The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column gave informed consent for the publication of the column.

Elevated clozapine levels and toxic effects after SARS-CoV-2 vaccination

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Case studies indicate that coronavirus disease 2019 (COVID-19) can be associated with toxic clozapine levels, requiring monitoring to maintain therapeutic levels and prevent relapses of psychosis.[1–4] High clozapine levels are consistent with infection-related inflammation inhibiting cytochrome P450 1A2 (CYP1A2) and slowing clozapine metabolism.[5] We report a case of elevated clozapine levels following administration of an mRNA vaccine.

A 51-year-old man with schizoaffective disorder treated with clozapine for more than 10 years was living at a mental health residential facility. He was a nonsmoker. Concomitant disorders included diabetes mellitus type 2, gastroesophageal reflux disease, hyperlipidemia, class II obesity and obstructive sleep apnea. Concurrent medications included divalproex, fenofibrate, linagliptin, metformin and pantoprazole. His history was notable for a past motor vehicle accident, with some residual gait impairment and infrequent incontinence.

The patient had received yearly influenza vaccinations without complication. During a hospital admission for pneumonia treated with intravenous antibiotics, while taking 500 mg/d clozapine, his clozapine level was elevated (Table 1) and he was over-sedated. Thereafter he was stabilized on 300 mg/d with a plan to monitor his clozapine level monthly.

As part of routine care, the patient received the Pfizer-BioNTech vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19. Adverse events began on the fourth day following vaccination. The patient became delirious, fell repeatedly and was increasingly incontinent. He was admitted to hospital out of concern for infection. There was no cough, diarrhea, nausea, vomiting or new rash. His temperature was 37.0 °C, pulse was 129 beats/minute, and blood pressure was 151/86 mm Hg. A chest radiograph showed subsegmental atelectasis or scarring; the lungs were otherwise clear, and an area of consolidation observed previously was resolved. Intravenous antibiotics were started empirically. Blood and urine cultures were negative, as was reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2, influenza and respiratory syncytial virus. A computed tomography scan of his head obtained to investigate delirium showed changes suggesting undiagnosed normal pressure hydrocephalus.

At admission, the patient's neutrophils and monocytes had increased, and lymphocytes were lower than they had been 3 days before vaccination while he was asymptomatic. The high-sensitivity C-reactive protein (hs-CRP) level was elevated well above a previous baseline. His clozapine level doubled; there was no history of stockpiling clozapine, and medication was dispensed daily by staff. The high C/D and C/N ratios were consistent with inhibition of CYP1A2 metabolism. Clozapine was held the next 2 days. Six days after vaccination, both the hs-CRP and clozapine levels had decreased. A repeat RT-PCR test for SARS-CoV-2 was negative. The patient improved to his pre-vaccination level of symptoms and was discharged back to residential care, with clozapine resumed at 150 mg that evening. As of 3 weeks following discharge, the patient remained clinically stable at that dose, with clozapine levels assessed weekly.

Infective or inflammatory stimuli are detected by cells of the innate immune system (including neutrophils and monocytes), and lymphocytes are redistributed from systemic circulation to

Table 1: Laboratory measures

		Pneumonia	Vaccination			
Variable	Reference range	3 months previous	3 days prior	4 days after	5 days after	6 days after
Leukocyte count, $\times 10^9$/L	4.0–11.0	8.4	5.7	11.1	6.3	—
Neutrophils, $\times 10^9$/L	2.0–8.0	6.3	2.7	9.1	4.3	—
Monocytes, $\times 10^9$/L	0.1–0.8	0.7	0.5	0.9	0.6	—
Lymphocytes, $\times 10^9$/L	1.0–4.0	1.3	2.3	1.1	1.5	—
High-sensitivity CRP, mg/L	≤ 7.5‡	65.6§	—	160.1	101.6	32.5
Clozapine dose, mg/d		500	300	300	0	0
Clozapine, nM/L (US ng/mL)	1070 (350)¶	3984 (1302)	1630 (533)	3296 (1078)		1212 (396)
Norclozapine, nM/L (US ng/mL)		1343 (439)	586 (192)	880 (288)		773 (253)
C/N*	≤ 2	2.95	2.78	3.75		1.57
C/D†	0.6–1.2	2.6	1.8	3.6		2.2

CRP = C-reactive protein.
*Ratio of clozapine to norclozapine level, value > 2 indicates slow metabolism.
†Ratio of clozapine level in ng/mL to clozapine dose in mg; requires a steady state or mean of 5 previous days used, a higher value indicates lower clearance.
‡Higher value indicates active inflammation or infection.
§Previous baseline 4.1; recovered in 6 days to 5.8.
¶Therapeutic level.

lymphoid tissues — all features observed in healthy volunteers given the mRNA vaccine, and consistent with findings in our patient.[6] Detection of a "danger signal" by immune cells leads to the production of proinflammatory cytokines, such as interleukin-6, that bind to receptors on hepatocytes, leading to release of acute phase proteins, such as CRP.[5,7] The CRP level is a highly sensitive inflammatory biomarker that can reach levels 1000-fold or more above baseline, with a response time of 6–12 hours and a rapid decrease 18–20 hours following termination of an inflammatory challenge.[7]

Inflammation can inhibit drug metabolizing enzymes through 3 proposed mechanisms: induction of transcriptional regulators, induction of nitric oxide–dependent proteosome degradation of enzymes, and epigenetic modification resulting in decreased gene expression.[5] Clozapine and theophylline levels are sensitive to inflammation-related inhibition of CYP1A2 activity.[5] These complex patterns of stimulation and response are incompletely understood and may explain why different stimuli affect drug levels in a specific manner. Notably, yearly vaccination for influenza had no symptomatic consequences in our patient, consistent with the reported absence of effect of influenza vaccination on clozapine levels reported by others.[8] Influenza vaccine has been associated with mild changes in immune cell profile and a wide range of CRP responses that may be related to dose, different adjuvant components of vaccines, or individual differences in immune system exposures or genetics.[9–11]

During the COVID-19 pandemic, the approach to managing clozapine in a patient with fever or flu-like symptoms includes obtaining clozapine levels in patients with symptoms possibly indicating toxicity, reducing the dose by as much as half, continuing the lower dose until symptoms subside, and then increasing stepwise to the previous dose.[12–15] This single case we report cannot establish a causal relationship between vaccination and elevated clozapine level; more clinical reports and research are required. Multiple predisposing factors may have contributed risk for symptomatic expression of the high clozapine level in our patient, including age, structural brain abnormalities, multiple medical comorbidities and concurrent medications. The complex immunomodulatory effects of clozapine may contribute to increased rates of pneumonia; the earlier pneumonia-related high clozapine level in our patient may represent individual sensitivity to specific types of inflammatory stimuli.[14,16,17]

In summary, patients can continue to be treated with clozapine during SARS-CoV-2 infection; similarly, there is no reason to avoid vaccination. Careful evaluation for symptoms consistent with clozapine toxicity following SARS-CoV-2 vaccination and obtaining clozapine and CRP levels when indicated may help maintain patients safely on clozapine — particularly patients with risk factors including previous high clozapine levels related to infection or inflammation — and prevent relapse of psychotic illness.[12]

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