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Delirium in COVID patients: recommendations for assessment and treatment

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Summary

COVID-19 patients, particularly those admitted to an Intensive Care Unit, are at high risk of Delirium due to the frequently observed concomitant presence of a series of factors which, taken together, constitute an increased risk factor. Factors thought to play a key role include: a direct action of the virus and state of inflammation on the Central Nervous System; secondary effects of organ failure; effect of sedative treatment; prolonged exposure to mechanical ventilation; prolonged immobilisation; environmental factors including social isolation and restricted interaction with relatives and healthcare operators. Bearing in mind the potential impact of delirium on clinical outcome, with an increased risk of death, appropriate prevention and management of this condition, particularly complex in COVID patients due to the frequently observed concomitant presence of numerous predisposing and precipitating factors, is fundamental.

Definition of delirium

Delirium is a severe neuropsychiatric syndrome characterised by an acute and fluctuating attention deficit. The condition develops in association with other cognitive or perceptual deficits as the direct physiological consequence of an ongoing medical condition, substance intoxication or withdrawal (substances of abuse or medications) or ingestion of prescribed medication, with symptoms manifested as a side effect of treatment. Delirium may be either *Acute* (duration from a few hours to a few days) or *Persistent* (duration of weeks or months) (Tabs. I, II).

Table I. DSM-5 criteria for delirium [1].

- A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)
- The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day
- An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception)
- The disturbances in Criteria A and C are not explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma
- There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies

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Conflict of interest
The Authors declare no conflict of interest.

Table II. Symptoms of delirium.

Hyperactive or hyperkinetic delirium	Psychomotor agitation, mood swings, illusions, hallucinations, delusions, increased response to external stimuli (e.g. light, noise), state of alert, signs of CNS activation (tachycardia, mydriasis, hypertension, sweating)
Hypoactive or bradykinetic delirium	Reduced psychomotor activity, reduced response to external stimuli, somnolence, lethargy
Mixed delirium	Fluctuating characteristics between the hyperkinetic and hypokinetic forms, with an at times "unpredictable" swing between lethargy and agitation

Prevalence

Delirium is very common in the elderly, in hospitalised patients, in patients in intensive or palliative care and in subjects affected by substance abuse. The risk is extremely high in elderly patients admitted to an intensive care unit.

- General population: from 1.2 to 14% (elderly population).
- Hospital population: 6-56%.
- Hospital population: post -surgery in 15-53% of elderly patients; in intensive care 70-87%.
- End-of-life patients: 83%.
- COVID-19 patients: 15% of hospitalised patients; up to 2/3 of patients admitted to intensive care.

How to prevent delirium

- Screen for delirium with periodic reassessment in at-risk subjects.
- Reduce the risk of onset of delirium by limiting known precipitating factors:
  - help the patient to achieve spatial and temporal reorientation;
  - facilitate interaction with relatives by means of phone calls or videocalls;
  - ensure that prescribed visual or hearing aids are used;
  - keep all transfers (room or ward transfers) to a minimum;
  - restrict the use of psychoactive drugs;
  - mobilise the patient as soon as possible;
  - ensure restorative sleep;
  - ensure adequate hydration and nutrition;
  - prevent constipation;
  - prevent urinary retention;
  - provide pain therapy;
  - maintain adequate oxygenation.
- Evidence has been provided relating to the use of melatonin in the prevention of delirium in patients in intensive care, leading to a proposed use of melatonin in COVID-19 patients [2].

Clinical assessment

Assess

- Vigilance, altered levels of awareness and attention, presence of cognitive disorders and fluctuation of symptomatology.
- Support assessments through use of rating scales (Confusion Assessment Method, CAM - Tab. III) [3].

Predisposing and precipitating factors for delirium

- Old age.
- Comorbidities.
- Severity of concomitant illness.
- Brain disorders (cognitive decline, dementia, stroke, Parkinson's disease).
- Cardiac disorders
- Endocranial disorders.
- Infections.
- Surgery.

Table III. The confusion assessment method (CAM) [3].

FEATURE 1: ACUTE ONSET OR FLUCTUATING COURSE
Is there evidence of an acute change in mental status from the patient's baseline? Did the abnormal behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?

FEATURE 2: INATTENTION
Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

FEATURE 3: DISORGANIZED THINKING
Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

FEATURE 4: ALTERED LEVEL OF CONSCIOUSNESS
Overall, how would you rate this patient's level of consciousness?

0 = alert (normal); 1 = vigilant (hyperalert), lethargic (drowsy, easily aroused), stupor (difficult to arouse) or coma (unarousable).

The diagnosis of delirium requires the presence of features 1 and 2 and either 3 or 4.

- Sensory deficits (auditory and/or visual).
- History of delirium.
- Malnutrition.
- Dehydration.
- Electrolyte and metabolic imbalances (e.g., hypernatremia).
- Urinary retention.
- Catheterisation.
- Multidrug therapy.
- Ongoing treatment with sedatives, anticholinergics, cortisones, analgesics.
- Introduction of new medications.
- Hospitalisation (particularly if prolonged).
- Admittance to an intensive care unit.
- Prolonged mechanical ventilation.
- Immobility.
- Sleep deprivation.
- Isolation.
- Restricted interaction with relatives or healthcare workers whilst in hospital.
- Restraints.
- Pain.
- Frailty.

Drugs are divided into three categories with a score of 1 to 3 based on the level of cognitive effects: the overall anticholinergic burden is yielded by the algebraic sum of the scores obtained of the relevant drugs (Tab. IV).

Non-pharmacological management of delirium

- Treatment of underlying causes.
- Management of hydration and nutrition.
- Verification of the need for oxygen.
- Treatment of pain as required.
- Treatment of urinary retention.
- Treatment of constipation.
- Correction of any electrolyte imbalances and metabolic alterations.
- Ensure monitoring and continuous assessment of patient's condition.
- Where possible, accommodate the patient in the vicinity of the nurses' station to allow for frequent monitoring.
- If the patient habitually uses glasses or hearing aids, ensure these are used to restore normal sensorial input.
- Excessive exposure to sensory stimuli (lights, noise, voices) and total isolation of the patient's room should be avoided.
- Ensure natural daylight during the day and artificial lighting at night.
- Promote movement whenever possible: keep the patient active (walking, exercises in bed).
- Refrain from prescribing sedatives unless absolutely necessary.
- Assess and re-evaluate ongoing treatments featuring a potential to predispose to/precipitate delirium.
- Promote a 24h presence of relatives where possible, or alternatively, set up phone calls or videocalls with family members.
- Monitor staff attitudes (e.g. ensure patient is not mocked).
- When addressing the patient refer to him/her using their name and explain the procedures being carried out. Avoid discussions with colleagues using strictly scientific terminology to avoid generating persecutory ideas.
- Speak slowly and calmly using an easily understandable terminology.
- Facilitate orientation: ward staff and relatives should provide frequent stimuli both to help the patient in reorientation and in responding to his autonomous interactions.
- Use a calm and reassuring attitude when dealing with the patient.
- Reassure the patient during the period of symptom remission.

Table IV. Anticholinergic cognitive burden scale.

Score 1		Score 2	Score 3	
Alprazolam	Furosemid	Amantadine	Amitriptyline	Orphenadrine
Haloperidol	Fluvoxamine	Belladonna Alkaloids	Atropine	Oxybutynin
Atenolol	Hydrocortisone	Carbamazepine	Chlorpheniramine	Paroxetine
Bupropion	Isosorbide	Cyclobenzaprine	Chlorpromazine	Perphenazine
Captopril	Loperamide	Cyproheptadine	Clemastine	Promazine
Chlorthalidone	Metoprolol	Oxcarbazepine	Clomipramine	Prometazine
Quinidine	Morfin	Pethidine	Clozapine	Propantheline
Cimetidine	Nifedipine	Pimozide	Desipramine	Quetiapine
Chlorazepate	Prednisone		Diphenhydramine	Scopolamine
Codeine	Ranitidine		Flavoxate	Thioridazine
Colchicine	Risperidone		Hydroxizine	Tolterodine
Diazepam	Theophyilline		Imipramine	Trifluoperazine
Digoxin	Trazodone		Nortriptyline	Trihexyphenidyl
Dipyridamole	Triamterene		Olanzapine	Trimipramine
Disopyramide	Warfarin			
Fentanyl				

From Boustani et al., 2008, mod. [4].

- Protect the patient and others by removing dangerous objects from the room and securing the area occupied by the patient.
- Place temporal references (clock, calendar) within sight of the patient.
- Invite relatives to bring the patient's personal belongings from home and leave by the bed.

Pharmacological management of delirium

General principles

- Only resort to pharmacological treatment following the failure of non-pharmacological measures.
- Use the lowest possible drug dose.
- Antipsychotics (APs) should be preferred over benzodiazepines (BDZ) unless delirium tremens is suspected: bear in mind that the sole indication for use of BDZ as monotherapy is delirium related to alcohol withdrawal (delirium tremens); in other cases BDZ as monotherapy should be avoided, being associated with a deterioration of state of confusion.
- Bear in mind that APs, particularly those with a higher sedative effect, as well as the combination of several APs, may increase the risk of respiratory depression.
- Monotherapy is the option of choice.
- Response to treatment should be assessed in the short term.
- Reduce and/or suspend prescribed treatment shortly (a few days) after achieving response.

Pharmacological management of delirium in COVID-19 patients

The following pharmacological proposals are based on the guidelines for delirium and on the recent recommendations relating to the management of delirium in COVID-19 patients.

These suggestions may be updated at any time in line with the continuous updating of scientific evidence.

Wherever possible, all guidelines should be adapted to suit each individual case at the time a need for therapeutic intervention is manifested and in the specific context in which this requirement is determined (Tabs. V, VI).

Table V. Effective drugs for use in clinical practice.

Tiapride
• First generation antipsychotic belonging to the class of benzamides • Indications: Severe Chorea in Huntington's Disease, behavioural disorders with agitation and anxiety, acute and chronic alcoholism, behavioural deficits in the elderly • Good sedative effect, of use in cases of hyperkinetic delirium • May be used in patients taking Lopinavir/Ritonavir (Lo/Ri) • Metabolism: renal • Does not interfere with cytochromes implicated in the metabolism of Lo/Ri or commonly used antibiotics • Therapeutic range: 50-300 mg/day • Available formulations: 100 mg tablets and vials containing 100 mg/2 mL • Indicated for both IM (in the absence of clotting disorders) and IV use (in the case of malabsorption): Tiapride should be commenced at a dose of 100 mg IM to be given up to three times daily • Oral administration should be established as soon as possible: reference dose 50+50+100 mg/day at 8am, 4pm and 10pm, respectively • The risk of prolonged QTc interval should be assessed • Risk of arrhythmias, particularly in association with lopinavir, although relatively slight • Caution should be applied when administering to patients with low K+ and Mg+ (e.g. vomiting and diarrhoea) • SpO_2 should be monitored to prevent onset of respiratory depression
Dexmedetomidine
• Selective alpha-2 adrenoceptor agonist • Sedative, anxiolytic and analgesic effect • Indicated for use in sedating adult patients in Intensive Care Units requiring a relatively superficial degree of sedation (patient able to respond to verbal stimuli: score ranging from 0-3 on the Richmond Agitation-Sedation Scale) • Difficult to manage on a ward: indicated for use solely in a hospital setting by staff specialised in the management of patients in Intensive Care • Does not produce respiratory depression • May be used in the presence of renal failure • Caution should be applied when using in the presence of liver failure • Alterations to blood pressure resulting in both hypotension and hypertension and bradycardia are frequently observed (particular attention should be paid to interaction with beta blockers) • Metabolised by means of oxidation: CYP2A6, 2D6 and others are involved • Possibly inductor of CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4: numerous antivirals are eliminated by means of oxidation (3A4 and 2D6); accordingly, dexmedetomidine may reduce the concentration of antivirals if co-administered

Promazine

- Antipsychotic belonging to the class of phenothiazines
- Marked antihistaminic properties and pronounced sedative effect, weak anti-alpha-adrenergic and anticholinergic activity
- Posology ranging from 50 to 300 mg IM/day (evaluate the presence of possible contraindications due to clotting deficiencies)
- Good sedative effect with low cardiovascular risk
- Monitor the risk of respiratory depression
- Metabolised in the liver by CYP1A2, 2C19, 3A4 and 2D6
- Bear in mind that both Lopinavir/Ritonavir and chloroquine/hydroxychloroquine may increase the bioavailability of promazine: implications are fewer if promazine is used only in the short-term (3-4 days), also in view of the short half-life of promazine (6h)
- Absence of significant interactions with antibiotics having a prevalently renal metabolism (tazobactam, piperacillin and doxycycline, the latter having a 50% hepatic metabolism)
- Caution should be applied when administering in association with sulfamethoxazole, clarithromycin, azithromycin and trimethoprim (increased toxicity and/or increased QTc) (association to be avoided preferably)
- Assess the risk of prolongation of QTc
- Low risk of arrhythmias, even in association with Lopinavir
- Low risk of hypotension
- Monitor SpO_2 for risk of onset of respiratory depression (relative risk in the case of short-term administration)
- Monitor K+ and Mg+: particular attention should be paid to patients with low K+ and Mg+ levels

Haloperidol

- Highly potent antipsychotic belonging to the class of butyrophenones
- Half-life: 20-24 hours
- The most widely used drug in the treatment of delirium
- Low risk of respiratory depression: caution should be applied and patients should be monitored
- Lower antihistaminic and anticholinergic effects compared to promazine, but a weaker sedative effect
- Absence of active metabolites
- Does not induce hypotension
- May increase QTc interval: lower risk if administered orally
- Use should be limited in patients treated with chloroquine/hydroxychloroquine and several antibiotics due to the risk of prolonged QTc
- Lopinavir/ritonavir and chloroquine/hydroxychloroquine increase blood plasma levels of haloperidol
- May induce acute dystonia/neurodyslectic syndrome, together with a lowering of the epileptogenic threshold
- Best suited for oral administration (1-15 mg/day: initial dose 0.5-1 mg 3 times daily with a potential increase and adjustment in daily distribution based on symptom evolution)
- Vial formulations should only be used for IM, and not IV, administration due to the increased risk of prolongation of QTc interval and onset of torsades de pointes
- Compared to oral use, IM administration is linked to a higher degree of cardiac toxicity (torsades de pointes)
- 2mg and 5mg immediate release vials are available: initial dosage ranging from 2 to 5 mg which, in the case of non-response or partial response, may be repeated after one hour. Oral administration should be implemented as soon as possible
- Use of a reduced dose should be considered in elderly patients, on the basis of patient's general clinical condition
- Oral administration of a fixed daily dose (rather than "as needed") represents the ideal solution and should be continued up until several days following remission of symptoms and then gradually withdrawn

Aripiprazole

- Second generation antipsychotic
- Long half-life: 75 h
- Immediate release oral or IM formulation (9.75 mg per IM vial)
- Of use in treating hyperkinetic (IM formulation should be used preferably) and hypokinetic delirium
- Low antihistaminic activity
- No anticholinergic activity
- Low risk of arrhythmia
- Low risk of respiratory depression
- Low risk of interactions
- The risk of onset of akathisia should be taken into account
- Metabolised by CYP2D6 and 3A4: blood plasma levels may increase in the presence of CYP2D6 and 3A4 inhibitors (e.g., atazanavir, lopinavir/ritonavir and, to a lesser extent, chloroquine/hydroxychloroquine); when co-administration is required, lower doses of aripiprazole should be used
- For IM administration, in the absence of CYP2D6 and 3A4 inhibitors, the maximum dose corresponds to 3 vials/day at intervals of no less than 2 hours

▶

Quetiapine

- Second generation antipsychotic
- Half-life: 6-12 hours
- Only available in oral tablet form
- The risk of prolonged QTc interval should be considered
- In Europe, association with lopinavir/ritonavir is contraindicated due to the potent inhibitory effects exerted by the drug on CYP3A4, which metabolizes quetiapine, resulting in an increase of quetiapine levels; a decrease of quetiapine to 1/6th of the original dose is recommended in the US
- Latency of action potential exceeding 1 hour
- The risk of hypotension at doses exceeding 100 mg should be taken into account, particularly in elderly patients
- Standard dosage ranges from 25-200 mg/day in one or two daily administrations
- Olanzapine
- Second generation antipsychotic
- Half-life: 33 hours
- Oral or IM formulation
- Association with lopinavir/ritonavir determines a reduction in blood plasma levels of olanzapine, which may result in the need for an increased dose of the antipsychotic in the case of co-administration
- Elevated anticholinergic action should be taken into account
- Displays a good sedative action and rapid onset of action
- IM formulation should not be associated with BDZ
- Standard dosage ranges from 2.5 to 10 mg/day in one or two daily administrations

Risperidone

- Second generation antipsychotic
- Half-life: 24 hours
- The risk of EPS should be considered
- The risk of prolongation of the QTc interval should be considered, particularly in association with Atazanavir, Lopinavir/Ritonavir, Chloroquine and Hydroxychloroquine
- Association with atazanavir, lopinavir/ritonavir, chloroquine and hydroxychloroquine determines an increase in blood plasma levels of risperidone, resulting in a potential need to reduce the dose of the antipsychotic in the case of co-administration
- Standard dosage ranges from 1-4 mg/day in one or two daily administrations

Recommendations for the use of benzodiazepines

- They may induce respiratory depression due to a central (depression of bulbar respiratory centres) or peripheral action (myorelaxant action)
- Use should be avoided in patients at high risk of impaired respiratory performance
- Caution should be applied in patients treated with BDZ with a long half-life, even in the absence of dyspnoea, as the latter may develop rapidly
- If required, use molecules with a short half-life
- The association of midazolam and diazepam with atazanavir and lopinavir/ritonavir increases benzodiazepine levels, thus recommending use of a reduced dosage in relation to the risk of respiratory depression

IM: intramuscolar injection.

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10 Liverpool drugs interaction group. Interactions with

Table VI. Drug interactions between psychotropic drugs commonly used in delirium and drugs used in COVID-19 patients.

	ATA	LPV/RIT	RDV	FAVI	CLO/ICLO	NITAZ	RBV	TCZ	ANTIBIOTICS
Haloperidol	↑HAL ♥	↑ HAL ♥	↔	↔	↑ HAL ♥	↔	↔	↔	♥ with SULF, TRIM, AZI and CLR
Promazine	♥	↑ PRO	↔	↔	↑ PRO ♥	↔	↔	↔	♥ with SULF, TRIM, AZI and CLR ↑toxicity of SULF
Aripiprazole	↑ ARI	↑ ARI	↔	↔	↔	↔	↔	↔	↑ ARI with CLR
Olanzapine	↔	↓ OLA	↔	↔	♥	↔	↔	↔	♥ with CLR
Quetiapine	↑ QTP ♥	↑ QTP ♥	↔	↔	♥	↔	↔	↔	♥ with AZI and CLR ↑ QUE with CLR
Risperidone	↑ RIS ♥	↑ RIS ♥	↔	↔	↑ RIS ♥	↔	↔	↔	♥ with SULF, TRIM, AZI and CLR
Lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔
Diazepam	↑ DIA	↑ DIA	↔	↔	↔	↔	↔	↔	↔
Midazolam parenteral	↑ MID	↑ MID	↔	↔	↔	↔	↔	↔	↔

ATV: atazanavir; LPV/RIT: lopinavir/litonavir; RDV: remdesivir; FAVI: favipiravir; CLQ/HCLQ: chloroquine/hydroxycloroquine; RBV: ribavirin; TCZ: tocilizumab; ALO: haloperidol; PRO: promazine; ARI: aripiprazole; OLA: olanzapine; QTP: quetiapine; RIS: risperidone; DIA: diazepam; MID: midazolam; SULF: sulfamethoxazole; TRIM: trimethoprim; AZI: azithromycin; CLR: clarithromycin; ↑: increased exposure of the co-medication; ↓: decreased exposure of the co-medication; ↔: no significant interactions; ♥ : increased risk of QTc prolongation (ECG monitoring is recommended).

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