Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Support'. Available from: https://dictionary.apa.org/social-support
2. House JS: Work stress and social support. Reading, MA: Addison-Wesley Educational Publishers Inc.; 1981.
3. Wills TA: Social support and interpersonal relationships. In: Clark MS, (ed.) Prosocial behavior. Newbury Park, CA: Sage; 1991. p. 265–289
4. Thoits PA: Stress, coping, and social support processes: where are we? What next? J Health Soc Behav 1996; 35:53–79
5. Nurullah AS: Received and provided social support: a review of current evidence and future directions. Am J Health Stud 2012; 27:173–188

Clozapine Toxicity in the Setting of COVID-19

TO THE EDITOR: The COVID-19 pandemic presents a variety of unique challenges for psychiatric practice including decreased in-person visits, difficulties obtaining lab work, and interruptions in medication supplies. These circumstances are particularly salient for patients with serious mental illnesses who are treated with clozapine. Prescribing this drug requires close monitoring for serious side effects (agranulocytosis, myocarditis, aspiration pneumonia) and clozapine toxicity (seizures, ileus, delirium).[1] In addition, discontinuing clozapine upon admission to an intensive care unit introduces the risk of clozapine withdrawal which can result in severe psychosis, catatonia, and medical complications including delirium.[2] Clinicians caring for patients with COVID-19 on clozapine may thus encounter clinical syndromes that are in part due to clozapine or require an adjustment of the clozapine dose. In the following paragraphs, we report 3 cases of elevated clozapine levels occurring in patients with COVID-19 who had been previously managed for several years on stable doses.

The first was a 76-year-old man with bipolar-type schizoaffective disorder complicated by recurrent catatonia. He had been stabilized for several years on clozapine 300 mg nightly (QHS) (trough level at this dose was 106 ng/mL) and monthly maintenance electroconvulsive therapy (ECT). He was admitted to the hospital with COVID-19 and catatonia 1 month after missing his last ECT treatment. A trough clozapine level from admission was 1360 ng/mL. Notably his hospital course was complicated by neutropenia with a nadir absolute neutrophil count (ANC) of 1100. Interpretation of this abnormality was complicated by the administration of an experimental COVID-19 medication (tocilizumab) that is associated with neutropenia. His ANC gradually rebounded to the 4000s, and his catatonia resolved with lorazepam and a reduction of clozapine to 200 mg QHS.

The second case was a 63-year-old woman with bipolar-type schizoaffective disorder stabilized for nearly a decade on citalopram 20 mg daily, olanzapine 20 mg QHS, and clozapine 50 mg in the morning and 350 mg QHS. She initially presented with nausea and confusion. She was found to have COVID-19, hyponatremia to 111, and an ileus. A clozapine level drawn at admission 4 hours before her normal nightly dose returned at 1060 ng/mL. No prior records were available for comparison. ANC at admission was elevated at 14,970. Her clozapine was held for 1 week without adverse consequences, and the drug was gradually reintroduced when her bowel function returned to normal.

The third case involved a 53-year-old woman with schizophrenia who had been maintained for many years on clozapine 250 mg QHS and fluphenazine 5 mg in the morning and 10 mg QHS. Her last clozapine level from when she was taking 200 mg was 458 ng/mL. She initially presented with delirium, fever, and vomiting. At admission, she was noted to have COVID-19 and an elevated trough clozapine level of 2154 ng/mL. ANC was 2200 at admission and remained stable throughout her stay. Her clozapine dose was decreased to 50 mg QHS with a temporary increase in her home fluphenazine to 10 mg twice daily (BID). She tolerated a gradual return to her home dose with normalization in her mental status.

These 3 cases (granulocytopenia with catatonia, ileus, and delirium) serve as a reminder to clinicians that clozapine is associated with a wide range of medical complications and toxicities that complicate the management of COVID-19. At the start of the pandemic, an international consensus statement was drafted to provide guidance on how to continue treating patients with this life-saving medication.[3] Recommendation 3 of these guidelines warns clinicians of possible clozapine toxicity in the setting of severe respiratory illnesses such as COVID-19. Recently it has been recognized that severe systemic inflammation can increase clozapine levels, in part due to cytokine-mediated inhibition of CYP1A2.[4] Therapeutic drug monitoring and consideration of dose reduction is generally recommended under such conditions.[3] Levels in the 200- to 450-ng/mL range are associated with

improved responses, while levels above 1000 ng/mL are associated with toxicity.[5] Consult psychiatrists should therefore be careful to monitor clozapine levels and signs of toxicity in patients diagnosed with COVID-19, while remaining vigilant for potentially life-threatening side effects necessitating a temporary dose reduction. On the outpatient side, liberalized ANC monitoring requirements do not equate to liberalized clinical monitoring requirements, and outpatient psychiatrists should continue to proactively engage their patients on clozapine.

Funding: None.

Disclosure: Dr. Freudenreich has received institutional research grants from Alkermes, Avanir, Janssen, Otsuka, and Saladax; consultant honoraria from Alkermes, Janssen, Neurocrine, Novartis, Roche, Global Medical Education, Elsevier, Medscape, and UpToDate; and royalties from Wolters-Kluwer, Springer Verlag, and UpToDate. The remaining authors have no competing financial interests to declare.

Samuel Dotson, M.D.*
Nathan Hartvigsen, M.D.
Department of Psychiatry, Massachusetts General Hospital Boston, MA
Department of Psychiatry, Harvard Medical School, Boston, MA
Behavioral Health Team, Boston Hope COVID-19 Field Hospital, Boston, MA
Tara Wesner, D.N.P., P.M.H.N.P.-B.C.
Timothy J. Carbary, Ph.D.
Behavioral Health Team, Boston Hope COVID-19 Field Hospital, Boston, MA
Gregory Fricchione, M.D.
Department of Psychiatry, Massachusetts General Hospital, Boston, MA
Department of Psychiatry, Harvard Medical School, Boston, MA
Behavioral Health Team, Boston Hope COVID-19 Field Hospital, Boston, MA
Oliver Freudenreich, M.D.
Department of Psychiatry, Massachusetts General Hospital, Boston, MA
Department of Psychiatry, Harvard Medical School, Boston, MA
*Send correspondence and reprint requests to Samuel Dotson, MD, Department of Psychiatry, Massachusetts General Hospital, Wang 8, 55 Fruit Street, Boston, MA 02114; e-mail: SJDotson@partners.org

References

1. Meltzer HY: Clozapine: balancing safety with superior antipsychotic efficacy. Clin Schizophr Relat Psychoses 2012; 6:134–144
2. Stanilla JK, De Leon J, Simpson GM: Clozapine withdrawal resulting in delirium with psychosis: a report of three cases. J Clin Psychiatry 1997; 58:252–255
3. Siskind D, Honer WG, Clark S, et al: Consensus statement on the use of clozapine during the COVID-19 pandemic. J Psychiatry Neurosci 2020; 45:200061
4. Clark SR, Warren NS, Kim G, et al: Elevated clozapine levels associated with infection: a systematic review. Schizophr Res 2018; 192:50–56
5. Freudenreich O: Clozapine drug levels guide dosing. Curr Psychiatry 2009; 8:78–79

Patients With the Novel SARS-Cov-2 Disease Require a Novel Standard of Care—Med-Psych

TO THE EDITOR: The severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) pandemic introduced a new way of caring for inpatients. Patients hospitalized because of infection with the virus are struggling with both the physical disease and the mental burden associated with isolation.

Abad et al.[1] have demonstrated the adverse effects of isolation on patients. The standards of precaution for prevention of disease transmission in their meta-analysis were significantly less "strict" than the standards currently practiced in isolation departments for patients with SARS-Cov-2.[1]

SARS-Cov-2 inpatients suffer from the physical impact of their disease and the forced quarantine, both of which contribute to their mental distress.[2] Prior mental health disorders worsen emotional responses brought on by the SARS-Cov-2. Relapses of an already existing mental health condition are observed as well.[3]

The isolation in departments caring for SARS-Cov-2 patients is multidimensional. Patients cannot leave the hospital, even if they are willing to bear the medical responsibility and consequences. They barely receive visits, and they are able to connect with the outer world mostly via electronic devices.

SARS-Cov-2 departments often have limited open spaces where patients can practice physical activity or roam about. Also, windows are partially shut, so daylight enters only to some extent, with no freedom to control this simple need.

Caring staff are fully covered by protective gear; therefore, their facial expressions are unseen. As a result of the multidimensional isolation, patients lose fundamental anchors of basic existence.

Internists are not well trained in diagnosing and treating mental