دلیریوم و کوید ۱۹

دکتر غلامرضا حاجتی
متخصص اعصاب و روان
انجمن آلزایمر ایران

COVID-19 causes significant morbidity and mortality. Despite the high prevalence of delirium and delirium- related symptoms in COVID-19 patients, data and evidence-based recommendations on the pathophysiology and management of delirium are limited.

Older people are at particular risk of delirium as well as COVID-19, and delirium may be one of the symptoms of COVID-19.

It can be a core symptom at presentation, even in the absence of respiratory symptoms.

Delirium is common in COVID-19 and may manifest from both indirect and direct effects on the central nervous system.

In a systematic review on 229 studies (2020), Delirium affected >50% of all patients with COVID-19 admitted to the ICU.

The etiology of COVID-19 delirium is likely multifactorial.

Journal of Psychosomatic Research 141 (2021) 110350

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

Review article

A rapid review of the pathoetiology, presentation, and management of delirium in adults with COVID-19

Michael Hawkins [a,*], Sanjeev Sockalingam [a,b,c], Sarah Bonato [b], Thiyake Rajaratnam [b,c], Mithunan Ravindran [d], Paula Gosse [d], Kathleen Ann Sheehan [a,c]

[a] Department of Psychiatry, University of Toronto, Toronto, Canada
[b] Centre for Addiction and Mental Health, Toronto, Canada
[c] Centre for Mental Health, University Health Network, Toronto, Canada
[d] Faculty of Medicine, University of Toronto, Toronto, Canada

Many papers hypothesized how complications of COVID-19 may exacerbate known risk factors and causes of delirium,

while others proposed potential mechanisms by which SARS-CoV-2 may directly impact the central nervous system .

It is important to recognize that social distancing and policies limiting non-essential patient contact can further precipitate delirium by limiting the support patients receive from familiar caregivers. This can be disorienting and isolating, especially in those already vulnerable to delirium.

Personal protective equipment (*PPE*), such as gowns, masks, and face shields, can also be disorienting to older patients who may have pre-existing sensory or cognitive impairments.

The complications of COVID-19 infection, such as pneumonia and ARDS, as well as the interventions used to manage them, are known risk factors for delirium.

ARDS, which results in hypoxia, respiratory acidosis, and respiratory failure, and, for some, disseminated intravascular coagulation (DIC) and systemic organ dysfunction, can contribute to delirium.

. Additionally, ARDS often necessitates prolonged admission to the ICU for ventilator support and sedation, interventions which can in and of themselves be deliriogenic .

COVID is also believed to be associated with a hypercoagulable state, which may predispose patients to further CNS insult through ischemic brain injury .

The role of systemic inflammation in precipitating delirium

The systemic inflammation seen in severe cases of COVID-19 can lead to the release of cytokines such as TNF-a, IL-1, and IL-6 and can increase the permeability of the blood-brain barrier (BBB) allowing inflammatory cells to enter the brain, where they too can release cytokines causing neuronal damage.

Direct entry of SARS-CoV-2 in the CNS as a possible etiology of delirium

Now that anosmia and hypogeusia are well-recognized presenting symptoms of COVID-19, numerous papers have considered whether SARS-CoV-2 can directly enter the CNS.

Hyperactive delirium may present particular challenges in the context of the COVID crisis

Standard non pharmacological measures may not be possible in isolation environments

Isolation environments and PPE may worsen symptoms of delirium; however PPE must be worn in line with national recommendations

PREVENTION

Risk of harm to others may exceed risk to individuals and earlier use of pharmacological measures may be necessary

Identify if patient is at risk:

older, dementia, comorbidities, recent hip fracture

Identify baseline level of functioning via collateral history if needed.

Drug and alcohol history is also important.

- Orientate,
- ensure people have their glasses and hearing aids,
- control pain,
- promote sleep hygiene,
- mobilise,
- maintain optimal hydration and nutrition,
- support with toileting,
- monitor and treat any pain or constipation,
- optimise oxygenation

Optimise medication and consider anticholinergic burden

Minimise number of changes of environment as far as possible (e.g. moves between wards)

DETECTION

- Are they different today? Listen to carers and family. Look for symptoms of delirium.
- Use the **4AT screening tool for delirium** (www.the4AT.com)
- Delirium due to withdrawal from drugs or alcohol should be considered
- Delirium can be hyperactive, hypoactive or mixed

SYMPTOMS/FEATURES OF DELIRIUM

Disorientation	**Acute onset (hours/days)**
Agitation and restlessness	**Disturbances in attention and awareness**
Withdrawal and drowsiness	**Fluctuating symptoms**
Mood disturbance	**Disrupted sleep/wake cycle**
Delusions	**Perceptual disturbance including hallucinations**

PINCH ME

Common causes of delirium

Pain

Infection

Nutrition

Constipation

Hydration & Hypoxia

Medication & Metabolic

Environment

MANAGEMENT

The management of delirium in patients with COVID-19 is in its infancy with no randomized clinical trials published to date.

Communicate clearly and carefully and allow plenty of time when assisting the patient .

. Consider risk to self and others due to current symptoms (e.g. aggression, accident, self-neglect, physical deterioration,

infection risk to others in context of COVID-19)

. Perform physical examination & investigations to identify causes

. Bloods ideally to include full confusion screen (FBC, U+E, LFTs, TFTs, vit B12, folate, vit D, bone profile, CRP)

. Consider CT if indicated

(possible fall, on anticoagulants...)

. Treat all underlying causes (SALT, dietician)

. Review current medications; ensure optimal pain management (use Bolton Pain Scale if required).

- treat any constipation

. Address sensory impairments

make sure people have their hearing aids and glasses

. Ensure proper hydration & nutrition –

- make sure people have their dentures

. Optimise environment - support with sleep hygiene,

use environmental cues (clock, calendar, radio etc) to aid orientation)

ensure adequate lighting and comfortable

Break down complicated tasks; regular reorientation and explanation;

acknowledge distress and validate feelings

Do not confront false beliefs (illusions, delusions),

offer reassurance and foster independence

Inform, educate and counsel the family; assist contact with family if possible; interact regularly as tolerated by patient

Use non-pharmacological interventions first wherever possible.

To date, the literature on the psychopharmacological management of patients with delirium has focused on prevention and a symptom-based treatment approach, such as insomnia and symptoms of agitation and psychosis.

Sher et al. (2020) recommends considering **dexmedetomidine** for acute agitation at nighttime .

Valproic acid is suggested for the management of hyperactive and/or mixed (i.e., fluctuating between agitation and hypoactivity) delirium.

Valproic acid has been described as having unique qualities including being potentially anti-inflammatory, neuroprotective and antioxidant; it may potentially decrease the transcription of interleukin-6 (implicated in cytokine storm) and may assist in reducing the need for sedative agents in delirious and/or agitated patients in the ICU.

Several authors propose using ***melatonin*** as a first-line agent in the management of delirium in COVID-19 patients given its safety compared to other agents (e.g. antipsychotics).

Melatonin has also been recommended to optimize sleep in the context of COVID-19 delirium . It has been found to have anti-inflammatory, antioxidative, and immune- enhancing features, which may reduce or interrupt the development of a cytokine storm for some patients .

It has also been proposed that melatonin can be advantageous for critically ill patients, reducing vascular permeability, agitation, and improving quality of sleep .

. However, no studies have examined the efficacy of melatonin in delirium treatment or prevention in COVID-19 patient populations.

Antipsychotics are considered for the management of delirium, ongoing agitation, and end-of-life care in patients with COVID-19 .

However, only one study has explored this, using intramuscular aripiprazole for the management of hyperactive delirium in a series of patients with COVID-19.

Aripiprazole appears to effectively reduce symptoms of delirium and agitation, and it was well tolerated.

Otherwise, no other antipsychotic has been studied in patients with COVID-19.

In general, antipsychotics should not be used unless there is a safety

risk to the patient or others . However, some anecdotal reports suggest using antipsychotic medications earlier in the treatment of COVID-19 patients with hyperactive delirium .

Sanders et al. (2020) propose using higher doses of antipsychotics when managing risky behaviors, which put the patient and others at risk of harm secondary to spreading infection, after accounting for the risks and benefits of such interventions.

In contrast, for the elderly and for people with neurological conditions, other guidelines suggest conservative dosing when treating delirium in patients with COVID-19 .

Experts cautioned the use of antipsychotics in the elderly and those with neurological conditions such as Parkinson’s disease .

Specific antipsychotic use varies among studies that described the pharmacological management of these patients.

Quetiapine has been suggested as

an option for the management of delirium in the elderly and in patients with neurological conditions based on its tolerability and wide therapeutic range

Olanzapine appears to be a preferred agent in

the management of agitation in delirious patients with COVID-19 due to

its sedative capacity and lower drug-drug-interaction potential with

antiviral medications.

In a recent review, Ostuzzi et al. suggests not using haloperidol, quetiapine, or lorazepam for the management of delirium in patients with COVID-19 due to the potential for drug-drug interaction with COVID-19 drugs .

At least two authors suggest close monitoring for respiratory depression in delirious patients treated with antipsychotics, based on a theoretical potential for antipsychotic related respiratory depression

It is important to also monitor for QTc prolongation in these patients if antipsychotics are prescribed .

- An ECG should be obtained prior to administering antipsychotics to check QTc (upper limits 440mS in men, 470mS in women)

However, haloperidol appears to offer some possible immunological benefits. It has been found to be an effective antagonist of sigma-1 receptors, which, in theory, might potently protect against oxidative stress-related cell death .

No papers recommend using medications to prevent delirium .

Finally, although benzodiazepines have been found to worsen

delirium, experts highlighted the use of benzodiazepines in COVID-19

patients with suspected alcohol-withdrawal delirium.

Medication may be needed for patients with agitation where there is intractable distress or high risk to self/ others

USE OF SEDATING MEDICATION FOR SEVERE AGITATION IN PATIENTS WITH DELIRIUM AND COVID-19

Psychotropic medications have major drug interactions with potential COVID-19 and many other drugs. Check for potential interactions - see table below & https://reference.medscape.com/druginteractionchecker or http://www.covid19-druginteractions.org/

There is ongoing debate as to which medication should be used first line for delirium. Current advice is to start with low dose lorazepam or haloperidol and increase dose and frequency slowly if needed.

Be aware that benzodiazepines may cause respiratory depression, and so haloperidol may be preferred in COVID delirium.

Prescribe flumazenil if needed.

Haloperidol can be given subcutaneously during palliative care

- Antipsychotics should not be used for patients with Parkinson's Disease or Lewy Body Dementia

- Haloperidol is not licensed for concomitant use with other QTc prolonging drugs (which include some antimicrobials and antiarrythmics)

- If antipsychotics are contraindicated low dose lorazepam can be used.

- In severe cases both antipsychotics and lorazepam may be needed

- Alternative antipsychotics can be used if needed, but please note they are not licensed for delirium.

Risperidone is licensed for use in Alzheimer's dementia for aggression, so can be considered if there is a history of this .

- Avoid polypharmacy and monitor for medication side effects, after sedation vital signs must be monitored as per rapid tranquillisation policy

- Doses listed are for older people - higher doses may be needed for younger patients – check BNF for upper limits

- For end of life last days/hours levopromazine and midazolam can be used in combination in a syringe driver - seek palliative care advice if needed

Medication	Route	Dose range (mg)	Daily frequency range	Recommended 24 hour max
Lorazepam	PO/IM/IV	0.5-1	OD - QDS	2mg
Haloperidol	PO/IM/SC (liquid form available)	0.5 – 2	OD - 2-4 hourly	5 mg
Risperidone	PO (liquid form available)	0.25 – 0.5	OD -BD	2 mg
Olanzapine	PO/IM (liquid form available)	2.5 - 5	OD - BD	10 mg
Quetiapine	PO (liquid form available)	12.5 - 50	OD - BD	100mg

If no improvement over 4 days, review diagnosis

Continue to treat underlying medical condition(s)

Continue to address common causes of delirium, e.g. constipation, dehydration, urinary tract infection, pain, medication side effects

Key

↑ Potential increased exposure of the co-medication

↓ Potential decreased exposure of the co-medication

⇑ Potential increased exposure of COVID drug

⇓ Potential decreased exposure of COVID drug

↔ No significant effect

♥ One or both drugs may cause QT and/or PR prolongation.

ECG Monitoring is advised if co-administered

	These drugs should not be co-administered
	Potential interaction which may require a dose adjustment or close monitoring.
	Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment unlikely to be required.
	No clinically significant interaction expected

ATV	Atazanavir	CLQ	Chloroquine
LPV/r	Lopinavir/ritonavir	HCLQ	Hydroxychloroquine
RDV	Remdesivir	NITAZ	Nitazoxanide
FAVI	Favipiravir	RBV	Ribavirin
		TCZ	Tocilizumab

Drug interactions between commonly used medications in delirium and COVID- 19 drugs

	ATV	LPV/r	RDV	FAVI	CLQ	HCLQ	NITAZ	RBV	TCZ
Aripiprazole	↑	↑	↔	↔	↔	↔	↔	↔	↔
Haloperidol	↑♥	↑♥	↔	↔	↔♥	↔♥	↔	↔	↔
Olanzapine	↔	↓	↔	↔	↔	↔	↔	↔	↔
Quetiapine	↑♥	↑♥	↔	↔	↔♥	↔♥	↔	↔	↔
Risperidone	↑♥	↑♥	↔	↔	↑♥	↑♥	↔	↔	↔
Diazepam	↑	↑	↔	↔	↔	↔	↔	↔	↔
Lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔
Midazolam (oral)	↑	↑	↔	↔	↔	↔	↔	↔	↔
Midazolam (parenteral)	↑	↑	↔	↔	↔	↔	↔	↔	↔
Oxazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔
Zaleplon	↑	↑	↔	↔	↔	↔	↔	↔	↔
Zolpidem	↑	↑	↔	↔	↔	↔	↔	↔	↔
Zopiclone	↑	↑	↔	↔	↔	↔	↔	↔	↔

NICE guidelines — managing COVID-19 symptoms [151]	**Agitation** Lorazepam 0.5-1 mg orally four times a day as required (maximum 4 mg in 24 hours) Lorazepam 0.25-0.5 mg in elderly or debilitated patients (maximum 2 mg in 24 hours) **Agitation** **patients with dysphagia** Midazolam 2.5-5 mg subcutaneously every 2-4 hours as required (reduce dose to 5 mg over 24 hours if estimated glomerular filtration rate (eGFR) is <30 mL per minute)	**Delirium** Haloperidol 0.5-1 mg orally at night and every 2 hours when required Increase dose in 0.5-1 mg increments as required (maximum 10 mg daily, or 5 mg daily in elderly patients) Similar doses subcutaneously as required, or a subcutaneous infusion of 2.5-10 mg over 24 hours Consider a higher starting oral dose (1.5-3 mg) if the patient is severely distressed or there are safety concerns to others Consider adding a benzodiazepine (e.g., lorazepam or midazolam if the patient remains agitated)	**Delirium** **patients with dysphagia** Levomepromazine 12.5-25 mg subcutaneously as a starting dose and then hourly as required (use 6.25-12.5 mg in elderly patients) Maintain with subcutaneous infusion of 50-200 mg over 24 hours increased according to response (doses >100 mg over 24 hours should be given under specialist supervision) Consider midazolam alone or in combination with levomepromazine if the patient also has anxiety

*Sher et al., 2020 [95] (Treatment of Hyperactive or Mixed COVID-19 Associated ICU Delirium) *Baller et al., 2020 [26] (no specific setting or patient population)	**Melatonin -** 10-15 mg enteric at night (given around sundown) **Alpha-2 agonists** Dexmedetomidine Guanfacine Dexmedetomidine IV: 0.1-2.4 mcg/kg/hr Guanfacine enteric: 0.5 mg twice daily – 1 mg thrice daily	**Antipsychotics** Haloperidol IV 0.5 mg – 30 mg per 24 hours consider antipsychotic for ongoing agitation. Low-potency agents preferred. May consider aripiprazole specifically for hypoactive delirium with perceptual disturbance. Use caution with antipsychotics if evidence of EPS, akinetic mutism or catatonia. – 1 mg thrice daily **Valproic acid** 250-500 mg IV/enteric twice daily and titrate up to 500 mg in the morning, 500 mg in the afternoon, and 1000 mg at night **or trazodone** 12.5-50mg every 6 hours as needed. titrate to effect	**Dopamine agonist** If evidence of akinetic mutism or catatonia, consider adding amantadine 100mg daily (titrated over 3-4 days to 600mg daily) or Methylphenidate 5-10mg twice daily. Monitor for seizures with amantadine and worsening psychosis. mutism or catatonia.

End of life [146] (no specific clinical setting)	**Dose** Midazolam 2.5-5 mg iv Morphine 5-20 mg with midazolam Haloperidol With midazolam and morphine 5-100 mg/daily	**Maintenance** Midazolam 10-120 mg/daily, 1200 mg iv Morphine with midazolam (morphine 0.01-0.02 mg/kg/h) Haloperidol With midazolam and morphine (haloperidol 5-100 mg/daily)	
End of life [164]^	Haloperidol Levomepromazine Levomepromazine and Midazolam		