

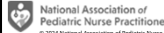
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on Pediatric Health Care

**Sedation & Analgesia
Outside of the Box:
Choices and Challenges**

Liz Espinoza, DNP, CPNP-AC
Lauren Flagg, DNP, CPNP-AC



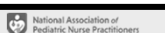
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Experts in pediatrics. Advocates for children.

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Speaker Disclosure

- No disclosures




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Learning Objectives

- Describe the mechanism of opioid induced pruritus and identify two strategies to help alleviate this common side effect.
- Explain two benefits of using a multimodal approach for pain and sedation management in pediatrics.
- Identify two agents that are commonly used for multimodal pain management in pediatrics and the risk and benefits of each.
- Define delirium and describe its three subtypes.
- Identify two agents used for sedation and/or analgesia that should be avoided in the prevention and management of pediatric delirium.




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**Sedation & Analgesia
Outside of the Box**

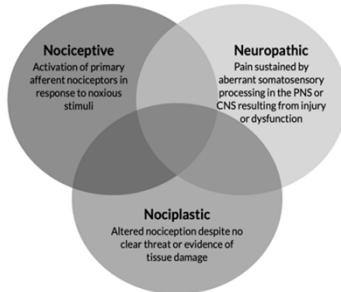
Liz Espinoza, DNP, CPNP-AC^{1,2}



¹Oregon Health & Science University School of Nursing
²Oregon Health & Science School of Medicine, Department of
Pediatrics, Division of Critical Care

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Pediatric Pain: The 30,000 Foot View



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Pain in the PICU

- Majority of children in the PICU will experience pain
- Risk factors include age and cognitive stage, mental status, underlying comorbidities, presence of mechanical ventilation (MV), need for invasive procedures or monitoring devices, sleep disturbance, mobility limitations
- Untreated pain has both physiological and psychological consequences including immunosuppression, delayed wound healing, impaired sleep, hyperalgesia, and increased risk for trauma and posttraumatic stress disorder

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Pain or Sedation..... or BOTH?!

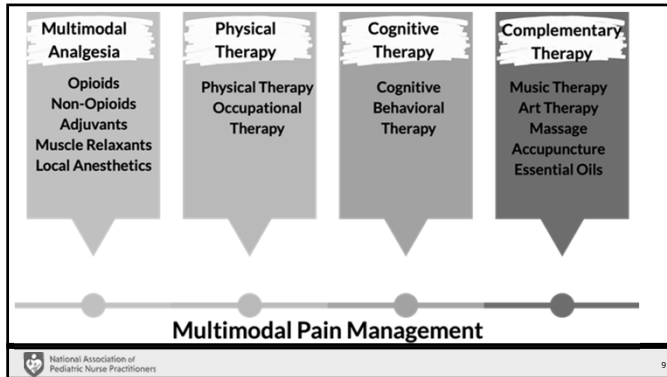
- Medications used for pain and sedation may help to decrease agitation, prevent accidental removal of invasive devices, improve vent synchrony, optimize hemodynamics, and decrease oxygen consumption
- Differentiating between pain and agitation is difficult in children
- Other plausible reasons for changes in child's condition must also be considered
- Many behavioral indicators overlap on commonly used pain and sedation assessment scales, causing confusion for nurses
- Nurses often rely on physiological variables when assessing pain, which may be influenced by other factors in the PICU, such as vasoactive medications or fluid status

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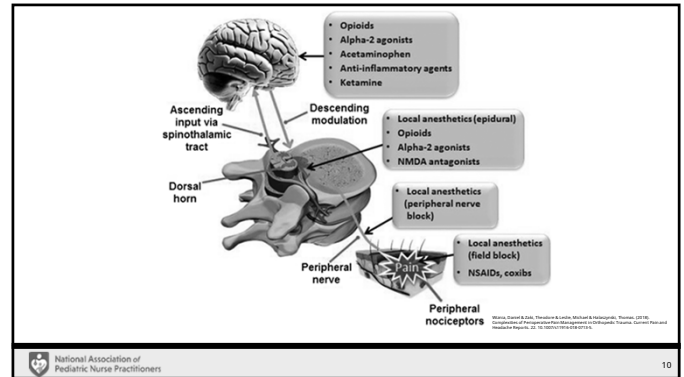
Why Does this Matter?

- Prolonged sedation with high doses of traditional agents (opioids and benzodiazepines) leads to risk of iatrogenic withdrawal syndrome (IWS), as well as potentially increase mechanical ventilation days and decrease enteral feeding tolerance
- Untreated pain increases risk for post-ICU trauma
- Oversedation leads to decreased mobility, increased muscle wasting, and increased risk of requiring inpatient rehab at discharge
- Patients without pain require less sedation, have more stable hemodynamics, and overall better outcomes

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Non-Opioid Analgesics: Acetaminophen & NSAIDS

- Similar pharmacological actions
- Good for mild pain and provides additive effect when used in combination with opioids
- Has a “ceiling” effect
- IV acetaminophen is opioid sparing, same effect has not been found with oral and rectal dosing
- IV route preferred for pain management for moderate to severe surgical pain and non-surgical pain when the PO route is unavailable

Non-Opioid Analgesics: Acetaminophen & NSAIDS



- Use of NSAIDS in both post op cardiac and noncardiac patients associated with improved pain scores and decreased opioid requirements
- Short term use not associated with bleeding, changes in renal function, or gastritis

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Opioids: Fentanyl, Morphine, Hydromorphone

- First line for moderate to severe pain in critically ill children
- Work by binding to mu, kappa, and delta opioid receptors to block nociceptive information both centrally and peripherally
- Increased risk of adverse effects over other agents
- Ideally should be used primarily to manage moderate to severe post operative or non-operative pain and then tapered

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Opioids: Fentanyl

- Shortest acting
- Preferred in patients with renal dysfunction due to lack of active metabolites
- Hemodynamically neutral with no effect on PVR
- Tachyphylaxis common
- Beware of rigid chest in neonates

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Opioids: Morphine

- Most sedative, but really its only benefit
- Broken down into 2 metabolites: morphine 3-glucuronide and morphine 5-glucuronide
- Caution in renal dysfunction as accumulation of metabolites can accumulate and prolong duration and effect
- High doses of morphine can cause histamine release, leading to peripheral vasodilation and hypotension.

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Opioids: Hydromorphone

- Longest onset of action
- Minimal histamine release
- Concentrated dosage forms and small per kg doses can limit use in pediatric population
- Increased risk of neuroexcitability from metabolites

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Benzodiazepines: Midazolam and Lorazepam

- Just say no for sedation (with few exceptions)!
- Provide sedation only, no pain control
- Adverse hemodynamic profile
- Disrupts sleep wake cycle
- Increases risk for delirium
- Neurotoxicity concerns, especially in infants
- Potential opioid antagonist
- May be useful adjunct for muscle spasms or anxiety



Alpha-2-Agonists: Dexmedetomidine & Clonidine

- Primarily used for sedation, though may have some analgesic properties
- Opioid sparing and anti-emetic properties
- Reduces emergence delirium in children awakening from anesthesia
- Use in post op cardiac patients may decrease risk of tachyarrhythmias
- Neuroprotective!
- Maintains normal sleep-wake cycle

Propofol

- Multiple receptors including GABA-A agonist, NMDA agonist, endocannabinoid agonist, sodium channel agonist
- Upregulates expression of mu-receptors
- Use in PICU controversial due to risk for Propofol infusion syndrome
- "Bridge to extubation" for patients at high risk for extubation failure
- Useful for weaning opioid and benzo drips
- Minimal respiratory depression, can be used for short procedural sedation

Ketamine

- Non-selective antagonist of the N-methyl-d-aspartate (NMDA) receptor
- Effective for both pain management and sedation
- Morphine sparing effect due to inhibition of central sensitization, opioid induced hyperalgesia, and acute opioid tolerance
- Low dose ketamine infusion can help reduce postoperative morphine requirements
- Recent literature suggests ketamine does not increase intracranial pressure
- Hemodynamically neutral
- Bronchodilatory properties useful for asthmatics, infants with BPD

Refractory Pain

- Frequent exposure to opioids may lead to opioid induced hyperalgesia (OIH)
- Evidence for rotating opioids is mixed
- NMDA receptor antagonists often useful as blocking glutamine leads to decreased pain sensitivity
- Gabapentin useful as a pain adjunct and may help with weaning of sedation as well
- Methadone is an opioid with racemic mixture of D/L enantiomers, where the D-isomer is a NMDA receptor antagonist, making it useful for refractory pain

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Key Takeaways

- Less is more! Limit exposure to additional agents as much as possible
- Pair opioids with known opioid sparing drugs to enhance effectiveness
- Consider around the clock dosing of pain medications for the first 24-48 hours post op to ensure pain is well managed, along with rescue doses for breakthrough pain
- Rule out other causes of hemodynamic changes or agitation prior to giving additional sedation
- Please don't forget the bowel regimen!

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Delirium: Choices and Challenges

Lauren Flagg, DNP, CPNP-AC^{1,2}

¹Yale University School of Nursing, ²Yale New Haven Hospital Pediatric Critical Care

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Definitions/Pathophysiology

Acute brain dysfunction due to physical illness.

- DSM-5 criteria
 - Fluctuating, develops over hours to days
 - Attention and awareness disturbance
 - Cognition change
 - Not due to existing disorder
 - Due to medical etiology
- Subtypes: Hyperactive, hypoactive, mixed types

(American Psychiatric Association, 2013; Liviskie et al., 2023; Traube, Silver, Gerber, et al., 2017)

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Pathophysiology

- Why does it occur?
- Nobody knows! Three hypotheses
 - Neuroinflammatory: Increased blood brain permeability
 - Reactive nitrogen/oxygen species: Energy failure, oxidative stress
 - Neurotransmitter dysregulation
- And a bit of common sense...

(Liviskie et al., 2023; Maldonado, 2018)

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History lesson

Adults

- Confusion Assessment Method (CAM) : 1990
- CAM-ICU : 2001 .
- ↑ mortality and morbidity, costs of care, LOS

Pediatrics

- pCAM-ICU 2011: >5 years old,
- CAPD: 2014: birth-21 years old.
- psCAM-ICU 2016, 2021
- ↑Mortality and morbidity
 - ↑ cost of care
 - Long-term outcomes ... in process

(Canter et al., 2021; Devan et al., 2022; Ely et al., n.d.; Inouye et al., 1990; Ita et al., 2022; Kaur et al., 2020; Selluh et al., 2015; Smith et al., 2016; Staveski et al., 2021; Traube et al., 2016; Traube, Silver, Gerber, et al., 2017; Traube, Silver, Reeder, et al., 2017)

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Risk Factors

Modifiable	Non-modifiable
Benzodiazepine use (4x more likely)	
Immobilization	Illness severity
Restraint use	Developmental delay
Inadequate sleep	Preexisting medical condition
*Anticholinergic use	
*Opiate use	
*Invasive lines	
Steroids	
	Vasoactive use
	Mechanical ventilation

(Ita et al., 2023; Meyburg et al., 2018; Siegel & Traube, 2020; Traube, Silver, Gerber, et al., 2017; Traube, Silver, Reeder, et al., 2017)

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Delirium & Pharmacologic Choices

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What can we do??

- **Addressing/preventing risk factors**
- Nursing led! 😊
- Non-pharmacologic
 - Hospital Elder Life Program (HELP), Yale 1999
- Medication choices, withdrawal/weaning plan
- Conflicting/limited data for most classes

Heron et al., 1999; Ista et al., 2023; Liviske et al., 2023; Meyburg et al., 2018; Smith et al., 2022; Stawski et al., 2023)

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Prevention and management

Physiologic	Pharmacologic	Environment
<ul style="list-style-type: none"> • Nutrition/hydration • Minimize tubes • Bladder/bowel • Day/night • Mobility • BRAINMAPS 	<ul style="list-style-type: none"> • Sedation goals • Pain management • Avoid polypharmacy • Prevent withdrawal • Precedex • + Melatonin • Antipsychotics • Minimize opiate, benzo, anticholinergic 	<ul style="list-style-type: none"> • Orientation • Noise reduction • Familiarity • Family • Reduce restraints • Educate Family

(Silver et al., 2019; Smith et al., 2013a)

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BRAINMAPS

B	Bring Oxygen
R	Remove/Reduce Drugs
A	Atmosphere
I	Infection, immobilization, inflammation
N	New Organ Dysfunction
M	Metabolic disturbances
A	Awake
P	Pain
S	Sedation

(Bettencourt & Mullen, 2017; Smith et al., 2013b)

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Benzodiazepines

- Up to a 4x risk delirium
 - Dose related links
- Linked to increased mortality and morbidity
- SCCM strongly recommend MINIMIZING

Crit Care Med. Author manuscript; available in PMC 2019 Sep 1.
Published in final edited form as:
Crit Care Med. 2019 Sep;46(9):1486-1491.
doi: 10.1097/CCM.0000000000003184

PMCID: PMC6606819
NLMID: NLM000000000
PMD: 20222303

BENZODIAZEPINES AND DEVELOPMENT OF DELIRIUM IN CRITICALLY ILL CHILDREN: ESTIMATING THE CAUSAL EFFECT

Sato-Maeda, MD, MPH, Steven K. Lee, MD
Boris M. Greenwald, MD, Gabrielle Silver
doi: 10.1097/CCM.0000000000000993

Patterns of Postoperative Delirium in Children

Jochen Meyburg¹, Mona-Lisa Dill, Chari Traube, Gabrielle Silver, Rebecca von Haden

Affiliations + expand

PMD: 27776085 DOI: 10.1097/PCC.0000000000000993

doi: 10.1097/PCC.0000000000000975

2022 Society of Critical Care Medicine Clinical Practice Guidelines on Prevention and Management of Pain, Agitation, Neuromuscular Blockade, and Delirium in Critically Ill Pediatric Patients With Consideration of the ICU Environment and Early Mobility

(Ista et al., 2023; Liviske et al., 2023; Meyburg et al., 2018; Mody et al., 2018; Smith et al., 2017, 2022; Stawski et al., 2023)

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Anticholinergics

- MOA= block acetylcholine...Acetylcholine – role in sleep/wake, stimuli processing.
- Traditional anticholinergic vs others
 - Antihistamines
 - H2-receptor antagonists
- Conflicting data

(Jata et al., 2023; Liviske et al., 2023; Madden et al., 2018, 2020; Meyburg et al., 2018, 2020; Mody et al., 2018; Traube, Silver, Reeder, et al., 2017)

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Propofol

- Less data re: pediatric ICU delirium, mostly emergency
- Limited long-term use in pediatrics
- Conflicting data – decreased emergence delirium, less effective than dexmedetomidine
- Possible benefits:
 - Wash-out
 - Bridge to extubation – SCCM recommendation

(Dervan et al., 2020; Meyburg et al., 2018; Smith et al., 2022; Uppuluri et al., 2022; Xiao et al., 2022)

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Ketamine

- Dissociative hypnotic →hallucinations, amnesic
- Commonly used for procedural sedation, data re: emergence delirium.
- Continuous infusion safety?
- Conflicting research, limited data
 - Speretto et al 2021: Decreased opioid infusion, reduced prns analgesedation. 1/70 delirium.

(Avidan et al., 2017; Dervan et al., 2020; Meyburg et al., 2018; Sperotto et al., 2021; Tessari et al., 2023; Wu et al., 2021)

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Dexmedetomidine

- Agreement! (mostly)
- Adults - Protective against delirium development.
 - Improved sedation levels
 - MOA: affect cholinergic dysregulation
- Pros:
 - SCCM guideline preferred agent
 - Linked to reduced mechanical ventilation, less opioid and benzo
- ?Cons: possible links, but may have reverse causality

(Bargnes et al., 2023; Cater et al., 2022; Christian et al., 2022; Dervan et al., 2020; Han et al., 2022; Riker et al., n.d.; Skrobik et al., 2018; Smith et al., 2022; Su et al., 2016; Traube, Silver, Reeder, et al., 2017)

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Opioids/Opiates

- Mixed research, umbrella term vs specific meds
 - Fentanyl vs Morphine vs hydromorphone: Fentanyl more delirium, morphine no relationship
 - Is lack of separation cause of variability?
- SCCM: optimize pain scoring, management, adjunctive therapies
- Withdrawal syndrome STRONG association with delirium

(Ista et al., 2023; Meyburg et al., 2018; Smith et al., 2022; Stawski et al., 2023)

Antipsychotics- atypicals

△ NOT FDA-approved in children for delirium△

- What can we agree on?
 - NO prophylaxis
 - Rule out underlying physiology cause
 - Consider with refractory/severe delirium
- Considerations
 - Monitoring: ECG, labs
 - PM administration
 - Risk for extrapyramidal side effects
 - May help wean other sedative infusions

(Campbell et al., 2020; Capino et al., 2020; Cronin et al., 2021; Hutchins et al., 2021; Joyce et al., 2015; Mody et al., 2018; Neufeld et al., 2016; Smith et al., 2013, 2022; Thelen et al., 2022; Turkel & Herff, 2014)

Common antipsychotic overview

Haloperidol	Quetiapine	Risperidone	Olanzapine
<ul style="list-style-type: none"> • IM, IV, PO • ↑ EPS • More cardiac side effects 	<ul style="list-style-type: none"> • PO • Half life 6 hours 	<ul style="list-style-type: none"> • PO, ODT • Half life 3-21 hours 	<ul style="list-style-type: none"> • PO, ODT. • IM adult

(Campbell et al., 2020; Capino et al., 2020; Cronin et al., 2021; Hutchins et al., 2021; Joyce et al., 2015; Thelen et al., 2022)

Conclusions

- Conflicting data for many agents
- Best practice per consensus: non pharmacologic, adjunctives, dexmedetomidine, morphine
- Atypical antipsychotics VERY limited data
- Many opportunities for research!



References