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Pharmacological treatment of hyperactive delirium in people with COVID-19: rethinking conventional approaches

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***Abstract*:** People with coronavirus disease (COVID-19) might have several risk factors for delirium, which could in turn notably worsen the prognosis. Although pharmacological approaches for delirium are debated, haloperidol and other first-generation antipsychotics are frequently employed, particularly for hyperactive presentations. However, the use of these conventional treatments could be limited in people with COVID-19, due to the underlying medical condition and the risk of drug–drug interactions with anti-COVID treatments. On these premises, we carried out a rapid review in order to identify possible alternative medications for this particular population. By searching PubMed and the Cochrane Library, we selected the most updated systematic reviews of randomised trials on the pharmacological treatment of delirium in both intensive and non-intensive care settings, and on the treatment of agitation related to acute psychosis or dementia. We identified medications performing significantly better than placebo or haloperidol as the reference treatment in each population considered, and assessed the strength of association according to validated criteria. In addition, we collected data on other relevant clinical elements (i.e. common adverse events, drug-drug interactions with COVID-19 medications, daily doses) and regulatory elements (i.e. therapeutic indications, contra-indications, available formulations). A total of 10 systematic reviews were included. Overall, relatively few medications showed benefits over placebo in the four selected populations. As compared with placebo, significant benefits emerged for quetiapine and dexmedetomidine in intensive care unit (ICU) settings, and for none of the medications in non-ICU settings. Considering also data from indirect populations (agitation related to acute psychosis or dementia), aripiprazole, quetiapine and risperidone showed a potential benefit in two or three different populations. Despite limitations related to the rapid review methodology and the use of data from indirect populations, the evidence retrieved can pragmatically support treatment choices of frontline practitioners involved in the COVID-19 outbreak, and indicate future research directions for the treatment of delirium in particularly vulnerable populations.

Keywords: agitation, antipsychotics, coronavirus disease, delirium

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Introduction

While we write, the novel coronavirus disease (COVID-19) pandemic is posing unparalleled challenges to healthcare systems globally.[1] It is estimated that about 1 out of 5 symptomatic cases will require hospitalisation for medical support, and 1 out of 20 will require intensive-care treatment because of severe respiratory impairment,[2] with higher fatality rates in older patients with medical comorbidities.[3] As in other life-threatening illnesses requiring intensive medical support, delirium occurs frequently and is associated with poorer prognosis, especially in the elderly.[4] A recent report of 214 cases in China found that about 15% of

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patients with severe COVID-19 developed states of impaired consciousness, including delirium.[5] Delirium is a multifactorial condition, characterised by a wide range of neuropsychiatric abnormalities, typically including changes in attention and consciousness, sleep problems, delusional thoughts and hallucinations, anxiety and restlessness, sometimes alongside frank psychomotor agitation. The disturbance develops quickly (usually hours to days) and tends to fluctuate over the course of the day.[6] Hypoactive presentations are the most frequent, although agitated/hyperactive presentations occur in about 25% of patients with delirium.[4] People with COVID-19 might have several risk factors for delirium, including disorientation caused by hospitalisation, old age, pre-existing multiple comorbidities and polypharmacy.[7,8] Moreover, potentially relevant additional risk factors are prolonged isolation, use of experimental medical treatments associated with neuropsychiatric side effects (e.g. antimalarial and antiviral drugs), direct or immunity-mediated neurologic effects, prolonged mechanical ventilation and acute renal impairment.[9–11]

Authoritative national and international guidelines recommend non-pharmacological interventions for the prevention and treatment of delirium, while pharmacological treatments should be considered only for hyperactive delirium with important behavioural issues (i.e. agitation, aggressiveness) or in severely distressed patients. In these cases, antipsychotics are recommended, and particularly first-generation antipsychotics, such as haloperidol or levomepromazine (also indicated as methotrimeprazine).[12,13] However, the efficacy and safety of antipsychotics for delirium remains actively debated.[4] Medications with anti-histaminergic and anti-cholinergic profiles can effectively induce short-term sedation, but medium- and long-term risks might be relevant (e.g. daytime sedation, respiratory distress and further worsening of cognitive performance). Other therapeutic targets of anti-delirium medications might include modulation of neurotransmission, neuroinflammation, oxidative stress and genetic transcription,[14] as well as cognitive enhancement and recovery.[15]

In patients with COVID-19, the treatment of hyperactive delirium poses additional challenges, considering that (a) non-pharmacological prevention and treatment are very limited due to the need for isolation and few contacts with personnel; (b) sedative agents might further impair the central respiratory drive and increase the risk of respiratory infections, with worsening of respiratory distress; (c) the risk of drug–drug interactions could be relevant, particularly regarding QTc-prolongation, due to both altered cytochromes activity and additive or synergistic activity of medications.[16] Therefore, conventional treatment routines are notably limited and should be rapidly rethought. Recently released guidelines on the management of delirium in people with COVID-19 mostly reflect previous recommendations for the general population, without fully considering the peculiarities of these patients and possible challenges of implementing recommendations.[17,18]

Based on these premises, we conducted a rapid review of the evidence in order to pragmatically summarise the elements supporting a tailored choice of medications for the management of delirium in people with COVID-19.

Methods

Considering the complete lack of direct data on delirium in people with COVID-19, we gathered data in people suffering from four conditions: (a) delirium in critically ill patients in intensive care units (ICUs); (b) delirium in non-ICU settings; (c) dementia-related agitation or aggressiveness; and (d) psychosis-related agitation or aggressiveness. As psychomotor agitation is a complex manifestation, key triggers and pathophysiology pathways might significantly differ in different populations, according to many factors (e.g. age, underlying medical and psychiatric conditions, altered states of consciousness). Thus, there are notable limitations in comparing data from such different populations. However, from a pragmatic standpoint, similar medications are generally prescribed to agitated patients irrespective of the underlying aetiology, probably because they target final common pathways (e.g. dysregulations of dopaminergic, serotonergic, noradrenergic, and GABAergic systems).[19,20] Furthermore, although data from indirect populations should be used carefully to provide practical recommendations,[21] they might generate useful insights for future research on promising interventions.

PubMed and the Cochrane Library were searched for high-quality and updated systematic reviews of randomised trials (RCTs) on the pharmacological treatment of delirium or agitation related to dementia or psychosis. The following terms were used: (delirium[Title] OR agitat*[Title] OR

confus*[Title] OR behav* [Title] OR dementia [Title]) AND (pharmacother*[Title/Abstract] OR psychopharm*[Title/Abstract] OR psychotropic* [Title/Abstract] OR antipsych*[Title/Abstract] OR benzodiazepin*[Title/Abstract] OR antidepress* [Title/Abstract]) AND (review[Title]* OR meta-analys*[Title] OR overview[Title] OR synthesis* [Title] OR random*[Title]). Results were limited to English language and to the last 10 years. The search was updated to 20 April 2020. We considered a number of medications typically used on- and off-label for delirium according to current clinical guidelines and common practice. Medications showing statistical superiority over placebo at study endpoint according to the most updated meta-analysis of RCTs were defined as having potential benefit on hyperactive delirium. When data from placebo-controlled trials were not available, we considered head-to-head RCTs showing no significant differences against haloperidol and narrow confidence intervals according to the GRADE approach for detecting imprecision,[21] provided that haloperidol was effective *versus* placebo in the same population. Strength of associations was assessed with validated criteria commonly employed to assess the strength of associations (umbrella review criteria – see Supplemental material).[22] Delirium duration or validated rating scales scores measuring overall symptoms of delirium, or agitation in the short-term (up to 72 h), were considered.

In addition, we searched additional sources to collect data on the pharmacological profile of psychotropic medications and the risk of drug–drug interactions with COVID-19 medications,[16,23,24] as well as regulatory data from the British National Formulary (BNF) and the European Medicines Agency (EMA) website.[25,26] The following information of practical relevance for the treatment of delirium in COVID-19 was retrieved for each medication: sedative and anticholinergic properties; risk of QTc prolongation; risk of drug-drug interactions with COVID-19 medical treatments (including commonly used antiviral and antimalarial drugs, antibiotics, antirheumatic drugs, low-molecular-weight heparin); EMA/BNF therapeutic indications; available formulations; and suggested daily doses according to existing authoritative guidelines.[17,18,23]

Results

The database search yielded 342 records. After removing duplicates, 259 records underwent title and abstract screening by one reviewer (CG). Ultimately, 44 full texts of potentially relevant studies were independently assessed by two reviewers (GO, CB), and 10 were finally selected by agreement (see Supplemental material).[27–36]

Medications showing evidence of benefit for the treatment of hyperactive delirium or other forms of agitation are reported in Table 1, along with other relevant clinical, pharmacological and regulatory data. Details on the search results, the study selection, the outcomes extracted from the selected reviews, the effect sizes and the strength of association are provided in the Supplement.

Overall, few medications showed potential benefits for the treatment of delirium, and the strength of associations was always weak according to the umbrella review criteria. Possible benefits emerged only for quetiapine and dexmedetomidine in ICU settings. Risperidone, quetiapine, aripiprazole and sodium valproate were effective in reducing the level of agitation in people with dementia. Haloperidol, olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone and lorazepam significantly reduced the level of agitation in people with agitation related to acute psychosis.

The risk of sedation, and potentially associated respiratory impairment, appears to be higher for first-generation antipsychotics, benzodiazepines, dexmedetomidine, and the antidepressants considered (i.e. mirtazapine and trazodone). All antipsychotics have warnings or explicit contraindications for the use in people with risk of QTc prolongation and for the association with some of the commonly used anti-COVID medical treatments. From a regulatory standpoint, only few medications have a marketing authorisation for at least one of the conditions considered. In particular, only haloperidol has an explicit indication for delirium according to the EMA, while midazolam and promazine have a generic indication for psychomotor agitation (Table 1). For many of the selected medications, rapidly acting formulations are not available on the market, although this aspect can notably vary according to the country and context (e.g. humanitarian and low-resources settings).

Discussion

Only quetiapine and dexmedetomidine showed benefits over placebo for the treatment of delirium in ICU settings, while no medications had

Table 1. Clinical elements, evidence of benefit and regulatory information of candidate medications for the treatment of hyperactive delirium in people with COVID-19.

Drugs	Clinical elements				Evidence of benefit				EMA/BNF therapeutic indications			Formulations available				Suggested daily doses
	Sedation	Anti-cholinergic effects	QTc prolongation	COVID-19 drug interactions	DEL ICU	DEL no ICU	DEM	PSY	DEL	DEM	PSY	TAB	DROPS	IM	IV	
ANTIPSYCHOTICS																
Aripiprazole	-	-	+ Ⓦ	++ Ⓦ			■	■		Ⓦ	■	■		■		10–30 mg
Chlorpromazine[a]	+++	++	++ Ⓦ	++ Ⓦ					■	■■ Ⓦ	■	■	■	■	■	25–300 mg (elderly 25–75 mg)
Haloperidol	+	+	++ ⊘	++ ⊘				■	■	■■ Ⓦ	■	■	■	■	■	1–10 mg (elderly 0.5–5 mg)
Olanzapine	++	+	+ Ⓦ	+ Ⓦ				■		Ⓦ		■		■		2.5–5 mg
Paliperidone	+	+	+ Ⓦ	+ Ⓦ						Ⓦ		■				3–6 mg
Promazine[b]	+++	++	++ Ⓦ	++ Ⓦ					■	■■ Ⓦ	■	■	■	■	■	100–200 mg × 4 (elderly 25–50 mg)
Quetiapine	++	+	+ Ⓦ	+++ ⊘	■		■	■		Ⓦ		■				25–50 mg
Risperidone[c]	+	+	+ Ⓦ	++ Ⓦ			■	■		■■ Ⓦ		■	■			0.5–2 mg
Tiapride	++	+	+ Ⓦ	++ Ⓦ					■	■■ Ⓦ		■		■	■	100–400 mg
Ziprasidone	+	-	++ ⊘	+++ Ⓦ				■		Ⓦ		■			■	10–80 mg
Zuclopenthixol	++	++	++ Ⓦ	++ Ⓦ						Ⓦ	■	■		■		20–150 mg (elderly 5–150 mg)
BENZODIAZEPINES																
Lorazepam	++	-	-	+ ⊘				■	■	■	■	■	■	■	■	1–4 mg (elderly 0.5–2)
Midazolam[d]	+++	-	-	++ Ⓦ					■				■	■	■	10–60 mg

(Continued)

Table 1. (Continued)

Drugs	Clinical elements				Evidence of benefit				EMA/BNF therapeutic indications			Formulations available				Suggested daily doses
	Sedation	Anti-cholinergic effects	QTc prolongation	COVID-19 drug interactions	DEL ICU	DEL no ICU	DEM	PSY	DEL	DEM	PSY	TAB	DROPS	IM	IV	
ANTIDEPRESSANTS																
Mirtazapine	+++	+	-	++								■				15–30 mg
Trazodone	+++	+	+ Ⓦ	++ Ⓦ								■				50–150 mg
OTHER DRUGS																
Dexmedetomidine	+++	-	++	++	■										■	0.2–1.4 mcg/kg/h
Rivastigmine[e]	-	-	+	-						■		■	■			3–12 mg
Donepezil[f]	-	-	+	-						■		■	■			5–10 mg
Sodium valproate	+	-	+	+			■					■	■		■	250–1000 mg

-, no risk; +, low risk; ++, moderate risk; +++, high risk; ⃠, contraindication according to EMA/BNF; Ⓦ, special warnings and precautions for use according to EMA/BNF; ■, presence of evidence of benefit, EMA/BNF therapeutic indication, or formulation; BNF, British National Formulary; DEL, delirium; DEM, aggressiveness/agitation/behavioural issues in dementia; DROPS, drops or other oral liquid formulations; EMA, European Medicines Agency; ICU, intensive care unit; IM, intramuscular injection; IV, intravenous infusion; mcg, micrograms; mg, milligrams; PSY, aggressiveness/agitation/behavioural issues in psychosis; QTc, corrected QT interval prolongation; RCT, randomised controlled trial; TAB, tablets or capsules.

Evidence of benefit was reported for treatments showing statistical superiority over placebo at study endpoint according to the most updated meta-analysis of RCTs. If data from placebo-controlled trials were lacking, we considered head-to-head RCTs showing no significant differences against haloperidol and narrow confidence intervals according to the GRADE approach for detecting imprecision, provided that haloperidol was effective *versus* placebo in the same population.

Notes on registered indications: (a) Registered indication (BNF): Psychomotor agitation, excitement, and violent or dangerously impulsive behaviour; (b) Registered indication (BNF): Short-term adjunctive management of psychomotor agitation; Agitation and restlessness in elderly; (c) Registered indication (BNF): Short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological interventions and when there is a risk of harm to self or others; (d) Registered indication (BNF): Adjunct to antipsychotic for confusion and restlessness in palliative care; (e) Registered indication (BNF): Mild to moderate dementia in Alzheimer's disease and in Parkinson's disease; (f) Registered indication (BNF): Mild to moderate dementia in Alzheimer's disease.

Notes on EMA/BFN warnings and precautions: all antipsychotics have a warning for (a) the increased risk QTc prolongation (and for haloperidol and ziprasidone there is contraindication if QTc ⩾500 ms) and (b) the increased risk of death in older people with dementia. Haloperidol is contraindicated in association with other QTc-prolonging medications, including certain antibiotics and chloroquine. The risk of QTc prolongation is likely to be greater with intravenous route. The associations quetiapine + cytochrome P450 3A4 inhibitors (e.g. HIV-protease inhibitors, clarithromycin) and lorazepam + HIV-protease inhibitors are contraindicated. Caution should be observed for any antipsychotic in association with other QTc-prolonging medications, for midazolam in association with HIV-protease inhibitors and macrolide antibiotics, and for trazodone in association with ritonavir and macrolide antibiotics.

evidence of benefit over placebo in non-ICU settings. A recent network meta-analysis pooling data from studies in both ICU and non-ICU settings found that only haloperidol (alone or combined with lorazepam) was slightly more effective *versus* inactive treatments in terms of response.[37] However, in this analysis, placebo-controlled studies and studies employing usual care as a control group were pooled together, notably limiting the interpretation of the results.

Only the second-generation antipsychotics risperidone and aripiprazole showed benefits in two different populations, and only quetiapine in three. Interestingly, like haloperidol, at least risperidone and aripiprazole are not generally characterized by a relevant sedative effect in the short-term, supporting the idea that sedation may not be the only therapeutic target for the management of delirium.

High heterogeneity emerged between medications regarding sedative proprieties, anticholinergic effect, QTc prolongation and interactions with anti-COVID treatments. These elements should be carefully weighed on a case-by-case basis, in light of underlying medical risk factors of patients (Table 1). Particularly, in patients with COVID-19, the risk of excessive sedation, respiratory distress, and QTc-prolonging drug–drug interactions should be routinely considered. Furthermore, most antipsychotics have an EMA warning on the increased risk of death in people with dementia.[38] This warning was issued on the basis of observational long-term studies showing a higher risk for a number of conditions (including infections, cerebrovascular events, and overall risk of death)[39]; however mortality was not increased in the included short-term studies.[30,31,34,37] Similarly, acceptability (total dropouts),[27,29] tolerability (dropouts due to adverse events),[29] and overall adverse events were not increased,[28,34] although for risperidone and olanzapine a higher risk of cerebrovascular events in people with dementia was found in short-term studies ($\leqslant$10 weeks).[34]

Regulatory data indicated that most of the medications considered are off-label in people with COVID-19 and delirium, and their prescription should therefore strictly follow the medico-legal procedures for off-label prescribing, being particularly alert of any unexpected safety issues.[40] This situation applies particularly to people with COVID-19, considering that many medical treatments are similarly being used off-label or compassionately.[41]

Pragmatically, some medications might have a limited use in clinical practice, as they may not be widely available as rapidly acting formulations, such as for example as sublingual tablets, drops, intramuscular injections, intravenous or subcutaneous infusions (Table 1).

This rapid review of the literature summarized previously provided an overview of the evidence base, the clinical aspects, and the regulatory elements that can help clinicians tailor the choice of antidelirium medications in different clinical scenarios. Clinically relevant specific elements for people with COVID-19 were critically considered. However, some limitations should be acknowledged. First, we employed a rapid review methodology, which carries intrinsic limitations in terms of accuracy of the search and selection process. Second, all available evidence suffers from a relevant degree of indirectness in terms of population, also considering that studies on delirium often included patients with hypoactive features (although relatively few in most cases). Third, we employed a minimum-threshold criterion for identifying evidence of benefit, and details on the magnitude of treatment effect were not provided in most cases.

In conclusion, while current guidelines recommend treating delirium in people with COVID-19 following the same pharmacological approach as used in the general population, COVID-19 provides a paradigmatic example of how standard treatment procedures, being designed around 'average' patients, are hardly applicable as complexity increases. Hopefully, the present tabular representation of the main clinical considerations relevant for the treatment of delirium in people with COVID-19 can help inform treatment choices that health care professionals need to make under real-world clinical circumstances. Quetiapine, risperidone and aripiprazole are potentially effective medications for the short-term treatment of hyperactive delirium, and might represent an alternative to conventional treatments, such as haloperidol. Of note, although the focus of this review was on pharmacological treatments, non-pharmacological approaches remain a cornerstone of the treatment and prevention of delirium, and should be provided whenever possible (e.g. reorientation of the patient, reviewing medications, managing visual and hearing impairment).

In terms of research priorities, we call for innovative approaches to establish the beneficial and harmful consequences of different medications in people with delirium, including in highly complex

populations (such as COVID-19) where standard treatments might be unfeasible. In particular, pragmatic randomised head-to-head studies enrolling real-world patients are urgently needed, which test promising medications with safe profiles (e.g. aripiprazole, quetiapine, risperidone, valproate, dexmedetomidine), and employ hard outcome measures resembling those routinely used in clinical practice.

Conflict of interest statement

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Supplemental material

Supplemental material for this article is available online.

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