

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/373727602>

Will ChatGPT₃ Substitute for us as Clozapine Experts?

Article in *Journal of Clinical Psychopharmacology* · September 2023

DOI: 10.1097/JCP.0000000000001734

CITATIONS

2

READS

144

2 authors:



Jose de Leon

University of Kentucky

589 PUBLICATIONS 21,913 CITATIONS

SEE PROFILE



Carlos De las Cuevas

Universidad de La Laguna

282 PUBLICATIONS 4,350 CITATIONS

SEE PROFILE

This is the first submitted version to the journal that was finally published as: de Leon J, De Las Cuevas C. Will ChatGPT3 Substitute for us as Clozapine Experts? J Clin Psychopharmacol. 2023 Sep-Oct 01;43(5):400-402. doi: 10.1097/JCP.0000000000001734. PMID: 37683226. The final published version is available in the journal webpage 10.1097/JCP.0000000000001734 or by requesting from the first author for private use. The final Word version will be available here after 12 months from initial publication. Please be aware that this version was substantially modified after peer-review, an abstract was added, the words increased from 1390 to 1862, the references from 17 to 20 and the Supplementary Boxes from 5 to 7.

No Abstract

Words in text: 1390

References: 17

Table/Figures: 0

5 Supplementary Boxes

Will ChatGPT substitute for us as clozapine experts?

Running title: chatbox and clozapine experts

Jose de Leon, MD^{a,b} Carlos De Las Cuevas, MD^c

Last names are in red font.

^aMental Health Research Center, Eastern State Hospital, Lexington, KY, USA

^bBiomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apóstol Hospital, University of the Basque Country, Vitoria, Spain

^cDepartment of Internal Medicine, Dermatology and Psychiatry and Instituto Universitario de Neurociencia (IUNE), Universidad de La Laguna, La Laguna, Canary Islands, Spain

*Corresponding author: Jose de Leon, M.D., Mental Health Research Center at Eastern State Hospital, 1350 Bull Lea Road, Lexington, KY 40511. E-mail: jdeleon@uky.edu Phone: 1-859-246-8440 Fax: 1-859-246-8446

E-mail and ORCID:

Jose de Leon jdeleon@uky.edu; <http://orcid.org/0000-0002-7756-2314>

Carlos De las Cuevas cdelascuevas@gmail.com; <https://orcid.org/0000-0001-5742-905X>

Acknowledgment

Lorraine Maw, M.A., at the Mental Health Research Center at Eastern State Hospital, Lexington, KY, USA, helped with editing.

Funding

This article was completed without any external funding. No commercial organizations had any role in the writing of this paper for publication.

Disclosure of interest

The authors had no conflicts of interest in the last 3 years.

Contributors

The two authors have contributed significantly and agree with the content of the manuscript.

Data availability

This article provides no new data but uses published data. All searches in ChatGPT and PubMed are carefully described and detailed in the Supplementary Material.

ChatGPT is a new artificial intelligence program that is receiving major attention in academia and other sectors of society in the United States (US) and Western Europe. It was initially released on November 30, 2022, but the stable release was on February 13, 2023. It is believed that similar programs may be released soon in China and Russia.

This article describes how the authors tested ChatGPT using their expertise on a very specific topic that has been the focus of their research since 2019, the effects of ethnic ancestry in the stratification of clozapine dosing.¹ Clozapine is mainly metabolized by CYP1A2, so this means smokers have higher metabolism than non-smokers since tobacco smoking induces CYP1A2; in addition males have higher metabolism than females because estrogens are CYP1A2 inhibitors.² There is general agreement in the literature that 350-600 ng/ml defines the therapeutic range for trough steady-state plasma concentrations. The minimum therapeutic dose needed to reach 350 ng/ml can be used to establish clozapine clearance across individuals or groups, including those associated with differences in ancestry.⁴ In the absence of inhibitors, inflammation, obesity or rare genetic CYP1A2 mutations,⁵ average patients of Asian⁶ or Indigenous American⁷ ancestry need, on average, clozapine minimum therapeutic dosages ranging from 166 mg/day (female non-smokers) to 270 mg/day (male smokers) to reach 350 ng/ml.⁸ In patients of European ancestry, average clozapine minimum therapeutic doses ranged from 236 mg/day (female non-smokers) to 368 mg/day (male smokers).⁹ These dosages for Asian and European patients are lower than typical doses used in the US, 300-600 mg/day.^{2,8}

These two sets of dosages (for Asians and Europeans) were introduced in an international clozapine guideline providing recommendations on titration and dosing.⁸ There has been no published information on clozapine concentrations for African-Americans or patients of African ancestry from other countries. However, the international guideline recommended that patients of African ancestry should be treated with the doses from 300 to 600 mg/day, which are the typically recommended by US textbooks and review articles.^{2,8} This decision was based on data from a small US double-blind study^{10,11} and an extrapolation from olanzapine data.^{11,12} Olanzapine metabolism is similar to clozapine metabolism; Asians

need lower olanzapine doses¹² to get the same olanzapine concentrations (24 mg/day in a patient of Asian ancestry provides the same concentration as 30 mg/day in a patient of European ancestry after stratification by sex and smoking and absence of confounding factors). An olanzapine population pharmacokinetic model using the plasma olanzapine concentrations from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)¹³ demonstrated that African-Americans need higher doses (1.3 times higher) than Whites to reach the same olanzapine concentrations. The predicted need for higher clozapine concentrations in patients of African ancestry¹⁴ to reach the minimum therapeutic dose had been verified by a population pharmacokinetic study from the United Kingdom that was published electronically on February 15, 2023.¹⁵

On February 20, 2023, the second author completed his first interaction with ChaptGTP (Supplementary Box S1) and communicated via Skype with the first author; that led to 4 other successive interactions (Supplementary Boxes S2 to S5) after successive discussions with the first author.

The second author uses English as a second language and, in the first interaction with ChatGPT, he asked 3 questions, “1) What is known about clozapine dose and clozapine plasma levels? 2) 2. What is known about slow and ultra-rapid metabolizers of clozapine? 3) What is known about ancestry and clozapine metabolism?”. The first author was very impressed: 1) ChatGPT knew that the second author meant “metabolism” when the first author wrote “metablolism”, and 2) the summary was very reasonable, very up-to-date, and included a comment on the effects of African ancestry on clozapine metabolism. “In contrast, individuals of African ancestry have been found to have higher CYP1A2 activity and faster clozapine metabolism, which may result in lower plasma concentrations and reduced therapeutic efficacy.” This topic had never received attention in the literature until the international clozapine guideline was published in March of 2022.⁸

The second author went back to ChatGPT and asked the relevant question, “What are the evidences about that individuals of African ancestry have been found to have higher CYP1A2 activity and faster clozapine metabolism?” ChatGTP provided 3 references: 1) 1999 in *Clin Pharmacol Ther*; 2) 2003

in *J Clin Psychopharmacol.* and 3) 2018 in *Pharmgenomics Pers Med.* After a quick PubMed search, the first author concluded that the 3 articles did not exist. Supplementary Box S2 describes a very detailed PubMed search that reached the same outcome; it was conducted on February 21, 2023.

Then the second author asked ChatGPT, “Please bring me adequate references”. The 5 new references¹⁶⁻²⁰ are described in Supplementary BoxS3. PubMed uses a number called the PMID, which provides a unique identifier for each article. PMID numbers allowed the first author to be sure on February 20, 2023, that those articles do not exist. Supplementary Box S3 describes a comprehensive and detailed PubMed search conducted by the first author on February 21, 2023, which demonstrated that: 1) Reference 1 includes the real PMID of another article and actual clozapine researchers, but a non-existent title, 2) Reference 2 includes a non-existent PMID and a non-existent title, but actual clozapine researchers, 3) Reference 3 includes the real PMID of another article and actual researchers, but a non-existent title, 4) Reference 4 includes the real PMID of another article and actual researchers, but a non-existent title, and 5) Reference 5 includes the real PMID of another article and actual researchers, but a non-existent title. The title of Reference 3 ("Pharmacokinetics of clozapine in African American patients with schizophrenia") can be used as an example to demonstrate how deceitful these titles were.

The second author confronted ChatGPT by writing, “The references are not the same that you mention previously.” Supplementary Box S4 describes ChatGPT’s answer, which was another reference relevant to CYP1A2 activity; the reference does not exist. Moreover, this time ChatGPT provided a plausible abstract for this non-existent article, “The authors also reported on differences in CYP1A2 activity between individuals of African and European ancestry, and how these differences may be due to genetic factors. However, the study did not specifically focus on the pharmacokinetics of clozapine.”

At the final interaction, the second author asked, “What's about Jose de Leon contributions in clozapine study” (Supplementary Box S5). ChatGPT wrote a very impressive statement, “In a study published in 2003, de Leon and colleagues examined the relationship between CYP1A2 activity and clozapine metabolism in patients with schizophrenia.... The study also reported that African-American

patients had significantly higher CYP1A2 activity than European-American patients, which is consistent with earlier studies on the subject.” This statement is false. Supplementary Box S5 provides a PubMed search that indicates the first author did not publish that article in 2003. As indicated previously, the first mention in the literature by the author or anyone else about African-Americans needing higher doses of clozapine was published in March of 2022.⁷ The second reference described by ChatGPT is, “In a review article published in 2013, de Leon and colleagues discussed the various genetic polymorphisms that can affect CYP1A2 activity and clozapine metabolism, and highlighted the importance of individualized dosing regimens to optimize treatment outcomes.” Supplementary Box S5 provides a PubMed search that indicates the first author did not publish a clozapine review article in 2013. He collaborated on a review article on CYP activity in 2015²¹ and that review article was the first time he described Asians as having lower clozapine metabolism and needing lower doses. That 2015 article²¹ did not mention African-Americans in the clozapine section. After providing references that the first author has never published, ChatGPT concluded a very laudatory description of his literature contributions, “Overall, Jose de Leon's contributions to the study of clozapine and its pharmacokinetics have been significant, and his work has helped to improve our understanding of how genetic and environmental factors can influence clozapine metabolism and treatment outcomes in patients with schizophrenia.”

Supplementary Boxes S1 to S5 provide the exact answers that ChatGPT gave to the questions by the second author and the precise and detailed PubMed searches done by the first author to demonstrate to the reader that the references provided by ChatGPT do not exist. The reader can make his or her own judgments, but the mix of truth, twisting of reality and non-existent facts reminds both authors of George Orwell's book “1984”.²²

References

1. de Leon J. Reflections on the lack of consideration of ethnic ancestry to stratify clozapine dosing. *Psychiatry Investig* 2023 (in press).
2. de Leon J, Ruan CJ, Schoretsanitis G, et al. A rational use of clozapine based on adverse drug reactions, pharmacokinetics and clinical pharmacopsychology. *Psychother Psychosom*. 2020;89:200-214, 2020.
3. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51:9-62.
4. Ruan CJ, Zang YN, Wang CY, et al. Clozapine metabolism in East Asians and Caucasians: a pilot exploration of the prevalence of poor metabolizers and a systematic review. *J Clin Psychopharmacol*. 2019;39:135-144.
5. Ruan CJ, de Leon J. Is there a future for CYP1A2 pharmacogenetics in the optimal dosing of clozapine? *Pharmacogenomics*. 2020;21:369-373.
6. Ruan CJ, Wang CY, Tang YL, et al. Exploring the prevalence of clozapine phenotypic poor metabolizers in 4 Asian samples: they ranged between 2% and 13. *J Clin Psychopharmacol*. 2019;39:644-648.
7. González-Esquivel DF, Jung-Cook H, Baptista T, et al. Amerindians may need clozapine dosing similar to that of Asians. *Rev Psiquiatr Salud Ment (Engl Ed)*. 2021;14:177-179.
8. de Leon J, Schoretsanitis G, Smith RL, et al. An international adult guideline for making clozapine titration safer by using six ancestry-based personalized dosing titrations, CRP, and clozapine levels. *Pharmacopsychiatry*. 2022;55:73-86.
9. Schoretsanitis G, Smith RL, Molden E, et al. European whites may need lower minimum therapeutic clozapine doses than those customarily proposed. *J Clin Psychopharmacol*. 2021;41:140-147.

10. Simpson GM, Josiassen RC, Stanilla JK, et al. Double-blind study of clozapine dose response in chronic schizophrenia. *Am J Psychiatry*. 1999;156:1744-1750.
11. Diaz FJ, Josiassen RC, de Leon J. The effect of body weight changes on total plasma clozapine concentrations determined by applying a statistical model to the data from a double-blind trial. *J Clin Psychopharmacol*. 2018;38:442-446.
12. Zang YN, Dong F, Li AN, et al. The impact of smoking, sex, infection, and comedication administration on oral olanzapine: a population pharmacokinetic model in Chinese psychiatric patients. *Eur J Drug Metab Pharmacokinet*. 2021;46:353-371.
13. Bigos KL, Pollock BG, Coley KC, et al. Sex, race, and smoking impact olanzapine exposure. *J Clin Pharmacol*. 2008;48:157-165.
14. Schoretsanitis G, de Leon J. C Best practices for starting clozapine in patients with schizophrenia: how to switch from the prior antipsychotic(s). *J Clin Psychiatry*. 2022;83:22ac14500.
15. Reeves S, Bertrand J, Obee SJ, et al. A population pharmacokinetic model to guide clozapine dose selection, based on age, sex, ethnicity, body weight and smoking status. *Br J Clin Pharmacol*. 2023 Feb 15. doi: 10.1111/bcp.15691. Epub ahead of print.
16. Cascorbi I, Roots I, Brockmüller J. Probing the substrate-specificity of human CYP1A2 by site-directed mutagenesis and molecular modeling. *Pharmacogenetics*. 1996;6:167-177.
17. Hagg S, Spigset O, Mjörndal T, et al. Pharmacokinetics of clozapine in Caucasians and the influence of smoking, CYP1A2 and CYP3A4 activity." *Acta Psychiatr Scand*. 2001;103:400-408.
18. Olufade AO, Sifontis NM, Johnson-Levonas AO, et al. Pharmacokinetics of clozapine in African American patients with schizophrenia. *J Clin Pharmacol*. 2002;42:850-858.
19. Llerena A, Berecz R, Dorado P, et al. CYP2D6, CYP2C9 and CYP1A2 activities in schizophrenia patients and related pharmacogenetic considerations. *Curr Drug Metab*. 2008;9:891-898.

20. Fonseca F, de Andrade TG, Ewald H, et al. Pharmacokinetics of clozapine in Brazilians with schizophrenia: Influence of CYP1A2 activity, smoking and ABCB1 polymorphisms. *Pharmacogenet Genomics*. 2011;21:506-514.
21. Spina E, de Leon J. Clinical applications of CYP genotyping in psychiatry. *J Neural Transm (Vienna)*. 2015;122:5-28.
22. Orwell, G. *Nineteen Eighty-Four*. London, UK: Secker & Warburg; 1949.

Supplementary Box S1. The first 4 questions on clozapine metabolism: reasonable and updated answers

1. What is known about clozapine dose and clozapine plasma levels?

- ‘Clozapine is an atypical antipsychotic medication that is primarily used to treat treatment-resistant schizophrenia. There is a well-established relationship between clozapine dose and clozapine plasma levels. When a patient takes a clozapine tablet, the medication is absorbed into the bloodstream and distributed throughout the body. The concentration of clozapine in the blood, or clozapine plasma level, can be measured through a blood test.
- Research has shown that there is a wide interindividual variability in clozapine metabolism and plasma levels. Some patients may require higher doses of clozapine to achieve therapeutic effects, while others may experience adverse effects at lower doses. As a result, monitoring clozapine plasma levels can be important for optimizing the medication's efficacy and safety.
- The therapeutic range for clozapine plasma levels is generally considered to be between 350-600 ng/mL. Plasma levels below this range may indicate that the patient is not receiving a sufficient dose of the medication, while plasma levels above this range may increase the risk of adverse effects, such as seizures, cardiac complications, and sedation.
- In clinical practice, clozapine plasma levels are typically monitored through regular blood tests, and the patient's dose is adjusted based on the results. However, it is important to note that other factors, such as drug interactions, smoking, and age, can also influence clozapine metabolism and plasma levels. As a result, the interpretation of clozapine plasma levels should always take into account the patient's individual characteristics and clinical context.’

2. What is known about slow and ultra-rapid metabolizers of clozapine?

- ‘Clozapine is metabolized by the liver enzyme cytochrome P450 1A2 (CYP1A2), which can result in wide variability in plasma concentrations of the drug. Some individuals may metabolize clozapine more slowly than others, leading to higher plasma concentrations and an increased risk of adverse effects. Others may metabolize the drug more rapidly, resulting in lower plasma concentrations and reduced therapeutic efficacy.
- Slow metabolizers of clozapine are individuals who have reduced CYP1A2 activity, which leads to slower metabolism of clozapine and higher plasma concentrations of the drug. Slow metabolizers are at increased risk of adverse effects, such as sedation, hypotension, and seizures, and may require lower doses of clozapine to achieve therapeutic effects.
- Ultra-rapid metabolizers of clozapine, on the other hand, are individuals who have increased CYP1A2 activity, leading to more rapid metabolism of clozapine and lower plasma concentrations of the drug. Ultra-rapid metabolizers may require higher doses of clozapine to achieve therapeutic effects, and may be at increased risk of treatment resistance.
- Genetic factors can play a role in determining an individual's CYP1A2 activity and, consequently, their clozapine metabolism. Specifically, genetic variations in the CYP1A2 gene can lead to differences in enzyme activity and affect clozapine metabolism. Testing for genetic variations can help identify slow and ultra-rapid metabolizers, which may aid in individualizing clozapine dosing and minimizing the risk of adverse effects.
- In clinical practice, monitoring clozapine plasma levels can also be used to assess a patient's metabolic rate and adjust their dose accordingly. However, it is important to note that other factors, such as smoking, caffeine consumption, and medication interactions, can also influence clozapine metabolism and plasma levels. Therefore, the interpretation of clozapine plasma levels and the choice of dose should always take into account the patient's individual characteristics and clinical context.’

3. Third paragraph: What is known about ancestry and clozapine metabolism^a?

- Ancestry can play a role in clozapine metabolism and plasma concentrations. Studies have shown that there is a higher prevalence of slow metabolizers among individuals of Asian ancestry, compared to those of European ancestry. This is thought to be due to genetic differences in the expression and activity of the CYP1A2 enzyme, which is responsible for clozapine metabolism.
- One genetic variant that is more common in Asian populations is the CYP1A2*1F allele, which has been associated with slower CYP1A2 activity and reduced clozapine metabolism. As a result, individuals with this allele may be at increased risk of higher clozapine plasma concentrations and adverse effects, such as sedation and seizures.
- In contrast, individuals of African ancestry have been found to have higher CYP1A2 activity and faster clozapine metabolism, which may result in lower plasma concentrations and reduced therapeutic efficacy. However, more research is needed to fully understand the impact of ancestry on clozapine metabolism and treatment outcomes.
- It is important to note that while ancestry can be a factor in clozapine metabolism, individual genetic variations and other factors, such as smoking, caffeine consumption, and medication interactions, can also influence clozapine metabolism and plasma concentrations. Therefore, the interpretation of clozapine plasma levels and the choice of dose should always take into account the patient's individual characteristics and clinical context.^a

4. What is known about clozapine metabolism inducers and inhibitors?

- ‘Clozapine metabolism can be influenced by drugs that act as inducers or inhibitors of the liver enzyme cytochrome P450 1A2 (CYP1A2), which is responsible for metabolizing clozapine.
- Inducers of CYP1A2, such as smoking, rifampin, and some anticonvulsants, can increase the rate of clozapine metabolism and lower plasma concentrations of the drug. This may reduce the therapeutic efficacy of clozapine and increase the risk of treatment failure or relapse. Therefore, patients who smoke or who are taking CYP1A2-inducing drugs may require higher doses of clozapine to achieve therapeutic effects.
- Inhibitors of CYP1A2, such as fluvoxamine, ciprofloxacin, and some antifungal agents, can reduce the rate of clozapine metabolism and increase plasma concentrations of the drug. This can increase the risk of adverse effects, such as sedation, hypotension, and seizures. Therefore, patients who are taking CYP1A2-inhibiting drugs may require lower doses of clozapine to minimize the risk of adverse effects.
- It is important to note that other factors, such as age, gender, liver function, and genetic variations, can also affect clozapine metabolism and plasma concentrations. Therefore, the interpretation of clozapine plasma levels and the choice of dose should always take into account the patient's individual characteristics and clinical context. Close monitoring of patients who are taking clozapine and other drugs that can affect its metabolism is recommended to ensure optimal treatment outcomes and minimize the risk of adverse effects.’

^aIt is very impressive that the AI program identified “metablolism” as “metabolism.”

Blue font for questions by the second author.

Red font for answers by ChatGPT.

Supplementary Box S2. Second interaction: What are the evidences about that individuals of African ancestry have been found to have higher CYP1A2 activity and faster clozapine metabolism?

1. A reasonable introduction
<ul style="list-style-type: none"> • ‘There are several studies that support the idea that individuals of African ancestry tend to have higher CYP1A2 activity and faster clozapine metabolism compared to other populations. Here are some examples:
2. The first reference that does not exist
<ul style="list-style-type: none"> • A study published in the journal <i>Clinical Pharmacology & Therapeutics</i> in 1999 examined the pharmacokinetics of clozapine in 20 healthy volunteers of African and European ancestry. The study found that the African volunteers had significantly faster clozapine metabolism and lower plasma concentrations of the drug than the European volunteers. The authors concluded that "the differences in clozapine pharmacokinetics between African and European Americans are likely due to genetic factors. • On February 20, 2023, a PubMed search for "Clin Pharmacol Ther"[Journal] AND clozapine AND 1999” provided 3 non-relevant clozapine articles: <ul style="list-style-type: none"> ○ 1: Sachse C, Ruschen S, Dettling M, Schley J, Bauer S, Müller-Oerlinghausen B, Roots I, Brockmöller J. Flavin monooxygenase 3 (FMO3) polymorphism in a white population: allele frequencies, mutation linkage, and functional effects on clozapine and caffeine metabolism. <i>Clin Pharmacol Ther.</i> 1999 Oct;66(4):431-8. doi: 10.1053/cp.1999.v66.a102203. PMID: 10546928. ○ 2: Holroyd S, Seward RL. Psychotropic drugs in acute intermittent porphyria. <i>Clin Pharmacol Ther.</i> 1999 Sep;66(3):323-5. doi: 10.1016/S0009-9236(99)70041-X. PMID: 10511069. ○ 3: Tschen AC, Rieder MJ, Oyewumi LK, Freeman DJ. The cytotoxicity of clozapine metabolites: implications for predicting clozapine-induced agranulocytosis. <i>Clin Pharmacol Ther.</i> 1999 May;65(5):526-32. doi: 10.1016/S0009-9236(99)70072-X. PMID: 10340918. • On February 20, 2023, a PubMed search for "Clin Pharmacol Ther"[Journal] AND clozapine AND (African-American OR Black)” provided non-relevant clozapine articles.
3. The second reference that does not exist
<ul style="list-style-type: none"> • ‘Another study published in the <i>Journal of Clinical Psychopharmacology</i> in 2003 examined the relationship between CYP1A2 activity and caffeine metabolism in African-American and white volunteers. The study found that the African-American volunteers had significantly higher CYP1A2 activity and faster caffeine metabolism than the white volunteers. The authors concluded that "the higher CYP1A2 activity in African-Americans may be an important factor to consider in the metabolism of drugs that are substrates for this enzyme. • On February 20, 2023, a PubMed search for "J Clin Psychopharmacol"[Journal] AND clozapine AND 2003” provided 12 clozapine articles. When the search was narrowed to "J Clin Psychopharmacol"[Journal] AND African-American AND clozapine AND 2003” there were no articles. Moreover, when the year was eliminated "J Clin Psychopharmacol"[Journal] AND African-American AND clozapine”, none of the 3 articles obtained had information on clozapine metabolism: <ul style="list-style-type: none"> ○ 1: Tiwari AK, Brandl EJ, Weber C, Likhodi O, Zai CC, Hahn MK, Lieberman JA, Meltzer HY, Kennedy JL, Müller DJ. Association of a functional polymorphism in neuropeptide Y with antipsychotic-induced weight gain in schizophrenia patients. <i>J Clin Psychopharmacol.</i> 2013 Feb;33(1):11-7. doi: 10.1097/JCP.0b013e31827d145a. PMID: 23277265. ○ 2: Pinninti NR, Houdart MP, Strouse EM. Case report of long-term lithium for treatment and prevention of clozapine-induced neutropenia in an African American male. <i>J Clin Psychopharmacol.</i> 2010 Apr;30(2):219-21. doi:

10.1097/JCP.0b013e3181d47b74. PMID: 20520308.

- 3: de Leon J, Diaz FJ, Josiassen RC, Cooper TB, Simpson GM. Weight gain during a double-blind multidosage clozapine study. *J Clin Psychopharmacol.* 2007 Feb;27(1):22-7. doi: 10.1097/JCP.0b013e31802e513a. PMID: 17224708.

4. The third reference that does not exist

- A more recent study published in the journal *Pharmacogenomics and Personalized Medicine* in 2018 examined the pharmacokinetics of clozapine in a large sample of patients with schizophrenia from different ethnic groups, including African-American, Hispanic, and white patients. The study found that the African-American patients had significantly faster clozapine metabolism and lower plasma concentrations of the drug than the Hispanic and white patients. The authors concluded that "race/ethnicity is an important factor to consider in the individualization of clozapine therapy."
- On February 20, 2023, a PubMed search for "Pharmgenomics Pers Med"[Journal] AND clozapine AND 2018" provided no articles. When the search was expanded to "Pharmgenomics Pers Med"[Journal] AND clozapine" there were 3 non-relevant articles:
 - 1: Puangpetch A, Srisawasdi P, Unaharassamee W, Jiratjintana N, Vanavanan S, Punprasit S, Na Nakorn C, Sukasem C, Kroll MH. Association between polymorphisms of *LEP*, *LEPR*, *DRD2*, *HTR2A* and *HTR2C* genes and risperidone- or clozapine-induced hyperglycemia. *Pharmgenomics Pers Med.* 2019 Aug 6;12:155-166. doi: 10.2147/PGPM.S210770. PMID: 31496784; PMCID: PMC6689662.
 - 2: Piatkov I, Caetano D, Assur Y, Lau SL, Jones T, Boyages SC, McLean M. *ABCB1* and *ABCC1* single-nucleotide polymorphisms in patients treated with clozapine. *Pharmgenomics Pers Med.* 2017 Aug 28;10:235-242. doi: 10.2147/PGPM.S142314. PMID: 28919802; PMCID: PMC5587196.
 - 3: Lally J, Gaughran F, Timms P, Curran SR. Treatment-resistant schizophrenia: current insights on the pharmacogenomics of antipsychotics. *Pharmgenomics Pers Med.* 2016 Nov 7;9:117-129. doi: 10.2147/PGPM.S115741. PMID: 27853387; PMCID: PMC5106233.

5. A reasonable conclusion regarding the limitations of studies that do not exist

- 'These and other studies provide strong evidence that individuals of African ancestry tend to have higher CYP1A2 activity and faster clozapine metabolism compared to other populations. However, it's important to note that individual variability in drug metabolism is high, and other factors such as age, sex, and co-administration of other drugs can also affect CYP1A2 activity and clozapine metabolism. Therefore, clinical decisions should always be based on a combination of factors, including genetic testing, drug monitoring, and individual patient characteristics.'

Blue font for questions by the second author.

Red font for answers by ChatGPT.

Supplementary Box S3. Third interaction: [Please bring me adequate references](#)

1. A reasonable introduction to results that are extremely misleading
<ul style="list-style-type: none"> • ‘Sure, here are some references to the studies I mentioned’
2. Reference 1 includes the real PMID of another article and actual clozapine researchers, but a non-existent title (on the surface plausible)
<ul style="list-style-type: none"> • Cascorbi I, Roots I, Brockmöller J. "Probing the substrate-specificity of human CYP1A2 by site-directed mutagenesis and molecular modeling." <i>Pharmacogenetics</i>. 1996 Apr;6(2):167-77. doi: 10.1097/00008571-199604000-00008. PMID: 8798343. • On February 20, a PubMed search for "8798343" provided a completely different article: <ul style="list-style-type: none"> ○ Wang W, Shakes DC. Molecular evolution of the 14-3-3 protein family. <i>J Mol Evol</i>. 1996 Oct;43(4):384-98. doi: 10.1007/BF02339012. PMID: 8798343. • On February 20, a PubMed search with the exact title "Probing the substrate-specificity of human CYP1A2 by site-directed mutagenesis and molecular modeling [Title]", provided no articles. • On February 20, a PubMed search for the authors: "Cascorbi I, Roots I, Brockmöller J" provided 26 articles. A PubMed search "Cascorbi I, Roots I, Brockmöller J AND clozapine" provided 1 non-relevant article: <ul style="list-style-type: none"> ○ Dettling M, Sachse C, Müller-Oerlinghausen B, Roots I, Brockmöller J, Rolfs A, Cascorbi I. Clozapine-induced agranulocytosis and hereditary polymorphisms of clozapine metabolizing enzymes: no association with myeloperoxidase and cytochrome P4502D6. <i>Pharmacopsychiatry</i>. 2000 Nov;33(6):218-20. doi: 10.1055/s-2000-8359. PMID: 11147929.
3. Reference 2 includes a non-existent PMID and a non-existent title, but actual clozapine researchers (on the surface plausible)
<ul style="list-style-type: none"> • Hagg S, Spigset O, Mjörndal T, Dahlqvist R. "Pharmacokinetics of clozapine in Caucasians and the influence of smoking, CYP1A2 and CYP3A4 activity." <i>Acta Psychiatrica Scandinavica</i>. 2001 May;103(5):400-8. doi: 10.1034/j.1600-0447.2001.00153.x. PMID: 11380345. • On February 20, 2023, a PubMed search for "11380345" provided a completely different article: <ul style="list-style-type: none"> ○ Falcoz C, Jenkins JM, Bye C, Hardman TC, Kenney KB, Studenberg S, Fuder H, Prince WT. Pharmacokinetics of GW433908, a prodrug of amprenavir, in healthy male volunteers. <i>J Clin Pharmacol</i>. 2002 Aug;42(8):887-98. doi: 10.1177/009127002401102803. PMID: 12162471. • On February 20, 2023, a PubMed search with the exact title: "Pharmacokinetics of clozapine in Caucasians and the influence of smoking, CYP1A2 and CYP3A4 activity. [Title]" provided no article. • On February 20, a PubMed search for the authors "Hagg S, Spigset O, Mjörndal T, Dahlqvist R." or with the authors and clozapine: "Hagg S, Spigset O, Mjörndal T, Dahlqvist R AND clozapine" provided the same 3 non-relevant articles: <ul style="list-style-type: none"> ○ 1: Hägg S, Spigset O, Mjörndal T, Dahlqvist R. Effect of caffeine on clozapine pharmacokinetics in healthy volunteers. <i>Br J Clin Pharmacol</i>. 2000 Jan;49(1):59-63. doi: 10.1046/j.1365-2125.2000.00111.x. PMID: 10606838; PMCID: PMC2014893. ○ 2: Hägg S, Spigset O, Mjörndal T, Granberg K, Persbo-Lundqvist G, Dahlqvist R. Absence of interaction between erythromycin and a single dose of clozapine. <i>Eur J Clin Pharmacol</i>. 1999 May;55(3):221-6. doi: 10.1007/s002280050621. PMID: 10379638. ○ 3: Hägg S, Joelsson L, Mjörndal T, Spigset O, Oja G, Dahlqvist R. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications.

J Clin Psychiatry. 1998 Jun;59(6):294-9. doi: 10.4088/jcp.v59n0604. PMID: 9671341.

4. Reference 3 includes the real PMID of another article and actual researchers, but a non-existent title (on the surface plausible)

- Olufade AO, Sifontis NM, Johnson-Levonas AO, et al. "Pharmacokinetics of clozapine in African American patients with schizophrenia." *Journal of Clinical Pharmacology*. 2002 Aug;42(8):850-8. doi: 10.1177/009127002236857. PMID: 12162471.
- On February 20, 2023, a PubMed search for "11380345" provided no article.
- On February 20, 2023, a PubMed search for the exact title "Pharmacokinetics of clozapine in African American patients with schizophrenia. [Title]" provided no article.
- On February 20, 2023, a PubMed search for the authors "Olufade AO, Sifontis NM, Johnson-Levonas AO" provided no articles. The PubMed search for the first author "Olufade AO" provided 9 articles but none on clozapine. The PubMed search for the second author "Sifontis NM" provided 11 articles but none on clozapine. The PubMed search for the third author "Johnson-Levonas AO" provided 85 articles but none on clozapine.

5. Reference 4 includes the real PMID of another article and actual researchers, but a non-existent title (on the surface plausible)

- Llerena A, Berecz R, Dorado P, de la Rubia A. "CYP2D6, CYP2C9 and CYP1A2 activities in schizophrenia patients and related pharmacogenetic considerations." *Current Drug Metabolism*. 2008 Dec;9(10):891-8. doi: 10.2174/138920008786049304. PMID: 19075654.
- On February 20, 2023, a PubMed search for "19075654" provided a completely different article:
 - Kaur C, Ling EA. Antioxidants and neuroprotection in the adult and developing central nervous system. *Curr Med Chem*. 2008;15(29):3068-80. doi: 10.2174/092986708786848640. PMID: 19075654.
- On February 20, 2023, a PubMed search for the exact title "CYP2D6, CYP2C9 and CYP1A2 activities in schizophrenia patients and related pharmacogenetic considerations [Title]" provided no article.
- On February 20, 2023, a PubMed search for the authors "Llerena A, Berecz R, Dorado P, de la Rubia A" provided 11 articles but none on clozapine.

5. Reference 5 includes the real PMID of another article and actual researchers, but non-existing title but existing researchers (on surface plausible)

- Fonseca F, de Andrade TG, Ewald H, Kanchan T, Scapinello C, Palha A, Belmonte-de-Abreu P, Tufik S, Hachul H. "Pharmacokinetics of clozapine in Brazilians with schizophrenia: Influence of CYP1A2 activity, smoking and ABCB1 polymorphisms." *Pharmacogenetics and Genomics*. 2011 Aug;21(8):506-14. doi: 10.1097/FPC.0b013e32833b97f2. PMID: 21765334.
- On February 20, 2023, a PubMed search for "19075654", provided a completely different article:
 - Snow M. Clostridium difficile: trouble for adults and children. *Nursing*. 2011 Aug;41(8):67-8. doi: 10.1097/01.NURSE.0000399594.28533.35. PMID: 21765334.
- On February 20, 2023, a PubMed search for the exact title "Pharmacokinetics of clozapine in Brazilians with schizophrenia: Influence of CYP1A2 activity, smoking and ABCB1 polymorphisms [Title]" provided no article.
- On February 20, 2023, a PubMed search for the authors "Fonseca F, de Andrade TG, Ewald H, Kanchan T, Scapinello C, Palha A, Belmonte-de-Abreu P, Tufik S, Hachul H." provided no articles. On February 20, 2023, a PubMed search for the first author "Fonseca F" provided 1421 articles but only one on clozapine, a schizophrenia guideline. On February 20, 2023, a PubMed search for the last author "Hachul H" provided 118 articles but none on clozapine.

5. Final wistful comment

- “I hope this helps!”

Blue font for questions by the second author.

Red font for answers by ChatGPT.

Supplementary Box S4. Fourth interaction: **the references are not the same that you mention previously**

1. Apology after confrontation
<ul style="list-style-type: none"> • 'I apologize for the confusion earlier. The reference for the study you are asking about is:'
2. Another reference is given that includes the real PMID of another article and actual researchers, but a non-existent title (on the surface plausible)
<ul style="list-style-type: none"> • Meyer, U.A., Gaertner, I., Manns, M.P. et al. "Variable expression of CYP1A2 in the human liver: impact of the CYP1A21F and CYP1A21D alleles." Clin Pharmacol Ther. 1998 Aug;64(2):180-90. doi: 10.1016/S0009-9236(98)90127-4. PMID: 9728895. • On February 20, 2023, a PubMed search for "9728895" provided a completely different article: <ul style="list-style-type: none"> ○ Rasmussen E, Eriksson B, Oberg K, Bondesson U, Rane A. Selective effects of somatostatin analogs on human drug-metabolizing enzymes. Clin Pharmacol Ther. 1998 Aug;64(2):150-9. doi: 10.1016/S0009-9236(98)90148-5. PMID: 9728895. • On February 20, 2023, a PubMed search for the exact title "Variable expression of CYP1A2 in the human liver: impact of the CYP1A21F and CYP1A21D alleles. [Title]" provided no article. • On February 20, 2023, a PubMed search for the authors "Meyer UA, Gaertner I, Manns MP" provided no articles. On February 20, 2023, a PubMed search for the first author "Meyer UA" provided 265 articles but none on clozapine.
2. Summary of this non-existent article
<ul style="list-style-type: none"> • The study examined the variability in CYP1A2 activity in the human liver, and the impact of different genetic polymorphisms on CYP1A2 expression and function. The authors also reported on differences in CYP1A2 activity between individuals of African and European ancestry, and how these differences may be due to genetic factors. However, the study did not specifically focus on the pharmacokinetics of clozapine.
3. Conclusion with apology
<ul style="list-style-type: none"> • I apologize for any confusion this may have caused.'

Blue font for questions by the second author.

Red font for answers by ChatGPT.

Supplementary Box S5. Fifth interaction: [what's about Jose de Leon contributions in clozapine study](#)

1. First paragraph: A reasonable description

- ‘Jose de Leon is a psychiatrist and researcher who has made significant contributions to the study of clozapine and its pharmacokinetics, particularly in relation to CYP1A2 metabolism.’

2. Second paragraph: A non-existent study by de Leon

- ‘In a study published in 2003, de Leon and colleagues examined the relationship between CYP1A2 activity and clozapine metabolism in patients with schizophrenia. The study found that CYP1A2 activity was a major factor in clozapine metabolism, and that patients with low CYP1A2 activity had significantly higher clozapine plasma concentrations than patients with high CYP1A2 activity. The study also reported that African-American patients had significantly higher CYP1A2 activity than European-American patients, which is consistent with earlier studies on the subject.’
- On February 20, 2023, a PubMed search for “de Leon J and clozapine and 2003” provided 5 articles, of which only 3 were published in 2003:
 - 3: de Leon J, Diaz FJ. Serious respiratory infections can increase clozapine levels and contribute to side effects: a case report. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003 Sep;27(6):1059-63. doi: 10.1016/S0278-5846(03)00148-9.PMID: 14499324.
 - 4: de Leon J, Odom-White A, Josiassen RC, Diaz FJ, Cooper TB, Simpson GM. Serum antimuscarinic activity during clozapine treatment. *J Clin Psychopharmacol*. 2003 Aug;23(4):336-41. doi: 10.1097/01.jcp.0000085405.08426.73. PMID: 12920408.
 - 5: de Leon J. Polydipsia--a study in a long-term psychiatric unit. *Eur Arch Psychiatry Clin Neurosci*. 2003 Feb;253(1):37-9. doi: 10.1007/s00406-003-0403-z.PMID: 12664312.
- You are welcome to read each word of these 3 studies but none of them mentioned anything about clozapine metabolism and African-Americans; moreover, de Leon did not take an specific interest in clozapine metabolism in African-Americans until 2021.

3. Third paragraph: A non-existent review article in this year; a review from another year did not address this topic

- ‘De Leon has also conducted research on the role of genetic factors in clozapine metabolism, and has published numerous papers on the topic. In a review article published in 2013, de Leon and colleagues discussed the various genetic polymorphisms that can affect CYP1A2 activity and clozapine metabolism, and highlighted the importance of individualized dosing regimens to optimize treatment outcomes.’
- On February 20, 2023, a PubMed search for “de Leon J and clozapine and 2013” provided 1 article:
 - Riesselman A, Strobl B, Cooley AT, de Leon J. A case report that suggested that aspirin's effects on valproic acid metabolism may contribute to valproic acid's inducer effects on clozapine metabolism. *J Clin Psychopharmacol*. 2013 Dec;33(6):812-4. doi: 10.1097/JCP.0b013e3182a4ea8f. PMID: 24113673. This letter to the editor described an African-American patient who metabolizes clozapine very fast. It does not comment that African-Americans as a group metabolize clozapine faster.
- In 2015, de Leon was the last author of Spina E, de Leon J. Clinical applications of CYP genotyping in psychiatry. *J Neural Transm (Vienna)*. 2015 Jan;122(1):5-28. doi: 10.1007/s00702-014-1300-5. Epub 2014 Sep 9. PMID: 25200585. This article describes clozapine metabolism and one can argue that ChatGPT was somewhat correct and confused the year of the review article (2,013 vs 2,015), but that review article did not mention the metabolism of African-Americans in the clozapine area.

4. Conclusion: A reasonable description

- ‘Overall, Jose de Leon's contributions to the study of clozapine and its pharmacokinetics have been significant, and his work has helped to improve our understanding of how genetic and environmental factors can influence clozapine metabolism and treatment outcomes in patients with schizophrenia.’

Blue font for questions by the second author.

Red font for answers by ChatGPT.