



## Special article

## [Translated article] Management of analgo-sedation and delirium in the critically ill patient



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## A B S T R A C T

The management of pain, agitation/sedation and delirium is a fundamental part of the treatment received by patients admitted to Intensive Care Units (ICU). The use of different strategies for the prevention and treatment of pain, agitation and delirium is one of the bases in the management of these patients. Knowledge of the different techniques for monitoring pain and delirium, pharmacokinetic behavior and the dosage used in this population, as well as the adverse effects and their management, is essential in order to provide optimal pharmacotherapeutic validation by the ICU clinical pharmacist.

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### Manejo de sedoanalgesia y delirium en el paciente crítico

## R E S U M E N

El manejo de la sedación, la analgesia y la relajación es parte fundamental del tratamiento que reciben los pacientes ingresados en unidades de cuidados intensivos. El empleo de diferentes estrategias para la prevención y tratamiento del dolor, la agitación y el delirio constituye una de las bases en el manejo de estos pacientes. Conocer las diferentes técnicas de monitorización del dolor y del delirio, el comportamiento farmacocinético y la posología utilizada en esta población, así como los efectos adversos y su manejo, es fundamental para poder proporcionar una validación farmacoterapéutica óptima por parte del farmacéutico clínico de la unidad de cuidados intensivos.

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## Introduction

The effective management of sedation, analgesia, and relaxation is crucial in the care of patients admitted to intensive care units (ICUs), with strategies to prevent and treat pain, agitation, and delirium being central to their overall management. The aim of analgosedation is therefore to provide patients with optimal comfort with the minimum necessary sedation, as well as to reduce agitation, disorientation, and anxiety, promote sleep, ensure adequate pain control, and facilitate compliance with mechanical ventilation (MV).<sup>1</sup> Insufficient sedation can result in poor compliance with MV, accidental extubations, and increased agitation, anxiety, and stress. By contrast, oversedation is associated with longer MV and ICU stays, an increased incidence of nosocomial infections, delirium, and long-term cognitive impairment, and impaired communication with patients.<sup>2</sup> The most recent guidelines recommend the use of sedation strategies based on analgesia,<sup>1,3–5</sup> proposing concepts such as early Comfort using Analgesia, minimal Sedatives, and maximal Human care. Effective analgesia should be prioritised, and the minimum sedative dose should then be used, always with a focus on patient care.<sup>6</sup> Thus, the Spanish Society of Intensive Care Medicine and Coronary Units promotes strategies such as the Zero Oversedation Project, which provides a practical teaching and collective awareness tool aimed at optimising clinical outcomes and minimising the harmful effects of excessive sedation. The tool comprises a package of measures that includes monitoring pain, analgesia, agitation, sedation, delirium, and neuromuscular blockade, implementing dynamic sedation, and avoiding deep sedation when not clinically indicated.<sup>7</sup>

Recommended activities for clinical pharmacists working in ICUs include validating pharmacotherapeutic regimens (dosage, interactions, drug allergies, adverse effects), identifying and preventing medication errors and drug-related problems, monitoring pharmacokinetics, and providing drug-related information and education to other healthcare professionals. Therefore, ICU clinical pharmacists must have a thorough knowledge of pharmacotherapy management related to analgosedation and delirium, participate in multidisciplinary teams to agree on treatment guidelines, implement protocols, provide information related to these treatments, and promote the evaluation of the impact of pharmacotherapeutic protocols.<sup>8,9</sup> Thus, the aim of this article was to provide a review of the strategies available for the assessment, prevention, and treatment of pain, agitation, and delirium in ICUs.

### Monitoring analgosedation and delirium in critically ill patients

It is recommended that the level of sedation and pain, as well as the presence of delirium, should be routinely assessed every 4–6 h in all patients admitted to critical care units. These assessments should be systematically documented in the patients' medical records.<sup>1,5</sup> Although there are several validated scales that provide an approximate assessment of critically ill patients, few tools are available to objectively monitor analgesia levels, particularly in sedated patients who are unable to communicate.

**Table 1**  
Richmond agitation-sedation scale.

Score	Name	Description	Examination
4+	Combative	Combative, violent, immediate danger to staff	Observe patient
3+	Very agitated	Aggressive, pulls or removes tubes or catheters	
2+	Agitated	Frequent nonpurposeful movement, fights ventilator	
1+	Restless	Anxious, but movements not aggressive or vigorous	Call patients by name and say "Open your eyes and look at me"
0	Alert and calm		
1–	Drowsy	Not fully alert, but remains ( $\geq 10$ s) awake (eye opening and contact)	
2–	Light sedation	Wakes briefly (<10 s) with eye contact to voice	
3–	Moderate sedation	Eye movement or opening to voice (but no eye contact)	Stimulate patients by shaking their shoulder or rubbing their chest
4–	Deep sedation	No response to voice, but eye movement or opening in response to physical stimuli	
5–	Unarousable	No response to voice or physical stimuli	

## Sedation scales

**Richmond Agitation Sedation Scale (RASS):** this tool assesses patients on a scale ranging from 5– to 4+, where 0 indicates an alert, calm patient with no signs of agitation or sedation (Table 1). A negative score indicates sedation, whereas a positive score indicates agitation. This scale is the preferred choice in ICUs, except when monitoring patients who are being treated with neuromuscular blockers.<sup>4</sup>

**Sedation-Agitation Scale (SAS):** this scale describes agitation and sedation in critically ill patients. It is valid for use with both intubated and non-intubated patients; however, it is not suitable for monitoring patients who are being treated with neuromuscular blockers. The SAS is scored on a scale ranging from 1 to 7, with 4 indicating a calm, cooperative patient<sup>5</sup> (Table 2).

**Ramsay scale:** this scale assesses the patients' responses to stimuli. It is scored on a scale ranging from 1 to 6. A score of 1 to 3 indicates a state of wakefulness, whereas a score of 4 to 6 indicates a state of sleep (Table 3). One of its limitations is that it only includes 1 category of agitation, making it less useful for quantifying its severity.<sup>10</sup> Furthermore, it is not suitable for monitoring patients who are being treated with neuromuscular blockers, since they are unable to respond to these stimuli.

**Bispectral index (BIS):** this index, derived from the analysis of electroencephalogram wave frequencies, estimates the level of brain electrical activity. The BIS scale ranges from 0 to 100, enabling continuous objective monitoring. It is indicated in patients who are being treated with neuromuscular blockers or who are deeply sedated. The goal is to maintain the BIS score within the range of 40–60.<sup>11</sup>

## Pain scales

In conscious and communicative patients, pain can be assessed using graphic scales such as the Visual Analogue Scale or the Visual Numeric Scale. Patients express their degree of pain on a scale ranging from 0 (no pain) to 10 (the worst pain imaginable).<sup>12</sup>

In noncommunicative patients or those on MV, indirect tools such as physiological indicators (e.g. high blood pressure, tachycardia, tachypnoea, sweating) or behavioural indicators (e.g. facial expression, presence of movement, or posture) can serve as an alert system for inadequate pain control.<sup>10</sup> These indicators have been used to develop validated scales, such as the Behavioural Indicators of Pain Scale, as there is currently no technique available to objectively assess the presence and intensity of pain.<sup>13</sup> This scale assesses pain on a scale of 0 to 10 based on facial expression, calmness, muscle tone, compliance with MV, and consolability. The aim is to maintain the pain level below 4 on the scale. It is recommended that pain is assessed before, during, and 15 min after any procedure is performed on noncommunicative patients on MV.<sup>1</sup> However, there is limited evidence of its use in patients with quadriplegia, those receiving treatment with neuromuscular blockers, patients in deep coma due to metabolic or neurological causes, or those with haemodynamic or respiratory instability. This limitation

**Table 2**  
Sedation-agitation scale.

Score	Level of sedation	Response
7	Dangerous agitation	Tries to remove endotracheal tube and catheters; attempts to get out of bed; strikes at staff
6	Very agitated	Does not calm down when spoken to, bites tube, needs physical restraint
5	Agitated	Anxious or moderately agitated, attempts to sit up, but calms down when spoken to
4	Calm and cooperative	Calm or easily awakened, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking, but quickly falls asleep again Obeys simple commands
2	Very sedated	May awaken to physical stimulation, but does not communicate or follow commands May move spontaneously
1	Unarousable	May move or gesticulate slightly to noxious stimuli, but does not communicate or follow commands

arises because this scale has not been evaluated in these clinical contexts, where patients may exhibit diminished responses to stimuli or reduced motor responses. These patients were therefore excluded from ESCID scale validation studies.<sup>14</sup>

**Campbell scale:** this instrument has been validated for assessing the presence and degree of pain in patients who are unable to communicate. It is scored on a scale ranging from 0 to 10. The objective is to maintain the score below 3. A score above 6 is considered to be very intense<sup>5</sup> (Table 4).

**Behavioural pain scale:** this scale assesses the presence of pain on a 12-point scale (Table 5). The main limitation of this scale is that it only indicates whether the stimulus is painful, offering little value in quantifying pain.<sup>15</sup>

**The analgesia nociception index:** this index measures heart rate variability based on electrocardiogram monitoring. It uses spectral analysis to generate an algorithm that converts nociception into an absolute value between 0 and 100. The target value is between 50 and 70, indicating a balance between analgesia and sedation.<sup>16</sup>

**Nociception level index:** this index measures nociception on a scale ranging from 1 to 100, based on the non-linear integration of physiological variables associated with pain perception (heart rate, photoplethysmogram amplitude, skin conductance, and skin conductance fluctuations along with their temporal derivatives). It has been used extensively during surgery, but its use in critical patients is limited.<sup>17</sup>

#### Scales for assessing delirium

**Confusion assessment method for the intensive care unit scale:** this scale assesses the state of consciousness, comprehension, memory, attention, and alertness. This dichotomous scale only detects the presence or absence of delirium (a positive or negative result) but does not distinguish between hypo- or hyperactive delirium or determine its severity.<sup>18</sup>

**Table 3**  
Ramsay scale.

Level	Description
<i>Awake</i>	
1	Anxious and agitated or restless
2	Cooperative, oriented, and calm
3	Drowsy Responds to normal verbal stimuli
<i>Asleep</i>	
4	Brisk response to loud noises or light glabellar tap
5	Sluggish response to loud noises or light glabellar tap
6	No response to loud noises or light glabellar

**Intensive Care Delirium Screening Checklist (ICDSC):** this checklist comprises an 8-item scale used to detect delirium over a period of 8 to 24 h. A score of 4 or higher on the ICDSC is positive and indicates the presence of delirium. It is particularly useful in sedated or uncommunicative patients.<sup>19</sup>

#### Sedation

Sedation involves reducing the patients' level of consciousness and their response to external stimuli. The ideal sedative should have an immediate onset of action, enable rapid recovery and easy dose adjustment, and have a wide therapeutic margin. It should also not accumulate or interact with other drugs, have no adverse effects, and be low cost.<sup>20</sup> However, as there is no ideal sedative, the choice of drug will depend on the patients' pathophysiological characteristics and any changes affecting pharmacokinetic and pharmacodynamic behaviour.

#### Sedation strategies

**Light or conscious sedation (RASS 0 to – 2):** at this level of sedation, consciousness is minimally depressed. Patients are calm but not asleep, and still maintain their airway reflexes, spontaneous ventilation, and appropriate responses to stimuli. Drugs such as dexmedetomidine are recommended for use over alternatives such as fentanyl, remifentanyl, or propofol.<sup>4</sup>

**Deep sedation (RASS – 4 to – 5):** for deep sedation, midazolam, propofol, or lorazepam are recommended as the sedatives of choice. This level may be accompanied by total or partial loss of defence reflexes, airway reflexes, or response to physical or verbal stimuli.

#### Sedative drugs (Table 6)

**Propofol:** this drug is indicated for short-term sedation or when sedation windows are required (e.g. frequent neurological assessments or early extubation), due to its rapid onset and quick recovery time. Lipid levels should be monitored and caloric intake maintained at a rate of 1.1 kcal/mL (i.e. 0.1 g of lipids per mL of 1% propofol). Propofol infusion syndrome may develop at high doses (greater than 5 mg/kg/h) and during prolonged infusions (greater than 48 h). This syndrome is life-threatening with a high mortality rate and is characterised by the development of arrhythmias, metabolic acidosis, hyperkalaemia, kidney failure, and rhabdomyolysis.

**Midazolam:** due to its high lipophilicity and strong binding to plasma proteins, there is a risk of accumulation in patients with hepatic failure, obesity, or hypoalbuminaemia. It should not be used in patients with cirrhosis. It has no analgesic effect. As it is a benzodiazepine, flumazenil can be used as an antidote to reverse its effects.

**Dexmedetomidine:** this drug is recommended for short-term sedation and patients at high risk of delirium. The advantages of dexmedetomidine for conscious sedation over other drugs include its lack of respiratory depression and its ability to reduce opioid requirements, shorten the duration of mechanical ventilation and ICU stays, and lower the incidence of delirium compared to propofol or midazolam<sup>4</sup>; however, due to its high risk of secondary cardiac block, it should be avoided in patients with cardiac decompensation.

**Remifentanyl:** this drug is indicated for short-term dynamic and sequential sedation in cases where repeated therapeutic procedures are required, such as aggressive treatments that necessitate potent analgesia. As remifentanyl is eliminated through plasma esterases, adjustment is not required in cases of renal or hepatic failure. It should not be administered as an intravenous (IV) bolus because of cardiovascular effects, such as the risk of bradycardia or hypotension.

**Table 4**  
Campbell scale.

Score	0	1	2
Facial expression	Relaxed	Tense, frowning, or grimacing	Regularly frowning or clenching teeth
Calmness	Calm, relaxed, normal movements	Occasional restless movements and shifting position	Frequent movement, including head or limbs
Muscle tone <sup>a</sup>	Normal	Increased. Flexion of fingers and toes	Rigid
Verbal response <sup>b</sup>	Normal	Occasional complaints, crying, moaning, or grunting	Frequent complaints, crying, moaning, or grunting
Consolability	Comfortable and calm	Reassured by touch and voice. Easy to distract	Difficult to console by touch or talking

<sup>a</sup> In cases of spinal cord injury or hemiplegia, assess the healthy side.

<sup>b</sup> It may be difficult to assess patients with an artificial airway.

**Ketamine:** this drug is an alternative for short-term sedation in patients with bronchospasm, as it preserves protective pharyngeal and laryngeal reflexes while avoiding respiratory depression. It has an analgesic effect by binding to sigma receptors. Due to its significant adverse effects, treatment should start with a low dose, which should then be increased gradually. Treatment should be monitored for the onset of persistent pain, haemodynamic instability, delirium, psychotic episodes, and tonic/clonic movements.

**Inhaled gases:** the use of inhaled anaesthetics in ICUs, such as isoflurane or sevoflurane, is increasing. They are a good alternative to IV anaesthesia, offering shorter recovery times and MV duration. These advantages are due to their excellent dose–response relationship and cardio- and neuroprotective properties, together with the availability of administration devices (AnaConDa or Mirus).<sup>21</sup>

## Analgesia

Opioids are the primary analgesics used for critical patients, with morphine and fentanyl being the preferred drugs for continuous IV administration. They act through  $\mu$ ,  $\kappa$ ,  $\delta$ , and  $\sigma$  opioid receptors at both central and peripheral levels, which mediate analgesic effects. These drugs interact synergistically with sedatives and require strict control due to their high inter- and intra-individual variability, their narrow therapeutic margin, and potential for adverse effects, such as respiratory depression, hypotension, decreased level of consciousness, urinary and gastric retention, ileus, nausea, and vomiting. Therefore, to minimise opioid consumption, strategies such as multimodal analgesia are recommended. This approach involves using nonopioid adjuvants, such as paracetamol (first step), metamizole (second step), or dexketoprofen (third step), as well as anticonvulsants or local anaesthetics.<sup>22</sup> Table 6 shows the main drugs used in ICUs for sedation, analgesia, and delirium in critically ill patients. The need for preventive analgesia should be assessed prior to handling patients or conducting routine procedures, such as patient care. In the event of opioid overdose, naloxone is the drug of choice as an antidote; it is a pure competitive opioid receptor antagonist.

**Table 5**  
Behavioural pain scale.

Item	Description	Points
Facial expression	Relaxed	1
	Partially tightened	2
	Fully tightened	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent. With finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerates movement	1
	Coughs, but tolerates ventilation most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

## Delirium

Neuropsychiatric syndrome is characterised by the onset of impaired consciousness and cognitive function, developing over a short period and following a fluctuating course. Its most characteristic manifestations include alterations in attention and perception of the environment (delusions or hallucinations) with agitation or hypoactivity.<sup>20</sup> It affects about 40% of patients in ICUs, although it often goes unnoticed, particularly the hypoactive forms.<sup>23</sup> Delirium in patients should be monitored every 8–12 h. It is associated with extended hospital stays, longer MV duration, higher costs, and increased mortality rates.<sup>24</sup>

Depending on the level of alertness and psychomotor activity, it is classified into 3 subtypes:

**Hyperactive:** agitation, aggression, restlessness, emotional instability, and a tendency to remove probes and catheters.

**Hypoactive:** decreased activity, lethargy, emotional indifference, apathy, and decreased response to external stimuli. The use of psychoactive drugs in ICUs makes hypoactive delirium more prevalent and harder to recognise than hyperactive delirium.

**Mixed:** this subtype is the most common. Patients alternate between the 2 subtypes described above.

## Risk factors

**Modifiable:** use of benzodiazepines, immobility, sleep deprivation, low exposure to sunlight, dehydration, and malnutrition.

**Non-modifiable:** advanced age, a high APACHE-II score on admission, dementia, previous episodes of delirium, high blood pressure, metabolic acidosis, emergency surgery, and multiple trauma.

**Prevention and treatment:** delirium can have multifactorial causes. The first step in managing delirium is to identify and correct the underlying cause. Table 6 shows the drugs used in this setting.

**Nonpharmacological measures:** it has been shown that the onset of delirium in ICUs can be reduced by strategies such as early mobilisation, stimulating patient orientation, controlling ambient light, maintaining a higher level of communication with patients, providing cognitive stimulation, reducing noise in the environment, maintaining adequate hydration, promoting the early removal of catheters, and performing early tracheostomy.

**Pharmacological treatment:** the guidelines suggest that drugs such as typical neuroleptics (haloperidol) or atypical neuroleptics (olanzapine, risperidone, or quetiapine) should not be routinely used to treat delirium. Although several studies have attempted to demonstrate the efficacy of pharmacological treatment, the results have not been conclusive.<sup>1,4,10</sup> If these drugs are used, they should be administered at the lowest possible concentration within their respective therapeutic range for this indication. The drugs should then be discontinued once clinical improvement or resolution has been achieved.

In conclusion, correctly implementing protocols for managing analgosedation and delirium in ICUs is crucial to individualise therapy in critically ill patients, improve safety, and optimise patient-centred

**Table 6**

Main drugs used for sedation, analgesia, and delirium in critically ill patients.

Sedation						
Drug	Mechanism of action	Dosage	Clinical effects	Indication/ characteristics	Metabolism/ elimination	Adverse effects
<i>Midazolam</i>	Benzodiazepine Action on GABA <sub>A</sub> receptor	IV bolus: 1–5 mg Infusion: 0.02–0.1 mg/kg/h <i>D</i> <sub>max</sub> : 0.25 mg/kg/h	Anxiolytic Hypnotic Amnesic Muscle relaxation Anticonvulsant	Status epilepticus, alcohol withdrawal syndrome, and prolonged sedation	Hepatic metabolism (CYP3A4) Active metabolite: α1-hydroxymidazolam Renal elimination	Hypotension Tachycardia Respiratory depression Tolerance Paradoxical reactions
<i>Propofol</i>	GABA <sub>A</sub> receptor agonist	IV bolus: 0.5–1 mg/kg Infusion: 5–50 µg/kg/min or 0.3–3 mg/kg/h <i>D</i> <sub>max</sub> : 4 mg/kg/h	Sedative Hypnotic Antiemetic Anticonvulsant	Recommended administration route Central Contraindicated in patients allergic to soy, peanuts, eggs Preferred choice if CRRT	Hepatic conjugation metabolism Renal elimination	Hypotension Respiratory depression Bradycardia Propofol infusion syndrome Hypertriglyceridaemia
<i>Dexmedetomidine</i>	Selective α-2 receptor agonist	0.2–0.7 µg/kg/h <i>D</i> <sub>max</sub> : 1.5 µg/kg/h	Hypnotic Analgesic Improves sleep quality	Light sedation Control of agitation during mechanical ventilation weaning	Hepatic metabolism (CYP2A6) Renal elimination	Hypotension Bradycardia Fever Avoid in cerebrovascular and cardiovascular disease
<i>Ketamine</i>	Noncompetitive NMDA receptor antagonist	Slow IV bolus: 0.25–1 mg/kg Infusion: 0.1–2.5 mg/kg/h	Dissociative anaesthesia Analgesic Bronchodilator Vasodilation	Bronchospasm or asthmatic state	Hepatic metabolism Renal elimination	Hypertension Sialorrhoea Arrhythmias Increased ICP Hallucinations and delirium
<i>Sodium thiopental</i>	Barbiturate anaesthetic Potentiates GABA receptor response	Bolus: 50–75 mg Infusion: 1–4 mg/kg/h	Hypnotic Anxiolytic Anticonvulsant	Neurocritical: refractory intracranial hypertension or status epilepticus	Hepatic metabolism Renal elimination	Hypotension Myocardial dysfunction Risk of infection Bronchospasm Paralytic ileus Bradycardia
<i>Remifentanyl</i>	µ-opioid receptor agonist	Infusion: 0.5–15 µg/kg/h	Sedative Analgesic	Dynamic sedation	Plasma esterases	Respiratory depression Muscle rigidity Paradoxical hyperalgesia Tolerance
<b>Analgesia</b>						
<i>Morphine</i>	µ, κ, δ, σ opioid receptor agonist	IV bolus: 2–4 mg or 0.05–0.1 mg/kg Infusion: 2–15 mg/h	Acute pain, postoperative pain Dyspnoea Long-term analgesedation	Hepatic metabolism Requires adjustment in RF		Nausea, vomiting Respiratory depression Hypotension Ileus and urinary retention Tolerance, dependence, and withdrawal syndrome Histamine release
<i>Fentanyl</i>	µ, κ, δ opioid receptor agonist	IV bolus: 50–100 µg Infusion: 0.7–5 µg/kg/h <i>D</i> <sub>max</sub> : 10 µg/kg/h	Severe acute pain Preferred in haemodynamically unstable patients	Hepatic metabolism Renal and biliary elimination		Respiratory depression Hypotension Muscle rigidity Decreases ICP
<i>Sufentanil</i>	µ-opioid receptor agonist	Induction: 5–20 µg or 0.1–2 µg/kg Maintenance: 0.2–2 µg/kg/h	Adjuvant analgesic during anaesthesia Induction and maintenance of analgesic anaesthesia	Hepatic metabolism		Respiratory depression Bradycardia, hypotension Nausea, vomiting Pruritus
<i>Methadone</i>	µ-opioid receptor agonist	Analgesic dose: 10–40 mg every 6–12 h orally	Opioid withdrawal syndrome	Hepatic metabolism Renal elimination		QT interval prolongation Serotonergic effect Drowsiness Respiratory depression
<i>Tramadol</i>	µ-opioid receptor agonist Minor centrally acting opioid	50–100 mg every 6–8 h <i>D</i> <sub>max</sub> : 400 mg/d	Acute postoperative pain Neuropathic pain	Reduce dose in elderly patients Requires adjustment in RF		Tachycardia Nausea, vomiting Orthostatic hypotension Seizures Tolerance, dependence, and withdrawal syndrome
<i>Paracetamol</i>	Inhibits prostaglandin synthesis	IV: 1 g every 6–8 h <i>D</i> <sub>max</sub> : 4 g/d	Mild to moderate pain Antipyretic	Hepatic metabolism Renal elimination		Hepatotoxicity Hypotension Hypoglycaemia

(continued on next page)

Table 6 (continued)

Sedation						
Drug	Mechanism of action	Dosage	Clinical effects	Indication/ characteristics	Metabolism/ elimination	Adverse effects
<i>Metamizole</i>	Pyrazolone derivative	IV: 1 g every 6–8 h $D_{max}$ : 8 g/d	Severe acute pain Antipyretic Anti-inflammatory Antispasmodic	Hepatic metabolism Renal elimination		Hypotension Agranulocytosis, thrombocytopenia Angioedema Bronchospasm
<i>Dexketoprofen</i>	NSAID	IV: 50 mg every 8–12 h	Moderate to severe pain Antipyretic Anti-inflammatory	Hepatic metabolism Renal elimination		Nephrotoxicity Hypertension Abdominal pain, constipation Peptic ulcer
<b>Delirium</b>						
<i>Haloperidol</i>	Typical neuroleptic Dopamine $D_2$ receptor agonist	IV, IM bolus: 2.5–5 mg every 20–30 min $D_{max}$ : 30 mg/d Continuous infusion: 5–25 mg/h $D_{max}$ : 40 mg/h oral : 0.5–2 mg/4–8 h	Agitation and psychosis Hyperactive delirium Hypoactive delirium	Hepatic metabolism, CYP2D6 CYP3A4		QT interval prolongation (ventricular arrhythmias), Torsades de Pointes Malignant neuroleptic syndrome Extrapyramidal symptoms Hypotension
<i>Quetiapine</i>	Atypical antipsychotic Acts on serotonergic and dopaminergic $D_1$ and $D_2$ brain receptors	Oral: 12.5–25 mg $D_{max}$ : 300 mg/d Use delayed-release tablets	Hyperactive delirium	Hepatic metabolism CYP3A4		QT interval prolongation Drowsiness and sedation Orthostatic hypotension Hyperglycaemia Extrapyramidal symptoms
<i>Olanzapine</i>	Atypical antipsychotic. Acts on serotonergic, histamine, and muscarinic receptors and has a moderate effect on $D_2$ dopaminergic receptors	Oral: 2.5–15 mg/d	Hyperactive delirium Positive psychotic symptoms	Hepatic metabolism CYP1A2 CYP2D6		QT interval prolongation Drowsiness and sedation Hyperglycaemia Increased appetite Monitor liver function Serotonin syndrome
<i>Risperidone</i>	Atypical antipsychotic	0.25–3 mg/12 h $D_{max}$ : 6 mg/d	Mild–moderate hyperactive delirium with active psychotic symptoms	Hepatic metabolism CYP2D6 CYP3A4		Drowsiness Hyperglycaemia QT interval prolongation Drowsiness and sedation Hyperglycaemia Monitor liver function Increased risk of acute stroke in patients >65 years
<i>Dexmedetomidine</i>	Selective $\alpha$ -2 adrenergic agonist	0.2–0.7 $\mu$ g/kg/h $D_{max}$ : 1.5 $\mu$ g/kg/h	Conscious sedation Better sleep quality Control of agitation during mechanical ventilation weaning	Hepatic metabolism CYP2D6		Hypotension Bradycardia Fever Avoid in cerebrovascular and cardiovascular disease
<i>Clonidine</i>	$\alpha$ -2 adrenergic agonist	Oral: 0.2–0.5 mg every 6–8 h or 0.15 mg every 12–24 h IV bolus: 300 $\mu$ g (stable haemodynamics) Infusion: $D_{max}$ : 3 $\mu$ g/kg/h	Hyperactive delirium	Renal elimination		Hypotension, bradycardia Dry mouth QT monitoring

NSAID, nonsteroidal antiinflammatory drug;  $D_{max}$ , maximum dose; GABA, gamma-aminobutyric acid; IM, intramuscular; RF, renal failure; IV, intravenous; NMDA, N-methyl-D-aspartate; ICP, intracranial pressure; CRRT, continuous renal replacement therapy; MV, mechanical ventilation.

health outcomes. Thus, clinical pharmacists can play a key role in selecting and individualising dosages, minimising medication errors and adverse events, and educating and training multidisciplinary teams to ensure continuous improvement in the quality of care for critically ill patients.

#### Declaration of authorship

All authors are members of the FARMIC Working Group. All authors participated in developing the concept, designing the project, defining the intellectual content, preparing the project, and reviewing it. The manuscript was written by María Martín-Cerezuela, Esther Domingo-

Chiva, and Fernando Becerril-Moreno. All of the authors have critically reviewed and approved the final version of the manuscript for publication.

#### CRediT authorship contribution statement

**María Martín Cerezuela:** Writing – review & editing, Conceptualization. **Esther Domingo Chiva:** Methodology. **Tatiana Betancor García:** Writing – review & editing, Conceptualization. **Irene Aquerreta González:** Writing – review & editing. **Carla Bastida Fernández:** Writing – review & editing. **Fernando Becerril Moreno:** Writing – review & editing, Writing – original draft, Conceptualization.

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## Conflicts of interest

None declared.

## References

- Celis-Rodríguez E, Birchenall C, de la Cal MA, Castorena Arellano G, Hernández A, Ceraso D, et al. Guía de práctica clínica basada en la evidencia para el manejo de la sedoanalgesia en el paciente adulto críticamente enfermo. *Med Intensiva*. 2013;37(8):519–574. doi:10.1016/j.medin.2013.04.001.
- Devlin JW. The pharmacology of oversedation in mechanically ventilated adults. *Crit Care Med*. 2018;46(9):e825–e873. doi:10.1097/CCM.0000000000003299.
- Barnes-Daly MA, Pun BT, Harmon LA, Byrum DG, Kumar VK, Devlin JW, et al. Improving health care for critically ill patients using an evidence-based collaborative approach to ABCDEF bundle dissemination and implementation. *Worldviews Evidence-Based Nurs*. 2018;15(3):206–216. doi:10.1111/wvn.12290.
- Lewis K, Balas MC, Stollings JL, McNett M, Girard TD, Chanques G, et al. A focused update to the clinical practice guidelines for the prevention and management of pain, anxiety, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2025;53(3):e711–e727. doi:10.1097/CCM.0000000000006574.
- 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(9):E825–E873. doi:10.1097/CCM.0000000000003299.
- Vincent JL, Shehabi Y, Walsh TS, Pandharipande PP, Ball JA, Spronk P, et al. Comfort and patient-centred care without excessive sedation: the eCASH concept. *Intensive Care Med*. 2016;42(6):962–971. doi:10.1007/s00134-016-4297-4.
- Caballero J, García-Sánchez M, Palencia-Herrejón E, Muñoz-Martínez T, Gómez-García JM, Cenicerós-Rozalén I, et al. Oversedation zero as a tool for comfort, safety and intensive care unit management. *Med Intensiva*. 2020;44(4):239–247. doi:10.1016/j.medin.2019.09.010.
- Lat I, Paciullo C, Daley MJ, MacLaren R, Bolesta S, McCann J, et al. Position paper on critical care pharmacy services: 2020 update. *Crit Care Med*. 2020;48(9):e813–e834. doi:10.1097/CCM.0000000000004437.
- Becerril-Moreno F, Valera-Rubio M, Acquerreta-González I, Domingo-Chiva E, Doménech-Moral L, Martín-Cerezueta M, et al. Activities of the clinical pharmacist in the intensive care units. *Farm Hosp*. 2025;49(3):188–193. doi:10.1016/j.farma.2024.09.004.
- 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(1):263–306. doi:10.1097/CCM.0b013e3182783b72.
- Kasuya Y, Govinda R, Rauch S, Mascha EJ, Sessler DI, Turan A. The correlation between bispectral index and observational sedation scale in volunteers sedated with dexmedetomidine and propofol. *Anesth Analg*. 2009;109(6):1811–1815. doi:10.1213/ANE.0b013e3181c04e58.
- Stephens J, Wright M. Pain and agitation management in critically ill patients. *Nurs Clin North Am*. 2016;51(1):95–106. doi:10.1016/j.cnur.2015.11.002.
- Latorre-Marco I, Acevedo-Nuevo M, Solís-Muñoz M, Hernández-Sánchez L, López-López C, Sánchez-Sánchez MM, et al. Validation of the behavioural indicators of pain scale ESCID for pain assessment in non-communicative and mechanically ventilated critically ill patients: a research protocol. *J Adv Nurs*. 2016;72(1):205–216. doi:10.1111/jan.12808.
- Latorre Marco I, Solís Muñoz M, Falero Ruiz T, Larrasquitu Sánchez A, Romay Pérez AB, Millán Santos I. Validación de la escala de conductas indicadoras de dolor para valorar el dolor en pacientes críticos, no comunicativos y sometidos a ventilación mecánica: resultados del proyecto ESCID. *Enferm Intensiva*. 2011;22(1):3–12. doi:10.1016/j.enfi.2010.09.005.
- Gélinas C. Pain assessment in the critically ill adult: recent evidence and new trends. *Intensive Crit Care Nurs*. 2016;34:1–11. doi:10.1016/j.iccn.2016.03.001.
- Cinco Huiqui AI, Beltrán Moguel J, Trejo Arteaga A, Cerón Díaz UW. Exactitud diagnóstica del índice de nocicepción analgesia para la evaluación del dolor en pacientes críticos. *Med Crítica*. 2022;36(2):82–90. doi:10.35366/104869.
- Shahiri TS, Richebé P, Richard-Lalonde M, Gélinas C. Description of the validity of the Analgesia Nociception Index (ANI) and Nociception Level Index (NOL) for nociception assessment in anesthetized patients undergoing surgery: a systematized review. *J Clin Monit Comput*. 2022;36(3):623–635. doi:10.1007/s10877-021-00772-3.
- Hughes CG, McGrane S, Pandharipande PP. Sedation in the intensive care setting. *Clin Pharmacol*. 2012;4:53–63. doi:10.2147/CPAA.S26582.
- Brummel NE, Vasilevskis EE, Han JH, Boehm L, Pun BT, Ely EW. Implementing delirium screening in the ICU: secrets to success. *Crit Care Med*. 2013;41(9):2196–2208. doi:10.1097/CCM.0b013e31829a6f1e.
- Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *N Engl J Med*. 2014;370(5):444–454. doi:10.1056/NEJMra1208705.
- Jabaudon M, Zhai R, Blondonnet R, Bonda WLM. Inhaled sedation in the intensive care unit. *Anaesth Crit Care Pain Med*. 2022;41(5):101133. doi:10.1016/j.accpm.2022.101133.
- Wheeler KE, Grilli R, Centofanti JE, Martin J, Gelinas C, Szumita PM, et al. Adjuvant analgesic use in the critically ill: a systematic review and meta-analysis. *Crit Care Explor*. 2020;2(7):e0157. doi:10.1097/CCE.000000000000157.
- Marra A, Pandharipande PP, Patel MB. Intensive care unit delirium and intensive care unit-related posttraumatic stress disorder. *Surg Clin North Am*. 2017;97(6):1215–1235. doi:10.1016/j.suc.2017.07.008.
- Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *Lancet Respir Med*. 2014;2(5):369–379. doi:10.1016/S2213-2600(14)70051-7.