

Suspected Recurrence of Symptomatic COVID-19: Management During Inpatient Psychiatric Treatment

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The widespread prevalence of coronavirus disease 2019 (COVID-19) means that inpatient psychiatric units will necessarily manage patients who have COVID-19 that is comorbid with acute psychiatric symptoms. We report a case of recurrence of respiratory symptoms and positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription-polymerase chain reaction (RT-PCR) testing in a patient on an inpatient psychiatric unit occurring 42 days after the initial positive SARS-CoV-2 RT-PCR test, 38 days after initial symptom resolution, and 30 days after the first of 3 negative SARS-CoV-2 RT-PCR tests. Over the course of the admission, the patient was safely initiated on clozapine. Recent literature on COVID-19's potential recurrence and neuropsychiatric effects is reviewed and implications for the management of COVID-19 on inpatient psychiatric units are discussed. In the era of COVID-19 and our still-developing understanding of this illness, psychiatrists' role as advocates and collaborators in our patients' physical health care has become even more critical.

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KEY WORDS: coronavirus disease 2019 (COVID-19), inpatient psychiatry, recurrence

After identifying the first case of severe acute respiratory syndrome-associated coronavirus (SARS-CoV-2) disease 2019 (COVID-19) on March 1, 2020,¹ New York City rapidly became the epicenter of the pandemic in the United States with 371,711 positive cases as of June 1, 2020.² The widespread prevalence of COVID-19 means that inpatient psychiatric units will necessarily manage patients who have COVID-19 comorbid with acute psychiatric symptoms including psychosis, depression, and suicidality. The challenges in preventing the spread of COVID-19 on inpatient psychiatric units include the impact of the patients' psychiatric illnesses on behaviors,³ the on-unit mobility of the patient population, the therapeutic use of

common spaces, peer-to-peer interactions, group treatment modalities, and longer lengths of stay. Evidence of these challenges can be seen in reports of COVID-19 outbreaks on inpatient psychiatric units in Wuhan, China,⁴ South Korea,⁵ and Seattle, WA.⁶

Limited published guidelines exist for the management of COVID-19 on inpatient psychiatric units,^{3,7-10} and much still remains unknown about the risk of reinfection or the time needed to maintain patients on contact, droplet, and eye precautions after symptoms resolve.¹¹ Guidelines from the United States Centers for Disease Control and Prevention (CDC) in place in May 2020, when this case report was being drafted, for discontinuing transmission-based precautions required either 72 hours of no fever without antipyretic use and improved respiratory symptoms at least 10 days from symptom onset or lack of fever without antipyretic use, improved respiratory symptoms, and 2 consecutive negative SARS-CoV-2 RNA tests at least 24 hours apart.¹²

Here, we report a case of recurrence of respiratory symptoms and positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) testing in a patient on an inpatient psychiatric unit occurring 42 days after the initial positive SARS-CoV-2 RT-PCR test, 38 days after initial symptom resolution, and 30 days after the first of 3 negative SARS-CoV-2 RT-PCR tests. Institutional review board approval was not obtained as case reports do not meet requirements set forth by the Federal Policy for the Protection of Human Subjects in research. The information in this report has been adequately deidentified to protect confidentiality.

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CASE PRESENTATION

The patient is a 44-year-old undomiciled male with a history of alcohol use disorder and no other formal psychiatric or medical history who was brought into NYU Winthrop Hospital (Mineola, NY) by ambulance on March 31, 2020, after he jumped in front of a train in a suicide attempt. The patient sustained right-sided 10th to 12th rib fractures, a scalp laceration, and a complete traumatic below-knee amputation of the right lower extremity for which he underwent emergency surgery.

Medical History and Hospital Course

On presentation to the emergency department, the patient endorsed a recent history of fever and cough, prompting him to be placed on COVID-19 precautions; he subsequently tested positive for SARS-CoV-2 via RT-PCR on April 1, 2020, via nasopharyngeal swab. A computed tomography (CT) scan of the chest, performed on March 31, 2020, demonstrated panlobar (middle and lower lobe predominant) ground-glass opacities most consistent with multifocal pneumonia (Figs. 1A, B). Bloodwork was notable for elevated C-reactive protein and D-dimer levels, although these results were likely increased in the setting of trauma. The patient received treatment for COVID-19 pneumonia which included dexamethasone on hospital day (HD) 1 and treatment with lopinavir-ritonavir, of which he received 3 doses during HD3 and HD4 and 3 doses over HD8 and HD9, with a gap in treatment due to patient refusal. The patient required supplemental oxygen from HD1 to HD4 and continued to be febrile over the course of HD3 to HD5 with temperatures up to 102.9°F, which were treated with acetaminophen. From HD5 onward, the patient remained afebrile, on room air, and without cough or other signs or symptoms of COVID-19. On HD6, a portable anterior-posterior chest x-ray revealed faint left basilar airspace opacity perhaps representing a small focus of residual atelectasis or pneumonia. While the patchy bilateral ground-glass opacities seen on CT can be difficult to appreciate by portable radiography, no new focal pulmonary consolidations were noted. The patient tested negative for SARS-CoV-2 via RT-PCR on HD13.

On HD15, the patient was medically stable and transferred to the inpatient psychiatry unit at NYU

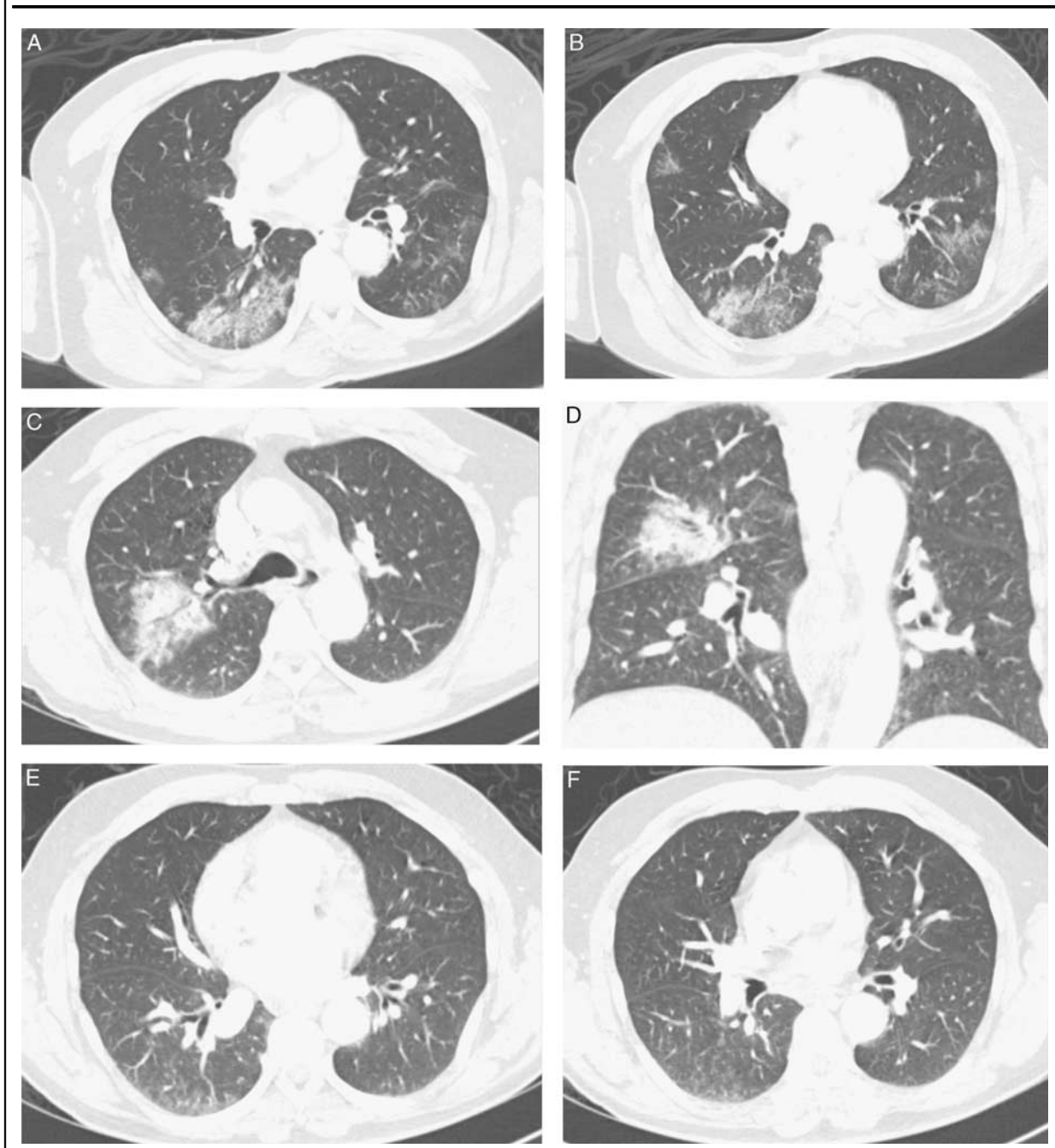
Langone Hospital–Brooklyn with diagnoses of alcohol use disorder and major depressive disorder with psychotic features. The patient was tested for SARS-CoV-2 via RT-PCR on 2 additional occasions, both prompted by elevated temperatures, with a temperature of 100.3°F on HD19 and a temperature of 99.6°F on HD42; both tests were negative. One day after the last negative SARS-CoV-2 result via RT-PCR test, the patient developed a cough, headache, and nasal congestion and subsequently tested positive for SARS-CoV-2 RNA on HD43. A COVID-19 immunoglobulin (Ig) G antibody test was also performed on this day and was positive (6.1 U).

A portable anterior-posterior chest x-ray was performed on HD44, which revealed a new hazy opacity in the right mid-lung to the upper-lung zone. On HD47, the patient developed dyspnea with elevated D-dimer (1276 ng/mL), prompting a repeat chest CT scan, which, in comparison to the CT performed on HD1, showed resolved infiltrates in the left lung and significantly decreased ground-glass opacities in the right lower lobe (Figs. 1E, F), with significantly increased patchy ground-glass opacities in the posterior segment of the right upper lobe (Figs. 1C, D).

Routine laboratory tests, including complete blood count and basic metabolic panel, were within normal limits. A nasopharyngeal respiratory pathogen panel via polymerase chain reaction for 20 common respiratory viral pathogens was negative; this result, along with low procalcitonin levels, negative interferon-gamma release assay, and positive measles IgG, made other potential respiratory infections unlikely. Ultimately, the patient's respiratory symptoms resolved, repeat SARS-CoV-2 testing via RT-PCR was performed twice 24 hours apart, on HD61 and HD62, with both tests negative, and the patient was removed from droplet/eye/contact precautions. As a requirement for transfer to a state psychiatric facility, the patient was retested on HD106 and HD112, with the results negative and positive, respectively. As a follow-up to the positive test on HD112, COVID-19 IgA, IgM, and IgG antibody tests were performed. COVID-19 IgA and IgM were negative (4 and 4.4 U, respectively) and IgG was positive (29.3 U). The assessment by the infectious disease physician was that the low viral load and the high IgG result without elevations in IgA/IgM in this patient indicated that the positive COVID-19 PCR test did not reflect new infection or infectiousness.

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FIGURE 1. Computed tomography of the patient's chest on the day of admission showing ground-glass opacities most pronounced in the right middle (A) and lower (B) lobes; follow-up computed tomography on hospital day 47 with increased ground-glass opacities in the posterior segment of the right upper lobe (C, D) and decreased ground-glass opacities in the right lower lobe (E, F).



Psychiatric History and Hospital Course

Although the patient denied any formal psychiatric diagnoses or past psychiatric treatment, he endorsed multiple years of occasional auditory hallucinations, delusions that other people were whispering about him, and feelings of depression in the context of social and financial stressors. These stressors included being away from his family overseas, losing his job as a dishwasher a few months before admission due to excessive alcohol use, and becoming homeless shortly thereafter due to lack of income. He denied any previous history of suicidal ideation or suicide attempts. On the days leading up to his suicide attempt, he reported feeling more depressed, characterized by hopelessness, decreased energy, decreased appetite, and poor sleep, leading to thoughts of suicide. He denied experiencing any auditory hallucinations at the time. He did not have any intent to commit suicide until the day of presentation when he began to hear a male voice commanding him to kill himself.

The patient also reported a history of alcohol use—reportedly drinking 2 to 4 beers, 1 to 2 times/wk before this admission—although he had had episodes of withdrawal, delirium tremens, and encephalopathy requiring inpatient management in the past. He never attended any rehabilitation programs. The patient denied any other substance use or family history of psychiatric illnesses. The patient's friend in New York City and his daughter overseas were contacted for collateral information and corroborated the patient's history of alcohol use disorder; both denied any known history of psychosis or suicidal ideation/attempts.

The course of the patient's psychiatric treatment was complicated by refusal or partial refusal of medications. While he was still on the surgery service, the patient endorsed command auditory hallucinations, some of which were telling him to kill himself. The patient was started on sertraline on HD2 for depression, which was titrated to 200 mg/d; he was maintained at this dose from HD18 to HD71. Following a brief period of refusal, sertraline was reinstated on HD77 and continued through discharge at a dose of 175 mg/d. Mirtazapine was added to the antidepressant regiment on HD52 and titrated to a total daily dose of 45 mg, which was continued through the hospitalization. With regards to antipsychotic medications, after a 1-day trial of risperidone (discontinued due to

prolonged QTc), the patient was started on olanzapine which was gradually increased to a dose of 25 mg/d by HD23. However, despite the absence of suicidal ideation, the patient continued to complain of command auditory hallucinations telling him to kill himself. Due to the persistence of these hallucinations, the patient was tapered off olanzapine and started on aripiprazole (up to a dose of 30 mg/d). An incomplete response was observed, and clozapine was initiated on HD35 for the ongoing and distressing command auditory hallucinations. The clozapine was titrated up to a dose of 200 mg by HD46 and continued through HD56. On that day, the patient began to consistently refuse blood draws, stating that he did not want to give blood "to the man upstairs." Therefore, the clozapine was discontinued and olanzapine was restarted at 15 mg/d at bedtime. The patient demonstrated some improvement in symptoms, which resulted in better engagement with the treatment team. He ultimately agreed to another trial of clozapine and the associated laboratory work, which was initiated on HD67 and continued through discharge. The blood monitoring levels of the patient's absolute neutrophil counts were within normal limits and unchanged from before the initiation of clozapine, ranging from 5000 to 8300/ μ L while on clozapine. However, due to the frequent recurrence of the command auditory hallucinations and the persistence of low mood due to hopelessness about his unemployment and amputation, the patient was discharged on HD119 to a state psychiatric facility for longer term treatment. His discharge diagnosis was severe, recurrent, major depressive disorder with psychotic features. While consideration was given to a diagnosis of schizoaffective disorder, the treatment team was unable to unequivocally identify a period of psychotic symptoms persisting for 2 or more weeks in the absence of mood symptoms. Despite not having a clear diagnosis of schizoaffective disorder, the serious nature of the patient's suicide attempt, the command auditory hallucinations he experienced in the hospital, and his history of psychotic symptoms warranted treatment with clozapine to which the patient was ultimately responsive. The patient's discharge medications were clozapine (250 mg/d), mirtazapine (45 mg/d), sertraline (175 mg/d), and gabapentin (for neuropathic pain, 1800 mg/d).

LITERATURE REVIEW

SARS-CoV-2 Testing and Potential COVID-19 Recurrence

Due to the novelty of the disease, our understanding of the potential for COVID-19 reinfection or reactivation has been constantly changing, with an increasing number of cases reported both in the scientific literature and in the news media. For most of the initial case reports, patients did not have a recurrence of fever or respiratory symptoms. In late February 2020, 3 patients in Wuhan, China tested positive for SARS-CoV-2 via RT-PCR between 5 and 13 days after recovering from confirmed symptomatic COVID-19 and having 2 consecutive negative tests.¹³ These patients did not develop fever or respiratory symptoms and similar cases have been documented in Wenzhou and Guangzhou, China.^{14,15}

However, more recently, attention has focused on cases of patients who seemed to have recovered from COVID-19 and later experienced a recurrence of symptoms with a subsequent positive test. On March 3, 2020, a study from the Guangdong Province of China found that 14% of patients who were discharged from hospitals after recovering from COVID-19 and testing negative twice subsequently tested positive for the virus again; an undisclosed number of patients had developed fever within 1 week from discharge.^{16,17} A study from Wuhan, China, published on March 17, 2020, found a 9% rate of retesting positive 4 to 17 days after a negative test, with 80% of those patients showing recurrence of symptoms.¹⁸ On May 16, 2020, the US Navy announced that at least 5 sailors developed influenza-like symptoms and retested positive after they were thought to have recovered from COVID-19 and had tested negative for the virus at least twice.¹⁹ Soon after, on May 18, 2020, the first case of potential COVID-19 recurrence in Italy was reported: a few weeks after recovery from confirmed COVID-19 with resolution of symptoms and 3 negative tests, the patient developed dyspnea and chest pain.²⁰ He was then tested for viral RNA and IgG antibodies, which were both positive. Of note, the patient was found to have a pulmonary embolism, which would at least partially explain his new symptoms.

The Korea Centers for Disease Control and Prevention (KCDC) has provided the most robust

analysis of this phenomenon, issuing a report on May 19, 2020, examining 285 cases in which patients tested positive after apparent recovery and release from isolation.²¹ Of these patients who tested positive again after having had negative tests (“re-positive” or repeat-positive patients), 44.2% had developed symptoms at the time of their repeat test. All patients were tested after meeting the criteria to discontinue isolation, which were similar to the criteria set by the United States CDC: the resolution of fever without antipyretic use, improvement in respiratory symptoms, and 2 negative RT-PCR tests 24 hours apart.²² The majority (96%) of the repeat-positive patients were found to have SARS-CoV-2 IgG antibodies, possibly indicating some degree of immunity. Contact tracing work by the KCDC determined that there were no new cases of COVID-19 in people who were solely exposed to these repeat-positive patients; the KCDC also reported that the virus was unable to be isolated from the cell culture of respiratory samples of the repeat-positive patients. Both of these factors indicate that, despite testing positive (with or without symptoms), these patients were no longer infectious. As a result, the KCDC decided to treat these repeat-positive patients as standard COVID-19-recovered patients and no longer requires isolation of repeat-positive patients or contacts of repeat-positive patients.

Neuropsychiatric Effects of COVID-19 and Concurrent Use of Clozapine

Multiple studies have reported increased rates of psychiatric illnesses in the general population during the COVID-19 pandemic and as well as during earlier pandemics, likely due to a preoccupation about getting sick and other stressors relating to isolation, unemployment, and loss of loved ones.^{23,24} In the setting of SARS-CoV-2 infection, patients without a history of psychiatric problems have developed new-onset psychotic symptoms.²⁵ Other neuropsychiatric sequelae include cerebrovascular events, encephalopathy, and delirium.²⁶ Various potential mechanisms for the neuropsychiatric symptoms associated with SARS-CoV-2 and other coronaviruses include viral infiltration into the central nervous system and immune system dysregulation, along with the aforementioned stressors.²⁷ Similarly, it has been speculated that those with

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chronic mental illnesses who are infected with SARS-CoV-2 may experience exacerbations in their symptoms.²⁴

Concerns have also been raised about the use of clozapine in COVID-19-positive patients. These reservations are based on earlier findings of an increased risk of infections, including pneumonia, in patients treated with clozapine compared with other antipsychotics.^{28,29} Proposed mechanisms include clozapine's immunomodulatory effects on cytokines and lymphocytes, leading to neutropenia and decreased levels of circulating Igs.^{30,31} Conversely, the increased levels of cytokines associated with COVID-19 infections can also decrease clozapine metabolism, leading to potential clozapine toxicity.²⁹ In addition, patients on clozapine usually have a history of treatment-resistant schizophrenia; these patients are more likely to have medical comorbidities such as diabetes and cardiovascular disease, which increase the risk associated with COVID-19 and other infections.^{28,29}

A retrospective cohort study in London, UK found that, of patients with schizophrenia spectrum disorders, those treated with clozapine had an increased risk of symptomatic COVID-19 infection compared to those treated with other antipsychotics.²⁸ However, multiple case reports have described patients with COVID-19 who were successfully continued or initiated on clozapine without any adverse effects including exacerbation of their respiratory illness or neutropenia.^{29,32} The general consensus is that, although treatment with clozapine introduces an increased risk of infection, it can be administered safely in patients with or at risk for COVID-19.^{28,33} Initiation should be considered on a case-by-case basis to find a balance between the risk of infection and the risk of leaving a patient's psychosis untreated. This is especially pertinent because patients with severe mental illness are already at a higher risk for medical illnesses at baseline.^{28,32} The current recommendations are that, if clozapine is given, patients should be monitored for new-onset infectious symptoms; in response to symptoms such as fever or cough, it is recommended for clinicians to assess the patient's absolute neutrophil counts and to adjust their clozapine dose to prevent toxicity.³³

DISCUSSION

There are several possible explanations for the recurrence of symptoms and positive RT-PCR testing in patients who had presumably recovered from

COVID-19. The most straightforward explanation for a patient testing negative in between positive tests lies in the sample itself. Variations in sampling technique, including the location of the sampling site and the time between sampling and testing, can affect the integrity of the sample.^{15,16} In addition, since the viral load of SARS-CoV-2 can be dependent on the course of the disease and symptom severity, test results can vary depending on the current clinical status of the patient.³⁴ As suggested by the KCDC, it is also possible that tests done later in the disease course may instead detect non-infectious viral shedding, leading to false concern about disease reactivation.^{21,35} For our patient, we were unable to track the changes in his viral load due to the qualitative nature of the Xpert Xpress SARS-CoV-2 test used at NYU Langone Health.³⁶ It is possible that our patient's RNA levels could have been low at baseline and fluctuated around the test's limit of detection (LoD), resulting in "non-detected" tests and a false impression that he had recovered from COVID-19 as he was asymptomatic for an extended period.

Consistent with this possibility, the sensitivity of RT-PCR tests has been a topic of concern for causing false-negative results.¹⁵ A study from Wuhan found that 21.4% of patients tested positive after 2 consecutive negative results, which was attributed to the false-negative rate of the RT-PCR test from Shanghai Huirui Biotechnology Co. Ltd.³⁵ Information on the sensitivity of this test is not readily available online, but the LoD (the lowest concentration level that can be detected with $\geq 95\%$ analytical sensitivity) of other commonly used RT-PCR test kits in China range from 484 to 774 copies/mL. In comparison, the Xpert Xpress SARS-CoV-2 test by Cepheid used at NYU Langone Health has a LoD of 250 copies/mL.³⁶ While the LoD may impact the likelihood of obtaining a false-negative result, particularly when combined with a poor sampling technique, it is unlikely that a test with a low LoD such as the one used with our patient would give 5 negative tests across 106 days and 2 different hospitals.

Even if our patient had never fully recovered and remained COVID-19-positive despite the negative RT-PCR results, it would be unexpected that he would have naturally redeveloped symptoms after resolution. In Shanghai, a retrospective study found that 249 patients with confirmed COVID-19 did not experience a recurrence of fever during the course of their infection.³⁷ The possibility of SARS-CoV-2 reactivation has been

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discussed in the literature. Various patient characteristics, including male sex, older age, comorbid health conditions, immunosuppression, and more severe clinical status, have all been proposed as potential risk factors for reactivation.^{16,18} However, potential mechanisms of reactivation have not been postulated, nor have other viruses in the group of coronaviruses previously been found to reactivate.³⁸ In our case, this patient did not carry any of these risk factors since he was previously healthy and only received a single dose of dexamethasone. There is also concern about reinfection of patients who have recovered from COVID-19, which has been speculated about but not formally documented. It has been suggested that patients may have incomplete immunity even with IgG antibodies for SARS-CoV-2 or that patients can be infected by a strain of SARS-CoV-2 with a different genotype, but to date, no large-scale studies have been published addressing these possibilities.^{16,18,20}

Finally, the temporal relationship between our patient experiencing a recurrence of symptoms and the initiation of clozapine must be considered. Clozapine was initiated on HD35 with the recurrence of symptoms occurring on HD43 (clozapine 125 mg/d), and at no point did the patient exhibit neutropenia. The current literature suggests that, in all likelihood, the initiation of clozapine did not play a role in the recurrence of COVID-19 symptoms and repeat-positive testing in our patient; however, as we are learning more about SARS-CoV-2, it would be prudent to use caution when initiating clozapine in the context of recent infection.

It should be noted that this patient's worsening psychosis and depression leading to a suicide attempt occurred in the setting of being infected with SARS-CoV-2. While in this case, all of the patient's psychotic and mood symptoms predated his SARS-CoV-2 infection, we cannot exclude the possibility that his acute decompensation was related to this infection. However, he did not report feeling particularly worried about the pandemic or his health, meaning the acute worsening of his psychiatric symptoms appeared unrelated to the pandemic or his fever and cough. During his admission, the patient's continued depressive symptoms were primarily linked to social and financial stressors, which were unrelated to the pandemic, and the injuries he sustained from his suicide attempt. His depressive and psychotic symptoms in the hospital did not appear to worsen with his COVID-19-related symptoms such as fever or cough. Therefore, it is unlikely that his acute decompensation was primarily

due to COVID-19; however, the infection certainly could have played a part in his presentation.

Recent findings that deemphasize the risk of reinfection and recurrence of infectivity may serve to inform policies for discontinuing isolation on inpatient psychiatric units.²¹ However, as our understanding of the infectiousness of SARS-CoV-2 over the course of COVID-19 develops, the management of COVID-19-positive patients should change accordingly. As we develop a better understanding of the various reasons why some patients retest positive, with or without the emergence of symptoms, we can develop better, more nuanced guidelines for patient care of inpatient psychiatric units that employ community interactions and group experiences as integral therapeutic modalities. In addition, increased knowledge of the neuropsychiatric effects of the virus and the safety of medications such as clozapine will provide insight into how to care for patients who rely on these treatments. Given the disproportionate prevalence of chronic medical illness among people with severe persistent mental illness^{39,40} and the significant barriers to care that our patients face, inpatient psychiatrists often act as advocates for timely, consistent, and optimal treatment of our patients' medical conditions. In the era of COVID-19 and our still-developing understanding of this illness and its potential psychiatric effects, our role as advocates and collaborators in our patients' physical health care has become even more critical.

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