CASE REPORT

Clozapine and nirmatrelvir/ritonavir coadministration without apparent interaction in a patient with mild COVID-19 infection: A case with review of other clozapine-related CYP3A4 interactions

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Purpose: Clozapine is primarily metabolized by cytochrome P450 (CYP) 1A2 and to a lesser extent by CYP2C19, CYP2D6, and CYP3A4. The global pandemic of coronavirus disease 2019 (COVID-19) and use of nirmatrelvir/ritonavir brought forth new challenges for those caring for patients prescribed clozapine. Prescribing information describes a consideration for a clozapine dose reduction while monitoring for adverse reactions when clozapine is used with nirmatrelvir/ritonavir. Other drug information resources consider the combination a contraindication. A case is reported in which therapeutic drug monitoring demonstrated a lack of interaction between clozapine and nirmatrelvir/ritonavir. The complexities of infection-associated clozapine toxicity are discussed and a review is provided of CYP3A4 drug and gene interactions with clozapine.

Summary: A 75-year-old woman with schizophrenia, prescribed clozapine 200 mg by mouth at bedtime, was initiated on nirmatrelvir/ritonavir after developing a mild COVID-19 infection. Two days later, the patient was brought to the emergency department after an unwitnessed fall. Clozapine toxicity was included in the differential diagnosis, although no other signs or symptoms of elevated clozapine levels were present. Nirmatrelvir/ritonavir was discontinued. Clozapine was withheld for 1 day while a clozapine level was pending, but this measurement revealed no interaction when compared to a baseline level of clozapine.

Conclusion: Although there are hypothetical concerns when initiating a CYP3A4 inhibitor with concomitant clozapine, the information derived from this case does not clearly support an interaction with the addition of nirmatrelvir/ritonavir during mild COVID-19 infection. It is important to understand the risks of withholding clozapine, although fortunately no psychiatric concerns developed. In reviewing the literature, CYP3A4 inhibitors or genetic polymorphisms seem to have a minimal impact on clozapine levels, although clinical monitoring is warranted.

Keywords: clozapine, drug interaction, infection, ritonavir, therapeutic drug monitoring

Am J Health-Syst Pharm. 2025;82:1228-1237

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https://doi.org/10.1093/ajhp/zxaf156

Clozapine is the only medication the Food and Drug Administration has approved for treatment-resistant schizophrenia and for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.[1] Clozapine is also beneficial for off-label uses such as in bipolar disorder and psychosis associated with Parkinson's disease.[1] Despite the therapeutic benefits, clozapine is widely underused in the US due to rigorous hematologic monitoring and the potential for multiple serious adverse drug reactions (eg, myocarditis, severe neutropenia,

and bowel obstruction). Monitoring clinically significant interactions is also important to avoid loss of therapeutic benefit or toxicity.

Clozapine is metabolized via cytochrome P450 (CYP) 1A2, CYP2C19, CYP2D6, and CYP3A4.[2] Metabolism of clozapine results in the formation of norclozapine as well as *n*-oxide clozapine, of which the former is considered the primary metabolite and is present at a relative concentration to the parent drug of up to 58%, whereas the latter is present at a relative concentration of only 17%.[3] While some in vitro data have suggested that CYP3A4 contributes 70% of clozapine metabolism, other data have suggested less of a contribution, at least in terms of the formation of norclozapine.[2–5] Conversely, the activity of CYP1A2 is considered most important in clozapine metabolism, and, clinically, the influence from CYP1A2 inducers (eg, cigarette smoking) and inhibitors (eg, fluvoxamine) can be substantial.[1] Yet, the introduction of any inducer or inhibitor of CYP2C19, CYP2D6, or CYP3A4 for those prescribed clozapine should still warrant monitoring.

The coronavirus disease 2019 (COVID-19) pandemic introduced 2 important considerations related to potential interactions with clozapine. First, infection itself is known to inhibit CYP function, especially that of CYP1A2, whereby cases of toxicity have been reported.[6] Limited evidence suggests that the severity of infection correlates with the degree of CYP inhibition.[7] Second, nirmatrelvir/ritonavir for the treatment of COVID-19 infection has a warning related to the potential inhibition of clozapine metabolism via CYP3A4. However, while ritonavir is also an inhibitor of CYP2D6, clozapine levels may be influenced by the medication's induction of CYP1A2 and CYP2C19.[8,9] The prescribing information for nirmatrelvir/ritonavir states that, when coadministration with clozapine is required, "consider reducing the clozapine dose and monitor for adverse reactions." Unfortunately, formal pharmacokinetic studies have not been completed and there is a lack of published clinical information to guide appropriate management of clozapine in the setting of prescribed nirmatrelvir/ritonavir. Additionally, a recent paper evaluating drug information resource warnings concluded that use of clozapine and nirmatrelvir/ritonavir should be considered contraindicated.[10] As such, mismanagement may occur, through the avoidance of nirmatrelvir/ritonavir when appropriate or unnecessary clozapine dose adjustment or even discontinuation.

A case is presented in which there was no apparent pharmacokinetic interaction between clozapine and nirmatrelvir/ritonavir in a patient with mild COVID-19 infection. A literature review was also undertaken to assess CYP3A4 drug inhibitor and gene interactions with clozapine.

KEY POINTS

- This case report supports the lack of a drug-drug interaction between nirmatrelvir/ritonavir and clozapine, as evidenced by therapeutic drug monitoring, and recommends further reporting of clozapine drug-drug interactions.
- Identification of contributing factors for altered clozapine metabolism is necessary as underlying disease states (eg, infection) may confound the results.
- Analysis of the literature regarding CYP3A4 inhibition and clozapine demonstrates a limited impact on clozapine metabolism, although monitoring is warranted.

Case report

A 75-year-old female with a history of schizophrenia was prescribed clozapine 200 mg by mouth at bedtime and risperidone 1 mg by mouth twice daily, a stable regimen over the prior year. Clozapine, norclozapine, and total levels (obtained 15 hours after the dose, 4 months before) while the patient was prescribed clozapine 200 mg by mouth at bedtime were 372 ng/mL (reference range, > 350 ng/mL), 221 ng/mL, and 593 ng/mL, respectively. The patient's other past medical history included type 2 diabetes, hypertension, gastroesophageal reflux disease, and a previously established right bundle branch block, for which she was prescribed insulin glargine 5 units subcutaneously at bedtime, lisinopril 5 mg by mouth daily, metformin 1,000 mg by mouth daily, and pantoprazole 20 mg by mouth daily. After developing cough, headache, and myalgias, testing for COVID-19 showed that the patient was positive for the infection. A community care prescriber initiated nirmatrelvir/ritonavir 300 mg/100 mg by mouth twice daily for 5 days to treat what was documented as a mild COVID-19 infection.

Two days after initiation of nirmatrelvir/ritonavir, having received 4 doses of nirmatrelvir/ritonavir in addition to her other medications, the patient had an unwitnessed fall and was subsequently taken to the emergency department. Upon presentation, she denied headache, cough, dyspnea, chest pain, abdominal pain, nausea, vomiting, diarrhea, and dysuria. Her vital signs were within normal ranges. A complete blood count with differential and electrolyte levels were also within normal limits. The serum creatinine concentration was 0.79 mg/dL and the estimated glomerular filtration rate was 78 mL/min. An electrocardiogram (ECG) showed normal sinus rhythm with a rate of 80 beats per minute, a QRS interval of 135 ms, and a corrected QT interval of 490 ms. The patient was also noted to have an incomplete right bundle branch block, which was preexisting to the current ECG. In the absence of other physical signs or symptoms, the patient was suspected to have had a vasovagal syncopal episode.

At the time of medication reconciliation, the electronic health record presented a warning flag related to the combination of nirmatrelvir/ritonavir and clozapine. The warning noted a "severe" interaction and recommended that (1) clozapine levels and signs of toxicity be monitored and (2)

clozapine might need discontinuation or dose adjustment. With clozapine toxicity due to an interaction as a potential explanation for the patient's fall, a clozapine level was obtained approximately 23 hours after the dose. Poison control was also contacted, who stated that nirmatrelvir/ritonavir may increase clozapine serum concentrations by 75%. Poison control recommended 12 hours of monitoring based on clozapine's half-life and monitoring for additional clozapine-related adverse effects. Subsequently, nirmatrelvir/ritonavir was discontinued and clozapine was held for 1 day.

Pending the results of the clozapine measurement, the patient was admitted to a general cardiology unit for telemetry cardiac monitoring. Her repeat ECGs were unchanged, and she denied any episodes of dizziness. The next day, inpatient psychiatry was consulted and recommended restarting clozapine at 150 mg by mouth at bedtime and risperidone 0.5 mg by mouth twice daily after 1 and 2 missed doses, respectively. Their instructions further recommended that the patient return to her previous home doses of 200 mg by mouth at bedtime and risperidone 1 mg by mouth twice daily the following day. The patient was discharged after 2 days in the hospital. The clozapine, norclozapine, and total levels from 23 hours after the dose, obtained at the time of admission, were available at 72 hours and were 259 ng/mL, 276 ng/mL, and 535 ng/mL, respectively. When accounting for differences in the timing of laboratory sampling, these levels were similar to her baseline reported levels. Assessment of this case using the Drug Interaction Probability Scale revealed a score of less than 2, indicating a "doubtful" interaction between clozapine and nirmatrelvir/ritonavir.[11]

Discussion

Following the initiation of nirmatrelvir/ritonavir with concurrent clozapine for 2 days, a patient experienced a possible syncopal episode resulting in presentation to the emergency department and was admitted to the hospital for monitoring. Although clozapine toxicity was on the differential diagnosis given the newly prescribed nirmatrelvir/ritonavir, the serum clozapine level did not confirm a significant elevation and there were no other signs or symptoms of clozapine toxicity (eg, sedation, sialorrhea, seizure, or gastrointestinal hypomotility).

Despite a warning prompt from the electronic health record, derived from a drug information resource, and concerns raised by the local poison control center, the discontinuation of nirmatrelvir/ritonavir and withholding of clozapine may not have been necessary. The suggestion from poison control that CYP3A4 inhibitors increase clozapine levels by 75% is based on a single case report and is not necessarily congruent with other literature.[12–14] Unfortunately, with delays in the return of clozapine level results, this conservative approach could still be considered appropriate. Yet, there are risks to abrupt clozapine discontinuation, including risks for severe return of psychosis, cholinergic rebound, and catatonia.[15] In addition to the potential interaction or lack thereof, this case also highlights the need for improvement in clozapine-related therapeutic drug monitoring turnaround times for use in real time, which has been noted in other reports.[16,17]

This case also raised the question of how CYP3A4 inhibition impacts clozapine metabolism, with seemingly more literature suggestive of a lack of the anticipated interaction between clozapine and CYP3A4 inhibitors. To explore this, a literature review was completed with the assistance of a medical librarian. Search strategies were created using a combination of related keywords and database-controlled vocabulary to focus on publications specifically evaluating the impact of CYP3A4 drug and gene interactions on clozapine metabolism. Searches were run on April 3, 2024, in the Ovid Cochrane Central Register of Controlled Trials (1991-), Ovid Embase (1974-), and Ovid Medline (1946-, including electronic publications ahead of print, in-process citations, and other nonindexed citations). The Embase search strategy is provided in eAppendix A. English-language publications involving individuals of any age were included if they met the search topic criteria. Conference abstracts, reviews, in vitro studies, and animal studies were excluded. Articles were excluded if the full text could not be obtained. Given the complexities of the CYP interactions described between clozapine and estrogen-containing oral contraception (eg, inhibitors of CYP1A2, CYP2C19, and CYP3A4) and in light of a recently published review,[18] this class of medication was not included in the search. From the initial search performed by the medical librarian, abstracts were imported into Covidence software (Covidence, Melbourne, Australia). Three authors independently screened titles and abstracts for eligibility by consensus. The full text of the abstracts included were then reviewed and again assessed by these 3 authors for eligibility with consensus. The references of papers were reviewed for additional citations.

The search retrieved a total of 266 citations after removal of non–English-language entries, conference abstracts, and animal studies. Deduplication was automatically performed by Covidence, leaving 263 citations to screen. The remaining titles and abstracts were screened with 170 initially excluded, resulting in 93 articles for full-text review. Subsequently, another 67 articles were excluded (28 did not involve an interacting drug or gene, 19 were review articles, 9 were abstracts or conference papers, 5 were not in English, 4 did not have the full text available, and 2 were in vitro studies), leaving 26 publications for inclusion. Three papers were included following citation review in addition to the 26 publications. In total, 29 articles were reviewed, of which 20 articles were related to CYP3A4-inhibiting medications coadministered with

clozapine and 9 articles discussed the potential impact of CYP3A4 genetic variation on clozapine metabolism.

The publications analyzing clozapine level outcomes in patients with CYP3A4-inhibiting medications are summarized in Table 1. These publications included case reports (n = 13), a case series (n = 1), small open-label studies (n = 5), and a randomized controlled trial (n = 1). The publications included various CYP3A4 inhibitors ranging from those with strong inhibitory effects to ones with weak inhibitory effects, with some medications impacting multiple CYP pathways in addition to CYP3A4. Three cases involved patients with human immunodeficiency virus and regimens that included ritonavir.[19–21] Two of these reports specifically noted the potential interaction via CYP3A4.[20,21] However, one of these recognized CYP1A2 induction by ritonavir and thus the potential for any clinically relevant interaction to be mitigated, owing to a lack of observed interaction in the case.[21] As reported, the patient was on clozapine 400 mg daily with a corresponding clozapine concentration of 490 ng/mL, which would not be unexpected. Another of these case reports noted similar clozapine levels before and after ritonavir prescribing.[19] Unfortunately, the clozapine doses were not reported, preventing interpretation of the potential for any interaction. In the third case, clozapine was titrated to 300 mg without mention of clinical concern for an interaction and no clozapine levels were reported.[20]

In terms of other strong CYP3A4 inhibitors (eg, itraconazole, nefazodone, grapefruit juice, and ketoconazole), 5 of 6 studies failed to identify significant changes in clozapine serum concentrations with clozapine coadministration.[13,14,22–24] One report by Khan et al[13] described a single case with an increase in serum clozapine concentration from 133 to 233 ng/mL after coadministration of nefazodone (300 mg/day), corresponding to a 40% decrease in clozapine clearance. This contrasts with a case series that found little to no change in serum clozapine concentration in patients on nefazodone 100 to 200 mg per day.[14] The authors of the latter study hypothesized that CYP3A4 inhibition may be negligible with other active metabolism pathways (ie, CYP1A2) available for clozapine.

There was variability in the conclusions for patients with coadministration of moderate CYP3A4 inhibitors (erythromycin, cimetidine, and fluconazole). Elevated serum clozapine concentrations were reported in 3 of 4 publications describing coadministration of clozapine with erythromycin.[25–28] However, one of these case reports was in the setting of clozapine overdose and 2 involved infection.[25–27] One study, conducted in healthy volunteers, reported no significant difference in serum clozapine levels when clozapine was given with vs without erythromycin. However, clozapine pharmacokinetics were assessed after only a single low dose (12.5 mg).[28] The authors concluded that the CYP3A4 inhibition from erythromycin is not significant to clozapine clearance and thus no clozapine dose modification is warranted. In a case report of a patient hospitalized for psychosis, the patient was given oral fluconazole and miconazole gel for oral candidiasis.[29] On the last day of fluconazole, clozapine was started and titrated to 225 mg over 16 days. A clozapine level after 3 weeks of clozapine was reported to be 542 ng/mL. The patient subsequently developed eosinophilia, nausea, vomiting, and palpitations and was found to have pericarditis. However, the patient was also continued on an estrogen-containing oral contraceptive throughout her hospitalization. The authors concluded that the clozapine level and pericarditis could have been precipitated by multiple interactions. In general, cases involving anti-infective agents in the setting of acute infection are confounded by the influence of the infection itself on clozapine metabolism.

The sleep aids suvorexant and lemborexant were found to increase clozapine concentrations by 2- and 3.85-fold, respectively.[30,31] Both case reports were in patients of East Asian ethnicity, and the authors hypothesized that ancestry could have contributed to the significant changes in clozapine concentration. In a third report, clozapine initiation was associated with the development of myocarditis in a patient prescribed lemborexant.[32] A clozapine concentration-to-dose ratio on day 8 was higher than expected, indicating decreased clearance. Symptoms of myocarditis developed on day 13. The authors suspected that rapid titration of clozapine in combination with lemborexant may have precipitated the adverse event.

Cimetidine was demonstrated to result in a modest increase in serum clozapine concentrations in 2 case reports, one of which used cimetidine to augment the clozapine concentration to a therapeutic level in a patient who refused to take more than 400 mg per day of clozapine.[33,34] While cimetidine inhibits CYP3A4, it also inhibits CYP1A2, CYP2C19, and CYP2D6, all of which are involved in clozapine metabolism, and conclusions cannot be made about CYP3A4 specifically. Finally, 2 studies analyzing patients initiated on amiodarone reported differing results; amiodarone also influences multiple CYP pathways. Stevens et al[35] reported a significantly increased clozapine concentration (from 242 to 1,580 ng/mL) requiring a 50% dose reduction. Kilciksiz et al[36] reported unchanged serum concentrations in a patient who received an empiric clozapine dose reduction of 25% with initiation of amiodarone. It is known that amiodarone's active metabolite, desethylamiodarone, is a potent CYP1A2 inhibitor, limiting the ability to definitively draw conclusions regarding amiodarone's weak CYP3A4 inhibition.

In summary, without the inhibition of other CYP pathways or acute infection, data do not support the notion that medications primarily inhibiting CYP3A4 are of clinical concern for patients taking clozapine. The cases of orexin inhibitors are interesting in that they involved patients of Asian ancestry. Several studies have demonstrated that individuals of Asian ancestry require lower clozapine dosing to achieve

Table 1. Publications Involving CYP3A4 Inhibitors and Clozapine

Offending agent: CYP influence[37,38,a]	Report (sample size, design)	Results and conclusion
Amiodarone: • CYP1A2: strong inhibitor (via active metabolite desethylamiodarone) • CYP2C9: weak to moderate inhibitor • CYP2D6: weak inhibitor • CYP3A4: weak inhibitor	Stevens et al[35] (n = 1, case report)	Clozapine levels increased 6.53-fold after initiation of amiodarone. It is possible that strong CYP1A2 inhibition by the amiodarone metabolite desethylamiodarone may lead to increased clozapine levels.
	Kilciksiz et al[36] (n = 1, case report)	Daily clozapine dosing was empirically decreased by 25% during a 6-day load of amiodarone. Serum clozapine levels were largely unchanged during this timeframe.
Cimetidine: • CYP1A2: weak inhibitor • CYP2C19: weak inhibitor • CYP2D6: weak inhibitor • CYP3A4: weak inhibitor	Szymanski et al[33] (n = 1, case report)	Clozapine levels increased 1.57-fold after initiation of cimetidine. The CYP inhibitory effect of cimetidine likely led to reduced clozapine metabolism.
	Sandson et al[34] (n = 1, case series)	In one case, cimetidine likely contributed to elevated clozapine concentrations.
Erythromycin: • CYP3A4: moderate inhibitor	Funderburg et al[26] (n = 1, case report)	The clozapine level was found to be 1,300 μg/mL after 7 days of coadministration with erythromycin. The drug-drug interaction leading to an elevated serum clozapine concentration contributed to a first-time seizure.
	Cohen et al[27] (n = 1, case report)	Clozapine levels increased 2.99-fold after initiation of erythromycin. Careful monitoring may be required when initiating a CYP3A4 inhibitor.
	Hagg et al[28] (n = 12, open label)	Serum clozapine levels were not significantly changed in healthy volunteers. CYP34 appears to have minimal effect on clozapine metabolism.
	Renwick et al[25] (n = 1, case report)	Clozapine metabolism appeared saturable in the setting of a 3- to 4-g ingestion. Clozapine metabolism may have further been reduced by the concomitant CYP3A4 inhibitor erythromycin.
Fluconazole: • CYP2C19: strong inhibitor • CYP2C9: moderate inhibitor • CYP3A4: moderate inhibitor	Cadeddu et al[29] (n = 1, case report)	A patient was initiated on clozapine at the end of a course of oral fluconazole and topical miconazole. A level was checked and was higher than expected. However, the patient was also on estrogen-containing contraception, known to inhibit clozapine through multiple potential pathways, including CYP1A2 and CYP2C19.
Grapefruit juice: • CYP3A4: moderate to strong inhibitor[b]	Vandel et al[24] (n = 9, open label)	Serum clozapine levels were not significantly changed. Clozapine metabolism did not appear to be altered by consumption of grapefruit juice.
	Lane et al[22] (n = 15, open label)	Serum clozapine levels were not significantly changed with coadministration of grapefruit juice.
	Lane et al[23] (n = 21, open label)	The pharmacokinetics of clozapine were not altered by grapefruit juice.
Itraconazole: • CYP3A4: strong inhibitor	Raaska et al[13] (n = 7, randomized trial)	Serum clozapine levels were unchanged. CYP3A4 inhibition by itraconazole did not appear to play a significant role in clozapine metabolism.
Ketoconazole: • CYP2C19: weak to moderate inhibitor • CYP3A4: strong inhibitor	Lane et al[23] (n = 21, open label)	A nonsignificant decrease in the clozapine area under the curve was found with coadministration of ketoconazole.
Lemborexant: • CYP2B6: weak inducer • CYP3A4: weak inhibitor	Watanabe et al[30] (n = 1, case report)	Clozapine levels increased significantly after initiation of lemborexant. Upon discontinuation, levels decreased approximately 3-fold. The authors concurrently published an in

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Table 1. Publications Involving CYP3A4 Inhibitors and Clozapine

Offending agent: CYP influence[37,38,a]	Report (sample size, design)	Results and conclusion
		vitro analysis, reporting lemborexant to be a weak inhibitor of CYP3A4.
Nefazodone: • CYP3A4: strong inhibitor	Taylor et al[14] (n = 6, open label)	Serum clozapine levels were not significantly changed. Other pathways of metabolism may be activated when CYP3A4 is inhibited.
	Khan et al[12] (n = 1, case report)	Clozapine levels increased 1.75-fold after initiation of nefazodone. CYP3A4 inhibition by nefazodone may have reduced clozapine metabolism.
Ritonavir: • CYP1A2: weak inducer • CYP2B6: moderate inducer • CYP2C9: weak inducer • CYP2C19: weak inducer • CYP2D6: weak inhibitor • CYP3A4: strong inhibitor	Nejad et al[19] (n = 1, case report)	In one of the cases, the authors noted that clozapine was initiated while the patient was prescribed zidovudine and lamivudine. A clozapine level during a period when they were not taking HIV medication was 341 ng/mL. Clozapine was stopped due to neutropenia. Years later, clozapine was restarted while the patient was on an HIV regimen involving ritonavir and a corresponding clozapine level of 357 ng/mL was obtained. Doses were not reported.
	Whiskey et al[21] (n = 1, case report)	Clozapine was initiated while the patient was on an HIV regimen including ritonavir. Clozapine reached a dose of 450 mg daily with ritonavir 100 mg twice daily. Neutropenia developed and clozapine was stopped. A rechallenge ensued, with clozapine reaching 400 mg daily and a corresponding level of 490 ng/mL.
	Gerken et al[20] (n = 1, case report)	Clozapine was initiated and titrated to 300 mg daily in conjunction with an HIV regimen involving ritonavir. Levels were not reported.
Suvorexant: • CYP1A2: weak to moderate inhibitor • CYP3A4: weak to moderate inhibitor	Kikuchi et al[31] (n = 1, case report)	Clozapine levels increased 2-fold after initiation of suvorexant. The authors hypothesized that the patient population (Japanese patients) may have more pronounced effects from this drug-drug interaction.

[a]CYP interactions and degree of inhibition or induction were derived from the Drug Interactions Flockhart Table and Adult Drug Information Handbook or, where information was lacking, from the corresponding citation.

[b]Although furanocoumarins, active chemical compounds in grapefruit, are known to be inhibitors of CYP3A4, they appear to inhibit gastrointestinal CYP3A4 and not liver CYP3A4. This is an explanation for the lack of interaction seen between grapefruit and clozapine in pharmacokinetic studies.

similar levels, as compared to individuals of European or African ancestry. It has been suggested that this may be related to differences in CYP1A2 activity across these populations.[1] Should clozapine's primary route of metabolism (ie, CYP1A2) be reduced, patients may be more susceptible to inhibition of other minor pathways, including CYP3A4. Additional research is needed to determine whether CYP3A4 inhibition is more likely to impact different populations prescribed clozapine.

Table 2 shows data from the 9 reports that assessed the pharmacogenetic variability in CYP3A4 activity and its impact on clozapine metabolism. Fluvoxamine was used to achieve therapeutic clozapine concentrations in a patient known to be a high metabolizer of CYP3A4.[39] Despite being a weak inhibitor of CYP3A4, escitalopram led to supratherapeutic clozapine concentrations in a patient known to have intermediate CYP3A4 metabolism status.[40] Three studies found that CYP3A4 metabolism played a larger role in cases where CYP1A2 was inhibited or in patients who had low expression of CYP1A2.[41–43] Two studies noted a lack of influence of CYP3A4 polymorphisms on clozapine metabolism.[41,44] One case report discussed a patient with refractory symptoms who underwent genotyping and was found to be an intermediate metabolizer of CYP1A2, CYP2D6, and CYP3A4. The authors suggested that the patient's elevated clozapine levels were partly attributable to her genetic polymorphisms but also questioned whether an unassessed drug-drug interaction was contributing.[45] A pharmacogenomic study of 96 patients with schizophrenia found an association between low CYP3A4 metabolizer status and elevated

Table 2. Pharmacogenomic Reports Involving CYP3A4 and Clozapine

Study (sample size)	Conclusions
Whiskey et al[39] (n = 1, case report)	Fluvoxamine coadministration with clozapine achieved a therapeutic clozapine concentration in a patient who was found to be a high metabolizer of CYP3A4.
John et al[40] (n = 1, case report)	The known intermediate CYP3A4 status prescribed escitalopram. The authors hypothesized that escitalopram, through weak CYP-inhibitory effects, led to supratherapeutic levels. The clozapine level decreased after discontinuation of escitalopram.
Jaquenoud Sirot et al[41] (n = 75)	This study suggested that CYP3A4 may influence clozapine metabolism to a larger extent in the presence of altered CYP1A2 activity. Patients with CYP2C19 and *ABCB1* polymorphisms also had altered clozapine metabolism. The study noted a lack of association between CYP3A4 polymorphisms and clozapine metabolism.
Ghassabian et al[42] (n = 11)	In vivo phenotyping found a significant correlation between CYP1A2 and CYP3A4 status in clozapine metabolism. The authors noted the caveat that the role of CYP3A4 could be understated due to their population including primarily people who smoked (CYP1A2 inducer).
Lee et al[44] (n = 96)	Analysis of 27 genes failed to identify an association between various CYP3A4 polymorphisms and clozapine metabolism.
Toth et al[43] (n = 92)	In patients with low expression of CYP1A2, CYP3A status was found to influence clozapine metabolism, where patients with normal to high expression of CYP3A4 required more than 2 times the clozapine dose.
Mian et al[45] (n = 1, case report)	The patient's multiple CYP polymorphisms could have contributed to the elevated clozapine concentrations.
Menus et al[46] (n = 96)	Patients with low CYP3A4 activity were more likely to have elevated clozapine concentrations, which correlated with patients having a higher BMI, abnormal glucose levels, and increased adverse effects.
Taylor et al[47] (n = 18)	1 of 4 models accounted for CYP3A4 and CYP3A5 status. All 4 models predicted the required dose to achieve a therapeutic concentration with moderate accuracy.

Abbreviation: BMI, body mass index.

clozapine concentrations, which were in turn associated with a higher incidence of metabolic adverse effects.[46] Finally, Taylor et al[47] described several models to predict clozapine dosing, which included either CYP3A4 activity scores as a variable or specific dose adjustment based on phenotype (ie, a 25-mg reduction in intermediate or poor CYP3A4 metabolizers). These models were described as providing "moderately accurate prediction of the clozapine dose to afford a plasma concentration of 350 ng/mL."[47] This suggests that a CYP3A4 activity score based on phenotype or phenoconversion could be considered to at least some degree in the dosing of clozapine. Although complex, the overall data suggest that a decrease in CYP3A4 function does not significantly impact clozapine metabolism without an influence on other pathways.

The pertinent medication mediating the interaction between nirmatrelvir/ritonavir and clozapine that affects clozapine metabolism is ritonavir. Ritonavir itself is a strong CYP3A4 inhibitor and, to a lesser extent, is an inhibitor of CYP2D6.[1] It is also a weak inducer of CYP1A2 and CYP2C19. All of these interactions are relevant to clozapine metabolism. However, while CYP3A4 and CYP2D6 are involved in metabolic pathways for clozapine clearance, both play small roles in comparison to clozapine's primary pathway involving CYP1A2. In the case reported here, given the package insert's interaction warning and the black box warning of syncope with clozapine, a conservative approach was taken in which nirmatrelvir/ritonavir was discontinued and clozapine was held initially.[2] A clozapine level was obtained to evaluate the degree of any potential clozapine toxicity but was found to be 259 ng/mL, below what is considered therapeutic (ie, 350 ng/mL). Unfortunately, the clozapine result was reported after the clinical decision to hold clozapine and even after hospital discharge. Alternatively, if the result had been obtained with a shorter turnaround time, an interruption of therapy might not have been warranted. The influence of nirmatrelvir/ritonavir on clozapine metabolism requires further evaluation to determine the clinical implications for patients with COVID-19 and treatment-resistant schizophrenia. More importantly, infection itself can significantly decrease clozapine metabolism and this factor needs to be accounted for in such cases, especially in those with more severe infections. In this case, the COVID-19 infection was mild, possibly explaining the lack of a meaningful change in the serum clozapine level relative to a prior baseline level due to infection alone.

One limitation of this report was that only 4 doses of nirmatrelvir/

ritonavir were given, which raises the questions of what duration of therapy is needed for robust CYP3A4 inhibition and whether the exposure was long enough to have caused significant inhibition. Ritonavir causes irreversible inhibition of CYP3A4 through complex mechanisms.[48,49] As the parent drug, ritonavir, is in part responsible for this inhibition, the onset of interaction can be expected to be rapid. This is one reason ritonavir has been leveraged to increase serum concentrations of other medications, including nirmatrelvir and certain medications used in the treatment of human immunodeficiency virus. In one pharmacokinetic study, over the first day of ritonavir exposure, the area under the curve (AUC) between 2 and 4 hours for midazolam, a CYP3A4 substrate, increased by over 5-fold and was increased by 10-fold on day 2 (although the ritonavir dose used was 300 mg twice daily).[50] The authors concluded that maximum inhibition occurred at 48 hours, with midazolam clearance 8.4% of that at baseline at this time. Additionally, there was strong inhibition 3 days after discontinuation of ritonavir. Greenblat et al[51] similarly reported that limited ritonavir exposure significantly impacted clearance of midazolam. In this crossover study, participants were given ritonavir 100 mg 3 times daily for 3 doses and subsequently administered midazolam 3 mg intravenously. Compared to placebo, given at least 1 week earlier, the AUC of midazolam was reported to be increased by 28-fold and the clearance was 4% of that during the control period. Second, differences in the timing of therapeutic drug monitoring were present in this case report, which has implications for interpretation. The time difference in sampling was approximately 8 hours. The half-life of clozapine is often cited to be 12 hours but may be longer (14 to 17 hours) with repeated exposure.[52] Additionally, based on general pharmacokinetic principles and other pharmacokinetic data in patients with advanced age, clozapine's half-life could be expected to extend beyond 12 hours in this patient. Using an assumption of a 16-hour half-life and a one-compartment model with first-order elimination kinetics, the expected baseline clozapine level before admission (372 ng/mL obtained 15 hours after the dose) could be estimated as 263 ng/mL when extrapolated to 23 hours after the dose (calculation is available in eAppendix B). This is very similar to the level obtained upon emergency department presentation of 259 ng/mL. To better characterize the potential lack of interaction, a follow-up clozapine level after discharge would have been useful but unfortunately was not obtained. A third limitation was the absence of a C-reactive protein level to assess whether inflammation was present, as acute inflammation can lead to clozapine toxicity on its own.[4] Fourth, no pharmacogenomic profile was available for review, which may have provided insight into the patient's metabolism of clozapine at baseline. Finally, adherence could only be assumed as the patient was at a nursing facility where medications were administered. However, at our facility, clozapine adherence is always assessed as a part of policy.

Conclusion

In a single case, data did not support a drug-drug interaction between nirmatrelvir/ritonavir and clozapine, as determined by therapeutic drug monitoring. The lack of clinical signs and symptoms of clozapine toxicity or an acute increase in the serum clozapine level, other than the initial syncopal episode resulting in presentation to the emergency department, is also notable. Ongoing investigation and reporting of cases is necessary to evaluate and better understand the interaction between nirmatrelvir/ritonavir and clozapine. However, formal pharmacokinetic evaluation would be challenging in a patient population with infection. Overall, based on the available literature, CYP3A4 does not appear to have a major role in clozapine clearance.

Data availability

No new data were generated or analyzed in support of this article.

Disclosures

The authors have declared no potential conflicts of interest.

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