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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Psychosomatics 2020:61:585–596 © 2020 Academy of Consultation-Liaison Psychiatry. Published by Elsevier Inc. All rights reserved.

Review Article

Neurocovid: Pharmacological Recommendations for Delirium Associated With COVID-19

Erica B. Baller, M.D., M.S., Charlotte S. Hogan, M.D., Mark A. Fusunyan, M.D., Ana Ivkovic, M.D., James W. Luccarelli, M.D., D.Phil., Elizabeth Madva, M.D., Mladen Nisavic, M.D., Nathan Praschan, M.D., M.P.H., Nadia V. Quijije, M.D., Scott R. Beach, M.D., Felicia A. Smith, M.D.

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.*
(Psychosomatics 2020; 61:585–596)

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.[1] Clinical presentations associated with COVID-19 are variable in severity, ranging from asymptomatic cases to severe pneumonia and acute respiratory distress syndrome (ARDS) requiring

Received May 4, 2020; revised May 15, 2020; accepted May 15, 2020. From the Department of Psychiatry (E.B.B., C.S.H., M.A.F., A.I., J.W.L., E.M., M.N., N.P., N.V.Q., S.R.B., F.A.S.), Massachusetts General Hospital, Boston, MA; Department of Psychiatry (E.B.B., C.S.H., M.A.F., A.I., J.W.L., E.M., M.N., N.P., N.V.Q., S.R.B., F.A.S.), Harvard Medical School, Boston, MA. Send correspondence and reprint requests to Erica B. Baller, MD, MS, Warren 6, 55 Fruit Street, Boston, MA 02114; e-mail: eballer@mgh.harvard.edu
© 2020 Academy of Consultation-Liaison Psychiatry. Published by Elsevier Inc. All rights reserved.

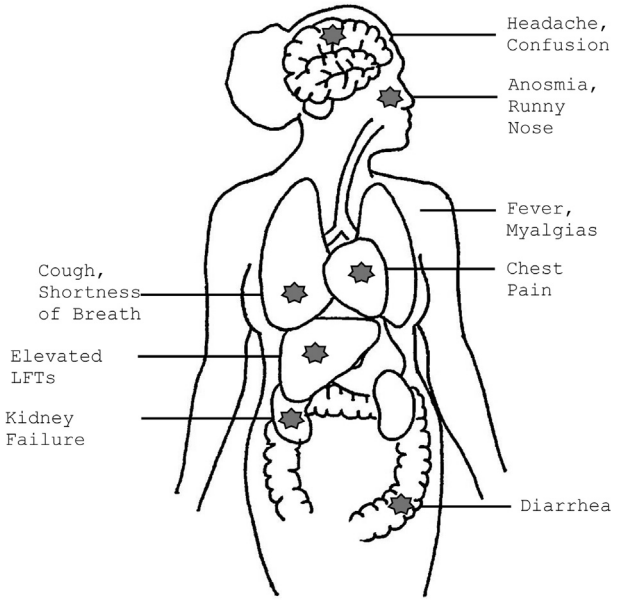
intensive care.[2,3] In symptomatic individuals, COVID-19 typically manifests as an influenza-like respiratory illness, with fever, cough, dyspnea, and malaise/myalgias.[4] Atypical presentations, however, are frequent and include extrapulmonary involvement such as gastrointestinal symptoms, multiorgan failure (liver, kidneys, heart), and neurologic manifestations (Figure 1).[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.[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.[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.[10] Coma, ataxia, focal motor deficits, weakness, and neuropathies have also been described.[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.[3] A case series of intensive care unit patients from Strasbourg, France, similarly reported a high incidence of altered mental status (85%).[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.[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.

FIGURE 1. COVID-19 symptoms. Infection with SARS-CoV-2 has been associated with multi-organ involvement. People most often report fever, cough, and shortness of breath.



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 encephalitis[15] 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.

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			
Dexmedetomidine	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
Clonidine	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
Guanfacine	Decreases NE release centrally > peripherally	Less systemic effects than clonidine	Only PO formulation; longer to peak effect
Antipsychotic agents			
Aripiprazole	D_2 partial agonist	Shortens QTc; less likely to cause EPS	PO only; akathisia; long half-life requires extensive washout period
Chlorpromazine	H_1, α_1, muscarinic antagonist. $5HT_{2A}$ antagonism > D_2 antagonism	PO, IM, IV formulations, very sedating, wide dose range, less EPS	Hypotension; anticholinergic side effects; greater QT prolongation
Haloperidol	D_2 antagonist	PO, IV, IM formulations; most evidence in hospital delirium literature	High risk of EPS with PO, reports of TdP with IV formulation
Olanzapine	D_2, H_1, α_1, and muscarinic antagonist	PO (tab and dissolvable) and IM formulations; sedating; fast-acting	IM formulation cannot be combined with benzodiazepines; anticholinergic side effects
Quetiapine	H_1, α_1, α_2, $5HT_{2A}$, D_1, and D_2 antagonist. $5HT_{1A}$ 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	D_2 and $5HT_{2A}$ antagonist	Tab and dissolvable available; minimally anticholinergic	High risk of EPS
Ziprasidone	D_2, $5HT_{2A}$, H_1 antagonist, $5HT_{1A}$ partial agonist	IM formulation available	Greater QT prolongation
Trazodone	$5HT_{2A}$ antagonist, $\alpha_1$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

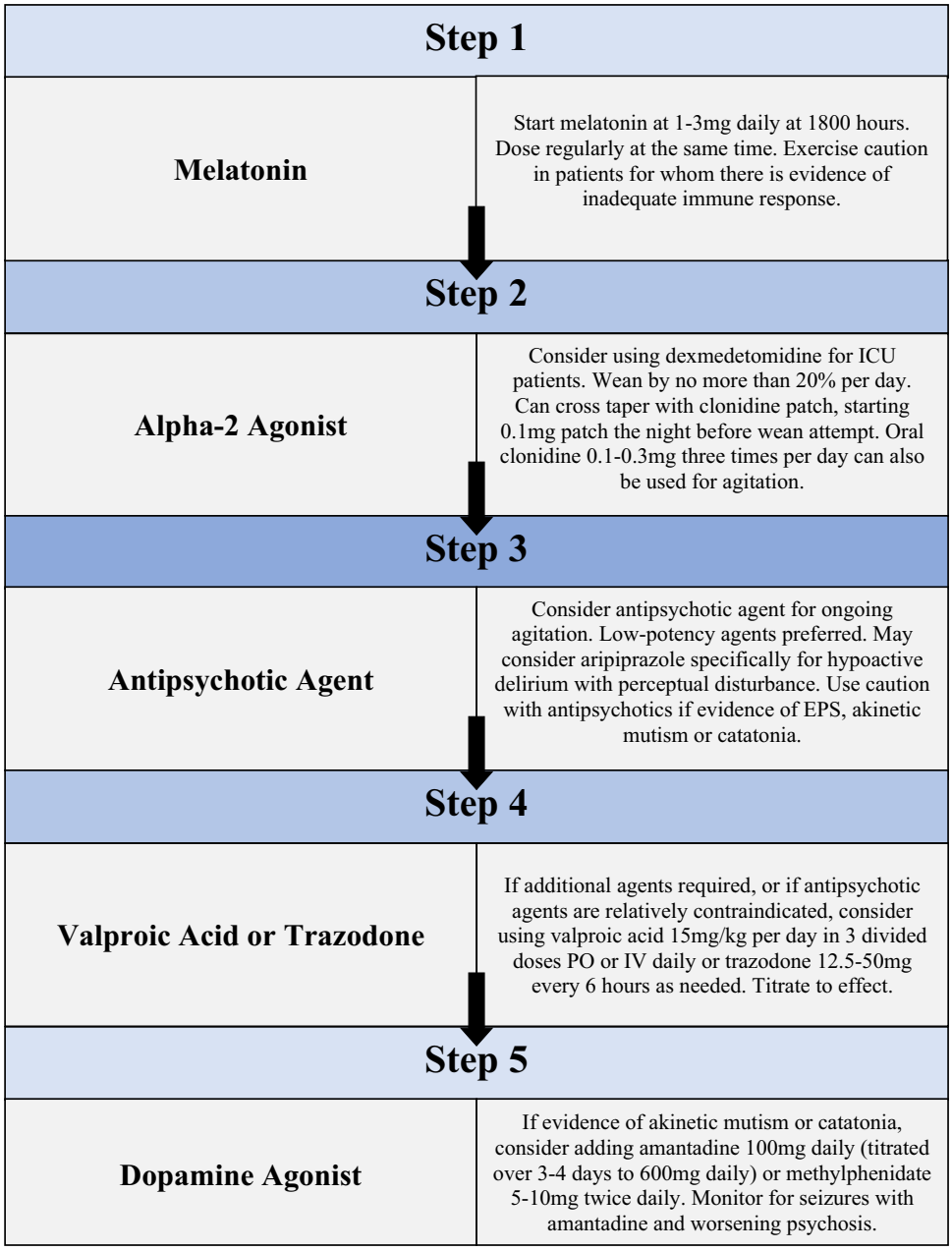
We review and summarize medications commonly used in the treatment of delirium. Attention is given to the advantages and disadvantages of medications specific to their use in patients with COVID-19.

5HT = 5-hyrdoxytryptamine; 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.[20,21] More recent data also suggest specific utility in COVID-19, perhaps due to its sleep-regulating, immunomodulatory, and neuroprotective factors.[20–22] In theory, the

FIGURE 2. **Pharmacologic treatment algorithm. Medication recommendations were extrapolated from previous delirium literature and adapted for patients with delirium in the setting of COVID-19 based on clinical experience from the Massachusetts General Hospital Consultation-Liaison Psychiatry COVID-19 Workgroup.**



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.[23–25] 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.[25,26] 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.[26] Critical care literature suggests that dexmedetomidine may improve delirium and shorten the time to recovery.[27–29] 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.[30–32] Similar to dexmedetomidine, clonidine decreases central norepinephrine production at the locus coeruleus via negative feedback presynaptically.[33] 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).[34] 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.[35] Patients with chronic obstructive pulmonary disease are at increased risk of respiratory failure and should be monitored closely.[36]

Aripiprazole

Although antipsychotics are not routinely recommended in hypoactive delirium, two open-label trials have suggested possible efficacy in the use of aripiprazole.[37,38] 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 $5HT_{2A}$ and D_2 receptors, chlorpromazine also has antihistaminergic, 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 halo- peridol 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 $5HT_{2A}$ and numerous other serotonergic targets; and at doses 400 mg and higher, it antagonizes D_2 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 D_2 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 $5HT_{2A}$ 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.[51] In a retrospective study of critically ill patients, VPA was associated with a reduction in agitation, delirium, and concomitant neuroleptic use.[52] 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.[53] 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.[54] 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.[54] Rapid tapering can lead to a withdrawal delirium.[55] 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.[56]

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.[57] Methylphenidate has also been used in catatonia, although commonly with worsening of underlying psychosis.[58]

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.[59] 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.[60] 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.[61,62] Low levels of vitamin D have been correlated with risk of delirium,[63,64] and omega-3 fatty acids significantly reduced patient-days with delirium and mechanical ventilation.[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.[66–68]

Special Considerations

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.[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.[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.[70]

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.[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.[58,71] Benzodiazepines may also be useful in this setting, despite the potential to worsen delirium.

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.[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.

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.

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.

Conflicts of Interest: The authors declare that they have no conflict of interest.

Funding: This work was supported by the National Institute of Mental Health (R25MH094612; E.M. and J.W.L.).

References

1. Peeri NC, Shrestha N, Rahman MS, et al: The SARS, MERS and novel Coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? Int J Epidemiol 2020; 49(3):717–726
2. Bai Y, Yao L, Wei T, et al: Presumed asymptomatic carrier transmission of COVID-19. JAMA 2020; 323:1406–1407
3. Mao L, Jin H, Wang M, et al: Neurologic manifestations of hospitalized patients with Coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020:e201127
4. Guan W-J, Ni Z-Y, Hu Y, et al: Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382:1708–1720
5. Wu Y, Xu X, Chen Z, et al: Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020; 87:18–22
6. Wang T, Du Z, Zhu F, et al: Comorbidities and multi-organ injuries in the treatment of COVID-19. Lancet 2020; 395:e52
7. Desforges M, Le Coupanec A, Stodola JK, Meessen-Pinard M, Talbot PJ: Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. Virus Res 2014; 194:145–158
8. Tsai L-K, Hsieh S-T, Chang Y-C: Neurological manifestations in severe acute respiratory syndrome. Acta Neurol Taiwan 2005; 14:113–119
9. Gu J, Gong E, Zhang B, et al: Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005; 202:415–424
10. Saad M, Omrani AS, Baig K, et al: Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. Int J Infect Dis 2014; 29:301–306
11. Arabi YM, Harthi A, Hussein J, et al: Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). Infection 2015; 43:495–501
12. Kim JE, Heo JH, Kim HO, et al: Neurological complications during treatment of Middle East respiratory syndrome. J Clin Neurol 2017; 13:227–233
13. Helms J, Kremer S, Merdji H, et al: Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 2020; NEJMc2008597
14. Beach SR, Praschan NC, Hogan C, et al. Delirium in COVID-19: a case series and exploration of potential mechanisms for central nervous system involvement, General Hospital Psychiatry, 2020.
15. Moriguchi T, Harii N, Goto J, et al: A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020; 94:55–58
16. Sedaghat Z, Karimi N: Guillain Barre syndrome associated with COVID-19 infection: a case report. J Clin Neurosci 2020; 76:233–235
17. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al: Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the Coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020; 17:13
18. Troyer EA, Kohn JN, Hong S: Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav Immun 2020; 68(5):947–949
19. LaHue SC, James TC, Newman JC, Esmaili AM, Ormseth CH, Ely EW: Collaborative Delirium Prevention in the Age of COVID-19. J Am Geriatr Soc [Internet]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/jgs.16480
20. Nishikimi M, Numaguchi A, Takahashi K, et al: Effect of administration of ramelteon, a melatonin receptor agonist, on the duration of stay in the ICU: a single-center randomized placebo-controlled trial*. Crit Care Med 2018; 46:1099–1105
21. Bourne RS, Mills GH, Minelli C: Melatonin therapy to improve nocturnal sleep in critically ill patients: encouraging results from a small randomised controlled trial. Crit Care 2008; 12:R52
22. Zhang R, Wang X, Ni L, et al: COVID-19: melatonin as a potential adjuvant treatment. Life Sci 2020; 250:117583

23. Bavithra S, Sugantha Priya E, Selvakumar K, Krishnamoorthy G, Arunakaran J: Effect of melatonin on glutamate: BDNF signaling in the cerebral cortex of polychlorinated biphenyls (PCBs)-exposed adult male rats. Neurochem Res 2015; 40:1858–1869
24. Skaper SD, Floreani M, Ceccon M, Facci L, Giusti P: Excitotoxicity, oxidative stress, and the neuroprotective potential of melatonin. Ann N Y Acad Sci 1999; 890:107–118
25. Azedi F, Mehrpour M, Talebi S, et al: Melatonin regulates neuroinflammation ischemic stroke damage through interactions with microglia in reperfusion phase. Brain Res 2019; 1723:146401
26. Use of Dexmedetomidine in Light to Moderate Sedation in the Patient in the Palliative Situation of a SARS-COV-2/COVID-19 Infection - Full Text View - ClinicalTrials.gov [Internet]. Available from: https://clinicaltrials.gov/ct2/show/NCT04350086
27. Shen Q-H, Li H-F, Zhou X-Y, Yuan X-Z: Dexmedetomidine in the prevention of postoperative delirium in elderly patients following non-cardiac surgery: a systematic review and meta-analysis. Clin Exp Pharmacol Physiol 2020; 47(8):1333–1341
28. Skrobik Y, Duprey MS, Hill NS, Devlin JW: Low-dose nocturnal dexmedetomidine prevents ICU delirium. A randomized, placebo-controlled trial. Am J Respir Crit Care Med 2018; 197:1147–1156
29. Neurocognitive Dysfunction Risk Alleviation With the Use of Dexmedetomidine in Perioperative Conditions or as ICU Sedation [Internet]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4554047/
30. Dobrydnjov I, Axelsson K, Berggren L, Samarütel J, Holmström B: Intrathecal and oral clonidine as prophylaxis for postoperative alcohol withdrawal syndrome: a randomized double-blinded study. Anesth Analg 2004; 98:738–744
31. Rubino AS, Onorati F, Caroleo S, et al: Impact of clonidine administration on delirium and related respiratory weaning after surgical correction of acute type-A aortic dissection: results of a pilot study. Interact Cardiovasc Thorac Surg 2010; 10:58–62
32. Gowing L, Farrell M, Ali R, White JM: Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev 2016:CD002024
33. De Sarro GB, Ascioti C, Froio F, Libri V, Nisticò G: Evidence that locus coeruleus is the site where clonidine and drugs acting at alpha 1- and alpha 2-adrenoceptors affect sleep and arousal mechanisms. Br J Pharmacol 1987; 90:675–685
34. Scholtysik G: Pharmacology of guanfacine. Br J Clin Pharmacol 1980; 10(suppl 1):21S–24S
35. Steinberg M, Lyketsos CG: Atypical antipsychotic use in patients with dementia: managing safety concerns. Am J Psychiatry 2012; 169:900–906
36. Wang M-T, Tsai C-L, Lin CW, Yeh C-B, Wang Y-H, Lin H-L: Association between antipsychotic agents and risk of acute respiratory failure in patients with chronic obstructive pulmonary disease. JAMA Psychiatry 2017; 74:252–260
37. Boettger S, Breitbart W: An open trial of aripiprazole for the treatment of delirium in hospitalized cancer patients. Palliat Support Care 2011; 9:351–357
38. Straker DA, Shapiro PA, Muskin PR: Aripiprazole in the treatment of delirium. Psychosomatics 2006; 47:385–391
39. Chlorpromazine [Internet]. Available from: https://www.drugbank.ca/drugs/DB00477
40. Shen Y, Peng K, Zhang J, Meng X, Ji F: Effects of haloperidol on delirium in adult patients: a systematic review and meta-analysis. Med Princ Pract 2018; 27:250–259
41. Menza MA, Murray GB, Holmes VF, Rafuls WA: Decreased extrapyramidal symptoms with intravenous haloperidol. J Clin Psychiatry 1987; 48:278–280
42. Gordon DE, Jang GM, Bouhaddou M, et al: A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 2020:1–13
43. Dumont M, Gottfried SB, Skrobik YK, Bergeron N: Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med 2004; 30:444–449
44. Olanzapine Pharmacokinetics - Psychopharmacology Institute [Internet]. Available from: https://psychopharmacologyinstitute.com/publication/olanzapine-pharmacokinetics-2159?canonical=/publication/olanzapine-pharmacokinetics-2159
45. Khorassani F, Saad M: Intravenous olanzapine for the management of agitation: review of the literature. Ann Pharmacother 2019; 53:853–859
46. Abraham MP, Hinds M, Tayidi I, et al: Quetiapine for delirium prophylaxis in high-risk critically ill patients. Surgeon 2020. https://doi.org/10.1016/j.surge.2020.02.002 [Epub ahead of print]
47. Maan JS, Saadabadi A: Quetiapine. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2020. Available from: http://www.ncbi.nlm.nih.gov/books/NBK459145/
48. Kodaka F, Ito H, Takano H, et al: Effect of risperidone on high-affinity state of dopamine D2 receptors: a PET study with agonist ligand [11C](R)-2-CH3O-N-n-propylnorapomorphine. Int J Neuropsychopharmacol 2011; 14:83–89
49. Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman JC: QTc prolongation, torsades de pointes, and psychotropic medications. Psychosomatics 2013; 54:1–13
50. Davies SJ, Burhan AM, Kim D, et al: Sequential drug treatment algorithm for agitation and aggression in Alzheimer's and mixed dementia. J Psychopharmacol 2018; 32:509–523
51. Sher Y, Miller Cramer AC, Ament A, Lolak S, Maldonado JR: Valproic acid for treatment of hyperactive or mixed delirium: rationale and literature review. Psychosomatics 2015; 56:615–625
52. Gagnon DJ, Fontaine GV, Smith KE, et al: Valproate for agitation in critically ill patients: a retrospective study. J Crit Care 2017; 37:119–125
53. Valproic Acid [Internet]. Available from: https://www.drugbank.ca/drugs/DB00313
54. Chang C, Ramphul K: Amantadine. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2020. Available from: http://www.ncbi.nlm.nih.gov/books/NBK499953/
55. Fryml LD, Williams KR, Pelic CG, et al: The role of amantadine withdrawal in 3 cases of treatment-refractory altered mental status. J Psychiatr Pract 2017; 23:191–199

56. Ene-Stroescu V, Nguyen T, Waiblinger BE: Excellent response to amantadine in a patient with bipolar disorder and catatonia. J Neuropsychiatry Clin Neurosci 2014; 26:E43
57. Fernandez F, Levy JK, Samley HR, et al: Effects of methylphenidate in HIV-related depression: a comparative trial with desipramine. Int J Psychiatry Med 1995; 25:53–67
58. Beach SR, Gomez-Bernal F, Huffman JC, Fricchione GL: Alternative treatment strategies for catatonia: a systematic review. Gen Hosp Psychiatry 2017; 48:1–19
59. Wu Y-C, Tseng P-T, Tu Y-K, et al: Association of delirium response and safety of pharmacological interventions for the management and prevention of delirium: a network meta-analysis. JAMA Psychiatry 2019; 76:526–535
60. Improvement NI for H and CE (NICE) in collaboration with NE and N: Managing COVID-19 symptoms (including at the end of life) in the community: summary of NICE guidelines. BMJ 2020; 369:m1461
61. Hemilä H, Chalker E: Vitamin C may reduce the duration of mechanical ventilation in critically ill patients: a meta-regression analysis. J Intensive Care 2020; 8:15
62. Carr AC: A new clinical trial to test high-dose vitamin C in patients with COVID-19. Crit Care 2020; 24:133
63. Bowman K, Jones L, Pilling LC, et al: Vitamin D levels and risk of delirium: a mendelian randomization study in the UK Biobank. Neurology 2019; 92:e1387–e1394
64. Quraishi SA, Litonjua AA, Elias KM, et al: Association between pre-hospital vitamin D status and hospital-acquired new-onset delirium. Br J Nutr 2015; 113:1753–1760
65. Naghibi T, Shafigh N, Mazloomzadeh S: Role of omega-3 fatty acids in the prevention of delirium in mechanically ventilated patients. J Res Med Sci 2020; 25:10
66. Choe J-Y, Kim S-K: Quercetin and ascorbic acid suppress fructose-induced NLRP3 inflammasome activation by blocking intracellular shuttling of TXNIP in human macrophage cell lines. Inflammation 2017; 40:980–994
67. Lu L, Lu Q, Chen W, Li J, Li C, Zheng Z: Vitamin D3 protects against diabetic retinopathy by inhibiting high-glucose-induced activation of the ROS/TXNIP/NLRP3 inflammasome pathway. J Diabetes Res 2018; 2018:8193523
68. Shen L, Yang Y, Ou T, et al: Dietary PUFAs attenuate NLRP3 inflammasome activation via enhancing macrophage autophagy. J Lipid Res 2017; 58:1808–1821
69. Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment for COVID-19 [Internet]. Am Coll Cardiol. Available from: http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2farticles%2f2020%2f03%2f27%2f14%2f00%2fventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19
70. Hajiesmaeili M, Afzal G, Sahraei Z: Poly pharmacy-induced Long-QT syndrome and torsades de pointes: a case report. J Pharm Care Health Syst 2017; 04
71. Yarns BC, Quinn DK: Telephone effect in akinetic mutism from traumatic brain injury. Psychosomatics 2013; 54:609–610
72. Remdesivir [Internet]. Available from: https://www.drugbank.ca/drugs/DB14761