Neonatal Abstinence Syndrome and Pain and Opioid Management in Children and Adolescents

March 11, 2018

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I have no conflicts of interest to disclose.
I will be discussing the off-label use of several drugs.
Objectives

- Examine current trends in the management of neonatal abstinence syndrome
- Discuss strategies for preventing prescription opioid misuse in adolescents and young adults
- Develop a plan for appropriate opioid prescribing and monitoring in children adolescents in your practice setting
Neonatal Abstinence Syndrome (NAS)

- Withdrawal symptoms experienced by neonates exposed to opioids in utero
- 5-fold increase over the past decade
  - 1 infant with NAS born every 25 minutes
- Hospital charges 2-3 times that of a healthy newborn
- NICU admissions for NAS
  - 7 per 1000 in 2004
  - 27 per 1000 in 2013

Map 4.

Neonatal Abstinence Syndrome Inpatient Discharges by Virginia Locality,
Rate per 1,000 Live Births, Q4 2014 through Q3 2015

NAS Symptoms

- Increased norepinephrine, corticotropin, and acetylcholine effects and reduced dopamine and serotonin effects

<table>
<thead>
<tr>
<th>CNS Symptoms</th>
<th>Vasomotor, Metabolic, Pulmonary Symptoms</th>
<th>GI Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability</td>
<td>Tachycardia</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Inability to sleep</td>
<td>Hypertension</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Tremors, myoclonic jerks</td>
<td>Fever</td>
<td>Poor feeding</td>
</tr>
<tr>
<td>Increased muscle tone</td>
<td>Frequent yawning</td>
<td>Excessive sucking</td>
</tr>
<tr>
<td>High-pitched crying</td>
<td>Sneezing, nasal stuffiness</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Excoriation (due to agitation)</td>
<td>Sweating</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>Tachypnea</td>
<td></td>
</tr>
</tbody>
</table>

Onset and Severity of NAS Symptoms

- Related to opioid half-life
  - Shortest onset with heroin and fentanyl
  - Longest with methadone (2-14 days)
- Buprenorphine
  - May produce milder symptoms and a shorter course
- Genetic variation may influence the severity of NAS
- Gabapentin use may increase the risk for NAS

NAS Guidelines

- **Assessment**
  - Standards for screening and duration of observation
  - Eat, Sleep Console (ESC) tool
  - Finnegan, Modified Finnegan, Lipsitz, MOTHER NAS

- **Standardized approach to treatment**
  - Non-pharmacologic care, breastfeeding
  - Morphine, methadone, or buprenorphine
  - Clonidine or phenobarbital

Ohio Children’s Hospital Association NAS Committee. [https://opqc.net/projects/NAS](https://opqc.net/projects/NAS)
UVA NAS Guideline: A Work in Progress

- Focused on family involvement
- Eat, Sleep, Console (ESC)
  - Breastfeed or take 1 ounce, sleep ≥ 1 hr, console in 10 min
- Modified Finnegan
- Morphine 0.05 mg/kg PO PRN
- Scheduled morphine only if necessary
- Clonidine for non-opioid use or as adjunct
Assessment of NAS Guidelines

- Ohio NAS collaborative
  - Reduced length of treatment (23 vs 34 days, $p < 0.001$)
  - Reduced length of stay (24 vs 32 days, $p < 0.001$)
  - Less adjunctive therapy (5% vs 21%, $p = 0.004$)

- Vermont Oxford Network
  - Reduced length of treatment (15 vs 16 days, $p = 0.02$)
  - Reduced length of stay (19 vs 21 days, $p = 0.002$)
  - Fewer patients discharged on meds (27% vs 40%, $p = 0.02$)

Pain and Opioid Management in Children and Adolescents
The Current State

- Drug overdose has been the most frequent cause of death not due to disease in Virginia since 2013, outpacing crashes and gun-related deaths
- 1,420 drug-related deaths in 2016
- 1,133 (80%) were from opioids
- Fentanyl and heroin accounted for 70% of those deaths; 30% were prescription opioids

Map 5.
Prescription Opioid Overdose Deaths (Excluding Fentanyl) 
by Virginia Locality, Rate per 100,000 Persons, 
Q4 2015 Through Q3 2016

Map 6.
Fentanyl and/or Heroin Overdose Deaths by Virginia Locality, 
Rate per 100,000 Persons, Q4 2015 Through Q3 2016

Gaining Perspective

- **Socioeconomic factors**
  - Associated with higher rates of depression, smoking, and alcohol use in adolescents as well as adults

- **Access and acceptance**
  - Changes in prescribing patterns

- **Transition to fentanyl and heroin**
  - Cost
  - Restricted access

Case A, Deaton A. PNAS 2015;112(49): 15078-83.
A Population at Risk

- 1 in 4 adolescents now report misusing prescription drugs; a 33% increase in 5 years
- Over 2/3 of people who abuse prescription medications report that they obtained them from a family member or friend for free
- Admissions for opioid overdoses in adolescents doubled and suicides increased by 50% between 2000 and 2015

Adolescent Opioid Misuse

- Analysis of the Nationwide Emergency Department Sample (NEDS) database of visits related to opioid dependence or misuse from 2008-2013
  - 257,165 visits made by patients < 21 years of age
    - 88.3% by 18-21 year-olds, 8.4% by 16-17 year-olds
  - 200 died in the ED and 325 died during hospitalization

Turning the Tide

- Help adolescents and young adults currently misusing opioids by referring them to medication-assisted treatment programs
- Providing naloxone to at-risk patients to reduce the risk of death due to opioid overdose
- Reducing opportunities for prescription opioid misuse

AAP Committee on Substance Use and Prevention. Pediatrics 2016;138(3):e20161893
Medication-Assisted Treatment

- Substance Abuse and Mental Health Services Administration
  [https://www.samhsa.gov/medication-assisted-treatment](https://www.samhsa.gov/medication-assisted-treatment)
- Methadone
- Buprenorphine
  - Approved by the FDA for patients 16 years and older
  - Can only be used by approved prescribers (physician, NP, PA)
  - Products
    - Bunavail® (buprenorphine and naloxone) buccal film
    - Suboxone® (buprenorphine and naloxone) film
    - Zubsolv® (buprenorphine and naloxone) sublingual tablets
    - Probuphine® (buprenorphine) implant
    - Buprenorphine products without naloxone – restricted use
- Naltrexone
MAT in Adolescents

- 2017 study of federally-funded treatment centers
  - Only 2.4% of adolescents in a recovery program received MAT, compared to 26% of adults
  - Only 0.4% with prescription opioid misuse received MAT
- A 2017 analysis of 20,822 15-25 year-olds with opioid use disorder found that only 25% received MAT
  - Younger patients, females, black, and Hispanic adolescents were less likely to receive MAT
- In a study of 103 young adults in a MAT program, retention was 45% at 60 days, with 85% abstinent

Naloxone

- Competitive opioid antagonist, approved in 1971
- Indicated for reversal of opioid overdose in all ages
- Requires rapid, efficient delivery
- Short duration of action (half-life 1-2 hours)

Considerations

- Limited efficacy with partial agonists (buprenorphine) or mixed agonists/antagonists
- Recurrent respiratory/CNS depression after effects wane
- Can precipitate severe opioid withdrawal
  - Vomiting, hypertension, tachycardia
Naloxone Standing Order

- Physician prescription
- State-wide standing orders provide expanded access
  - Currently in 48 states
  - Virginia standing order issued in November 2016
- Dispensed by pharmacists under protocol
  - Patients
  - Families
  - Community members/groups

Naloxone Products: Pros and Cons

- Naloxone 2 mg/2 mL syringe with nasal atomizer*
  - Longer preparation time
  - $71.28 per 2-dose kit at UVA Pharmacies
- Narcan® 4 mg/0.1 mL nasal spray *
  - $145 per 2-dose bottle
- Evzio® auto-injector 2 mg/0.4 mL SC or IM
  - Talk the user through the process
  - $3,800 per 2-dose kit

*preferred by Virginia Medicaid, covered by most major insurers
Opioid Prescribing Regulations
Virginia Regulations Governing Prescribing of Opioids
Acute Pain (≤ 90 days)

- Initiation of therapy
  - Restricted to use of short-acting opioids
  - Acute Pain limited to ≤ 7-day supply
  - Post-surgical use limited to ≤ 14-day supply
- Must take a history, perform a physical exam, and assess the patient’s history and risk for substance misuse
- Must check PMP
- Must document reason for prescribing a dose > 50 Morphine Milligram Equivalent (MME)/day in the medical record

https://www.dhp.virginia.gov/medicine/
Virginia Regulations Governing Prescribing of Opioids
Acute Pain (< 90 days)

- Prescribing a dose > 120 MME/day requires documentation in the medical record justifying the dose or referring to consultation with a pain management specialist
- Naloxone must be prescribed if:
  - Dose > 120 MME/day
  - Patient is also taking a benzodiazepine
  - Patient has a history of substance misuse
  - Patient has a history of a previous overdose
- Due to the risk for fatal overdose in patients taking an opioid and a benzodiazepine, the following medication should not be used: sedative hypnotics, carisoprodol, or tramadol

- Enacted 8/24/17
Virginia Regulations Governing Prescribing of Opioids Chronic Pain (> 90 days)

- Must take a history, perform a physical exam and urine drug screen, and assess the patient’s pain history, current and past treatments, and history or risk of substance misuse
- Must check PMP
- Medical record must contain informed consent and a treatment plan
- Must document reason for prescribing a dose > 50 Morphine Milligram Equivalent (MME)/day in the medical record
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- Due to the risk for fatal overdose in patients taking an opioid and a benzodiazepine, the following medication should not be used: sedative hypnotics, carisoprodol, or tramadol

- Must document the rationale for continued use every 3 months, recheck PMP, obtain a urine drug screen, and reassess for opioid use disorder

- Enacted 8/24/17
Virginia Prescription Drug Monitoring Program

- Interoperable with 22 other states
- Licensed prescribers, or their agents, are required to check the PMP before prescribing opioids
- Exemptions:
  - Patients receiving hospice or palliative care
  - Hospitalized patients
  - Patients in an assisted living facility with one pharmacy
  - Emergencies

https://www.dhp.virginia.gov/dhp_programs/pmp/default.asp
Efficacy of Prescription Monitoring Programs

National Survey of Drug Use and Health 2004-2014

- 80% reduction in opioid prescriptions from multiple prescribers in states with mandatory PMPs
- 75% reduction in fake prescriptions
- 56% reduction in opioid prescriptions from multiple prescribers in states with voluntary PMPs
- 50% reduction in fake prescriptions
- No increase in heroin use associated with PMPs

CALCULATING TOTAL DAILY DOSE OF OPIOIDS FOR SAFER DOSAGE

Higher Dosage, Higher Risk.

Higher dosages of opioids are associated with higher risk of overdose and death—even relatively low dosages (20-50 morphine milligram equivalents (MME) per day) increase risk. Higher dosages haven’t been shown to reduce pain over the long term. One randomized trial found no difference in pain or function between a more liberal opioid dose escalation strategy (with average final dosage 52 MME) and maintenance of current dosage (average final dosage 40 MME).

Dosages at or above 50 MME/day increase risks for overdose by at least 2x the risk at <20 MME/day.

WHY IS IT IMPORTANT TO CALCULATE THE TOTAL DAILY DOSAGE OF OPIOIDS?

Patients prescribed higher opioid dosages are at higher risk of overdose death.

In a national sample of Veterans Health Administration (VHA) patients with chronic pain receiving opioids from 2004–2009, patients who died of opioid overdose were prescribed an average of 98 MME/day, while other patients were prescribed an average of 48 MME/day.

Calculating the total daily dose of opioids helps identify patients who may benefit from closer monitoring, reduction or tapering of opioids, prescribing of naloxone, or other measures to reduce risk of overdose.

HOW MUCH IS 50 OR 90 MME/DAY FOR COMMONLY PRESCRIBED OPIOIDS?

50 MME/day:
- 50 mg of hydrocodone (10 tablets of hydrocodone/acetaminophen 5/300)
- 33 mg of oxycodone (~2 tablets of oxycodone sustained-release 15 mg)
- 12 mg of methadone (~3 tablets of methadone 5 mg)

90 MME/day:
- 90 mg of hydrocodone (9 tablets of hydrocodone/acetaminophen 10/325)
- 60 mg of oxycodone (~2 tablets of oxycodone sustained-release 30 mg)
- ~20 mg of methadone (4 tablets of methadone 5 mg)

**HOW SHOULD THE TOTAL DAILY DOSE OF OPIOIDS BE CALCULATED?**

1. **DETERMINE** the total daily amount of each opioid the patient takes.

2. **CONVERT** each to MMEs—multiply the dose for each opioid by the conversion factor. (See table)

3. **ADD** them together.

<table>
<thead>
<tr>
<th>OPIOID</th>
<th>Conversion Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Fentanyl transdermal (in mcg/hr)</td>
<td>2.4</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.0</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>4.0</td>
</tr>
<tr>
<td>Methadone</td>
<td>4.0</td>
</tr>
<tr>
<td>1-20 mg/day</td>
<td>4.0</td>
</tr>
<tr>
<td>21-40 mg/day</td>
<td>8.0</td>
</tr>
<tr>
<td>41-60 mg/day</td>
<td>10.0</td>
</tr>
<tr>
<td>&gt; 61-90 mg/day</td>
<td>12.0</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.0</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*These dose conversions are estimated and cannot account for all individual differences in genetics and pharmacokinetics.*

**CAUTION:**
- Do not use the calculated dose in MMEs to determine dosage for converting one opioid to another—the new opioid should be lower to avoid unintentional overdose caused by incomplete cross-tolerance and individual differences in opioid pharmacokinetics. Consult the medication label.

**USE EXTRA CAUTION:**
- Methadone: the conversion factor increases at higher doses.
- Fentanyl: dosed in mcg/hr instead of mg/day, and absorption is affected by heat and other factors.

**HOW SHOULD PROVIDERS USE THE TOTAL DAILY OPIOID DOSE IN CLINICAL PRACTICE?**

- Use caution when prescribing opioids at any dosage and prescribe the lowest effective dose.
- Use extra precautions when increasing to ≥50 MME per day* such as:
  - Monitor and assess pain and function more frequently.
  - Discuss reducing dose or tapering and discontinuing opioid if benefits do not outweigh harms.
  - Consider offering naloxone.
- Avoid or carefully justify increasing dosage to ≥50 MME/day*

*These dosage thresholds are based on overdose risk when opioids are prescribed for pain and should not guide dosing of medication-assisted treatment for opioid use disorder.

Learn More [www.cdc.gov/drugoverdose/prescribing/guideline.html](http://www.cdc.gov/drugoverdose/prescribing/guideline.html)
Opioid Prescribing in Children, Adolescents, and Young Adults
Opioid Exposures

- National Hospital Ambulatory Medical Care Survey
  - Opioid prescriptions in pediatric Emergency Depts rose from 6.4% in 1994 to 14.5% in 2010
- A 2014 study of claims data found 46% of 8,373 adolescents with newly diagnosed migraine were given a prescription for an opioid, despite treatment guidelines recommending against their use

Managing Pain

- Setting appropriate goals
- Selecting the best drug and an appropriate duration
  - A randomized study of morphine and ibuprofen in children after orthopedic surgery found no difference in efficacy, but more adverse effects in the morphine group (69% vs 39%, p < 0.001)
  - In a study of 672 children after adenotonsillectomy, addition of an opioid to ibuprofen delayed time to resumption of normal activity and diet by 1-2 days

Opioid Use after Discharge

- In a 2015 study of 243 families only 56% complied with scheduled morphine after surgery
  - Only 9% of prescribed doses were given

Opioid Use after Discharge

- A team at Johns Hopkins interviewed parents of 343 children given a prescription for opioids at discharge
  - Median number of doses prescribed: 43 (IR 30-85)
  - Median number of doses taken: 16 (IR 2-39)
  - 58% of doses prescribed were not used
  - Most parents stopped opioids because they were no longer needed; 18% of patients had adverse effects
  - Only 19% of parents reported receiving instructions for disposal of unused drug; just 4% followed them

Matching Pain to Opioid Prescribing

- Children who underwent orthopedic procedures or Nuss surgery received an average of 25 more doses than other patients

Duration of Therapy

- Evidence and Experience
  - Treatment guidelines rarely include duration
  - In a review of 4,075 opioid prescriptions from pediatric EDs and urgent care clinics, the odds of receiving a prescription for > 5 days were higher if prescribed by residents or in an urgent care clinic

- Limiting the quantity prescribed
  - ≤ 7 days for acute pain
  - ≤ 14 days for postoperative pain

Probability of Continued Opioid Use Among Opioid-Naïve Patients by Number of Days’ Supply, United States 2006-2015

* Days’ supply of the first prescription is expressed in days (1–40) in 1-day increments. If a patient had multiple prescriptions on the first day, the prescription with the longest days’ supply was considered the first prescription.

Unused Opioids

- Multiple studies have shown that most parents keep unused opioids prescribed for their children.
- In a study of 5,330 adults given opioids, 72% had leftover medication; of those, 71% kept it and 2.3% gave it to someone else.
- In a recent systematic review of 6 studies in adult surgery patients, those that tracked drug disposal found rates < 10%.

Safe Storage and Disposal

- 60% of pediatric opioid exposures resulting in hospital admission involved children < 6 years of age
- Survey of 681 adults with an opioid prescription
  - Locked or latched storage in only 32% of families with children < 7 yrs and 12% in families of children 7-17 years

Disposal
- Disposal bags and kits
- Drop-off sites
- Take back programs

The Future

- Practice change and an acceptance of alternatives
- Declining adolescent prescription opioid exposure and misuse

Without health, there is no happiness. An attention to health, then, should take the place of every other object.

- Thomas Jefferson 1787