2024

Lesche, D., Mostafa, S., Everall, I., Pantelis, C., & Bousman, C. A. (2020). Impact of CYP1A2, CYP2C19, and CYP2D6 genotype- and phenoconversion-predicted enzyme activity on clozapine exposure and symptom severity. *Pharmacogenomics Journal*, *20*(2), 192–201. https://doi.org/10.1038/s41397-019-0108-y

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews*, *30*, 67–76. https://doi.org/10.1093/epirev/mxn001

Mendoza, M. C. N., & Lindenmayer, J.-P. (2009). N-Desmethylclozapine: Is There Evidence for its Antipsychotic Potential? *Clinical Neuropharmacology*, *32*(3), 154–157. https://doi.org/10.1097/WNF.0b013e31818d46f5

Nahdiyin, N. A. (2023). Jurnal Kajian Perpustakaan dan Informasi. *Bibliotika*, *7*(2),

227–239. https://doi.org/http://dx.doi.org/10.17977/um008vi12017p001

Patel, K. R., Cherian, J., Gohil, K., & Atkinson, D. (2014). Schizophrenia: overview and treatment options. *P & T: A Peer-Reviewed Journal for Formulary Management*, *39*(9), 638–645. http://www.ncbi.nlm.nih.gov/pubmed/25210417

Pfeifervan, C. O., der Horst, M. Z., Bousman, C. A., Lin, B., van Eijk, K. R., Ripke, S., Ayhan, Y., Babaoglu, M. O., Bak, M., Alink, W., van Beek, H., Beld, E., Bouhuis, A., Edlinger, M., Erdogan, I. M., Ertuğrul, A., Yoca, G., Everall, I. P., Gö, C., van der Horst, M. Z., … Luykx, J. J. (2022). Genome-wide association analyses of symptom severity among clozapine-treated patients with schizophrenia spectrum disorders. *Translational Psychiatry*, *12*(1), 1884-1896. https://doi.org/10.1038/s41398-022-01884-3

PharmVar. (2017). *CYP1A2*. PharmVar. https://www.pharmvar.org/gene/CYP1A2. Accessed on 17Th July 2024

Quednow, B. B., Geyer, M. A., & Halberstadt, A. L. (2020). Serotonin and schizophrenia. *Handbook of Behavioral Neuroscience*, *31*, 711–743. https://doi.org/10.1016/B978-0-444-64125-0.00039-6

Ros, J. E. K., Smallegoor, W., & van der Weide, J. (2005). The cytochrome P450 CYP1A2 genetic polymorphisms *1F and *1D do not affect clozapine clearance in a group of schizophrenic patients. *Annals of Clinical Biochemistry*, *42*(3), 216–219. https://doi.org/10.1258/0004563053857798

Ruan, C. J., Wang, C. Y., Tang, Y. L., Lin, S. K., Lee, S. T., Hong, K. S., Rajkumar, A. P., Jacob, K. S., & De Leon, J. (2019). Exploring the Prevalence of Clozapine Phenotypic Poor Metabolizers in 4 Asian Samples: They Ranged Between 2% and 13%. *Journal of Clinical Psychopharmacology*, *39*(6), 644–648. https://doi.org/10.1097/JCP.0000000000001125

Sheffler, Z. M., Reddy, V., & Pillarisetty, L. S. (2024). Physiology, Neurotransmitters. In *StatPearls*. http://www.ncbi.nlm.nih.gov/pubmed/29893445. Accessed on 17Th July 2024

Silva, C.R., Semedo, A. T., Neri, H. F. D. S., Vianello, R. P., Galaviz-Hernández, C., Sosa-Macías, M., de Brito, R. B., & Ghedini, P. C. (2020). The CYP2C19*2 and CYP2C19*17 Polymorphisms Influence Responses to Clozapine for the Treatment of Schizophrenia. *Neuropsychiatric disease and treatment*, *16*, 427–432. https://doi.org/10.2147/NDT.S228103

Smith, R. L., O'Connell, K., Athanasiu, L., Djurovic, S., Kringen, M. K., Andreassen, O. A., & Molden, E. (2020). Identification of a novel polymorphism associated with reduced clozapine concentration in schizophrenia patients—a genome-wide association study adjusting for smoking habits. *Translational Psychiatry*, *10*(1), 1–10. https://doi.org/10.1038/s41398-020-00888-1

SNPedia. (2018). *CYP1A2*. https://www.snpedia.com/index.php/CYP1A2. Accessed on 17Th July 2024

Sriretnakumar, V., Huang, E., & Müller, D. J. (2015). Pharmacogenetics of clozapine treatment response and side-effects in schizophrenia: an update. *Expert Opinion on*

Drug Metabolism & Toxicology, *11*(11), 1709–1731. https://doi.org/10.1517/17425255.2015.1075003

Thorn, C. F., Müller, D. J., Altman, R. B., & Klein, T. E. (2018). PharmGKB summary. *Pharmacogenetics and Genomics*, *28*(9), 214–222. https://doi.org/10.1097/FPC.0000000000000347

Vasudev, K., Choi, Y. H., Norman, R., Kim, R. B., & Schwarz, U. I. (2017). Genetic Determinants of Clozapine-Induced Metabolic Side Effects. *Canadian Journal of Psychiatry*, *62*(2), 138–149. https://doi.org/10.1177/0706743716670128

WHO. (2022). *Schizophrenia*. World Health Organitation. https://www.who.int/news-room/fact-sheets/detail/schizophrenia. Accessed on 17Th July 2024

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by all authors. The first draft of the manuscript was submited by [**Fathina Annajla**]. All authors contributed on previous version and revisions process of the manuscript. All authors read and approved the final manuscript.