Journal of Chemical Health Risks

www.jchr.org

MINI REVIEW ARTICLE

Pharmacokinetics of Clozapine: An Investigate the Potential Molecular Mechanisms of Action

Vajagathali M., Iyshwarya B.K, Ramakrishnan V.*

Human Cytogenetics and Genomics Laboratory, Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamilnadu, India

(Received: 22 September 2021 Accepted: 20 November 2021)

KEYWORDS

Pharmacokinetics;
Clozapine;
Atypical antipsychotics;
Cytochrome;
Therapeutics

ABSTRACT: Pharmacological surveillance research has usually focused on maintaining chronic experience to marginally efficient blood levels to manage adherence and prevent withdrawal symptoms. The reasoning to use targeted therapies checking in regards to atypical antipsychotics is being discussed, at least in the context of its actual therapeutic efficacy. However, there is proof that it can enhance utility, particularly when psychotic individuals do not react or improve adverse effects while using an effective dose. Moreover, plasma drug levels identifications may be helpful in medical-legal conditions. This study focused on the therapeutic pharmacokinetic information for clozapine and briefly discussed the relationship with plasma levels. Clozapine research showed a link between plasma levels and therapeutic signs, with a 350–420 m m^{-1}limit related to positive therapeutic outcomes. Since elevated plasma concentration levels of clozapine can raise the threat of epilepsy, targeted therapies surveillance is well defined. Several components impact plasma clozapine levels, including modified cytochrome P450 1A4 action, age, sex, and cigarette smoking.

INTRODUCTION

Several medical pharmacotherapy experiments are based on identifying the plasma concentration of a drug because the therapeutic consequences of a drug, both beneficial and poisonous, commonly match up quite accurately to the concentration of blood than dosage. These researches revealed that plasma concentrations are not explicitly linked to delivered dose levels and rather accurately reflect brain levels (approximately 20 % greater in the brain than blood) [1], owing to the action of various enzymes such as absorption glycoprotein. Observing plasma levels has also helped us know drug non-response by differentiating between 'pseudo' and 'true' drug ability to resist. The former has minimal plasma levels as an effect of enhanced cell metabolism or poor response, while it has suitable plasma levels in connection to the dosage but inadequate antibody responsiveness or pharmacological drug interrelations [2]. Numerous drugs dosages interactions differ significantly among patients, owing primarily to pharmacokinetic distinctions impacted by age, modifications in the first pass effects, and the initiation or reduction of the process of microsomal metabolism [3, 4]. The most significant origin of pharmacokinetic variations in the drug chemical process, a physiologic mechanism precipitated by the cytochrome P450 (CYP) enzymatic reaction (Figure 1), the interaction of which differs significantly between subject areas sensitivity to ecological impacts and genetic variation [3]. Even though mainly considered a component of the process under which drugs are eliminated from the body, the metabolic activity could also result in the creation of active constituents, whose action may be equivalent to that of the parent molecule or be entirely different [4]. Physiologic experiments have already shown that determining the plasma levels between the active ingredient and its metabolic products, such as

*Corresponding author: rkgenes@gmail.com (Ramakrishnan V.)
DOI: 10.22034/jchr.2021.1941063.1415

paliperidone (PLP), a new medicine, is helpful in diagnostically handling prescription medication.

Moreover, the physiologic ratio (the proportion of biosynthesis to primary compound plasma levels) could become an informal genetic predictor of a patient's metabolism and an indicator of a pharmacoresistant component which can be valid or obtained (i.e., as an outcome of enzyme action or formation) [5]. Therapeutic drug monitoring (TDM) can also be beneficial when adjusting regular doses to accomplish the most incredible treatment outcome with the slightest risk of severe symptoms and harmful effects [3, 6]. Preskorn [7] enumerated the pharmacokinetic and pharmacodynamic qualities of a drug that anticipate the diagnostic value of TDM: numerous processes of activity, the substantial inter-individual variance of its human physiology, a limited therapeutic indicator, a disrupted duration of action, and problems in discovering harmful effects. The multidisciplinary TDM group [8] recommended compromise regulations to fully utilize TDM for psychiatric medications. There were five research-based different levels of suggestion for continuous analysis of plasma levels for dose adjustment among most psychiatric substances: (1) highly suggested, (2) suggested, (3) beneficial, (4) potentially helpful, and (5) not suggested. The authors also discussed dosage ranges based on legalized and constructed experimental studies on the plasma levels commonly observed at therapeutic doses with molecular targets of each drug is mentioned in Table 1.

The main objective of medical drug formulations studies is to describe a chemical's kinetic description (uptake, dispersion, and removal) after a single and several dosages, including its major metabolic processes and the impact of the parent molecule and active ingredients on clinical reaction and withdrawal symptoms, and any relationship among plasma levels and clinical reactions. This study aims to update the pharmacokinetics of clozapine in determining the relationship between medication plasma concentration levels and therapeutic symptoms.

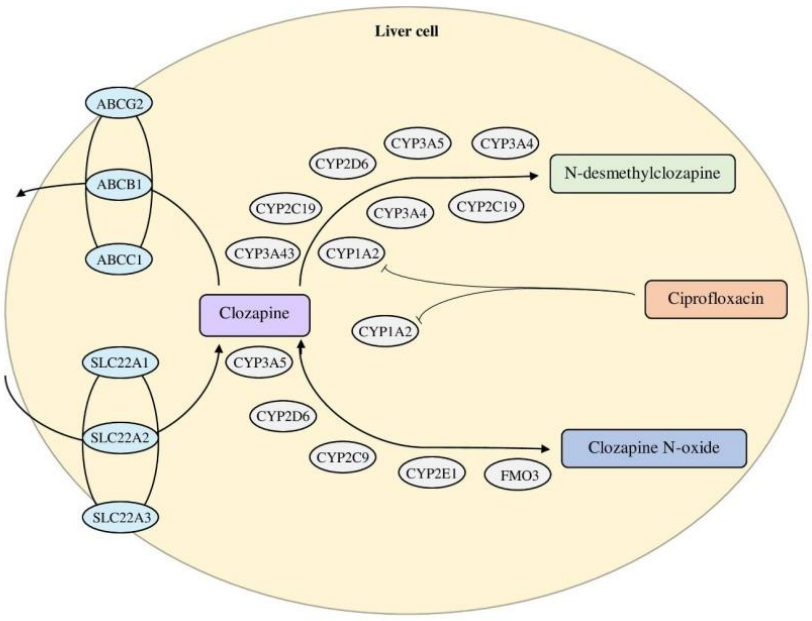

Figure 1. Physiological mechanism and drug-drug interaction of clozapine.

Table 1. Therapeutic range plasma concentration and molecular targets of different atypical antipsychotics

Drug	Dosage PC ($m\ m^{-1}$)	Laboratory alert PC ($m\ m^{-1}$)	Level (1–4) of recommendation to use TDM	Molecular target	Actions	Organism
Amisulpride (AMI)	100-320	640	1	-Dopamine D2, D3 receptor -5-hydroxytryptamine receptor 2A, 7	Antagonist	Humans
Aripiprazole (ARI)	100-350	1000	2	-Dopamine D2 receptor -5-hydroxytryptamine receptor 2A	Antagonist	Humans
Asenapine	1-5	10	4	-Dopamine D2 receptor -5-hydroxytryptamine receptor 2A	Antagonist	Humans
Brexiprazole (BRX)	40-140	280	3	-5-hydroxytryptamine receptor 1A -Dopamine D2 receptor -5-hydroxytryptamine receptor 2A -Alpha-2C and 1B adrenergic receptor	Partial agonist Antagonist	Humans
Cariprazine (CRP)	010-20	40	3	-Dopamine D2, D3 receptor -5-hydroxytryptamine receptor 1A -5-hydroxytryptamine receptor 2B, 2A -Histamine H1 receptor	Partial agonist Antagonist	Humans
Clozapine (CLZ)	350-600	1000	1	-Dopamine D2 receptor -5-hydroxytryptamine receptor 2A	Antagonist	Humans
Iloperidone	05-100	20	3	-Dopamine D2 receptor -5-hydroxytryptamine receptor 2A	Antagonist	Humans
Lurasidone	15-40	120	3	-Dopamine D2 receptor -5-hydroxytryptamine receptor 2A	Antagonist	Humans
Olanzapine	20-80	100	1	-Dopamine D2 receptor -5-hydroxytryptamine receptor 2A	Antagonist	Humans
Paliperidone (PLP)	20-60	120	2	-Dopamine D2, D4, D3 receptor -5-hydroxytryptamine receptor 2A, 2C	Antagonist	Humans
Quetiapine (QTP)	100-500	1000	2	-Dopamine D2 receptor -5-hydroxytryptamine receptor 2A	Antagonist	Humans
Risperidone	20-60	120	2	-Dopamine D2 receptor -5-hydroxytryptamine receptor 2A	Antagonist	Humans
Sertindole	50-100	200	2	-Dopamine D2 receptor -5-hydroxytryptamine receptor 2A, 2C, 6	Antagonist	Humans
Sulpiride	200-1000	1000	2	-Dopamine D2 receptor	Antagonist	Humans
Ziprasidone	50-200	400	2	-Dopamine D2 receptor -5-hydroxytryptamine receptor 2A, 1D, 2C -5-hydroxytryptamine receptor 1A	Antagonist Agonist	Humans
Zotepine	10-150	300	3	- D (1) dopamine & D2 receptor -5-hydroxytryptamine receptor 2A	Antagonist	Humans

Clozapine-mechanism of action

Clozapine, which is still the central part of atypical antipsychotics, corresponds to the dibenzodiazepine compound group. It has several different clinical benefits over classic antipsychotic substances, including adequacy in treatment-resistant mental disorders, a little proclivity to stimulate neuropsychiatric side effects,

especially tardive dyskinesia and a lack of serum lactate elevation [9]. CLZ may be effective in curing depression symptoms, restricting mental issues, and treating a few forms of psychological imbalances related to schizophrenia (SCZ) (Figure 2), in addition to being effective against positive side effects [9]. Clozapine has far more inhibitory activities on the cerebral cortex and midbrain dopamine receptors (D4 than D2). It also inhibits serotonin 5-HT2 receptor subgroups (5-HT2C and 5-HT2A), as well as muscarinic (M1), histamine (H1), adrenergic (a1) neurotransmitters [10]. Multiple research findings [11–15] explored the correlation between plasma CLZ levels and clinical response. Observing plasma CLZ levels was already recommended to be essential in clinical administration, but the impactful plasma CLZ display is even now being discussed [16, 17]. Antipsychotic adequacy never looked to be directly linked to plasma dose levels in previous studies [18–20]. However, these were defined by systematic insufficiencies, such as consequent treatment with other medications, different times between the next dose and sample size, weak evaluations of therapeutic outcome, specimen sizes too limited for precise analysis methods, including the use of variable-dose instead of fixed-dose patterns [21].In addition, plasma CLZ levels differ significantly between individuals. Hence the oral treatment is not a good predictor of plasma levels. As it is required to consider the significance of patient-related parameters on plasma CLZ levels [22, 23], the diversity of drug metabolism and the dosages neurotoxicity of CLZ (seizures, hypotension, sedation) has prompted TDM to enhance medication techniques [17].

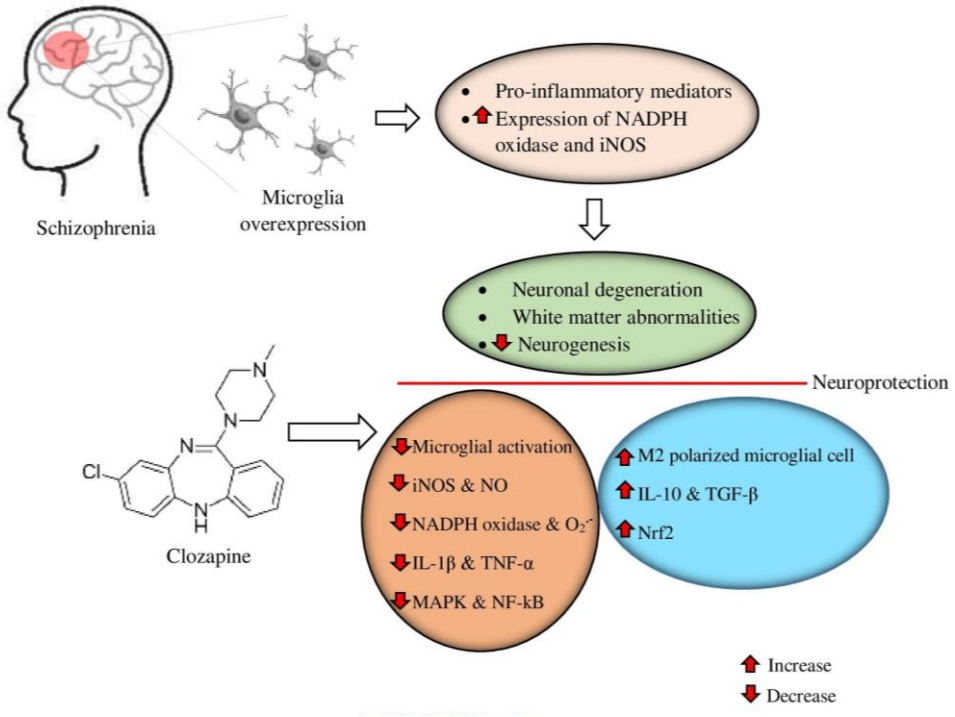

Figure 2. Mechanism of action of clozapine in the treatment of schizophrenic effects.

Pharmacokinetic studies

Intense pharmacokinetic information revealed a considerable cross variation, with average half-lives varying from 9 to 18 hrs. [24]. The optimum plasma levels were between 1 and 3.5 h, plasma discharge was between 8 and 54 L/h, and the dosage was between 1.5 and 7.1 L/kg [24]. After 7 to 10 days of dosages, stable plasma levels are achieved. The medicine is quickly consumed upon oral administration. Due to substantial first-pass metabolism, hardly 27 to 50 percent of the dosages attain the circulatory system. Clozapine is 95% tied to plasma proteases, mainly a1- glycoprotein. Food appears to have no impact on the amount of drug assimilated [25, 26].However, clozapine has several hematological side effects; a study done by Blackman

and co-workers measure the hematological changes after the admission of clozapine drug. It was found that clozapine initiation is linked with increased platelet, neutrophil, and WBC count in treatment-resistant SCZ patients. Thus, despite extensive examination, the study gives information in favor of clozapine, causing initial hematological implications in psychotic patients [27].Similarly, the meta-analysis results of Tan et al. showed that triglycerides, heart rate, and shared ADRs are substantially associated with lipids, clozapine levels, weight gain, and total cholesterol with nor-clozapine levels [28].

Association between plasma concentrations and clinical response

Most scientists claim that CLZ plasma levels of 350 to 420 $mm^{-1}$are related to the higher likelihood of an excellent medical reaction to the medicine. Furthermore, the majority of the information suggests that improving the oral CLZ pill in non-responders to accomplish plasma levels of at least 350 to 420 mm^{-1}can boost the amount of CLZ responders [13, 29 and 30]. Several factors, including sex, age, and cigarette smoking, can impact plasma CLZ levels (and the likelihood of achieving a specified limit) [31]. Therapeutic drug tracking is effective in situations of presumed lack of adherence and for patients with modified drug metabolism, like those with hyper CYP1A2 interaction, which results in decreased plasma CLZ levels and non-response, requiring the use of highly increased CLZ dose levels or the sub-administration of a robust CYP1A2 suppressor (e.g., fluvoxamine) [32]. Furthermore, the excellent internal consistency fluctuation and limited intraindividual variation of plasma CLZ levels support the functionality of tracking them [33]. Recent research [34] foundthat potential CYP3A recognition testing (CYP3A4 indication, CYP3A5 genotype) can help distinguish patients at a greater risk of inadequate or detrimental responses and drastically enhance customized CLZ treatment.

Moreover, more diagnostic research is needed to demonstrate the value of CYP3A screening for patients who received CLZ treatment. TDM is significant in overtaking clozapine increases the risk of epilepsies, directly connected to plasma concentrations. Due to the increasingly significant levels of adverse drug reactions, TDMs are highly suggested for personalized dosing in CLZ pediatrics. Dose adjustments in females may also be appropriate due to gender differences in serum levels [35]. Positron emission tomography (PET) investigations in many sufferers [34] prove that CLZ is unusual in terms of D2 receptor tenancy, which may describe the non-appearance of neuropsychiatric symptoms. CLZ has a rare amalgamation of reasonably increased D1, low D2, and high 5-HT2 neurotransmitter utilization levels. Serum CLZ levels have never been revealed to anticipate physiological efficacy unambiguously, and the intensity in this research did not anticipate the point of neurotransmitter occupancy in the neurological pathways. When improving CLZ therapies in specific patients, the thorough clinical procedure cannot be overtaken by drug levels observed [36].

Moreover, conditional research has exposed that the concentration levels to stop 75% of D4 neurotransmitters correspond to the treatment doses [37]. Some other research suggested that genetically determined D4 variations could describe a few of the cross alterations in patients' responses to CLZ [38]. Molins et al. [39] discovered that the N-desmethylclozapine (NDMC) proportion, rather than CLZ or NDMC plasma levels alone, was a predictor of mental function, particularly supervisory capacities. In diagnostically controlled subjects, decreased NDMC proportions are linked with greater neurocognitive capacities.

CONCLUSIONS

Antipsychotic plasma levels are a valuable but unutilized tool in various healthcare settings where patients with psychiatric disorders deal with these types primarily based on inaccurate details. Practitioners are much less likely to determine the specific reason for complex antipsychotic therapies course work and make the appropriate therapeutic decisions if there is a lack of actual data. Rather than establishing pro-adherence initiatives or dosage modifications targeted at maximizing or creating the intervention extra endurable, practitioners may unnecessarily withdraw an otherwise exciting drug. Enhancing strategic planning by improving accessibility to antipsychotic plasma levels details can profoundly impact the care performance and

results of individuals with schizophrenia. It is necessary to recognize that TDM is not entirely required for all new antipsychotic drugs because the connection between plasma dose levels and patient outcomes or adverse effects is not clearly stated. However, the concentration-related pro-convulsant influence of CLZ is a demonstrative excuse that makes TDM strongly regarded in the AGNP-TDM recommendations to prevent overdosing. Moreover, there is no evidence from clinical data, especially lengthy information, for a few atypical antipsychotics, requiring further research in the upcoming future.

ACKNOWLEDGEMENTS

The authors thank the Chettinad Academy of Research and Education for the constant support and encouragement

Conflicts of interests

No relevant financial or non-financial competing interests to report.

REFERENCES

1. Brodie B.B., 1965. Displacement of one drug by another from carrier or receptor sites. Proc R Soc Med. 58, 946–55.

2. McCutcheon R., Beck K., D'Ambrosio E., Donocik J., Gobjila C., Jauhar S., Kaar S., Pillinger T., Reis Marques T., Rogdaki M., Howes O.D., 2018. Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia. ActaPsychiatr Scand. 137(1), 39–46.

3. Buur-Rasmussen B., Brosen K., 1999. Cytochrome P450 and therapeutic drug monitoring with respect to clozapine. Eur Neuropsychopharmacol. 9, 453–9.

4. Prior T.I., Chue P.S., Tibbo P., Baker G.B., 1999. Drug metabolism and atypical antipsychotics. Eur Neuropsychopharmacol.9, 301–9.

5. Mauri M.C., Volonteri L., Dell'Osso B., Regispani F., Papa P., Baldi M.L., Bareggi S.R., 2003. Predictors of clinical outcome in schizophrenic patients responding to clozapine. J Clin Psychopharmacol. 23(6), 660–4.

6. Steen N.E., Aas M., Simonsen C., Dieset I., Tesli M., Nerhus M., Gardsjord E., Mørch R., Agartz I., Melle I., Ueland T., Spigset O., Andreassen O.A., 2017. Serum levels of second-generation antipsychotics are associated with cognitive function in psychotic disorders. World J Biol Psychiatry. 18(6), 471–82.

7. Preskorn S.H., 2014. Therapeutic drug monitoring (TDM) in psychiatry (part I): why studies attempting to correlate drug concentration and antidepressant response don't work. J Psychiatr Pract. 20(2), 133–7.

8.Hiemke C., Bergemann N., Clement H.W., Conca A., Deckert J., Domschke K., Eckermann G., Egberts K., Gerlach M., Greiner C., Gründer G., 2018. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology. Pharmacopsychiatry. 51(1–02), 9–62.

9. Meltzer H.Y., Bastani B., Ramirez L., Matsubara S., 1989. Clozapine: new research on efficacy and mechanism of action. Eur Arch Psychiatry Neurol Sci. 238, 332–9.

10. Meltzer H.Y., 1982. The mechanism of action of clozapine in relation to its clinical advantages. In: Meltzer HY, editor. Novel antipsychotic drugs. New York: Raven Press Ltd. pp. 1–13.

11. Perry P.J., Miller D.D., Arndt S.V., Cadoret R.J., 1991. Clozapine and norclozapine plasma concentrations and clinical response treatment-refractory schizophrenic patients. Am J Psychiatry. 148, 231–5.

12. Hasegawa M., Gutierrez-Esteinou R., Way L., Meltzer H.Y., 1993. Relationship between clinical efficacy and clozapine concentration in plasma in schizophrenia: effect of smocking. J Clin Psychopharmacol. 13, 383–90.

13. Potkin S.G., Bera R., Gulasekaram B., Costa J., Hayes S., Jin Y., Richmond G., Carreon D., Sitanggan K., Gerber B., Telford J., Plon L., Plon H., Park L., Chang Y.J., Oldroyd J., Cooper T., 1994. Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. J Clin Psychiatry. 55, 133–6.

14. Kronig M.H., Munne R.A., Szymansky S., Safferman A.Z., Pollack S., Cooper T., Kane J.M., Lieberman J.A., 1995. Plasma clozapine levels and clinical response for treatment-refractory schizophrenic patients. Am J Psychiatry. 152, 179–82.

15.Mauri M.C., Volonteri L.S., Fiorentini A., Invernizzi G., Bareggi S.R., 2004. Clinical outcome and plasma

levels of clozapine and norclozapine in drug-resistant schizophrenic patients. Schizophr Res. 66,197–8.

16. Freeman D.J., Oyewumi L.K., 1997. Will routine therapeutic drug monitoring have a place in clozapine therapy? Clin Pharmacokinet.32, 95–100.

17. Khan A.Y., Preskorn S.H., 2005. Examining concentration-dependence toxicity of clozapine: role of therapeutic drug monitoring. J Psychiat Pract. 11, 289–301.

18.Ackenheil V.M., Brau H., Burkhart A., Franke A., Pacha W., 1976. Antipsychotic efficacy in relation to plasma levels of clozapine. Arzneimttelforschung. 26, 1156–8.

19. Thorup M., Fog R., 1977. Clozapine treatment of schizophrenic patients: plasma concentration and coagulation factors. Acta Psychiatr Scand. 66, 123–6.

20.Brau V.H., Burkhart A., Pacha W., Ackenheil V.M., 1978. Relationships between effects and plasma levels of clozapine. Arzneimttelforschung. 28, 1300.

21. Bell R., Mc Laren A., Galanos J., Copolov D., 1998. The clinical use of plasma clozapine levels. Aust N Z J Psychiatry. 32, 567–74.

22.Volpicelli S.A., Centorrino F., Puopolo P.R., Kando J., Frankenburg F.R., Baldessarrini R.J., Flood J.G., 1993. Determination of clozapine, norclozapine and clozapine-N-oxide in serum by liquid chromatography. Clin Chem. 39, 1656–9.

23.Palego L., Biondi L., Giannaccini G., Sarno N., Elmi S., Ciapparelli A., Cassano G.B., Lucacchini A., Martini C., Dell'Osso L., 2002. Clozapine, norclozapine plasma levels, their sum and ratio in 50 psychotic patients. Influence of patient-related variables. Prog Neuropsychopharmacol Biol Psychiatry. 26, 473–80.

24.Jann M.W., Grimsley S.R., Gray E.C., Chang W.H., 1993. Pharmacokinetics and pharmacodynamics of clozapine. Clin Pharmacokinetic. 24, 161–76.

25.Choc M.G., Lehr R.G., Hsuan F., Honigfeld G., Smith H.T., Borison R., Volavka J., 1987. Multiple-dose pharmacokinetics of clozapine in patients. Pharm Res. 4, 402–5.

26.Choc M.G., Hsuan F., Honigfeld G., Robinson W.T., Ereshefsky L., Crismon M.L., Saklad S.R., Hirschowitz J., Wagner R., 1990. Single- vs multiple-dose pharmacokinetics of clozapine in psychiatric patients. Pharm Res. 7, 347–51.

27. Blackman G., Lisshammar J.E., Zafar R., Pollak T.A., Pritchard M., Cullen A.E., Rogers J., Carter B., Griffiths K., Nour M., David A.S., 2021Clozapine Response in Schizophrenia and Hematological Changes. Journal of Clinical Psychopharmacology. 41(1), 19.

28.Tan M.S., Honarparvar F., Falconer J.R., Parekh H.S., Pandey P., Siskind D.J., 2021. A systematic review and meta-analysis of the association between clozapine and norclozapine serum levels and peripheral adverse drug reactions. Psychopharmacology. 7, 1-23.

29.Fabrazzo M., La Pia S., Monteleone P., Esposito G., Pinto A., De Simone L., Bencivenga R., Maj M., 2002. Is the time corse of clozapine response correlated to the time course of clozapine plasma levels? A one-year prospective study in drug-resistant patients with schizophrenia. Neuropsychopharmacology. 27, 1050–5.

30.Miller D.D., Fleming F., Holman T.L., Perry P., 1994. Plasma clozapine concentrations as a predictor of clinical response: a follow-up study. J Clin Psychiatry. 55, 117–21.

31. Schulte P., 2003. What is an adequate trial with clozapine? Therapeutic drug monitoring and time to response in treatment-refractory schizophrenia. Clin Pharmacokinet. 42, 607–18.

32. Eap C.B., Bender S., Jaquenoud S.E., Cucchia G., Jonzier-Perey M., Baumann P., Allorge D., Broly F., 2004. Nonresponse to clozapine and ultrarapid CYP1A2 activity: clinical data and analysis of CYP1A2 gene. J Clin Psychopharmacol. 24, 214–9.

33. Akamine Y., Sugawara-Kikuchi Y., Uno T., Shimizu T., Miura M., 2017. Quantification of the steady-state plasma concentrations of clozapine and N-desmethylclozapine in Japanese patients with schizophrenia using a novel HPLC method and the effects of CYPs and ABC transporters polymorphisms. Ann Clin Biochem. 54(6), 677–85.

34.To 'the K., Csukly G., Sirok D., Belic A., Kiss A., Ha' fra E., De' ri M., Menus A., Bitter I., Monostory K., 2017. Potential role of patients' CYP3A-status in clozapine pharmacokinetics. Int J Neuropsychopharmacol. 20(7), 529–37.

35.Wohkittel C., Gerlach M., Taurines R., Wewetzer C., Unterecker S., Burger R., Schreck D., Mehler-Wex C., Romanos M., Egberts K., 2016. Relationship between clozapine dose, serum concentration, and clinical

outcome in children and adolescents in clinical practice. J Neural Transm (Vienna). 123(8), 1021–31.

36.Nordstrom A.L., Farde L., Nyberg S., Karlsson P., Halldin C., Sedvall G., 1995. D1, D2, and 5-HT2 receptor occupancy in relation to clozapine serum concentration: A PET study of schizophrenic patients. Am J Psychiatry. 152, 1444–9.

37.Seeman P., Van Tool H.H.M., 1995. Deriving the therapeutic concentrations for clozapine and haloperidol: the apparent dissociation constant of a neuroleptic at the D2 or D4 receptor varies with the affinity of the competing radioligand. Eur J Pharmacol Mol Pharmacol. 291, 59–66.

38.Zhao A.L., Zhao J.P., Zhang Y.H., Xue Z.M., Chen J.D., Chen X.G., 2005. Dopamine D4 receptor gene exon III polymorphism and interindividual variation in response to clozapine. Int J Neurosci. 115, 1539–47.

39.Molins C., Carceller-Sindreu M., Navarro H., Carmona C., Pin ˜eiro M., Martı ´nez E., A ´lvarez E., Portella M.J., 2017. Plasma ratio of clozapine to N-desmethylclozapine can predict cognitive performance in treatment-resistant psychotic patients. Psychiatry Res. 258, 153–7.