Pain Management and Sedation in the Critically ill

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Disclaimers Conflict of interest

- None

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Goals

Identify	Causes of **Stress** and the need for sedation
Identify	**Anxiolytics** their advantages and disadvantages
Identify	**Narcotics** their advantages and disadvantages
Identify	**Hypnotics** and their use
Identify	**Neuromuscular** Blocking agents

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Causes of Distress

Anxiety/dyspnea

- **Fear of death/pain**
- Difficulty communicating
- **Shortness of breath**
- Perceived threats
- **Paralyzed patients**

Pain

- **Initial trauma**
- Procedures
- **Ventilator discomfort**
- Immobility

Delirium

- **Electrolyte imbalance**
- Hyperglcemia
- **Hepatorenal disease**
- Hyperamylasemia
- **Drug withdrawal**
- Malnutrition
- **Medications antihistamines, antiarrythmics, atropine**

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Effects of Sedative Meds

Effects of sedative drugs

Drug	Anxiolysis	Hypnosis	Amnesia	Analgesia
Benzodiazepines	+	+	+	-
Dexmedetomidine	+	-	-	+
Haloperidol	+	+*	+*	-
Opioid analgesics	-	-	-	+
Propofol	+¶	+	+*	-

* Minimal effect.
¶ Only at low doses.

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Sedatives

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Benzodiazopines Bind GABA Receptor and enhances inhibition

Advantages

- Midazolam/ Lorazepam mostly used
- Anxiolytic
- Amnesia
- Anticonvulsant
- Muscle relaxant
- Strength Lorazepam>Midazolam>valium
- Midazolam fastest onset 2-5 min (2-4h)
- Lorazepam onset 5-20 min (6-8h) no metabolites

Disadvantages

- Respiratory and cardiovascular depression
- Prolonged vent days comp to propofol
- Prolonged LOS comp to Propofol
- Accumulate with repeated dosing
- Midazolam accumulates in renal/hepatic impaired or CYP3A4 inhibitors meds like fluconazole, macrolide antibiotics
- Valium has 2 active metabolites accumulates in obese, old, renal hepatic impaired
- Increase delirium especially lorazepam
- Propylene glycol toxicity- hyperosmolar, acidosis possibly needs dialysis (lorazepam/valium)

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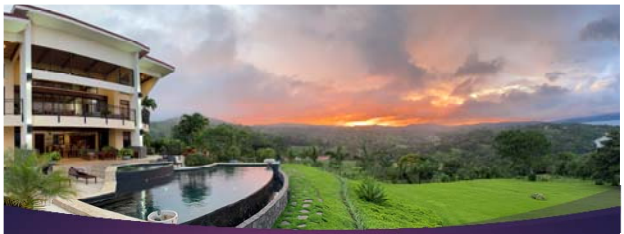

Pain Killers

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Opioids- bind mu opioid receptor and alpha 2 block in the spinal cord

Most Common Medications

- Morphine
- Fentanyl
- Hydromorphone
- Remifentanil- rapidly cleared not dependent on liver/renal metabolism
- Meperidine has no role
- *Tylenol

Disadvantages

- No amnestic properties
- Induce Tolerance
- Interactions with other medications
- Prolonged opioid effect CYP3A4 inhibition antifungals and macrolides
- Respiratory depression
- May cause delirium
- Ileus/urinary retention
- Nausea vomiting
- Pruritis

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Opioids- commonly used

Morphine

Histamine release may lower BP- could be advantage or disadvantage

Histamine may. Cause bronchospasm

Fentanyl

No metabolites- best in Hepato-renal disease

Minimal increased ICP

Remifentanil-

Ultra short action 5-10min

Use if limited narc use needed

hydromorphone

Twice the strength of morphine

Useful in Hepatorenal disease

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Hypnotics

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Hyponotics

- Propofol
- Dexmedetomidine
- Ketamine
- Barbituates- Methohexital

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Propofol- Activates central GABA-A receptors and hypothalamic sleep center

Advantages

- **Rapid sedation and awakening**
- Amnestic effects
- **Anxiolytic**
- Anticonvulsant*
- **Muscle Relaxant- broncho-dialation**
- No elimination difference Hepatic/ Renal impairment
- **Duration of action 6-10 min (<48hr)**
- Lower mortality earlier discharge less vent days

Disadvantage

- **Water insoluble- egg lecithin/soy/glycerol**
- No direct Analgesic effect
- **Long term use may lead to accumulation in fat**
- Cardiac suppressant 15-25% hypotension
- **Risk for contamination -12 hr use window**
- Elevated triglycerides CK, myoglobin, lactate, myoclonus
- **Propofol related infusion syndrome<1% high dose 4mg/Kg/hr for >48h (67mcg/Kg/min**

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Dexmedetomidine Central alpha 2 agonist

Advantages

- **Sedation/anxiolytic and analgesic effects**
- FDA-Use for 24 hrs longer use risk withdrawal and hypertension
- **Possibly shortens vent days and LOS** 1624 patients in 7 studies
- Possibly reduces delirium (compared to placebo)

Disadvantages

- **Does not improve mortality**
- Does not reduce vent days compared to other meds
- **Does not reduce delirium compared to other meds**
- Bradycardia/ hypotension
- **Bolus doses mixed BP result:**
  HTN if PNS Alpha 2B.
  Hypotension if central Alpha 2A
- Cytochrome P450 metabolism

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Ketamine Non-competatively blocks glutamate NMDA receptors opioid/muscarinic agonist, nicotinic blockade

Advantages

- **Rapid onset (1min and)**
  Rapid metabolism (10-15min)
- Liver metabolism
- **Dissociated anesthesia**
- Sympathetic stimulation supports BP, HR, Bronchodialation
- **Best analgesia for burn patients**

Disadvantages

- **Psychoactive effects**
- Hallucinations, delirium
- **Hypersalivation**
- Respiratory and cardiac depression

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Odd balls

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Antipsychotics **antagonize Dopamine**

Haloperidol

- Given IV onset 5-20 min (4-12h)
- Mild sedation
- Low cardiac/ respiratory depression
- No FDA approval for use
- Dosing .2-20 mg q6h (divide load dose by 4 and give every 6h)

Disadvantages

- Tardive Dyskinesia
- No reduction in delirium
- Increases QTc interval leading to torsades de pointes and sudden death
- No reduction in vent days
- No reduction in mortality
- No reduction in LOS

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Barbiturates bind GABA receptor complex different site than benzodiazepines

Methohexital

- Rapid onset
- Helpful if all else fails

Disadvantages

- Severe cardio respiratory effects
- Prolonged elimination
- Accumulation in renal/hepatic impairment
- Induces cytochrome P450

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Baclofen GABA type B receptor agonist

Advantages
- High levels are sedating
- May be useful for alcohol withdrawal

Disadvantages
- No impact on mortality
- Longer vent days
- Longer ICU stay

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Neuromuscular blockers

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Neuromuscular Blockers

Advantages
- Improve ventilation by preventing spontaneous breathing
- Lessen O2 demand by abolishing muscle tone
- Lower ICP in patients fighting a ventilator
- Use in status Asthmaticus
- May facilitate procedure if mentally altered state
- Intubation for acute respiratory failure

Disadvantages
- Not First line for movement/ agitation
- No sedative properties
- No Analgesia
- No amnesia

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Neuromuscular Blocking Bind Acetylcholine motor endplate

Depolarizing

- Succinylcholine on type in US
- Bind the endplate and cause a depolarization
- Only use if for intubation due to rapid onset
- Never use succinylcholine if hyperkalemia is present

Nondepolarizing

- Competitively inhibit Ach receptor but obstructs the ion channel so no depolarization occurs
- Aminosteroid: Pancuronium, Vecuronium, Rocuronium
- Benzylisoquinolinium: Atricurium, Cisatricurium, Mivacurium

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Drugs that look alike

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Neuromuscular Blockers

Aminosteroids

- Vecuronium and Pancuronium were the most frequently used- now replaced by Cisatracurium
- Rocuronium may be used as an alternative to Succinylcholine for intubation

Benzolisoqinoliniums

- Cisatracurium is 2/3 of all used NMB due to metabolism unrelated to liver or Renal failure
- Atracurium has no Hepatorenal dependence
- Metabolized by Hoffman elimination which is a plasma enzyme
- Mivacurium is short acting

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Neuromuscular Blockers-Factors

Reduced block

- Burn patients – less susceptable due to up regulation of receptors
- Hypercalcemia decreases sensitivity and durationl
- Sepsis- delayed and reduced response to NMB

Prolonged Block

- Hyperkalemia- no succinylcholine
- Hypokalemia-
- Hyper-Magnesium
- Acidosis
- Hypothermia
- Myasthenia Gravis
- Advanced age- low cardiac output/ body water
- Obesity Atracurium (dose based on body weight)

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Neuromuscular Blockers

Initiation

Need to reduce metabolic oxygen requirements (shivering/fighting the ventilator)

Control movement not necessarily 100% paralysis

Allergic reactions-rare with Cisatracurium

Hypotension- blockade of ANS and histamine release

Maintenance

Dose to TOF stimulation q3h-qshift

May be used a bolus or infusion

If infusion do a daily wake up

Pt must get sedation/amnesia

Corneal lubrication

Prevent skin breakdown

DVT prophylaxis

Pupil reflexes

Bispectral –processed EEG

Weaning

No weaning- maintain some sedation

May be reversed (neostigmine/Sugammadex)

Prolonged weakness- most often in Sepsis/steroid use/prolonged NMB/renal-hepatic insufficiency

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Administration of medication

- Continuous Infusion
- Intermittent Infusion

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Make Good Choices

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Best options:

Opioid	Benzodiazopine	NMB
Fentanyl	**Midazolam**	**Cisatracurium**
	Lorazepam	**Atracurium**
Propofol	**Etmedetomidate**	**Ketamine**

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Meds used to Sedate Critically Ill

Drugs used to sedate critically-ill patients

Analgesics
Remifentanil
Sedative-hypnotics
Benzodiazepines
Diazepam
Lorazepam
Midazolam
Anesthetic-sedatives
Propofol
Alpha-2 agonists
Dexmedetomidine
Neuroleptics
Haloperidol
Olanzapine
Quetiapine
Risperidone

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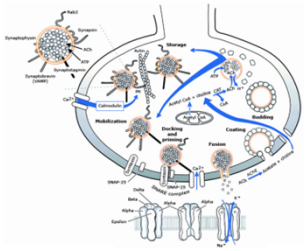
Neuromuscular Junction

Neuromuscular junction



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Richmond agitation –Sedation scale

Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tubes or catheters; aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, sustained (>10 seconds) awakening, eye contact to voice
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation
Procedure		
1.	Observe patient. Is patient alert and calm (score 0)?	
2.	Does patient have behavior that is consistent with restlessness or agitation?	
	Assign score +1 to +4 using the criteria listed above.	
3.	If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.	
	Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score -1).	
	Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score -2).	
	Patient has any movement in response to voice, excluding eye contact (score -3).	
4.	If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response.	
	Patient has any movement to physical stimulation (score -4).	
	Patient has no response to voice or physical stimulation (score -5).	

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Dexmedetomidine

Drug	Loading dose	Maintenance dose range	Onset (minutes)	Duration of intermittent dose (minutes)	Characteristics and role
	(maximum dose 2 mg/kg in a 30 minute period)				management, severe agitation, or as an ingredient analgesic in patients with severe refractory pain in clinical settings where increased myocardial oxygen demand and sympathetic tone are tolerable.
Central alpha$_2$ agonist					
Dexmedetomidine	Optional: 1 mcg/kg over 10 minutes if hemodynamically stable Usually not given	0.2 to 1.5 mcg/kg/hour Initiate at 0.2 mcg/kg/hour and titrate every 30 minutes**	5 to 10 (optional loading dose) 15 (without loading dose)	60 to 120	**Advantages:** Effective sedative sympatholytic (central alpha$_2$ agonist) with moderate anxiolysis and analgesia. Character and depth of sedation may permit critically ill, mechanically ventilated patients to be interactive or easily awakened, yet comfortable. Can be used in non-mechanically ventilated ICU patients and continued as needed following extubation. Reduces shivering in the rewarming phase of induced hypothermia following resuscitation from cardiac arrest. May be less likely to cause delirium than other sedative choices. **Disadvantages:** Potentially significant hypotension and bradycardia or hypertension that do not resolve quickly upon abrupt discontinuation. Metabolized hepatically by glucuronidation and CYP2A6. Dose reduction recommended with renal and/or hepatic impairment. Rapid administration of loading dose may be associated with cardiovascular instability, tachycardia, bradycardia, or heart block. Does not induce the deep sedation needed for neuromuscular blockade. **Role:** A good choice for short- and long-term sedation in critically ill patients without relevant cardiac conditions. May be useful for sedation of patients with or at high risk of developing delirium, although this has not been well established.

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Fentanyl Hydromorphone

Intravenous* sedative and analgesic dosing regimens for managing pain, agitation, and delirium in the intensive care unit

Drug	Loading dose	Maintenance dose range	Onset (minutes)	Duration of intermittent dose (minutes)	Characteristics and role
Opioid analgesics¶					
Fentanyl¶	1 to 2 mcg/kg¶ (25 to 100 mcg)¶	0.35 to 0.5 mcg/kg every 0.5 to 1 hour intermittent (25 to 50 mcg)¶ **AND/OR** 0.7 to 10 mcg/kg/hour infusion (50 to 700 mcg/hour) (1) For most patients, 1 to 3 mcg/kg/hour infusion (50 to 200 mcg/hour)¶ with as-needed intermittent bolus doses is sufficient	<1 to 2	30 to 60^	**Advantages:** Potent analgesic-sedative with immediate onset and less hypotension than other opioid analgesic choices due to relative lack of histamine release. Metabolized hepatically by cytochrome P450-3A4 (CYP3A4) to inactive metabolites. **Disadvantages:** Highly lipophilic parent drug accumulates in adipose and other tissue with repeated or prolonged administration. Chest wall rigidity may occur with higher dosing¶. **Role:** A good choice for analgesia for most critically ill patients.
Hydromorphone	0.5 to 2 mg¶	0.2 to 0.6 mg every one to two hours intermittent **AND/OR** 0.5 to 3 mg/hour infusion	5 to 10	240 to 300	**Advantages:** IV administration requires small volumes relative to other opioids. Non-CYP metabolism (glucuronidation) may be an advantage for patients receiving drugs that significantly alter CYP3A4 metabolism and thereby interact with fentanyl. **Disadvantages:** Potentially neurotoxic (excitatory) metabolite(s) may accumulate in hepatic and/or renal dysfunction¶. **Role:** Analgesic option alternative to fentanyl or morphine. Dose adjustment and gradual titration needed for patients with renal and/or hepatic impairment.

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Ketamine

Drug	Loading dose	Maintenance dose range	Onset (minutes)	Duration of intermittent dose (minutes)	Characteristics and role
					sedation or a general critical care physician trial is likely to be ready soon for ventilator weaning trials.
Ketamine	0.25 to 0.5 mg/kg bolus IV Bolus doses may be used for sedation with an infusion of ketamine or as a single bolus (eg, patients with burns prior to dress changes or for procedural sedation). Bolus dosing may be repeated if necessary during the procedure (maximum dose 2 mg/kg in a 30 minute period)	0.05 to 0.4 mg/kg/hour	≤1	10 to 15 (single dose)	**Advantages:** A potent dissociative sedative-anesthetic with marked analgesia that maintains cardiac output and mean arterial pressure without inhibition of respiratory drive. Does not inhibit protective reflexes. May reduce acute opioid tolerance. **Disadvantages:** Sympathetic stimulation (ie, increased heart rate and myocardial oxygen demand, elevated intracranial pressure and systemic blood pressure) may be intolerable depending upon clinical setting. Rarely, laryngospasm may occur with rapid bolus dose administration or higher doses. Adverse effects may include hallucinations, delirium upon withdrawal, tonic-clonic movements, dissociative experiences, unpleasant recall, hypersalivation, nausea, and vomiting. Complex metabolism includes CYP3A4, 2C9, 2B6, and non-CYP hepatic transformations and an active metabolite (norketamine), which may accumulate in renal and/or hepatic dysfunction. Long half-life. **Role:** An alternate choice for postoperative pain management, severe epilepsies, or as an adjunctive analgesic in patients with severe refractory pain in clinical settings where increased myocardial oxygen demand and sympathetic tone are tolerable.

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Lorazepam

Lorazepam¶	0.02 to 0.04 mg/kg¶ (1 to 2 mg)¶	0.02 to 0.06 mg/kg every two to six hours intermittent (1 to 4 mg)¶ **AND/OR** 0.01 to 0.1 mg/kg/hour infusion (0.5 to 10 mg/hour)¶	15 to 20	360 to 480^	**Advantages:** Sedative, amnestic, potent anxiolysis with anticonvulsant properties. Hepatically metabolized by glucuronidation to inactive metabolites. Relatively low risk of drug interactions and safety in mild to moderate hepatic and renal impairment. **Disadvantages:** Relatively slow onset. Risk of over-sedation when titrating due to delayed response and accumulation in peripheral tissues. Risk of delirium. IV incompatibilities and risk of line precipitate. Propylene glycol solvent may accumulate with prolonged use or high dosing causing metabolic acidosis and end-organ dysfunction (refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dose regimens, and adverse effects). Long half-life, with significant risk of accumulation in older adults or in patients with significant renal or hepatic impairment. **Role:** A good choice for sedation and anxiolysis for most patients, including those who may require long-term ongoing sedation. Although intermittent bolus dosing may be preferred, a continuous infusion may be initiated for patients requiring frequently repeated higher dosing.

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Midazolam

Benzodiazepines¶					
Midazolam¶	0.01 to 0.05 mg/kg[1] (0.5 to 4 mg)¶	0.02 to 0.1 mg/kg/hour infusion (2 to 8 mg/hour)¶ with intermittent bolus dose(s) if needed. While the patient is on a continuous infusion, periodic re-bolus may be needed to maintain the sedation goal. This approach may help prevent unnecessary dose creep of the infusion.	2 to 5	30[9]	**Advantages:** A potent amnestic and anxiolytic agent with an immediate onset of action and a short duration of effect when administered short term (<48 hours). It is the only IV benzodiazepine that is not delivered in propylene glycol. **Disadvantages:** Hepatically metabolized by CYP3A4 to active metabolites that may accumulate and cause prolonged sedation if delivered long term. Half-life may be prolonged in critically ill patients with hepatic or renal impairment. Risk of delirium. Also, it interacts with drugs used in the ICU (eg, some antiretrovirals, azole antifungals) that alter CYP metabolism such that excess sedation can occur with concomitant use of midazolam and drugs metabolized by CYP3A4. **Role:** A good choice for short-term anxiolysis and treatment of acute agitation. Dose adjustment and gradual titration are needed for patients with renal and/or hepatic impairment.

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Remifentanil

Drug	Loading dose	Maintenance dose range	Onset (minutes)	Duration of intermittent dose (minutes)	Characteristics and role
Remifentanil¶	Optional: 1.5 mcg/kg[4][11] Most ECU patients can be managed without bolus doses; if required, a bolus of 0.3 mcg/kg is usually sufficient; larger boluses are associated with significant reductions in HR and MAP	0.5 to 15 mcg/kg/hour infusion Use ideal body weight to determine dose for obese patients¶	1 to 3	5 to 10 (after cessation of infusion)	**Advantages:** Ultra-short-acting. Cleared by nonspecific plasma esterases to inactive metabolites. Does not accumulate in renal or hepatic impairment. Prompt reversal of analgesia and sedation upon discontinuation. **Disadvantages:** Anticipate pain and discomfort upon abrupt cessation. Glycine excipient may accumulate in renal impairment[4]. **Role:** An alternative to fentanyl for patients requiring frequent neurologic assessments or those with multiorgan failure.

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Opioid analgesics¶					
Fentanyl¶	1 to 2 mcg/kg[4] (25 to 100 mcg)¶	0.35 to 0.5 mcg/kg every 0.5 to 1 hour intermittent (25 to 50 mcg)¶ **AND/OR** 0.7 to 10 mcg/kg/hour infusion (50 to 700 mcg/hour) [1] For most patients, 1 to 3 mcg/kg/hour infusion (50 to 200 mcg/hour)¶ with as-needed intermittent bolus doses is sufficient	<1 to 2	30 to 60[10]	**Advantages:** Potent analgesic-sedative with immediate onset and less hypotension than other opioid analgesic choices due to relative lack of histamine release. Metabolized hepatically by cytochrome P450-3A4 (CYP3A4) to inactive metabolites. **Disadvantages:** Highly lipophilic parent drug accumulates in adipose and other tissue with repeated or prolonged administration. Chest wall rigidity may occur with higher dosing[4]. **Role:** A good choice for analgesia for most critically ill patients.
Hydromorphone	0.5 to 2 mg[2]	0.2 to 0.6 mg every one to two hours intermittent **AND/OR** 0.5 to 3 mg/hour infusion	5 to 10	240 to 300	**Advantages:** IV administration requires small volumes relative to other opioids. Non-CYP metabolism (glucuronidation) may be an advantage for patients receiving drugs that significantly alter CYP3A4 metabolism and thereby interact with fentanyl. **Disadvantages:** Potentially neurotoxic (excitatory) metabolite(s) may accumulate in hepatic and/or renal dysfunction[4]. **Role:** Analgesic option alternative to fentanyl or morphine. Dose adjustment and gradual titration needed

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Morphine

Drug	Loading dose	Maintenance dose range	Onset (minutes)	Duration of intermittent dose (minutes)	Characteristics and role
					Role: Analgesic option alternative to fentanyl or morphine. Dose adjustment and gradual titration needed for patients with renal and/or hepatic impairment.
Morphine sulfate	2 to 10 mg[a]	2 to 4 mg every one to two hours intermittent **AND/OR** 2 to 30 mg/hour infusion	5 to 10	240 to 300	**Advantage:** Non-CYP metabolism (glucuronidation) may be an advantage for selected patients receiving drugs that significantly alter CYP3A4 metabolism and thereby interact with fentanyl. **Disadvantages:** Can accumulate in hepatic or renal dysfunction and prolong effects. Histamine release and vagally mediated vasodilation, hypotension, and bradycardia can be significant[b]. **Role:** Analgesic alternative to fentanyl or hydromorphone where preload reduction and myocardial depressive effects are desirable or tolerable. Dose adjustment and gradual titration needed for patients with renal and/or hepatic impairment. Avoid in patients with advanced or decompensated liver disease with renal impairment due to risk of accumulation of neurotoxic metabolite. Infusions are not generally used for sedation or analgesia in the ICU but are more commonly used for palliative purposes.

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For Each Medication type the “how to” and “why to”

initiation

Identify medications

Pharmacokinetic characteristics

When and why to choose an agent

Maintenance

Assessing if a medication is reaching the goals you want.

Adjustment of medication to reach goals

Weaning

When and how to withdraw the medication treatments

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Outline

Sedative Analgesics

Identify a number of agents

Advantages and disadvantages for specific disease states

Pain Treatment

Identify agents

Advantages and disadvantages in specific disease states

Neuromuscular Blocking Agents

Identify agents

Advantages and disadvantages in specific disease states

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For Each Medication type the “how to” and “why to”

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