


**Pediatric Pharmacy Advocacy Group**

## Hush Little Baby

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**Pediatric Pharmacy Advocacy Group**

## Objectives

- Summarize the historical perspective of midazolam use for analgo-sedation in the PICU
- Discuss the advantages of midazolam for analgo-sedation in the PICU
- Determine the disadvantages of midazolam for sedation in the PICU
- Compare and contrast the risks and benefits of midazolam for sedation
- Discuss midazolam-sparing strategies



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## A long long time ago....in a PICU far far away...or maybe really close

- Benzodiazepines, specifically midazolam, has been the workhorse of the PICU for many years
- Patented 1976, medical use 1982
- 1986, efficacy study in Peds
- Publication in critically ill peds, 1991
- 2006 Guidelines recommend midazolam or clonidine
- Midazolam and fentanyl most common sedative agents in PICU
- Last year approval as IM agent for seizures (Seizalam)



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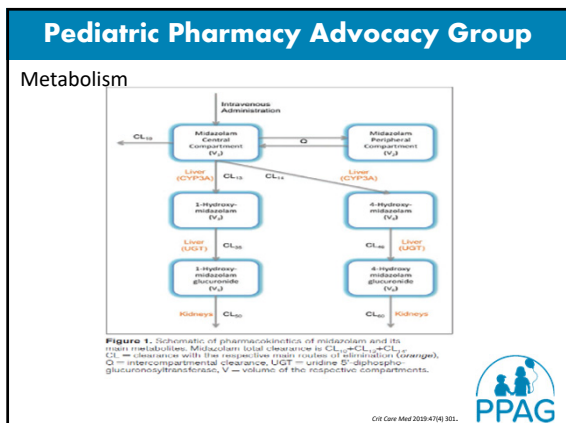
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- ### Metabolism
- 152 subjects rs62298861 (UGT2B7)
    - 96 patients (63%) homozygous wild type
    - 48 (32%) heterozygous
    - 7 (5%) homozygous for minor allele
  - Heterozygous had increased clearance by 10%
  - Homozygous for minor allele had 20% increase in clearance
  - Genetics likely play a role
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- ### Where did the hoopla come from?
- FDA Safety Communication, Dec 2016
    - Resulted in labeling changes
  - Cochrane review in neonates, 2017
    - No efficacy of midazolam, concern for safety
  - Adult data about increased morbidity
    - Increased wakefulness and cooperative sedation
- [FDA: https://www.fda.gov/oc/2016/12/safety-communication-midazolam-056644](https://www.fda.gov/oc/2016/12/safety-communication-midazolam-056644)  
 Cochrane Database Syst Rev 2017;1:CD002032  
 Crit Care Med 2018;46:e25  
<https://doi.org/10.1093/crm/ckz014>

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### Risk vs Reward

Risk	Benefit
Delirium	Sedation
Neuroapoptosis	Anxiolysis
Excitatory effects	Antegrade amnesia
Reduced sedation efficacy (tachyphylaxis)	Easily titratable (rapid onset)
Withdrawal	Compatibility
Hypotension	High lipophilicity
Paradoxical Reactions	High therapeutic index
Withdrawal	Decreased pain at injection site
Active metabolites	Reversible
	Less cardiovascular effects



Crit Care Med. 1998;26(5): 941  
Crit Care Med. 2007;22(5):173

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### Midazolam Sedation Efficacy

- Historical benefit; Over 20 years of use
- 1986, 50 children (6mo-9yrs) after cardiac surgery
  - Morphine + midazolam (0.1-0.5 mg/kg/h)
  - Efficacy determined by response, alertness
  - 48hrs after ICU d/c, >6 yrs no recollection of ICU stay
- 2002 (1997 respondents) survey
  - 145 hospitals 90% routinely or frequently use midazolam
- 2014 survey of 341 intensivists all over the world
  - 72% used opioid and benzo, 12% opioid alone and 8 % opioid and dex.
  - For those using benzo midazolam 86% and 12% for lorazepam.



Br J Anaesth. 1986;58:1104  
Crit Care Med 2014; 42:1002  
Pediatr Crit Care Med. 2002; 3(2): 183

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### Midazolam Efficacy

- 2017 Cochrane Review in neonates
  - No differences in mortality
  - No differences in days on ventilator or pneumothorax
  - Longer length of stay (5 days)
  - Increased risk of poor neurological outcomes (NNH 4)
- 2004 RCT of midazolam and dexmedetomidine cont infusions
  - Dex reached better sedation efficacy based on COMFORT, Ramsey scores
  - Dex less supplemental morphine use
  - Dex less titrations vs midaz



Cochrane Database Syst Rev. 2017;1:CD002092  
South Med J 97:453

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### Midazolam Efficacy

- 2017 Cochrane review
  - 3 studies
- Tobias 2004 - 24 hours at most
  - Small number of patients
  - One patient discontinued due to bradycardia (and dex group had lower HR overall)
  - Two doses of DEX compared, higher dose (0.5 mg/kg/h) more efficacious but midazolam dose stayed at 0.1mg/kg/hr
  - DEX less effective at < 12months

Cochrane Database Syst Rev 2017;1:CD002052  
Search Med 1/17/15



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### Midazolam and Delirium

- Established in adult trials
- Pediatrics? maybe 12-30%
- Is it really delirium? How do you know?
- No consensus regarding assessing/diagnosing delirium in pediatrics
- Is it only midazolam causing the delirium?

Crit Care Med 2018;46:125  
Semin Respir Crit Care Med. 2013;34:244



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### Midazolam and Delirium

- 2015 study of 187 post op cardiac patients
  - Everyone received fentanyl; 77 received dex; 97 received midazolam
  - Dex spent less time on mechanical ventilator, lower doses of adjunct drugs, and had lower delirium scales.
- 2017 study of 300 PICU patients
  - Benzo exposure significantly associated with lower likelihood of ICU discharge (dex had increased likelihood)
  - 2.5 incidence rate of delirium (even with only 0.7 mg/kg/day)
  - Higher benzo exposure increased delirium duration

Crit Care Med 2017;45:1427  
JAMA Netw Open. 2018;1(6):e180189



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### Midazolam and Delirium

- 2013 RCT adolescents post-op scoliosis surgery
  - Pain scores, fentanyl consumption, and vent days higher in the midaz group
  - Level of sedation higher in midaz group (only 0.4 mcg/kg/hr of dex)
  - Delirium 31.3% midaz group vs 12.5% in dex group
  - 25% of patients in the midaz group received haloperidol vs 4% dex
- 2018 retrospective study of 310 PICU patients
  - Receiving BZD prior risk factor for delirium (38% vs 14%) and OR 2
  - Opioid use was not independently associated with delirium
  - BZD use increased future delirium rates 4 times compared to normal cognition in patients who did not receive BZD

Pediatric Anesth 2013; 23:446  
Crit Care Med 2018; 46:1488



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### Midazolam and Neuroapoptosis

- FDA Safety communication
  - Exposure for >3 hours associated with decreased brain development
  - No specific sedation agent isolated, all anesthetics and sedatives
- In vitro and animal data, since 1999
- Affects brain development
- Localized and epidural administration
- Clinical evidence?

FDA: <https://www.fda.gov/oc/oa/CDUgSafety/comm54624.htm>  
Pediatr Crit Care Med 2010;11:217  
Pediatr Drugs 2012;14:53



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### Midazolam and Neurological Morbidity

- Guerra 2014, Infants w/ congenital heart disease
  - 91 infants, 54 month follow up
  - Negative association w/ cumulative benzos and Visual Motor Integration score (small effect size and may not be clinically significant)
- Shein 2017, Database study -PICU bronchiolitis (n=3751, 9516)
  - 1.3-8.7 months of age
  - All meds (morphine, fentanyl, midazolam, NMBs, and diuretics) assoc w/ increased neurofunctional morbidity.
  - DEX associated w/ decreased neurofunctional morbidity

Pediatric Anesthesia 2014;24:257  
Pediatr Crit Care Med 2017;18:1106



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### Long-term outcomes?

- Most PICU patients have good Quality of Life after discharge
- Meyberg 2018, found no association between PICU delirium and long-term cognition or behavior
- In UK, study found children 5x more likely to have long-term (Post ICU) delusional memories when benzos/opiates > 2 days

J Pediatr Child Health 2007;43:673  
Intensive Care Med 2015;41:1235  
Ann N Y Acad Sci 2016;1375:1916  
Pediatr Crit Care Med 2018;10:e511



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### Midazolam Withdrawal

- Duration (>5-7 days)
- Dose (60mg/kg)
- Neuromuscular blockade use
- Patients intermittent weaning vs continuous weaning longer mechanical ventilation and length of stay
- Hard to elucidate due to opioid exposure

Pediatr Crit Care Med. 2016; 17(1): 10  
Med Intensiva. 2013; 37(2): 67



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### Midazolam Sparing Approaches

- When used in combination with opioids can use less. (0.1 vs 0.07 mg/kg/hr in one study)
- Windows
- Lighting
- Noise reduction
- Private rooms
- Other medications

J Korean Med Sci. 2019; 24(18): e21  
Pediatr Crit Care Med. 2018; 19: 538



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**What are other options?**

- Opioids
- Propofol
- Ketamine
- Etomidate
- Barbituates
- Clonidine (even IV)
- Dexmedetomidine



Br Med J. 2017; 7:4056031

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**Closing Argument FOR Midazolam**

- Midazolam isn't the bad guy!
- First, Save the patient
  - Keep patient from interfering with care
- Less is always more



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**Closing Argument AGAINST Midazolam**

- It is the bad guy!!
- Could cause delirium
- Neuroapoptosis
- Potential long term neurological deficits
- Withdrawal is a huge issue



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Questions



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