First Lines and Lifelines:
Analgesia and Sedation During Drug Shortages

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Disclosure

I have no financial and/or commercial conflicts of interest to disclose.

Disclaimer: There is no substitute for identifying waste, good collaboration, or effective communication.

Objectives

- Identify key concepts for analgesia and sedation in intensive care unit (ICU) patients
- Discuss first line and alternative pharmacotherapeutic agents
- Design a therapeutic regimen for a difficult ICU case

Case #1: RF

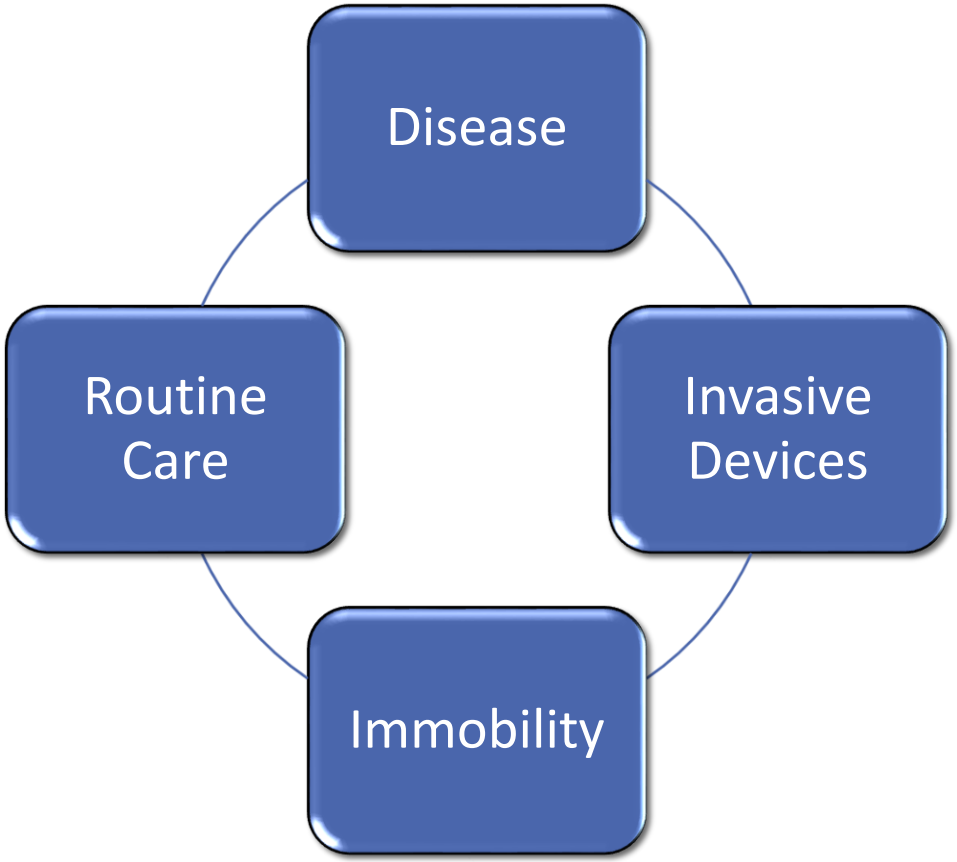
- 62 year old male
- PMH: Heavy EtOH use, HTN
- CC: Respiratory failure due to COVID19 pneumonia
- Mechanically ventilated

Case #2: CD

- 47 year old male
- History of methamphetamine use
- CC: Polysubstance ingestion, motor vehicle collision
- Intubated to protect airway

Pain

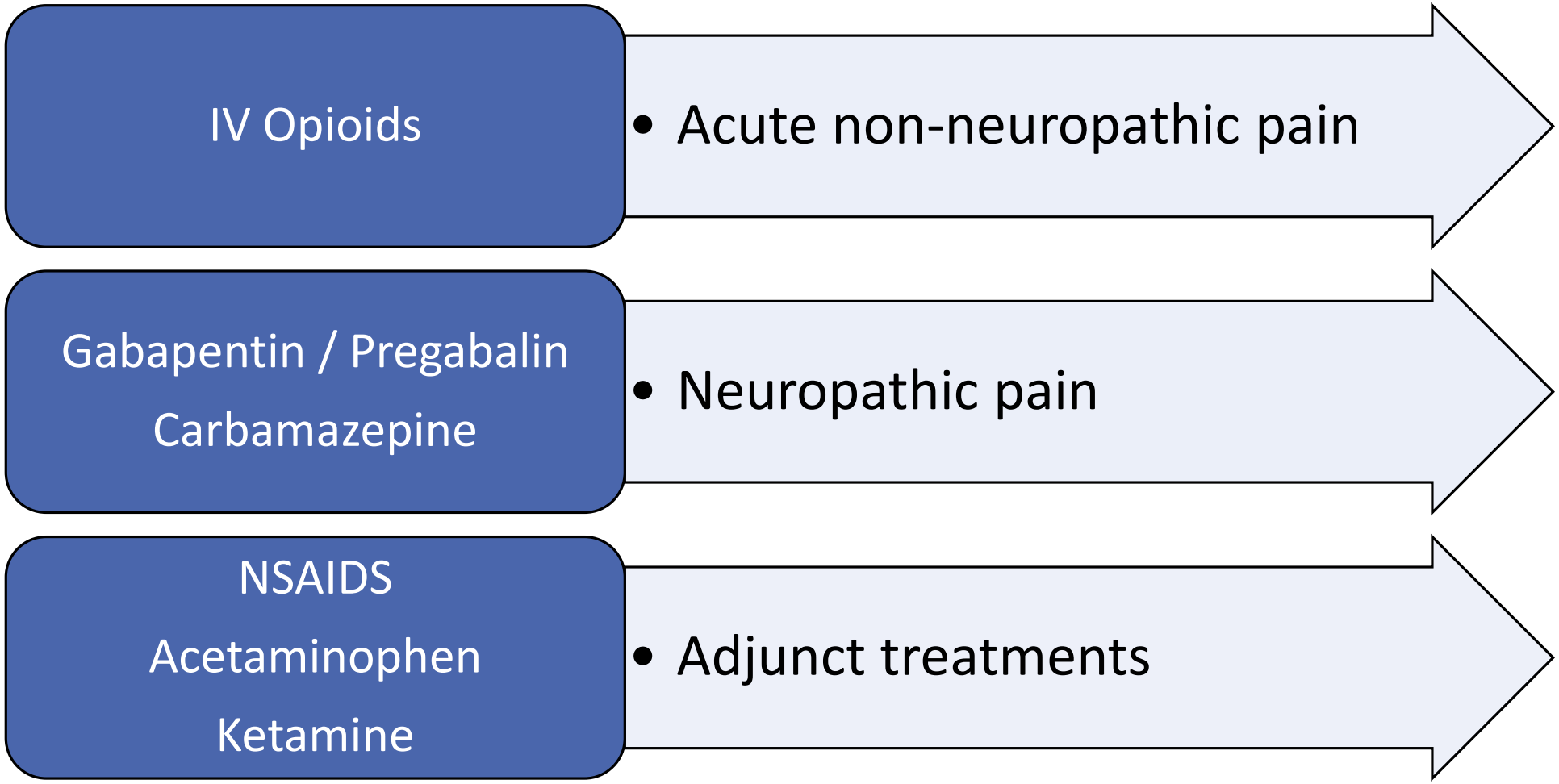
"An unpleasant sensory and emotional experience associated with actual or potential tissue damage."



Complications	
Chronic pain	Stress
Sleep-loss	Hyper-metabolism
Impaired wound healing	Impaired immune function
Feelings of Helplessness	Post-traumatic stress disorder

SIGAKIS, ET AL. CRIT CARE MED. 2015;43(11):2468-78

Options for Pain



Opioid Analgesia

- Aim for lowest effective dose
- Route will depend on clinical scenario
- Continuous infusions may be necessary
  - Used (almost) exclusively in ventilated patients
  - Drug accumulation can occur with prolonged infusions
  - Daily interruptions are beneficial

Opioid Infusions – Possible Dosing

PRIMARY

- Fentanyl 25-200 mcg/hr
- Hydromorphone 0.5-3 mg/hr

SECONDARY / TERTIARY

- Morphine 2-30 mg/hr
- Remifentanil 0.008-0.25 mcg/kg/min
- Sufentanil 0.05-1 mcg/kg/**hr**

BARR, ET AL. CRIT CARE MED. 2013;41(1):263-306
MOHRIEN KM, ET AL. CRIT CARE NURS Q, 2014
MEMIS D, ET AL. CRIT CARE 2003

Strategies to Reduce Opioids

- "Multi-modal" analgesia
  - Who should receive this?
- Acetaminophen up to 1g q6h (any route)
- Ketorolac or Ibuprofen in select patients
- Gabapentin, even as low as 300 mg/day
- Ketamine, 0.2-0.5 mg/kg IV bolus
  - If positive response, consider infusion at 1-2 mcg/kg/min

Strategies to Prolong Opioid Supply

- Flat rather than weight-based dosing
- Enteral opioid to supplement infusion
  - Functioning GI tract
  - Oxycodone 5-20 mg q4h
  - Likely best for those with lower opioid needs (fentanyl <150 mcg/hr)
- Transdermal fentanyl (1:1 IV to TD dosing)
  - Probably better than enteral if high opioid needs (>150 mcg/hr)
  - Wean infusion at 6, 8, and 10 hours after application
- Methadone to facilitate weaning
  - If on opioid infusion for prolonged duration (>7-10d)

ZECH, DF, ET AL. PAIN. 1992;50(3):293-301.

Ketamine

- Blocks NMDA receptors in peripheral/central nervous system
- Activates mu and kappa opioid receptors
- Analgesic at lower doses (1-2 mcg/kg/min)
  - Can limit opioid tolerance and reduce requirements
- Sedative at higher doses (10-80 mcg/kg/min)
  - Produces dissociative sedation
- Pay attention to product concentrations

MOHRIEN KM, ET AL. CRIT CARE NURS Q. 2014;37(2):137-51.

Methadone

- Consider in difficult to wean patients
- Dose considerations:
  - Incomplete cross-tolerance
  - Not aiming for equivalent dose
  - Long half life, steady state at 3-7 days
  - 10 mg q8h per tube may be a reasonable starting dose
- Weaning
  - Over 5-10 days
  - Decrease by 10-25% every 2-3 days
  - Stop when total daily dose <10-15 mg

AGITATION

"A syndrome of excessive motor activity, usually non-purposeful and associated with internal tension."

Photo: "Lumex Nightmare" by Ralph Sirianni

SOURCES

- Pain
- Hypoxia
- Withdrawal
- Hypoglycemia
- Delirium
- Hypotension

READE, CRIT CARE. 1999;3(3):R35-R46.
BARR, ET AL. CRIT CARE MED. 2013;41(1):263-306.

Assessment of Agitation

Richmond Agitation Sedation Scale (RASS)

Target RASS	RASS Description
+ 4	Combative, violent, danger to staff
+ 3	Pulls or removes tube(s) or catheters; aggressive
+ 2	Frequent nonpurposeful movement, fights ventilator
+ 1	Anxious, apprehensive , but not aggressive
0	Alert and calm
- 1	awakens 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. 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

RIKER, ET AL. CRIT CARE MED 1999;27:1325-1329

Assessment of Agitation

Richmond Agitation Sedation Scale (RASS)

Target RASS	RASS Description
+ 4	
+ 3	
+ 2	
+ 1	
0	
- 1	
- 2	
- 3	
- 4	
- 5	

Sedation–Agitation Scale (SAS)

7	Dangerous agitation	Pulling at ET tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing side-to-side
6	Very agitated	Does not calm, despite frequent verbal reminding of limits; requires physical restraints, biting ET 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 not communicate or follow commands

RIKER, ET AL. CRIT CARE MED 1999;27:1325-1329

Keys to Sedation Use

GOALS

- Patient comfort, safety
- Facilitate mechanical ventilation
- Facilitate neuromuscular blockade

PRINCIPLES

- Lighter sedation is better
- Daily interruption is useful
- Non-benzodiazepines preferred

Options for Sedative Infusions

PRIMARY

Propofol 5-100 mcg/kg/min

Dexmedetomidine 0.1-1.5 mcg/kg/**hr**

SECONDARY OR TERTIARY

Midazolam 1-10 mg/hr

Ketamine 10-80 mcg/kg/min

BARR, ET AL. CRIT CARE MED. 2013;41(1):263-306.

Options for Sedative Infusions

	Midazolam	Propofol	Dexmedetomidine	Ketamine
Amnesia	X	X		X
Analgesia			X	X
Anticonvulsion	X	X		X
Antiemesis		X		
Anxiolysis	X	X		X
Hypnosis	X	X		X
Sedation	X	X	X	X
Bradycardia			X	
Hypotension	X	X	X	
Respiratory Depression	X	X		

BARR, ET AL. CRIT CARE MED. 2013;41(1):263-306.

Strategies to Reduce Sedation Use

- Encourage lighter sedation
- Eliminate modifiable sources of agitation
  - Pain, hypernatremia, drug withdrawal
- Resume home neuropsychiatric meds
- Prevent delirium

Strategies to Prolong Sedative Supply

- Consider supplementing with enteral agent
  - Quetiapine, risperidone
  - Clonidine
  - Lorazepam, if already on benzodiazepine (up to 4 mg q4h)
- Adjunctive ketamine infusion

GROETZINGER LM, ET AL. PHARMACOTHERAPY. 2018;38(2):181-188.

Neuromuscular Blockade (NMB)

* Deeper sedation levels needed prior to starting (RASS -4 to -5)

- Severe ARDS
  - Data initially showed possible mortality benefit (ACURASYS, NEJM 2010)
  - Recent study demonstrated no clinical benefit (PETAL, NEJM 2019)
- Impaired patient-ventilator synchrony
- Targeted temperature management

Options for NMB Infusions

PRIMARY

Cisatracurium 0.5-10 mcg/kg/min

Vecuronium 0.8-1.7 mcg/kg/min

SECONDARY OR TERTIARY

Rocuronium 4-16 mcg/kg/min

Atracurium 5-20 mcg/kg/min

Monitoring:

-Physiologic parameters (skeletal muscle movement, spontaneous breathing, plateau pressures)

-Train of four devices (many limitations)

Strategies to Prolong NMB Supply

- Attempt intermittent boluses first
  - Vecuronium 0.1-0.2 mg/kg
  - Rocuronium 0.6-1.2 mg/kg
  - Cisatracurium 0.1-0.2 mg/kg
- Daily release from NMB
- Educate providers on lack of benefit in recent ARDS trial
- Infusions >48 hours should be questioned

SMETANA KS, ET AL. CRIT CARE NURS Q. 2017;40(4):323-343.

Case #1: RF

- 62 year old male
- PMH: Heavy EtOH use, HTN
- CC: Respiratory failure due to COVID19 pneumonia
- Mechanically ventilated

CASE #1: RF

- 62 year old male
- CC: Respiratory failure due to COVID19 pneumonia
- **Day 2:**
  - Ventilator settings are increasing (FiO2 70% / PEEP 14)

Pain: Fentanyl 75 mcg/hr
Sedation: Propofol 50 mcg/kg/min
NMB: None

Assume fentanyl and propofol shortage

Pain: Start hydromorphone 0.5-3 mg/hr
Sedation: Start midazolam 2 mg IVP q10 min + infusion 1-10 mg/hr
NMB: None

Case #1: RF

- 62 year old male
- CC: Respiratory failure due to COVID19 pneumonia
- **Day 4:**
  - Pneumonia progresses to severe ARDS
  - Clinician wants neuromuscular blockade

Assume fentanyl and propofol shortage

Pain: Hydromorphone 1 mg/hr
Sedation: Midazolam 4 mg/hr → Bolus 2 mg and increase to 6 mg/hr for RASS -4
NMB: Vecuronium 0.2 mg/kg, if multiple doses needed within several hours, start drip 0.8-1.7 mcg/kg/min

Case #1: RF

- 62 year old male
- CC: Respiratory failure due to COVID19 pneumonia
- **Day 18:**
  - ARDS improved, attempts at ventilator weaning occur
  - Refractory agitation, discomfort occur when drips

Assume fentanyl and propofol shortage

Pain: Hydromorphone 3 mg/hr, add methadone 10 mg q8h per tube
Sedation: Dexmedetomidine 1.2 mcg/kg/min
NMB: Off

Case #1: RF

- 62 year old male
- CC: Respiratory failure due to COVID19 pneumonia
- **Day 20:**
  - Hydromorphone maintenance rate reduced
  - Hydromorphone turned off during awakening trial
  - Dexmedetomidine is maintained at low rate during breathing trial
  - Patient is able to be successfully extubated
  - Wean methadone over 5-10 days

Assume fentanyl and propofol shortage

Pain: Hydromorphone 1.5 mg/hr, methadone 10 mg q8h (day 3)
Sedation: Dexmedetomidine 1 mcg/kg/min
NMB: Off

Case #2: CD

- 47 year old male
- History of methamphetamine use
- CC: Polysubstance ingestion, motor vehicle collision
- **Day 1:**
  - Intubated to protect airway

Pain: Fentanyl 125 mcg/hr
Sedation: Propofol 60 mcg/kg/min
NMB: None

Assume fentanyl and propofol shortage

Pain: Start hydromorphone 0.5-3 mg/hr
Sedation: Dexmedetomidine 0.1-1.5 mcg/kg/hr
NMB: None

Case #2: CD

- 47 year old male
- History of methamphetamine use
- CC: Polysubstance ingestion, motor vehicle collision
- **Day 2:**
  - Intubated to protect airway
  - Consistently in pain, agitated, attempting to pull at lines/tubes

Assume fentanyl and propofol shortage

Pain: Hydromorphone 3 mg/hr, schedule APAP 1g q6h, Gabapentin 100 mg TID
Sedation: Dexmedetomidine 1.5 mcg/kg/hr, midazolam 4 mg/hr
NMB: None

Case #2: CD

- 47 year old male
- History of methamphetamine use
- CC: Polysubstance ingestion, motor vehicle collision
- **Day 3:**
  - Intubated to protect airway
  - Consistently in pain, agitated, attempting to pull at lines/tubes

Assume fentanyl and propofol shortage

Pain: Hydromorphone 3 mg/hr, schedule APAP 1g q6h, Gabapentin 100 mg TID
Sedation: Stop dexmedetomidine, add ketamine infusion, midazolam 4 mg/hr
NMB: None

Case #2: CD

- 47 year old male
- History of methamphetamine use
- CC: Polysubstance ingestion, motor vehicle collision
- **Day 5:**
  - Pain control much improved, less agitated
  - Ventilator weaning, ready for breathing trials

Assume fentanyl and propofol shortage

Pain: Hydromorphone 1 mg/hr, stop APAP, continue gabapentin
Sedation: Ketamine 20 mcg/kg/min
NMB: None

Case #2: CD

- 47 year old male
- History of methamphetamine use
- CC: Polysubstance ingestion, motor vehicle collision
- **Day 6:**
  - Awakening trail and breathing trial
  - Successfully extubated

Assume fentanyl and propofol shortage

Pain: HOLD hydromorphone infusion, stop APAP, continue gabapentin
Sedation: Drop ketamine to 1-2 mcg/kg/min, have PRN midazolam available
NMB: None

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