Medication-based Treatment: A Guide to Managing Opioid Use Disorder for the Pediatric-Focused APRN

Kristin Hittle Gigli, PhD, RN, CPNP-AC, CCRN
Post-doctoral Scholar
Department of Critical Care Medicine
University of Pittsburgh

Speaker Introduction
• Dr. Kristin Hittle Gigli has worked in pediatric critical care for 15 years. After earning her PhD in nursing at Vanderbilt University, she assumed a research position at the University of Pittsburgh School of Medicine where she currently works as a post-doctoral fellow in the Department of Critical Care CRISMA Center conducting research in pediatric health policy and APRN outcomes in critical care. She also works as a pediatric nurse practitioner at the Children’s Home in Pittsburgh. She is a past NAPNAP Executive Board member and current member of the Health Policy Committee. She has presented at numerous international conferences and authored multiple publications on both clinical practice and professional issues in nursing.

Disclosures
• I will not discuss off label use and/or investigational use of any drugs or devices in my presentation.
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Learning Objectives
• Describe the pathophysiologic effects of short- and long-term opioid use in pediatric patients.
• Identify developmental implications associated with opioid exposure in pediatric patients.
• Discuss medication-based treatment options available for management of neonatal abstinence syndrome and pediatric opioid use disorder.
• Examine barriers and opportunities for pediatric-focused advanced practice registered nurses to prescribe medication-based treatment.

Pediatric Opioid Mortality
• 0.81: 100,000 Children in U.S
  • A 268% increase 1999 – 2016
  • 80% were unintentional deaths
  • 73% attributed to prescription opioids
  • Racial disparity
    • Black mortality 391%
    • White non-Hispanic mortality 289%
    • Hispanic mortality 188%
  • 1/3 of adolescents died of co-ingestion

Hospital Impact

Gaither et al., JAMA Network Open. 2018
National opioid prescribing trends

Opioid Use for Pain Management

Long-term opioid use for pain and sedation creates tolerance
Increased long-term use of opioid medications
Unrelieved pain

Unrelieved pain

• Physiological
  • Stress activation of:
    • Hypothalamic–pituitary–adrenal axis
    • Renin–angiotensin–aldosterone axis
      • Can result in fluid retention, generalized edema, hypertension, impaired tissue oxygenation, increased oxygen consumption, delayed wound healing, and compromised immunity
  • Psychological
    • Can result in:
      • Anxiety, depression, impaired sleep, or PTSD

Pain pathways

Ascending pathways
Descending pathways

Martyn, Mao, & Bittner, NEJM, 2019

Transmission of pain

Martyn, Mao, & Bittner, NEJM, 2019

Local response

Martyn, Mao, & Bittner, NEJM, 2019
Don’t be afraid to treat pain

• Acute pain guidelines
  • National Academy of Medicine
    • Framing Opioid Prescribing Guidelines for Acute Pain: Developing the Evidence (2019a)
  • American Dental Association
    • Pain Management in Infants, Children, Adolescents and Individuals with Special Health Care Needs (2017)
  • Society for Pediatric Anesthesia
    • Recommendations for the Use of Opioids in Children during the Perioperative Period (2019)

• Chronic pain guidelines
  • Centers for Disease Control and Prevention
    • CDC Guideline for Prescribing Opioids for Chronic Pain (2017)

Short-term Opioid Treatment

• Imbalance between pro-nociceptive and antinociceptive pathways
  • Lessened analgesic effects
  • Aggravated pain behaviors
  • Increased tolerance, and
  • Opioid-induced hyperalgesia

Long-term Opioid Treatment

• 60% for children of opioid-naïve patients undergoing major and minor elective surgery fill an opioid prescription after surgery

Pediatric opioid prescribing practices

• Between 2010 to 2017, opioid use after pediatric surgery decreased 20%
• Institutional guidelines for prescribing opioids have reduced opioid use and shifted primary prescribing to nonopioid alternatives for postoperative pain management

Prescription opioids to opioid misuse

• Receiving a provider-prescribed opioid before the 12th grade is associated with a 33% increase in the risk of nonmedical opioid use by 23 years of age

Overall opioid prescription misuse is on the decline
Neonatal abstinence syndrome is on the rise

- 32,000 births per year
- One baby every 15 minutes
- $560 million to treat in infancy
- Admissions 13-23 days
- Higher likelihood of 30-day readmission

Effect on development?

- Neonates
  - Mixed studies; conducted prior to current opioid epidemic
  - Cognitive development similar to non-exposed children
    - When control age, race, and socioeconomic status
    - Scores were lower in both groups compared with the general population
  - Lower IQ scores and poor social skill
    - Small sample sizes
    - Poor retention rates to do 5-year follow-up studies
- Adolescents
  - Effects of opioid exposure on adolescent development is unclear
  - Adolescent Brain Cognitive Development (ABCD) Study
    - 11,000+ adolescents in longitudinal study

Medication-based Treatment

- Monitor for symptoms for at least 5 days – there are many assessment tools
- Promote breastfeeding, if safe
- Support non-pharmacologic interventions (swaddling, rooming in*) and,
- Coordinate necessary help for the mother
- 50-80% require medical management
- Risk factors associated with needing MBT
  - CNS active agents: nicotine, benzodiazepines, gabapentin, SSRIs, and marijuana
  - Genetic and epigenetic factors
  - Exposure to buprenorphine versus methadone prenatally

How should we treat NAS

- Most recent, blinded RCT
  - Dose determined by scoring
  - Morphine q4 versus Methadone and placebo alternating q8

<table>
<thead>
<tr>
<th></th>
<th>Methadone (N=58)</th>
<th>Morphine (N=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay</td>
<td>21.8 (15.0)</td>
<td>23.3 (8.8)</td>
</tr>
<tr>
<td>Length of stay attributed to NAS</td>
<td>18.9 (7.9)</td>
<td>21.1 (6.9)</td>
</tr>
<tr>
<td>Length of treatment</td>
<td>14.7 (8.0)</td>
<td>16.6 (6.9)</td>
</tr>
<tr>
<td>Needed a dose increase</td>
<td>22 (37.9)</td>
<td>28 (48.3)</td>
</tr>
<tr>
<td>Needed Phenobarbital</td>
<td>10 (17.2)</td>
<td>17 (29.3)</td>
</tr>
</tbody>
</table>

NAS Treatment studies

- 1 Meta-analysis
- 18 studies

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine</th>
<th>Methadone</th>
<th>Phenytoin</th>
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</thead>
<tbody>
<tr>
<td>Length of Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for Adjunct</td>
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</table>
Which treatment may be best for NAS

Recommendations with SO much still to be learned

• Morphine should not be our first choice for treatment, but currently it is used the most often
• Methadone or Buprenorphine should be considered first
• We have more questions than answers about diagnosing, treatment and outcomes for patients with NAS

Helping young children in families with addiction

Scale of adolescent opioid misuse

• 1 in 5 adolescents will misuse opioids
• Use without a prescription or not as prescribed
• Misuse associated with:
  • Mental health problems: depression, anxiety, ADHD
  • Genetic predisposition
  • Trouble with family
  • Housing instability
  • History of victimization
  • School problems
  • Friends who misuse opioids
  • Live in rural areas

Adolescent Treatment

• Screening, brief intervention, and referral to treatment (SBIRT)
  • Some states offer in schools: Massachusetts, Wisconsin, New Mexico, and New York
• Medications (methadone, buprenorphine, and naltrexone)
• Behavioral therapy, and
• Family-centered approaches

FindTreatment.gov

Medication-based treatment in adolescent OUD

• <3% of pediatric patients with OUD receive MBT
• Variation in the prescribing rates between the states
  • Discrepancy largely based upon Medicaid expansion
    • Biggest barriers to treatment in the South and for low-income
  • Access to Buprenorphine
    • In Medicaid-expanding states, increased from 40 to 138 per 1,000 enrollees
    • In non-Medicaid-expanding states, increased from 16 to 41 per 1,000 enrollees
Pediatric access to MBT has decreased

![Graph showing trends in buprenorphine use in the United States per 1000 population, by age group, 2000-2018](image)

MBT in adolescents

![Graph showing proportion of adolescents prescribed MBT](image)

MBT rates are particularly low among youngest adolescents

![Graph showing prescribing of any buprenorphine or naltrexone by age of OUD diagnosis](image)

Treatment for OUD in adolescents

- MBT + behavioral therapy = better treatment retention
- Overall pediatric retention is worse than adults

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Well studied in adolescents</th>
<th>Limited data in adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All data supports using MBT in adolescents

Buprenorphine

<table>
<thead>
<tr>
<th>Receptor activity</th>
<th>High affinity partial opioid agonist</th>
<th>This is not a full opioid substitute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on OUD</td>
<td>Decreases withdrawal symptoms</td>
<td>Decreases reward if also using opioids</td>
</tr>
<tr>
<td>Key timing around starting</td>
<td>Start 12-24 hours after stopping opioids, beginning of withdrawal symptoms</td>
<td>Takes a few days to become therapeutic</td>
</tr>
<tr>
<td>Risk of overdose on treatment</td>
<td>Lowest of treatments, less respiratory depression than methadone</td>
<td></td>
</tr>
<tr>
<td>Dosage</td>
<td>4.24mg daily</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>Low testosterone levels</td>
<td></td>
</tr>
<tr>
<td>Who can prescribe</td>
<td>MD or APP with specialized training and DEA waiver</td>
<td></td>
</tr>
<tr>
<td>Where is treatment received</td>
<td>Prescription to home pharmacy</td>
<td>Treatment at home***</td>
</tr>
</tbody>
</table>

Methadone

<table>
<thead>
<tr>
<th>Receptor activity</th>
<th>Fully activates the mu receptor</th>
<th>This is a full opioid substitute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on OUD</td>
<td>Decrease “lows” of withdrawal symptoms</td>
<td>Therapeutic, does not substitute, high of short-acting opioids</td>
</tr>
<tr>
<td>Key timing around starting</td>
<td>No need to have withdrawal symptoms before starting treatment</td>
<td>Takes days to weeks to become therapeutic</td>
</tr>
<tr>
<td>Risk of overdose on treatment</td>
<td>Most significant in first two weeks of treatment</td>
<td></td>
</tr>
<tr>
<td>Dosage</td>
<td>Daily – individualized</td>
<td>Missing dose can lead to withdrawal</td>
</tr>
<tr>
<td>Side effects</td>
<td>Low testosterone levels</td>
<td>Prolonged QTc</td>
</tr>
<tr>
<td>Who can prescribe</td>
<td>MD or APP working at certified opioid treatment programs</td>
<td></td>
</tr>
<tr>
<td>Where is treatment received</td>
<td>Outpatient methadone treatment centers</td>
<td>Given in conjunction with counseling by clinic providers</td>
</tr>
</tbody>
</table>
Extended-release Naltrexone

<table>
<thead>
<tr>
<th>Receptor activity</th>
<th>Full antagonist of mu receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on OUD</td>
<td>Completely block euphoric and analgesic effect of all opioids</td>
</tr>
<tr>
<td>Key timing around starting</td>
<td>Starting can cause severe withdrawal symptoms – need to be supervised</td>
</tr>
<tr>
<td>Start 4 to 7 days after no opioid use</td>
<td></td>
</tr>
<tr>
<td>Risk of overdose on treatment</td>
<td>Greatest risk at end of 28-day period of extended formulation</td>
</tr>
<tr>
<td>Dosage</td>
<td>380mg IM q 28 days</td>
</tr>
<tr>
<td>Side effects</td>
<td>Not appropriate for treatment in setting of acute pain (fractures, surgery)</td>
</tr>
<tr>
<td>Who can prescribe</td>
<td>MD or APP in an office-based setting</td>
</tr>
</tbody>
</table>

Where is treatment received
Office-based setting

Special populations to consider using Naltrexone
Those who have been compliant on other MBT treatment
Those who have not used in 2 weeks but are at high risk of relapse
Intermittent users

Oral Naltrexone

- Daily dose of oral medication
- No better than placebo in treating OUD
- Increased risk of opioid overdose

*Oral naltrexone is not approved by the FDA for OUD

Narcan

- All patients on MBT also need a prescription for Narcan
- Opioid antagonist to treat respiratory depression that causes fatal overdose
- Can be obtained from a pharmacy without seeing a provider
- Often available at low or no cost in community-based organizations

MBT research

- Slow-release morphine
- Supervised injectable opioid agonist therapy
  - Pharmaceutical grade heroin and dilaudid
- Cannabinoids
- Vaccination

Treatment duration

- Better OUD outcomes if MBT continues for at least 6-12 months
- Only half of patients aged of 18 and 64 who initiate buprenorphine therapy remain on therapy for 180 days or more.
- Ideas to improve retention in treatment
  - Increase availability of medication – more convenient
  - Pair with evidence-based CBT
  - Prevent periods of time without insurance

Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Use &amp; Mode</th>
<th>Frequency of administration</th>
<th>Route of administration</th>
<th>Who can prescribe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>Full agonist binds to and activates opiate receptors, providing pain relief in patients that were addicted by the drug, but is a safer option than pharmaceutical grade heroin and dilaudid.</td>
<td>Daily</td>
<td>Oral to treat lifelong dependence on opioids or prevent relapse</td>
<td>Physicians, nurse practitioners, and physician assistants with a national waiver. Prescriptions must be written by a licensed physician. Narcan can be used for patients when needed or for naloxone, also for nalorphine, at home.</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Partial agonist agonist binds to and activates opiate receptors but with less euphoria than full agonists.</td>
<td>Daily or less frequent (every 3-6 months)</td>
<td>Oral tablet or film strips (buprenorphine)</td>
<td>Physicians, nurse practitioners, and physician assistants with a national waiver. Prescriptions must be written by a licensed physician. Narcan can be used for patients when needed or for nalorphine, also for nalorphine, at home.</td>
</tr>
<tr>
<td>Subutex (buprenorphine e injection)</td>
<td>300mg/mL injection (for moderate to severe opioid use disorder)</td>
<td>Monthly</td>
<td>Subcutaneous injection (for moderate to severe opioid use disorder)</td>
<td>Physicians, nurse practitioners, and physician assistants with a national waiver. Prescriptions must be written by a licensed physician. Narcan can be used for patients when needed or for nalorphine, also for nalorphine, at home.</td>
</tr>
<tr>
<td>Naltrexone (oral)</td>
<td>Antagonist: blocks in and reduces the activity of certain enzymes or cells, preventing a physiological response</td>
<td>Monthly</td>
<td>Injection into the gluteal muscle in a methadone or buprenorphine program or by qualified staff.</td>
<td></td>
</tr>
</tbody>
</table>

National Academy of Medicine, 2019b; SAMHSA, 2020

Foney & Mace, 2019

National Academy of Medicine, 2019b
Policy to Support MBT

Legislation to increase access to MBT

- **October 2000**: Drug Addiction Treatment Act of 2000 (DATA)
  - Physicians can prescribe buprenorphine in office-based settings

- **July 2016**: Comprehensive Addiction and Recovery Act (CARA 2016)
  - Extends buprenorphine waiver eligibility to NPs and PA
  - NPs and PAs can begin taking waiver training

- **November 2016**: SUPPORT for Patients and Communities Act (2018)
  - NPs and PAs begin receiving buprenorphine prescribing waivers

- **February 2017**: Waiver eligibility extended to CNM, CNS, and CRNAs

- **October 2018**: SUPPORT for Patients and Communities Act (2018)

New MBT Providers 2002 - 2017

SUPPORT for Patients and Communities Act (2018)

- Increase access – pregnant women, children, rural areas
- CHIP must provide mental health and SUD benefits on par with those for physical health
- Medicaid funding can cover NAS treatment
- Children age out of foster care qualify for Medicaid until age 26
- Expands access to inpatient addiction treatment
  - Cover up to 30 days of inpatient treatment per year

SUPPORT for Patients and Communities Act (2018)

- Clarifies that MAT can be prescribed via telehealth
- Increases access to Narcan
- Supports addiction and pain research
- Promotes provider education
- Expands MAT prescribing
  - Permanently for NPs, expands to other APRN roles

APRN MAT Prescribing

- All APRNs can be MAT prescribers
  - 24 hours of initial training available from multiple sources
  - Certification through the DEA
  - Gradually increase to treat up to 275 patients on MAT
  - Not contingent on collaborating physician to be a MAT prescriber
  - Provider education resources:
    - SAMHSA Provider Clinical Support System for Opioid Therapies
      - https://pcss-o.org
    - SAMHSA Provider Clinical Support System for Medication-Assisted Treatment
NPs and PAs with DEA waivers to prescribe buprenorphine

State scope-of-practice is associated with number of providers

Where is MBT being prescribed?

How many OUD patients do MAT prescribers treat

Significant gaps in capacity to provide MBT

MBT high need areas
Innovative Ways to Increase Access

- **Primary care**
  - Stigma among PCPs regarding MAT treatment (Wakeman & Barnett, 2018 NEJM)
  - Efforts to make treatment with MAT comparable to antiretroviral therapy during AIDS crisis
- **ED**
  - Safe and cost-effective to start treatment for patients with opioid related visits (not just overdose)
  - Requires partnership with treatment clinic

Methadone Innovations in Delivery

- Allow office-based administration of methadone
- Outside of outpatient treatment programs
- Mobile methadone vans
  - Used in several states to reach patients who can’t travel to a treatment program
- Create “medication units” associated with a treatment program but provide off-site medication at places more convenient for patients
  - “addiction schools”
- Loosen restrictions on the number of treatment programs in a state

Narcan Prescribing

- Less than 1% of people prescribed opioids, deemed to be at risk of overdose receive a concurrent Narcan prescription
- Surgeon General’s Advisory on Naloxone and Opioid Overdose
- HHS is taking action to increase Narcan awareness
  - Stand alone guideline on when to prescribe Narcan
  - FDA taking steps to make Narcan available as an OTC medication

FindTreatment.gov

- 13,000+ providers
- Search by:
  - Inpatient and outpatient services
  - Pediatric
  - LGBTQ community
  - Kind of insurance
  - Type of medication

The Mental Health Parity and Addiction Equity Act (2008)

- Requires coverage of mental health and substance use disorder treatment
  - Public and private health insurance markets
  - Covers care that meet standards of other evidence-based treatments
- Enforcement has been limited
  - Patients must engage in appeal/complaint process to gain access
  - 1/10th of patients who need substance use treatment receive it
**Good Samaritan Laws**

- Provide immunity from arrest, charge, or prosecution for controlled substance possession and paraphernalia when 911 is called in an overdose
- When 4+ people present
- Particularly among adolescents
- Awareness of law increase use in all ages, genders and races!!
- National Conference of State Legislators – state specific law

**References**