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# COVID-19 infection, fluctuations in the clozapine/norclozapine levels and metabolic ratio and clozapine toxicity: An illustrative case-report

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*To the Editors,*

A 45-year-old African American female (BMI = 28.27 kg/m$^2$) with schizophrenia was titrated to 350 mg/day of clozapine over 4 weeks with significant improvement noted in treatment-resistant positive symptoms. She was discharged to a residential treatment facility for further stabilization. On admission, she was fully alert and oriented exhibiting residual delusions. Against advice, she resumed smoking eight cigarettes per day. Caffeine intake (3 cups of coffee/day) continued unchanged. Six days after admission, she tested positive for SARS-CoV-2 (RT-PCR test) and a day later exhibited chills and fever, and nasal congestion (Table 1). One day after exhibiting these symptoms she was markedly lethargic and sedated, with excess salivation. She had difficulty holding up her head during a treatment team meeting and required assistance with walking (suggestive of clozapine toxicity confirmed when the clozapine/norclozapine levels were available 3 days later). At the same time, she exhibited low blood pressure and tachycardia and remained febrile with mild hypoxemia suggesting ongoing COVID-19 infection. The daily dose of clozapine was cut immediately to 200 mg (57 percent decrease). Clonazepam was decreased from 2 to 1 mg daily and valproate 1000 mg daily was continued throughout. Area hospitals, urgent care facilities and emergency departments were overrun with COVID-19 Omicron surges and requested facilities to only send moderately to severely symptomatic patients for possible admission. Thus, following the positive COVID test, she was quarantined and monitored in her room with every 15-minute observations for mental state, delirium, shortness of breath, rapid breathing, cough and gastro-intestinal symptoms. Vital signs were monitored each shift for fever, systolic/diastolic blood pressure, tachycardia and pulse oximetry. Fluid and food intake were monitored closely. She would frequently increase her room temperature to 84 °F and staff would recalibrate it down to ambient room temperature.

Trough levels (11–12 h after last dose) of serum clozapine/norclozapine and its ratio, clozapine daily dosage, clozapine concentration/dose (C/D) ratio, vital signs and mental state parameters are detailed in Table 1, especially as these relate to the onset and offset of COVID-19 infection and clozapine toxicity. All clozapine/norclozapine levels were drawn presumably at steady state (at least 7-days) at 350 mg or 200 mg per day except for one measurement during the symptomatic COVID-19 phase (Table 1). White cells including absolute neutrophil counts were normal throughout. Renal functions were essentially unchanged, therefore unlikely to have impacted norclozapine elimination. C-Reactive Protein (CRP) and valproate levels were not obtained during COVID-19 infection.

Within 24–48 h of lowering the clozapine dosage, her alertness and

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**Table 1**
Clozapine, laboratory and vital sign parameters, and symptoms of clozapine toxicity and/or COVID-19 infection.

| | Pre-Covid-19 3–4 weeks | SARS-CoV-2 positive (RT-PCR) | | Resolving Covid-19 2 weeks |
|---|---|---|---|---|
| | | Asymptomatic 8 days | Symptomatic 6 days | |
| Clozapine dosage mg/day | 350 | 350 | 350/200 | 200 |
| Clozapine level µg/L | 867 | 928 | 1050[a] | 406 |
| Norclozapine level µg/L | 278 | 186 | 284[a] | 149 |
| Clozapine/norclozapine metabolic ratio | 3.12 | 4.99 | 3.70[a] | 2.72 |
| Clozapine concentration to dose (C/D) ratio | 2.48 | 2.65 | 3.0[a] | 2.03 |
| Smoking (8 cig/day) | No | Yes | Yes | Yes |
| Covid-19 symptoms | None | None | Chills, fever, nasal congestion | Dissipated |
| Clozapine toxicity symptoms | None | None | Markedly sedated lethargic, excess salivation, walking with assistance | Fully alert and oriented, walking on her own, less salivation |
| Vital signs (range) | | | | |
| • BP (mm Hg) | 102–118/70–82 | | 77–93/53–68 | 95–103/68–78 |
| • Pulse rate/min | 102–119 | | 128–133 | 108–117 |
| • Pulse Ox-$SpO_2$% (room air) | 96–100 | | 92–95 | 95–100 |
| • Temperature (°F) | 97.2–98.6 | 97.4–98.7 | 96.4–101.2 | 97.2–98.4 |

[a] Not at steady state, only one day of clozapine at 200 mg (C/D ratio calculated using 350 mg). C/D ratio is an indicator of clozapine clearance, low to very low ratios indicate presence of cytochrome inducers or rapid metabolizers, and high to very high ratios indicate presence of cytochrome inhibitors or poor metabolizers. Average C/D ratios in Caucasians are estimated to range from 0.6 to 1.2 ng/ml per day (Ng et al., 2005; Spina and de Leon, 2015), and in Chinese and East Asians range from 1.2 to 2.4 (or higher) ng/ml per day (Ng et al., 2005; Ruan et al., 2019), data for African Americans is not yet available.

lethargy levels improved significantly, the excess salivation diminished considerably, and she was able to walk on her own. Over the next 5 days, COVID-19 symptoms dissipated, and she continued to benefit from the lower 200 mg dose of clozapine. Physician-Nurse-Pharmacist-Administrator communication occurred at least twice daily until she stabilized over a 5-day period. The higher clozapine/nor-clozapine levels and ratios seen during the asymptomatic and symptomatic stages of COVID-19 infection normalized with clozapine dosage reduction and resolution of COVID-19 symptoms (Table 1).

These longitudinal data strongly suggest that the resumption of cigarette smoking a week earlier had little if any impact on clozapine/norclozapine levels compared to the powerful impact that COVID-19 infection and inflammation had on the inhibition of hepatic cytochrome enzymes which are involved in the metabolism of clozapine. Nevertheless, a review of several studies indicated that the clozapine/norclozapine ratio is not a good measure of CYPIA2 activity or of clinical response, but the authors also noted none of reviewed studies assessed *a single* subject longitudinally with regards to the clozapine/norclozapine ratio (Schoretsanitis et al., 2019). A recent Swiss study assessed SARS-CoV-2 infection's impact on hepatic cytochromes and reported a 53% inhibition of CYP1A2, 23% inhibition of CYP3A and 75% inhibition of 2C19 enzyme activity, all major metabolic pathways for clozapine during the infection with normalization upon resolution (Lenoir et al., 2021).

Prescriber knowledge and competence in managing side-effects of clozapine is crucial for patients to derive long-term benefits from this efficacious medicine. There is consensus on remaining vigilant to clozapine toxicity with COVID-19 infection (Siskind et al., 2020). Furthermore, the mortality associated with pneumonia and infections with reference to clozapine treatment (possible causes include hypersalivation, sedation and aspiration, infection and cytokine-mediated factors) have been described previously (Clark et al., 2018; de Leon et al., 2020).

The succinct but consensus-based **bottom-line** advice to front-line prescribers is to "*cut the dose of clozapine by half*" (Siskind et al., 2020) or in extreme cases to stop clozapine and reassess later. However, the daily clozapine dosage will likely be determined by individual patient factors. While clinical assessment of COVID-19 symptoms and potential clozapine toxicity in clozapine-treated patients is paramount, the use of clozapine/norclozapine levels and ratios *longitudinally* in individual patients may prove useful to guide clozapine dosing. Acute symptoms of COVID-19 may mask clozapine-withdrawal symptoms following clozapine dosage reduction or stoppage (e.g. cholinergic rebound, Ahmed et al., 1998). Therefore, it is important for the prescriber to factor this possibility into clinical decision making, even though we did not encounter clozapine withdrawal symptoms in our patient. As COVID-19 resolves, if positive symptoms re-emerge, then titration back to the pre-COVID-19 clozapine target dose will have to be made on an individualized patient basis. In our patient, we have slowly titrated clozapine back to 300 mg per day to successfully treat re-emergent positive symptoms.

It is also pertinent to prescribers that a combination of two protease inhibitors, nirmatrelvir and ritonavir (Paxlovid) was recently granted emergency use authorization by the FDA to treat mild to moderate COVID-19 but is contraindicated in clozapine-treated patients (https://www.fda.gov/media/155050/download). Ritonavir's inhibition of CYP3A4 could potentially elevate clozapine to toxic levels. Pimozide and lurasidone are also on the nirmatrelvir and ritonavir combination medication's contraindicated list. Nevertheless, physicians should remain alert for signs of clozapine toxicity just in case this medication combination is co-prescribed with clozapine. Finally, targeted education of prescribers, nurses, caregivers, family members and staff caring for clozapine-treated patients, and the patients themselves is clinically prudent in anticipating and managing clozapine toxicity especially during COVID-19 infections or in yet other infections (especially respiratory and urinary).

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## Declaration of competing interest

None of the authors have any conflicts of interest to disclose in connection with this submission.

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