Jurnal Pharmascience, Vol. 12, Issue 2, October 2025, page: 367-379
ISSN-Print 2355 – 5386
ISSN-Online 2460-9560
https://dx.doi.org/10.20527/jps.v12i2.23111
Research Article

Effectiveness of Clozapine and Its Potential Drug-Drug Interactions in Patients with Schizophrenia: A Study in Referral Psychiatric Hospital

Salma Fajar Puspita[1], Rifa Salsabila[1], Wahyu Ratna Dewi[2], Vitarani Dwi Ananda Ningrum[1]*

[1]Department of Pharmacy, Universitas Islam Indonesia, Yogyakarta, Daerah Istimewa Yogyakarta, Indonesia
[2]Pharmacy Unit, Prof. Dr. Soerojo Psychiatric Hospital, Magelang, Central Java, Indonesia
Email: vitarani.ningrum@uii.ac.id

ABSTRAK

Penelitian terkait efektivitas klozapin pada populasi Asia, baik sebagai monoterapi atau kombinasi, masih sangat terbatas. Selain itu, potensi interaksi antar-obat sering dijumpai pada pasien skizofrenia. Penelitian ini bertujuan untuk menganalisis respon terapeutik klozapin dan faktor-faktor yang memengaruhinya, serta interaksi obat-obat yang bersifat potensial. Penelitian cross-sectional retrospektif ini menggunakan data sekunder dari rekam medik pasien di rumah sakit jiwa rujukan di Jawa Tengah, Indonesia. Analisis data menggunakan uji Chi-square atau Fisher's exact dengan SPSS versi 23. Studi melibatkan 149 pasien skizofrenia dengan mayoritas laki-laki dan terdiagnosis undifferentiated schizophrenia. Sebanyak 89,93% pasien mengalami perbaikan gejala klinis, sesuai yang dinyatakan dokter pada rekam medik, baik pada penggunaan klozapin tunggal maupun kombinasi terutama dengan risperidon. Respon terapeutik klozapin dipengaruhi secara signifikan hanya oleh usia ($p<0,05$). Sementara itu, interaksi obat potensial dengan klozapin berkategori mayor ditemukan pada 8,1% pasien. Penggunaan bersama risperidon diidentifikasi sebagai interaksi obat mayor terbanyak (79,25%) yang berisiko menimbulkan permasalahan kardiovaskular atau pernapasan. Penelitian ini merekomendasikan studi prospektif dengan penilaian efektivitas klozapin menggunakan PANSS-ES maupun dampak klinis interaksi obatnya.

Kata Kunci: Klozapin, Skzofrenia, Efektivitas, Faktor Yang Memengaruhi, Interaksi Obat-Obat

ABSTRACT

Studies on clozapine effectiveness among Asian populations, either as monotherapy or in combination, are quite limited. In addition, potential drug-drug interactions (DDI) are common in schizophrenic patients. This study aimed to analyze the therapeutic response to clozapine, its influencing factors, and the potential DDI. A

cross-sectional study design *retrospectively collected secondary data from medication records* at the referral psychiatric hospitals in Central Java, Indonesia. Data analysis was performed using the Chi-square test or Fisher's exact test in SPSS version 23. This study included 149 patients, predominantly male, who were diagnosed with undifferentiated schizophrenia. As many as 89.93% of patients experienced symptom improvement, as stated by the physician in the medical record, either as monotherapy or in combination, especially with risperidone. The therapeutic response to clozapine was significantly influenced only by age ($p<0.05$). Meanwhile, potential major drug interactions were found in 8.1% of patients. The combined use of clozapine with risperidone has been identified as having the most significant risk for drug interactions (79.25%), which can lead to cardiovascular or respiratory problems. This study recommends conducting prospective studies on the effectiveness of clozapine using the PANSS-ES scale and examine the clinical impact of the drug interactions.

Keywords: Clozapine, Schizophrenia, Effectiveness, Influencing Factor, Drug-Drug Interactions

I. INTRODUCTION

Clozapine is a second-generation antipsychotic or also known as an atypical antipsychotic. Atypical antipsychotics have different receptor affinities from typical antipsychotics. Typical antipsychotics have a high affinity to dopamine receptor type 2 (D2 receptors), while atypical antipsychotics have low affinity to dopamine receptors but show a strong affinity to serotonin 5-HT_{2A} receptors. In addition, atypical antipsychotics have some advantages compared to typical antipsychotics, such as a lower risk of extrapyramidal syndrome (EPS) and their ability to control positive and negative symptoms that may be present in schizophrenic patients. Therefore, atypical antipsychotics are more widely prescribed than typical antipsychotics nowadays (Pai et al., 2022). Clozapine is usually administered to patients with schizophrenia who are resistant or intolerant to conventional antipsychotics as a single or combination therapy with other antipsychotics. Clozapine is effective in managing positive and negative symptoms and reducing relapse rates (Wagner et al., 2021). Clozapine is combined with other antipsychotics to improve effectiveness in controlling schizophrenia. However, data on its effectiveness among Asian populations, either as monotherapy or in combination, are quite limited.

Most of the research related to drug effectiveness involves Caucasian population. Currently, the response variability of each patient to drug therapy is gaining significant attention in the health sector (Goodman & Brett, 2021). Differences in therapeutic response among races are caused by genetic variations that can affect physiological conditions, particularly for the protein function (i.e.,

transporter, enzyme, receptor). These physiological differences can affect the pharmacodynamic and pharmacokinetic aspects of a drug (Olafuyi et al., 2021). For instance, a research conducted revealed that single-nucleotide polymorphisms (SNPs) that occur in the ABCB1 and DRD3 genes affect clinical response to clozapine therapy (Naveen et al., 2020). In addition, a systematic review has documented that Asians have a different clearance of clozapine than Caucasians (Ruan et al., 2019). Besides polymorphism, other factors that can affect antipsychotic response are gender, age and route of clozapine administration. However, previous study has only examined clozapine monotherapy and has not investigated factors that influence response to clozapine (Harjaningsih et al., 2021).

Administering two or more antipsychotics or other medications for comorbidities may lead to potential drug-drug interactions. These interactions sometimes cause significant clinical effects in certain patients, which may disrupt the therapy effectiveness or have a toxic effect. Since most clinicians prescribed clozapine in combination with other antipsychotics or medication for the comorbidities experienced by the patients, it is crucial to examine and monitor the interaction to improve patient safety. Therefore, this study aimed to analyze the therapeutic response to clozapine and its influencing factors, as well as the potential drug-drug interactions.

II. METHOD

A. Design

This retrospective cross-sectional study involved 149 subjects in the inpatient wards of Prof. Dr. Soerojo psychiatric hospital in Magelang in 2022. The inclusion criteria of this study were patients aged ≥18 years, diagnosed with schizophrenia, and receiving clozapine therapy (either as monotherapy or in combination. Meanwhile, patients experiencing switch therapy during hospitalization were excluded from the study.

B. Research Ethics

This research fulfilled the ethical requirements and obtained ethics approval from the Ethics and Legal Committee of Prof. Dr. Soerojo psychiatric hospital Magelang and the Research Ethics Committee for Medicine and Health of Islamic University of Indonesia (project numbers 01/KEH/I/2023 and 373/Dek/70-TA/Bag.TA/XII/2022f) respectively.

C. Data Collection

Due to the limited number of patients per year (< 200 patients), this study

used a saturated sampling technique. Demographic data such as gender and age, type of diagnosis, antipsychotics doses, and therapeutic outcomes were obtained from medical records. Therapeutic outcome was defined as an improvement of psychiatric clinical symptoms as stated by the physician. The patient's clinical symptoms can be either dominant positive symptoms or negative symptoms, or both.

As written on the medical record, psychiatric symptoms were considered improved if the patient showed a relatively calm condition, coherent verbal communication, relaxed expression, stable emotions, was cooperative, displayed quite a good level of conversational initiative, could control hallucinations, was able to follow a series of activities and exercises, and recognize the problem. Patients with more than one symptom of psychosis were categorized to improve with clozapine therapy when clinical symptoms show improvement as stated by the doctor on the medical record.

The independent variables in this study were gender, age, and type of diagnosis, while the dependent variable was the therapeutic outcome.

D. Data Analysis

Descriptive data were analyzed using SPSS 23 version with the frequencies feature and presented as percentages. While the correlation between the 2 variables was analyzed with the Chi-square test and alternative Fisher's exact test. Correlation between 2 variables was considered significant if the *p*-value <0.05. Drug-drug interactions were determined by referring to electronic drug interaction databases from Medscape confirmed by using website drugs.com at the professional section. The potential drug-drug interactions were further classified by severity level.

III. RESULTS AND DISCUSSION

This study involved 149 subjects who had met the inclusion and exclusion criteria. The research subjects were dominated by males (72.48%). Based on the age distribution, the percentage of young adults in the age range of 18-39 years (65.77%) was greater than patients in the middle age range (34.23%). More than half of the patients suffered from undifferentiated schizophrenia (57.71%), a schizophrenia with more than one type of symptoms and therefore cannot be classified into other schizophrenia subtypes. The demographic and clinical data of the subjects were enumerated in Table I.

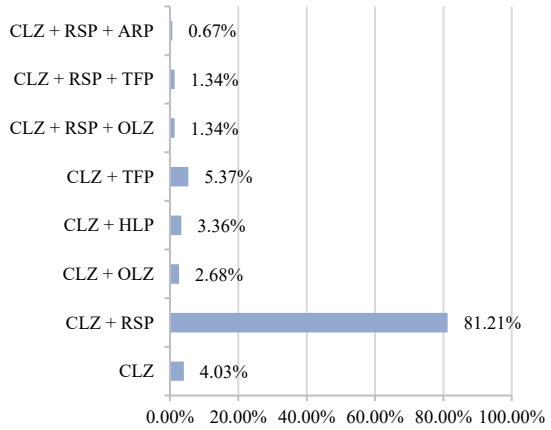
Table I. Research Subject Characteristics

Characteristics	Number (n=149)	Percentage (%)
Sex		
Male	108	72.48
Female	41	27.52

Characteristics	Number (n=149)	Percentage (%)
Age		
18 – 39 years (young adult)	98	65.77
40 – 59 years (middle age)	51	34.23
Diagnosis		
Catatonic Schizophrenia	12	8.05
Paranoid Schizophrenia	54	36.24
Undifferentiated Schizophrenia	83	57.71
Type of Medication		
Monotherapy	6	4.03
Combination of 2 antipsychotics	138	92.62
Combination of 3 antipsychotics	5	3.35
Clozapine Dose		
Monotherapy		
50 mg/day	1	0.67
200 mg/day	5	3.36
Combination Therapy		
12.5 mg/day	1	0.67
25 mg/day	53	35.57
50 mg/day	65	43.63
100 mg/day	20	13.42
200 mg/day	4	2.68

This study showed similar results to those of prior research, which showed that the incidence of schizophrenia mostly occurred in men (Li et al., 2022). Estrogen seems to play an important role in preventing psychosis in women because of its neuroprotective effects (Brand, de Boer, et al., 2021). The incidence of schizophrenia is more common in young adults than middle-aged people because generally the onset of schizophrenia symptoms occurs at the age of 20-25 years (Solmi et al., 2022).

Most patients received a combination therapy of 2 antipsychotics. The combination of 2 types of antipsychotic therapy is currently preferred by most physicians. A combination of clozapine with the other atypical antipsychotics, especially risperidone, was the most frequently prescribed therapy for schizophrenic patients. The distribution of antipsychotic prescriptions is displayed in Figure 1.



Notes: CLZ = Clozapine; RSP = Risperidone; OLZ = Olanzapine; HLP = Haloperidol; TFP = Trifluoperazine; ARP = Aripiprazole

Figure 1. Antipsychotic Prescription

Pharmacologic synergism is the main reason for prescribing a combination of several antipsychotics. Moreover, it could reduce the side effects of each drug. Both clozapine drugs are second-generation antipsychotics or atypical antipsychotics. However, they have different affinities for

several receptors (Siafis et al., 2018). In this study, there is a wide range of clozapine dose either as monotherapy or combination therapy. The Monotherapy patient group received 50-200mg/day clozapine. While in the combination group, patients received 12,5-200mg/day clozapine. In this group, patients seemed to receive lower dose than monotherapy group. Physicians typically taper off clozapine and may introduce an additional antipsychotic if there is no symptom improvement despite reaching the maximum dose.

A total of one hundred thirty-four subjects (89.93%) demonstrated an improvement in symptoms, while 15 subjects (10.07%) did not show any improvement. Among the participants receiving clozapine monotherapy, 12 subjects (85.71%) showed a positive response in symptom improvement, whereas 2 subjects (14.29%) did not. On the other hand, 122 subjects (90.37%) prescribed with clozapine in combination with another antipsychotic showed symptom improvement, while 13 (9.63%) subjects did not. According to prior systematic reviews, comparisons of the effectiveness between clozapine monotherapy and combination cannot be justified because patients in combination group have a higher symptom severity than those in monotherapy group (Ortiz-Orendain et al., 2017). Table II shows the factors influencing the therapeutic outcomes of clozapine.

Table II. Factors Affecting Clinical Outcomes

Factor	Symptom Improvement (n,%)		Number of Patient (n)	*p-value*
	Yes	No		
Gender				
Male	93 (86.1)	15 (13.9)	108	*
Female	41 (100)	0 (0)	41	
Age				
18 – 39 years (young adult)	84 (85.7)	14 (14.3)	98	0.020
40 – 59 years (middle age)	50 (98)	1 (2)	51	
Diagnosis				
Catatonic Schizophrenia	6 (75)	2 (25)	8	0.113
Paranoid Schizophrenia	48 (96)	2 (4)	50	
Undifferentiated Schizophrenia	68 (88.3)	9 (11.7)	77	
Administration of Clozapine				
Once daily	75 (90.4)	8 (9.6)	83	1,000
Divided dose	59 (89.4)	7 (10.6)	66	

*does not meet requirements for bivariate test

Several studies have been conducted to assess the effectiveness of the combination of clozapine and the other antipsychotics in schizophrenic patients, but the results were inconclusive (Barber et al., 2017). Other studies revealed that the combination of both drugs was effective in managing the symptoms of schizophrenic patients, but the number of subjects was limited. In addition, the dose of clozapine used in the study was quite high (450 mg/day) and was administered over a

period of 8 weeks (Sulejmanpasic & Bise, 2017). In contrast, in this study, the patients showed symptom improvement with a dose of clozapine 12.5-200 mg/day within 2 weeks of administration. The difference findings of the current and prior studies might occur due to the differences in the methods of the therapeutic outcome assessment used in both studies. Prior studies used instruments such as the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS) and the Scale for the Assessment of Negative Symptoms (SANS). As a result, the measurement of therapeutic outcomes was semi-quantitative and less subjective aspects in determining clinical symptom improvement.

Current study found that only age significantly affected the clinical outcome (p <0.05). The number of patients who showed symptom improvement was higher in the middle age group than the young age group. The gender, subtype of schizophrenia and frequency of clozapine administration did not affect the clinical symptoms. Although this research found no influence of gender on clinical outcomes, the differences in pharmacodynamic and pharmacokinetic aspects in women and men might have different expression of D2 receptors in the frontal cortex, temporal cortex, and thalamus, with its impact related to the receptor binding (Williams et al., 2021). Women have a longer gastric emptying time and intestinal transit time than men, so the antipsychotic absorption process is more optimum (Walters & Levitan, 2020). Differences in gastric emptying time and intestinal transit of antipsychotics cause different antipsychotic levels in plasma. In prior studies, detectable level of clozapine in the blood plasma of women was higher than that of men, even though the dose exposed to men was higher than the dose exposed to women (Thorn et al., 2018). Clozapine plasma level is a strong predictor of the effectiveness of clozapine therapy (Siskind et al., 2021).

In addition, the response to therapy might be influenced by the expression of P-glycoprotein (P-gp) transporter as well. This transporter is an efflux transporter that affects the distribution of drugs to the brain by preventing drugs, including antipsychotics, from penetrating the blood-brain barrier (Chai et al., 2022). The expression of P-gp in the blood-brain barrier in men is two-fold greater than that in women (Brand, Haveman, et al., 2021). Therefore, antipsychotics penetrate the blood-brain barrier more easily in women. However, the effect of gender on the clinical response of each antipsychotic type could not be generalized (Hoekstra et al., 2021). Therefore, further analysis is necessary to assess the influence of gender

on each type of antipsychotic clinical response.

This study also found that the number of patients who showed symptom improvement was higher in the middle-aged group (40-59 years) than in the young adult group. Physiologically, the integrity of the blood-brain barrier declines along with age (Knox et al., 2022). Therefore, it is easier for antipsychotics to penetrate the blood-brain barrier in the middle-aged group. In addition, albumin levels in the blood also generally decrease along with age. The antipsychotics used in this study were highly bound to albumin (≥90%). Thus, the lower the albumin levels, the higher the free antipsychotics levels in plasma. An increase in unbound drug may increase the effect of antipsychotics (Schoretsanitis et al., 2020).

Additionally, an increase in antipsychotic level could lead to a better therapeutic response (Thorn et al., 2018). To date, no further studies about the relationship between plasma risperidone levels and therapeutic outcomes have been conducted. Previous studies have been conducted in a population aged ≤18 years and ≥45 years (Aichhorn et al., 2005; Kloosterboer et al., 2021). The study conducted on subjects aged ≤18 years found that plasma levels of risperidone had an effect on therapeutic response (Kloosterboer et al., 2021). Another factor that might influence the improvement of symptoms in young adults is adherence. Adherence to antipsychotics regiment is sometimes poor among schizophrenic outpatients (El Abdellati et al., 2020). However, in this study the adherence factor was omitted because inpatients were always supervised by healthcare providers to take their medication as prescribed.

In this study, clozapine was given to patients in 2 ways, once a day and in divided doses twice a day. Clozapine has a terminal half-life of 12-14 hours and dissociates rapidly from the D2 receptor. Administration of clozapine once a day could produce trough levels below the minimum effective level of clozapine in the pharmacokinetic profile. It could potentially lead to a relapse at certain times (Procyshyn et al., 2014). However, the result of this study showed that there was no significant relationship between the frequency of clozapine administration and symptom improvement. This result was similar to that of a study conducted by Takeuchi et al., (2016). Clozapine is given in divided dose if the patient is prescribed with high doses of clozapine (>200mg/day) and in combination with other drugs such as other antipsychotics, anticholinergics and benzodiazepines (Kuzo et al., 2022).

In this study, subjects received clozapine in divided doses if the daily dose prescribed was 50 mg or higher, either as

monotherapy or in a combination with other drugs.

A combination of 2 or more drugs could increase the risk of potential drug interactions. There were 159 cases of potential interactions in this study, and some patients prescribed with more than 2 antipsychotics were more likely to have potential drug interactions. Interactions between 2 atypical antipsychotics dominate the number of potential interaction cases. On the other hand, other interactions that could potentially occur were interactions between typical and atypical antipsychotics, antipsychotics and antidepressants, antipsychotics and anticonvulsants as well as antipsychotics and proton pump inhibitors.

Most of the potential drug interactions were classified as major interaction found in 12 patients (8.1%). DDIs are categorized as major if the interaction is possibly life-threatening or could cause permanent damage. The impact of these interactions according to the findings is related to cardiovascular and respiratory system to fatal consequences such as cardiac or respiratory arrest. The potential drug-drug interactions profile were summarized in Table III.

In this study, most of the interactions that could potentially occur were severe interaction caused by concomitant use of 2 atypical antipsychotics, especially clozapine and risperidone. Concurrent use of 2 antipsychotics might increase the risk of orthostatic hypotension. Orthostatic hypotension could occur due to inhibition of alpha-adrenergic receptors, causing vasodilation (Willner et al., 2023). Receiving atypical antipsychotics such as clozapine, olanzapine and risperidone is associated with a high prevalence of orthostatic hypotension (Parks et al., 2018). Orthostatic hypotension mainly affects elderly patients with reduced cardiovascular homeostasis. However, this condition is relatively uncommon in adults, and in patients with existing hypertension, it can be beneficial.

Some potential interactions are inevitable and considered since the interacting drugs are crucial to control schizophrenic symptoms. In the other words, the advantage of administering a combination of antipsychotics outweighs the risk of potential interaction. But this does not mean that the interaction will not develop hereafter. Thus, the healthcare providers are encouraged to closely monitor any sign and symptom of DDI, especially for major type. Drug discontinuation can be advised to the physician if the DDI is life-threatening.

A thorough assessment of antipsychotic clinical therapy using quantitative/semi-quantitative scoring method needs to be applied to all cases of

schizophrenia. Prospective follow-up studies related to therapeutic outcomes, including adverse drug reactions (ADR) and the clinical impact of major drug interactions, are recommended to better manage schizophrenic disorders using clozapine. In addition, this research does not have genetic information on patient which was an essential determinant of drug responses. Thus, it is important to conduct future research to find out genetic influence on clinical outcome.

Table III. Drug-Drug Interactions

Type of Drug Interaction	Number of Case (N=159)	
Major (n=143; 89.94%)		
Clozapine – Risperidone	126	(79.25%)
Clozapine – Trifluoperazine	8	(5.03%)
Clozapine – Haloperidol	5	(3.15%)
Clozapine – Olanzapine	2	(1.26%)
Clozapine – Aripiprazole	1	(0.63%)
Clozapine – Clobazam	1	(0.63%)
Moderate (n=12; 7.55%)		
Risperidone – Trifluoperazine	8	(5.03%)
Risperidone – Olanzapine	2	(1.26%)
Clozapine – Omeprazole	1	(0.63%)
Risperidone – Aripiprazole	1	(0.63%)
Minor (n=4; 2.51%)		
Clozapine – Divalproex Sodium	4	(2.52%)

IV. CONCLUSION

Most patients showed symptom improvement after clozapine administration. The only factor that significantly influenced the clinical response to antipsychotic therapy was age. Major drug interactions, although rare in less than 10% of patients, require special attention to prevent less effective or toxic effects of clozapine use.

CONFLICT OF INTEREST

The author(s) do not have any conflict of interest.

ACKNOWLEDGEMENT

The authors would like to thank the management of Dr. Soerojo Hospital for facilitating the location of this study.

REFERENCES

Aichhorn, W., Weiss, U., Marksteiner, J., Kemmler, G., Walch, T., Zernig, G., Stelzig-Schoeler, R., Stuppaeck, C., & Geretsegger, C. (2005). Influence of age and gender on risperidone plasma concentrations. *Journal of Psychopharmacology (Oxford, England)*, *19*(4), 395–401. https://doi.org/10.1177/0269881105053306

Barber, S., Olotu, U., Corsi, M., & Cipriani, A. (2017). Clozapine combined with different antipsychotic drugs for treatment-resistant schizophrenia. *The Cochrane Database of Systematic Reviews*, *2017*(3), CD006324. https://doi.org/10.1002/14651858.CD006324.pub3

Brand, B. A., de Boer, J. N., & Sommer, I. E. C. (2021). Estrogens in schizophrenia: Progress, current challenges and opportunities. *Current Opinion in Psychiatry*, *34*(3), 228–237. https://doi.org/10.1097/YCO.0000000000000699

Brand, B. A., Haveman, Y. R. A., de Beer, F., de Boer, J. N., Dazzan, P., & Sommer, I. E. C. (2021). Antipsychotic medication for women with schizophrenia spectrum disorders. *Psychological Medicine*, *52*(4), 649–663. https://doi.org/10.1017/S0033291721004591

Chai, A. B., Callaghan, R., & Gelissen, I. C. (2022). Regulation of P-Glycoprotein in the Brain. *International Journal of Molecular Sciences*, *23*(23), Article 23. https://doi.org/10.3390/ijms232314667

El Abdellati, K., De Picker, L., & Morrens, M. (2020). Antipsychotic Treatment Failure: A Systematic Review on Risk Factors and Interventions for Treatment Adherence in Psychosis. *Frontiers in Neuroscience*, *14*. https://www.frontiersin.org/articles/10.3389/fnins.2020.531763

Goodman, C. W., & Brett, A. S. (2021). Race and Pharmacogenomics—Personalized Medicine or Misguided Practice? *JAMA*, *325*(7), 625–626. https://doi.org/10.1001/jama.2020.25473

Harjaningsih, W., Ayunirrahmah, L., & Putri, N. J. V. (2021). IAI CONFERENCE: The therapeutic outcomes and adverse drug reactions study of Clozapine on Schizophrenia inpatients in the Grhasia psychiatric hospital Yogyakarta, Indonesia. *Pharmacy Education*, *21*(2), Article 2. https://doi.org/10.46542/pe.2021.212.287295

Hoekstra, S., Bartz-Johannessen, C., Sinkeviciute, I., Reitan, S. K., Kroken, R. A., Løberg, E.-M., Larsen, T. K., Rettenbacher, M., Johnsen, E., & Sommer, I. E. (2021). Sex differences in antipsychotic efficacy and side effects in schizophrenia spectrum disorder: Results from the BeSt InTro study. *NPJ Schizophrenia*, *7*, 39. https://doi.org/10.1038/s41537-021-00170-3

Kloosterboer, S. M., de Winter, B. C. M., Reichart, C. G., Kouijzer, M. E. J., de Kroon, M. M. J., van Daalen, E., Ester, W. A., Rieken, R., Dieleman, G. C., van Altena, D., Bartelds, B., van Schaik, R. H. N., Nasserinejad, K., Hillegers, M. H. J., van Gelder, T., Dierckx, B., & Koch, B. C. P. (2021). Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. *British Journal of Clinical Pharmacology*, *87*(3), 1069–1081. https://doi.org/10.1111/bcp.14465

Knox, E. G., Aburto, M. R., Clarke, G., Cryan, J. F., & O'Driscoll, C. M. (2022). The blood-brain barrier in aging and neurodegeneration. *Molecular Psychiatry*, *27*(6), Article 6. https://doi.org/10.1038/s41380-022-01511-z

Kuzo, N., Haen, E., Ho, D. M., Takeuchi, H., Piras, M., Eap, C.-B., de Filippis, R., Homan, P., Kane, J. M., Roy, M.-A., Paulzen, M., & Schoretsanitis, G. (2022). Clozapine once- versus multiple-daily dosing: A two-center cross-sectional study, systematic review and meta-analysis. *European Archives of Psychiatry and Clinical Neuroscience*. https://doi.org/10.1007/s00406-022-01542-1

Li, X., Zhou, W., & Yi, Z. (2022). A glimpse of gender differences in schizophrenia. *General Psychiatry*,

35(4), e100823. https://doi.org/10.1136/gpsych-2022-100823

Naveen, M., Patil, A. N., Pattanaik, S., Kaur, A., Banerjee, D., & Grover, S. (2020). ABCB1 and DRD3 polymorphism as a response predicting biomarker and tool for pharmacogenetically guided clozapine dosing in Asian Indian treatment resistant schizophrenia patients. *Asian Journal of Psychiatry*, *48*, 101918. https://doi.org/10.1016/j.ajp.2019.101918

Olafuyi, O., Parekh, N., Wright, J., & Koenig, J. (2021). Inter-ethnic differences in pharmacokinetics—Is there more that unites than divides? *Pharmacology Research & Perspectives*, *9*(6), e00890. https://doi.org/10.1002/prp2.890

Ortiz-Orendain, J., Obeso, S. C., Colunga-Lozano, L. E., Hu, Y., Maayan, N., & Adams, C. E. (2017). Antipsychotic combinations for schizophrenia. *Cochrane Database of Systematic Reviews*, *6*. https://doi.org/10.1002/14651858.CD009005.pub2

Pai, N., Acar, M., Juneja, P., Kouhkamari, M. H., Siva, S., & Mullan, J. (2022). Antipsychotic prescribing patterns in Australia: A retrospective analysis. *BMC Psychiatry*, *22*(1), 110. https://doi.org/10.1186/s12888-022-03755-z

Parks, K. A., Parks, C. G., Yost, J. P., Bennett, J. I., & Onwuameze, O. E. (2018). Acute Blood Pressure Changes Associated With Antipsychotic Administration to Psychiatric Inpatients. *The Primary Care Companion for CNS Disorders*, *20*(4), 26587. https://doi.org/10.4088/PCC.18m02299

Procyshyn, R. M., Vila-Rodriguez, F., Honer, W. G., & Barr, A. M. (2014). Clozapine administered once versus twice daily: Does it make a difference? *Medical Hypotheses*, *82*(2), 225–228. https://doi.org/10.1016/j.mehy.2013.11.043

Ruan, C.-J., Zang, Y.-N., Wang, C.-Y., Cheng, Y.-H., Sun, C., Spina, E., & de Leon, J. (2019). Clozapine Metabolism in East Asians and Caucasians: A Pilot Exploration of the Prevalence of Poor Metabolizers and a Systematic Review. *Journal of Clinical Psychopharmacology*, *39*(2), 135. https://doi.org/10.1097/JCP.0000000000001018

Schoretsanitis, G., Kane, J. M., Correll, C. U., Marder, S. R., Citrome, L., Newcomer, J. W., Robinson, D. G., Goff, D. C., Kelly, D. L., Freudenreich, O., Piacentino, D., Paulzen, M., Conca, A., Zernig, G., Haen, E., Baumann, P., Hiemke, C., Gründer, G., Psychopharmacology, A. S. of C., & Pharmakopsychiatrier, T. D. M. T. F. of the A. für N. und. (2020). Blood Levels to Optimize Antipsychotic Treatment in Clinical Practice: A Joint Consensus Statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie. *The Journal of Clinical Psychiatry*, *81*(3), 3649. https://doi.org/10.4088/JCP.19cs13169

Siafis, S., Tzachanis, D., Samara, M., & Papazisis, G. (2018). Antipsychotic Drugs: From Receptor-binding Profiles to Metabolic Side Effects. *Current Neuropharmacology*, *16*(8), 1210–1223. https://doi.org/10.2174/1570159X15666170630163616

Siskind, D., Sharma, M., Pawar, M., Pearson, E., Wagner, E., Warren, N., & Kisely, S. (2021). Clozapine levels

as a predictor for therapeutic response: A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *144*(5), 422–432. https://doi.org/10.1111/acps.13361

Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J. B., Jones, P., Kim, J. H., Kim, J. Y., Carvalho, A. F., Seeman, M. V., Correll, C. U., & Fusar-Poli, P. (2022). Age at onset of mental disorders worldwide: Large-scale meta-analysis of 192 epidemiological studies. *Molecular Psychiatry*, *27*(1), Article 1. https://doi.org/10.1038/s41380-021-01161-7

Sulejmanpasic, G., & Bise, S. (2017). Clozapine augmented with risperidone in treatment-resistant schizophrenia. *European Psychiatry*, *41*, S385. https://doi.org/10.1016/j.eurpsy.2017.02.424

Takeuchi, H., Powell, V., Geisler, S., DeSanti, M., Fervaha, G., Agid, O., Kane, J. M., & Remington, G. (2016). Clozapine administration in clinical practice: Once-daily versus divided dosing. *Acta Psychiatrica Scandinavica*, *134*(3), 234–240. https://doi.org/10.1111/acps.12593

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

Wagner, E., Siafis, S., Fernando, P., Falkai, P., Honer, W. G., Röh, A., Siskind, D., Leucht, S., & Hasan, A. (2021). Efficacy and safety of clozapine in psychotic disorders—A systematic quantitative meta-review. *Translational Psychiatry*, *11*(1), Article 1. https://doi.org/10.1038/s41398-021-01613-2

Walters, S. H., & Levitan, E. S. (2020). Vesicular Antipsychotic Drug Release Evokes an Extra Phase of Dopamine Transmission. *Schizophrenia Bulletin*, *46*(3), 643–649. https://doi.org/10.1093/schbul/sbz085

Williams, O. O. F., Coppolino, M., George, S. R., & Perreault, M. L. (2021). Sex Differences in Dopamine Receptors and Relevance to Neuropsychiatric Disorders. *Brain Sciences*, *11*(9), 1199. https://doi.org/10.3390/brainsci11091199

Willner, K., Vasan, S., & Abdijadid, S. (2023). Atypical Antipsychotic Agents. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK448156/