Therapeutic options for agitation in the intensive care unit

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A B S T R A C T

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 α2 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.

Contents

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1. Introduction

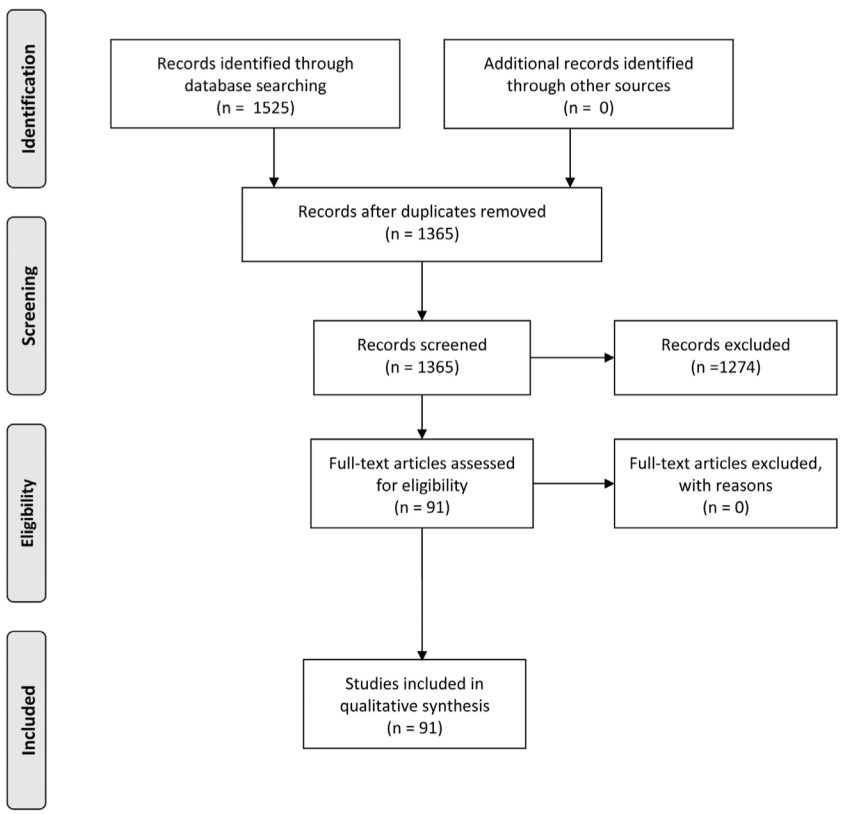
Although agitation is a common event in the intensive care unit (ICU), limited data exist about its management [1–3]. An agitated patient is exposed to the life-threatening risk of accidental removal of devices, the continued use of sedatives, and prolonged duration of mechanical ventilation and ICU 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 (ketamine, nefopam, fluoroquinolones and anticonvulsive drugs) are commonly used in ICU.

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:
– β-lactam antibiotics and carbapenems
– Fluoroquinolones
– Linezolid
Corticosteroids
Angiotensin-converting enzyme inhibitors
Digoxin
Amiodarone
Proton-pump inhibitor

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

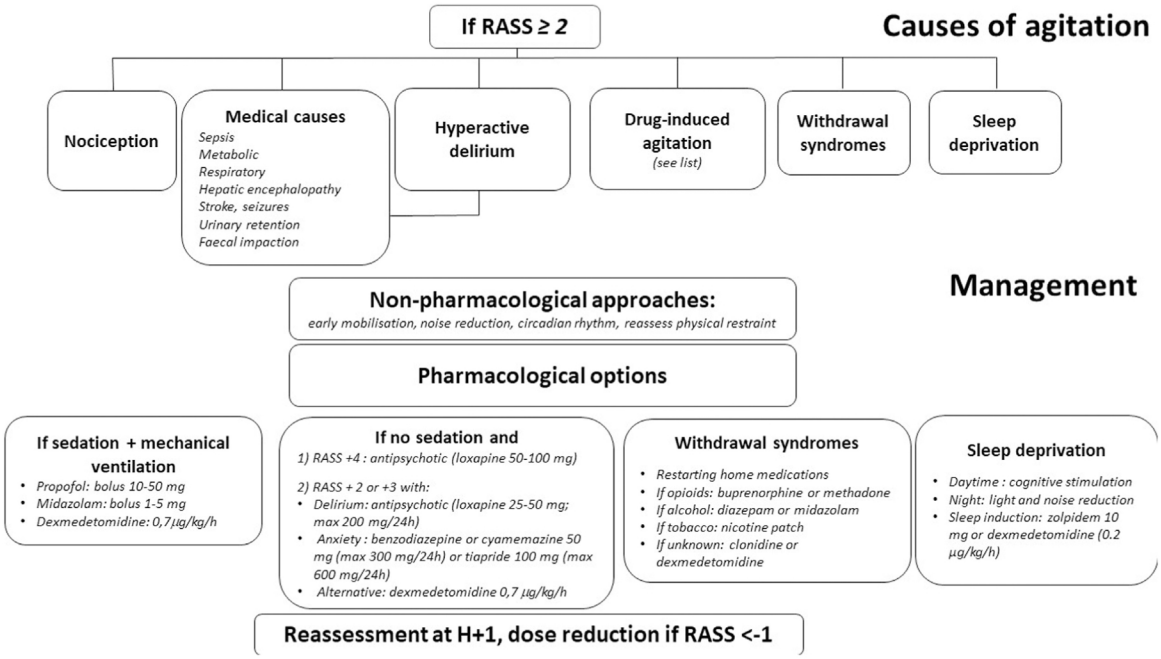


Fig. 2. A practical algorithm proposed in managing agitation in the intensive care unit.

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 clorazepate (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	
	Tiapride	Antipsychotic/sedative	PO/IM/IV	15 min	3 h		Heart failure, prolonged QT Agranulocytosis
	Haloperidol	Antipsychotic/sedative	PO/IM/(IV)	15 min	21 h		
	Cyamemazine	Antipsychotic/sedative	PO/IM/(IV)	15 min	10 h		
	Risperidone	Antipsychotic	PO	4 h (PO)	24 h		
α2 agonists	Clonidine	Sedative/analgesia	IV/PO	10 min	12–16 h	Heart rate and blood pressure disturbances	Kidney failure Severe heart/liver failure
	Dexmedetomidine		IV	15 min	2 h		
Benzodiazepines	Clorazepate	Anxiolytic/sedative	IV/IM/PO	30 min	30–150 h	Respiratory depression, hypotension, addiction	Liver failure
	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. *α2 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 α2 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, amnestic 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.

References

[1] Fraser GL, Prato BS, Riker RR, Berthiaume D, Wilkins ML. Frequency, severity, and treatment of agitation in young versus elderly patients in the ICU. Pharmacotherapy 2000;20:75–82. http://dx.doi.org/10.1592/phco.20.1.75.34663.

[2] Chanques G, Jaber S, Barbotte E, Violet S, Sebbane M, Perrigault P-F, et al. Impact of systematic evaluation of pain and agitation in an intensive care unit. Crit Care Med 2006;34. http://dx.doi.org/10.1097/01.CCM.0000218416.62457.56. 1691–9.

[3] de Almeida TML, de Azevedo LCP, Nosé PMG, de Freitas FGR, Machado FR. Risk factors for agitation in critically ill patients. Rev Bras Ter Intensiva 2016;28. http://dx.doi.org/10.5935/0103-507X.20160074. 413–9.

[4] Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, Agitation/Sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018;46. http://dx.doi.org/10.1097/CCM.0000000000003299. e825–73.

[5] Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263–306. http://dx.doi.org/10.1097/CCM.0b013e3182783b72.

[6] Siegel MD. Management of agitation in the intensive care unit. Clin Chest Med 2003;24. 713–25.

[7] Ely EW, Truman B, Shintani A, Thomason JWW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 2003;289. http://dx.doi.org/10.1001/jama.289.22.2983. 2983–91.

[8] Barr J, Pandharipande PP. The pain, agitation, and delirium care bundle: synergistic benefits of implementing the 2013 Pain, Agitation, and Delirium Guidelines in an integrated and interdisciplinary fashion. Crit Care Med 2013;41:S99–115. http://dx.doi.org/10.1097/CCM.0b013e3182a16ff0.

[9] Jaber S, Chanques G, Altairac C, Sebbane M, Vergne C, Perrigault P-F, et al. A prospective study of agitation in a medical-surgical ICU: incidence, risk factors, and outcomes. Chest 2005;128. http://dx.doi.org/10.1378/chest.128.4.2749. 2749–57.

[10] Burk RS, Grap MJ, Munro CL, Schubert CM, Sessler CN. Predictors of agitation in critically ill adults. Am J Crit Care 2014;23. http://dx.doi.org/10.4037/ajcc2014714. 414–23.

[11] Woods JC, Mion LC, Connor JT, Viray F, Jahan L, Huber C, et al. Severe agitation among ventilated medical intensive care unit patients: frequency, characteristics and outcomes. Intensive Care Med 2004;30. http://dx.doi.org/10.1007/s00134-004-2193-9. 1066–72.

[12] Liptzin B, Levkoff SE. An empirical study of delirium subtypes. Br J Psychiatry 1992;161. http://dx.doi.org/10.1192/bjp.161.6.843. 843–5.

[13] Brummel NE, Girard TD. Preventing delirium in the intensive care unit. Crit Care Clin 2013;29:51–65. http://dx.doi.org/10.1016/j.ccc.2012.10.007.

[14] Girard TD, Thompson JL, Pandharipande PP, Brummel NE, Jackson JC, Patel MB, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. Lancet Respir Med 2018;6. http://dx.doi.org/10.1016/S2213-2600(18)30062-6. 213–22.

[15] Mostaghimi L, Obermeyer WH, Ballamudi B, Martinez-Gonzalez D, Benca RM. Effects of sleep deprivation on wound healing. J Sleep Res. https://doi.org/10.1111/j.1365-2869.2005.00455.x.

[16] Figueroa-Ramos MI, Arroyo-Novoa CM, Lee KA, Padilla G, Puntillo KA. Sleep and delirium in ICU patients: a review of mechanisms and manifestations. Intensive Care Med 2009;35. http://dx.doi.org/10.1007/s00134-009-1397-4. 781–95.

[17] Patel J, Baldwin J, Bunting P, Laha S. The effect of a multicomponent multidisciplinary bundle of interventions on sleep and delirium in medical and surgical intensive care patients. Anaesthesia 2014;69. http://dx.doi.org/10.1111/anae.12638. 540–9.

[18] Cammarano WB, Pittet JF, Weitz S, Schlobohm RM, Marks JD. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. Crit Care Med 1998;26. http://dx.doi.org/10.1097/00003246-199804000-00015. 676–84.

[19] Fraser GL, Riker RR, Prato BS, Wilkins ML. The frequency and cost of patient-initiated device removal in the ICU. Pharmacotherapy 2001;21:1–6. http://dx.doi.org/10.1592/phco.21.1.1.34444.

[20] Vasilevskis EE, Ely EW, Speroff T, Pun BT, Boehm L, Dittus RS. Reducing iatrogenic risks: ICU-acquired delirium and weakness–crossing the quality chasm. Chest 2010;138. http://dx.doi.org/10.1378/chest.10-0466. 1224–33.

[21] Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California community hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. Crit Care Med 2017;45. http://dx.doi.org/10.1097/CCM.0000000000002149. 171–8.

[22] Balas MC, Vasilevskis EE, Olsen KM, Schmid KK, Shostrom V, Cohen MZ, et al. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. Crit Care Med 2014;42. http://dx.doi.org/10.1097/CCM.0000000000000129. 1024–36.

[23] Arora VM, Chang KL, Fazal AZ, Staisiunas PG, Meltzer DO, Zee PC, et al. Objective sleep duration and quality in hospitalized older adults: associations with blood pressure and mood. J Am Geriatr Soc 2011;59. http://dx.doi.org/10.1111/j.1532-5415.2011.03644.x. 2185–6.

[24] Dammeyer J, Dickinson S, Packard D, Baldwin N, Ricklemann C. Building a protocol to guide mobility in the ICU. Crit Care Nurs Q 2013;36. http://dx.doi.org/10.1097/CNQ.0b013e3182750acd. 37–49.

[25] Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373. http://dx.doi.org/10.1016/S0140-6736(09)60658-9. 1874–82.

[26] Schaller SJ, Anstey M, Blobner M, Edrich T, Grabitz SD, Gradwohl-Matis I, et al. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. Lancet 2016;388. http://dx.doi.org/10.1016/S0140-6736(16)31637-3. 1377–88.

[27] Freeman R, Maley K. Mobilization of intensive care cardiac surgery patients on mechanical circulatory support. Crit Care Nurs Q 2013;36:73–88. http://dx.doi.org/10.1097/CNQ.0b013e31827532c3.

[28] De Jonghe B, Constantin J-M, Chanques G, Capdevila X, Lefrant J-Y, Outin H, et al. Physical restraint in mechanically ventilated ICU patients: a survey of French practice. Intensive Care Med 2013;39. http://dx.doi.org/10.1007/s00134-012-2715-9. 31–7.

[29] Benbenbishty J, Adam S, Endacott R. Physical restraint use in intensive care units across Europe: the PRICE study. Intensive Crit Care Nurs 2010;26. http://dx.doi.org/10.1016/j.iccn.2010.08.003. 241–5.

[30] Perren A, Corbella D, Iapichino E, Di Bernardo V, Leonardi A, Di Nicolantonio R, et al. Physical restraint in the ICU: does it prevent device removal? Minerva Anestesiol 2015;81. 1086–95.

[31] Pan Y, Jiang Z, Yuan C, Wang L, Zhang J, Zhou J, et al. Influence of physical restraint on delirium of adult patients in ICU: a nested case-control study. J Clin Nurs 2018;27. http://dx.doi.org/10.1111/jocn.14334. 1950–7.

[32] Chang L-C, Liu P-F, Huang Y-L, Yang S-S, Chang W-Y. Risk factors associated with unplanned endotracheal self-extubation of hospitalized intubated patients: a 3-year retrospective case-control study. Appl Nurs Res 2011;24:188–92. http://dx.doi.org/10.1016/j.apnr.2009.09.002.

[33] Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early sedation with dexmedetomidine in critically ill patients. N Engl J Med 2019;380. http://dx.doi.org/10.1056/NEJMoa1904710. 2506–17.

[34] Van den Boogaard M, Slooter AJC, Brüggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW, et al. Effect of haloperidol on survival among critically ill adults with a high risk of delirium: the REDUCE randomized clinical trial. JAMA 2018;319:680–90. http://dx.doi.org/10.1001/jama.2018.0160.

[35] Chanques G, Conseil M, Roger C, Constantin J-M, Prades A, Carr J, et al. Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients (SOS-Ventilation): a randomised, parallel-group clinical trial. Lancet Respir Med 2017;5:795–805. http://dx.doi.org/10.1016/S2213-2600(17)30304-1.

[36] La MK, Thompson Bastin ML, Gisewhite JT, Johnson CA, Flannery AH. Impact of restarting home neuropsychiatric medications on sedation outcomes in medical intensive care unit patients. J Crit Care 2018;43. http://dx.doi.org/10.1016/j.jcrc.2017.07.046. 102–7.

[37] Liatsi D, Tsapas B, Pampori S, Tsagourias M, Pneumatikos I, Matamis D. Respiratory, metabolic and hemodynamic effects of clonidine in ventilated patients presenting with withdrawal syndrome. Intensive Care Med 2009;35:275–81. http://dx.doi.org/10.1007/s00134-008-1251-0.

[38] Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for managing opioid withdrawal. Cochrane Database Syst Rev 2017;2:CD002025. http://dx.doi.org/10.1002/14651858.CD002025.pub5.

[39] Wanzuita R, Poli-de-Figueiredo LF, Pfuetzenreiter F, Cavalcanti AB, Westphal GA. Replacement of fentanyl infusion by enteral methadone decreases the weaning time from mechanical ventilation: a randomized controlled trial. Crit Care 2012;16:R49. http://dx.doi.org/10.1186/cc11250.

[40] Reynaud-Davin I, Francony G, Fauvage B, Canet C, Coppo F, Payen J-F. A protocol for the cessation of sedation in brain-injured patients. Ann Fr Anesth Reanim 2012;31:109–13. http://dx.doi.org/10.1016/j.annfar.2011.10.018.

[41] Awissi D-K, Lebrun G, Fagnan M, Skrobik Y. Regroupement De Soins Critiques, réseau de soins respiratoires, québec. alcohol, nicotine, and iatrogenic withdrawals in the ICU. Crit Care Med 2013;41:S57–68. http://dx.doi.org/10.1097/CCM.0b013e3182a16919.

[42] De Jong B, Schuppers AS, Kruisdijk-Gerritsen A, Arbouw MEL, Van den Oever HLA, Van Zanten ARH. The safety and efficacy of nicotine replacement therapy in the intensive care unit: a randomised controlled pilot study. Ann Intensive Care 2018;8:70. http://dx.doi.org/10.1186/s13613-018-0399-1.

[43] Etchegoyen CV, Keller GA, Mrad S, Cheng S, Di Girolamo G. Drug-induced QT interval prolongation in the intensive care unit. Curr Clin Pharmacol 2017;12:210–22. http://dx.doi.org/10.2174/1574884713666180223123947.

[44] Bourin M, Dailly E, Hascöet M. Preclinical and clinical pharmacology of cyamemazine: anxiolytic effects and prevention of alcohol and benzodiazepine withdrawal syndrome. CNS Drug Rev 2004;10:219–29.

[45] Lemoine P, Kermadi I, Garcia-Acosta S, Garay RP, Dib M. Double-blind, comparative study of cyamemazine vs. Bromazepam in the benzodiazepine withdrawal syndrome. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:131–7. http://dx.doi.org/10.1016/j.pnpbp.2005.08.015.

[46] Currier G, Walsh P. Safety and efficacy review of inhaled loxapine for treatment of agitation. Clin Schizophr Relat Psychoses 2013;7:25–32. http://dx.doi.org/10.3371/CSRP.CUWA.032513.

[47] Gaudry S, Sztrymf B, Sonneville R, Megarbane B, Van Der Meersch G, Vodovar D, et al. Loxapine to control agitation during weaning from mechanical ventilation. Crit Care 2017;21:235. http://dx.doi.org/10.1186/s13054-017-1822-y.

[48] Robert PH, Allain H. Clinical management of agitation in the elderly with tiapride. Eur Psychiatry 2001;16. 42s–7s.

[49] Chanques G, Conseil M, Roger C, Constantin JM, Prades A, Carr J, et al. Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients (SOS-Ventilation): a randomised, parallel-group clinical trial. Lancet Respir Med 2017;5:795–805. http://dx.doi.org/10.1016/S2213-2600(17)30304-1.

[50] Kram BL, Kram SJ, Brooks KR. Implications of atypical antipsychotic prescribing in the intensive care unit. J Crit Care 2015;30. http://dx.doi.org/10.1016/j.jcrc.2015.03.030. 814–8.

[51] Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, et al. Haloperidol and ziprasidone for treatment of delirium in critical illness. N Engl J Med 2018;27:2506–16. http://dx.doi.org/10.1056/NEJMoa1808217.

[52] Weaver CB, Kane-Gill SL, Gunn SR, Kirisci L, Smithburger PL. A retrospective analysis of the effectiveness of antipsychotics in the treatment of ICU delirium. J Crit Care 2017;41. http://dx.doi.org/10.1016/j.jcrc.2017.05.034. 234–9.

[53] Gesin G, Kane-Gill SL, Dasta JF, Birrer KL, Kolnik LJ, Cheatham ML. Diazepam as a component of goal-directed sedation in critically ill trauma patients. J Crit Care 2011;26. http://dx.doi.org/10.1016/j.jcrc.2010.09.008. 122–6.

[54] Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. JAMA 2016;315. http://dx.doi.org/10.1001/jama.2016.2707. 1460–8.

[55] Wu X-H, Cui F, Zhang C, Meng Z-T, Wang D-X, Ma J, et al. Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: a pilot randomized controlled trial. Anesthesiology 2016;125. http://dx.doi.org/10.1097/ALN.0000000000001325. 979–91.

[56] Maccioli GA. Dexmedetomidine to facilitate drug withdrawal. Anesthesiology 2003;98:575–7. http://dx.doi.org/10.1097/00000542-200302000-00041.

[57] Beg M, Fisher S, Siu D, Rajan S, Troxell L, Liu VX. Treatment of alcohol withdrawal syndrome with and without dexmedetomidine. Perm J 2016;20:49–53. http://dx.doi.org/10.7812/TPP/15-113.

[58] Mueller SW, Preslaski CR, Kiser TH, Fish DN, Lavelle JC, Malkoski SP, et al. A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. Crit Care Med 2014;42:1131–9. http://dx.doi.org/10.1097/CCM.0000000000000141.

[59] Linn DD, Loeser KC. Dexmedetomidine for alcohol withdrawal syndrome. Ann Pharmacother 2015;49:1336–42. http://dx.doi.org/10.1177/1060028015607038.

[60] Frazee EN, Personett HA, Leung JG, Nelson S, Dierkhising RA, Bauer PR. Influence of dexmedetomidine therapy on the management of severe alcohol withdrawal syndrome in critically ill patients. J Crit Care 2014;29:298–302. http://dx.doi.org/10.1016/j.jcrc.2013.11.016.

[61] Su X, Meng Z-T, Wu X-H, Cui F, Li H-L, Wang D-X, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 2016;388:1893–902. http://dx.doi.org/10.1016/S0140-6736(16)30580-3.

[62] Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet 2014;383:911–22. http://dx.doi.org/10.1016/S0140-6736(13)60688-1.

[63] Tune LE, Damlouji NF, Holland A, Gardner TJ, Folstein MF, Coyle JT. Association of postoperative delirium with raised serum levels of anticholinergic drugs. Lancet 1981;2:651–3.

[64] Flacker JM, Cummings V, Mach JR, Bettin K, Kiely DK, Wei J. The association of serum anticholinergic activity with delirium in elderly medical patients. Am J Geriatr Psychiatry 1998;6:31–41.

[65] Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001;161:1099–105. http://dx.doi.org/10.1001/archinte.161.8.1099.

[66] Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry 2013;21:1190–222. http://dx.doi.org/10.1016/j.jagp.2013.09.005.

[67] Maldonado JR. Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. Crit Care Clin 2008;24:789–856. http://dx.doi.org/10.1016/j.ccc.2008.06.004.

[68] O'Keeffe ST, Chonchubhair Ní. A. Postoperative delirium in the elderly. Br J Anaesth 1994;73:673–87.

[69] Balas MC, Happ MB, Yang W, Chelluri L, Richmond T. Outcomes associated with delirium in older patients in surgical ICUs. Chest 2009;135:18–25. http://dx.doi.org/10.1378/chest.08-1456.

[70] Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. Eur J Clin Pharmacol 2013;69:1485–96. http://dx.doi.org/10.1007/s00228-013-1499-3.

[71] Gareri P, Segura-García C, Manfredi VGL, Bruni A, Ciambrone P, Cerminara G, et al. Use of atypical antipsychotics in the elderly: a clinical review. Clin Interv Aging 2014;9:1363–73. http://dx.doi.org/10.2147/CIA.S63942.

[72] Trifirò G, Gambassi G, Sen EF, Caputi AP, Bagnardi V, Brea J, et al. Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. Ann Intern Med 2010;152:418–25. http://dx.doi.org/10.7326/0003-4819-152-7-201004060-00006.

[73] Markota M, Rummans TA, Bostwick JM, Lapid MI. Benzodiazepine use in older adults: dangers, management, and alternative therapies. Mayo Clin Proc 2016;91:1632–9. http://dx.doi.org/10.1016/j.mayocp.2016.07.024.

[74] Inouye SK, Bogardus ST, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340:669–76. http://dx.doi.org/10.1056/NEJM199903043400901.

[75] Gramish JA, Kopp BJ, Patanwala AE. Effect of amantadine on agitation in critically ill patients with traumatic brain injury. Clin Neuropharmacol 2017;40:212–6. http://dx.doi.org/10.1097/WNF.0000000000000242.

[76] McNett M, Sarver W, Wilczewski P. The prevalence, treatment and outcomes of agitation among patients with brain injury admitted to acute care units. Brain Inj 2012;26:1155–62. http://dx.doi.org/10.3109/02699052.2012.667587.

[77] Van der Naalt J, Van Zomeren AH, Sluiter WJ, Minderhoud JM. Acute behavioural disturbances related to imaging studies and outcome in mild-to-moderate head injury. Brain Inj 2000;14:781–8.

[78] Williamson DR, Frenette AJ, Burry L, Perreault MM, Charbonney E, Lamontagne F, et al. Pharmacological interventions for agitation in patients with traumatic brain injury: protocol for a systematic review and meta-analysis. Syst Rev 2016;5:193. http://dx.doi.org/10.1186/s13643-016-0374-6.

[79] Singh R, Venkateshwara G, Nair KPS, Khan M, Saad R. Agitation after traumatic brain injury and predictors of outcome. Brain Inj 2014;28:336–40. http://dx.doi.org/10.3109/02699052.2013.873142.

[80] Nott MT, Chapparo C, Baguley IJ. Agitation following traumatic brain injury: an Australian sample. Brain Inj 2006;20:1175–82. http://dx.doi.org/10.1080/02699050601049114.

[81] Grof TM, Bledsoe KA. Evaluating the use of dexmedetomidine in neurocritical care patients. Neurocrit Care Juin 2010;12(3):356–61. http://dx.doi.org/10.1007/s12028-008-9156-x.

[82] Humble SS, Wilson LD, Leath TC, Marshall MD, Sun DZ, Pandharipande PP, et al. ICU sedation with dexmedetomidine after severe traumatic brain injury. Brain Inj 2016;30:1266–70. http://dx.doi.org/10.1080/02699052.2016.1187289.

[83] Chanques G, Nelson J, Puntillo K. Five patient symptoms that you should evaluate every day. Intensive Care Med 2015;41:1347–50. http://dx.doi.org/10.1007/s00134-015-3729-x.

[84] Drouot X, Roche-Campo F, Thille AW, Cabello B, Galia F, Margarit L, et al. A new classification for sleep analysis in critically ill patients. Sleep Med 2012;13:7–14. http://dx.doi.org/10.1016/j.sleep.2011.07.012.

[85] Toublanc B, Rose D, Glérant J-C, Francois G, Mayeux I, Rodenstein D, et al. Assist-control ventilation vs. Low levels of pressure support ventilation on sleep quality in intubated ICU patients. Intensive Care Med 2007;33:1148–54. http://dx.doi.org/10.1007/s00134-007-0659-2.

[86] Van Rompaey B, Elseviers MM, Van Drom W, Fromont V, Jorens PG. The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients. Crit Care 2012;16:R73. http://dx.doi.org/10.1186/cc11330.

[87] Rivosecchi RM, Kane-Gill SL, Svec S, Campbell S, Smithburger PL. The implementation of a nonpharmacologic protocol to prevent intensive care delirium. J Crit Care 2016;31(1):206–11. http://dx.doi.org/10.1016/j.jcrc.2015.09.031.

[88] Schmidt M, Demoule A, Polito A, Porchet R, Aboab J, Siami S, et al. Dyspnea in mechanically ventilated critically ill patients. Crit Care Med 2011;39:2059–65. http://dx.doi.org/10.1097/CCM.0b013e31821e8779.

[89] Babkoff H, Sing HC, Thorne DR, Genser SG, Hegge FW. Perceptual distortions and hallucinations reported during the course of sleep deprivation. Percept Mot Skills 1989;68:787–98. http://dx.doi.org/10.2466/pms.1989.68.3.787.

[90] Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents ICU delirium. A randomized, placebo-controlled trial. Am J Respir Crit Care Med 2018;197:1147–56. http://dx.doi.org/10.1164/rccm.201710-1995OC.

[91] Alexopoulou C1, Kondili E, Diamantaki E, Psarologakis C, Kokkini S, Bolaki M, et al. Effects of dexmedetomidine on sleep quality in critically ill patients: a pilot study. Anesthesiology 2014;121:801–7. http://dx.doi.org/10.1097/ALN.0000000000000361.