Rational Approach to Psychotropic Use in COVID-19 Cases With Psychiatric Comorbidities: Lesson Learnt From a Case Series

Jigyansa Ipsita Pattnaik[1], Sudipta Das[2], Hemlata Sarkar[2], Rajnarayan Mahasuar[3,4] and Jayprakash Russell Ravan[2,4]

The treatment of individuals with major psychiatric disorders suffering from severe COVID-19 disease is a challenge to clinicians in view of hypoxia and psychotropic-related adverse effects. The multifaceted proximity of psychiatric manifestations with COVID-19 is noteworthy. The management of COVID-19 in the first wave of the pandemic mostly included hydroxychloroquine, doxycycline, antivirals, ivermectin, azithromycin, etc., and possible drug interactions with psychotropic medications have been highlighted.[1] Treatment regimens are more streamlined in the second wave, with the mild cases being managed with home isolation and close observation to detect early signs of cytokine storm and other markers of progression.[2] Oxygen therapy, steroids, and low-molecular-weight heparin (LMWH) are reserved for moderate to severe cases only.[3] The complex interactions of psychotropics pertaining to hypoxia, steroid therapy, and coagulability have now become more relevant. A set of practical recommendations was drawn up to aid frontline resident doctors posted at COVID hospitals to identify the risk of psychotropic-related unfavorable events and determine when to withdraw, switch, or adjust the dose of the psychotropic medication.[4] However, the treating physicians often hesitate to continue psychotropics during a COVID-19 infection,[5] and there is a lack of consensus even among mental health professionals about dose adjustment considerations in patients with psychiatric comorbidities.

We present a series of patients with psychiatric comorbidities who developed COVID-19, highlighting the various therapeutic challenges and rational considerations for psychotropic use in this population. Those who provided valid informed consent were included.

Case 1

A 35-year-old female, separated from husband, staying with parents, with ten years history of treatment-resistant schizophrenia was maintaining on 200 mg of clozapine for eight years. Her psychotic symptoms were well-controlled, but she had sialorrhea and oversedation as the side effect of clozapine. A trial of reducing clozapine was tried eight years back when the psychotic symptoms worsened. However, the sialorrhea persisted even at 25 mg. Currently, she presented with fever and throat pain and tested positive for COVID, with an oxygen saturation (spO_2) of 86%. She was categorized as severe COVID. She had a computerized tomography (CT) score of 18/25. She was hospitalized and started on oxygen therapy, methylprednisolone, and LMWH. Psychiatry consultation was sought.

The potential of clozapine to cause leukopenia (lymphopenia and neutropenia)

[1]Department of Psychiatry, St Johns Medical College, Bengaluru, India. [2]Dept. of Psychiatry, Kalinga Institute of Medical Sciences, KIIT University, Bhubaneswar, Odisha, India. [3]Wyndham Clinic Private Hospital, Melbourne, Australia. [4]Consultant Psychiatrist, BIIPbSAR, Bhubaneswar, Odisha, India.

HOW TO CITE THIS ARTICLE: Pattnaik JI, Das S, Sarkar H, Mahasuar R and Ravan JR. Rational Approach to Psychotropic Use in COVID-19 Cases With Psychiatric Comorbidities: Lesson Learnt From a Case Series. *Indian J Psychol Med*. 2021;43(6):542–545.

Address for correspondence: Jayprakash Russell Ravan, Dept. of Psychiatry, Kalinga Institute of Medical Sciences, KIIT University, Bhubaneswar, Odisha 751024, India. E-mail: jpr_219@yahoo.co.in

Submitted: 11 Jun. 2021
Accepted: 23 Jul. 2021
Published Online: 28 Sep. 2021

ACCESS THIS ARTICLE ONLINE
Website: journals.sagepub.com/home/szj
DOI: 10.1177/02537176211040260

and the risk of clozapine complicating the pneumonia were considered. Continuing clozapine with close monitoring of blood counts and dose reduction for sialorrhea could have been attempted. However, in view of severe COVID, need for oxygen, increased risk of aspiration because of clozapine-induced sialorrhea, and a prior trial of dosage reduction for persistent sialorrhea, clozapine was stopped. In the meantime, she was prescribed haloperidol to prevent any exacerbation of schizophrenia. Her D-dimer, serum ferritin, C-reactive protein (CRP), blood counts (particularly for leucopenia), and blood sugar were monitored regularly. The COVID symptoms improved gradually. She maintained a saturation of 95% at room air; she had no complaint of breathlessness and no fever spikes. Therefore, she was discharged after two weeks of hospital stay with a tapering dose of steroid, and clozapine was restarted as per protocol. Post-COVID, the patient had mild chest pain, exertional dyspnea, and occasional breathlessness, but maintained saturation above 94% and was closely monitored for cardiac side effects.

Case 2

A 28-year-old male electrician with a family history of mood disorder in his father, with the first episode of mania with psychotic symptoms in 2017, with an inadequate response with single mood stabilizer, was maintaining well on lithium carbonate 800 mg/day, sodium valproate 1 g/day, and risperidone 3 mg/day, but had discontinued medications since January 2021. On the sixth day following his marriage, in March 2021, he had a relapse, with sleep disturbance, overtalkativeness, and increased psychomotor activity. Within the next 48 h, he also developed cough and breathlessness. He was brought restrained to the fever clinic, where he tested positive for COVID-19, with a CT severity score of 18/25 and spO_2 of 78%. The patient was uncooperative, restless, aggressive, and hyperactive. He was sedated with Inj haloperidol, shifted to the high-dependency unit, and put on noninvasive ventilation, methylprednisolone, and LMWH. He was simultaneously restarted on lithium gradually, with 400 mg/day, and it was titrated up to 800 mg/day in divided doses over a week, with valproate 1 gm in divided doses. Risperidone up to 3 mg twice daily was given to control severe agitation and bring down his psychotic symptoms. The patient was closely monitored for hydration status, urine output, serum lithium levels, and D-dimer. No significant adverse drug reaction because of psychotropics was observed during the hospital stay. With medications, improvement in psychomotor and COVID symptoms was noted. He was discharged after a ten-day hospital stay and was closely followed up in psychiatry OPD until remission was achieved.

Case 3

A 52-year-old married male administrative officer, with a diagnosis of recurrent depressive disorder, maintaining well on venlafaxine 75 mg and clonazepam 0.5 mg, with diabetes and hypertension, developed fever and muscle pain, and tested positive for COVID. He was started on favipiravir and vitamin supplements and was in home isolation. On the tenth day, he developed high fever, severe headache, and breathlessness. He was admitted to the COVID hospital with a CT severity score of 12/25, D-dimer 0.8 mcg/mL, and CRP 20. Other blood parameters were within the normal range. His spO_2 of 90% in room air improved to 94% with proning. Venlafaxine was continued but clonazepam was discontinued as he had no sleep difficulty or anxiety. Although benzodiazepine can be administered if need be, judicious use and careful monitoring for respiratory depression are warranted. He was started on steroids and LMWH for three days, with regular monitoring of blood sugar. He improved after 72 h of hospitalization and was discharged after one week on a tapering steroid regimen.

Case 4

A 67-year-old female, a known case of ovarian malignancy operated two years back and subsequently on adjuvant chemotherapy, had a history of three episodes of depression with catatonic features. The most recent episode was in April 2021, and she was maintaining well since then with mirtazapine 15 mg and lorazepam 6 mg/day to 8 mg/day. She developed fever and cough in May 2021, and tested positive for COVID, with a CT severity score of 15/25 and spO_2 of 98%. She was admitted and managed with steroids and LMWH. The risk of respiratory depression with lorazepam was weighed against the efficacy of tofisopam for catatonia without any sedation or respiratory depression. Mirtazapine was continued, and cross-titration of lorazepam with tofisopam was tried. Lorazepam was reduced to 2 mg twice daily, and tofisopam 50 mg twice a day was simultaneously added; after four days, lorazepam was tapered gradually by 1 mg/day over the next four days. The patient was closely monitored for vitals, catatonic/psychomotor symptoms, and relapse of mood symptoms, with a plan to add tofisopam 50 mg as and when needed if needed. The cross-tapering was successful, without the appearance of any catatonic symptoms. The patient improved and was discharged with a tapering dose of oral steroids for two weeks, with advice for close follow-up in both post-COVID and psychiatry clinics.

Case 5

A 42-year-old male with COVID-19 and alcohol dependence was admitted to the COVID hospital. He had a CT severity score of 15/25 and was maintaining spO_2 of 90% with 8 L to 10 L of O_2/min. Within 48 h of admission, he developed complicated alcohol withdrawal characterized by tremors, confusion, and tactile hallucinations. In this state of delirium tremens, he was restless and kept removing his mask, thus resulting in a drop in spO_2. Although benzodiazepines are known to cause respiratory depression, in the backdrop of his refusing oral medications, need for rapid tranquilization, and worsening spO_2, the risk-benefit analysis supported the use of injectable benzodiazepines with close monitoring for respiratory depression (in the absence of any other injectable alternative). He was started on injection lorazepam, and thiamine was supplemented along. With the improvement of withdrawal symptoms, the patient was cooperative for COVID treatment, and his oxygen saturation could be maintained with a face mask. Once the patient stabilized and started accepting oral medications, in addition to tablet lorazepam, low-dose haloperidol and sodium valproate (an alternate GABAergic medication) were also initiated in order to reduce the required dose of lorazepam and therefore counter its cumulative dose-related

respiratory depressive effect. Close monitoring of liver functions was regularly done. The patient improved in the next two weeks and was discharged from the COVID hospital and followed up in the de-addiction clinic.

Discussion

Clozapine has been associated with worse outcomes in some pneumonias;[6] it may, in theory, worsen outcomes in COVID-19. COVID-19 is known to induce an acute immune response, which can affect hematological parameters monitored during clozapine therapy like the total and differential counts, and systemic infection may reduce clozapine clearance.[7] Despite these concerns, data indicates it is safe to continue clozapine in mild COVID-19.[6] However, in our first case, the patient had clozapine-induced sialorrhea and oversedation, both with potential for respiratory complications. Hence, clozapine was withheld temporarily, and the patient was closely monitored for re-emergence of psychotic symptoms. Other antipsychotics like haloperidol and amisulpride may be considered, which are safer alternatives in such an interim period. However, if clozapine can be excluded as a cause of the presenting symptoms, it is reasonable to continue treatment, with the serum level closely monitored. Post-COVID cardiopulmonary changes may influence decisions surrounding clozapine monitoring, particularly for myocarditis and cardiomyopathies.[8]

As seen in the second case, delayed presentation with severe COVID may be because of unawareness of physical distress subsequent to mania, which can also hinder management of COVID, and thus, needs urgent consideration. For rapid tranquilization, avoiding benzodiazepine is pertinent to prevent the worsening of hypoxia, while injectable haloperidol is a safe option. Among mood stabilizers, lithium has antiviral properties and may be helpful in COVID-19 via inhibition of the phosphatidylinositol signaling FC pathway,[8] the regulation of autophagy, and inhibition of the glycogen synthase kinase-3. However, the narrow therapeutic range warrants close observation of serum levels, hydration status, and renal and cardiac functions. Among other mood stabilizers, no potential drug interactions have been noted for valproate or carbamazepine with oxygen therapy, steroids, or LMWH. However, significant drug interactions with other COVID-19 medications like antiretrovirals (which were used in the first wave) have been reported.[1] Close monitoring of the coagulability profile is also suggested, considering the possibility of valproate-induced thrombocytopenia and subsequent implications with LMWH use. Considering the bone marrow suppression and liver toxicity effects of both valproate and carbamazepine, liver function and blood count monitoring are also suggested.

Case three is a case of depressive disorder with severe COVID. Hypercoagulability and high levels of several pro-inflammatory mediators like CRP, ferritin, and fibrin lead to complications in patients of severe COVID. Antidepressants have been reported to have a beneficial role in COVID by three different mechanisms. Firstly, antidepressants are associated with reduced plasma levels of pro-inflammatory mediators and less need for intubation, with better outcomes. Secondly, in-vitro antiviral effects on SARS-CoV-2 via inhibition of acid sphingomyelinase by some antidepressants, which prevents the infection of epithelial cells with SARS-CoV-2, have also been demonstrated.[9, 10] Lastly, antidepressants have been demonstrated to modify hemostasis by causing decreased platelet activity and aggregability and prolongation of bleeding time.[11] Thus, although the antihemostatic properties when used in isolation may be desirable to prevent COVID-19 complications secondary to hypercoagulability, the potential risk of bleeding with LMWH needs to be highlighted here. However, the risk of sedation and respiratory depression associated with benzodiazepine use and the significance of these effects in the COVID treatment protocol should be evaluated on a case-to-case basis by the COVID treating team, with a review by the pulmonologist. No significant drug interactions between antidepressants and steroids or remdesivir have been reported.

The fourth case is a case of recurrent catatonia with underlying recurrent depressive disorder and postop ovarian malignancy on chemotherapy. The need of continuing benzodiazepine for catatonia versus the potential risk of COVID-19-related hypoxia deserves attention. The respiratory depressant effect of classical benzodiazepines like lorazepam limits its use in such patients. However, a nonsedative alternative, tofisopam, has a chemical backbone common to "classical" 1, 4-benzodiazepines, but does not interact with the classical benzodiazepine-binding-site of the Gamma Amino Butyric Acid (GABA) receptor; hence, it does not cause respiratory depression, providing an added advantage in COVID hypoxia. Although evidence is limited, tofisopam was thus preferred over lorazepam.[12,13] Additional possibilities include considering the use of benzodiazepines for a short duration to improve sleep and reduce autonomic panic symptoms, which would aid recovery in mild to moderate COVID patients with severe anxiety or insomnia. Nonjudicious use of benzodiazepines may lead to respiratory depression and drug dependence.[14]

The fifth case highlights the clinical dilemma of risk versus benefit of benzodiazepine use in the case of alcohol withdrawal. Although benzodiazepine was initiated, keen efforts were made to use the lowest possible dose of lorazepam and use less effective alternative medications like haloperidol and sodium valproate.[15] Close monitoring is extremely important in such cases. In addition to reducing the total dose of benzodiazepines needed, haloperidol helps to reduce the symptoms of tactile hallucinations, and valproate helps with withdrawal-related agitation.

Recommendations and Conclusions

In cases of treatment-resistant schizophrenia, although clozapine can worsen outcomes in severe viral pneumonia, evidence exists for the safety of clozapine in mild to moderate COVID-19 infection. The clinical decision should be individually tailored depending on the severity of COVID hypoxia and clozapine-induced adverse drug reactions. As a general rule, clozapine can be continued in mild to moderate COVID cases. In contrast, in severe cases with high oxygen dependency, it is prudent to keep clozapine on hold in case of significant sialorrhea, neutropenia, or any other complication, and treat the patient with alternative antipsychotics like haloperidol, amisulpride, etc. until the patient is adequately stabilized.

All mood stabilizers are relatively safe in COVID-19; however, close monitoring of serum levels, hydration status, and renal and liver functions, as appropriate, is advised. Therefore, mood stabilizers can be continued in all cases of bipolar disorder with COVID hypoxia. Antidepressants are safe in COVID hypoxia and are associated with lesser incidence of acute respiratory distress syndrome and decreased need for intubation in patients with COVID hypoxia, thereby improving outcome, and should be continued.

Benzodiazepine use needs to be judicious in delirium tremens and other drug withdrawal, and close monitoring is essential. It is recommended to use a symptom-triggered therapy with the lowest possible dose of benzodiazepine, and adjunctive use of alternatives like haloperidol/valproate[14] should be tried. The decision-making should be undertaken by a multidisciplinary team including psychiatrists, pulmonologists, and others.

In conclusion, an individually tailored approach with close drug-specific side-effect monitoring is suggested in patients with severe COVID hypoxia and comorbid mental illness.

Declaration of Conflicting Interests

The study was conducted in accordance with ethical principles as per declaration of Helsinki. We acknowledge the patients and their caregivers for their consent and support.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Jigyansa Ipsita Pattnaik https://orcid.org/0000-0001-8563-7200

Sudipta Das https://orcid.org/0000-0001-8598-4499

Jayprakash Russell Ravan https://orcid.org/0000-0002-8315-2573

References

1. Mohebbi N, Talebi A, Moghadamnia M, et al. Drug interactions of psychiatric and COVID-19 medications. Basic Clin Neurosci 2020; 11: 185–200.
2. Ragab D, Salah Eldin H, Taeimah M, et al. The COVID-19 cytokine storm; what we know so far. Front Immunol 2020; 11: 1446.
3. Government of India Ministry of Health and Family Welfare. *Clinical management protocol for COVID-19.* Government of India Ministry of Health and Family Welfare, 2021. https://www.mohfw.gov.in/pdf/UpdatedDetailedClinicalManagementProtocolforCOVID19adultsdated24052021.pdf (accessed June 9, 2021).
4. Ostuzzi G, Papola D, Gastaldon C, et al. Safety of psychotropic medications in people with COVID-19: Evidence review and practical recommendations. BMC Med 2020; 18: 215.
5. Luykx JJ, Veen SMP van, Risselada A, et al. Safe and informed prescribing of psychotropic medication during the COVID-19 pandemic. Br J Psychiatry 2020; 217: 471–474.
6. Leon Jde, Ruan C-J, Verdoux H, et al. Clozapine is strongly associated with the risk of pneumonia and inflammation. Gen Psychiatr 2020 April 16; 33(2): e100183.
7. Butler M, Bano F, Calcia M, et al. Clozapine prescribing in COVID-19 positive medical inpatients: A case series. Ther Adv Psychopharmacol 2020; 10. DOI: 10.1177/2045125320959560
8. Oleszak F, Maryniak A, Botti E, et al. Myocarditis associated with COVID-19. Am J Med Case Rep 2020; 8: 498–502.
9. Hoertel N, Sánchez-Rico M, Vernet R, et al (AP-HP/Universities/INSERM COVID-19 Research Collaboration and AP-HP COVID CDR Initiative). Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVID-19: Results from an observational study. Mol Psychiatry 2021. DOI: 10.1038/s41380-021-01021-4.
10. Yu W and Greenberg ML. Inositol depletion, GSK3 inhibition and bipolar disorder. Future Neurol 2016; 11: 135–148.
11. Halperin D and Reber G. Influence of antidepressants on hemostasis. Dialogues Clin Neurosci 2007; 9: 47–59.
12. Ravan JR, Pattnaik JI, Padhy SK, et al. Tofisopam as an alternative intervention in organic catatonia: An open label study. KC Dube Awards. Indian J Psychiatry 2019; 61: S364–S378.
13. Pattnaik J ipsita, Deepthi RA, Dua S, et al. Role of tofisopam in post COVID neuro-psychiatric sequelae: A case series. Indian J Psychol Med 2021; 43: 174–176.
14. Agrawal R. Careful prescribing of benzodiazepines during COVID-19 pandemic: A review. J Ment Health Clin Psychol 2020; 4: 13–16.
15. Lambie DG, Johnson RH, Vijayasenan ME, et al. Sodium valproate in the treatment of the alcohol withdrawal syndrome. Aust N Z J Psychiatry 1980 September; 14(3): 213–215.