

## Consensus document

# Consensus of the Liaison-Psychiatry Committee of the Colombian Psychiatric Association on the diagnosis and treatment of delirium in the context of the COVID-19 pandemic



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## ABSTRACT

The pandemic caused by the new coronavirus named SARS-CoV-2 poses unprecedented challenges in the health care. Among them is the increase in cases of delirium. The severe SARS-CoV-2 disease, COVID-19, has common vulnerabilities with delirium and produces alterations in organs such as the lungs or the brain, among others, which have the potential to trigger the mental disorder. In fact, delirium may be the first manifestation of the infection, before fever, general malaise, cough or respiratory disturbances. It is widely supported that delirium increases the morbidity and mortality in those who suffer from it during hospitalization, so it should be actively sought to carry out the relevant interventions. In the

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absence of evidence on the approach to delirium in the context of COVID-19, this consensus was developed on three fundamental aspects: diagnosis, non-pharmacological treatment and pharmacological treatment, in patients admitted to the general hospital. The document contains recommendations on the systematic use of diagnostic tools, when to hospitalize the patient with delirium, the application of non-pharmacological actions within the restrictions imposed by COVID-19, and the use of antipsychotics, taking into account the most relevant side effects and pharmacological interactions.

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## Consenso del Comité de Psiquiatría de Enlace de la Asociación Colombiana de Psiquiatría sobre el diagnóstico y tratamiento del delirium en el contexto de la pandemia por COVID-19

### R E S U M E N

#### Palabras clave:

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La pandemia por el nuevo coronavirus denominado SARS-CoV-2 plantea retos sin precedentes en la atención de la salud. Entre ellos se cuenta el aumento en los casos de delirium. La enfermedad grave por SARS-CoV-2, COVID-19, tiene vulnerabilidades comunes con el delirium y produce alteraciones en órganos como el pulmón o el cerebro, entre otros, que tienen potencial para precipitar el trastorno mental; de hecho, este puede ser la primera manifestación de la infección, antes de la fiebre, el malestar general, la tos o las alteraciones respiratorias. Está ampliamente sustentado que el delirium incrementa la morbilidad y la mortalidad de quienes lo padecen durante una hospitalización, por lo que se debe buscar activamente para realizar las intervenciones pertinentes. Ante la ausencia de evidencia sobre el abordaje del delirium en el contexto de la COVID-19, se elaboró este consenso sobre tres aspectos fundamentales: diagnóstico, tratamiento no farmacológico y tratamiento farmacológico, en pacientes ingresados en el hospital general. El documento contiene recomendaciones sobre uso sistemático de herramientas diagnósticas, cuándo hospitalizar al paciente con delirium, la aplicación de acciones no farmacológicas dentro de las restricciones que impone la COVID-19 y la utilización de antipsicóticos teniendo en cuenta los efectos secundarios más relevantes y las interacciones farmacológicas.

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### Statement of the problem

Coronavirus disease 2019 (COVID-19) caused by the novel coronavirus SARS-CoV-2 was declared a pandemic by the World Health Organization (WHO) on 11 March 2020.<sup>1</sup> The first case in Colombia had been reported on 6 March 2020, and as of the latest update to this manuscript, on 14 September 2020, the Colombian Ministry of Health and Social Protection and the Colombian National Institute of Health had reported 716,319 confirmed cases, 22,924 deaths and 599,385 recoveries in that country (which has a population of 48,258,498), despite the public health measures adopted, including population lockdown and a clinical management protocol for positive cases.<sup>2</sup>

The virus, with a tropism for angiotensin converting enzyme II receptors — which are present in the lungs, heart, kidneys, gastrointestinal system and brain, among other organs — causes a broad spectrum of symptoms, including malaise, pneumonia, impairment of various systems and death.<sup>3,4</sup> Although other modes of transmission have not been ruled out, COVID-19 is spread in a manner similar to influenza.<sup>5</sup> According to the WHO, it has a basic reproduc-

tion number of 2–4, 15% of cases are serious, 5% are critical and the global gross mortality rate is 7%.<sup>6</sup> The risk of having a serious/critical case or dying increases with age or if one suffers from cardiovascular disease, respiratory disease, diabetes or cancer.<sup>7–9</sup>

Lines of research on COVID-19 treatment include searching for a vaccine and studying the plasma of recovered patients.<sup>10,11</sup> While awaiting more high-quality empirical evidence, proposed treatment regimens include public health measures such as population lockdown, isolation of positive cases and drugs ranging from symptomatic treatment to antiviral agents.<sup>12</sup> Staff who care for patients with the disease must follow strict protective measures, and the need to have these measures in place at institutions as well as the possibility of transmission in said staff have placed restrictions on medical care.<sup>13</sup>

Delirium is acute brain failure triggered by health conditions that cause inflammation, abnormalities in cell homeostasis or central neural activity and other changes.<sup>14</sup> Patients with delirium have cortical and deep-structure dysfunction related to consciousness, which may be reflected

in the onset of cognitive symptoms, abnormalities in executive function, changes in circadian rhythm and frontal release signs.<sup>15</sup> It is not a categorically “present” or “absent” disorder; rather it is an altered mental state on a spectrum from mild changes to very serious changes.<sup>16</sup>

To understand the causes of delirium, both individual vulnerability and precipitating factors must be taken into account.<sup>17</sup> Several conditions increase vulnerability, such as major neurocognitive disorder and other predisposing factors,<sup>18,19</sup> largely coinciding with those stated for serious/critical SARS-CoV-2 infection, which for its part has the potential to precipitate mental disorder, as a result of abnormalities caused in various systems.<sup>20</sup>

Several mechanisms account for the novel virus’s capacity to precipitate delirium. Regarding central nervous system (CNS)-specific impairment, the virus likely gains access to the brain parenchyma through the olfactory nerve, and gets as far as the thalamus and brainstem, which are directly involved in the pathophysiology of delirium.<sup>21</sup> Other abnormalities caused by SARS-CoV-2 that affect both the CNS and other systems include excessive cytokine production, clot formation and hypoxia, all with the potential to alter consciousness.<sup>22,23</sup>

Under normal conditions, delirium already affects one out of every five hospitalised patients,<sup>24</sup> and in Colombia more than 30% of geriatric patients will ultimately get it.<sup>25,26</sup> Since COVID-19 features a confluence of vulnerabilities and precipitating factors, to which must be added the pharmacological interventions required in serious/critical cases, an increase in the prevalence of delirium has been observed.<sup>27–30</sup> In fact, the disorder may be the first sign of COVID-19.<sup>31,32</sup> This is concerning because delirium usually has low detection and treatment rates,<sup>33</sup> and furthermore lengthens stays and increases care costs, morbidity, functional/cognitive difficulties upon discharge and mortality in those who suffer from it,<sup>34</sup> to date there is a dearth of specific evidence on how to address it in the context of the pandemic.

## Scope of the consensus

Taking the above considerations into account, the Comité de Psiquiatría de Enlace [Liaison Psychiatry Committee] of the Asociación Colombiana de Psiquiatría [Colombian Psychiatry Association] developed this consensus on three essential aspects of clinical treatment of delirium in relation to the current pandemic: a) diagnosis; b) general measures and non-pharmacological interventions; and c) drug treatment. To this end, a member of the committee prepared the initial version and sent it to the other authors for critical analysis and comments in two rounds before a final consensus was reached.

The context of this document is a general hospital, and it is intended for general physicians, psychiatrists, specialists in other areas and nurses responsible for treating adults with suspected or confirmed COVID-19.

It must be stressed that these are not guidelines for treating delirium in general; rather, they are a specific consensus on care for the disorder in the scenario caused by infection with the novel SARS-CoV-2 virus. There is not enough high-quality evidence on the treatment of delirium under these specific circumstances, and this article emphasises the relevant points

taking into account variability in resources and interventions in the infection.

Table 1 features the consensus recommendations and the subsequent sections show the detailed discussion. Table 2 offers instructions on antipsychotic use and the section on drug treatment includes online sources, where updates can be found.

## Diagnosis

Given the importance of timely diagnosis of delirium, physicians and nurses lacking in-depth knowledge of psychiatric disease must use screening instruments or, better yet, instruments for provisional diagnosis, which ideally can also be used in patients who lack the capacity to give verbal responses due to intubation or limitations on communication. In Colombia, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and Delirium Diagnostic Tool-Provisional (DDT-Pro) are validated.<sup>35</sup> The former is an algorithm to screen for delirium on intensive care units (ICUs),<sup>36</sup> and the latter is the first tool developed for provisional diagnosis of delirium in the absence of an expert to verify it.<sup>37</sup>

The CAM-ICU has four items that can be evaluated even in the absence of a verbal response from the patient: a) acute change or fluctuating course; b) inattention; c) disorganised thinking; and d) level of consciousness according to the Richmond Agitation Sedation Scale (RASS). It is scored as positive or negative for delirium. A patient is positive if they have abnormalities in the first and second item plus failures in either of the other two items. The Colombian version has very good interevaluator agreement ( $\kappa=0.8$ ), with 93% sensitivity and 87% specificity for people on ventilation and delirium according to the DSM-IV-TR.<sup>38</sup>

Since the prevalence of delirium in critically ill and intubated patients can exceed 80% and the condition can develop at any time during ICU admission,<sup>39</sup> the consensus recommendation is to use the CAM-ICU at least every 12–24 hours in patients with COVID-19. Those positive for delirium should be periodically assessed and it should be determined whether they cease to be positive once treatment measures are instated. The CAM-ICU validated in Colombia is available online (<https://n9.cl/sbad>).

The DDT-Pro has three items that can be evaluated even in the absence of verbal responses: a) comprehension, b) vigilance and c) sleep-wake cycle. Each is scored from 0 (serious abnormality) to 3 (no abnormality). The total score ranges from 0 to 9. The Colombian version was validated in patients admitted to internal medicine and its subspecialisations. Agreement between a physician and a nursing professional is very good (intraclass correlation index=0.9) and is not affected in major neurocognitive disorder. Diagnostic accuracy for delirium according to the DSM-V is 94%. A cut-off point  $\leq 6$  is the one recommended as indicative of a diagnosis of delirium. DDT-Pro scores are sensitive to changes in clinical stages, and therefore serve to monitor the patient’s course.<sup>40</sup>

Given the needs for staff isolation and protection in accident and emergency departments and hospitalisation departments with large numbers of admissions, and

**Table 1 – Consensus of the Comité de Psiquiatría de Enlace [Liaison Psychiatry Committee] of the Asociación Colombiana de Psiquiatría [Colombian Psychiatric Association] on the diagnosis and treatment of delirium related to SARS-CoV-2 infection and COVID-19.**

#### Diagnosis of delirium

- Implement guidelines for delirium treatment at all centres with hospital services, articulating the actions of all professionals according to their role
- Use screening instruments or instruments for provisional diagnosis of delirium validated in Colombia, without neglecting to screen for other common disorders such as anxiety and depression
- On the ICU:
  - The CAM-ICU algorithm is recommended; intensivists and nurses can use it in patients with or without the ability to give verbal responses
  - The CAM-ICU should be used at least every 12–24 hours in patients with confirmed or suspected COVID-19
  - Patients screened as positive for delirium should be periodically assessed with the CAM-ICU to determine whether they remain positive
  - The version in Spanish of the CAM-ICU can be downloaded at:  
[https://uploads\\_ssl.webflow.com/5b0849daec50243a0a1e5e0c/5bb41b525e9306c1d636d785\\_CAM-ICU\\_training.Spanish.pdf](https://uploads_ssl.webflow.com/5b0849daec50243a0a1e5e0c/5bb41b525e9306c1d636d785_CAM-ICU_training.Spanish.pdf)
- In other hospital departments:
  - The DDT-Pro is recommended; it can be used by physicians or nurses, even in patients who cannot give verbal responses or have major neurocognitive disorder
  - The DDT-Pro should be used in all patients with recent alteration of their behaviour/mental state
  - If delirium is diagnosed, the DDT-Pro should be used at least once daily to evaluate the seriousness or resolution of the case
  - The version in Spanish of the DDT-Pro can be downloaded at: <https://n9.cl/sbad>
  - Although no known data validate the general CAM in Colombia, those who are already using it should not switch instruments during the pandemic and should consider the instructions provided
  - To use the general CAM, the patient must be able to give verbal responses
  - To use the general CAM, it is necessary to register at: [https://help.agscicare.org/chapter\\_abstract/chapter/H00101/H00101\\_PART001\\_002](https://help.agscicare.org/chapter_abstract/chapter/H00101/H00101_PART001_002)

#### General measures and non-pharmacological interventions

- Delirium prevention:
  - Maintain proper patient hydration and, depending on their possibilities and restrictions, allow mobility, promote sleep hygiene and care for cognitive function
- Decision to hospitalise a patient with delirium from the accident and emergency department:
  - When the patient's delirium symptoms are serious
  - When the patient's clinical condition is progressively declining
  - When the aetiologies of the delirium have not been identified or if it is suspected or confirmed that the disorder may be in some way related to COVID-19
  - When in-home care or outpatient follow-up cannot be ensured or when delirium overlaps with a known cognitive disorder
- General non-pharmacological actions for the care of patients with delirium:
  - Tolerate, anticipate and not agitate (TANA): tolerate minor behavioural disturbances, anticipate fall and injury risk, and evaluate risk of aggression
  - When behavioural disturbances are present, verbal behavioural interventions are initially used
- Only for patients in whom it is strictly necessary, mechanical restraint:
  - If, despite other non-pharmacological and pharmacological interventions, the risk that they will harm themselves or that their behaviour will interfere with their treatment persists
  - Always bear in mind that mechanical restraint itself can cause agitation
  - Whenever this measure is necessary, strict records of the patient's condition and the continuity of the indication for restraint must be kept
  - Always as brief as possible
- Specific non-pharmacological actions for delirium treatment:
  - Considering restrictions that come with patient isolation and possible limitations on staff and space, communication with the patient must be maintained
  - Circumstances and characteristics of the centre, specific department and patient permitting, electronic means should be used to maintain frequent contact with the patient
  - The use of any eyeglasses or hearing equipment that the patient may require is allowed, whenever possible
  - Orientate and give frequent, clear explanations, insofar as is possible: where you are, who is caring for you, what procedure/treatment is being performed, etc.
- Although involving companions in delirium care is beneficial, the pandemic restricts the possibility of doing so regularly

#### Drug treatment

- Preventive prescription of medicines intended to prevent the onset of delirium related to COVID-19 is not recommended
- For all patients, with or without delirium, a rational drug prescription must be made, and this must be reviewed daily
- It is necessary to investigate causes of delirium and behavioural abnormalities in the context of COVID-19 and to intervene in those that can be treated
- In investigating causes, vulnerability factors and specific precipitating factors must be analysed in each case in order to rationalise interventions to the extent possible
- As the pandemic restricts some non-pharmacological interventions, an increase in drug treatment for delirium is anticipated
- When delirium in the context of COVID-19 does not resolve with the other actions described, it is recommended that an antipsychotic be administered at the minimum effective dose
- The most important side effects of antipsychotics used to treat delirium in the context of COVID-19 are:
  - Extrapyramidal effects, especially with typical antipsychotics
  - Effects on metabolism, especially with atypical antipsychotics, which may appear at the start and be more significant in at-risk populations

**Table 1 (Continued)**

- Cardiovascular and cerebrovascular effects, especially in patients with risk factors for QT prolongation and the geriatric population with neurocognitive disorders
- Gastrointestinal effects (among them, constipation is significant in inpatient settings and may worsen delirium)
- In the context of COVID-19, cardiovascular abnormalities may occur due combining antipsychotics with drugs to manage viral disease
- Decision-making as to which antipsychotic to administer must be personalised based on the patient's clinical characteristics and the medicines that the patient is already taking (see [Table 2](#))
- Treatment with antipsychotics should be as brief as possible, depending on the patient's clinical course and comorbidities
- Benzodiazepines should not be administered as a first-line pharmacological option in the treatment of delirium in patients with COVID-19
- Lorazepam should only be used for timely control of behavioural changes when it is not possible to prescribe an antipsychotic, and it should always be used at low doses with monitoring of respiratory function

**Table 2 – Profile of particularly significant side effects in the context of COVID-19 of antipsychotics used to treat delirium.\***

Antipsychotic	Extrapyramidal effects	Effects on metabolism	Cardiac/cerebrovascular effects	Risk of constipation	Comments
Haloperidol	Common, not suitable for patients with parkinsonism of any origin	Less pronounced than with atypical agents	High risk of QT interval prolongation with ritonavir and atazanavir and with chloroquine and hydroxychloroquine. Risk of cerebrovascular accident and death in geriatric patients with major neurocognitive disorder	Constipation is a significant side effect and should be weighed particularly heavily in geriatric patients and patients with other risk factors	Ritonavir and chloroquine double haloperidol bioavailability. Does not significantly interact with tocilizumab, dexamethasone, interferon beta, remdesivir, favipiravir or ribavirin. Atazanavir could increase haloperidol levels
Quetiapine	Uncommon, especially at low doses	The higher the dose, the worse the blood glucose and lipid control; long term, there is weight gain	High risk of QT interval prolongation with lopinavir, atazanavir, chloroquine and hydroxychloroquine. Risk of cerebrovascular accident and death in geriatric patients with major neurocognitive disorder	Constipation is a significant side effect and this risk should be weighed particularly heavily in geriatric patients and patients with other risk factors	Quetiapine has significant anxiolytic and hypnotic effects. Ritonavir increases quetiapine bioavailability by up to six times. There are no significant interactions with tocilizumab, dexamethasone, interferon beta, remdesivir or ribavirin. Favipiravir is metabolised by aldehyde oxidase, which is inhibited <i>in vitro</i> by quetiapine (the clinical significance of this interaction is unknown). Atazanavir significantly increases quetiapine levels
Risperidone	Dose-dependent	The higher the dose, the worse the blood glucose and lipid control; long term, there is weight gain	Simultaneous combination with hydroxychloroquine (or chloroquine) and lopinavir is contraindicated due to QT interval prolongation. Moderate risk of QT prolongation with atazanavir. Orthostatic hypotension (significant in geriatric patients). Risk of cerebrovascular accident and death in geriatric patients with major neurocognitive disorder	Constipation is a significant side effect and this risk should be weighed particularly heavily in geriatric patients and patients with other risk factors	Orthostatic hypotension is more common during the initial dose increase. Ritonavir and chloroquine increase its bioavailability. Does not significantly interact with tocilizumab, dexamethasone, interferon beta, remdesivir, favipiravir or ribavirin. Atazanavir may increase risperidone levels, so it may be necessary to reduce the patient's risperidone dose when administering it.

**Table 2 (Continued)**

Antipsychotic	Extrapyramidal effects	Effects on metabolism	Cardiac/cerebrovascular effects	Risk of constipation	Comments
Olanzapine	Less common than with typical antipsychotics	The higher the dose, the worse the blood glucose and lipid control; long term, there is weight gain	With chloroquine or hydroxychloroquine, there is mild QT interval prolongation. Orthostatic hypotension (especially in combination with benzodiazepines). Risk of cerebrovascular accident and death in geriatric patients with major neurocognitive disorder	Constipation is a significant side effect; this risk should be weighed particularly heavily in geriatric patients and patients with other risk factors	Hypnotic effects. Ritonavir reduces its levels. Does not significantly interact with tocilizumab, dexamethasone, interferon beta, remdesivir, favipiravir, ribavirin or atazanavir
Aripiprazole	Less than with the other antipsychotics described in the table	Fewer metabolic and weight effects than other atypical agents	With lopinavir or hydroxychloroquine, it causes mild QT interval prolongation. Possible QT interval prolongation with atazanavir. Occasional orthostatic hypotension, during the initial dose increase. Risk of cerebrovascular accident and death in geriatric patients with major neurocognitive disorder	The risk of constipation increases with the dose and is less significant than with the other antipsychotics described in the table	Ritonavir doubles its bioavailability. Does not significantly interact with tocilizumab, dexamethasone, interferon beta, remdesivir, favipiravir or ribavirin. Atazanavir may increase aripiprazole levels, so it may be necessary to reduce the patient's aripiprazole dose when administering it
Amisulpride	Dose-dependent	Long term, there is weight gain in some patients, as well as increased incidences of diabetes and hyperlipidaemia	QT interval prolongation, which is dose-dependent and when combined with hydroxychloroquine. Risk of cerebrovascular accident and death in geriatric patients with major neurocognitive disorder	Constipation is a significant side effect; this risk should be weighed particularly heavily in geriatric patients and patients with other risk factors	Hypnotic effects may become significant, especially at high doses. Does not significantly interact with chloroquine, tocilizumab, dexamethasone, interferon beta, remdesivir, lopinavir, ritonavir, favipiravir, ribavirin or amisulpride

\* The decision to administer a specific antipsychotic depends on the individual risk of serious side effects and on whether the patient is taking a drug associated with significant interactions. Outside of what is specified herein, antipsychotics have other side effects, as well as other drug interactions. Although hydroxychloroquine and lopinavir/ritonavir do not reduce mortality from COVID-19, the WHO leaves open the possibility of using and evaluating them in patients exposed to the virus; hence, their interactions with antipsychotics are reviewed. Some online sources that can be checked for updates on drug interactions between antipsychotics and the drugs reviewed or other antivirals or drugs that may be used in patients with COVID-19 are: <https://www.drugs.com/> and <https://www.covid19-druginteractions.org/>.

given that delirium should be suspected in all patients with acute or subacute changes in behaviour while in hospital,<sup>41</sup> it is advisable to use the DDT-Pro in any patient with recent alteration in their behaviour/mental state and, if delirium is diagnosed, continue using it at least once daily during treatment to assess the course. The DDT-Pro validated in Colombia can be downloaded online (<https://www.dropbox.com/s/2bahekw4679wf8d/DDT-Pro-Spanish.pdf?dl=0>).

Finally, we are not aware of any validations in Colombia of the CAM algorithm for general use. It is a screening instrument with items similar to those of the CAM-ICU, which requires prior training and verbal responses from the patient. It was constructed according to the criteria of the DSM-III-R and is very well known.<sup>42</sup> Its adaptation in Spain has very good agreement as it is applied by physicians ( $\kappa=0.9$ ) and has 90% sensitivity and 100% specificity.<sup>43</sup> Although quantitative data on the performance of the CAM in the country are unknown, it is recommended that those with experience not switch instruments and that they use this in the context of the pandemic with patients who are able to give verbal responses, according to the recommendations mentioned for accident and emergency departments and hospitalisation departments. To download the CAM in Spanish, it is necessary to register beforehand ([https://help.agscicare.org/chapter-abstract/chapter/H00101/H00101\\_PART001\\_002](https://help.agscicare.org/chapter-abstract/chapter/H00101/H00101_PART001_002)).

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## General measures and non-pharmacological interventions

Non-pharmacological measures for preventing delirium are widely used.<sup>44</sup> The most important ones are care for baseline cognition, promotion of sleep hygiene, mobilisation according to the patient's circumstances and hydration.<sup>45</sup> The fourth should always be done, and the first through third can be done to some degree, given the need for isolation of COVID-19 cases and potential staff and space restrictions.

On the accident and emergency department, a decision should be made as to whether a patient with delirium should be hospitalised. Patients with delirium who visit accident and emergency departments and are not hospitalised are at higher risk of dying and hospitalisation is the best option when delirium symptoms are serious, clinical status is declining, outpatient care or follow-up cannot be ensured, or underlying neurocognitive disorder is present.<sup>46</sup> Although the decision to hospitalise or not hospitalise should be personalised, the recorded evidence indicates that the best option is to hospitalise patients with delirium of indeterminate cause or suspected or confirmed to be related to COVID-19. It should be borne in mind that delirium may be the only clinical sign of the infection.<sup>47</sup>

Non-pharmacological interventions are among first-line treatment options. In any case of delirium, the "tolerate, anticipate and not agitate" (TANA) strategy should be used. Minor behavioural abnormalities can be tolerated, fall and injury risk must be anticipated and risk of self-aggression or heteroaggression must be evaluated.<sup>48</sup>

Although most disruptive or dangerous behaviours can be reduced with verbal interventions, behavioural measures or pharmacological interventions (see the following section), mechanical restraint may be required in specific cases: if there is a risk of self-harm on the part of the patient or if the behaviours are interfering with treatment. Whenever this measure is necessary, it should be applied according to each institution's protocols, with recording of clinical status and the continuity of the indication to use it, endeavouring to keep it as brief as possible. Mechanical restraint can cause agitation in itself.<sup>49</sup>

The guidelines of the National Institute for Health and Care Excellence recommend maintaining communication with the patient, who insofar as is possible should be wearing any required eyeglasses or hearing aids. For example, it should be explained to the patient: where they are, who is caring for them and what procedure is being performed. In addition, efforts should be made to calm them; to this end, under normal conditions, families and carers can be involved.<sup>50</sup> Unfortunately, indications for isolation and staff and space restrictions limit the possibility of including companions.

Since non-pharmacologic preventive and therapeutic measures may be restricted, prescription of medicines for managing delirium can be anticipated to increase during the pandemic.

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## Drug treatment

There are no clear instructions on the preventive use of drugs for delirium; there is not even agreement on whether they decrease its duration or reduce its incidence, or on identification of patients who would benefit from it.<sup>51</sup> It is not possible to recommend this strategy for those affected by COVID-19.

On the other hand, there is a unanimous agreement on the need to identify and treat the cause of delirium. This also involves rationalising the various pharmacological interventions in patients (this rationalisation being preventive and therapeutic).<sup>52</sup> In the context of COVID-19, it is necessary to analyse the factors of vulnerability to delirium that a given patient has, as well as specific precipitating factors, among which drug treatment plans must be considered,<sup>53</sup> in order to maximise personalisation of interventions in mechanisms of brain failure.

Traditionally, drug treatment of delirium has been based on antipsychotics at the lowest possible doses. Although research is inconclusive and debate persists,<sup>51</sup> the drugs with the most empirical support are haloperidol, quetiapine, risperidone and olanzapine.<sup>54</sup> According to a survey on delirium treatment in Colombia, these same drugs, in that order, are the most commonly used ones in that country, with the fifth most common option being aripiprazole.<sup>55</sup> Although there is less evidence on aripiprazole, there are reports on it, as well as amisulpride, indicating that they are effective.<sup>56,57</sup>

Antipsychotics should be used with caution if other measures have not worked, especially when there is increased motor activity, and they should be used only as long as strictly necessary.<sup>50</sup> Special care should be taken with: a) extrapyramidal effects, especially, but not exclusively, with typical antipsychotics; b) effects on metabolism, especially with atyp-



ical agents; c) cardiac/cerebrovascular effects, with virtually all antipsychotics, in people with risk factors for QT interval prolongation and in geriatric patients with neurocognitive disorders; d) gastrointestinal effects (among them, constipation can worsen delirium); and e) in the current situation, drug interactions with drugs to treat viral disease.

Table 2 describes recommendations for antipsychotic use according to the five sources of caution listed. Relevant side effect recommendations are based on the Stahl Prescriber's Guide (<https://n9.cl/9qe7k>), and remarks on interactions are based on the widely recognised websites <https://www.drugs.com/> and <https://www.covid19-druginteractions.org/>, which are regularly updated. It should be clarified that we are not offering a categorical recommendation as to which drug to use; guidelines are presented according to patients' demographic, clinical and pharmacological profiles. That is, the decision to administer or not administer an antipsychotic depends on individual risk factors for side effects and on whether antivirals or other drugs are being administered.

Regarding antipsychotic interactions, Table 2 describes the safety and risks of concomitant administration of antivirals such as remdesivir, lopinavir, ritonavir, favipiravir, ribavirin and atazanavir, which are being used and studied in the context of COVID-19.<sup>58,59</sup> Although the WHO announced that, according to the Solidarity trial, neither hydroxychloroquine nor a combination of lopinavir/ritonavir reduces mortality, it left open the option of using and evaluating them as prophylaxis against exposure to SARS-CoV-2.<sup>60</sup> Therefore, as it is possible to encounter patients who are taking them, their interactions are described. The safety of tocilizumab, dexamethasone and interferon beta, used in the treatment of the inflammatory response to the virus, is also reviewed.<sup>61–63</sup>

On the other hand, the risk of side effects must not be overestimated. The best evidence available in 2019 in relation to delirium treatment indicated that, although those who took antipsychotics tended to experience cardiac side effects, mortality did not increase and it could not be confirmed that taking them for short periods negatively impacted other systems.<sup>64</sup>

Except when delirium is due to central nervous system depressants, routine use of benzodiazepines is not recommended.<sup>65</sup> Although they have a sedative effect, they alter sleep architecture, attention, memory and motor skills, and their anticholinergic effects and effects on GABA worsen the prognosis of delirium. In geriatric patients and patients with lung disease, in combination with other central depressants, they cause respiratory complications.<sup>66</sup> Even so, the British Geriatrics Society, the European Delirium Association and the Royal College of Psychiatrists recommend lorazepam in patients with COVID-19, when antipsychotics cannot be administered, always with monitoring of respiratory function.<sup>67</sup>

Information on other first-line and adjuvant drugs in the treatment of delirium is less conclusive, so no instructions can be given on using or not using them.<sup>68</sup> The recommendation in the context of COVID-19 is not to supply them without first weighing the reasons for doing so and the risks in each case.

## Conclusions

Given the large numbers of cases of delirium related to COVID-19 and environmental factors of isolation and potential restrictions on human and technical resources, systematic detection and monitoring of the disorder should be structured with validated tools. In all cases, the aetiology must be actively sought in order to intervene, and non-pharmacological interventions must be adapted to suit the resources available. When pharmacological interventions for delirium are necessary, adverse effects should be taken into account in light of patient profiles and drug interactions.

## Conflicts of interest

José G. Franco coordinated the validation in Colombia of the Confusion Assessment Method-Intensive Care Unit and the Delirium Diagnostic Tool-Provisional. He co-owns the copyright for the Delirium Diagnostic Tool-Provisional. He also worked with the team that validated the Confusion Assessment Method for general use in Spain. He receives no remuneration for the use of any of these instruments. Gabriel Fernando Oviedo has sat on Janssen's advisory board. Liliana Patarroyo Rodríguez has been a speaker for Lundbeck. The other authors declare that they have no conflicts of interest.

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