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Intermountain Project ECHO TeleCritical Care Medicine

Sedation Pearls & Pitfalls

March 2, 2022

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Objectives

1. Understand how to improve patient outcomes using analgosedation principles for sedation management

2. Apply existing evidence in order to thoughtfully consider a bolus vs. continuous sedation approach

3. Review sedation options and pearls for nonintubated patients

No disclosures

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Analgosedation

Sedation: Long Term Impact, Mortality

Outcome	Incidence	Risk Factors
Cognitive impairment	30-80%	Delirium, presence and duration Sedation Hypo and hyperglycemia Hypoxemia, Hypotension
Psychiatric illness, PTSD	Up to 57%	Sedation Poor recall of intensive care unit (ICU) stay Younger age
Physical impairment	25-80%	Acute Respiratory Distress Syndrome (ARDS) Prolonged mechanical ventilator (MV) time Sepsis, Multi-organ failure Steroid use

Devlin JW et al. Crit Care Med 2018; 46e825-873
Colbenson GA et al. Breath. 2019 Jun; 15(2): 98-101
Marra A, et al. Crit Care Clin. 2017 Apr; 33(2): 225-243.

Treatment Guidance

PADIS

- **P**ain
- **A**gitation/Sedation
- **D**elirium
- **I**mmobility
- **S**leep Disruption

ABCDEF Bundle

- **A**ssess and manage pain
- **B**reathing trials, spontaneous awakening
- **C**hoice of sedative
- **D**aily delirium monitoring
- **E**arly mobility
- **F**amily engagement and empowerment

Marra A et al. Crit Care Clin. 2017 Apr; 33(2):225-243
Devlin JW et al. Crit Care Med 2018; 46e825-873

Key Principles

Non-modifiable Risk: Delirium

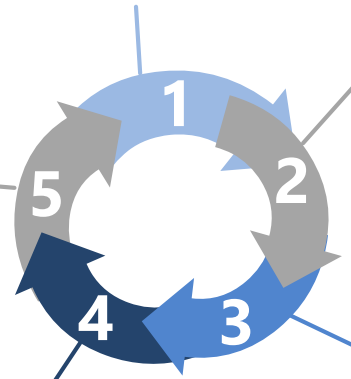
Older age
Dementia
Emergency surgery or trauma
High APACHE

Non-medication

Music, pet therapy
Cold packs
Cognition exercises
Reorientation
Early mobility
Hearing/vision
Sleep/wake cycle

Analgosedation

Treat pain first
Exceptions exist



Validated Scales

Behavioral Pain Scale (BPS)
Critical care pain observation tool (CPOT)
Richmod Agitation-Sedation Scale (RASS)

Establish Goals

Patient-specific
Least-effective doses

Devlin JW et al. Crit Care Med 2018; 46e825-873

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Behavioral Pain Scale (BPS)

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	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with Ventilation	Tolerating movement	1
	Coughing with movement	2
	Fighting ventilator	3
	Unable to control ventilation	4

Payenet al. CritCare Med 2001;29(12):2258-63.

Critical Care Pain Observation Tool (CPOT)

Indicator	Description	Score	
Facial Expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening	Tense	1
	All of the above plus eyelids tightly closed	Grimacing	2
Body Movement	Does not move at all	Absence of movement	0
	Slow cautious movements, touching site, seeks attention through movement	Protection	1
	Pulling tube, attempting to sit up or climb out of bed, moving limbs/thrashing/striking out, not following commands	Restlessness	2
Muscle tension	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
Compliance with ventilator (intubated)	Alarms not activated, easy ventilation	Tolerating vent or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
Vocalization (extubated)	Talking in normal tone or no sound	Talking normal or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2

Gélinaset al. *Am J CritCare.*2006 Jul;15(4):420-7.

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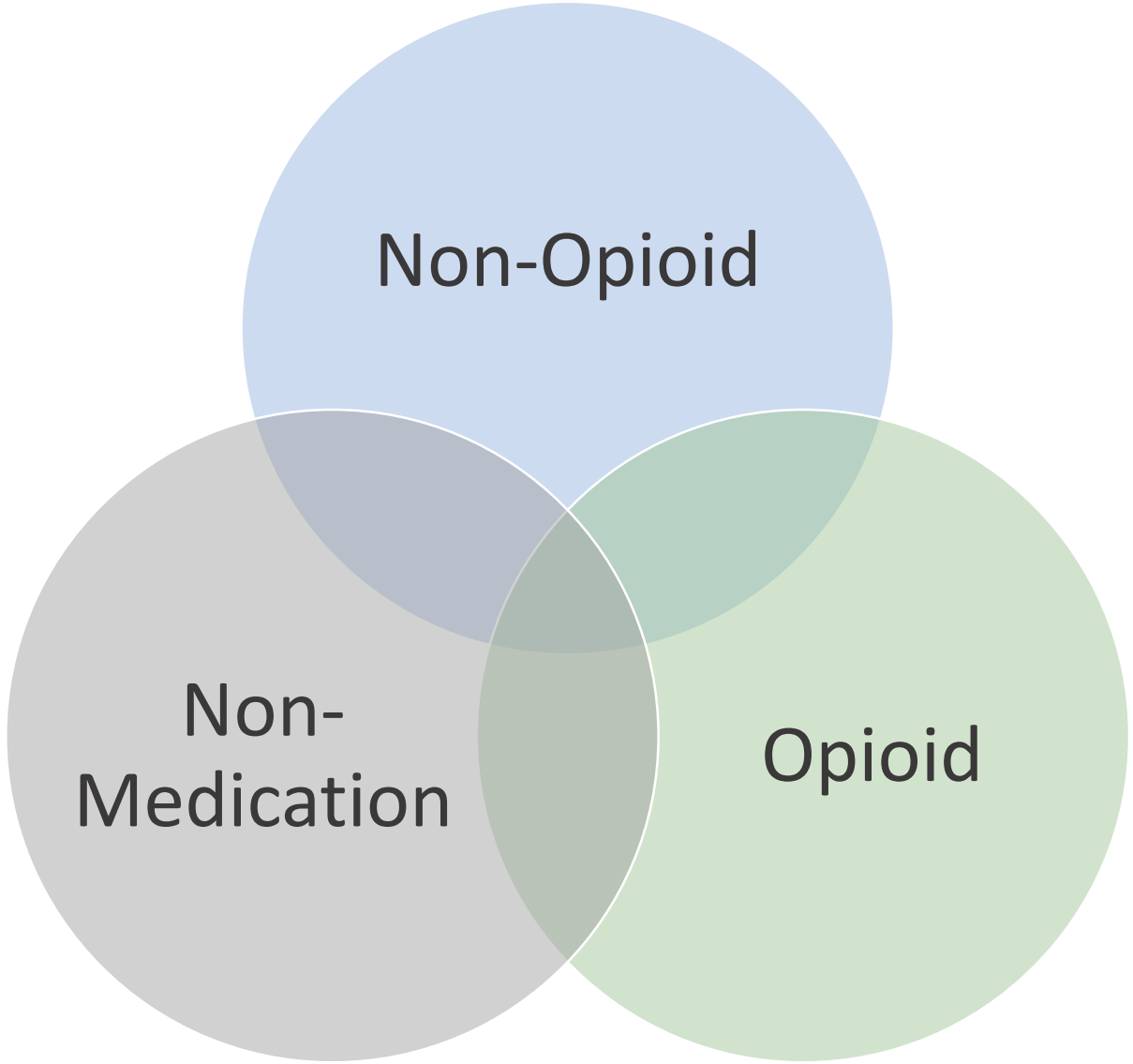
Multimodal Approach

Non-Opioid:

- Acetaminophen
- Gabapentin, Pregabalin
- Carbamazepine
- Lidocaine patches
- Ketamine

Non-Medication:

- Ice packs/Heat
- Cognitive distraction
- Music/Pet therapy
- Massage
- Setting Expectations



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Opioids & Ketamine

Drug	Onset	Duration	Bolus Dosing	IV Infusion Rates	Pearls
Fentanyl	10-30 sec	30-60 min	25-100 mcg q1h PRN	10-200 mcg/h	Less hypotension than morphine
Hydromorphone	5 min	3-4 h	0.5-1 mg q1h PRN	0.2-3 mg/h	Option if tachyphylaxis to fentanyl Increased drug exposure in renal impairment
Morphine	5-10 min	3-5 h	2–8 mg q2h PRN	1-10 mg/h	Histamine release Active metabolites
Ketamine	30-40 sec	15-20 min	0.25-1 mg/kg q2h PRN	1-10 mg/h	Adjunct pain dosing Attenuates opioid tolerance

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Non-Opioids

Drug	Onset	Duration	Dosing	Pearls
APAP (PO,PR)	30-60 min	4-6 h	325-1000 mg Q4-6h (MDD 4g/d)	Hepatic dysfunction max 3g/d or avoid
APAP (IV)	5-10 min	4-6 h	1000 mg IV Q6H (MDD 4g/d)	
Ketorolac (IM/IV)	10-20 min	4-6 h	15-30 mg IM/IV Q6H up to 5 days (MD = 120 mg/d x 5d)	Avoid NSAIDs in most ICU patients Increased drug exposure in geriatric
Ibuprofen	25 min	4-6 h	400 mg PO Q4H (MDD 2.4 g/d)	
Gabapentin	1-4 h	5-7h	100 mg PO TID; (MDD 900-3600 mg/d)	Sedation, confusion, dizziness, ataxia Adjust in renal failure May have impaired absorption

Lexicomp; Wolters Kluwer 2022 UpToDate, Inc.

Bolus vs Continuous Infusion

Pain & Sedation

Sedation

Goals

- Reduce anxiety and stress
- Prevent harm
- Ventilator compliance

Morbidity

- ICU length of stay (LOS)
- Duration of MV
- Physical function
- Neurocognitive and psychologic outcomes

ICU Pitfalls

- Validated scales
- Unpredictable pharmacokinetics
- Drug interactions
- Organ dysfunction
- Absorption variability
- Hemodynamic instability

Devlin JW et al. Crit Care Med 2018; 46e825-873

Light Sedation

How to apply in practice with the available evidence

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Salgado DR, et al

Purpose: Is minimal sedation feasible and without major adverse events?		
Design	Prospective, observational 2-month period	
Population	ICU patients > 12 hours	
Descriptive outcomes	• Admit diagnosis • Severity of illness • Sedatives/opiates • Self-extubation	• Duration of MV • ICU LOS • 28-day mortality

Salgado DR et al. *Journal of Critical Care* (2011) 26, 113-121

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Salgado DR, et al

- Total = 335 patients; MV = 145 (46%)
- Sedation received = 142 (42%)
  - 85% MV
  - Intermittent bolus = 20 (14%)
  - Continuous infusion = 122 (86%)
    - MV (92% vs 18%) and ARDS (19% vs 0%)
    - Longer median ICU LOS [24 (12-36) vs 16 (8-24) $p < 0.01$]
    - Greater risk of death [HR 2.82 (0.66-12) p 0.16]
- Self-extubation = 6; 1 reintubated
- 14 patients received haloperidol

Salgado DR et al. *Journal of Critical Care* (2011) 26, 113-121

Table 4 Sedation and analgesia data in mechanically ventilated and nonmechanically ventilated patients

		No mechanical ventilation (n = 180)	Mechanical ventilation (n = 155)	*P*
Sedation				
Strategy of sedation, n (%)	Continuous	2 (1)	120 (77)	<.001
	Intermittent	9 (5)	11 (7)	
Type of sedative drug, n (%)	Midazolam	6 (3)	70 (45)	<.001
	Propofol	1 (1)	68 (44)	
	Diazepam	9 (5)	7 (5)	
	Thiopental	0	2 (1)	
Duration of sedation (h)		0 (0-0)	5 (1-18)	<.001
Sedative max dose	Midazolam (mg/h)	2.5 (2-3)	5 (2.5-10)	<.001
	Propofol (mg/h)	20	200 (100-240)	NA
Sedative total dose	Midazolam (mg)	3.5 (3-4)	74.5 (18-178)	<.001
	Propofol (mg)	40	470 (240-1170)	NA
Analgesia				
Strategy of analgesia, n (%)	Continuous	15 (8)	108 (70)	<.001
	Intermittent	71 (39)	25 (16)	
Type of analgesic drug, n (%)	Morphine	65 (36)	115 (74)	<.001
	Remifentanil	0	42 (27)	
	Fentanyl	0	1 (1)	
	Paracetamol	88 (49)	60 (39)	
	Others [a]	8 (4)	7 (11)	
Duration of analgesia (h)		0 (0-2)	19 (3-41)	<.001
Analgesia max dose	Morphine (mg/h)	2 (2-2)	2 (2-4)	<.001
	Remifentanil (mg/h)	0	0.5 (0.2-1.1)	NA
Analgesia total dose	Morphine (mg)	8 (3.5-17)	67 (25.5-162)	<.001
	Remifentanil (mg)	0	24 (22.1-99.1)	NA
Coinfusion of sedation and opiates, n (%)		0 (0)	96 (62)	<.001

Data are presented as n (%) or median (25%-75% interquartile range). NA indicates not applicable; max: maximum.

[a] Nonsteroidal anti-inflammatory drugs, tramadol.

Salgado DR et al. *Journal of Critical Care* (2011) 26, 113-121

Salgado DR, et al

MV without continuous sedation was safely achieved more than 80% of the time

- Continuous infusion and intermittent bolus approaches used
- No direct comparison of intermittent vs continuous strategy

No major adverse effects

- Not well evaluated

No difference in ICU LOS or time on MV

Other long-term sequelae not evaluated

Salgado DR et al. *Journal of Critical Care* (2011) 26, 113-121

Strom T, et al

Purpose: Is duration of MV reduced when using a no sedation vs daily sedation interruption protocol?		
Design	Prospective, randomized controlled trial	
Population	ICU patients requiring MV for > 24h	
Intervention	<u>No Sedation (n = 55)</u> • Morphine 2.5-5 mg bolus prn	<u>Sedation (n = 58)</u> • Propofol x48h → midazolam infusion; daily interruption • Morphine 2.5-5 mg bolus prn
Outcomes	• Days without MV (28d period) • ICU and hospital LOS	

Strom T et al, *Lancet* 2010; 375: 475-80.

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	No sedation (n=55)	Sedation (n=58)	p value
Days without mechanical ventilation (from intubation to day 28)	13·8 (11·0); 18·0 (0–24·1)	9·6 (10·0); 6·9 (0–20·5)	0·0191*†
Length of stay (days)			
Intensive care unit	13·1 (5·7–··)‡	22·8 (11·7–··)‡	0·0316*§
Hospital	34 (17–65)	58 (33–85)	0·0039*§¶
Mortality			
Intensive care unit	12 (22%)	22 (38%)	0·06
Hospital	20 (36%)	27 (47%)	0·27
Drug doses (mg/kg)‖			
Propofol (per h of infusion)**	0 (0–0·515)	0·773 (0·154–1·648)	0·0001
Midazolam (per h of infusion)	0 (0–0)	0·0034 (0–0·0240)	<0·0001
Morphine (per h of mechanical ventilation)	0·0048 (0·0014–0·0111)	0·0045 (0·0020–0·0064)	0·39
Haloperidol (per day of mechanical ventilation)	0 (0–0·0145)	0 (0–0)	0·0140
Tracheostomy	16 (29%)	17 (29%)	0·98
Ventilator-associated pneumonia	6 (11%)	7 (12%)	0·85

Data are mean (SD), median (IQR), or number (%). ··=data not available because of censoring at day 28. *Corrected for baseline variables: age, sex, weight, acute physiology and chronic health evaluation (APACHE II), simplified acute physiology score (SAPS II), and sequential organ-failure assessment (SOFA) at day 1. †Calculated from multiple linear regression. ‡More than 25% of patients remained in the intensive care unit for more than 28 days (figure 2). §Calculated from Cox regression analysis. ¶Calculated for the first 30 days to agree with the proportional hazards assumption. ‖Drug dose (mg) as a proportion of bodyweight (kg). **Maximum dose during 48 h of treatment.

Table 2: **Outcome data**

Strom T et al, *Lancet* 2010; 375: 475-80.

Strom T, et al

Providing analgesia with intermittent boluses may be an effective strategy to maintain ventilator compliance, while reducing duration of MV and ICU LOS

Pitfalls:

- Change from propofol to midazolam infusion
- Morphine not commonly used
- Delirium detection was not a primary outcome
- Did not evaluate other patient centered outcomes

Strom T et al, *Lancet* 2010; 375: 475-80.

Continuous Infusion

Specific patient populations

- Severe ARDS
- Ventilator compliance
- Withdrawal syndromes
- Intracranial hypertension or seizure management
- Neuromuscular blockade

Non-benzodiazepine preferred

- Shorter ICU LOS
- Shorter duration of MV
- Reduced incidence of delirium

Daily sedation vacations

Devlin JW et al. Crit Care Med 2018; 46e825-873

Continuous Infusion

Evidence Pitfalls

- Benzodiazepine-heavy approach
  - Finfer, et al: intermittent diazepam vs continuous midazolam
    - No difference: hours to or within target sedation, over sedation
  - Carson, et al: intermittent lorazepam vs continuous propofol
    - Propofol group: fewer days on ventilator, reduced ICU LOS
- Evidence supporting sedation vacation is in the setting of continuous infusion
- “Light sedation” not well-defined
  - RASS -2 to +1
  - Need more robust correlation with clinical outcomes

Kress JP, *CHEST Counterpoint* 2012, 142:5.

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Intermittent Bolus

May be a reasonable approach for some patients

- Wean continuous infusions
- Avoid dose escalations
- In place of continuous infusions
  - Minimal ventilator settings
  - Anticipated short duration of MV
  - Altered mental status due to unknown cause
  - Hemodynamic compromise

Drug Shortages

- Often require lower cumulative doses

Nassar et al *Annals of Intensive Care* 2014, 4:14.
Vinayak AG *CHEST Counterpoint* 2012, 142:5.

Traditional Sedatives

Drug	Bolus Dosing	IV Infusion	Pearls
Midazolam	2-5 mg q1-2h PRN	0.5-10 mg/h	One active metabolite
Lorazepam	2-4 mg q1-2h PRN	Avoid	Propylene glycol toxicity
Diazepam	5-10 mg q2-4h PRN	Avoid	Vesicant: can cause phlebitis Longer acting: two active metabolites
Propofol	0.5-2 mg/kg Procedural or to avoid dose escalation	5-75 mcg/kg/min	+/- Hypotension Hypertriglyceridemia Propofol Related Infusion Syndrome (PRIS)
Dexmedetomidine	Avoid	0.1-1.5 mcg/kg/h	Bradycardia Start low, go slow Does not cause amnesia or deep sedation
Ketamine	0.5-2 mg/kg Procedural or to avoid dose escalation Stand-alone	5-75 mcg/kg/min	Continuous sedation dosing Emergence reactions Hallucinations/Agitation Catecholamine depletion → myocardial depression

Devlin JW et al. Crit Care Med 2018; 46e825-873
Reade, et al. N Engl J Med. 2014;370:444-54.
Lexicomp Onlinee, Lexi-Drugs, Hudson, Ohio: Lexi-Comp, Inc; April 29, 2018

Non-traditional Sedatives

Phenobarbital (MDD = 400 mg)

- PRN Bolus: 2-5 mg/kg IV q4h PRN vs. 130-260 mg IV q4h PRN
- Load: 5-10 mg/kg IV x1
- Pearls:
  - Slow IV push, max 60 mg/min. Large doses in IVPB
  - Many drug interactions
  - +/- bradycardia, hypotension

Valproic Acid

- 500 mg IV or enteral BID to TID, +/- 30 mg/kg loading dose
- Pearls:
  - +/- thrombocytopenia, transaminitis, hyperammonemia
  - Drug interaction with carbapenems

Clonidine: alpha-2 agonist

- 0.2-0.3 mg q6-8h scheduled, up to 0.4 mg q6h
- If tapering off dexmedetomidine, reduce infusion by 25% with each dose

Gagnon DJ et al. Pharmacotherapy 2017;37(10):1309-1321)

Agitation Management in the Nonintubated Patient

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Agitation in the ICU

- Pain
- Delirium
- Sleep-wake disturbances
- Fear, anxiety
- Encephalopathy
- Infection/Fever
- Brain injury/Trauma
- Medications
- Metabolic disorders
- External stimuli
- Underlying psychiatric disorders
- Substance abuse or withdrawal
- Toxins

Reade MC et al, *N Engl J Med* 2014; 370: 444-454.
Chevrolet JC, Jolliet P, Crit Care 2007; 11(3):214.
Devlin JW et al. Crit Care Med 2018; 46e825-873.

Medication Options for Nonintubated Patients

- Antipsychotics
- Benzodiazepines
- Ketamine (low dose)
- Dexmedetomidine (low dose)
- Clonidine
- Valproic Acid
- Phenobarbital
- Opioids
- Non-opioid analgesics
- Sleep promoting medications

Delirium

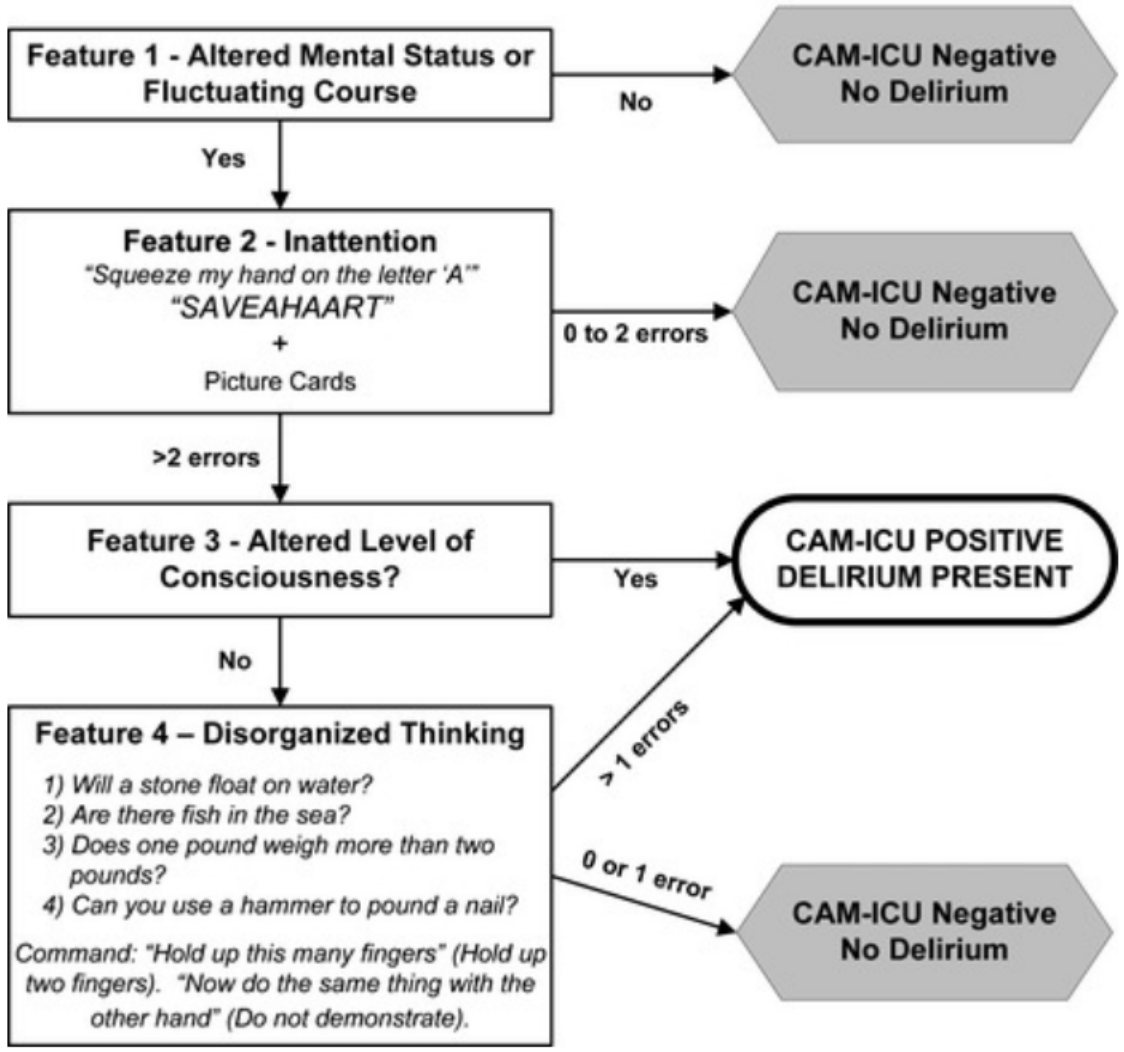
Strong Modifiable Risk Factors

- Benzodiazepine use
- Blood transfusions

Moderate Modifiable Risk Factors

- Use of psychoactive medication
- Hypertension
- Neurologic disease on admission
- Trauma
- Dialysis or CVVHD
- History of respiratory disease

Confusion Assessment Method - ICU



Journal of Intensive Care Medicine. 2016;31(1):14-23
Devlin JW et al. Crit Care Med 2018; 46e825-873

Delirium Prevention & Treatment

Multimodal non-medication interventions, ABCDEF bundle

- Reduce modifiable risk factors
- Improve cognition
- Optimize sleep, improve daytime wakefulness
- Increase early mobilization, physical rehabilitation
- Hearing and vision
- Re-direct, de-escalate

Significant distress: anxiety, fear, hallucinations, self harm, harm to others

- Short term use of atypical antipsychotics or haloperidol

Violent/aggressive agitation or prohibiting cares

- IM sedatives or antipsychotics
- Dexmedetomidine
- Physical restraints

Devlin JW et al. Crit Care Med 2018; 46e825-873

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Antipsychotics

First line use

- Psychosis

Possible use

- Undifferentiated agitation
- Agitated Delirium
- Intoxication-related agitation

First Generation (FGA)

- Haloperidol
- Droperidol

Second Generation (SGA): less sedating, fewer extrapyramidal side effects

- Olanzapine
- Quetiapine
- Risperidone
- Ziprasidone

Roppolo LP et al. *JACEP Open* 2020;1:898–907.

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SGA

Drug	Onset	Duration	Dosing	Pearls
Olanzapine	ODT: <60 min IM: 15 min IV: 5-10 min	ODT: n/a IM: 2 hr IV: n/a	ODT: 5-10 mg TID (MDD 30 mg/d) IM: 5-10 mg x1, repeat at 2 hr then 4 hr (MDD 30 mg/d) IV: 5 mg x1, repeat 2.5-5 mg in 10 min (MDD 10 mg/d)	Avoid IV use due to risk of respiratory depression Least QTc prolonging Faster oral onset compared to oral risperidone
Risperidone	60 min	Variable	ODT: 1-2 mg q2-6 hr (MDD 6 mg/d)	Higher doses in schizophrenia
Ziprasidone	IM: 15-30 min PO: n/a	IM: 2-8 hr PO: 8-12 hr	IM: 10-20 mg x1, repeat at 2-4 hr (MDD 40 mg/d) PO: 20-40 mg BID (MDD 80 mg)	Highest QTc prolongation of SGA
Quetiapine	30-90 min	6-12 hr	12.5-400 mg/d, can be divided BID or TID (MDD 400 mg/d for agitation)	Higher doses in schizophrenia

Lexicomp; Wolters Kluwer 2022 UpToDate, Inc.

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FGA

Drug	Onset	Duration	Dosing	Pearls
Haloperidol	IM: 15 min IV: 3-15 min	IM: 2 hr IV: 3-24 hr	IM or IV: 2-10 mg every 15 min – 6 hr (MDD 30 mg/d)	Lactate formulation may be given IV or IM Decanoate formulation can only be given IM PO rarely used
Droperidol	IM/IV: 2-10 min	2-4 hr	IM or IV: 2.5-10 mg x1 (MDD 10-20 mg/d)	Decreased combativeness significantly more than haloperidol when given IM

Lexicomp; Wolters Kluwer 2022 UpToDate, Inc.

Sleep Disruption in the ICU

Often normal in ICU patients:

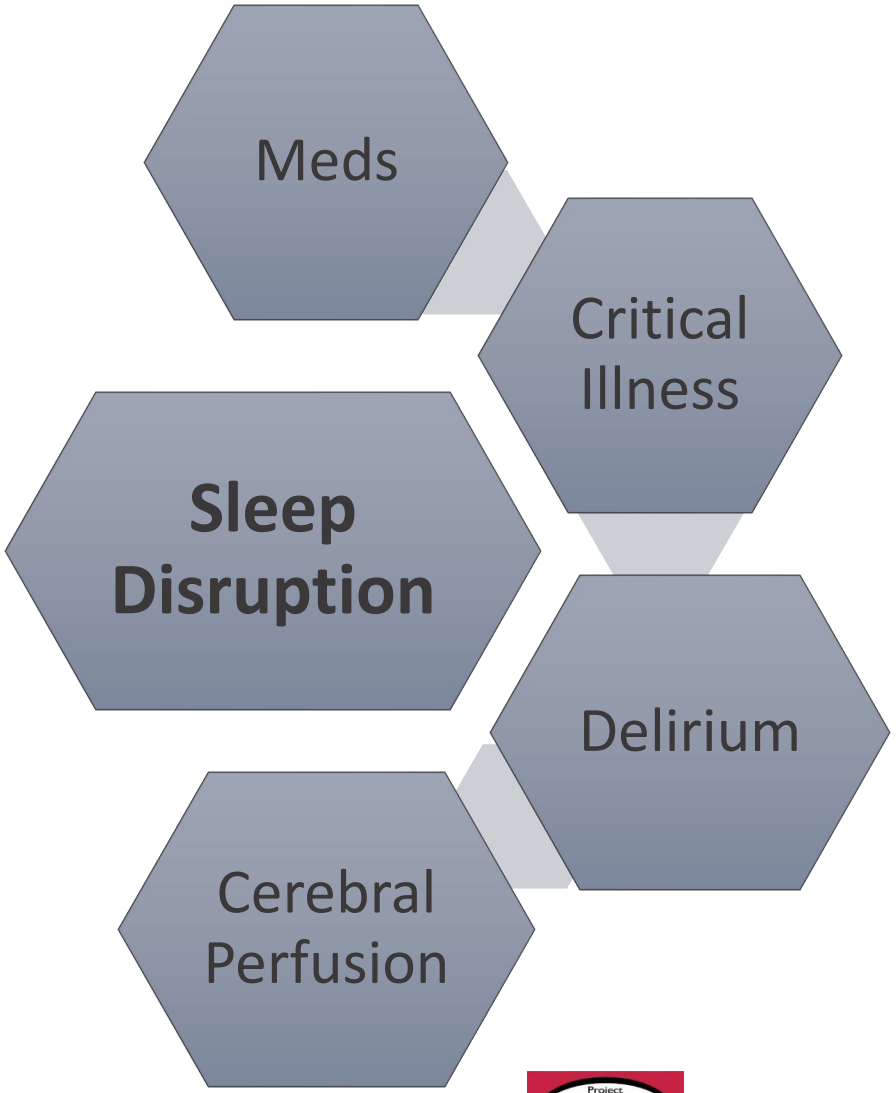
- Total sleep time
- Sleep efficiency

Often greater in ICU patients:

- Sleep fragmentation
- Light sleep (stages 1 & 2)
- Daytime Sleep (up to 57%)

Often decreased in ICU patients:

- Deep sleep (REM, slow wave)
- Sleep quality



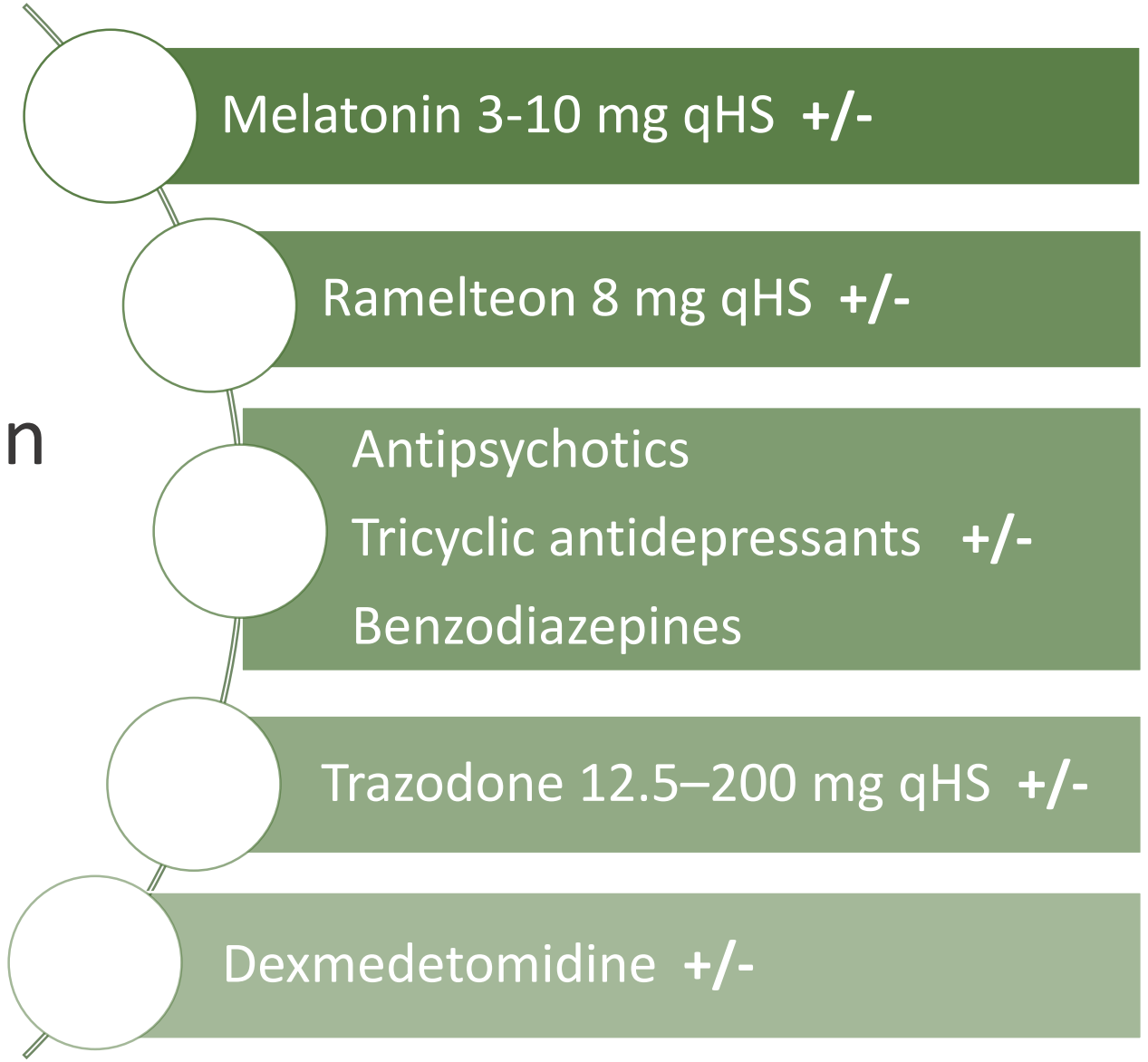
Devlin JW et al. Crit Care Med 2018; 46e825-873

Sleep Improvement

Prioritize non-medication strategies

- Noise and light reduction
- Daytime activity
- Earplugs, eyeshades

Medications only after careful consideration



Devlin JW et al. Crit Care Med 2018; 46e825-873
Matthews EE, AACN Adv Crit Care. 2011; 22(3):204-224

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Dexmedetomidine and Sleep

Sleep architecture

- Endogenous sleep-promoting pathway
- Animal and preclinical settings

Sleep in MV patients

- Alexopoulou C et al: 13 patients on MV, no other sedation
  - Significantly higher sleep efficiency, reduced stage 1 and 2 sleep, increased proportion of night time sleep

Sleep in non-MV patients

- Wu XH et al: RCT of 76 patients age ≥65 admitted to ICU after noncardiac surgery without MV
  - Significantly increased % stage N2 sleep (15.8% vs 43.5%), but no difference on N3 or REM sleep
  - Longer total sleep time, increased sleep efficiency, improved subjective sleep quality
  - Increased incidence of hypotension in dexmedetomidine group

Alexopoulou C et al. *Anesthesiology* 2014, 121, 801-807.
Wu XH et al. *Anesthesiology* 2016, 125, 979-991.

Today's Accomplishments

1. Understand how to improve patient outcomes using analgosedation principles for sedation management

2. Apply existing evidence in order to thoughtfully consider a bolus vs. continuous sedation approach

3. Review sedation options and pearls for nonintubated patients

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Discussion & Questions