



## **Therapeutic options for agitation in the intensive care unit**

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# Therapeutic options for agitation in the intensive care unit

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## ABSTRACT

Agitation is common in the intensive care unit (ICU). There are numerous contributing factors, including pain, underlying disease, withdrawal syndrome, delirium and some medication. Agitation can compromise patient safety through accidental removal of tubes and catheters, prolong the duration of stay in the ICU, and may be related to various complications. This review aims to analyse evidence-based medical literature to improve management of agitation and to consider pharmacological strategies. The non-pharmacological approach is considered to reduce the risk of agitation. Pharmacological treatment of agitated patients is detailed and is based on a judicious choice of neuroleptics, benzodiazepines and  $\alpha 2$  agonists, and on whether a withdrawal syndrome is identified. Specific management of agitation in elderly patients, brain-injured patients and patients with sleep deprivation are also discussed. This review proposes a practical approach for managing agitation in the ICU.

## Keywords:

Psychomotor agitation  
Delirium  
Pain  
Anxiety  
Intensive care unit  
Pharmacology

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## 1. Introduction

Although agitation is a common event in the intensive care unit (ICU), limited data exist about its management [1–3]. An agitated patient is exposed to the life-threatening risk of accidental removal of devices, the continued use of sedatives, and prolonged duration of mechanical ventilation and ICU length of stay, as well as related complications, in particular healthcare-related infections, ICU-acquired weakness and potentially impaired long-term quality of life. The 2013 and 2018 clinical practice guidelines of the Society of Critical Care Medicine (SCCM) for the management of pain, agitation and delirium in adult patients in the ICU suggested using local protocols for agitation management [4,5]. In routine clinical practice, the choice of medication used to treat agitation is often left at the discretion of the physician in charge. Although several antipsychotic drugs are available, their properties are not always fully understood and/or appropriate for ICU patients. We therefore decided to perform a review of the literature about the management of agitation in the ICU, to identify options for preventing agitation and treating agitated patients.

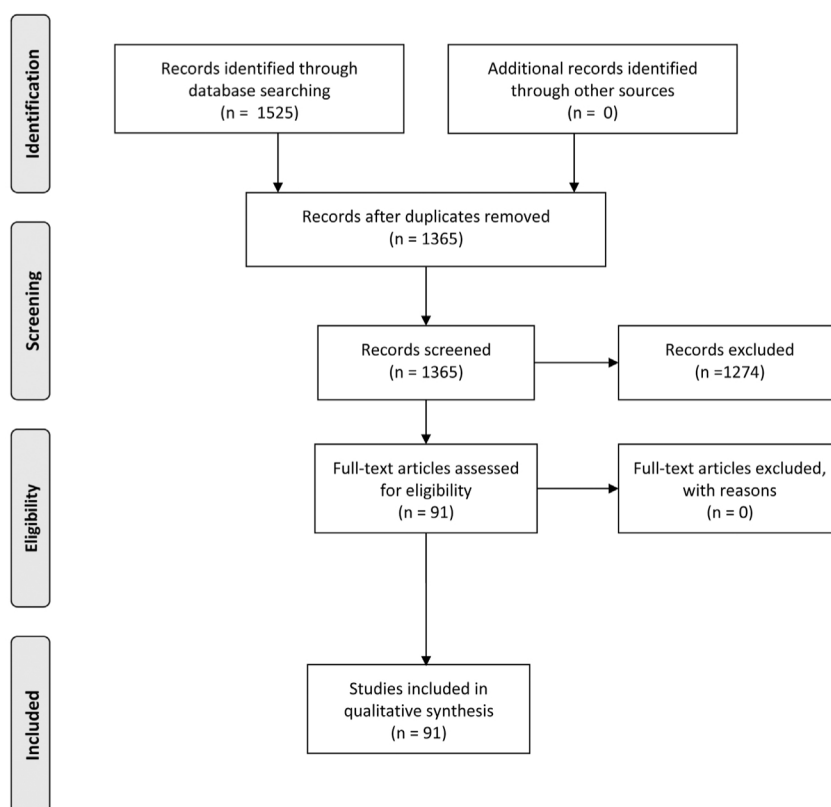
We conducted an exhaustive review of indexed studies on PubMed based on the MeSH terms: “psychomotor agitation”, “intensive care unit”, “delirium”, “critical care”, “aged”, “brain injuries”, “antipsychotic agents”, and on drugs used in the ICU: “diazepam”, “clorazepate”, “cyamemazine”, “tiapride”, “haloperidol”, “loxapine”, “levomepromazine” and “dexmedetomidine”. The Boolean operators (AND/OR) were also used to combine search

terms. Due to the limited number of articles written in French or English, the time period for search analysis was extended from 1981 to 2019. The database search strategies yielded 1525 records, and 161 duplicates were identified and excluded. The authors excluded 1274 studies after screening the titles and abstracts. The full texts of the remaining 91 studies were retrieved for further assessment (Fig. 1). They were all selected, including guidelines, clinical studies, pharmacological studies and reviews.

## 2. Epidemiology and risk factors

Agitation can be defined as an important elevation of motor and psychological activity and may be associated with disorganised thinking [6]. Agitation can be classified as a score equal to or higher than + 2 using the Richmond Agitation–Sedation Scale (RASS), whether the patient is mechanically ventilated or not [2,7]. However, the reported incidence of agitation in the ICU is highly variable, ranging between 12% and 70% [1–3,8]. This is probably due to the heterogeneity in qualifying agitation, as a wide range of behaviours may constitute aggression, including verbal abuse, rage, sudden mood change, and lack of cooperation.

Risk factors for agitation have been identified, such as preadmission use of psychotropic drugs and/or chronic alcohol intoxication, hyperthermia, sepsis, dysnatremia, and use of sedative drugs during the ICU stay [9]. Other suggested risk factors include delirium, moderate-to-severe pain, mechanical ventilation and smoking habits [3]. Predictors of agitation on admission to the ICU



were the use of illicit substances, the use of physical restraint during the ICU stay, and respiratory and central nervous system components on the Sequential Organ Failure Assessment [10].

### 3. Causes of agitation

#### 3.1. Medical causes

Sepsis is an important source of agitation even in the absence of symptoms of delirium. Sepsis must be suspected in agitated patients with hypo/hyperthermia, arterial hypotension, tachycardia and arrhythmia [8]. Metabolic disturbances (hypo/hypernatremia, hypo/hyperglycaemia), respiratory dysfunction (hypoxic hypoxia, hypercapnia), hepatic encephalopathy, stroke and non-convulsive seizures can also be associated with agitation [8,11]. Urinary retention and faecal impaction are common causes of agitation, particularly in elderly patients.

#### 3.2. Pain

Pain is a classic cause of agitation. Nociception should be regularly assessed in communicating and non-communicating patients using appropriate instruments, i.e., self-report scales and behavioural assessment tools [4].

#### 3.3. Delirium

Delirium is an acute rapidly developing brain dysfunction including disturbed cerebral microcirculation and brain inflammation. A delirious patient has memory fluctuations, attention deficiency and spatiotemporal disorientation. The clinical picture of delirium is more often hypoactive than hyperactive or a combination of the two [12,13]. In the hyperactive form, the patient is agitated, even combative, with or without hallucinations, and this form is associated with a prolonged duration of hospital stay and persistent cognitive dysfunction [4]. Assessment of delirium is recommended by using validated tools such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) [4,5]. Many factors predispose patients to the development of delirium: sepsis, hypoxemia, sedation exposure and metabolic dysfunction [14], as well as increased age, multiple co-morbidities, preadmission dementia, admission for a surgical emergency or severe trauma, increased Acute Physiology and Chronic Health Evaluation (APACHE) score and sleep deprivation [4,15–17].

#### 3.4. Withdrawal syndromes

Withdrawal syndromes are possible in patients who have used hypnotics, opioids or psychoactive drugs, as well as in patients who smoke and consume alcohol in excess. Clinical signs include tachycardia, hypertension, fever, nausea, vomiting, diarrhoea, sweating, tremors, headache, pupil dilation, lacrimation, rhinorrhoea, paraesthesia, myoclonus and/or myalgia. The patient experiencing a withdrawal syndrome shows agitation, anxiety, irritability and restlessness, and may have increased sensitivity to pain, light and sound. Pre-existing psychiatric disorders, prolonged use (> 7 days) of high-dose opioids (the equivalent of fentanyl > 200 mcg/day) and/or benzodiazepines (the equivalent of midazolam > 4 mg/h) are risk factors for the development of a withdrawal syndrome [18].

#### 3.5. Drug-induced agitation

Unrelated to withdrawal syndromes, some drugs can induce agitation (Table 1). It should be noted that many of these drugs

**Table 1**

Drugs that may cause agitation in the intensive care unit or other settings.

Benzodiazepines
Opioids
Anticholinergic drugs (see Table 3)
Nefopam
Antidepressant drugs (serotonin syndrome):
– Selective serotonin reuptake inhibitors
– Tricyclic antidepressants
– Monoamine oxidase inhibitors
– Lithium
Ketamine
Anticonvulsive drugs:
– Levetiracetam
– Lamotrigine
– Valproic acid
– Pregabalin/gabapentin
Anti-infective drugs:
– $\beta$ -lactam antibiotics and carbapenems
– Fluoroquinolones
– Linezolid
Corticosteroids
Angiotensin-converting enzyme inhibitors
Digoxin
Amiodarone
Proton-pump inhibitor

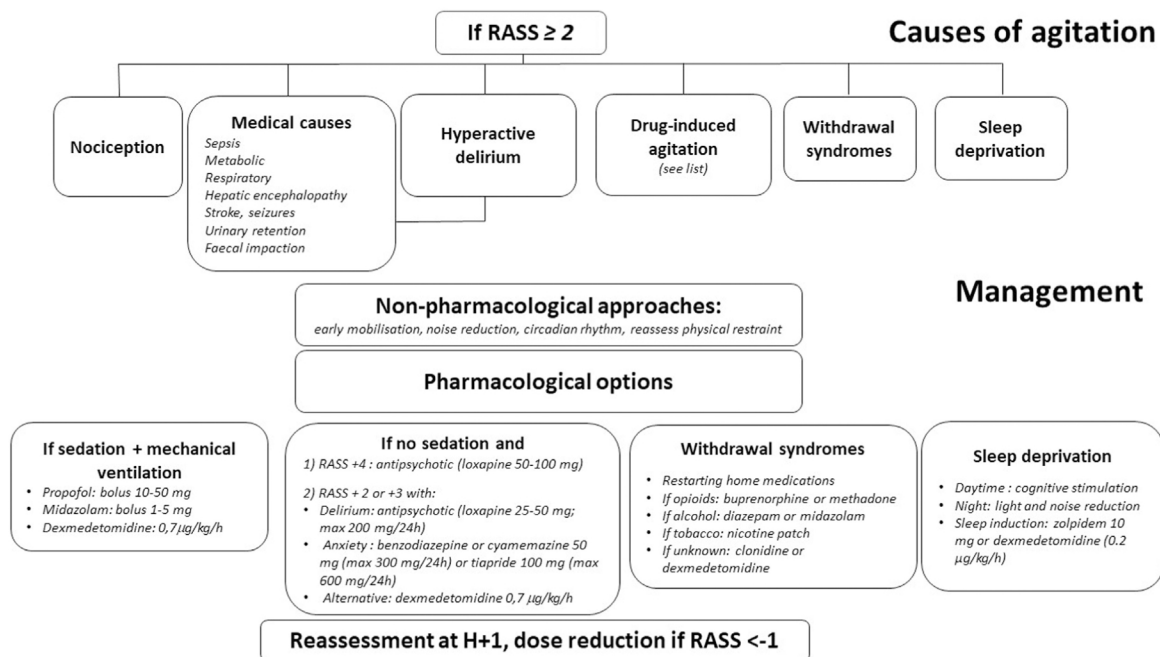
(ketamine, nefopam, fluoroquinolones and anticonvulsive drugs) are commonly used in ICU.

### 4. Consequences of agitation

Agitation can be responsible for accidental or self-removal of catheters, tubes, drains or medical devices that occurs in 20–25% of cases [8,11]. These unexpected events expose the patient to life-threatening risks and/or to a prolonged duration of both mechanical ventilation and hospital stay [8,11]. The economic impact of unplanned removal of medical device was estimated to be around \$250,000 annually in a 42-bed unit [19]. Agitation is also associated with more frequent related infections and surgical re-interventions [9]. If sepsis can explain agitation, agitation per se can favour the development of infection (self-removal of catheters, tubes) and surgical re-intervention (self-removal of drains, evisceration). Surprisingly, the long-term consequences of agitation have not been explored so far.

### 5. Prevention of agitation

Non-pharmacological approaches can be considered to anticipate potential causes of agitation and reduce delirium through optimisation of the environment and improvement of patient comfort [5]. An ICU measure termed the ABCDE bundle, for awakening and breathing coordination, delirium monitoring and exercise/early mobility, was created to fill the gap between current practices and the ideal process [20]. With a protocol aiming to sequentially reduce sedation, perform daily spontaneous awakening and breathing trials, and encourage exercise, a significant reduction in the duration of mechanical ventilation, delirium incidence and mortality was observed [21,22]. Noise reduction at night was associated with a reduced consumption of sedative and anxiolytic drugs [23]. Early passive and active mobilisation combined with spontaneous awakening and breathing trials reduced the duration of mechanical ventilation as well as delirium [24–26]. Mobilisation is possible even for patients under mechanical ventilation or extracorporeal circulation [25,27]. Therefore, the 2013 and 2018 guidelines proposed various measures to enhance cognitive stimulation, improve vision and hearing, perform active



**Fig. 2.** A practical algorithm proposed in managing agitation in the intensive care unit.

and passive mobilisation in dedicated periods, and respect circadian rhythms [4,5].

The use of physical restraint is common in the ICU to prevent agitated patients from self-extubation and accidental removal of drains and tubes. In a French survey, physical restraint was reported to be used for > 50% of the duration of mechanical ventilation [28]. Factors associated with physical restraint were mechanical ventilation, sedation, a large ICU and a high patient/nurse ratio [29]. Although the presence of physical restraint was shown to reduce cases of adverse events [30], it was associated with a higher risk for delirium [31]. Overall, the use of physical restraint is mainly driven by local habits and carried out by nurses without specific medical orders. Thus, the use of physical restraint when not specifically recommended must be limited, since it is a source of agitation and prevents actions that can guard against the risks associated with agitation [10,32]. These findings underscore the need for the development of measures to prevent agitation.

It should be emphasised that no drug preventing agitation has been identified. In particular, the preemptive use of antipsychotic agents or dexmedetomidine has consistently failed to abolish or diminish the incidence of agitation in ICU patients [33,34]. The best strategy to prevent agitation due to hyperactive delirium or withdrawal syndromes is probably to refrain from indicating the use of sustained sedation. Accordingly, immediate interruption of sedation after unplanned surgeries for peritonitis with septic shock was associated with a lower incidence and duration of delirium compared to 1.5 days of moderate sedation [35]. In addition, the duration of sedation-associated delirium was a good predictor of cognitive function 12 months later [14].

## 6. Treatment of agitation

Treating agitated patient depends on a judicious choice of drugs once a treatable cause of agitation has been eliminated, i.e., sepsis, hypoxic hypoxia, metabolic disturbances, pain and drug-induced agitation. We arbitrarily distinguished between the treatment of withdrawal syndromes and the treatment of agitation symptoms. A practical algorithm in managing agitation is proposed in Fig. 2.

### 6.1. Withdrawal syndromes

Various strategies exist to prevent and treat drug withdrawal, although few data exist. The 2013 guidelines suggested tapering drugs over several days to reduce the risk of drug withdrawal [5]. Restarting home medications may be beneficial. For example, early initiation of home neuropsychiatric medications within the first 5 days of ICU admission was associated with a lighter sedation level and less delirium [36]. High-dose clonidine (1.8–2.5 mg/24 h) was effective in normalising haemodynamic and respiratory changes induced by withdrawal syndromes in 25 ICU patients [37]. Buprenorphine and methadone are two options used to treat opioid withdrawal [38]. The introduction of enteral methadone during fentanyl weaning was associated with a reduced weaning time from mechanical ventilation [39]. Buprenorphine was successfully tested in a cohort of brain-injured patients during weaning from sedation and analgesia [40]. In that study, patients received a 48 h-infusion of clonazepam (3 mg/kg/24 h) to prevent benzodiazepine withdrawal, followed by cessation of sedatives and a possible introduction of buprenorphine (0.01 mg/kg/24 h) in cases of opioid withdrawal. Alcohol withdrawal can be treated with benzodiazepines (diazepam, midazolam, lorazepam) [41]. In patients who smoked more than 10 cigarettes a day before ICU admission, nicotine replacement therapy did not affect the number of serious adverse events or delirium-free days [42].

### 6.2. Management of agitation symptoms

The pharmacological treatment of agitation symptoms preferably requires a choice of short-acting drugs, so that neurological assessment can occur (Table 2).

#### 6.2.1. Neuroleptics

It should be noted that, except for tiapride, the intramuscular route remains the authorised route for administration of neuroleptics, which is an issue in critically ill patients. Although off-label, the intravenous route is the route of choice in the ICU for neuroleptics as it enables delivery of limited doses within a limited time.



**Table 2**

Pharmacological profile of drugs for the management of agitation symptoms in the intensive care unit.

Therapeutic class	Drug	Pharmacology	Route	Onset (IV)	Elimination half-life	Side effects common to the therapeutic class	Precaution/Contraindication
Neuroleptics	Loxapine	Antipsychotic	PO/IM/(IV)/inhaled	30 min	8 h	Heart rate disturbance, prolonged QT, anticholinergic and extrapyramidal symptoms, hypotension, neuroleptic malignant syndrome, liver function test abnormalities	Heart failure, prolonged QT Agranulocytosis
	Tiapride	Antipsychotic/sedative	PO/IM/IV	15 min	3 h		
	Haloperidol	Antipsychotic/sedative	PO/IM/(IV)	15 min	21 h		
	Cyamemazine	Antipsychotic/sedative	PO/IM/(IV)	15 min	10 h		
$\alpha 2$ agonists	Risperidone	Antipsychotic	PO	4 h (PO)	24 h	Heart rate and blood pressure disturbances	Kidney failure Severe heart/liver failure Liver failure
	Clonidine	Sedative/analgesia	IV/PO	10 min	12–16 h		
	Dexmedetomidine		IV	15 min	2 h		
Benzodiazepines	Clorazepate	Anxiolytic/sedative	IV/IM/PO	30 min	30–150 h	Respiratory depression, hypotension, addiction	
	Diazepam		IV/PO	5 min	32–47 h		

PO: per os; IM: intramuscular; IV: intravenous; (IV): off-label intravenous route.

- Haloperidol is a butyrophenone antipsychotic with a strong sedative activity. This is the most studied drug used to treat agitation and delirium in the ICU. Despite its short onset of action when given intravenously, haloperidol has been associated with prolonged QT interval and a risk of *torsade de pointes* [43]. The 2018 guidelines recommended against the routine use of haloperidol to treat delirium [4].
- Cyamemazine is a typical antipsychotic drug of the phenothiazine class with marked sedative and anxiolytic effects. Cyamemazine can be considered an appropriate agent to treat agitation given its short onset of action, its intravenous or oral administration, and its availability in a wide range of doses (50–300 mg/24 h). Cyamemazine has been studied in the treatment of alcohol or benzodiazepine withdrawal [44,45]. Surprisingly, its use remains unexplored in an ICU setting.
- Loxapine is a typical antipsychotic drug used to treat agitated patients in the context of schizophrenia and bipolar disorder. Inhaled loxapine has been recently proposed in psychiatric acute care settings [46]. Due to its short onset of action, short half-life elimination and intravenous availability (50–200 mg/24 h), loxapine can be considered for agitated patients in the ICU. Loxapine has been tested in the treatment of agitated patients in the ICU who were candidates for weaning from mechanical ventilation: unfortunately, this trial was prematurely terminated because of slow patient accrual [47].
- Tiapride is a selective dopamine antagonist used to treat alcohol withdrawal, negative symptoms of psychosis and agitation in elderly patients [48]. This neuroleptic drug offers advantages over haloperidol in reducing drug-induced extrapyramidal symptoms. However, no study testing tiapride in agitated patients in the ICU has been conducted yet. Due to pharmacological properties allowing regular neurological reassessment and its intravenous administration route, tiapride (50–200 mg/24 h) can be considered for the treatment of moderate agitation with an anxious or delirious component.
- Levomepromazine is a phenothiazine neuroleptic drug. Because of a prolonged half-life elimination (15–80 h), a marked sedative effect and specific routes for administration (i.e., oral or intramuscular), levomepromazine is not particularly appropriate in the ICU setting. This drug may be considered in cases of severe episodes of agitation (5 mg every 5 min until a 50 mg maximum is reached) [2,49].
- Atypical neuroleptic drugs such as risperidone, olanzapine and ziprasidone are serotonin and dopamine antagonists. They are more effective at treating positive and negative symptoms of psychosis and result in fewer extrapyramidal effects than typical neuroleptics. Their half-life elimination ranges between 7 h (ziprasidone) to 30 h (olanzapine). A slow onset of action and an exclusive oral administration make their use difficult in the ICU.

In one study, a QT prolongation occurred in 31% of patients receiving these drugs in the ICU [50]. Two other studies reported no reduction in the incidence of delirium in patients receiving these drugs in the ICU [51,52].

#### 6.2.2. Benzodiazepines

Although the 2013 and 2018 guidelines suggest that benzodiazepines should not be used for sedation in the ICU because their use can delay the time to liberation from mechanical ventilation and result in an increased risk of delirium [4,5], these drugs could be considered for the treatment of agitation in cases of alcohol withdrawal syndrome, prolonged benzodiazepine administration or severe anxiety.

- Clorazepate is a 1–4 benzodiazepine with anxiolytic, anticonvulsant and muscle relaxant actions. Its prolonged half-life elimination along with mild sedative effects was advantageous in treating brain-injured patients with benzodiazepine withdrawal syndrome [40].
- Diazepam is a drug of choice to treat alcohol withdrawal syndrome. Although successfully tested to provide goal-directed sedation in the ICU at 40 mg/24 h [53], diazepam has prolonged half-life elimination and marked sedative effects, making its use inappropriate in the treatment of agitation episodes.

#### 6.2.3. $\alpha 2$ adrenergic receptor agonists

- Dexmedetomidine is a highly selective agonist with a rapid onset of action during a continuous infusion (15–30 min) and a half-life elimination of 2 h. In the 2018 guidelines, dexmedetomidine and propofol were recommended as first-line sedatives for critically ill patients [4]. Dexmedetomidine facilitated tracheal extubation in patients where agitation precluded liberation from mechanical ventilation [54]. The drug may improve sleep quality in elderly non-intubated patients [55]. Dexmedetomidine may be used for alcohol and drug withdrawal in association with benzodiazepines [56–60]. However, there is little evidence regarding the use of dexmedetomidine to treat severe agitation. Dexmedetomidine exposes the patient to the risks of bradycardia and arterial hypotension, as well as hypertension in cases where patients have received excessive doses. Dexmedetomidine is contraindicated in patients with severe heart or liver failure.
- Clonidine is another agonist of central  $\alpha 2$  adrenergic receptors and has a longer duration of action than dexmedetomidine.

**Table 3**  
Drugs with anticholinergic effects [70].

Drug		
Alprazolam	Colchicine	Oxepine
Amitriptyline	Doxylamine	Oxybutynin
Atropine	Furosemide	Paroxetine
Baclofen	Hydroxyzine	Quetiapine
Chlorphenamine	Imipramine	Scopolamine
Clomipramine	Ipratropium	Solifenacin
Clorazepate	Nortriptyline	Trospium
Clozapine	Olanzapine	

Clonidine was successfully used to treat withdrawal syndromes in ICU patients [37]. However, few data exist about its use in treating agitation symptoms in adults. The dose of clonidine must be adjusted according to the patient's renal function.

### 6.3. Specific populations

#### 6.3.1. Elderly patients

It is difficult sometimes to distinguish between agitated delirium and dementia in elderly critically ill patients (> 75 years) due to possible pre-existing alterations of cognitive function. No data exists concerning the specific aspect of agitation in this population. After major surgery, the incidence of delirium in this population was found to be 11–51% [61]. A wider range of incidence (19–82%) was reported in elderly patients admitted to the ICU [62]. Delirium is related to a dysfunction of cholinergic neurotransmission, which is aggravated by the frequent occurrence of hepatic and renal dysfunction in this population; this in turn may alter drug pharmacokinetics [63–67]. Long-term consequences of hypo- and hyperactive delirium in elderly patients are cognitive alteration, loss of autonomy and decreased likelihood of returning home [68]. The development of early complications in the ICU is strongly associated with delirium [68,69].

Treatment of agitation in this fragile population should start with the withdrawal of any drug with anticholinergic properties (Table 3) [70]. Typical antipsychotic drugs inhibit central dopaminergic neurotransmission then result in extrapyramidal symptoms and orthostatic hypotension. Atypical antipsychotic drugs have novel receptor binding profiles and reduced extrapyramidal symptoms [46]. However, the mortality risk may be raised 1.7 times with the use of these drugs in elderly patients [71]. Atypical antipsychotic drugs are associated with an increased risk of pneumonia, probably related to their anticholinergic action favouring swallowing disorders and aspiration pneumonia [72]. In addition, the American Geriatric Society has suggested avoiding benzodiazepines for elderly people due to the risk of cognitive impairment, agitation, falls and fractures [73]. Low-dose dexmedetomidine (0.1 mcg/kg/h for 24 h) decreased the incidence of delirium within 7 days after non-cardiac surgery in patients of > 65 years with no major side effects [61]. Delirium was also reduced in non-surgical elderly patients with standardised management of dehydration, sleep deprivation, immobility, and visual, hearing and cognitive impairments [74].

#### 6.3.2. Brain-injured patients

Agitation is reported in 11–70% of patients during their recovery from brain injury [75–78]. The development of agitation in brain-injured patients may reflect hidden neurological complications, e.g., cerebrospinal fluid infection, extended or new intracerebral lesions, seizures or systemic complications. The severity and/or duration of agitation were associated with greater cognitive

dysfunction, a longer ICU stay and a poorer outcome after traumatic brain injury (TBI) [79,80].

Treating agitation symptoms is challenging, as the above-cited drugs can interfere with neurological assessment. On the other hand, agitation in this population may require the use of physical restraint, and delays recovery and rehabilitation [77,79,81]. In patients with TBIs, beta-blockers were proposed for the treatment of hyperadrenergic responses and anticonvulsants for the control of behavioural disorders [82]. Minimising the use of benzodiazepines and typical antipsychotic agents was also suggested, as their use can result in confusion, amnesic effects and impairment of motor recovery [82]. Dexmedetomidine was first tested in six brain-injured patients with no major problems [79]. In a retrospective cohort of 85 TBI patients, dexmedetomidine (0.5 mcg/kg/h) was initiated at 63 h after hospital admission. The drug was associated with reduced requirements for sedatives and opioids along with no significant changes in haemodynamic parameters [82].

#### 6.3.3. Patients with sleep deprivation

Poor sleep quality and/or insomnia is one of the five most stressful symptoms reported by patients in the ICU [83]. This is consistent with polysomnography studies highlighting frequent sleep disruption and sleep deprivation in the ICU [16]. Sleep disturbances, i.e., reduction in restful sleep, circadian sleep cycle disruption and increased daytime sleep, are closely linked with delirium and agitation [4,16,84], as well as with difficult liberation from mechanical ventilation [85]. Ventilator settings should be therefore adjusted at night to avoid both alkalosis and muscular fatigue/dyspnoea, which may cause delirium, agitation and sleep interference [85]. Adjustment of light, noise and alarms, and/or use of earplugs and eye masks can provide a calm environment at night, and have been shown to be effective in reducing the risk of delirium and poor quality of sleep in the ICU setting [86,87]. Before administering sedatives or hypnotics for sleep, clinicians should address delirium, dyspnoea, anxiety, pain and other stressful symptoms, medications (e.g., steroids) or ventilator settings that can interfere with restful sleep [88]. However, sedatives may be considered in patients who are unable to fall asleep, in the hope of reducing the risk of agitation and/or delirium. Indeed, healthy volunteers who were kept awake for more than 48 h developed visual and hearing distortions prior to having delirium [89]. There are cases where observers feel that a patient is “somewhere else”, with delusions, despite the patient being classed as being delirium-free. In such cases, dexmedetomidine may be of interest to preserve sleep and/or to reduce delirium and agitation when administered at night [90,91].

## 7. Conclusion

There are several pharmacological and non-pharmacological therapeutic options for agitated patients in the ICU. Identifying the exact cause of agitation is a prerequisite prior to considering the use of medication.

### Author contributions

Study design/planning: SA, CC and JFP  
Study conduct: SA, FB, CC and JFP  
Data analysis: SA, FB, GC and CC  
Writing the paper: SA, FB, GC and JFP  
Revising the paper: all authors

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## Declaration of interest

None.

## Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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