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Taper Tantrums:
Diffusing Pediatric Sedation Tapers

PPAG Annual Meeting April 2019
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Objectives

- Summarize sedation and analgesia practices that contribute to the need for tapers
- Discuss strategies to assess and prevent withdrawal
- Apply literature and pharmacokinetic properties of medications to develop taper recommendations
- Understand when adjustments to taper recommendations are necessary

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Root of the Problem: Pain

Pain
- A protective mechanism that leads one to avoid tissue damage

ICU patients cannot escape painful stimuli
- Trauma, surgery, burns, chest tubes, ET tubes, physical therapy, suctioning, repositioning, etc.

Physiologic effects of pain
- Increase HR, BP, O_2 consumption
- Increase in BEE, Na and H_2O retention
- Hyperglycemia, Hypercoagulability

Neonates may have a lower pain threshold due to underdeveloped descending pain pathways

- Osterweis M, et al. The Anatomy and Physiology of Pain. National Academies Press (US); 1987.
- Anand KJS. *J Perinatol*. 2007; 54-511.
- Mummel P and M Puchalski. *Newborn Infant Nurs Rev*. 2001; 1:114-121.

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Root of the Problem: Anxiety

Anxiety
- The sustained state of apprehension and autonomic arousal in response to real or perceived threats

Causes of anxiety
- Inability to communicate, intubation, separation from parents, fear

Physiologic effects of anxiety
- Increased sympathetic tone, HR and BP
- Increased plasma prostaglandin → increased pain
- Protein catabolism →increase caloric requirements

- Osterweis M, Kleinman A, Mechanic D. The Anatomy and Physiology of Pain. National Academies Press (US); 1987.
- Anand KJS. *J Perinatol*. 2007; 54-511.
- Mummel P and M Puchalski. *Newborn Infant Nurs Rev*. 2001; 1:114-121.

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Analgesia and sedation are necessary parts of care for critically ill children

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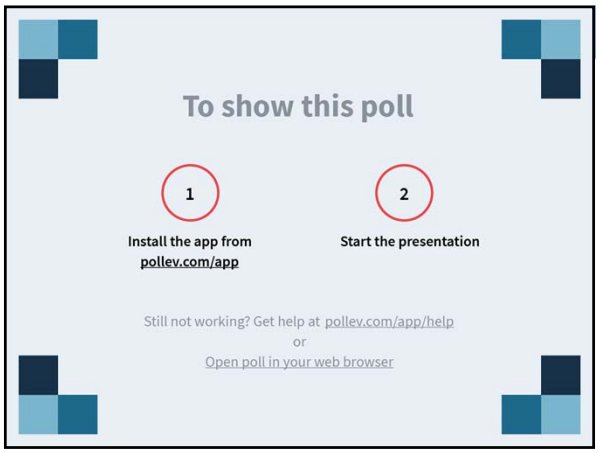
Polling Question 1

- You are asked to provide an analgesia and sedation regimen for an intubated patient in your ICU. What do you recommend?
  - Opioid infusion
  - Opioid and benzodiazepine infusion
  - Opioid and dexmedetomidine infusion
  - Opioid, benzodiazepine and dexmedetomidine infusion



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Analgesia Practices

Opioids

- Mainstay of analgesia in mechanically ventilated patients
- Short acting agents are ideal for continuous infusions
- Drug selection based on PK and adverse effects of each drug

- Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Accessed 2/25/19.
- Harthan, et al. *J Pediatr Pharmacol Ther.* 2014; 19(4): 288-295.

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Fentanyl	• Tachyphylaxis develops quickly • Little effect on hemodynamics • High binding to ECMO circuit
Morphine	• Histamine release leading to hemodynamic changes and itching
Hydromorphone	• Often used 2nd or 3rd line after other opioids

- Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Accessed 2/25/19.
- Harthan, et al. *J Pediatr Pharmacol Ther.* 2014; 19(4): 288-295.

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Sedation Practices

Benzodiazepines

- Historically most common sedative to facilitate mechanical ventilation and prevent anxiety
- Data in preterm neonates shows correlation with abnormal hippocampal growth
- Contributes to the development of delirium

- Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Accessed 2/25/19
- Duerden EG, et al. *Ann Neurol.* 2016; 79: 548-559
- Smith HAB, et al. *Crit Care Med.* 2017; 45:1427–35

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Midazolam	• Most commonly used continuous infusion due to short half-life
Lorazepam	• Limited use as a continuous infusion • Longer half-life • Potential for propylene glycol toxicity

- Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Accessed 2/25/19
- Duerden EG, et al. *Ann Neurol.* 2016; 79: 548-559
- Smith HAB, et al. *Crit Care Med.* 2017; 45:1427–35

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Sedation Practices

Alpha-2 Agonist

- Inhibit presynaptic release of NE resulting in termination of pain signals
- Physiologic response is dependent on location of receptor
- Sedation and analgesia with no respiratory depression

- Gertler R, et al. *Proc (Bayl Univ Med Cent).* 2001;14(1):13-21.
- Alpinar H, et al. *Scientific Reports.* Sci. Rep. 6, 37196; doi: 10.1038/srep37196 (2016).
- Wang Y, et al. *Br J of Anaesthesia.* 2016; 116 (3): 384–92.

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Dexmedetomidine

- Only approved for 24 hours in pediatric patients
- Large body of data supporting longer use
- More expensive than midazolam
- Animal data shows a neuroprotective effect following subarachnoid hemorrhage and cerebral ischemia

- Gertler R, et al. *Proc (Bayl Univ Med Cent).* 2001;14(1):13-21.
- Akpinar H, et al. *Scientific Reports. Sci. Rep.* 6, 37196; doi: 10.1038/srep37196 (2016).
- Wang Y, et al. *Br J of Anaesthesia.* 2016; 116 (3): 384–92.

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Clinical Practice Guidelines

Pediatric

- 2012: AAP Clinical report on neonatal withdrawal included section on the management of acquired opioid and benzodiazepine dependency
- 2014: AAP report on opioid iatrogenic dependence and withdrawal for children
- Coming soon: Pediatric clinical practice guidelines

Adult

- 2013: Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients
- 2018: Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients

- Hudak ML, Tan RC. *Pediatrics.* 2012; 129(2):e540-60
- Barr J, et al. *Crit Care Med.* 2013; Jan;41(1):263-306
- Galinkin J, Koh J. *Pediatrics.* 2014; 133 (1):152-155.
- Devlin JW, et al. *Crit Care Med.* 2018; 46:1532–1548

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Adult Guideline Recommendations

Analgesia

- Routine monitoring of pain with a validated tool
- Vital signs should only be used as cues to investigate further
- Pain should be treated before sedative agents are considered
- Opioids at the lowest effective dose should be used first line for non-neuropathic pain
- Non-opioid analgesics (acetaminophen, ketamine and non-COX-1 NSAIDs) should be used to reduce the amount of opioid analgesic needed
- Addition of neuropathic pain meds (gabapentin, carbamazepine, pregabalin) for neuropathic pain and post CV surgery

- Devlin JW, et al. *Crit Care Med.* 2018; 46:1532–1548

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Adult Guideline Recommendations

Agitation/Sedation

- Maintaining a light level of sedation rather than deep sedation
- Promoting daily spontaneous awakening defined by specific actions such as eye opening in response to voice
- Utilization of BIS monitoring for sedative titration when deep sedation is used
- Non-benzodiazepines (propofol and dexmedetomidine) rather than benzodiazepines

- Devlin JW, et al. *Crit Care Med.* 2018; 46:1532–1548

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Adult Guideline Recommendations

Delirium

- Should be assessed routinely in all ICU patients using a validated tool
- Reduction of modifiable risk factors for delirium (blood transfusions and use of benzodiazepines)
- Reorientation of the patient, use of clocks, increase of wakefulness (reduce sedation), improve sleep (minimize light and noise), early rehabilitation and mobilization
- Do not use pharmacologic therapy to 'prevent'
- Avoid routine use of haloperidol and atypical antipsychotics to prevent or treat delirium
- If needed, use dexmedetomidine to facilitate ventilator weaning

- Devlin JW, et al. *Crit Care Med.* 2018; 46:1532–1548

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Adult Guideline Recommendations

Sleep

- Sleep-promoting, multicomponent protocol is suggested
- Reduce noise and light
- Do not suggest aromatherapy, acupuncture or music to improve sleep
- Do not recommend melatonin, dexmedetomidine or propofol to improve sleep

- Devlin JW, et al. *Crit Care Med.* 2018; 46:1532–1548

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Case

- Patient:
  - 3.5 kg, HLHS post op day 3 from Norwood with an open chest on mechanical ventilation
  - RASS goal of -3 but currently at RASS of 0
- Current analgesia and sedation regimen:
  - Fentanyl at 5 mcg/kg/hr
  - Midazolam at 0.1 mg/kg/hr

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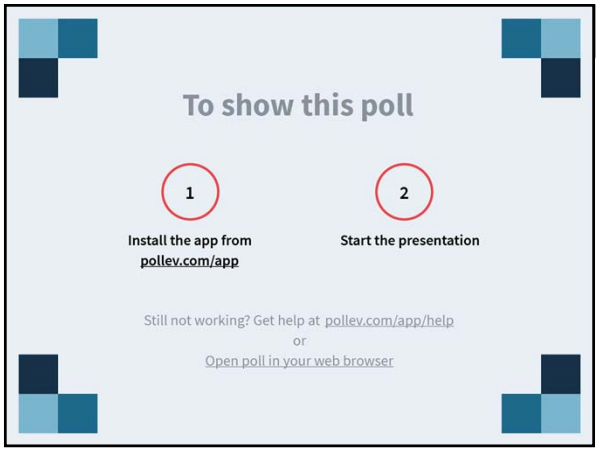
Polling Question 2

- What changes would you make to the patient's regimen?
  - Reassess RASS goal
  - Increase the fentanyl and/or midazolam dose
  - Add dexmedetomidine
  - Switch fentanyl to hydromorphone
  - Switch opioids and add dexmedetomidine
  - Switch opioids and increase the benzo dose



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Assessment of Withdrawal

WAT-1: Withdrawal Assessment Tool, Version 1

- First validated scale to assess for opioid and benzodiazepine withdrawal
- Score of ≥ 3 correlates with withdrawal
- Not validated for dexmedetomidine withdrawal but has been used

SOS: Sophia Observational Withdrawal Symptoms Scale

- Validated scale to assess for opioid and benzodiazepine withdrawal
- Score of ≥ 4 correlates with withdrawal
- Differs from WAT-1 in that Tachycardia and Tachypnea are assessed

Finnegan scale

- Intended for neonates with Neonatal Abstinence Syndrome (NAS)
- May have utility in preterm neonates with iatrogenic dependence

- Franck, et al. *Pediatr Crit Care Med*. November 2008; 9(6): 573–58.
- Franck, et al. *Pain*. 2012 January; 153 (1): 142-148.
- Iqta, et al. *Pediatr Crit Care Med*; October 2013; 14(8): 761-769.
- Maguire, et al. *Advances in Neonatal Care*. December 2013; 13(6):430-437.

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Risk Factors for Withdrawal: Opioids and Benzodiazepines

Fernandez-Carrion, et al.

- Retrospective, single cohort study
- 48 intubated PICU patients, aged 15 days-13 years, who received sedation and analgesia with midazolam and fentanyl for at least 48 hours
- Withdrawal was measured on Finnegan scale
  - ≥8-12: Mild withdrawal
  - 12-16: Moderate withdrawal
  - > 16: Severe withdrawal

- Fernandez-Carrion F, et al. *Med intensive*. 2013; 37(2):67-74.

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Risk Factors for Withdrawal: Opioids and Benzodiazepines

Fernandez-Carrion, et al.

- 50% developed withdrawal symptoms
- 80% of patients on therapy > 5 days developed withdrawal symptoms
- Risk factors for opioid withdrawal
  - Cumulative fentanyl dose >0.48 mg/kg
  - Duration >5.75 days
- Risk factors for benzodiazepine withdrawal
  - Cumulative midazolam dose of > 40 mg/kg
  - Duration > 5.75 days

- Fernandez-Carrion F, et al. *Med intensive*. 2013; 37(2):67-74.

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Risk Factors for Withdrawal: Opioids and Benzodiazepines

Franck, et al.

- Multicenter, prospective, repeated measures study to test the validity of the WAT-1
- Conducted during baseline, pre-randomization phase of the RESTORE study
- 126 patients from 21 centers exposed to ≥ 5 days of continuous, intermittent and PRN opioids were assessed for withdrawal symptoms twice a day
- Withdrawal defined as WAT-1 score of ≥ 3

• Franck L, et al. *Pain*. 2012 January; 153 (1): 142-148.

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Risk Factors for Withdrawal: Opioids and Benzodiazepines

Franck, et al.

- Opioid withdrawal
  - Cumulative opioid exposure was higher in patients who experienced withdrawal: 40.2 mg/kg vs 17.6 mg/kg (morphine equivalents)
  - Length of opioid treatment prior to weaning was associated with withdrawal: 7 days vs 5 days
  - Length of time to wean from opioids was longer in patients who experienced withdrawal: 10 vs 6 days
- Benzodiazepine withdrawal
  - Cumulative benzodiazepine exposure was higher in patients who experienced withdrawal: 24.7 mg/kg vs 10.8 mg/kg (midazolam equivalents)
  - Total cumulative dose: 32.2 mg/kg vs 18 mg/kg
  - Length of benzo treatment prior to weaning: 7 vs 5 days
  - Length of time to wean from benzos: 10 vs 6 days

• Franck L, et al. *Pain*. 2012 January; 153 (1): 142-148.

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Risk Factors for Withdrawal: Opioids and Benzodiazepines

Amigoni, et al.

- Prospective observational study
- PICU patients birth to 18 years who received opioids and/or benzodiazepine continuous infusions for ≥ 3 days
- Withdrawal defined as WAT-1 ≥3 and a SOS of ≥4
- 60 patients with 89 periods of weaning
- Highest doses and cumulative doses of opioids and benzodiazepines were collected
- Incidence of withdrawal was 37%
  - Only highest benzodiazepine dose was associated with withdrawal
  - 0.2 mg/kg/hr vs 0.1 mg/kg/hr

• Amigoni, et al. *Acta Paediatrica*. 2014; 103:e538–e543.

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Risk Factors for Withdrawal: Dexmedetomidine

Haenecour, et al.

- Retrospective study
- PICU patients < 18 years who received dexmedetomidine infusions for > 48 hours
- Withdrawal assessment
  - WAT-1
  - All reported withdrawal episodes were reviewed by 2 investigators
  - Withdrawal was categorized as related to dexmedetomidine alone or dexmedetomidine plus additional analgesics or sedatives

• Haenecour, et al. *J Pediatr Pharmacol Ther*. 2017; 22(6): 453-460.

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Risk Factors and Symptoms of Withdrawal: Dexmedetomidine

- Haenecour, et al.
  - 52 patients with 68 courses of dexmedetomidine
  - 24 episodes of withdrawal were observed
  - Dexmedetomidine alone: 38% incidence of withdrawal
  - Cumulative dose of 107 mcg/kg (pre-weaning) was associated with withdrawal
  - Duration of opioids was also a risk factor for withdrawal

Withdrawal symptoms reported in dexmedetomidine alone group	
• Agitation (100%) • Fever (77.8%) • Vomiting/Retching (33.3%) • Decreased sleep (44.4%) • Tremors/jitteriness (22.2%)	• Diaphoresis (33.3%) • Uncoordinated movements (33.3%) • Startle to touch (22.2%) • Increased tone (33.3%)

• Haenecour, et al. *J Pediatr Pharmacol Ther*. 2017; 22(6): 453-460.

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Risk Factors and Symptoms of Withdrawal: Dexmedetomidine

Takahashi, et al.

- Retrospective review
- Infants receiving dexmedetomidine continuous infusions for post-op sedation following cardiovascular surgery
- Evaluated different tapering methods
  - Gradual: Tapering of dose by 0.1 mcg/kg/hr every 12-24 hours
  - Abrupt: Sudden discontinuation of > 0.4 mcg/kg/hr

• Takahashi, et al. *Brain & Development*. 2016; 38: 648–653.

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Risk Factors and Symptoms of Withdrawal: Dexmedetomidine

Takahashi, et al.

- 28 patients in abrupt discontinuation group and 114 patients in gradual discontinuation group
- 9 patients experienced generalized clonic or generalized tonic-clonic seizures
  - 8 in abrupt discontinuation group
  - 1 in gradual discontinuation group
- Seizures were preceded by fever >38°C
- Occurred 4-8 hours after discontinuation
- Associated with higher cumulative dose: 72.2 mcg/kg vs 38 mcg/kg

- Takahashi, et al. *Brain & Development*. 2016; 38: 648–653.

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Risk Factors and Symptoms of Withdrawal: Dexmedetomidine

Burbano, et al.

- Retrospective review
- Patients < 18 years old who received dexmedetomidine continuous infusion for > 3 days at doses > 1.5 mcg/kg/hr
- No standard weaning process in place, but typically weaned at a rate of 0.1-0.4 mcg/kg/hr every 8-24 hours
- Withdrawal symptoms reported were tachycardia (27%), transient hypertension (35%) and agitation (27%)
- More frequent when stopped abruptly (42% vs 14%)

- Burbano , et al. *Intensive Care Med*. 2012; 38(2): 300–307.

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Symptoms of Opioid, Benzodiazepine and Dexmedetomidine Withdrawal

GI	Autonomic	Neurologic
• Feeding intolerance • Vomiting • Retching • Gagging • Diarrhea	• Sweating • Tachycardia • Increased muscle tone • Tremors • Dilated pupils • Yawning • Sneezing	• Agitation • Easily startled • Irritability • Difficult to calm • Insomnia • Seizures

- Galinkin, et al. *Pediatrics*. 2014; 133 (1):152-155.
- Haenecour, et al. *J Pediatr Pharmacol Ther*. 2017; 22(6): 453-460.
- Johnson, et al. *Pharmacotherapy*. 2012; 32(2): 148-57.

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Patient Case continued

- Patient is post-op day 10
  - Chest closed post-op day 5
  - Weaning mechanical ventilation
  - Almost at full NG feeds
- Current sedation and analgesia regimen
  - Hydromorphone 30 mcg/kg/hr
  - Midazolam 0.15 mg/kg/hr
  - Dexmedetomidine 0.7 mcg/kg/hr

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Polling Question 3

- The team would like to start weaning sedation in preparation for extubation. What would you recommend?
  - Wean each drip slowly over the next few days
  - Convert to equivalent doses of methadone, lorazepam and dexmedetomidine and stop drips
  - Add low dose methadone, lorazepam and dexmedetomidine and wean drips over the next few days

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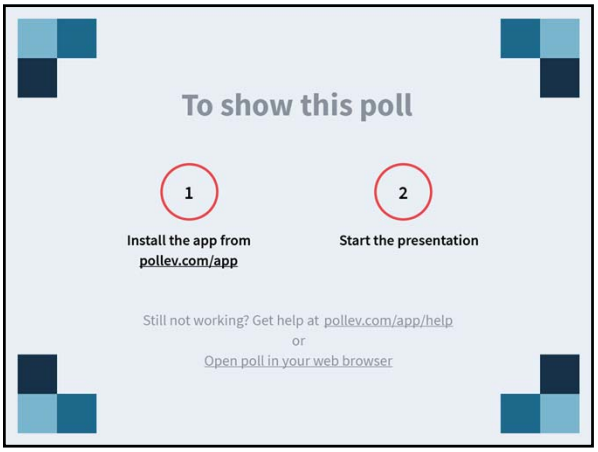

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Clinical Pearls for Reducing Withdrawal Risk

Take steps to decrease the total cumulative dose of sedation and analgesia
- Daily sedation holidays/daily dose reduction
- Sedation goal should be for light sedation when possible

Slow taper of continuous infusions
- May not be feasible if transitioning to lower level of care (floor or home)

Transition to short-acting oral agents
- Limited by frequency of dosing

Transition to long-acting oral agents
- Opioids: methadone
- Benzodiazepines: lorazepam or diazepam
- Dexmedetomidine: clonidine

- Sanchez-Pinto, et al. *J Crit Care*. 2018; 43: 214-9.
- Aminovin, et al. *Pediatr Crit Care Med*. 2018; 19 (11):1024-32.
- Curley, et al. *JAMA*, 2015; 313 (4): 379-89.

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Management of Opioid Withdrawal: Methadone

Mechanism
- L-methadone is responsible for analgesia via opioid receptors and by blocking serotonin and norepinephrine re-uptake
- L- and D-methadone block the NMDA receptors

PK/PD
- Onset 10-20 minutes with peak at 1-2 hours
- Duration 6-8 hours with single doses, 24-48 hours with repeat dosing
- Hepatic metabolism to inactive metabolites
- Half-life: median 15.3 hours (range: 4-62) in children

- Clark, M. Lippincott's Illustrated reviews. Baltimore, MD, 2012.
- Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Accessed 7/5/18
- Johnson, et al. *Pharmacotherapy*. 2012; 32(2): 148-57.

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Management of Opioid Withdrawal: Methadone

Equianalgesic potency:
- ~ 1-2 times as potent as morphine
- May not be necessary to use equianalgesic conversion
- Requires less drug to prevent withdrawal than to treat pain
- IV:PO conversion: Changes from 1:1 to 1:2 with duration of therapy

Considerations:
- Long half-life and relatively long duration of action make it a good option for weaning off other opioids
- Withdrawal symptoms may take a few days to appear due to long half-life
- NMDA antagonism may add benefit

- Lugo, et al. *Pharmacotherapy*. 2001; 21 (12): 1566-73
- Nelson Sanchez-Pinto L et al. *J Crit Care*. 2018; 43: 214-9
- Aminovin R et al. *Pediatr Crit Care Med*. 2018; 19 (11):1024-32

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Polling Question 4

- In our patient case, what would you do to wean off hydromorphone 30 mcg/kg/hr?
  - Start morphine at equianalgesic doses
  - Start methadone 0.1 mg/kg IV Q6h
  - Start methadone 0.1 mg/kg PO Q6h

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Managing Benzo Withdrawal: Lorazepam

PK/PD
- Onset 2-3 minutes (IV)
- Duration of action 6-8 hours (adults)
- Metabolism in liver to inactive metabolites
- No CYP450 drug interactions
- Clearance is prolonged in neonates due to immature enzymes at birth

Considerations
- Long duration of action limits use as a continuous infusion
- Ideal for oral/IV intermittent dosing and tapering (1:1 switch IV to PO)

- Clark, M. Lippincott's Illustrated reviews. Baltimore, MD, 2012.
- Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc; Accessed 7/5/18

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Managing Benzo Withdrawal: Diazepam

PK/PD

- Onset 4-5 minutes for sedation (IV)
- Long T ½ (33-44 hrs) with short duration (1-2 hrs)
- Hepatic metabolism by CPY3A4 and 2C19 to active metabolites, eliminated by glucuronidation
- Decreased glucuronidation in neonates and young infants may lead to accumulation

Considerations

- Long T ½ limits use as a continuous infusion
- Short duration of action can cause challenges with intermittent doses
- Oral product does NOT contain propylene glycol

- Clark, M. Lippincott's illustrated reviews. Baltimore, MD, 2012.
- Lexicomp Online™, Pediatric & Neonatal Lexi-Drugs™, Hudson, Ohio: Lexi-Comp, Inc; Accessed 7/5/18

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Polling Question 5

- For our patient case, what would you suggest for weaning midazolam of 0.15 mg/kg/hr?
  - Convert total daily dose of midazolam to diazepam, decrease by 20% and divide Q6h
  - Convert total daily dose of midazolam to lorazepam, decrease by 20% and divide Q6h
  - Lorazepam 0.1 mg/kg/dose PO Q8h
  - Lorazepam 0.1 mg/kg/dose IV Q6h

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Managing Dexmedetomidine Withdrawal: Clonidine

Mechanism

- Selective α_2 agonist
- α_2:α_1 ratio = 200:1 (Dexmedetomidine = 1600:1)
- Eight times less specific for the α_{2A} than dexmedetomidine

Considerations

- Oral, Transdermal or Epidural; Hypotension if given IV
- Dose unknown for sedation/withdrawal
- Start low and titrate to effect while avoiding hypotension
- Antihypertensive dose (5-10 mcg/kg/day)

- *Anesth Prog.* 2015; 62:31–38
- *RUMC P ROCCEDINGS* 2001;14:13–21

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Polling Question 6

- For our patient, what would you suggest for weaning dexmedetomidine of 0.7 mcg/kg/hr?
  - Nothing; wean the drip off over 24 hours
  - Start a 0.1 mg/24 hr clonidine patch
  - Start clonidine 1 mcg/kg/dose q6h
  - Start clonidine 3 mcg/kg/dose q6h

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Clinical Evidence: Devising a Taper Plan

Lugo, et al.

- Retrospective review of patients on fentanyl infusions ≥ 9 days and concomitant methadone
- Methods:
  - Methadone initiated at 0.1 mg/kg every 6 hours enterally 1-2 days prior to fentanyl discontinuation
  - Fentanyl weaned over 2-3 days by reducing original dose 10-15% every 8 hours
  - Methadone taper started 2 days after fentanyl discontinued
  - Increased interval to q8h and q12h every 2 days then reduced original dose by 25% every 2-3 days until off
- Implemented benzo tapering guidelines at same time that typically lasted ~14 days upon extubation

• Lugo, et al. *Pharmacotherapy*. 2001; 21 (12): 1566-73.

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Clinical Evidence: Devising a Taper Plan

Lugo, et al. Results

- 704 patients on continuous fentanyl infusion; 22 met criteria
- Total fentanyl duration was 17.8 ± 8.4 days
- Peak fentanyl dose: 5.9 ± 3.8 mcg/kg/hr
- Median cumulative dose was 1300 mcg/kg (1.3 mg/kg)
- Fentanyl was able to be discontinued in a median of 2.6 days

• Lugo, et al. *Pharmacotherapy*. 2001; 21 (12): 1566-73.

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Clinical Evidence: Devising a Taper Plan

Lugo, et al.

- 21 out of 22 patients had no withdrawal
  - 15 patients required no methadone dose increase (0.5 ± 0.22 mg/kg/day)
  - 7 patients methadone increased empirically (0.53 ± 0.27 mg/kg/day to max of 0.91 ± 0.37 mg/kg/day)
  - One patient in group 2 required restart of fentanyl and methadone dose escalation to 0.3 mg/kg q6 hrs
- Methadone was weaned off over 18.2 ± 11.9 days
  - 19 patients were off prior to discharge

• Lugo, et al. *Pharmacotherapy*. 2001; 21 (12): 1566-73.

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Clinical Evidence: Devising a Taper Plan

Meyer, et al.

- Evaluated a 10 day enteral methadone taper in patients who received fentanyl infusions
- Prospective, observational study of 29 patients ages 1 day to 19.8 years old
- Protocol
  - Converted fentanyl infusion to morphine q4h
  - Followed NAS scores q2 hrs until NAS score consistently <8
  - Converted morphine to methadone (2 mg po methadone = 1 mg IV morphine)
  - Initial dose every 12 hours x 3 doses
  - Then once daily at bedtime with 10% reduction daily

• Meyer, et al. *Pediatr Crit Care Med*. 2001; 2:329–333

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Clinical Evidence: Devising a Taper Plan

Meyer, et al.

- Results:
  - Fentanyl duration was 14.5 ± 9.2 days
  - Cumulative fentanyl dose was 1.93 ± 1.53 mg/kg
  - 86% (29) of patients successfully completed the 10 day taper without withdrawal symptoms
  - 3 of 4 who did not complete the 10 day taper, completed a 21 day taper

• Meyer, et al. *Pediatr Crit Care Med*. 2001; 2:329–333

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Clinical Evidence: Devising a Taper Plan

- Johnson et al reviewed eight reports and studies
- Compiled formula-based and weight-based strategies

Table 2. Initial Methadone Dosing Regimen for a 5-kg Patient Receiving Continuous-Infusion Fentanyl at a Rate of 5 µg/kg/hour

Initial Dosing Strategy	Example Dosing Calculations	Initial Methadone Dosing Regimen
Weight-based[20]	0.1 mg/kg/dose x 5 kg = 0.5 mg/dose	0.5 mg p.o. q12h
Weight-based[21, 22]	0.05 mg/kg/dose x 5 kg = 0.25 mg/dose	0.25 mg p.o. q12h
Weight-based[23, 27, a]	0.1 mg/kg/dose x 5 kg = 0.5 mg/dose	0.5 mg p.o. q6h
Formula-based[24]	5 µg/kg/hr x 5 kg = 25 µg/hr; 0.001 mg/kg x (x)/0.1 mg/kg x 0.025 mg; solve for "x" = 2.5 mg	2.5 mg i.v. q6h
Formula-based[25]	5 µg/kg/hr x 5 kg x 24 hrs x 3 = 1800 µg/day; (1800 µg/day)/(3 doses/day) = 600 µg/dose	0.6 mg i.v. t.i.d.
Formula-based[26]	5 µg/kg/hr x 5 kg = 25 µg/hr; 25 µg/hr x 60 = 1.5 mg i.v. morphine; methadone = 1.5 mg i.v. morphine x 2 = 3 mg	3 mg p.o. q12h
Formula-based[27, b]	0.1 mg/kg x 5 kg x 5 µg/kg/hr = 2.5 mg	2.5 mg p.o. q6h

[a]Studies included a comparison of weight-based and formula-based approaches. This reflects the method of calculation for the weight-based group.
[b]This study included a comparison of weight-based and formula-based approaches. This reflects the method of calculation for the formula-based group.

• Johnson, et al. *Pharmacotherapy*. 2012; 32(2): 148-57

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Clinical Evidence: Devising a Taper Plan

- Vipond, et al
  - Implemented a standardized, pharmacist-managed methadone and lorazepam taper protocol
  - Protocol separated patients into 4 risk categories depending on duration of opioid and benzodiazepine infusions and cumulative morphine dose
  - Sedation practices were already standardized

Vipond JM et al. *Pediatr Qual Saf*. 2018 May-Jun; 3(3): e079

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Clinical Evidence: Devising a Taper Plan

Risk Category	Length of opioid and benzodiazepine infusion	Cumulative morphine (or equivalent) dose	Duration of taper	Starting doses of methadone and lorazepam *all doses PO
Low Risk	< 5 days	N/A	3 days	M = 0.05 mg/kg q8h L = 0.05 mg/kg q6h
Moderate Risk	5-9 days	N/A	6 days	M = 0.1 mg/kg q8h L = 0.1 mg/kg q6h
High Risk	≥ 10 days	60-100 mg/kg	13 days	0.1 mg/kg q6h for both
Very High Risk	≥ 28 days	> 100 mg/kg	17 days	M = 0.2 mg/kg q6h L = 0.1 mg/kg 4h

- Vipond, et al. *Pediatr Qual Saf*. 2018 May-Jun; 3(3): e079

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Vipond et al Results

	Methadone Pre-protocol	Methadone Post protocol	p value	Lorazepam Pre-protocol	Lorazepam Post protocol	p value
Age of patient (median months)	7 ± 10.5	26.6 ± 42.2	0.0326	8.7 ± 12.1	28.5 ± 41.1	0.0641
Taper length, median days (IQR)	9.5 (5.5 - 14.5)	6 (3 - 9)	0.0145	13 (8 - 18)	6 (4 - 7)	0.0006
Low risk*	6.5	3	0.0047	7	3	0.0016
Mod risk*	13	6	0.0104	16	6	0.0013
High risk*	11	14	0.4945	11	15	0.1573

*median days for taper length; Note: No patients fell into the very high risk group based on results reported

- Vipond, et et al. *Pediatr Qual Saf*. 2018 May-Jun; 3(3): e079

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Clinical Evidence: Devising a Taper Plan

- Children's Hospital Los Angeles
  - Studied a weaning protocol pre- and post-implementation
    - PICU study: opioid taper protocol
    - PCICU study: opioid and benzo taper protocol
    - Same dosing recommendations for opioids in both
    - Sedation at discretion of provider (no standard protocol)
  - Baseline WAT-1 score determined
  - Significant withdrawal defined as:
    - WAT-1 score ≥ 4 AND >2 above baseline
    - 3 or more PRNs (doses as defined in protocol)
    - Held wean for that day; evaluate for other causes (i.e. delirium)

- Sanchez-Pinto, et al. *J Crit Care*. 2018; 43: 214-9 (PICU study)
- Aminovin, et al. *Pediatr Crit Care Med*. 2018; 19 (11):1024-32 (PCICU study)

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CHLA Weaning Protocol

Risk Category	Length of opioid and benzodiazepine infusion	Duration of taper	Taper recommendations
Low Risk	< 5 days	No taper necessary	No scheduled opioids prescribed
Moderate Risk	5-7 days	5 days	Dose decreased each day by 20% of original dose
High Risk	8-30 days	13 days	Dose decreased every other day by 20% of original dose
Very High Risk	> 30 days	17 days	Dose decreased every other day by 10% of original dose

- Sanchez-Pinto, et al. *J Crit Care*. 2018; 43: 214-9 (PICU study)
- Aminovin, et al. *Pediatr Crit Care Med*. 2018; 19 (11):1024-32 (PCICU study)

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CHLA Results---Opioid Study

	Pre-implementation	Post-implementation	p value
*Days on opioid	22.5	17.5	0.01
*Days on taper	18	12	0.01
*Total opioid dose per patient	48.8 mg/kg	33.2 mg/kg	0.02
Hospital LOS	33	29	0.06

*primary outcome

- No difference in discharges w/methadone taper
- No difference in withdrawal symptoms

- Sanchez-Pinto, et al. *J Crit Care*. 2018; 43: 214-9 (PICU study)

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CHLA Results---Opioid and Benzo Study

CHLA Study---Opioid & Benzo	Opioid Pre-protocol	Opioid Post protocol	Benzo Pre-protocol	Benzo Post protocol	p value
Days on medication median (IQR)	30 (19-51)	19 (13-28)	24 (8.7-60.6)	5 (1.8-17)	<0.001
Days on taper median (IQR)	23 (15-35)	12 (7-16.5)	15 (7.2-28.2)	2 (2.1-10.4)	<0.001
Total med exposure (mg/kg/pt)	48.4 (31.2-91.6)	31.2 (21.4-44.2)	3.9 (1.7-10.3)	1.3 (0.4-3)	<0.001 opioids <0.01 benzos

- Amirnovin,et al. *Pediatr Crit Care Med.* 2018; 19 (11):1024-32 (PCICU study)

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Clinical Evidence: Devising a Taper Plan

- CHLA Results---Opioid and Benzos
  - Secondary Outcomes
    - Decreased hospital length of stay as median days (IQR) 42 (35-75) vs 34 (25-50), p < 0.01
    - Discharged on wean: 16.4% vs 6.3 %, p = 0.14
    - Time to discharge post wean as median days (IQR) 8 (3-21) vs 13 (5-22) days, p = 0.25
    - Total hospitalization costs per patient as median (IQR) $207k ($62-313k) vs $190k ($133-258k), p < 0.04

- Amirnovin, et al. *Pediatr Crit Care Med.* 2018; 19 (11):1024-32 (PCICU study)

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Putting It All Together: Devising a Taper Plan

Identify patients at risk for withdrawal

- Opioids, benzos, dexmedetomidine > 5-7 days
- Shorter duration with high total cumulative dose

Determine method of taper

- Slow wean of continuous infusions when possible
- Convert to long acting agents

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Putting It All Together: Devising a Taper Plan

Determine starting dose of long acting agents

- Convert to equivalent doses of long acting agents
- Start at a lower dose of a long acting agent
  - Less drug may be needed to prevent withdrawal than to treat pain and agitation

Estimate the length of a taper

- In general, a taper with long acting agents should not be longer than the duration of continuous infusions

Devise a plan for weaning multiple drugs

- Consider the half-life of each drug

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Putting It All Together: Devising a Taper Plan

Identify other factors that may interfere with taper

- Vapotherm weaning, advancing feeds, painful procedures
- Patient should no longer require continuous analgesia or sedation
  - Treat acute pain or anxiety when needed

Implement the use of a withdrawal assessment score

- All staff should be trained on how to use the tool and aware of its limitations

Provide guidance for treatment of withdrawal

- Determine if any degree of withdrawal is acceptable
- Rescue PRN therapy verses reverting to previous taper step

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Putting It All Together: Devising a Taper Plan

Avoiding taper deviation

- Ensure understanding of taper process and goals by other members of the medical team
- Understand risk involved with methadone and lorazepam in the developing brain
- Still discovering long-term effects
- Benzodiazepines: contribute to delirium

Fussy baby versus true withdrawal

- Non-pharmacologic measures
- Parent/caregiver involvement

- Vestal-Laborde, et al.*Dev Neurosci.* 2014; 36(5): 409–421.
- Smith, et al.*Pediatr Clin N Am.* 2013; 60: 741–760.
- Smith, et al. *Crit Care Med.* 2017; 45:1427–1435.

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Pharmacist Role

- Guideline development in conjunction with other members of the medical team
- Writing taper recommendations using an evidence based approach
- Adjusting taper recommendations based on patient specific responses
- Transitions of Care: Insuring all areas utilize the same withdrawal assessment tool
- Educating parents/patients prior to discharge

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QUESTIONS?

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Taper Tantrums:
Diffusing Pediatric Sedation Tapers

PPAG Annual Meeting April 2019
Alison G. Grisso, PharmD, BCPPS
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References

- Osterweis M, Kleinman A, Mechanic D. The Anatomy and Physiology of Pain. National Academies Press (US); 1987.
- Anand KJS. Pharmacological approaches to the management of pain in the neonatal intensive care unit. *J Perinatol.* 2007; S4-S11.
- Mummel P and M Puchalski. Assessment and Management of Pain in Infancy. *Newborn Infant Nurs Rev.* 2001; 1:114-121.
- Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Accessed 2/25/19.
- Harthan AA, Buckey KW, Heger ML, Fortuna RS, Mays K. Medication Adsorption into Contemporary Extracorporeal Membrane Oxygenator Circuits. *J Pediatr Pharmacol Ther.* 2014; 19(4): 288-295.
- Duerden EG, Guo T, Dodbiba L, Chakravarty MM, Chau V, Poskitt KJ, Synnes A, Grunau RE, Miller SP. Midazolam dose correlates with abnormal hippocampal growth and neurodevelopmental outcomes in preterm infants. *Ann Neurol.* 2016; 79: 548-559.
- Smith HAB, Gangopadhyay M, Goben CM, et al: Delirium and benzodiazepines associated with prolonged ICU stay in critically ill infants and young children. *Crit Care Med.* 2017; 45:1427–1435
- Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. *Proc (Bayl Univ Med Cent).* 2001;14(1):13-21.
- Akpinar H, Nazıroglu M, Ovey IS, Cig B, Akpinar O. The neuroprotective action of dexmedetomidine on apoptosis, calcium entry and oxidative stress in cerebral ischemia-induced rats: Contribution of TRPM2 and TRPV1 channels. *Sci. Rep.* 6, 37196; doi: 10.1038/srep37196 (2016).
- Wang Y, Han R, Zuo Z. Dexmedetomidine post-treatment induces neuroprotection via activation of extracellular signal-regulated kinase in rats with subarachnoid haemorrhage. *British Journal of Anaesthesia.* 2016; 116 (3): 384–92.
- Hudak ML, Tan RC; American Academy of Pediatrics Committee on Drugs; Committee on Fetus and Newborn. Neonatal drug withdrawal. Pediatrics. 2012; 129(2):e540-60.
- Barr J, et al. Clinical practice guidelines for the management of pain, agitation and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013; Jan;41(1):263-306.
- Galinkin J and Koh J. Recognition and management of iatrogenically induced opioid dependence and withdrawal in children. *Pediatrics.* 2014; 133 (1):152-155.
- Devlin JW, et al. Executive Summary: Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med.* 2018; 46:1532–1548
- Fernandez-Carrion F, et al. Withdrawal syndrome in the pediatric intensive care unit. Incidence and risk factors. *Med intensive.* 2013; 37(2):67-74.
- Amigoni A, Vettore E, Brugnolaro V, Brugnaro L, Masola M, Marzollo A, Pettenazzo A. Hight doses of benzodiazepine predict analgesic and sedative drug withdrawal syndrome in paediatric intensive care patients. *Acta Paediatrica.* 2014; 103:e538–e543.
- Franck LA, Scoppettuolo LA, Wypij D, Curley MAQ. Validity and generalizability of the withdrawal assessment tool-1 (WAT-1) for monitoring iatrogenic withdrawal syndrome in pediatric patients. *Pain.* 2012 January; 153 (1): 142-148.
- Franch LS, Harris SK, Soetenga DJ, Amline JK, Curley MAQ. The withdrawal assessment tool –version 1 (WAT-1). *Pediatr Crit Care Med.* November 2008; 9(6): 573–58.
- Ista E, Hoog M, Tibboel D, Duivenvoorden HJ, van Dijk M. Phychometric evaluation of the Sophia observation withdrawal symptoms scale in critically ill children. *Pediatr Crit Care Med.* October 2013; 14(8): 761-769

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References

- Maguire D, Cline GJ, Parnell L, Tai C. Validation of the Finnegan neonatal abstinence syndrome tool-short form. *Advances in Neonatal Care.* December 2013; 13(6):430-437.
- Fernandez-Carrion F, et al. Withdrawal syndrome in the pediatric intensive care unit. Incidence and risk factors. *Med intensive.* 2013; 37(2):67-74.
- Amigoni A, Vettore E, Brugnolaro V, Brugnaro L, Masola M, Marzollo A, Pettenazzo A. Hight doses of benzodiazepine predict analgesic and sedative drug withdrawal syndrome in paediatric intensive care patients. *Acta Paediatrica.* 2014; 103:e538–e543.
- Haenecour AS, Seto W, Urbain CM, Stephens D, Laussen PC, Balt CR. Prolonged Dexmedetomidine Infusion and Dug Withdrawal in Critically Ill Children. *J Pediatr Pharmacol Ther.* 2017; 22(6): 453-460.
- Takahashi Y, Ueno K, Ninomiya Y, Eguchi T, Nomura Y, Kawano Y. Potential risk factors for dexmedetomidine withdrawal seizures in infants after surgery for congenital heart disease. *Brain & Development.* 2016; 38: 648–653.
- Burbano, NH, Otero AV, Berry DE, Orr RA, Munoz RA. Discontinuation of prolonged infusions of dexmedetomidine in critically ill children with heart disease. *Intensive Care Med.* 2012; 38(2): 300–307.
- Curley MA, Wypij D, Watson Rs, Grant MJ, Asaro LA, Cheifetz IM, Dobson BL, Franck LS, Gedeit RG, Angus DC, Matthay MA. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. *JAMA,* 2015; 313 (4); 379-89.
- Lugo RA, MacLaren R, Cash J, Pribble C and DD Vernon. Enteral methadone to expedite fentanyl discontinuation and prevent opioid abstinence syndrome in the PICU. *Pharmacotherapy.* 2001; 21 (12): 1566-73.
- MT Meyer and RJ Berens. Efficacy of an enteral 10-day methadone wean to prevent opioid withdrawal in fentanyl-tolerant pediatric intensive care unit patients. *Pediatr Crit Care Med.* 2001; 2:329–333
- Johnson PN, Boyles KA and JL Miller. Selection of the initial methadone regimen for the management of iatrogenic opioid abstinence syndrome in critically ill children. *Pharmacotherapy.* 2012; 32(2): 148-57.
- Vipond JM, Heibeiger AL, Thompson PA, and JN Huber. Shortened taper duration after implementation of a standardized protocol for iatrogenic benzodiazepine and opioid withdrawal in pediatric patients: results of a cohort study. *Pediatr Qual Saf.* 2018 May-Jun; 3(3): e079.
- Sanchez-Pinto LN, Nelson LP, Lieu P, Koh JY, Rodgers JW, Larson KA, Huson JM and R Amirnovin. Implementation of a risk-stratified opioid weaning protocol in a pediatric intensive care unit. *J Crit Care.* 2018; 43: 214-9.
- Amirnovin R, Nelson Sanchez-Pinto L, Okuhara C, Lieu P, Koh JY, Rodgers JW and L Nelson. Implementation of a risk-stratified opioid and benzodiazepine weaning protocol in a pediatric cardiac ICU. *Pediatr Crit Care Med.* 2018; 19 (11):1024-32.
- Vestal-Laborde AA, Eschenroeder AC, Bigbee JW, Sobinson SE, Sato-Bigbee C. The opioid system and brain development: methadone effects on the oligodendrocyte lineage and the early stages of myelination. *Dev Neurosci.* 2014; 36(5): 409–421.
- Smith HA, Brink E, Fuchs DE, Ely EW, Pandharipande PP. Pediatric delirium: monitoring and management in the pediatric intensive care unit. *Pediatric Clin N Am.* 2013; 60: 741–760.