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# Clozapine plasma level toxicity induced by a pharmacokinetic interaction with bupropion: A case report

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## Abstract

**Introduction:** Clozapine is the gold-standard antipsychotic treatment for patients with treatment-resistant schizophrenia. Prescribers must be vigilant in ensuring that all risk evaluation mitigation strategies requirements and routine cardiac and metabolic monitoring are maintained. Clozapine therapeutic drug monitoring is not a routine part of patient care; however, it can be clinically valuable to confirm the achievement of therapeutic dosages, address tolerability concerns, assess the impact of smoking habit changes, and identify concerning drug–drug interactions.

**Case Report:** A 52-year-old patient with a diagnosis of schizoaffective disorder was co-prescribed clozapine, bupropion, escitalopram, buspirone, and haloperidol since at least 2019. Clozapine/norclozapine levels were drawn in 2024 due to patient reports of daytime sedation. It was determined that the bupropion should be discontinued, and it was reduced from 300 mg to 150 mg daily for 1 week and then completely stopped. A final documented clozapine/norclozapine plasma level was obtained 4 weeks later, demonstrating a significant decrease in levels. The experience of daytime sedation was reported to be mildly improved by the patient.

**Discussion:** There are multiple published reports of established pharmacokinetic and pharmacodynamic drug–drug interactions with clozapine. In this case report, there was a direct correlation between clozapine (CYP2D6 substrate) plasma levels decreasing and the discontinuation of bupropion (CYP2D6 inhibitor).

**Conclusion:** This case demonstrates a low-patient harm example of how a pharmacokinetic drug interaction with clozapine can unexpectedly impact patient care. Clozapine plasma level or concentration monitoring can serve as one of the tools necessary to guide the identification of drug–drug interactions.

**Keywords:** clozapine, plasma, monitoring, drug–drug interaction

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## Introduction

Clozapine is the gold-standard antipsychotic treatment for patients with treatment-resistant schizophrenia.[1,2] For many taking it long-term, it has the potential to dramatically improve quality of life and reduce overall symptom burden. Despite the numerous values it adds to patient care, it remains one of the more challenging antipsychotics to take long-term due to tolerability concerns and more extensive monitoring requirements. When clozapine is prescribed within a primary care setting, providers must be vigilant in ensuring that all risk evaluation mitigation strategy requirements and routine cardiac and metabolic monitoring are maintained.[3,4] Clozapine therapeutic drug monitoring (measurement of plasma clozapine and its metabolite norclozapine) is not a routine part of patient care; however, it can be clinically valuable to confirm the achievement of therapeutic dosages, address tolerability concerns, assess the impact of smoking habit changes, and identify concerning

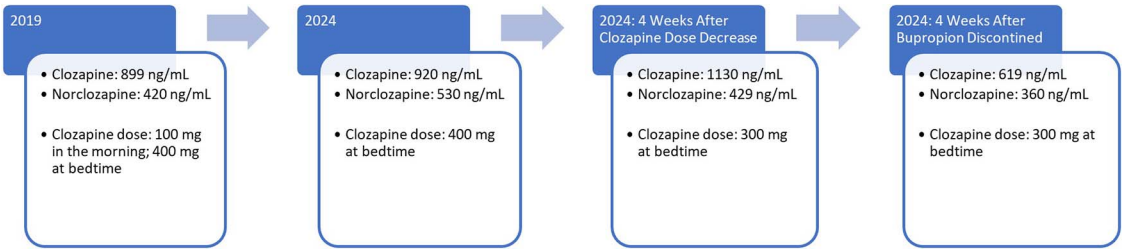


**FIGURE: Clozapine/norclozapine documented plasma levels over time. A clozapine plasma therapeutic window of 350–550 ng/mL is generally recommended. The upper therapeutic limit is between 600 and 800 ng/mL. Plasma levels > 1000 ng/mL are more associated with seizure risk[3]**

drug–drug interactions.[5,6] Clozapine is a substrate for multiple CYP450 isoenzymes, including CYP1A2 (primary), CYP3A4, CYP2C9, CYP2C19, and CYP2D6.[7] When co-prescribed medications are initiated or discontinued, the risk becomes greater that these changes may influence clozapine plasma levels, leading to unintended toxicity or subtherapeutic levels. Schmitz et al[8] published a case report of seizure activity resulting from the prescribed combination of bupropion and clozapine; however, plasma levels were not used to verify a pharmacokinetic interaction. Yang et al[9] describe a case involving seizure activity after just 1 dose of bupropion was taken by a patient prescribed long-term clozapine. Clozapine plasma levels were not assessed in this case, but the authors concluded that a CYP450 drug–drug interaction was a proposed etiology.[9] In primary care settings or when multiple prescribers are involved in patient care, more concerning drug interactions have the potential to be overlooked or missed.

## Case Report

A 52-year-old patient with a diagnosis of schizoaffective disorder, type 2 diabetes, hyperlipidemia, and chronic pain was receiving care in an outpatient primary care setting and was prescribed the following psychiatric medication regimen: clozapine 100 mg in the morning and 400 mg at bedtime, buspirone 30 mg twice daily, bupropion XL 300 mg daily, escitalopram 20 mg daily, and haloperidol decanoate 100 mg intramuscular every 4 weeks. Their non-psychiatric medications included meloxicam 15 mg daily, atorvastatin 20 mg daily, liraglutide 1.2 mg subcutaneous injection daily, famotidine 20 mg daily, levothyroxine 100 mcg daily, insulin aspart 13 units injected with meals, and aspirin 81 mg daily. They have a documented history of taking clozapine consecutively for more than 12 years. Clozapine, bupropion, escitalopram, buspirone, and haloperidol have all been co-prescribed since at least 2019 when the patient transitioned psychiatric care to their current established primary care clinic. Exact medication start dates before 2019 were not accessible to the care team. The patient attended monthly psychiatric-focused appointments at their primary care clinic and obtained a complete blood count with differential, per risk evaluation mitigation strategies monitoring requirements, at each visit. They have no reported drug allergies, have never smoked cigarettes or used other nicotine products, and do not currently consume alcohol or any other substances derived outside of prescriptions. They have a documented positive antinuclear antibody from a previous lab assessment but no autoimmune disease diagnosis.

The patient had their first documented clozapine/norclozapine plasma levels drawn in 2019 when they initiated care in the primary care clinic and reported daytime sedation to their new psychiatric treating provider. Based on the plasma level results (clozapine 899 ng/mL/norclozapine 420 ng/mL) and the patient's reported sedation, the clozapine dose was reduced from 100 mg in the morning and 400 mg at bedtime to only 400 mg at bedtime. The patient reported that the daytime sedation was only mildly approved; however, they described it as manageable and agreed to remain at this dose. Clozapine/norclozapine levels were checked again in 2024 because of re-emerging patient reports of daytime sedation and to determine if elevated plasma levels may be contributing to this sedation. After receiving these results (clozapine 920 ng/mL/norclozapine 530 ng/mL), the clozapine dose was reduced from 400 to 300 mg at bedtime. Plasma levels were drawn approximately 4 weeks after this dose change, and levels remained elevated (clozapine 1130 ng/mL/norclozapine 429 ng/mL). The patient, however, was not reporting or displaying any other signs of clozapine toxicity outside of the continued report of daytime sedation. Because clozapine levels greater than 1000 ng/mL have a higher association with seizure risk, to reduce this risk, other efforts to reduce the plasma level were explored. It was determined that discontinuing the bupropion was an overall better option for this patient to avoid the risk of re-emerging psychiatric symptoms from a continued taper of the clozapine dose. The bupropion was selected because of the possible clozapine plasma level influence from a pharmacokinetic drug interaction. It was reduced from 300 to 150 mg daily for 1 week and then completely stopped. All other medications and dosages remained the same. A final documented clozapine/norclozapine plasma level (clozapine 619 ng/mL/norclozapine 360 ng/mL) was obtained approximately 4 weeks after the bupropion was discontinued, demonstrating a significant decrease in levels (>40%). See the Figure for detailed plasma value changes over time. All plasma levels were drawn between 12 and 16 hours after the last clozapine dose taken by the patient and after steady-state plasma levels were achieved. Despite

**TABLE: Patient medication list - pharmacokinetic/pharmacodynamic drug interaction risk**

| Medication | CYP450 Metabolic Pathway (If Applicable)[16] | Pharmacodynamic (Concomitant Risk)[16] |
|---|---|---|
| Clozapine | 1A2 (primary), 3A4, 2C19, 2D6 | Lowered seizure threshold; CNS depression; QTc prolongation effect |
| Aspirin | N/A | Antiplatelet effect |
| Atorvastatin | 3A4 | |
| Bupropion | 2B6<br>2D6 inhibitor (strong) | Lowered seizure threshold |
| Buspirone | 3A4 | Serotonin syndrome risk |
| Escitalopram | 2C19, 3A4, 2D6 | Serotonin syndrome risk; QTc prolongation effect; antiplatelet effect |
| Famotidine | N/A | |
| Haloperidol | 3A4, 2D6 | Lowered seizure threshold; CNS depression; QTc prolongation effect |
| Insulin aspart | N/A | Hypoglycemic effect |
| Levothyroxine | N/A | |
| Liraglutide | N/A | Hypoglycemic effect |
| Meloxicam | 2C9, 3A4 | Antiplatelet effect |

CNS = central nervous system; N/A = not applicable; QTc = corrected QT.

this significant decrease and return to non-toxic clozapine levels, the patient reported only mild improvement in levels of daytime sedation; however, there is also clinical value in decreasing overall seizure risk for this patient.

## Discussion

There are multiple published reports of established pharmacokinetic drug–drug interactions between clozapine and CYP450 enzyme inducers (eg, omeprazole, carbamazepine, hydrocarbons from smoking) and CYP450 enzyme inhibitors (eg, fluvoxamine, ciprofloxacin, oral ethinyl estradiol, antifungals).[7,10-12] Pharmacodynamic drug–drug interactions include lowered seizure threshold (eg, tramadol, bupropion) and central nervous system depression (eg, benzodiazepines, z-hypnotics, alcohol, opioids).[7,10-12] When assessing clozapine plasma levels, a therapeutic window has generally been established to be between 350 and 550 ng/mL. Levels between 600 and 800 ng/mL are considered the upper therapeutic limit, and levels greater than 1000 ng/mL have a higher association with seizure risk. Plasma norclozapine (a metabolite of clozapine) levels are commonly measured along with clozapine levels when chromatographic methods are used. If the norclozapine to clozapine ratio is high ($\geq$3), this may suggest inhibition of clozapine N-demethylation through a pharmacokinetic drug interaction.[5,6]

In this patient case, because there had been no recent medication changes, alternative rationales for the elevated clozapine plasma level were explored. The case was initially debriefed by the primary care clinic behavioral health consultant team, and several clozapine plasma level or concentration monitoring guides were reviewed. In addition, queries were disseminated on SMIadviser.org and through the American Association of Psychiatric Pharmacists member listserv.[13,14] A more extensive drug–drug and drug–disease assessment were completed during this process. See the Table for patient-specific drug interaction risk stratification. Initially, the following were proposed as likely causes of the clozapine plasma level elevation: (1) drug–drug interaction, (2) recent viral infection but with no reported symptoms or autoimmune or inflammatory process (+ antinuclear antibody in history with only arthritic symptoms reported), and (3) unpredictable variation in clozapine plasma levels from laboratory draw to draw that is established in the literature.[15] In this case report, because there was a direct correlation between clozapine (CYP2D6 substrate) plasma levels decreasing and the discontinuation of bupropion (CYP2D6 inhibitor), this pharmacokinetic drug–drug interaction was identified as the most likely cause (scoring as "probable" on the Drug Interaction Probability Scale).[16,17] Most established interactions with clozapine involve the primary CYP450 metabolic pathways of CYP1A2 and CYP3A4.[7,10-12] Because CYP2D6 plays a minor role, it is oftentimes less implicated. While there was no identified harm to the patient related to this pharmacokinetic drug interaction, the long-term consequences of clozapine plasma levels maintained beyond the established therapeutic range must be considered, including lowered seizure threshold and hypersomnia, as reported by this patient.

## Conclusion

Psychiatric care that is embedded within primary care settings allows for expanded long-term access to holistic care for patients with serious mental illnesses.[18] However, the risk of drug–drug interaction occurrence in this setting cannot be underestimated. This case demonstrates a low-patient harm example of how a pharmacokinetic drug interaction with clozapine can unexpectedly impact patient care. The clinical use of therapeutic clozapine plasma monitoring can be challenging in primary care settings, lending to unpredictable levels and unnecessary clozapine dose reductions.[15] In this case, it served as one of the tools necessary to guide the identification of an interaction that allowed for the established therapeutic dose of clozapine to remain consistent without any further dose reductions.

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