The Impact of the Opioid Epidemic on the Pediatric Surgical Population

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Learning Objectives

- Describe development of the fetus and the impact of maternal chronic opioid abuse
- Outline treatment options for neonatal abstinence syndrome
- Recognize factors that put pediatric surgical patients at risk for persistent opioid abuse
- Characterize prevalence of opioid abuse in pediatric and adult populations
Disclosures

- None
Opioids by the Numbers

214,881,622
Number of opioid prescriptions

84.9
Prescriptions per 100 people in MI

130
Americans die every day
Opioid-involved Overdose Deaths, 1999-2017

Figure 3. National Drug Overdose Deaths Involving Any Opioid, Number Among All Ages, by Gender, 1999-2017

Opioids

- Natural, endogenous and synthetic compounds
- μ-receptors
- Supraspinal analgesia
- Low molecular weight
- Lipophilic
- Cross placental and blood-brain barriers
- Physical and psychological dependence
The Maternal-Fetal Dyad

- Opioids during pregnancy
- Increase since 1997
- Costs associated
- Screening mothers
- Optimize outcomes for baby and mom
- Legal/ethics of drug testing

https://www.fitpregnancy.com/24-weeks-pregnant
Risks to fetus

- Risk of preterm birth
- Intrauterine growth restriction
- Neonatal abstinence syndrome
- Medication-assisted treatment for moms—methadone, Buprenorphine
- High-risk behaviors in moms with OUD
Prenatal Exposure

- Difficult to assess in human studies
- Congenital defects
- Neurocognitive/Behavioral effects? Lots of confounding factors!
- Increased infant mortality
**TABLE 2**

**Associations between maternal opioid analgesic treatment and specific major birth defects**

<table>
<thead>
<tr>
<th>Birth defect</th>
<th>Total no.*</th>
<th>No. exposed</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothesis-testing analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>6701</td>
<td>134</td>
<td>Reference</td>
</tr>
<tr>
<td>Anencephaly/craniorachischisis</td>
<td>340</td>
<td>9</td>
<td>1.7 (0.84-3.4)</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>718</td>
<td>26</td>
<td>2.0 (1.3-3.7)</td>
</tr>
<tr>
<td>Any of included heart defects</td>
<td>7724</td>
<td>211</td>
<td>1.4 (1.1-1.7)</td>
</tr>
<tr>
<td>Laterality defects with CHD</td>
<td>188</td>
<td>4</td>
<td>1.2 (0.49-3.2)</td>
</tr>
<tr>
<td>Atrioventricular septal defect</td>
<td>175</td>
<td>9</td>
<td>2.4 (1.7-6.8)</td>
</tr>
<tr>
<td>Anomalous pulmonary venous return</td>
<td>206</td>
<td>4</td>
<td>0.71 (0.22-2.3)</td>
</tr>
<tr>
<td>Single ventricle complex</td>
<td>261</td>
<td>4</td>
<td>1.1 (0.45-2.9)</td>
</tr>
<tr>
<td>Conotruncal defects</td>
<td>1481</td>
<td>41</td>
<td>1.3 (1.0-2.1)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>872</td>
<td>21</td>
<td>1.7 (1.1-2.8)</td>
</tr>
<tr>
<td>D-transposition of great arteries</td>
<td>461</td>
<td>10</td>
<td>1.1 (0.58-2.1)</td>
</tr>
<tr>
<td>Atrioventricular septal defect conoventricular</td>
<td>110</td>
<td>6</td>
<td>2.7 (1.1-6.9)</td>
</tr>
<tr>
<td>Left ventricular outflow tract obstruction defects</td>
<td>1195</td>
<td>36</td>
<td>1.5 (1.0-2.3)</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>357</td>
<td>17</td>
<td>2.4 (1.4-4.1)</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>630</td>
<td>11</td>
<td>0.88 (0.47-1.6)</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>253</td>
<td>9</td>
<td>1.3 (0.61-2.9)</td>
</tr>
<tr>
<td>Right ventricular outflow tract obstruction defects</td>
<td>1175</td>
<td>40</td>
<td>1.6 (1.1-2.3)</td>
</tr>
<tr>
<td>Pulmonary valve stenosis</td>
<td>887</td>
<td>34</td>
<td>1.7 (1.2-2.6)</td>
</tr>
<tr>
<td>Septal defects</td>
<td>3482</td>
<td>87</td>
<td>1.2 (0.93-1.6)</td>
</tr>
<tr>
<td>Ventricular septal defect perimembranous</td>
<td>1402</td>
<td>29</td>
<td>0.99 (0.85-1.3)</td>
</tr>
<tr>
<td>Atrial septal defect secondum</td>
<td>1507</td>
<td>43</td>
<td>1.3 (0.84-1.9)</td>
</tr>
<tr>
<td>Atrial septal defect not otherwise specified</td>
<td>511</td>
<td>17</td>
<td>2.0 (1.2-3.6)</td>
</tr>
<tr>
<td>CHD association: ventricular septal defect + atrial septal defect</td>
<td>528</td>
<td>17</td>
<td>1.7 (1.0-2.9)</td>
</tr>
<tr>
<td>CHD association: pulmonary valve stenosis + ventricular septal defect</td>
<td>131</td>
<td>4</td>
<td>1.3 (0.46-3.7)</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>936</td>
<td>25</td>
<td>1.3 (0.84-2.0)</td>
</tr>
<tr>
<td>Cleft lip with cleft palate</td>
<td>1162</td>
<td>33</td>
<td>1.4 (0.96-2.1)</td>
</tr>
<tr>
<td>Cleft lip without cleft palate</td>
<td>614</td>
<td>9</td>
<td>0.68 (0.34-1.3)</td>
</tr>
</tbody>
</table>

Neonatal Abstinence Syndrome

- Array of signs and neurobehaviors experienced by the newborn following abrupt discontinuation of gestational exposure to substances taken by the mother
- Inhibit release of noradrenaline
- Abrupt discontinuation → supranormal release of noradrenaline → autonomic and behavioral signs and symptoms
NAS symptoms and timing

- Onset depends on exposure
- Preterm infants LESS at risk
- Seizures in 2-11%
- Subacute signs may last for up to 6 months
- Modified Finnegan’s Neonatal Abstinence Scoring Tool
  - CNS disturbances
  - Metabolic/Respiratory/Vasomotor disturbances
  - GI disturbances
Incidence of NAS

**Figure 1** US incidence of neonatal abstinence syndrome (NAS), 2000–2012.

NAS management

- Non-pharmacologic
  - Minimize environmental stimuli
  - Avoid auto-stimulation—swaddling
  - Respond early to signals
  - Frequent, small volume feeds

- Pharmacologic
  - Opioids
  - Benzodiazepines
  - Barbiturates
  - Clonidine
  - 5-HT₃ antagonists

Implications for anesthesia

- Electrolyte abnormalities, hydration status
- Feeding patterns (NPO status)
- Autonomic instability
- Seizure incidence
- Lower pain threshold
- Hyperthermia
- Sweating

http://www.susannahshouse.org/faq.html
Role of Clonidine in Neonatal Abstinence Syndrome: A Systematic Review

- Disarray of symptoms
- Noradrenaline largely regulated by locus coeruleus
- a2-adrenergic receptor agonist
- Central and peripheral alterations
- Half-life in neonates up to 16.9 hours
- May lessen treatment time
- Hypotension, rebound hypertension, atrioventricular block, bradycardia

Annals of Pharmacotherapy 2016, Vol. 50(4) 301–310
Methadone and NAS

- Long half-life
- Cytochrome P450's immature at birth
- Prolongs QT interval
- Use of volatile anesthetics
- Intractable nystagmus
- Strabismus

Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome

Walter K. Kraft, M.D., Susan C. Adeniyi-Jones, M.D., Inna Chervoneva, Ph.D., Jay S. Greenspan, M.D., Diane Abatemarco, Ph.D., Karol Kaltenbach, Ph.D., and Michelle E. Ehrlich, M.D.

- μ-opioid agonist; antagonist at κ-opioid and δ-opioid receptors
- Long half-life, active metabolites
- Decreased duration of treatment
- Decreased length of hospital stay
- No significant impact on respiratory rate
- Buprenorphine-induced hyperalgesia?
- Multimodal analgesia
Neonatal abstinence syndrome and early childhood morbidity and mortality in Washington state: a retrospective cohort study

CE Witt¹,²,³, KE Rudd¹,⁴, P Bhatraju¹,⁴, FP Rivara¹,²,⁵, SE Hawes¹ and NS Weiss¹

- Very little data
- Animal models—neurocognitive and behavioral issues
- 2017 US study
  - Population-based cohort study
  - First 5 years
  - Differences beyond effects of socioeconomic status
  - Increased risk for re-hospitalization for variety of diagnoses
  - Limitations

Journal of Perinatology (2017) 37, 1124–1129
Poisoning risk in young children

- 188,468 prescription opioid exposures among children <20 yo
- Annual number and rate of exposures declined after 2009
- Exception for buprenorphine
Figure 2. Opioid-involved Overdose Deaths by Age in 2015
(Number of deaths)

Most opioid-involved overdose deaths in the United States occur among those between the ages of 25 and 55 years old.

Source: CDC Wonder database, multiple cause of death files

Hospitalizations for Opioid Poisonings

JAMA Pediatrics  December 2016  Volume 170, Number 12
Opioid-Related Critical Care Resource Use in US Children’s Hospitals

Jason M. Kane, MD, MS, FAAP, FCCM, a,b Jeffrey D. Colvin, MD, JD, c Allison H. Bartlett, MD, MS, d Matt Hall, PhD e

- 3647 opioid-related hospitalizations in 31 children’s hospitals
- 42.9% required critical care
- Overall mortality, 1.6%
- PICU requirements nearly doubled
- 37% required mechanical ventilator support
- 20.3% required pressors

Rate of opioid admissions
Outcomes for Patients Age 1-5 Years of Age

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. cases</td>
<td>1249</td>
<td>274</td>
<td>481</td>
<td>494</td>
<td>—</td>
</tr>
<tr>
<td>Home</td>
<td>1195 (95.7)</td>
<td>260 (94.9)</td>
<td>455 (94.6)</td>
<td>480 (97.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Died</td>
<td>18 (1.4)</td>
<td>11 (4)</td>
<td>3 (0.6)</td>
<td>4 (0.8)</td>
<td>—</td>
</tr>
<tr>
<td>Home health</td>
<td>9 (0.7)</td>
<td>2 (0.7)</td>
<td>5 (1)</td>
<td>2 (0.4)</td>
<td>—</td>
</tr>
<tr>
<td>Short-term care</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>—</td>
</tr>
<tr>
<td>Other care</td>
<td>12 (1)</td>
<td>1 (0.4)</td>
<td>8 (1.7)</td>
<td>3 (0.6)</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>15 (1.2)</td>
<td>0 (0.0)</td>
<td>10 (2.1)</td>
<td>5 (1)</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>3</sup> Data for 2015 include quarter 1 through quarter 3 only because of the ICD-10 conversion.

PEDIATRICS Volume 141, number 4, April 2018
Most Opioids Prescribed for Outpatient General Surgery Procedures Go Unused

72% OF PRESCRIBED PILLS WENT UNUSED

### Leftover Prescription Opioids After Minor Procedures: An Unwitting Source for Accidental Overdose in Children

<table>
<thead>
<tr>
<th>Table. Leftover Opioid Doses and Estimated Days of Treatment Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td><strong>Opioids prescribed</strong></td>
</tr>
<tr>
<td>Hydrocodone/acetaminophen</td>
</tr>
<tr>
<td>Codeine/acetaminophen</td>
</tr>
<tr>
<td>Oxycodone</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td><strong>Procedures</strong></td>
</tr>
<tr>
<td>Tonsillectomy</td>
</tr>
<tr>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Minor abdominal, genitourinary tract, or peripheral procedures</td>
</tr>
</tbody>
</table>
Leftover Prescription Opioids

Guidelines:

- Medication Disposal
Non-medical use of prescription opioids

- ~10% of high school seniors
- Own prescription—40%
- Prescribed for 22% of visits among adolescents with back pain
- FDA labeling for oxycodone now extended to 11 years—but mostly for cancer pain
- No recommendations by CDC included for patients <18 years old
Persistent Opioid Use Among Pediatric Patients After Surgery

Calista M. Harbaugh, MD, a Jay S. Lee, MD, a Hsou Mei Hu, PhD, b Sean Esteban McCabe, PhD, c Terri Voepel-Lewis, PhD, RN, d Michael J. Englesbe, MD, e Chad M. Brummett, MD, d Jennifer F. Waljee, MD, MPH, MS f

- 88,637 patients age 13 to 21
- Opioid naïve
- Common surgical procedures
- Prolonged opioid refill after surgery as proxy for persistent opioid use
- Compared to random sample of non-surgical patients
- One or more additional opioid prescriptions filled between 90 and 180 days after the procedure

Pediatrics. 2018; 141(1):e20172439
Prolonged Opioid Refills

![Graph showing frequency of prolonged opioid refills after surgery for various procedures](image)

Pediatrics. 2018; 141(1):e20172439
Adolescent context of exposure to prescription opioids and substance use disorder symptoms at age 35: a national longitudinal study

Association of the context of prescription opioid exposure with the risk of nonmedical use (NMUPO) at age 35

Main outcome measures: past-year NMUPO and substance use disorder symptoms

Data from Monitoring the Future study

17,000 US high school seniors

Surveys mailed every 5 years

PAIN 157 (2016) 2173–2178
<table>
<thead>
<tr>
<th>Baseline context of lifetime prescription opioid exposure at age 18</th>
<th>Past-year nonmedical use of prescription opioids at age 35, %</th>
<th>Alcohol use disorder symptoms at age 35, 2+ symptoms %</th>
<th>Marijuana use disorder symptoms at age 35, 2+ symptoms %</th>
<th>Other drug use disorder symptoms at age 35, 2+ symptoms %</th>
<th>Any substance use disorder symptoms at age 35, 2+ symptoms, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medical or nonmedical use (n = 3014)</td>
<td>2.4</td>
<td>24.6</td>
<td>4.9</td>
<td>2.7</td>
<td>25.7</td>
</tr>
<tr>
<td>Medical use only (n = 527)</td>
<td>4.4</td>
<td>26.2</td>
<td>5.1</td>
<td>3.4</td>
<td>28.7</td>
</tr>
<tr>
<td>Medical and nonmedical use (n = 207)</td>
<td>8.4</td>
<td>31.8</td>
<td>6.9</td>
<td>8.9</td>
<td>35.3</td>
</tr>
<tr>
<td>Nonmedical use only (n = 116)</td>
<td>5.8</td>
<td>44.7</td>
<td>14.8</td>
<td>13.0</td>
<td>52.8</td>
</tr>
<tr>
<td>Sample size*</td>
<td>n = 3576*</td>
<td>n = 3768*</td>
<td>n = 3817*</td>
<td>n = 3631*</td>
<td>n = 3549*</td>
</tr>
</tbody>
</table>

* Sample sizes vary due to missing data on the dependent measures (i.e., substance use disorder symptoms at age 35).
Are adolescents more vulnerable?

- Balance of rewarding vs aversive effects
- Adolescents consistently less sensitive to withdrawal effects
- Adolescents **NOT** consistently more sensitive to reinforcing or locomotor effects of drugs
- Differences in neuronal structure and function in brain areas related to reward and habit formation
- Correlation does not imply causation
EPA Disposal Recommendations

- First choice: drug take-back events
- Second choice:
  1. remove prescription drugs from original container
  2. mix drugs with undesirable substance (cat litter, coffee grounds)
  3. put mixture into tub with lid or sealable bag
  4. conceal or remove any personal information on empty container
  5. place in trash

Drug Disposal Guidelines, Office of National Drug Control Policy, October 2009
DEA Disposal Recommendations

- Take-back events
- Mail-back programs
- Collection receptacle locations
- No specific standards for destruction

Federal Register/Vol. 79, No. 174/Tuesday, September 9, 2014/Rules and Regulations
Walmart Disposal

01 Open vial

02 Add warm tap water until vial is 2/3 full

03 Add DisposeRX Powder & shake for ~30 seconds, contents solidifies in <10 min.
2.4 million Americans have an opioid-use disorder

$78.5 billion in 2013

Value of a statistical life

<table>
<thead>
<tr>
<th>VSL Assumption</th>
<th>Fatality Costs</th>
<th>Non-fatality Costs</th>
<th>Total Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-dependent</td>
<td>$431.7 billion</td>
<td>$72.3 billion</td>
<td>$504.0 billion</td>
</tr>
<tr>
<td>Low</td>
<td>$221.6 billion</td>
<td>$72.3 billion</td>
<td>$293.9 billion</td>
</tr>
<tr>
<td>Middle</td>
<td>$393.9 billion</td>
<td>$72.3 billion</td>
<td>$466.2 billion</td>
</tr>
<tr>
<td>High</td>
<td>$549.8 billion</td>
<td>$72.3 billion</td>
<td>$622.1 billion</td>
</tr>
</tbody>
</table>

The Council of Economic Advisers. The Underestimated Cost of the Opioid Crisis, November 2017
Michigan Legislation

- Public Act 247: Requires prescribers to have a bona fide relationship with the patient receiving a schedule II-V controlled substance (CS)
- Public Act 248: Mandatory checking of MAPS prior to writing more than 3 days of a DEA schedule II-V CS
- Public Act 246: Parental Consent for Opioid Prescription
- Public Act 251: Prescribing Limits for Opioids
- Passed 89-21, signed by Governor Snyder 12/2017
Legislation Specific to Pediatrics

- Must discuss with minor or minor’s parent
  - Risks of addiction and overdose
  - Increased risk with mental and substance abuse disorders
  - Danger of taking an opioid with a CNS depressant
- Does not apply if associated with surgery
- Does not apply to emergency situations
- Minor defined as anyone <18 years old
- Must be signed by minor or their guardian
Prescribing Trends

Narcotic Analgesic Dispensed Volume in Morphine Milligram Equivalents (MME) Bn


Chart notes: Prescription counts are adjusted for length of prescriptions and re-aggregated. Prescriptions referred to as 90-day are calculated based on transactions with 84 days supply or more to include medicines with up to one week fewer treatment days. Prescriptions for 84 days supply or more or factored by three, and those under 84 days unchanged.

Report: Medicine Use and Spending in the U.S.: A Review of 2017 and Outlook to 2022, Apr 2018
More research needed for impact of in utero exposure

Changing management strategies for treatment of neonatal abstinence syndrome

Better-aligned prescribing practices to decrease potential opioid exposures in young children

Increased awareness of impact on adolescent population

Changes to opioid legislation
Bittersweet Side Effect

Organ Donors Who Died From Drug Overdoses (U.S.)

Data: United Network for Organ Sharing; Lindsey Cook for USN&WR