

Evidence-Based Management Of Pain, Sedation, and Delirium in the Intensive Care Unit and Clinical Pharmacists' Contribution: A Practical Review

ABSTRACT

Pain, anxiety, agitation, and delirium are common in intensive care unit (ICU) patients, particularly in those undergoing invasive procedures such as intubation and mechanical ventilation. Initiating sedation without first evaluating and treating pain is not rational, as it may mask underlying discomfort and delay appropriate management. Deep sedation, when applied without careful assessment, is associated with prolonged mechanical ventilation, extended ICU stay, and increased mortality; therefore, it should be reserved only for specific clinical indications, as emphasized in the Society of Critical Care Medicine Pain, Agitation, and Delirium Guidelines. Pain, a major trigger of agitation, requires systematic assessment and early, multimodal analgesia—combining opioid and non-opioid strategies—to reduce adverse outcomes, minimize opioid exposure, and support faster recovery. Agitation may otherwise result in complications including self-extubation, catheter dislodgement, and ventilator asynchrony, necessitating judicious use of sedatives and analgesics in ICU care. Delirium, characterized by disturbances in attention, consciousness, and cognition, is strongly linked to increased mortality and long-term cognitive impairment. Guidelines recommend routine delirium screening, environmental modifications, structured sleep protocols, and early mobilization, along with careful pharmacological strategies. Antipsychotics are not advised for prophylaxis, while dexmedetomidine may be considered in selected ventilated patients. Optimal triad management requires individualized drug selection, validated assessment tools, and minimal benzodiazepine use except in cases such as withdrawal. In addition to guideline-based strategies, growing evidence highlights the role of clinical pharmacists, whose interventions in drug selection, dose titration, monitoring, and interprofessional education have been shown to reduce sedative and opioid exposure, shorten mechanical ventilation and ICU stay, and improve cost-effectiveness. This review synthesizes guideline-based recommendations, recent evidence, and the expanding contributions of clinical pharmacists to provide practical, evidence-based strategies for clinicians managing pain, sedation, and delirium in the ICU.

Keywords: Clinical pharmacist, delirium, intensive care unit, pain, sedation

INTRODUCTION

The intensive care unit (ICU) is a highly specialized setting that provides advanced monitoring and therapeutic support to critically ill patients with life-threatening organ dysfunction.^{1,2} In this environment, patients frequently experience pain, anxiety, dyspnea, agitation, and delirium, often related to invasive procedures such as intubation and mechanical ventilation. Agitation, which may result in patient-initiated removal of tubes or catheters, ventilator asynchrony, and heightened sympathetic activity, is a major reason for the frequent use of sedatives and analgesics in ICU practice.^{3,4}

Only a small proportion of patients require continuous deep sedation for specific clinical indications, such as intracranial hypertension, refractory status epilepticus, or the use of neuromuscular blockers.⁴ Evidence consistently shows that unnecessary deep sedation is associated with prolonged mechanical ventilation, longer ICU stays, and increased mortality, underscoring the importance of individualized, goal-directed sedation strategies.^{4,5}

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Among the most important causes of agitation in the ICU are pain and delirium. These 3 interconnected phenomena—pain, agitation, and delirium—are often referred to as the “ICU triad” due to their overlapping pathophysiology and management strategies. Initiating sedation without prior evaluation of pain and delirium may obscure underlying conditions, leading to suboptimal outcomes.⁶ Therefore, comprehensive management of these processes is essential for ensuring patient comfort and optimizing ventilator synchrony. Sedation depth and appropriateness should be assessed using validated scoring tools, and pharmacological choices must be tailored to the patient’s clinical profile.⁷

This paper is a narrative review synthesizing evidence from PubMed, Scopus, and Web of Science databases. Literature published between 2000 and 2025 was considered, with emphasis on international guidelines, randomized controlled trials, meta-analyses, and key observational studies directly relevant to ICU pain, sedation, and delirium management. The review integrates pharmacological evidence with practical clinical strategies, presenting current data on efficacy, safety, pharmacokinetics, dosing approaches, and the advantages and limitations of sedative and analgesic agents. By highlighting practical implementation challenges and emphasizing individualized, multimodal strategies, it aims to support informed, patient-centered decisions and multidisciplinary, guideline-based care. In addition, this review underscores the expanding contribution of clinical pharmacists, who play a pivotal role in drug selection, dose optimization, interaction management, monitoring of adverse effects, education, and interprofessional collaboration in the ICU. While the 2018 Society of Critical Care Medicine (SCCM) Pain, Agitation, and Delirium guidelines (PADIS) guidelines provide a comprehensive framework for ICU practice, the rapid evolution of evidence in recent years underscores the need for updated and practice-oriented syntheses. In this way, the review not only complements existing guidelines but also highlights the indispensable role of clinical pharmacists, serving as a concise and clinically applicable resource for ICU clinicians.

PAIN

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.”⁸ This comprehensive definition highlights that pain is not merely a physiological phenomenon, but also a psychological and highly individual experience. Studies have shown that approximately 70% of patients discharged from the ICU report experiencing moderate to severe pain during their stay.^{4,9}

Primary causes of pain in the ICU include underlying illness, surgical procedures, endotracheal intubation, mechanical ventilation, patient repositioning, physiotherapy, nasogastric tube placement, and the use of invasive catheters.¹⁰ If left untreated, pain can lead to a range of

adverse effects. In the short term, it may cause hypermetabolism, increased oxygen consumption, hypercoagulability, and immune dysfunction.^{11,12} In the long term, it may result in chronic pain and psychiatric conditions such as post-traumatic stress disorder.¹³ Therefore, pain management is considered a cornerstone of comprehensive ICU patient care. Current guidelines—particularly the SCCM PADIS guidelines—recommend assessing and addressing pain before initiating sedative therapy. This approach is known as “analgesia-first sedation” or “analgo-sedation.”¹⁴⁻¹⁶

Pain Assessment

Since pain is a subjective parameter, the gold standard for its assessment is the patient’s own report.¹⁷ However, in situations where communication is impaired—as is often the case in ICU settings—both physiological and behavioral indicators can guide the assessment process. Given the multitude of factors in the ICU that can influence physiological responses, relying solely on vital signs is not recommended.⁴ Instead, validated and reproducible pain assessment tools that evaluate both behavioral signs (e.g., facial grimacing, restlessness, combativeness, diaphoresis) and physiological indicators (e.g., tachycardia, hypertension, hyperventilation) are recommended.¹⁸

The choice of assessment tool should be based on the patient’s ability to communicate:

- For patients who can communicate:
 - **Numeric Rating Scale (NRS):** Patients rate their pain on a scale from 0 (no pain) to 10 (worst possible pain).¹⁹
 - **Visual Analog Scale (VAS):** Patients mark their level of pain on a visual line representing a pain continuum.²⁰
 - **Verbal Rating Scale (VRS):** Patients select descriptive terms that best represent their pain intensity.²¹
- For patients who cannot communicate:
 - **Behavioral Pain Scales:** Tools such as the Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) assess observable indicators such as facial expressions, body movements, and physiological responses.^{4,22} (Supplementary)

Pain Management

Pain arises from inflammatory mediators such as bradykinin, prostaglandins, and substance P released in response to tissue injury. These mediators stimulate peripheral nerve endings, resulting in pain signals transmitted to the central nervous system.²³ The therapeutic goal is to reduce pain perception by blocking one or more of these pathways. The medications used exert their effects by inhibiting prostaglandin synthesis, reducing perception at the central nervous system level, or blocking nerve conduction.²⁴

In the ICU setting, opioids are the most frequently used drugs for pain control. They are preferred due to their short half-lives, effective analgesic profiles, and the ability to titrate doses according to clinical response. However,

opioid use can lead to various side effects such as respiratory and consciousness depression, delirium, nausea, vomiting, hypotension, urinary retention, decreased bowel motility, pruritus, tolerance development, and risk of dependence. Therefore, it is recommended to use the lowest effective dose possible and to prefer multimodal approaches by combining other analgesic agents.^{25,7}

Opioids exert their analgesic effects by binding to μ -opioid receptors.²⁶ Given the variability in pharmacokinetic properties, metabolic pathways, and side effect profiles among different opioids, individualized drug selection is necessary. Factors influencing the choice include the expected duration of action, the patient's hepatic and renal function, concomitant medications, presence of extracorporeal organ support therapies, drug availability, and cost.^{4,16,7} Table 1 summarizes the pharmacokinetic properties of commonly used opioid analgesics. The general characteristics and drug-specific advantages in terms of clinical use are discussed below under each respective opioid heading.

Morphine

Morphine is the prototype opioid. Due to its hydrophilic nature, it crosses the blood-brain barrier more slowly than other opioids, resulting in a delayed onset of action. It is less commonly used for pain control in the ICU and is mainly employed in palliative care.^{4,27} Morphine is metabolized by hepatic glucuronidation; while this confers some advantage in drug interactions, accumulation can occur in cases of hepatic or renal impairment, increasing the risk of prolonged effects and toxicity.²⁸ It can induce histamine release causing side effects such as hypotension and bronchospasm.⁴ Additionally, morphine can induce histamine release, which may result in hypotension and bronchospasm, limiting its use particularly in hemodynamically unstable patients. These pharmacodynamic disadvantages contribute to its infrequent preference in emergency and critical care settings.^{4,7,28}

Fentanyl

Fentanyl, a synthetic derivative of morphine, is approximately 100 times more potent. Its lipophilic nature results in a rapid onset of action; however, prolonged infusions may cause accumulation in adipose tissue leading to prolonged

sedation. Due to less histamine release, its hemodynamic side effects are lower compared to morphine.²⁹ This makes fentanyl more suitable for use in hemodynamically unstable patients. Additionally, its favorable pharmacological profile—characterized by potency, rapid onset, and ease of titration—allows for safe use in patients with bronchospasm or those breathing spontaneously. With appropriate dose adjustments, it can also be safely administered in cases of renal or hepatic impairment. Rapid bolus doses can cause skeletal muscle rigidity. It is metabolized hepatically, and in obese patients, standard dosing independent of weight or dose adjustment based on adjusted body weight is recommended due to altered volume of distribution.³⁰

Remifentanyl

Remifentanyl has analgesic potency similar to fentanyl but is rapidly degraded by plasma esterases, with effects dissipating within 5-10 minutes after infusion cessation. This pharmacokinetic profile is independent of organ function, allowing safe use in patients with hepatic or renal failure. Due to its ultra-short duration of action, remifentanyl permits frequent and accurate neurological assessments, which is particularly advantageous in critically ill patients requiring serial evaluations.^{4,7} Although remifentanyl is used as a first-line agent in some centers, its use in the United States is limited by concerns over tachyphylaxis, cost, and the potential for opioid-induced hyperalgesia following discontinuation. Despite these pharmacokinetic advantages, a large meta-analysis conducted in 2009 showed no significant benefit of remifentanyl regarding mortality, ventilation duration, or agitation.³¹ The formulation contains glycine as an excipient, which poses a risk of neurotoxicity in renal failure. Additionally, due to its lipophilicity and altered volume of distribution in obese patients, dose adjustments based on adjusted body weight are necessary, while in geriatric patients, a 50% reduction in starting dose is advised due to decreased clearance.³²

Hydromorphone

Hydromorphone is a semi-synthetic opioid that is more potent and somewhat more lipophilic than morphine, with a faster onset of action and a shorter half-life.³³ Unlike morphine, it produces fewer active metabolites, which can

Table 1. Pharmacokinetics of Opioid Analgesics¹⁶

Equi-Analgesic Dose (mg)						
Opiates	IV	PO	Onset (IV)	Elimination Half-Life	Context Sensitive Half-Life	Metabolic Pathway
Fentanyl	0.1	N/A	1-2 min	2-4 hr	200 min (6-hr infusion), 300 min (12-hr infusion)	N-dealkylation CYP3A4/5 substrate
Hydromorphone	1.5	7.5	5-15 min	2-3 hr	N/A	Glucuronidation
Morphine	10	30	5-10 min	3-4 hr	N/A	Glucuronidation
Methadone	N/A	N/A	1-3 d	15-60 hr	N/A	N-demethylation, CYP3A4/5, 2D6, 2B6, 1A2 substrate
Remifentanyl	N/A	N/A	1-3 min	3-10 min	3-4 min	Hydrolysis by plasma esterases

d, day; hr, hour; IV, intravenous; min, minutes; N/A, not applicable; PO, peroral.

be an advantage in patients with renal impairment. It is metabolized in the liver to hydromorphone-3-glucuronide (H3G), a compound that may cause neuroexcitatory effects such as agitation or myoclonus, and is renally excreted. Although H3G can be removed by hemodialysis, accumulation between treatments is possible and requires careful monitoring. Compared with fentanyl, hydromorphone is less lipophilic, resulting in a more predictable offset and lower risk of prolonged sedation after discontinuation. In patients with hemodynamic instability, it may be preferable to morphine because of less histamine release and reduced risk of hypotension. Typical ICU dosing includes intermittent intravenous administration (0.2-0.6 mg every 2-3 hours as needed) or continuous infusion (0.5-3 mg/hour), titrated according to pain scores and clinical response. While clinical data in ICU settings are more limited than for fentanyl or morphine, available studies suggest comparable efficacy and safety, supporting its role as an alternative opioid in selected critically ill patients.³⁴

Methadone

Methadone is a long-acting synthetic opioid that acts additionally via NMDA receptor antagonism and monoamine reuptake inhibition. It can be used to prevent opioid withdrawal, manage hyperalgesia, and facilitate weaning from mechanical ventilation. Its prolonged duration of action allows for intermittent bolus administration, either orally or intravenously, making it suitable for managing chronic pain conditions such as burn injuries. Methadone is utilized for preventing opioid withdrawal, managing opioid-induced hyperalgesia, and facilitating weaning from mechanical ventilation. Due to its highly variable half-life, ranging from 8 to over 59 hours, there is a significant risk of drug accumulation. Methadone may also prolong the QTc interval, necessitating regular electrocardiographic monitoring. The drug is metabolized hepatically, and dose adjustments are recommended in patients with severe renal impairment.³⁵

In ICU pain management, instead of using opioids alone, a multimodal analgesia approach involving agents with different mechanisms of action is recommended. This strategy helps reduce opioid requirements and thus minimize side effects. The commonly used agents include^{14,15,16}:

- Pharmacological agents:
- Acetaminophen
- Non-steroidal anti-inflammatory drugs (Ibuprofen)
- Ketamine (low-dose NMDA antagonism)
- Dexmedetomidine (α_2 -agonist providing analgesic and sedative effects)
- Gabapentinoids/Carbamazepine (especially for neuropathic pain)
- Non-pharmacological approaches:
- Supportive methods such as massage, music therapy, and relaxation techniques

Certain opioids and non-opioid agents are recommended to be avoided in the ICU setting. These include meperidine,

due to its neurotoxic metabolite normeperidine which increases seizure and delirium risk; codeine, due to low analgesic efficacy; alfentanil and sufentanil, because of cost inefficiency; tramadol due to unpredictable interaction profiles; opioid agonist-antagonists (e.g., buprenorphine, nalbuphine), which may precipitate withdrawal symptoms in chronic opioid users; and intravenous lidocaine, for which sufficient evidence supporting efficacy in critically ill patients is lacking.⁷

SEDATION

In the ICU, continuous deep sedation is indicated for only a small subset of patients, except in certain conditions such as status epilepticus, intracranial hypertension, severe respiratory failure, and the use of neuromuscular blocking agents.⁴ Since the 1990s, awareness of the adverse effects associated with deep sedation has increased, leading to the development of protocol-based titration strategies aimed at achieving light sedation. When adequate sedation cannot be achieved through targeted analgesic titration alone, the use of additional sedative agents is recommended, with an emphasis on avoiding deep sedation.³⁶

Monitoring the depth and quality of sedation is a critical practice that directly impacts clinical outcomes in critically ill patients. However, studies conducted across different countries reveal that sedation depth is frequently insufficiently monitored in clinical practice, representing a significant gap in patient management.³⁷

Sedation Assessment

Distinguishing between sedation and agitation can be challenging. Therefore, patient sedation levels should be systematically monitored using validated assessment tools. Currently, widely used scales include the Richmond Agitation-Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS), both regarded as the gold standard for sedation monitoring in the ICU. Routine assessments facilitate daily re-evaluation and adjustment of individualized sedation targets^{4,14,15,16} (Supplementary).

Electroencephalography-based monitoring systems are used as alternative assessment tools, particularly in patients under neuromuscular blockade where behavioral evaluation is impossible. Nevertheless, their widespread clinical use is limited due to decreased reliability in elderly patients, cost, and susceptibility to movement artifacts.³⁸

Sedation Management

Sedative selection should be guided by the underlying etiology of patient distress^{4,14,15,16}:

- Pain/dyspnea: Opioids or non-opioid analgesics
- Anxiety/agitation: Propofol, dexmedetomidine, benzodiazepines
- Delirium: Antipsychotics

- Withdrawal syndrome: Benzodiazepines, methadone, clonidine, among others

Additionally, patient hemodynamic status, organ function, concurrent therapies, and potential drug interactions should inform agent choice.

Dexmedetomidine

Dexmedetomidine, an α_2 -adrenergic receptor agonist, exerts moderate anxiolytic, sedative, and analgesic effects and is preferred in mechanically ventilated patients.³⁹ Numerous randomized controlled trials and meta-analyses have demonstrated its capacity to reduce delirium incidence, ICU length of stay, and duration of mechanical ventilation, though it has no significant impact on mortality. A meta-analysis of 29 randomized studies included in the 2025 SCCM guidelines reported a significant reduction in delirium prevalence (RR 0.55), shortened delirium duration, and a modest but statistically significant decrease in ICU stay length. Compared to other sedatives, dexmedetomidine did not show a significant difference in mechanical ventilation duration or mortality but was associated with an increased risk of bradycardia (RR 1.65) without significant changes in hypotension risk.¹⁴ Another large 2022 meta-analysis corroborated these findings, reporting reduced delirium risk (RR 0.67), ventilation duration (mean difference (MD) -1.8 hours), and ICU length of stay (MD -0.32 days), alongside increased hypotension and bradycardia rates (4% and 6%, respectively).⁴⁰ A 2018 network meta-analysis involving 4491 patients revealed that benzodiazepines and propofol were associated with a higher delirium risk compared to dexmedetomidine.⁴¹

Dexmedetomidine may also serve as an adjunctive agent in alcohol withdrawal, potentially reducing the need for alternative sedatives. Loading doses are not recommended due to risks of cardiovascular instability, tachycardia, bradycardia, and atrioventricular block. Dose adjustment based on adjusted body weight is suggested for obese patients, and geriatric patients should start at lower doses with cautious titration to minimize adverse effects.⁴²

Propofol

Propofol is an intravenous, lipophilic phenol derivative that modulates GABA_A receptors, producing amnestic, anxiolytic, anticonvulsant, and muscle-relaxant effects. It lacks direct analgesic properties and is typically administered alongside analgesics. Its formulation contains soybean oil, egg lecithin, and glycerol; therefore, it is contraindicated in patients with allergies to egg or soy.⁴³ A 2018 network meta-analysis of 31 randomized trials found that benzodiazepines prolonged ICU stay compared to propofol (HR 3.62, 95% CI 0.834-6.2) without affecting mortality.⁴¹ Similarly, a large randomized open-label trial reported fewer ventilation days with propofol infusion plus daily sedation interruption compared to lorazepam bolus (mean propofol dose 24.4 ± 16.3 mcg/kg/min; median lorazepam dose 11.5 mg/day).⁴⁴

Given its high caloric density (1.1 kcal/mL), prolonged infusions beyond 24-48 hours may cause excessive caloric load, necessitating metabolic monitoring. Biochemical

parameters, including serum triglycerides, should be closely monitored, especially during the first 3 days. Vigilance for propofol infusion syndrome is essential, with suspected cases requiring evaluation of serum lactate, creatine kinase, and myoglobin.⁴⁵

Propofol offers rapid onset, short duration, and effective sedation but demands cautious monitoring and limited duration of use due to potential adverse effects and metabolic burden.^{4,7}

Benzodiazepines

Although first-line agents for alcohol withdrawal, benzodiazepines have limitations in ICU sedation of critically ill patients. Despite their anxiolytic efficacy, benzodiazepines increase delirium risk, prolong mechanical ventilation and ICU stay, and may cause prolonged sedation due to accumulation of lipid-soluble metabolites. These findings suggest benzodiazepines are less favorable than propofol or dexmedetomidine in terms of patient outcomes.^{4,7}

Midazolam, the only benzodiazepine without propylene glycol in its intravenous formulation, acts as a short-acting sedative and anxiolytic with an onset of 2-5 minutes and a duration of approximately 30 minutes for single doses. It is preferred for acute agitation control in short-term (<48 hours) sedation due to rapid onset and potent amnestic effects. However, midazolam is metabolized by CYP3A4 into active metabolites, which may accumulate during prolonged use, leading to unwanted sedation. Due to multiple drug interactions and increased delirium risk, its use requires caution. Dosing in obese patients is preferably weight-independent or adjusted based on adjusted body weight if weight-based dosing is applied.⁴⁶

DELIRIUM

Delirium is characterized by acute and severe confusion and rapid fluctuations in brain function occurring in association with physical or mental illness. The pathophysiology of ICU delirium is not fully elucidated and varies with multiple etiologies.⁴⁷ The increased risk associated with GABA_A agonists and anticholinergic drugs suggests critical roles for GABAergic and cholinergic neurotransmitter systems. Other proposed mechanisms include excessive dopaminergic activity and direct neurotoxic effects of inflammatory cytokines. However, the lack of definitive proof results in largely empirical pharmacologic management strategies.^{4,48}

Delirium Assessment

Delirium manifests clinically in hypoactive, hyperactive, and mixed forms^{47,49}:

- Hypoactive delirium is marked by a notable reduction in the consciousness level and carries higher mortality than other forms.
- Hyperactive delirium presents with increased psychomotor and autonomic activity.

- Mixed delirium is diagnosed when features of both forms coexist intermittently.

Two common scales are used for delirium diagnosis:

- Confusion Assessment Method for the ICU (CAM-ICU): A rapid assessment tool for delirium presence at a single time point.⁵⁰
- Intensive Care Delirium Screening Checklist (ICDSC): Evaluates delirium symptoms observed over a defined period.⁵¹

Delirium Management

Management of ICU delirium is predominantly based on expert consensus and observational studies, as controlled clinical trials remain limited. The most effective preventive approaches are multicomponent and nonpharmacological strategies, particularly when targeted to high-risk patients. Core principles of prevention and treatment include avoidance of exacerbating factors such as polypharmacy, dehydration, immobility, sensory impairment, and sleep-wake cycle disruption; identification and treatment of underlying acute illness; and supportive care to prevent physical and cognitive decline.⁴⁹ Maintaining adequate hydration and nutrition, promoting mobility and range of motion, treating pain and discomfort, preventing skin breakdown, improving incontinence—which affects more than half of delirium patients—and minimizing the risk of aspiration pneumonia are essential supportive measures.^{49,52}

To address agitation, frequent reassurance, gentle touch, and verbal redirection are recommended, preferably delivered by family members or familiar individuals, though professional caregivers may also be effective. Physical restraints should be considered only as a last resort, since they often exacerbate agitation and increase the risk of complications such as pressure ulcers, aspiration, loss of mobility, and prolonged delirium.^{49,53}

Pharmacological therapy is reserved for severe behavioral disturbances, particularly hyperactive delirium associated with self-harm risk, when non-pharmacological strategies are insufficient. Antipsychotics remain the mainstay in this context. Haloperidol, the most commonly used agent in ICU delirium, has a long clinical track record and continues to be the standard treatment, although it has not been shown to prevent or shorten delirium duration.^{54,55} Newer atypical antipsychotics—such as quetiapine, risperidone, ziprasidone, and olanzapine—appear to have comparable efficacy with potentially fewer adverse effects, though head-to-head trials in critically ill patients remain limited.⁵⁶ Importantly, haloperidol requires careful monitoring due to risks of extrapyramidal side effects and QT prolongation.^{54,56}

Benzodiazepines have a limited role in delirium management and are primarily indicated in cases of alcohol or sedative withdrawal or when antipsychotics are

contraindicated. Despite this, surveys suggest they remain overprescribed in practice. Other sedatives, including dexmedetomidine and propofol, are frequently used in the ICU to manage anxiety and pain and are occasionally applied to control agitation, although they may themselves contribute to delirium.^{4,57} Hypoactive delirium, by contrast, is generally managed with supportive care alone, without specific pharmacological intervention.⁵⁸

Clinical Pharmacists' Contributions to Pain, Sedation, and Delirium Management in the Intensive Care Unit

The American College of Clinical Pharmacy defines clinical pharmacy as an area of pharmacy concerned with the science and practice of rational medication use.⁵⁹ Clinical pharmacists contribute significantly to the quality of pharmacotherapy and patient outcomes in the ICU by participating in ward rounds, reconciling medications, supporting appropriate drug selection, adjusting and titrating doses, managing drug-drug interactions, monitoring adverse effects, tracking treatment durations, educating the healthcare team, and improving medication administration procedures.⁶⁰ Additionally, intensive care pharmacists play a valuable role in optimizing the use of analgesics and sedatives in critically ill patients, owing to their understanding of the pharmacokinetic and pharmacodynamic complexities of these agents.⁶¹

Several studies have highlighted the specific contributions of clinical pharmacists to the management of sedatives and analgesics. Marshall et al⁶² (2008) demonstrated that pharmacist-led interventions during and after ward rounds—focusing on sedation planning, titration to Sedation-Agitation Scale targets, pain and delirium management, and individualized dose adjustments—resulted in significant reductions in the duration of mechanical ventilation, ICU stay, and hospital length of stay. Similarly, Louzon et al⁶³ (2017) implemented a 2-phase initiative in which pharmacists enhanced adherence to pain-agitation-delirium protocols, encouraged the use of non-benzodiazepine sedatives, and collaborated within an interprofessional team applying the bundle. These interventions led to reductions in sedation exposure, ventilator days, and ICU stay. In addition, pharmacist-directed sedation management achieved a 46% reduction in continuous sedative infusions, shorter ICU and hospital stays, and cost savings exceeding \$1 million, with further improvements observed when pharmacists collaborated on bundle implementation. The overall evidence base further supports these findings. A recent systematic review by Buckley et al⁶¹ (2023), synthesizing 9 studies with a total of 3769 patients, concluded that pharmacist-led interventions reduced sedative and opioid utilization, decreased the duration of mechanical ventilation, and shortened ICU and hospital stays in several studies. Although effects on mortality and delirium were not consistent, the review highlighted meaningful improvements in resource utilization and significant cost savings, with reported reductions ranging from \$1.2 to \$7.2 million.

Taken together, the growing body of evidence clearly demonstrates that the integration of clinical pharmacists into ICU teams provides tangible benefits in the management of pain, sedation, and delirium. Beyond optimizing pharmacotherapy, their active participation fosters multidisciplinary collaboration, enhances adherence to clinical guidelines, and supports cost-effective care. Clinical pharmacists therefore play a pivotal role in ensuring safer and more rational medication use, improving both clinical and economic outcomes in critically ill patients.⁶¹⁻⁶³

Conclusion

Despite significant advances in the management of ICU pain, sedation, and delirium, many clinical and pharmacological questions remain unresolved. Further investigation into the pharmacokinetics and pharmacodynamics of sedatives and analgesics in vulnerable subgroups—such as obese, elderly, and patients with organ dysfunction—is essential to optimize dosing and minimize adverse effects.^{64,65} Personalized treatment approaches, guided by multimodal analgesia and goal-directed sedation protocols, are critical to improving both safety and efficacy.¹⁶ Incorporating pharmacogenetic insights into

clinical practice may further enable individualized therapy, reducing variability in treatment response and adverse outcomes.⁶⁶ The overarching goal of ICU pain and sedation management strategies should be to enhance patient comfort, improve long-term functional outcomes, and preserve quality of life.

Future progress will rely on expanding the number of prospective randomized controlled trials evaluating multimodal strategies and on integrating emerging technologies into clinical practice. Artificial intelligence-driven decision support systems hold promise for predicting delirium risk, optimizing sedation depth, and generating real-time alerts for adverse drug interactions.⁶⁷

Ultimately, advancing ICU pain, sedation, and delirium management requires a comprehensive, multidisciplinary approach that integrates guideline-based care with innovative tools from precision medicine. By leveraging these strategies, future practice has the potential to shorten ICU stays, reduce complications, improve survival, and enhance the long-term quality of life for critically ill patients.

Table 2. Commonly Used Sedative-Analgesic Drug Doses Unadjusted for Renal and Hepatic Function

Medication	Dosage
Fentanyl	0.35-0.5 mcg/kg every 0.5-1 hour intermittent and/or 0.7-10 mcg/kg/hr infusion
Morphine sulphate	2-4 mg every 1-2 hours intermittently and/or 2-30 mg/hr infusion
Remifentanyl	Loading: 1.5 mcg/kg; ¹ 0.5-15 mcg/kg/hr infusion maintenance
Propofol	5 mcg/kg/min 5 minute infusion loading; ² 5-50 mcg/kg/min maintenance Titrate in 5-10 mcg/kg/min increments every 5-10 minutes ³
Dexmedetomidine	Loading: 1 mcg/kg for 10 minutes; ⁴ 0.2 to 0.7 mcg/kg/hr maintenance ⁵ Start at 0.2 mcg/kg/hr and titrate every 30 minutes
Midazolam	Loading: 0.01-0.05 mg/kg; ⁶ 0.02-0.1 mg/kg/hr infusion ⁷ maintenance
Haloperidol	0.03-0.15 mg/kg loading, various intermittent regimens have been used (e.g., 1.25-5 mg every 8-12 hours depending on severity of agitation, age, and cardiovascular risk factors. Continuous infusions are rarely indicated (e.g., 0.5-2 mg/hr)
Quetiapine	Oral: Initially, 50 mg every 12 hours; increase up to 400 mg/day every 24 hours if necessary
Olanzapine	Optional loading: 5-10 mg IM. May be repeated every 2-4 hours if necessary (maximum 30 mg total). Oral: 5-10 mg once daily initially; increase by 5 mg increments every 24 hours as needed up to 20 mg/day

IM, intramuscular; min, minutes.

1. Most ICU patients can be treated without bolus doses; if necessary, a bolus of 0.5 mcg/kg is usually sufficient; larger boluses are associated with significant decreases in heart rate and mean arterial pressure.

2. An IV loading dose of propofol should be administered only to patients who are unlikely to develop hypotension.

3. Some patients may require doses up to 70 mcg/kg per minute, which may increase the risk of propofol infusion syndrome.

4. Avoid IV loading doses of dexmedetomidine in hemodynamically unstable patients.

5. The maintenance infusion rate of dexmedetomidine may be increased up to 1.5 µg/kg/hour if tolerated.

6. 0.5-4 mg; this non-weight-based dosage may be preferred.

7. 2-8 mg/hour; this non-weight-based dosage may be preferred) with intermittent bolus dose(s) if necessary. Periodic re-boluses may be required to maintain sedation target while the patient is on continuous infusion. This approach may help prevent unnecessary dose escalation of the infusion.

One or more loading doses may be required. See onset of action data for minimum interval between re-dosing. The loading dose should be reduced or omitted in patients who are elderly, hypovolemic, have increased vasopressor requirements, or are at risk of hemodynamic compromise.

When using propofol, serum triglyceride levels should be measured before initiating treatment and every 3-7 days thereafter, especially if treatment is administered for more than 48 hours and/or at doses ≥50 mcg/kg/min.

Special Patient Groups

In obese patients, fentanyl, remifentanyl, propofol, dexmedetomidine and midazolam are dosed according to adjusted body weight.

In geriatric patients, the starting dose of remifentanyl is reduced by 50%.

Table 3. Approach to Pain, Sedation, and Delirium According to SCCM Guidelines.¹⁶

	Pain	Agitation	Delirium
Assess	x4/h and assess as needed. Recommended assessment tools: Patient who can express: NRS (0-10) Patient who cannot express: BPS (3-12) or CPOT (0-8) If NRS ≥ 4 , BPS >5 or CPOT ≥ 3 , the patient is experiencing significant pain, treatment is recommended.	x4/h and assess as needed. Recommended assessment tools: RASS (-5 to +4) or SAS (1-7) Agitated: RASS +1 to +4 or SAS 5-7 Awake and calm: RASS=0 or SAS=4 Light sedation: RASS=-1 to -2 or SAS=3 Deep sedation: RASS=-3 to -5 or SAS=1-2	Assess at every shift and as needed. Recommended assessment tools: CAM-ICU (+ or -) ICDSC (0-8) If CAM-ICU is positive or ICDSC ≥ 4 , delirium is present.
Manage	Non-pharmacological treatment: Relaxation therapy (massage, music) Pharmacological treatment: Non-neuropathic pain: IV opioid + non-opioid analgesic Neuropathic pain: gabapentin or carbamazepine + IV opioid	Target sedation: RASS=-2 to 0 or SAS=3-4 If below target (RASS >0 , SAS >4): Assess/treat pain, then start sedative as needed (do not start benzodiazepines unless alcohol or benzodiazepine withdrawal). If above target (RASS <-2 , SAS <3): Withhold sedation until target is reached, then restart at 50% of previous dose.	Treat pain as needed. Reorient patients, familiarize them with their surroundings, use patient's glasses or hearing aids if available. Pharmacological treatment of delirium: Avoid benzodiazepines unless patients requiring sedation are in alcohol or benzodiazepine withdrawal, use dexmedetomidine. Avoid rivastigmine. Avoid antipsychotics if high risk of Torsades de Pointes.
Prevent	Administer pharmacologic and/or nonpharmacologic analgesia prior to procedure. Treat pain first, sedate later.	Consider trying daily spontaneous breathing, early mobilization, and exercise.	Identify delirium risk factors: Dementia, hypertension, coma, benzodiazepine use, alcohol abuse. Avoid benzodiazepines. Mobilize patient early. Manage sleep (light, noise control). Restart baseline psychiatric medications if indicated.

BPS, Behavioral Pain Scale; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; CPOT, Critical-Care Pain Observation Tool; ICDSC, Intensive Care Delirium Screening Checklist; IV, intravenous; NRS, Numeric Rating Scale; RASS, Richmond Agitation-Sedation Scale; SAS, Sedation-Agitation Scale.

An overview of the approaches to assess, manage, and prevent pain, sedation, and delirium in critically ill patients is illustrated in Table 2. Additionally, dosages of commonly used sedative-analgesic drugs are presented in Table 3.

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SUPPLEMENTARY

Behavioral Pain Scale		
Subscale	Definition	Point
Facial Expression	Relaxed	1
	Partially Tightened	2
	Fully Tightened	3
	Grimacing	4
Upper Extremity	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Ventilator Synchrony	Tolerating movement	1
	Coughing but tolerating ventilation	2
	Fighting ventilatör	3
	Unable to control ventilation	4

Behavioral Pain Scale: Analgesia is considered for scores ≥ 6 .

Critical-Care Pain Observation Tool		
Subscale	Definition	Point
Facial Expression	Relaxed	0
	Tense	1
	Grimacing	2
Body Movements	No movement	0
	Protection	1
	Restlessness	2
Muscle Ton	Relaxed	0
	Tense, rigid	1
	Very tense or rigid	2
Ventilator Synchrony	Tolerant movement	0
	Coughs but mostly tolerates	1
	Fighting the ventilatör	2
Vocalization (for extubated patients)	Speaking in a normal tone or silent	0
	Sighing or moaning	1
	Crying out, sobbing	2

Critical Care Pain Observation Tool: Analgesia is considered for scores >2 .

Richmond Agitation-Sedation Scale		
Point	Criteria	Definition
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive vigorous
0	Alert and calm	Shows spontaneous interest in caregiver
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable sedation	No response to voice or physical stimulation

Richmond Agitation-Sedation Scale

Riker Sedation-Agitation Scale.

Point	Criteria	Definition
7	Dangerous agitation	Tries to remove monitors and devices or climb out of bed; tosses and turns; lashes out at staff
6	Very agitated	Remains restless despite frequent verbal reassurance; bites endotracheal tube; requires restraint
5	Agitated	Anxious or restless; attempts to move; calms down with reassurance
4	Calm and cooperative	Calm; easy to arouse; able to follow instructions
3	Sedated	Difficult to awaken; responds to verbal prompts or gentle shaking but drifts off again
2	Very sedated	Incommunicative; responds to physical stimuli but not verbal instructions; may move spontaneously
1	Unarousable	Incommunicative; little or no response to painful stimuli

Riker Sedation-Agitation Scale.