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Background: The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as one of the biggest health threats of our generation. A significant portion of patients are presenting with delirium and neuropsychiatric sequelae of the disease. Unique examination findings and responses to treatment have been identified. Objective: In this article, we seek to provide pharmacologic and treatment recommendations specific to delirium in patients with COVID-19. Methods: We performed a literature search reviewing the neuropsychiatric complications and treatments in prior coronavirus epidemics including Middle Eastern respiratory syndrome and severe acute respiratory syndrome coronaviruses, as well as the emerging literature regarding COVID-19. We also convened a work group of consultation-liaison psychiatrists actively managing patients with COVID-19 in our hospital. Finally, we synthesized these findings to provide preliminary pharmacologic recommendations for treating delirium in these patients. Results: Delirium is frequently found in patients who test positive for COVID-19, even in the absence of respiratory symptoms. There appears to be a higher rate of agitation, myoclonus, abulia, and alogia. No data are currently available on the treatment of delirium in patients with COVID-19. Extrapolating from general delirium treatment, Middle Eastern respiratory syndrome/severe acute respiratory syndrome case reports, and our experience, preliminary recommendations for pharmacologic management have been assembled. Conclusions: COVID-19 is associated with neuropsychiatric symptoms. Low-potency neuroleptics and alpha-2 adrenergic agents may be especially useful in this setting. Further research into the pathophysiology of COVID-19 will be key in developing more targeted treatment guidelines.

Key words: consultation-liaison psychiatry, delirium, neuropsychiatry, psychopharmacology, coronavirus, COVID-19.

BACKGROUND

The pandemic of coronavirus disease 19 (COVID-19) marks the emergence of the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been associated with significant global morbidity and mortality. Clinical presentations associated with COVID-19 are variable in severity, ranging from asymptomatic cases to severe pneumonia and acute respiratory distress syndrome (ARDS) requiring
intensive care.\textsuperscript{2,3} In symptomatic individuals, COVID-19 typically manifests as an influenza-like respiratory illness, with fever, cough, dyspnea, and malaise/myalgias.\textsuperscript{4} Atypical presentations, however, are frequent and include extrapulmonary involvement such as gastrointestinal symptoms, multiorgan failure (liver, kidneys, heart), and neurologic manifestations (Figure 1).\textsuperscript{3,5,6} Recently, there has been increasing recognition of neuropsychiatric manifestations of COVID-19, prompting this review of treatment strategies for the management of delirium in these patients.

Human coronaviruses are known to have neuroinvasive potential.\textsuperscript{7} SARS-CoV was associated with cases of polyneuropathy, myopathy, and large artery ischemic stroke, and autopsy studies identified SARS-CoV RNA in hypothalamic and cortical neurons.\textsuperscript{8,9} Middle Eastern respiratory syndrome coronavirus may have been linked to even greater central nervous system (CNS) involvement; a retrospective study in Saudi Arabia found that a fourth of cases developed “confusion” and nearly 9% experienced seizures.\textsuperscript{10} Coma, ataxia, focal motor deficits, weakness, and neuropathies have also been described.\textsuperscript{11,12}

Early literature is also recognizing the neuropsychiatric manifestations of COVID-19. A recent case series in Wuhan, China, described the occurrence of neurological syndromes such as altered mental status and ischemic stroke in 36% of all admitted patients with COVID-19.\textsuperscript{3} A case series of intensive care unit patients from Strasbourg, France, similarly reported a high incidence of altered mental status (85%).\textsuperscript{13} This encephalopathy was often characterized by agitation (69%), corticospinal tract signs (67%), and executive dysfunction (36%). In this cohort, 8 patients had enhancement of the leptomeningeal spaces, and 11 had bilateral frontotemporal hypoperfusion on perfusion imaging. Many patients continued to experience altered cognition even upon discharge.\textsuperscript{13}

To date, no pharmacologic guidelines have been published for the treatment of delirium specifically associated with COVID-19. In this narrative review, we synthesize the current literature regarding the neurologic manifestations of COVID-19, propose a possible pathophysiologic hypothesis, and provide preliminary guidance for management.

**METHODS**

First, we performed a literature search for reviews, case reports, case series, and pharmacologic trials related to Middle Eastern respiratory syndrome, SARS, and COVID-19. The literature search took place between April 1, 2020, and April 29, 2020 (see Supplemental Material for details). Database search yielded a total of 43 articles. We excluded articles that were not written in English.

In addition to a literature review, we formed a consultation-liaison (C-L) psychiatry COVID-19 workgroup. The workgroup consisted of a panel of expert C-L psychiatrists in the Massachusetts General Hospital (MGH) Department of Psychiatry who were actively engaged in the care of patients with COVID-19 on inpatient medical and surgical units. Treatment courses were discussed and summarized by the workgroup.

Finally, literature review and anecdotal evidence from emerging cases were synthesized to provide a working hypothesis of neurocovid pathophysiology as well as pharmacologic guidance for the treatment of delirium in patients with COVID-19.
RESULTS

C-L Psychiatry COVID-19 Delirium Workgroup Experience

Practicing on a psychiatry consult service in a large general hospital, we have seen 19 patients with delirium in the setting of COVID as of May 1, 2020. It is the experience of these authors that there may be unique characteristics of delirium in some patients with SARS-CoV-2. We have seen that some patients are admitted with confusion and agitation as their presenting symptoms, in the absence of respiratory symptoms or other signs of infection. In addition to significant agitation and attentional impairment, examinations have been notable in varying degrees for myoclonus, rigidity, alogia, and abulia.14 As such, we have tailored our examinations to specifically evaluate for catatonia and akinetic mutism. We also focus our chart review on ruling out alternative causes of delirium and potential neurologic manifestations of COVID-19 (i.e., stroke, seizure).

Pathophysiologic Hypothesis

The pathophysiology by which SARS-CoV-2 causes encephalopathy is yet to be elucidated. The severity of systemic illness (and the associated metabolic derangements and inflammatory cascades) in some patients with COVID-19 is likely sufficient to cause the toxic-metabolic encephalopathy often seen in hospitalized patients. However, some features of SARS-CoV-2 and specifically the presentation of patients with severe confusional states in the absence of respiratory symptoms or other organ failure have raised questions about alternative mechanisms of CNS injury. Cases of SARS-CoV-2–associated encephalitis15 and Guillain-Barré syndrome have been recently described.16 Anosmia and ageusia may be early features of SARS-CoV-2 infection,17 implying direct invasion of the olfactory bulb. These revelations have led several investigators to propose multiple potential mechanisms by which SARS-CoV-2 may induce mental status changes in its victims, including infectious spread to the CNS by retrograde transport or hematogenous spread, dysregulation of cytokine activation leading to CNS inflammation, induction of cell-mediated CNS inflammation, postinfectious autoimmune reactions via molecular mimicry, and hypoxemic/thrombotic neuronal injury.5,18 Some authors have also hypothesized that hematogenous spread of SARS-CoV-2 through the periventricular system may lead to a clinical picture of akinetic mutism even in the absence of a lesion detected on neuroimaging.14

Treatment Overview

Given our cursory understanding of the pathophysiology of delirium in patients with COVID-19, treatment decisions must be based on symptom presentation, underlying medical comorbidities, and consideration of medication interactions. Similar to general delirium management, behavioral modifications are first line, but pharmacologic options may be needed for management of agitation and perceptual disturbances.

Behavioral Management

Every patient who is admitted to the hospital with COVID-19 should be considered at high risk for developing delirium, and prevention should be optimized.19 Given new limitations and challenges related to staffing and visitor restrictions in the hospital during COVID-19, we also recommend ensuring patients have supervised access to charged phones or a tablet for communication with families, in addition to typical environmental and stimulus control, early ambulation, and care clustering to daytime.19 When observation is needed, baby monitors can be used if available. If a patient is severely agitated for a prolonged time, net beds can reduce the risk of rhabdomyolysis and thrombosis by decreasing time in restraints.

Pharmacologic Management

When behavioral strategies alone are not sufficient to keep patients and staff safe, pharmacologic management is necessary. Of note, there are no Food and Drug Administration (FDA)-approved treatments for delirium, and to our knowledge, there is no literature reviewing management of agitation in cases of COVID-19. The recommendations discussed here are for off-label use (Table 1). They have been extrapolated from SARS and Middle Eastern respiratory syndrome literature and reflect the general practice patterns of the C-L Psychiatry COVID-19 Delirium Workgroup at MGH. Figure 2 outlines a potential management algorithm for COVID-19 delirium.
We review and summarize medications commonly used in the treatment of delirium. Attention is given to the advantages and disadvantages of medications specific to their use in patients with COVID-19.

5HT = 5-hydroxytryptamine; D = dopamine; ECT = electroconvulsive therapy; EPS = extrapyramidal symptoms; ER = extended release; ETOH = ethanol; GABA = gamma aminobutyric acid; H = histamine; ICU = intensive care unit; IM = intramuscular; IR = immediate release; IV = intravenous; NE = norepinephrine; NMDA = N-methyl-D-aspartate; PO = per oral; QTc = corrected QT interval; TBI = traumatic brain injury; TdP = torsades de pointes.

### TABLE 1. Pharmacologic Agents With Potential Utility in Treating Delirium in COVID-19

| Medication | Mechanism | Advantages | Disadvantages |
|------------|-----------|------------|---------------|
| **Melatonin** | Circadian rhythm regulation; anti-inflammatory | Minimal side effects | PO formulation only; caution in the immunosuppressed |
| **Alpha-2 agonists** | Decreases NE release both centrally and peripherally | Available in IV; can be rapidly titrated; no respiratory sedation; analgesic properties | Use restricted to ICU setting; expensive; occasional shortages; hypotension, bradycardia |
| **Dexmedetomidine** | Decreases NE release both centrally and peripherally | PO and patch formulation; short time to peak concentration and short half-life | Hypotension and bradycardia acutely, rebound tachycardia and hypertension if not tapered |
| **Clonidine** | Decreases NE release centrally > peripherally | Less systemic effects than clonidine | Only PO formulation; longer to peak effect |
| **Guanfacine** | Decreases NE release centrally > peripherally | | |
| **Antipsychotic agents** | | | |
| **Aripiprazole** | D2 partial agonist | Shortens QTc; less likely to cause EPS | PO only; akathisia; long half-life requires extensive washout period |
| **Chlorpromazine** | H1, z1, muscarinic antagonist, 5HT2A antagonism > D2 antagonism | PO, IM, IV formulations, very sedating, wide dose range, less EPS | Hypotension; anticholinergic side effects; greater QT prolongation |
| **Haloperidol** | D2 antagonist | PO, IV, IM formulations; most evidence in hospital delirium literature | High risk of EPS with PO, reports of TdP with IV formulation |
| **Olanzapine** | D2, H1, z1, and muscarinic antagonist | PO (tab and dissolvable) and IM formulations; sedating; fast-acting | IM formulation cannot be combined with benzodiazepines; anticholinergic side effects |
| **Quetiapine** | H1, z1, z2, 5HT2A, D1, and D2 antagonist. 5HT1A partial agonist. | Wide dose range; different receptors targeted at different doses; minimal EPS | PO only; onset of action up to 1 h; hypotension at doses > 100 mg |
| **Risperidone** | D2 and 5HT2A antagonist | Tab and dissolvable available; minimally anticholinergic | High risk of EPS |
| **Ziprasidone** | D2, 5HT2A, H1 antagonist, 5HT1A partial agonist | IM formulation available | Greater QT prolongation |
| **Trazodone** | 5HT2A antagonist, z1 antagonist | Preferred hypnotic for geriatric patients; low EPS and QTc risk | PO formulation only; onset of action up to 1 h |
| **Valproic acid** | Unclear; regulated GABA/glutamate, D, NE, and 5HT sodium channel blocker | PO and IV formulations; weight-based loading possible; useful in comorbid seizure d/o, TBI, and ETOH withdrawal | CYP450 inhibitor; contraindicated in patients with pancreatic or hepatic failure |
| **Dopamine agonists** | | | |
| **Amantadine** | Indirect D agonist and NMDA-receptor antagonist | Useful for abulia, akinetic mutism, and catatonia when lorazepam/ECT contraindicated | PO formulation only in United States; contraindicated in end-stage renal disease; lowers seizure threshold; can worsen delirium and psychosis |
| **Methylphenidate** | D and NE reuptake inhibition | PO (IR and ER) and patch formulations; short-half life for ease of titration; useful for abulia | Increases heart rate and blood pressure; may worsen appetite; can worsen delirium and psychosis |
| **Lorazepam** | Enhances the activity of GABA at the GABA-A receptor | PO, IV and IM formulations; rapid onset; very sedating; can decrease neuroleptic requirement | Respiratory suppression, especially when combined with opioids; can worsen delirium |

We review and summarize medications commonly used in the treatment of delirium. Attention is given to the advantages and disadvantages of medications specific to their use in patients with COVID-19.

5HT = 5-hydroxytryptamine; D = dopamine; ECT = electroconvulsive therapy; EPS = extrapyramidal symptoms; ER = extended release; ETOH = ethanol; GABA = gamma aminobutyric acid; H = histamine; ICU = intensive care unit; IM = intramuscular; IR = immediate release; IV = intravenous; NE = norepinephrine; NMDA = N-methyl-D-aspartate; PO = per oral; QTc = corrected QT interval; TBI = traumatic brain injury; TdP = torsades de pointes.

### Melatonin

There is significant interest in using melatonin and melatonin-receptor agonists in delirium management. More recent data also suggest specific utility in COVID-19, perhaps due to its sleep-regulating, immunomodulatory, and neuroprotective factors. In theory, the
Age-related decline in melatonin levels may be one factor contributing to increased delirium risk and worse COVID-19 outcomes among elderly patients. Melatonin exerts its soporific effects through circadian entrainment and may also offer neuroprotection via increased brain-derived neurotrophic factor (BDNF) expression and attenuation of N-methyl-D-aspartate receptor–mediated glutamate excitotoxicity, as well as the prevention of kainic acid–induced neuronal lesions, glutathione depletion, and reactive oxygen species–mediated apoptotic nerve cell death. It also has a relatively good safety profile. We recommend considering the addition of...
melatonin in all patients with COVID-19. It is worth noting, however, that for patients with severe immunocompromise, the immunosuppressive effects of melatonin may be detrimental. Although speculative, it is possible that there is heterogeneity in the patients with COVID-19 who develop ARDS: those who do not mount enough of an immune response, and those in whom overactive immune response leads to cytokine storm. Melatonin might be particularly useful in the latter group.

**Alpha-2 Agonists**

As a class, alpha-2 agonists have been shown to be effective as prophylaxis against delirium as well as in management of agitation related to delirium. Given their relatively safe side effect profile for patients with SARS-CoV-2, we recommend them as first-line agents for management of delirium in this population.

**Dexmedetomidine**

Dexmedetomidine may be particularly useful in COVID-19 delirium and is actively being studied. Critical care literature suggests that dexmedetomidine may improve delirium and shorten the time to recovery. While critical care teams most commonly manage dosing of the agent, C-L psychiatrists may play a role in advocating for dexmedetomidine over other sedating agents, helping to manage dexmedetomidine in combination with other psychotropic agents and providing guidance for weaning dexmedetomidine.

Dexmedetomidine decreases norepinephrine release and sympathetic tone both centrally and peripherally. Intravenous (IV) infusion allows for quick titration, and it also has analgesic properties. Unlike other sedative agents, dexmedetomidine does not cause respiratory depression, which may be particularly advantageous for patients with ARDS. The use of dexmedetomidine is currently restricted to intensive care settings, although a sublingual form is under investigation. Relative to other sedatives, dexmedetomidine is expensive and occasionally subject to hospital shortages. Notably, dexmedetomidine can cause hypotension and bradycardia.

**Clonidine**

Anecdotal experience suggests that clonidine may also be an appropriate first-line treatment for COVID-19 delirium. Clonidine has efficacy in delirium as well as alcohol and opioid withdrawal. Similar to dexmedetomidine, clonidine decreases central norepinephrine production at the locus coeruleus via negative feedback presynaptically. Clonidine is available in pill and patch forms and is useful in transitioning patients off dexmedetomidine. The patch typically takes 12 hours to impact behavior once applied. Clonidine may cause hypotension and bradycardia; rebound hypertension and tachycardia may occur with rapid taper.

**Guanfacine**

Guanfacine has a similar mechanism of action to clonidine but a longer half-life (allowing for once daily dosing). It also causes less hypotension than clonidine and has less potential for rebound tachycardia. While these properties make it theoretically appealing, it should be noted that there is currently no evidence for guanfacine in delirium. In addition, it can only be given orally, and it is more difficult to rapidly titrate when transitioning a patient from dexmedetomidine.

**Antipsychotic Agents**

Antipsychotics may be used for the management of behavioral dysregulation or perceptual disturbances. Based on clinical manifestations of COVID-19 delirium and possible pathophysiology, we recommend starting with low-potency antipsychotics to minimize the risk of extrapyramidal side effects and catatonia. As always, psychiatrists should use additional caution in treating elderly patients with antipsychotics given warnings related to increased risk of death and stroke in patients with dementia. Patients with chronic obstructive pulmonary disease are at increased risk of respiratory failure and should be monitored closely.

**Aripiprazole**

Although antipsychotics are not routinely recommended in hypoactive delirium, two open-label trials have suggested possible efficacy in the use of aripiprazole. Because aripiprazole acts as a partial agonist at the dopamine receptor, it may be a good choice for patients experiencing perceptual disturbances in the setting of hypoactive delirium or for those in a dopamine-depleted state and displaying hypokinetic movements or rigidity on examination. While dystonic reactions and parkinsonism are uncommon, akathisia
may occur, and aripiprazole is only available in pill form on most hospital formularies.

**Chlorpromazine**

Chlorpromazine, one of the oldest neuroleptics, is known for its rapid sedating effects. As a low-potency agent, it carries less risk for extrapyramidal symptoms and has the added advantages of being available in parenteral form and having a wide dose range, allowing for dose escalation. In addition to effects on 5HT2A and D2 receptors, chlorpromazine also has anti-histaminergic, anticholinergic, and alpha-1 blocking effects, which can lead to hypotension, urinary retention, and constipation.39

**Haloperidol**

Haloperidol is typically the first-line agent for management of agitation in delirium.40 Given preliminary observations that patients with COVID-19 may be at higher risk for motor symptoms suggesting a dopamine-depletion state, we recommend using it with caution. As a high-potency agent, haloperidol carries a significant risk of extrapyramidal symptoms and catatonia. That being said, the IV formulation appears to carry a much lower risk of these side-effects.41 IV haloperidol is blood pressure neutral, without anticholinergic side effects, calming but not sedating, and has a wide dose range. Interestingly, in recently accepted publication in Nature, Gordon and colleagues demonstrated that medications that affect sigma1/sigma2 receptors including haloperidol may have antiviral activity against SARS-Cov-2.42 Future studies clarifying the role of haloperidol will be extremely important.

**Olanzapine**

Olanzapine is often used for sedation and management of agitation in delirious patients.43 Similar to quetiapine, it has actions on a number of different receptors although it is more anticholinergic. In contrast to quetiapine, it is relatively quick-acting, and the availability of a dissolvable form allows for use in patients who cannot swallow pills. Intramuscular olanzapine can be administered in severely agitated patients but should not be combined with benzodiazepines.44 Some physicians have administered intramuscular olanzapine intravenously, but this is not a common or recommended strategy given the lack of safety data.45

**Quetiapine**

Quetiapine is commonly used to manage symptoms related to delirium in the hospital setting.46,47 It is a relatively low-potency agent and has a wide dose range. At low doses, it primarily acts as an antihistamine; at doses at or above 100 mg, it exerts alpha-1 blockade; from 150–300 mg, it additionally binds to 5HT2A and numerous other serotonergic targets; and at doses 400 mg and higher, it antagonizes D2 receptors. Quetiapine is only available in oral form and can take one hour from administration to exert effect. Hypotension is an additional risk, particularly in older patients.

**Risperidone**

Risperidone is considered to be the most haloperidol-like of the atypical antipsychotics given its tight binding and antagonism at the D2 receptor, which makes it less compelling in patients with COVID-19.48 However, flexibility in routes of administration, including dissolvable tablets, may make it useful in certain circumstances.

**Ziprasidone**

In psychosis and acute agitation settings, ziprasidone can be very useful. However, we recommend against using it routinely for COVID-19 delirium given its more significant effects on the QT interval.49

**Trazodone**

Trazodone is often used for management of sleep and behavioral dysregulation in the hospital setting. It can be particularly effective for daytime impulsivity and restlessness in older patients who may not tolerate antipsychotic agents, a profile consistent with many patients experiencing COVID-19 delirium.50 Trazodone is thought to exert its action through effects on 5HT2A and has relatively few side effects. It has a wide dose range but is only available in pill form.

**Valproic Acid**

Valproic acid (VPA) has demonstrated utility in managing impulsivity and dysexecutive syndromes in patients with traumatic brain injury, and this approach
has been extended to the treatment of behavioral dysregulation in delirious patients. In a retrospective study of critically ill patients, VPA was associated with a reduction in agitation, delirium, and concomitant neuroleptic use. Similar to SARS and Middle Eastern respiratory syndrome literature, early COVID-19 literature has demonstrated a variety of neurological findings, including increased risk of strokes and some reports of seizures and abnormal electroencephalogram findings, suggesting that VPA could be especially useful in these patients. VPA is thought to exert its actions through effects on dopamine, glutamate, norepinephrine, and serotonin and may decrease CNS oxidative stress and neurotoxicity. In addition to being available in IV form, VPA has a wide dose range. In patients with COVID-19, monitoring for pancreatitis and liver dysfunction may be particularly important. If mental status worsens and hyperammonemia develops, VPA should be discontinued.

**Dopamine Agonists**

Dopamine agonists, including amantadine and methylphenidate, should be considered in patients with akinetic mutism or catatonia. All dopamine agonists have the potential to worsen delirium and perceptual disturbances, however.

**Amantadine**

Amantadine is approved by the FDA for the treatment of influenza A, drug-induced extrapyramidal symptoms, and Parkinson disease and has also been used in patients with low-dopamine conditions such as and dementia with Lewy bodies. It is sometimes used off-label to stimulate activity in patients with hypoactive delirium. Amantadine has a dual mechanism of action, serving as an N-methyl-D-aspartate-receptor antagonist and a dopamine-receptor agonist. It has a wide dose range and is usually well-tolerated, although it can lower the seizure threshold and is contraindicated in end-stage renal disease. Rapid tapering can lead to a withdrawal delirium. Although an IV form is available internationally, only the pill form is available in the United States. Amantadine may be especially useful for treating catatonia in patients with COVID-19 pneumonia, as benzodiazepines would be relatively contraindicated because of respiratory suppression, and electroconvulsive therapy can aerosolize virus particles.

**Methylphenidate**

Methylphenidate has been used anecdotally for behavioral activation in patients with hypoactive delirium or apathy states. It blocks the reuptake of dopamine without increasing dopamine release and has the distinct advantage of being available in a long-acting patch form. It can cause a mild increase in heart rate and blood pressure. Notably, methylphenidate was used during the early AIDS epidemic, when patients were exhibiting symptoms similar to those described in some COVID-19 delirium cases, including depression, abulia, and alogia. Methylphenidate has also been used in catatonia, although commonly with worsening of underlying psychosis.

**Lorazepam**

Classically, benzodiazepines are felt to be “bad” for delirium, outside of gamma aminobutyric acid withdrawal states. While a recent meta-analysis suggests that haloperidol in combination with lorazepam may be the best management strategy for acute agitation in delirium, it is also well known that benzodiazepines can worsen delirium and cause paradoxical behavioral dysregulation. Nonetheless, for patients with COVID-19 and severe agitation, the use of lorazepam in combination with antipsychotic agents may allow for greater sedation and lower the risk of extrapyramidal symptom. This is especially true for patients who have been on prolonged high-dose benzodiazepine drips in the intensive care unit setting and may experience withdrawal if tapered too quickly. Recommendations for the management of delirium in the United Kingdom have also commented on the potential utility of benzodiazepines in COVID-19 delirium. Lorazepam has the advantage of being quick-acting and available in a variety of forms. Lorazepam may still be useful for catatonia assessment in patients with abulia and alogia, but extreme caution is necessary given the risk of respiratory suppression in patients with pneumonia or ARDS.

**Vitamins and Micronutrients**

Vitamin or other micronutrient administration is not presently a standard of care for delirium management, except for situations when a particular deficiency is thought to explain the cause of the delirium (e.g., thiamine deficiency causing Wernicke encephalopathy).
However, given the pro-oxidant and proinflammatory state that accompanies COVID-19 delirium and the limited knowledge surrounding effective treatments, we advocate that a lower threshold be maintained for the use of safe and relatively inexpensive nutritional interventions with known antioxidant and anti-inflammatory benefits. A recent meta-regression analysis demonstrated strong evidence that vitamin C shortens the duration of mechanical ventilation in critically ill patients, particularly severely ill patients who required mechanical ventilation for more than 10 hours, and it is currently being studied as a COVID-19 intervention.\textsuperscript{51,62} Low levels of vitamin D have been correlated with risk of delirium,\textsuperscript{63,64} and omega-3 fatty acids significantly reduced patient-days with delirium and mechanical ventilation.\textsuperscript{65} Indeed, vitamin C, vitamin D, and omega-3 fatty acids have all been shown to inhibit the NLRP3 inflammasome and may work synergistically against the cytokine storm associated with COVID-19 and specifically against the neuroinflammation associated with its delirium.\textsuperscript{66–68}

Special Considerations

\textbf{QT Prolongation}

Patients with COVID-19 are at increased risk of QT prolongation and torsades de pointes by virtue of their age, illness burden including direct effects of COVID-19 on the heart, electrolyte disturbances, and other medications, including hydroxychloroquine and azithromycin.\textsuperscript{6,69} It is challenging to risk-stratify antipsychotic agents, but current evidence suggests that chlorpromazine and ziprasidone may carry a greater risk of QT prolongation, whereas aripiprazole appears to carry a lower risk.\textsuperscript{49} All other antipsychotics, including IV haloperidol, probably cannot be separated out in terms of overall risk. It should also be noted that although dexmedetomidine and clonidine do not prolong the QT interval, they can increase the risk for torsades de pointes by virtue of bradycardia.\textsuperscript{70}

\textbf{Akinetic Mutism and Catatonia}

Anecdotal reports of catatonia-like syndromes, which are also considered to be low-dopamine states, have been reported in COVID-19 delirium.\textsuperscript{14} It remains unclear whether these patients are suffering from catatonia, which may be related to underlying psychiatric illness, delirium, or the infection itself or a related phenomenon, such as akinetic mutism, which may have features overlapping with catatonia. For patients exhibiting alogia, abulia, immobility, and withdrawal, C-L psychiatrists should consider using dopamine agonists and avoiding antipsychotics. Amantadine has been recommended as a third-line agent in catatonia and is also the treatment of choice for akinetic mutism.\textsuperscript{58,71} Benzodiazepines may also be useful in this setting, despite the potential to worsen delirium.

\textbf{Remdesivir}

Remdesivir, an antiviral that was originally designed for the treatment of Ebola virus, was granted emergency authorization by the FDA for the treatment of COVID-19 on May 1, 2020. Many patients admitted with COVID-19 will likely receive this medication. Remdesivir is metabolized by CYP450 2C8, 2D6, and 3A4 and could potentially interact with psychiatric medications; blood levels of remdesivir may decrease when administered with CYP450 inducers such as phenobarbital and carbamazepine.\textsuperscript{72} Consultation-psychiatrists are strongly encouraged to perform an interaction check when selecting pharmacologic agents for delirium in patients receiving remdesivir. Of note, we performed a Lexicomp (Wolters Kluwer Health, Hudson, OH) interaction check for all medications reviewed in this article with remdesivir and found no significant interactions.

\textbf{CONCLUSIONS}

To date, there are no guidelines for the management of delirium in patients with COVID-19, and the evidence base is exceedingly thin. In our narrative review of the literature and clinical experience, we have provided a possible framework and algorithm for pharmacologic selection in COVID-19 delirium. Our recommendations take into account anecdotal observations that some patients with COVID-19 delirium appear to have increased rates of myoclonus, rigidity, alogia, and abulia, suggesting a dopamine-depletion state or catatonia-spectrum condition. When there are no absolute contraindications to any particular class of medication, we preferentially use alpha-2 agonists and low-potency antipsychotics to manage behavioral disturbance. We nonetheless recommend a thoughtful, individualized, step-based approach to management.
Pharmacological Recommendations for Delirium with COVID-19

It is probable that there is heterogeneity in COVID-19 delirium. While some patients may become delirious because of the likely proinflammatory burden of ARDS, it may be that others experience direct invasion of the virus into the CNS, although this is yet to be determined. Future directions include amassing a more extensive collection of COVID-19 delirium cases. Objective measures such as magnetic resonance imaging, electroencephalogram, and cerebrospinal fluid studies would be particularly useful in understanding the neurobiology of the condition but are currently limited by the necessity of minimizing staff exposure to COVID-19. We expect that as more cases are identified and treated, our understanding of the pathophysiology will improve, and recommendations for managing delirium may evolve.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://doi.org/10.1016/j.psym.2020.05.013.

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