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## Abstract

As the opioid epidemic continues to grow throughout the country, so too does the impact on children in all stages of development. Whether due to actual opioid exposure, drug endangerment due to unstable home environs, or adolescent addiction, the effects are pervasive throughout the life of an affected child. As pediatricians we need to be aware of opioid-related hazards in a child's environment to identify and mitigate risk.

## Introduction

Few issues in healthcare have gained as much attention in recent years as the opioid epidemic. What once seemed confined to specific populations and geographic locales has become widespread, as has the popularity of both prescription and illicit opioids. To worsen matters, the illicit drug supply has become more dangerous than ever as fentanyl and fentanyl analogues have become a dominant presence, causing death rates to skyrocket. An oft-overlooked facet of the epidemic is the impact on the nation's young people. This ripples through all aspects of care provided to children, including stresses on the foster care system (As cited in the NYT "Young Victims of the Opioid Epidemic" (January 16, 2017)). It is estimated that up to 2/3 of children currently in foster care have some contribution of opioid addiction to their circumstances.

A child can be impacted by opioids (or any drugs of abuse) all along the course of development. Opioid use disorder has not spared the pregnant population, and the effects of opioid exposure in utero begin in the neonatal period with a ballooning incidence of neonatal abstinence syndrome. Children under 6 are the prime age for poisoning exposures in general, and opioids are increasing annually as a cause of serious poison exposures. All throughout development, a child may be "drug-endangered"—a concept used to describe children living in homes where drug abuse, manufacture, and distribution can imperil their basic needs for care and safety. Lastly, the impact in adolescence ranges from the mental health consequences of severe stress in childhood, to addiction of the teen themselves.

## Prenatal exposure, neonatal consequences

According to the National Institutes on Drug Abuse,<sup>1</sup> a baby is born suffering from opioid withdrawal every 15 minutes. The Centers for Disease Control estimate a 433% increase in Neonatal Abstinence Syndrome (NAS) since 2000.<sup>2</sup> Although this has not surprisingly risen in parallel with the incidence of opioid prescribing, abuse and overdose in the adult population, many important questions arise.

A pregnant woman may encounter opioids either as treatment for a painful condition, or in the context of opioid use disorder (the umbrella term used to encapsulate terms such as abuse, misuse, and addiction). Opioid agents cross the placenta into the fetal circulation, due to the same lipophilic characteristics that allow them to cross the blood-brain barrier and confer central nervous system effects. The longer the in utero exposure, and the higher the overall opioid dose, the more likely a newborn infant is to develop the neonatal abstinence syndrome.

Opioids cross the placenta easily via passive diffusion, exposing the fetus for the same length of time as the mother is exposed. High amounts of opioid usage in the mother, regardless of opioid agent, create a withdrawal syndrome which is distinct from opioid withdrawal outside the neonatal period. In contrast to the classic symptoms of withdrawal (vomiting, diarrhea, flu-like illness, yawning, piloerection), the neonatal abstinence syndrome is characterized by extreme irritability, tremor, myoclonus, muscle rigidity, hypertonia, and seizures in up to 10% of patients.<sup>3,4</sup> Recognition and treatment is essential to avoid morbidity and mortality, and the course may be complicated by polysubstance dependence.

The time of onset and duration of symptoms varies depending on the particular opioid in question. Newborns with heroin-associated neonatal abstinence syndrome will generally manifest some symptoms within 48 hours. In contrast, a methadone-exposed newborn may not develop symptoms until 72 hours after delivery. Initial symptoms of NAS may be mild, which is why newborns at risk for NAS are generally observed for a period of up to 5 days before discharge, if asymptomatic. The time of onset and duration of illness generally follows the pharmacokinetic profile of the opioid involved: heroin has a short half-life of elimination and duration of effect (8-10 days), whereas methadone is specifically prescribed to exploit its long duration of action with a concomitant length of illness up to 30 days. Agents such as buprenorphine and oxycodone are intermediate in time of onset to NAS. Table 1 (on the following page) summarizes the most common opioid exposures and characteristics of NAS.<sup>3</sup>

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**Table 1. Characteristics of NAS according to maternal opioid exposure (Adapted in part from Kocherlakota P, Neonatal Abstinence Syndrome. *Pediatrics* 2014; 134:e547-61.)**

Drug	Onset, h	Duration, d
Heroin	24–48	8–10
Methadone	48–72	Up to 30 or more
Buprenorphine	36–60	Up to 28 or more
Prescription opioids	36–72	10–30

Treatment of NAS involves recognition, usually via a standardized measurement tool such as the Finnegan scoring system. Milder cases can be managed non-pharmacologically with methods such as rooming in, quiet environments, skin-to-skin contact, massage, high-calorie supplementation, and encouragement of breastfeeding. Infants with more severe NAS require opioid replacement therapy with morphine, buprenorphine, or methadone. Practice patterns vary. Recent data suggests buprenorphine is associated with a shorter length of stay and duration of NAS symptoms compared to morphine pharmacotherapy.<sup>5</sup>

Talking to expectant mothers about the risks of maternal opioid abuse is essential prior to delivery. Adopting a non-punitive interviewing style to obtain necessary information may ameliorate risk by modifying behavior. In some states, mothers may fear divulging opioid abuse for fear of incarceration. Fortunately, New Jersey law does not regard opioid use disorder in pregnancy as a criminal offense, which can certainly contribute to adverse neonatal outcomes for a wealth of reasons.

## Opioid Poisoning Exposures

As the child progresses out of the neonatal period into toddlerhood, the risk of self-poisoning with medications in the home environment emerges. The circumstance by which a young child obtains a toxic substance in the home is by no means unique to opioids. Sometimes referred to as “unintentional” or “accidental”, the preferred term for this injury model is *exploratory*, which reflects the child’s curious intent to ingest a given substance, without knowledge of the toxic effect. Exploratory exposures, which demonstrated a decreased incidence and severity in the 1990’s, have shown a more concerning trend in recent years as opioids are responsible in more and more of these cases.<sup>6</sup>

It is estimated that Poison Control Centers manage a case of pediatric opioid poisoning at least 32 times daily.<sup>7</sup> This has risen in concert with opioid prescribing patterns, particularly in the 1-5 year age group most susceptible to exploratory exposure. In almost all cases, the opioid agent with which the child becomes poisoned belongs to an adult in the home: a parent, grandparent, or other caregiver.<sup>8</sup> Fatalities are reported annually from pediatric prescription opioid poisoning, often with a delay to seeking care on the part of caregivers.<sup>9</sup>

While any prescription opioid can certainly qualify for the “One Pill Can Kill” description, the severity of poisoning worsens considerably when a child ingests methadone.<sup>9</sup> This effect is also seen with buprenorphine,<sup>10</sup> highlighting the fact that parents undergoing addiction treatment warrant targeted counseling about the hazards of opioids to young children in the home. In one survey of patients in addiction treatment, only 40% of participants reported knowing that opioids were dangerous to children.<sup>11</sup> Buprenorphine and methadone are the two opioids currently used in the treatment of opioid use disorder, in what some refer to as Medication Assisted Therapy. This moniker will likely fall into disuse as it implies that medication for opioid addiction is merely adjunctive, whereas research demonstrates it to be essential.

Methadone is a unique hazard due to formulation and dispensing methods. It is dispensed in methadone treatment centers as a colored liquid and is stored in the refrigerator. Concentrations vary but can be as high as 10mg/mL. Although methadone is not typically prescribed in children, a therapeutic dose in a 10-kg child would be approximately 2mg. It is not difficult to imagine, then, how a potent yet enticing liquid medication, in an unlocked refrigerator, can fall into the hands of a toddler with tragic result.

Buprenorphine is safer by comparison, but still causes serious and fatal pediatric poisonings annually. While buprenorphine has been a truly lifesaving addition to the armamentarium of opioid use disorder treatment, and has been associated with a decline in prescription opioid deaths in other countries after its introduction,<sup>12</sup> the oft-touted ceiling effect seen in adults is not true in children. Adult patients are much less likely to experience respiratory depression from buprenorphine than other opioids, due to its partial agonism at the mu opioid receptor causing a plateau at high doses. However, fatal respiratory depression in children has been reported several times. Even in controlled anesthesia studies comparing equianalgesic doses of morphine and buprenorphine, respiratory depression was more pronounced in children receiving buprenorphine for pain (a very uncommon indication).<sup>13</sup> The development of an individually-wrapped sublingual film alternative to tablets may provide some preventative effect, although some patients may use only part of the film in one dose, leaving the remainder opened and accessible.



It is clear that education of parents with opioids in the home is essential and, in many cases, overdue. Opioid medications certainly qualify for the “one pill can kill” category in young children, with methadone at the top of the list. Containers with a 2-mechanism child-resistant closure, such as lock boxes and locked medication pouches, can confer some degree of protection. Caregivers should be instructed never to transfer medications, particularly liquid medications, out of the original container. Adults who obtain opioids through illicit diversion may store them in unsecured locations, such as handbags, mint or cigarette containers, and tissues. We must talk to parents about how to keep their children safe from opioids in the home, regardless of how they were obtained. Table 2 summarizes key messages in anticipatory guidance for safe opioid storage.

**Table 2. Safe Storage of Opioids: Targets for Anticipatory Guidance**

Never transfer a medication, particularly liquid, outside of its original container. Children are easily attracted to medications in beverage bottles, for example.
Medications obtained via illicit means are more likely to be stored in an unsafe place.
Liquid methadone is particularly hazardous, due to its palatable appearance and storage in the refrigerator.
Lock boxes and locked pouches for high-risk medications such as buprenorphine, oxycodone, methadone.
If you suspect a child has ingested an opioid medication, contact Poison Control immediately.

## The Drug-Endangered Child

A concept historically espoused to capture the plight of children living in illicit methamphetamine labs, the idea of drug-endangerment has expanded to include all children living in environments where there is drug abuse, misuse, manufacture, or distribution. Here unique hazards arise. Chemicals used to synthesize drugs pose a dangerous poisoning risk – for example, highly concentrated acids in methamphetamine exposure and powdered fentanyl analogues in illicit “pill mills”. Drug paraphernalia such as needles and pipes bring the spectre of infectious disease and burn hazards. Unsanitary conditions with decreased resources can mean a child lives in a house where waste, vermin, insects and clutter abound. Food insecurity and homelessness are additional challenges. Traffic through the home environment of “customers” or other persons with drug abuse increases the potential for child abuse and human trafficking. And having a parent or caregiver in the clutches of drug addiction too often means a child does not get the care they need.<sup>14</sup> The media is full of heartbreaking stories of children found with unconscious caregivers.

Children living in drug-endangered homes are three times more likely to undergo physical, emotional, or sexual abuse, and four times more likely to suffer neglect. This is more pronounced in the neonatal period, where the intersection of the mother’s recovery from delivery, substance use disorder, and sleep deprivation combine with the near-constant needs of a newborn baby.<sup>14</sup> Resources for recognition and assistance with these challenges are essential, including agencies such as the National Alliance for Drug Endangered Children ([www.nationaldec.org](http://www.nationaldec.org))

## Adolescents and Opioids

The seemingly chaotic period of adolescence creates a uniquely fertile ground for opioid misuse, abuse, and addiction to take hold. Developmentally, adolescents are risk-takers, seeking increasingly more stimulating and rewarding activities as they age. This has been attributed by many to the relative over-activity of the dopamine-rich limbic system, making what feels good to the average person, feel really good, and perhaps irresistible, to an adolescent. This of course does not only include opioids, but other risky, stimulating behaviors like other drug use, alcohol use, sexual behaviors, dangerous driving, and a variety of online activities including pornography.

In addition, the areas of the brain most responsible for judgement—the “brakes” in this operation—do not fully develop until the early 20s. The prefrontal cortex is vital to weighing in on whether something *should* be done, but is critically underdeveloped in adolescents. The perfect storm for drug abuse ensues. The average age of onset of addiction is 19 years old,<sup>15</sup> driving home the fact that addiction is a pediatric disease.

Adolescents prescribed opioids may be at increased risk, although multiple studies suggest teens obtain opioids through a variety of avenues, including accessing the leftover prescription medications within their home.<sup>16</sup> This emphasizes the importance of getting opioids out of the home, and talking to parents about drug take-back opportunities. While designated “Drug Take-Back” Days are scheduled throughout the year, this does not require a special occasion. Leftover prescription medications can be disposed of throughout the year at police stations or even flushed down the toilet, in small quantities. Getting that spare oxycodone out of the house keeps it out of the hands of teens.

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We do have to take a hard look at prescribing as well. In a potent campaign “Would you give him heroin?” (Partnership for a Drug-Free New Jersey, [drugfreenj.org](http://drugfreenj.org)) emphasized the need to reduce opioid prescriptions, and parental expectations of them, in the context of an acute sports injury. The adolescent athlete faces a multifaceted challenge in this regard: the pressure to play despite injury, the pattern of repeated injuries and cumulative prescriptions, and the potential for ‘sharing’ of opioids with teammates both for analgesic and recreational purposes. We must be vigilant when prescribing opioids in this scenario, especially where non-opioid analgesics have equal effectiveness.

We also must improve on access to care in these teens. It is estimated that fewer than 5% of active buprenorphine-waivered prescribers care for patients under the age of 18. In a time where addiction services to the general population are in critical shortage, adolescents are truly unable to find care. We must increase our number and advocate to remove obstacles such as the buprenorphine waiver and insurance pre-authorization requirements.<sup>17</sup>

## Conclusion

As pervasive as the opioid epidemic is in our society, so are the implications throughout a child’s development from conception through adulthood. As pediatricians we are poised to make a difference in intercepting these risks through knowledge, education, and intervention.

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**CME Quiz on page 10**

# CME Quiz

1. A child's curious intent to ingest a given substance without knowledge of its toxic effect is preferably termed as exploratory.  
a. True      b. False
2. The "One Pill Can Kill" concept applies to which of the following:  
a. Methadone  
b. Buprenorphine  
c. Both Methadone and Buprenorphine  
d. Any prescription opioid
3. Which of the following statements is not true?  
a. Drug-endangerment includes all children living in environment where there is drug abuse, misuse, manufacture, or distribution.  
b. Children residing in drug-endangered homes are three times more likely to undergo sexual, physical, or emotional abuse.  
c. There is a surplus of addiction services, where adolescents are truly able to find care.  
d. The average age of onset of addiction is 19 years old.
4. According to the Centers for Disease Control, what is the percentage of increase in Neonatal Abstinence Syndrome (NAS) since 2000?  
a. 100%      c. 200%  
b. 150%      d. 433%
5. A case of pediatric opioid poisoning is managed at the Poison Control Center at least \_\_\_\_\_ times daily. (Fill in the blank).  
a. 28      c. 32  
b. 30      d. 35
6. The \_\_\_\_\_ year age group is most susceptible to exploratory exposure. (Fill in the blank.)  
a. 1-5      c. 12-17  
b. 6-11      d. 18 and over
7. Fatalities are reported annually from pediatric prescription opioid poisoning, often associated with a delay to seeking care on the part of caregivers.  
a. True      b. False
8. A reduction of fatalities from pediatric prescription opioid poisoning requires:  
a. Education about safe opioid storage  
b. Getting opioids out of the home (e.g., Drug Take-Back opportunities)  
c. Counseling parents undergoing addiction treatment about the hazards of opioids to young children in the home.  
d. All of the above
9. As compared to buprenorphine, respiratory depression was more pronounced in children receiving morphine for pain.  
a. True      b. False
10. The term drug-endangered refers to:  
a. Opioid exposure in utero  
b. Children under 6 – the prime age for poisoning exposures  
c. Children living in homes where drug abuse, manufacture, and distribution can imperil their basic needs for care and safety.  
d. Neonatal abstinence syndrome

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