Sedation and Analgesia in Critically Ill Patients

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TUMS

Light Sedation

- No consensus definition
- Light sedation usually ranges from –1 to –2 on the Richmond Agitation-Sedation Scale.
- RASS score in the –2 to +1 range has also been considered light sedation in a few studies.

✓Target range from 0 (alert and calm) to -1 (drowsy) is more realistic.

Score	Term	Description
		Richmond Agitation-Sedation Scale
4	Combative	Violent, immediate danger to staff
3	Very agitated	Pulls at or removes tubes, aggressive
2	Agitated	Frequent non-purposeful movements, fights ventilator
1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert & calm	
−1	Drowsy	Not fully alert, sustained awakening to voice (eye opening & contact >10 sec)
−2	Light sedation	Briefly awakens to voice (eye opening & contact <10 sec)
−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	Unrousable	No response to voice or physical stimulation
		Riker Sedation-Agitation Scale
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, trashing side-to-side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting endotracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
4	Calm and cooperative	Calm, awakens easily follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
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 or communicate or follow

Light Sedation

- ↓ Time to extubation
- ↓ Frequency of tracheostomy
- ↓ ICU LOS

How to Maintain Light Sedation

- Daily Sedative Interruption (DSI)
- Nurse-Protocolized Sedation (NPS)

DSI/ SAT	Waking up
	Arousal/alertness
	Eye opening
	RASS -1 to +1
	SAS 4-7

Pain Management

- Treatment of underlying conditions.
- Treatment of pain is often done in combination with a sedative medication.
- Analgesics should be administered as a continuous IV infusion.
- Analgosedation using opioids may increase the risk of delirium in a dose-dependent manner, such that we avoid oversedation with opioids alone if not indicated for pain.

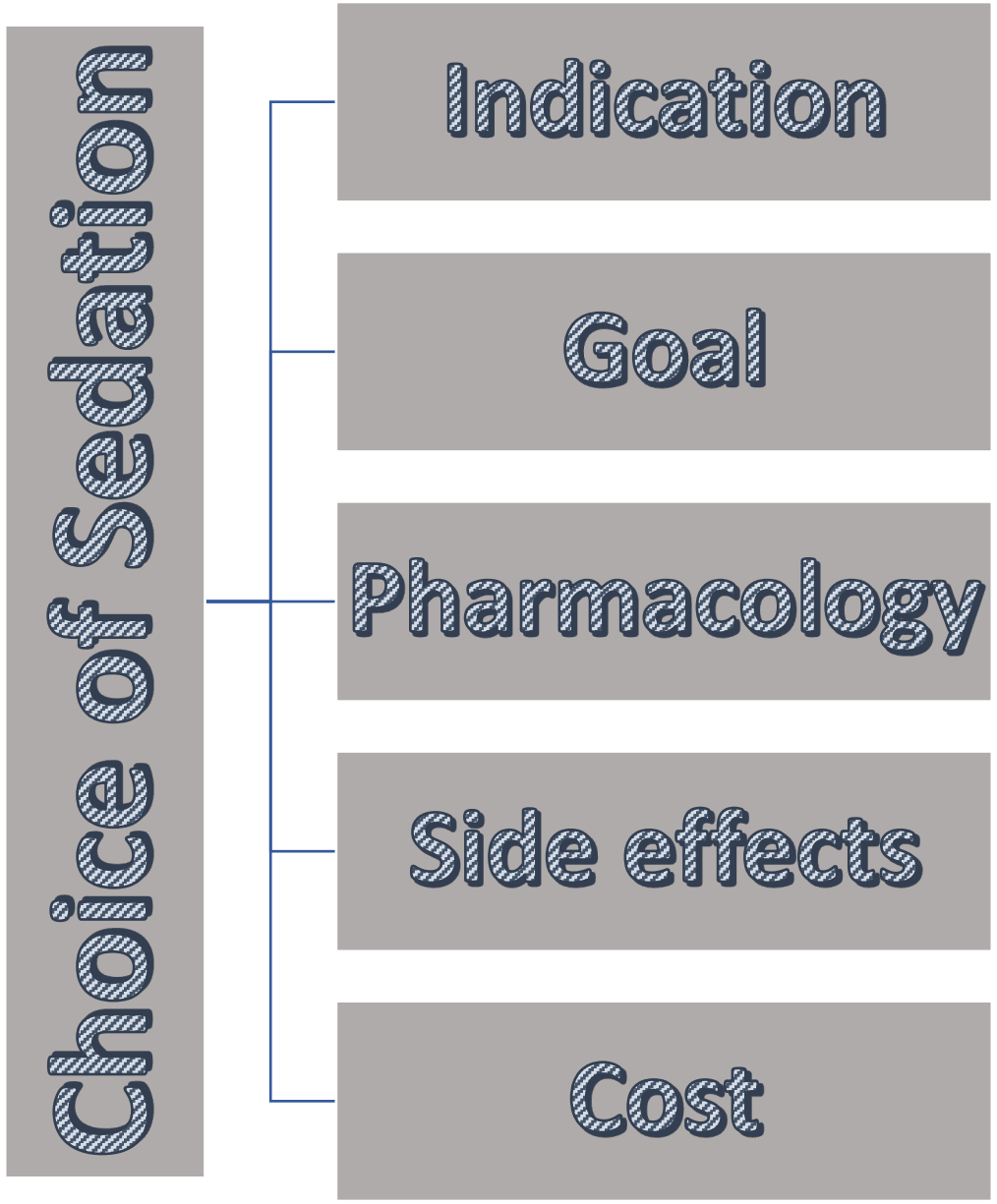
In critically ill adults who cannot self-report pain with observable behaviors, the BPS and CPOT demonstrate the greatest validity and reliability for monitoring pain (KSCCM).

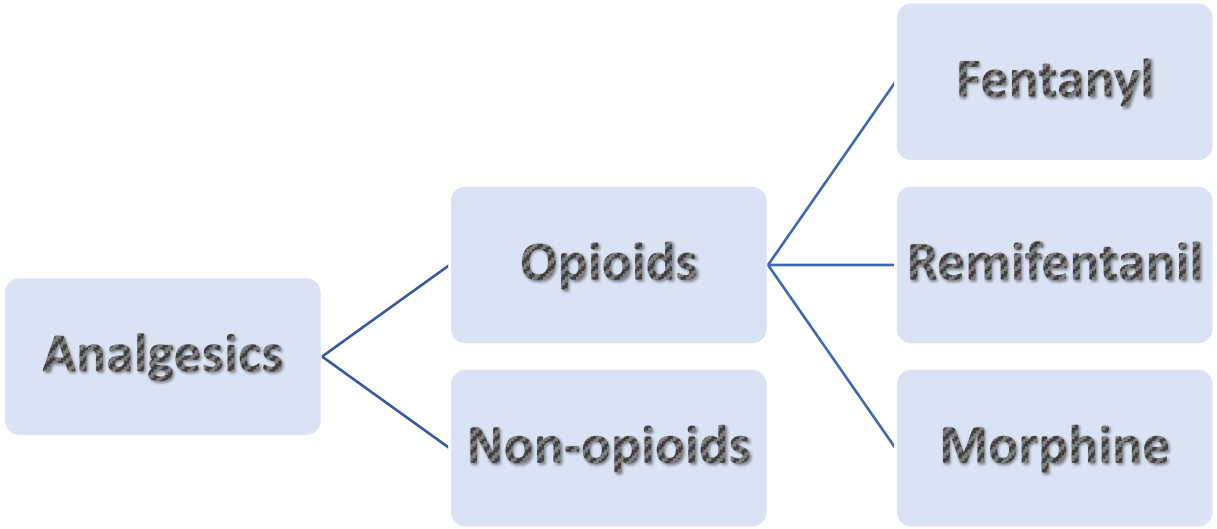
Table 1. Description of the Behavior Pain Scale [10]

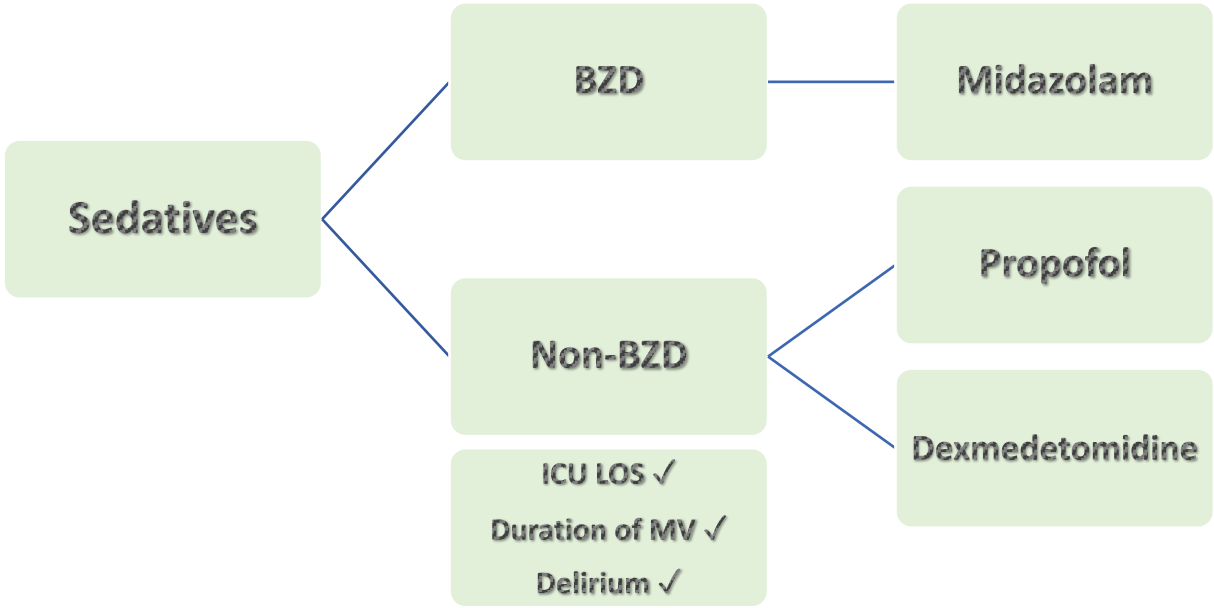
Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limbs movement	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating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

Table 2. Description of the Critical-Care Pain Observation Tool [11]

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movement	Does not move at all (does not necessarily mean absence of pain)	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
Muscle tension: evaluating by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movement, inability to complete them	Very tense or rigid	2
Compliance with the ventilator (intubated patients) or vocalization (extubated patients)	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
	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


Choice of Sedation
Indication
Goal
Pharmacology
Side effects
Cost


Analgesics
Opioids
Non-opioids
Fentanyl
Remifentanil
Morphine


Sedatives
BZD
Non-BZD
Midazolam
Propofol
Dexmedetomidine
ICU LOS ✓
Duration of MV ✓
Delirium ✓

Fentanyl

- A good choice for analgesia for most critically ill patients.
- Loading dose: 1-2 mcg/kg (25-100 mcg)
- Maintenance dose: 0.7-1 mcg/kg/h
- Onset: <1 to 2 min; * Duration: 30-60 min

Advantages	Disadvantages
Potent analgesic-sedative Immediate onset ✖ Histamine release Metabolized hepatically to inactive metabolites	Highly lipophilic (greater than morphine) Chest wall rigidity may occur with higher dosing CYP 3A4 interactions High first pass metabolism

Remifentanil

- An alternative to fentanyl
- Loading dose: 1.5 mcg/kg
- Maintenance dose: 0.5-15 mcg/kg/h
- Onset: 1-3 min; Duration: 3-10 min

Advantages	Disadvantages
Ultra-short-acting Cleared by plasma esterases to inactive metabolites Does not accumulate in renal or hepatic impairment	Anticipate pain and discomfort upon abrupt cessation

Morphine Sulfate

- Analgesic alternative to fentanyl when reduction and myocardial depressive effects are desirable or tolerable.
- Avoid in advanced/decompensated liver disease or renal impairment
- Loading dose: 2-10 mg
- Maintenance dose: 4-8 mg every 3-4h; 2-30 mg/h infusion
- Onset: 5-10 min; Duration: 4-5h

Advantages	Disadvantages
No CYP interactions	Accumulation in hepatic/renal dysfunction Histamine release Vagally mediated venodilation Hypotension Bradycardia

Methadone

- Avoidance of withdrawal syndromes during weaning (prolonged opioid infusion)
- Alternative opioid to alleviate high-dose OIH
- Acute pain management in patients previously taking methadone

Advantages	Disadvantages
Mu-receptor agonist with NMDA receptor antagonism ⬇ Opioid-induced hyperalgesia ⬇ Withdrawal symptoms	Widely variable response among individuals ⬆ QTc Accumulation in hepatic/severe kidney impairment CYP interactions

Adverse Effects

- Respiratory depression
- Depressed consciousness
- Cardiovascular side effects
- Gastrointestinal: nausea/vomiting/ileus/constipation

If ileus is severe and opioids are used for sedation rather than analgesia, we may discontinue the continuous infusion completely and use a different sedative.

- Hallucination/delirium

✓ Drug interactions

- The azole antifungals (eg, fluconazole, itraconazole, posaconazole, ketoconazole, voriconazole) and the macrolides and related antibiotics (eg, clarithromycin, erythromycin) may prolong fentanyl activity by inhibiting CYP3A4.
- The rifamycins decrease serum concentration and effects of opioids.

Midazolam

- A good choice for short-term anxiolysis/acute agitation
- Limit administration to 48 hours
- Loading dose: 0.5-4 mg
- Maintenance dose: 0.02-0.1 mg/kg/h (2-8 mg/h)
- Onset: 1-5 min; Duration: 30 min

Advantages	Disadvantages
Potent amnestic/anxiolytic agent Immediate onset Short duration of action	Risk of delirium High level of fat solubility Accumulation in hepatic/renal impairment CYP interaction

Dexmedetomidine

- A good choice for short- and long-term sedation
- Used in non-intubated patients
- May be useful for sedation in patients with high risk of delirium
- * Loading dose: 1 mcg/kg over 10 min
- Maintenance dose: 0.2-1.5 mcg/kg/h
- Onset: 5-15 min; Duration: 60-120 min

Advantages	Disadvantages
Effective sedative sympatholytic Moderate anxiolysis and analgesia Easy awakening Comfortable ⬇ Shivering	⬇ BP ⬇ HR Accumulation in hepatic/renal impairment

Propofol

- A good choice in conjunction with appropriate analgesia for short-term sedation
- Loading dose: -
- Maintenance dose: 5-50 mcg/kg/min (up to 70 mcg/kg/min)
- Onset: <1 to 2 min; Duration: 3-10 min

Advantages	Disadvantages
Potent sedative-hypnotic Immediate onset/rapid awakening Metabolism unaltered in hepatic/renal impairment Few significant drug interactions ↓ ICP, cerebral metabolism, shivering Controls intractable seizures	↓ BP ↓ HR ↓ Myocardial contractility ↑ TG Propofol infusion syndrome

PRIS

- Metabolic acidosis
- Fever
- Hyper TG
- Hypotension
- Arrhythmia
- Bradycardia
- AKI
- Hepatic dysfumction
- Rhabdomyolysis
- Hyperkalemia

Ketamine

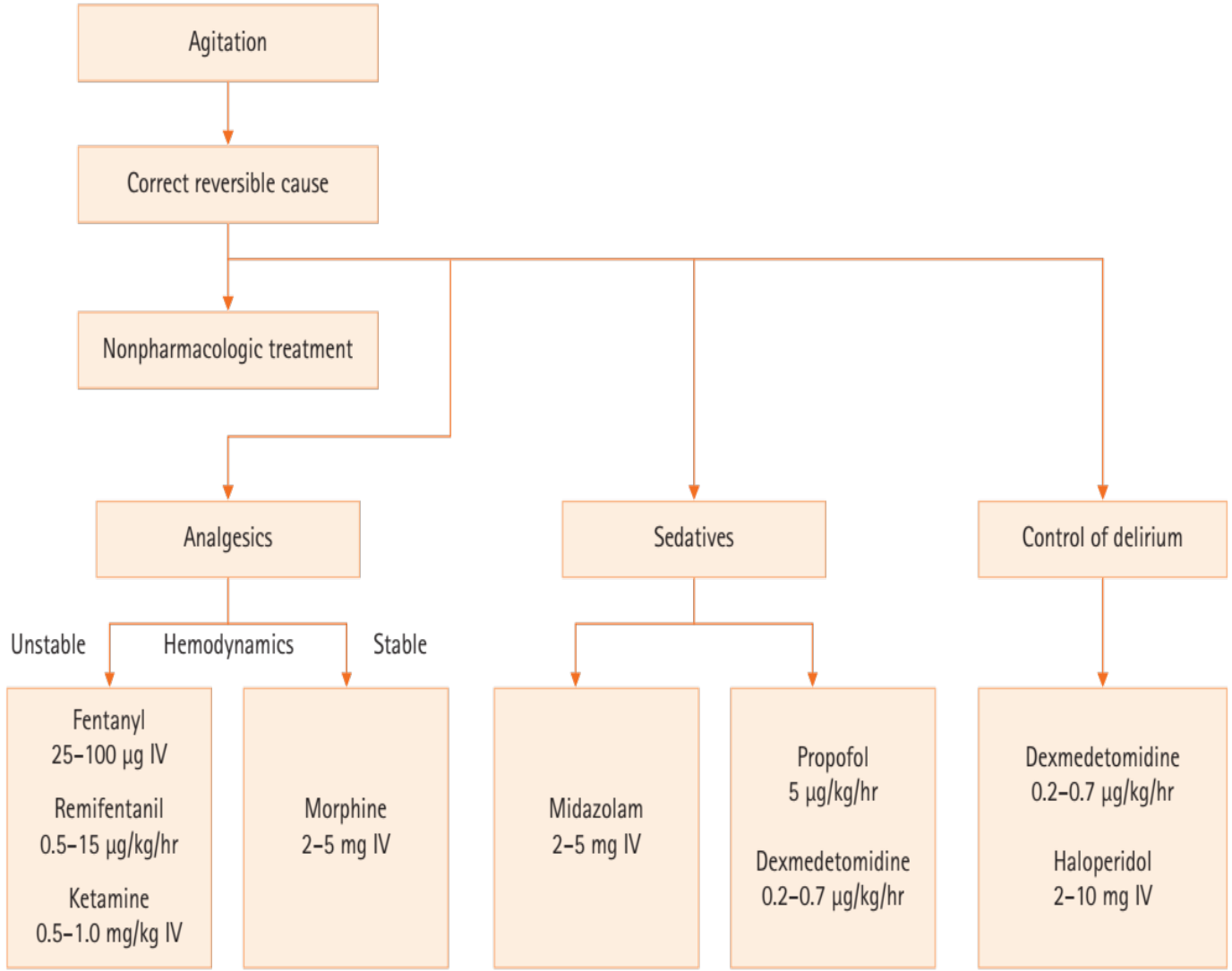
- An alternate choice for pain management/severe agitation
- Adjunctive analgesic in severe refractory pain with ⇩ acute opioid tolerance
- Loading dose: 0.25-0.5 mg/kg
- Maintenance dose: 0.05-0.4 mg/kg/h
- Onset: ≤1 min ; Duration: 10-15 min

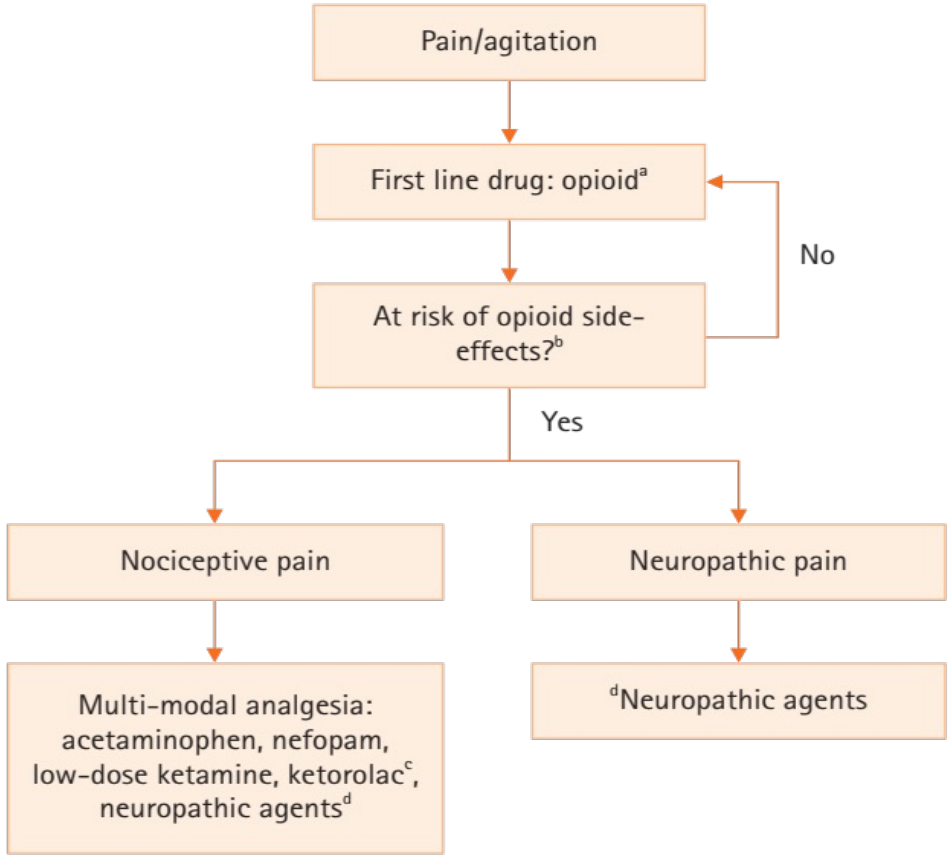
Advantages	Disadvantages
A potent dissociative sedative-anesthetic Marked analgesia ✖ Inhibition of respiratory drive Does not inhibit protective reflexes	⇧ HR/BP ⇧ ICP Hallucinations, dissociative experiences, unpleasant recall, N/V, tonic-clonic movements, hypersalivation Accumulation in hepatic/renal impairment Drug interactions (CYP metabolism)

Summary

Opioids (route)	Equianalgesic dose	Onset	Elimination half-life	Intermittent dosing	IV infusion rate	Side effect and other information
Morphine (IV)	10 mg	5–10 min	3–4 hr	2–4 mg q1-2 hr	2–30 mg/hr	Accumulation in patients with liver dysfunction
Hydromorphone (IV)	1.5 mg	5–15 min	2–3 hr	0.2–0.6 mg q1-2 hr	0.5–3 mg/hr	Accumulation in patients with kidney and liver dysfunction
Fentanyl (IV)	100 μg	1–2 min	2–4 hr	0.35–0.5 μg q 0.5-1 hr	0.7–10 μg/kg/hr	Accumulation in patients with kidney and liver dysfunction, release of histamine
Remifentanil (IV)		1–3 min	3–10 min		Loading dose: 1.5 μg/kg Maintenance dose: 0.5–15 μg/kg/hr	Available regardless of liver and kidney dysfunction

Sedative	Onset	Elimination half-life	Active metabolite	Intermittent dosing	IV infusion rate
Midazolam	2–5 min	3–11 hr	Yes (prolonged sedation, especially with renal failure)	0.01–0.05 mg/kg over several minutes	0.02–0.1 mg/kg/hr
Lorazepam	10–40 min	8–15 hr	None	0.02–0.04 mg/kg (≤2 mg)	0.02–0.06 mg/kg q 2–6 hr prn or 0.01–0.1 mg/kg/hr (≤10 mg/hr)
Diazepam	2–5 min	20–120 hr	Yes (prolonged sedation)	5–10 mg	0.03–0.1 mg/kg q0.5–6 hr prn
Propofol	1–2 min	Short-term use: 3–12 hr Long-term use: 50±18.6 hr	None	5 μg/kg/min over 5 minutes	5–50 μg/kg/min
Dexmedetomidine	5–10 min	1.8–3.1 hr	None	1 μg/kg/min over 10 minutes	0.2–0.7 μg/kg/hr


Agitation
Correct reversible cause
Nonpharmacologic treatment
Analgesics
Sedatives
Control of delirium
Unstable
Hemodynamics
Stable
Fentanyl
25–100 μg IV
Remifentanil
0.5–15 μg/kg/hr
Ketamine
0.5–1.0 mg/kg IV
Morphine
2–5 mg IV
Midazolam
2–5 mg IV
Propofol
5 μg/kg/hr
Dexmedetomidine
0.2–0.7 μg/kg/hr
Dexmedetomidine
0.2–0.7 μg/kg/hr
Haloperidol
2–10 mg IV


Pain/agitation
First line drug: opioid[a]
No
At risk of opioid side-effects?[b]
Yes
Nociceptive pain
Neuropathic pain
Multi-modal analgesia: acetaminophen, nefopam, low-dose ketamine, ketorolac[c], neuropathic agents[d]
[d]Neuropathic agents

Discontinuation of Sedatives

- Patients taking analgesics or sedatives for more than a week may develop neurological changes or physiological dependence.

References

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Any
Questions?