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# Management of Pain, Agitation, and Delirium in Mechanically Ventilated Oncology Patients

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Additional information is available at the end of the chapter

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## Abstract

Attention has heightened over the last several years to the importance of managing pain, agitation, and delirium in mechanically ventilated patients due to the multiple long-term adverse effects patients experience after an intensive care unit (ICU) admission. Furthermore, clinical practice is being molded not just by the guidelines and randomized controlled trials, but also by the information gathered from real patient experiences to improve care at the bedside. The literature continues to remain sparse for providing guidance specifically in the oncology population. Therefore, several resources have been combined to better assist clinicians on making sound decisions for keeping patients comfortable on the ventilator while recognizing the differences in treatment that may need to be employed due to these patients' medical condition.

**Keywords:** Ventilation, Pain, Agitation, Delirium, Sedation

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## 1. Introduction

One of the leading causes of an intensive care unit (ICU) admission is acute respiratory failure where approximately 44–69% of patients with malignancies requiring mechanical ventilation due to the progression of cancer or chemotherapy toxicity [1]. Improved survival of critically ill oncology patients has been due to the advances in the treatment of malignancies and more appropriate triage of patients for ICU admission [2]. Thus, not all families of intubated patients are met with discussions for end of life or hospice care of their loved one. Goals of weaning and extubation to allow the resumption of cancer treatment have become more common.

There is a potential increase in number of oncology patients that clinicians will manage on mechanical ventilation in the future. Therefore, the need for appropriate protocols to treat pain,

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agitation, and delirium is especially crucial for a population on chronic pain and anxiety medications prior to admission. However, national guidelines published by the Society of Critical Care Medicine (SCCM) in 2013 were primarily based on data from the nononcology population, which poses challenges in applying such concepts to these patients. Such protocol outcomes lack support from clinical trials in oncology patients. Studies involving ICU patients with cancer have largely focused on mortality outcomes, rather than improvement of care, due to these patients' overall poor prognosis. Thus, the concepts described in the SCCM guidelines must be applied simultaneously with literature on effective treatment of pain and agitation in noncritically ill oncology patients.

In addition to clinical trials, patient interviews conducted in the ICU are gaining more attention to help the clinician better predict the needs of the patient on mechanical ventilation. A prospective study, conducted in a medical ICU, evaluated the symptom experience of patients with a present or past diagnosis of cancer admitted during an 8-month period. The patients expressed the procedures associated with the greatest pain or discomfort were endotracheal suctioning, endotracheal and nasogastric tubes, mechanical ventilation, arterial puncture, and turning. The aspects of the environment reported to be most stressful were inability to communicate, communicate, sleep disturbances, and limited family visitation hours [2]. In this study, patients still experienced significant discomfort despite liberal administration of opioids and sedatives, along with the implementation of palliative care recommendations. This could be explained by the challenge of accurately assessing pain in mechanically ventilated patients, as well as the rate in which patients felt their stress was not relieved by medications. For these reasons, it is imperative that a multidisciplinary team acquires a consistent and universal method by which these patients' pain, agitation, and delirium are managed. More importantly, the clinicians should have a strong understanding of the pharmacology of opioids and sedatives to ensure the safest agents are chosen.

## 2. Pain

The prevalence of pain has not been shown to differ between patients actively receiving anticancer treatment and those with an advanced- or terminal-phase disease. Studies have also published that on average 56–82.3% of cancer patients' pain is not adequately treated [3]. This emphasizes the importance of performing accurate and timely assessments of pain to ensure appropriate treatment. As recommended by SCCM guidelines, the gold standards for pain assessments in ICU patients are the numerical rating scale or visual analog scale (VAS) if a patient is communicative enough to express their level of pain. In some instances, such assessments can be challenging in ICU patients receiving high-dose sedatives during mechanical ventilation or those with altered level of consciousness [4]. If the patient is unable to self-report his/her pain, then the most valid and reliable assessments for pain are the behavioral pain scale (BPS) and the critical pain observation tool (CPOT) outlined in **Tables 1** and **2** [5], which are consistent with recommendations by NCCN guidelines for adult cancer pain. Vital signs alone are no longer recommended for detecting symptoms of pain. They only should be used as a cue to perform further assessments [4].

Indicator	Descriptor	Score	
<b>Facial expression</b>	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tensed	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
<b>Body movements</b>	Does not move at all (does not necessarily mean absence of pain)	The absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
<b>Muscle tension evaluation by passive flexion and extension of upper extremities</b>	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
<b>Compliance with the ventilator (intubated patients)</b> OR	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
<b>Vocalization (extubated patients)</b>	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2

**Table 1.** Critical pain observation tool (CPOT) [5].

Chronic pain affects greater than 60% of oncology patients, with upwards of 66% experiencing failure of therapy [6]. Subsequently, the majority of these patients are opioid tolerant and on high doses of narcotics prior to being admitted. Upon ICU admission, many patients do not have oral access or have multisystem failure that can preclude them from receiving specific types of opioids. It becomes imperative that thorough medication reconciliations are performed to determine the amount of daily opioids the patient takes at home so that they can be converted to the most appropriate and safest formulation in the ICU. When performing such conversions, clinicians must consider incomplete cross tolerance if the patient is placed on an opioid they are not receiving prior to admission. Long-term exposure to one drug can result in the development of tolerance to those with similar structures. However, this tolerance is rarely complete with agents that bind to different receptors, thus the analgesic effect of the

new agent is enhanced in the patient. Without appropriate conversions, the patient is at risk of withdrawal or overdose when rotating opioids. However, the heightened analgesic effect due to incomplete cross tolerance can also lead to excessive side effects such as respiratory depression, nausea, sedation, and dysphoria [7]. The total daily dose of the patient's regimen, both IV and oral, should be converted to the opioid to be initiated in the ICU using **Table 3** and reduced by 20–30% for cross intolerance. Persistent or chronic pain should be controlled using a combination of long-acting agents, either extended or sustained release oral formulations or continuous IV infusions, in conjunction with short-acting agent. Long-acting opioid typically comprises 50% of the total daily requirement [11].

Item	Description	Score
<b>Facial expression</b>	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
<b>Upper limb movements</b>	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
<b>Compliance with mechanical ventilation</b>	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

**Table 2.** Behavioral pain scale (BPS) [5].

Society of Critical Care Medicine Guidelines emphasize that many sources of pain have been identified in ICU patients related to not only surgery, trauma, burns, or cancer but also procedures. In a comparative, descriptive study, data were obtained from over 6000 patients to describe pain intensity and procedural distress. Procedures were defined as wound dressing changes, turning, tracheal suctioning, and wound drainage removal. The average pain score was 5–7, and the most distressful procedures were turning and wound care. Unfortunately, less than 20% of these patients actually received opiates before the procedures. With procedures performed so frequently in the ICU, this remains one of the areas that is poorly managed [12]. Therefore, it is highly encouraged patients are pre-treated with bolus doses of opioids.

Unrelieved pain leads to long-term negative outcomes, such as patients recalling traumatic memories of pain during their ICU admission. It has also been shown that inadequately treated pain is associated with physiological consequences such as increase in catecholamines leading to arteriolar vasoconstriction, impaired tissue perfusion, catabolic hypermetabolism resulting in hyperglycemia, lipolysis, and breakdown of muscle [4].

Drug	Oral (mg)	Parenteral (mg)
Morphine	30	10
Codeine	200	100
Oxycodone	20	n/a
Hydrocodone	30	n/a
Hydromorphone	7.5	1.5
Fentanyl	n/a	0.1
Methadone	Use ratio of 3:1 (morphine/methadone) to convert methadone to morphine equivalents and then convert to desired opioid	
Tramadol	120	100

**Table 3.** Opioid equianalgesic doses [8–10].

Managing pain in ICU patients, especially the mechanically ventilated, is almost always in conjunction with managing agitation and delirium. Therefore, pain can be managed more effectively and appropriately with several simple concepts employed:

1. Nurses should perform consistent and accurate pain assessments using the tools validated in ICU patients with reassessments performed after analgesics are administered to evaluate response to therapy.
2. Intermittent boluses versus continuous IV infusion strategies should be selected based on the frequency and severity of pain and/or patient's mental status. The use of patient-controlled administration (PCA) should be highly considered for patients responsive and cognitive to control delivery of boluses.
3. The type of opioid selected for each patient should be based on the drug pharmacokinetics/ pharmacodynamics including any risks for altered clearance if the patient has evidence of organ dysfunction (see **Tables 4** and **5**).
4. Oral formulations should be limited to those patients with adequate gastrointestinal absorption.
5. Regional or neuraxial (spinal or epidural) modalities can be considered for postoperative analgesia.
6. Administer analgesics pre-emptively prior to procedures (i.e., chest tube removal, line insertion, turning the patient).
7. Analgesic agents should be started prior to sedative agents if there is any suspicion of pain. After sedatives are initiated, pain assessments can be harder to perform and less accurate in ensuring the patient is comfortable.
8. Pain medications should be titrated upward by 10–25% and doses selected based on the pain assessments using nursing driven scales. Opioid rotation should be considered if pain is inadequately controlled or persistent adverse effects are experienced [11].
9. Use of nursing-driven protocol with effective multidisciplinary discussions for adjustment of such medication orders should occur on a routine basis.

Analgesic	Onset (IV)	Duration of action	$t_{1/2}$	Dosing <sup>1</sup>	Common toxicities/major precautions
Fentanyl IV	1–2 min	0.1–5 h	1.5–6 h	25–100 mcg every 15 min PRN pain <b>Infusion:</b> 25–500 mcg/h	Large volume of distribution and high lipophilicity increasing risk of accumulation in tissues and sedation with prolonged infusions; less hypotension effect than morphine; accumulation with hepatic failure; rare: chest wall rigidity at high doses serotonin syndrome
Hydromorphone IV	5–15 min	4–5 h	2–3 h	0.2–0.6 mg every 15 min PRN pain <b>Infusion:</b> 0.5–5 mg/h	Alternative to fentanyl and morphine if long-acting agent is needed; accumulation in hepatic failure
Morphine IV	5–10 min	3–6 h	3–7 h	2–4 mg PRN pain <b>Infusion:</b> 2–15 mg/h	Common: bradycardia/hypotension, respiratory depression, and sedation especially at higher doses. Caution with risk of bronchospasm, histamine release, accumulation of active metabolite (3-morphine glucuronide) in renal failure that can lead to seizures
Methadone oral	1–3 days	4–6 h	8–59 h	2.5–10 mg every 8–12 h (titrated slowly every 3–5 days)	Common: prolongation of QTc, sedation Caution with multiple drug interactions; unpredictable pharmacokinetic/pharmacodynamics; hepatic and renal failure will delay clearance. Rare: serotonin syndrome
Tramadol (for polyneuropathies as second-line agent in patients who did not respond to opioids)	1 h	9 h	6–8 h	50 mg once or twice daily titrated to max of 400 mg/day	Common: somnolence, constipation, dizziness, and hypotension. Reduce dose in renal or hepatic dysfunction; precipitates seizures in patients with history of seizures or those receiving medications that reduce seizure threshold; may increase risk of serotonin syndrome with SSRIs and SNRIs

<sup>1</sup>More aggressive dosing recommendations based on higher tolerance to opioids in most cancer patients. More conservative dosing is recommended for opioid-naïve patients.

PRN, as needed;  $t_{1/2}$ , half-life of elimination; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; IV, intravenous; QTc, corrected QT interval.

**Table 4.** Comparison of most common opioids used in oncology ICU mechanically ventilated patients [4, 13–19].

### 2.1. Route of administration/formulation

The route of administration preferred for non-ICU patients is often oral, whereas for critically ill patients, intravenous is optimal when there is known or suspected altered gastrointestinal (GI) tract absorption. Furthermore, other routes such as intramuscular (IM), subcutaneous, or transdermal requiring systemic absorption are frequently avoided in critically ill patients due

to erratic and unpredictable absorption [13]. Risks of changes in perfusion due to hemodynamic instability and fluid shifts can lead to potentiated or subtherapeutic effects.

## 2.2. Pharmacokinetic/pharmacodynamic properties and side effect profile

**Table 4** illustrates the comparison of the most common analgesics used in ICU mechanically ventilated patients, with the exception of meperidine, which is discouraged in an ICU setting due to the high risk of neurotoxicity. Methadone is occasionally avoided due to the risk of QT prolongation, interaction with common ICU medications, and difficulty dosing. In the oncology setting, patients taking methadone at home can be encountered, and due to its multiple side effects, it should be converted to alternative opioids if the patient is unstable or lacks oral access. Methadone should not be discontinued abruptly without adequate alternative opioids initiated as replacement therapy to prevent withdrawal.

When the patient is hemodynamically unstable or has renal insufficiency, then fentanyl or hydromorphone is recommended as first line agents. Either of two agents, in addition to morphine, can be used for patients with no renal insufficiency or those who are stable [24]. Clinicians should also be cognitive of possible inadequate metabolism and/or clearance of medications in patients with renal and hepatic cancers which may not be evident by laboratory values.

## 2.3. Nonopioid analgesics

Opioid analgesics are most often the first line agents employed in general ICU patients with the ease of administration and ability to titrate. However, in patients with cancer, nonopioid agents provide a novel approach to better controlling their pain long term and helping to reduce opioid requirements. The WHO analgesic ladder provides guidelines for the treatment of cancer pain by suggesting a sequential three step approach based on severity of pain. Nonopioids are recommended for mild pain, weak opioids for moderate pain, and strong opioids for severe pain with fixed scheduled dosing according to the pharmacokinetic properties of the drugs. Typically, the nonopioids initiated in step 1 should be continued in conjunction with opioids added in the next step to allow for agents with different mechanisms of actions to improve analgesic control. There are several common nonopioid agents used to treat cancer pain that can be continued in an ICU if the patient has appropriate access. **Table 5** compares the various classes of nonopioid agents and pharmacokinetics as well as common toxicities of which to be aware when using such agents in the ICU setting. Other nonopioids found to effective in the oncology population are bisphosphonates for bone metastases and medicinal cannabinoids that are not encouraged in the ICU due to their unsafe profile.



Drug/Class	Onset of action	t <sub>1/2</sub>	Dosing	Place in therapy	Common toxicities/major precautions
APAP IV	5–10 min	2.4 h	650 mg q4 h– 1000 mg IV q 6 h (max 4 gm/day)	Opioid sparing effect. IV is a suitable agent for the treatment of	Adjust dose with CrCl <30 mL/min or with CRRT
APAP PO	30–60 min	2 h	325–1000 mg q4–6 h (max 4 gm/day)	mild to moderate pain in patients with no oral access or to assist with reaching peak levels with the first dose faster	Risk for hepatotoxicity; use lower doses in older adults, heavy alcohol use or those who are malnourished
Ketorolac (IM/IV)	10 min	2.4– 8.6 h	30 mg IM/IV, then 15–20 mg IM or IV q6 h up to 5 days (max 120 mg/day × 5 days)	Ketorolac for acute pain postsurgery Benefit has been shown when added to an opioid in	Avoid in renal failure, GI bleeding, platelet abnormality, concomitant angiotensin converting enzyme inhibitory therapy, congestive heart failure; risk of drug interactions with anticoagulants and corticosteroids
Ibuprofen (PO)	25 min	1.8– 2.5 h	400 mg q4 h (max 2.4 gm/day)	WHO Step 3 More effective for cancer pain associated with inflammation	
Ketamine	30–40 sec	2–3 h	Loading dose: 0.1– 0.5 mg/kg Maintenance dose: 0.05–0.4 mg/kg/h	May decrease doses of concurrently used opioids; provides analgesia and sedation as a “dissociative anesthetic”; the treatment of chronic cancer pain not controlled by opioids or opioids plus adjuvant analgesics	Mild to severe emergence reactions (e.g., confusion, excitement, irrational behavior, hallucinations, delirium) [rare]; hypertension; arrhythmias
Steroids	N/A	N/A	Dexamethasone 2–8 mg oral, IV, or	Useful at any step in the WHO analgesic	Gastrointestinal bleeding; increase risk of infection;

Drug/Class	Onset of action	t <sub>1/2</sub>	Dosing	Place in therapy	Common toxicities/major precautions
*Dexamethasone most often prescribed because it causes less fluid retention due to its lower mineralocorticoid effect			SQ q8 h Prednisone 7.5–10 mg daily	ladder when pain is due to edema or inflammation such as metastatic bone pain, neuropathic, and visceral pain	increased blood pressure; metabolic abnormalities; psychiatric disturbances; increased appetite, weight gain; insomnia Regimens should be tapered rather than abruptly discontinued if therapy exceeds 2 weeks
Gabapentin (PO)	N/A	5–7 h	Starting dose=100 mgTID 900–3600 mg/day in three divided doses	Neuropathic pain	CNS depression (common); confusion; ataxia; adjust dose in renal impairment; abrupt discontinuation associated with drug withdrawal syndrome; seizures; adjust for renal impairment
Carbamazepine (PO)	4–5 h	26–65 h, then 12–17 h	Starting dose = 50–100 mg BID; 100–200 mg q4–6 h (max 1200 mg/day)	Neuropathic pain	Somnolence (common); nystagmus; lethargy; Stevens-Johnson syndrome (rare); toxic epidermal necrolysis; agranulocytosis; adjust for CrCl <10 or hemodialysis; caution with hepatic impairment

PO, by mouth; IM, intramuscular; IV, intravenous; CrCl, creatinine clearance; BID, twice daily; TID, three times daily; APAP, acetaminophen; t<sub>1/2</sub>, half-life of elimination; SQ, subcutaneous; CRRT, continuous renal replacement therapy; q, every; N/A, non-applicable; GI, gastrointestinal; CNS, central nervous system.

**Table 5.** Comparison of major non-opioid analgesic classes [4,20–23].

#### 2.4. Unconventional modes of administration

Breathlessness is often a distressing symptom in oncology patients especially during end of life. Alternative routes of opioid administration, via inhaled nebulization and intranasal, have

been studied. Unfortunately, data are still lacking on the efficacy of such routes of administration. However, benefit has been seen due to the short onset of action with these modes of delivery. Both morphine and fentanyl have been administered through nebulization, and fentanyl is preferred intranasally due its lipophilic properties allowing for better absorption [21].

### 2.5. Protocolized management of pain

In mechanically ventilated patients, use of protocols can greatly reduce the delay in treating pain, ICU length of stay, high dose analgesics, and duration of mechanical ventilation. It is advised to initiate orders that allow nurses to select the appropriate dose of an analgesic agent based on the pain scale score. Minimal data exist on the incremental doses that should be administered with various pain scores. However, orders for the analgesic agent of choice have been applied to our current practice in an oncology ICU and proven to be effective which are listed as follows:

- Fentanyl 25 mcg IV every 15 min as needed for numeric pain score 1–2, critical pain observation tool (CPOT) 0–2, and/or Richmond agitation-sedation scale (RASS) +1.
- Fentanyl 50 mcg IV every 15 min as needed for numeric pain score 3–4, CPOT 3–4, and/or RASS +2.
- Fentanyl 75 mcg IV every 15 min as needed for numeric pain score 5–7, CPOT 5–6, and/or RASS +3.
- Fentanyl 100 mcg IV every 15 min as needed for numeric pain score 8–10, CPOT 7–8, and/or RASS +4.

Initial doses are defaulted but can be changed by the prescriber if more aggressive or more conservative doses are needed.

Pain should be assessed routinely especially after analgesic agents are administered. Most nursing standards expect pain to be reassessed within 15–30 min after treatment, and thus, the frequency of analgesic medications should be written to allow redosing in a timely manner if needed [4].

## 3. Analgesia-First Sedation

Recent literature now emphasizes the importance of adequately treating pain prior to use of sedatives. The most common source of agitation identified in intubated patients is pain. If agitation is treated immediately with sedatives, then the patient is at risk of experiencing the physiologic consequences previously discussed because pain remains untreated. Therefore, it may be beneficial to have intermittent analgesic medication orders written to PRN RASS scores in addition to incremental pain scores to allow the nurse to adequately use such medications for agitation (as shown in example above).

If pain is ruled out as the cause of agitation, then other causes should be promptly considered such as hypoxemia, hypoglycemia, hypotension, or withdrawal from alcohol or other drugs [4]. Aside from treating such underlying causes, strategies should be used to help reduce agitation by maintaining comfort for the patient, frequent reorientation, and optimization of the environment to maintain normal sleep patterns. After addressing such issues, sedatives only then should be considered if the patient remains agitated with a goal sedation level established: light for goals of extubation (i.e. the patient is alert, calm, arousable, and able to follow commands) or deep sedation with goals of synchronization with the ventilator, or the prevention of movement in severe trauma/burns/paralysis (i.e. patient is unresponsive to painful stimuli, unable to follow commands) with goals of synchronization with the ventilator, or the prevention of movement severe trauma/burns). Most patients should have goals of light sedation as many studies have demonstrated increased ICU length of stay, mechanical ventilation, delirium, and muscle deconditioning with deep, prolonged sedation [25–27].

Agitation should be assessed as frequently as pain is assessed using the RASS or SAS scales (Tables 6 and 7). Recommendations for options to treat agitation are in Table 8.

Scale	Label	Description
+4	Combative	Combative, violent
+3	Very agitated	Pulls to remove tubes or catheters; aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive, movements not aggressive
0	Alert and calm	Spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening & contact >10 s)
-2	Light sedation	Briefly awakens to voice (eyes open & contact < 10 s)
-3	Moderate sedation	Movement or eye opening to voice (no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

**Table 6.** Richmond agitation sedation scale (RASS) [28].

Score	Term	Descriptor
7	Dangerous agitation	Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
6	Very agitated	Requiring restraint and frequent verbal reminding of limits, biting ET tube
5	Agitated	Anxious or physically agitated, calms to verbal instructions
4	Calm and cooperative	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follow simple commands but drifts off again

Score	Term	Descriptor
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands ET, endotracheal.

Table 7. Sedation agitation scale [29].

Drug/MOA	Onset of action	$t_{1/2}$	Effects	Dosing	Place in therapy	Common toxicities/major precautions
Dexmedetomidine Selective $\alpha_2$ -agonist	5–10 min	1.8–3.1 h	Anxiolytic, sedative, analgesic/opioid sparing	Bolus: 1 mcg/kg over 10 min. Infusion: 0.2–0.7 mcg/kg/h	Assists in keeping patient calm and arousable to wean off the ventilator or for the treatment of acute hyperactive delirium; causes minimal respiratory depression	<b>Common:</b> bradycardia and hypotension, hypertension with loading dose. <b>Rare:</b> loss of airway reflexes, risk for withdrawal after prolonged (7 days) use. Infusion must be tapered slowly to prevent rebound agitation; slower emergence with hepatic failure
Propofol Binds to GABA <sub>A</sub> , glycine, nicotinic, and M <sub>1</sub> muscarinic receptors	1–2 min	26–32 h	Sedative, hypnotic, anxiolytic, amnestic, antiemetic, anticonvulsant	Bolus: 5 mcg/kg/min Infusion: 5–50 mcg/kg/min	Light or heavy sedation; ideal for neurosurgery patients to allow for daily neurological assessments or medical ICU patients requiring deep sedation for vent synchronization; treatment of seizures and elevated intracranial pressure	Hypotension; respiratory depression; hypertriglyceridemia (with prolonged use), rhabdomyolysis (rare), pancreatitis (rare), deep sedation with propofol is associated with longer emergence times; lipid emulsion delivering 1.1 kcal/mL
Midazolam Activate $\gamma$ -aminobutyric acid A (GABA <sub>A</sub> ) neuronal receptors	2–5 min	3–11 h	Sedative, hypnotic, anxiolytic, amnestic, antiemetic, anticonvulsant	1–14 mg/h (max ~0.1 mg/kg/h)	Patients requiring deep sedation; treatment of seizures or alcohol withdrawal	Respiratory depression; hypotension; accumulates in hepatic dysfunction; active metabolite accumulates in renal dysfunction; drug has potential to accumulate in adipose

Drug/MOA	Onset of action	$t_{1/2}$	Effects	Dosing	Place in therapy	Common toxicities/major precautions
Lorazepam Activate $\gamma$ -aminobutyric acid A (GABA A) neuronal receptors	15–20 min	8-15 h	Sedative, hypnotic, anxiolytic, amnestic, antiemetic, anticonvulsant	1–10 mg/h	Patients requiring deep sedation; treatment of seizures or alcohol withdrawal	tissue with continuous infusions Respiratory depression; hypotension; propylene glycol-related acidosis (rare); nephrotoxicity evident by an osmolar gap greater than 10–12 mOsm/L; accumulates in hepatic dysfunction; emergence from lorazepam after prolonged infusions will be longer than midazolam due to its greater potency and slower clearance; drug has potential to accumulate in adipose tissue with continuous infusions

$t_{1/2}$ , half-life of elimination; MOA, mechanism of action.

**Table 8.** Sedative agents [4,23,30].

## 4. Delirium

Delirium is defined as a syndrome with acute onset of cerebral dysfunction due to a change or fluctuation in baseline mental status, inattention, or disorganized thinking [4]. Two forms of delirium can exist: hyperactive (agitated, associated with hallucinations or delusions) or hypoactive (calm, lethargic, confused, and sedated). With delirium now being shown to be a strong predictor of negative long-term outcomes, it is imperative that regular assessments are performed to identify incidences of delirium and implementing preventative measures [24,31]. Such strategies include early mobilization, maintenance of light sedation while avoiding benzodiazepines in those with underlying risk factors for delirium, promoting sleep in adult ICU patients by optimizing environmental factors such as light, noise, clustering patient care activities, and decreasing stimuli at night.

Medication-induced delirium is not well studied and the exact onset, duration, or severity has yet to be confirmed. Delirium is multifactorial and, therefore, medications should not be solely considered as the cause in a patient experiencing changes in mental status. Most common causes of delirium are in **Table 9**. Benzodiazepines have been studied extensively as a possible risk factor for delirium. The data concerning benzodiazepines and outcomes with causing delirium remain controversial. The MENDS and SEDCOM studies had similar results showing higher delirium free days with or without coma when dexmedetomidine was administered compared to midazolam or lorazepam. Furthermore, both have similar results in showing no

difference in mortality and the length of ICU stay [33,34]. However, another meta-analysis including six trials comparing benzodiazepine versus nonbenzodiazepine sedatives found opposite results. The ICU length of stay and duration of mechanical ventilation were significantly higher in the benzodiazepine group with no difference found in delirium prevalence or all-cause mortality [35]. Until further research can clarify such effects, caution is still warranted when using these sedatives and other risk factors shown in **Table 10** should be considered as well.

<b>Iatrogenic</b>	Exposure to sedative and opioid medications
<b>Environmental</b>	Prolonged physical restraints
	Immobilization
	Disorientation to time and space
<b>Other</b>	Drug or alcohol withdrawal
	Sepsis
<b>Medication induced</b>	Anticholinergics
	Benzodiazepines
	Opiates
	Antipsychotics
	Antispasmodics
	Anticonvulsants
	Corticosteroids

**Table 9.** Common causes of delirium [4,32].

Age
Pre-existing delirium
History of baseline hypertension
Sedative-associated coma
Mechanical ventilation
Polytrauma
Emergency surgery prior to ICU admission
APACHE II score
Metabolic acidosis
Delirium on the previous day

**Table 10.** Risk factors for delirium [36].

Two scales for assessing delirium with the highest psychometric (e.g., validity and reliability) scores are the CAM-ICU and the ICDSC [37]. Delirium should be assessed every 8–12 hours, only after sedatives are decreased or interrupted and preferably during daytime hours.

Drug	Usual starting dose/ available formulations	Short-term adverse effects		Additional considerations
		Low risk	Moderate to high risk	
Olanzapine	5 mg (PO, disintegrating tablet, IM)	EPS, NMS	Anticholinergic, weight gain, dyslipidemia	Increased risk of accumulation in elderly, female, and hepatic/ renal impairment; QT prolongation
Quetiapine	12.5–25 mg (PO)	NMS, weight gain, tardive dyskinesia, seizures, EPS	Anticholinergic (dry mouth, constipation), sedation, dizziness, Hypotension (with rapid titration), weight gain, dyslipidemia	Associated with lowest risk of EPS and tardive dyskinesia
Risperidone	0.5–1 mg (PO, disintegrating tablet)	Anticholinergic, NMS, cardiac conduction abnormalities	Orthostatic hypotension (with rapid titration),	EPS associated with doses >6 mg/day
Ziprasidone	20 mg PO 10 mg IM	Anticholinergic, sedation, EPS, NMS	QTc prolongation	IM formulation contains a nephrotoxin called cyclodextrin that can accumulate in renal impairment; reduce dose in hepatic impairment

PO, by mouth; IM, intramuscular; EPS, extrapyramidal symptoms; NMS, neuroleptic malignant syndrome.

**Table 11.** Atypical antipsychotics for the treatment of delirium [24,30,38,39].

Treatment of delirium should be directed at the probable underlying causes (e.g., alcohol or drug withdrawal, infection, dehydration, discomfort) and consider pharmacologic agents only if needed. SCCM guidelines provide a Grade C recommendation that “atypical antipsychotics may reduce the duration of delirium in adult ICU patients.” No evidence exists on the efficacy of haloperidol in reducing delirium and is associated with higher incidences of extrapyramidal and cardiac side effects [38]. The atypical antipsychotics, which have been studied and shown to be beneficial, are listed in **Table 11**. If such agents are initiated, it is crucial to ensure they are discontinued upon discharge or follow-up strategies are in place in the outpatient setting. Patients should also be monitored carefully for the adverse effects listed.

The fundamental component of implementing successful protocols to manage pain, agitation, and delirium in mechanically ventilated patients is a multidisciplinary team. Developing a comprehensive protocol can help reduce costs, improve ICU outcomes, and create more consistent practices. As presented earlier, the SCCM PAD Guideline concepts can be employed but the basic principles established in cancer patients for managing pain and anxiety must also be considered to achieve optimal outcomes.



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