Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

Neonatal Opioid Withdrawal Syndrome (NOWS): A Transgenerational Echo of the Opioid Crisis

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The incidence of neonatal opioid withdrawal syndrome (NOWS) has increased substantially in the setting of the opioid epidemic, a major public health problem in the United States. At present, NOWS has commonly used assessment and treatment protocols, but new protocols have questioned old practices. However, because of limited access to opioid use disorder (OUD) treatment and socioeconomic factors, many pregnant (and postpartum) women with OUD do not receive treatment. The pathophysiology of NOWS is not completely understood, although limited research studies have been conducted in humans and animals to better understand its etiology. Moreover, there is evidence that epigenetic and genetic factors play a role in the development of NOWS, but further study is needed. Animal models have suggested that there are deleterious effects of *in utero* opioid exposure later in life. Clinical research has revealed the harmful long-term sequelae of NOWS, with respect to cognitive function and childhood development. Many psychiatric disorders begin during adolescence, so as infants born with NOWS approach adolescence, additional clinical and molecular studies are warranted to identify biologic and psychosocial risk factors and long-term effects of NOWS. Additionally, access to specialized OUD treatment for pregnant women must be more readily available in the United States, especially in rural areas.

The opioid epidemic has developed into an overwhelming public health issue over the past three decades. One major contributing factor to the opioid epidemic over the past 25 years is the common use of prescription opioids (POs) to treat chronic, nonprogressive musculoskeletal pain (Brady et al. 2016). Approximately 80% of new heroin users engaged in illicit opioid use after the use of POs (Jones 2013; Muhuri et al. 2013; Compton et al. 2016). From 1999 to 2016, a total of 231,264 men and 120,366 women died from opioid-related causes across the entire United States (Kiang et al. 2019). The current opioid epidemic is notable for its appearance in rural areas, placing pressure on nonurban legal and medical systems, which have inadequate resources to deal with large numbers of opioid use disorder (OUD) patients (U.S. Department of Health and Human Services [HHS], Office of the Surgeon General 2018). Current trends

Editors: R. Christopher Pierce, Ellen M. Unterwald, and Paul J. Kenny
Additional Perspectives on Addiction available at www.perspectivesinmedicine.org

 doi: 10.1101/cshperspect.a039669
Cite this article as *Cold Spring Harb Perspect Med* 2021;11:a039669

show that the situation is becoming more deadly: opioid overdose deaths increased 30% from July 2016 to September 2017 in 52 jurisdictions across 45 states (Vivolo-Kantor et al. 2018).

The current opioid epidemic has resulted in a similarly large increase of pregnant women using opioids, which has led to an epidemic of newborns with neonatal opioid withdrawal syndrome (NOWS) (Winkelman et al. 2018). NOWS is a condition seen among infants born to mothers who have used opioids during the course of their pregnancy; it occurs because opioids readily cross the placenta causing the fetus to become dependent on opioids (Griffiths and Campbell 2014). The term NOWS is often used interchangeably with the more established term, neonatal abstinence syndrome (NAS). More recently, the term NOWS has been used to refer to infants born to opioid-using mothers, whereas NAS has been used by some professionals to refer to infants born to mothers with polysubstance use (Sutter et al. 2014; McQueen and Murphy-Oikonen 2016; MacMullen and Samson 2018).

From 2004 to 2014, the incidence of NOWS increased 433% in the United States from 1.5 to 8.0 per 1000 hospital births (Jilani et al. 2019). In 299 neonatal intensive care units (NICUs) across the United States from 2004 to 2013, the rate for NICU admission for NOWS increased from seven cases per 1000 admissions to 27 cases per 1000 admissions, and the median length of stay for NICU admissions increased from 13 days to 19 days, largely because of NOWS infants (Tolia et al. 2015). Furthermore, the percentage of NICU days as a result of NOWS increased from 0.6% to 4.0% during this period (Tolia et al. 2015). One retrospective cohort study at a single medical center showed that 5.6% of the 177 infants born to women who used POs for ≥1 month during their pregnancy developed clinical signs of withdrawal consistent with NOWS (Kellogg et al. 2011). There is an association between increased NOWS incidence and geographical areas with higher long-term unemployment and with a shortage of mental health clinicians, typical of many rural areas of the United States (Patrick et al. 2019).

The severity of the NOWS epidemic in rural areas of the United States has been demonstrated by data at Geisinger, an integrated health care system covering a rural area in northeastern and central Pennsylvania. Geisinger uses the Epic electronic health record (EHR) system. Per Epic records at Geisinger, from January 1, 2016 to August 31, 2018, there were 672 pregnant women who had an OUD diagnosis. *This represents 5% of all women who were pregnant and delivered during this 30-month period* (K Moran, pers. comm., May 16, 2019). Seven percent of pregnant women received an opioid prescription during their pregnancy. However, only 72% of opioid-exposed infants were born to mothers carrying a diagnosis of OUD (K Moran, pers. comm., May 16, 2019). This last statistic suggests that not all of the mothers with OUD are being identified during pregnancy. A routine urine drug screen is not part of prenatal care at Geisinger, nor is it recommended by the American College of Obstetricians and Gynecologists (ACOG). Among this cohort of 672 pregnant women with OUD, only 14% of women with OUD received medication-assisted treatment (MAT) during pregnancy. Only 45% of women with OUD attend their postpartum appointment within the Geisinger health system, compared to 72% of women without OUD (K Moran, pers. comm., May 16, 2019). More must be done to identify mothers with OUD and engage them to seek treatment both for themselves and for their infants.

CLINICAL PRESENTATION

NOWS is a heterogeneous condition that consists of central nervous system hyperactivity, autonomic nervous system dysfunction, and gastrointestinal problems, with symptoms typically beginning within 24–72 h after birth (Table 1; Sutter et al. 2014; Kraft et al. 2016). Seizures are seen in 2%–11% of newborns with NOWS (Kocherlakota 2014). NOWS infants are often born prematurely, and have smaller head circumferences, even when adjusted for gestational age (McQueen and Murphy-Oikonen 2016).

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Table 1. Acute neonatal opioid withdrawal syndrome (NOWS) symptoms in infants

Symptoms[a]
High-pitched cry
Irritability
Difficulty sleeping
Increased muscle tone
Tremors
Skin excoriation (due to excessive movement)
Hyperthermia
Loose stools
Yawning
Sweating
Nasal stuffiness
Sneezing

[a]Data adapted from Kraft et al. (2016).

ASSESSMENT AND DIAGNOSIS

NOWS is a clinical diagnosis (ICD10 code: P96.1) and is defined by common signs of opioid withdrawal (Kraft et al. 2016). The diagnosis is based on a history of opioid exposure *in utero* of the fetus and symptoms in the neonate consistent with opioid withdrawal. The clinical landscape is frequently complicated by the mother's polysubstance use (Abdel-Latif et al. 2013).

Several clinical instruments are available to assess the severity of NOWS in infants and are used to guide pharmacotherapy. The most commonly used screening instrument in clinical settings is the Finnegan Neonatal Abstinence Scoring System (Finnegan et al. 1975; Hudak and Tan 2012). However, a limitation of the Finnegan scoring system is its length and complexity (McQueen and Murphy-Oikonen 2016). The Lipsitz Neonatal Drug Withdrawal Scoring System is another commonly used screening assessment (Lipsitz 1975). Scoring for the Lipsitz tool is simple and practical to use (McQueen and Murphy-Oikonen 2016). The Neonatal Withdrawal Inventory is an alternative screening instrument that was designed for speed and ease of administration (Zahorodny et al. 1998). At this time, there is no evidence that any assessment tool is superior to another (Jansson 2019).

One new method used in the assessment and management of infants with NOWS is the Eat, Sleep, Console (ESC) approach (Grossman et al. 2018). According to this protocol, an infant is evaluated by the ability to eat at least 1 oz at a feeding, sleep at least 1 h uninterrupted, and when crying, be consoled within 10 min by a caregiver (Grossman et al. 2018). Nonpharmacologic interventions are then used as first-line treatment before administering doses of opioids. This approach was devised to reduce the amount of opioids required by infants for NOWS management and to shorten hospitalizations for NOWS infants. Studies have shown that the ESC approach is a promising intervention for the management of NOWS infants (Achilles and Castaneda-Lovato 2019; Blount et al. 2019; Dodds et al. 2019; Grisham et al. 2019; Parlaman et al. 2019). It is unclear whether there is sufficient evidence to recommend the ESC approach as part of standard-of-care.

TREATMENT

Rooming-in of the NOWS infant with the mother in the mother's hospital room has been found to reduce NOWS severity (MacMillan et al. 2018). Small, frequent feedings should be given to the infant. Although methadone and buprenorphine are secreted in breast milk from mothers receiving those medications, MAT is not a contraindication for breastfeeding (Pritham 2013; Sutter et al. 2014). In fact, breastfeeding can decrease the severity of NOWS symptoms in infants born to these mothers (Malpas et al. 1997; Abdel-Latif et al. 2006; Pritham et al. 2012; Pritham 2013; Welle-Strand et al. 2013; Kocherlakota 2014). The mother should be supported to attend to the infant and be given patient education as needed (Jansson 2019).

Pharmacologic management is also an important component in the treatment of NOWS. At present, opioid replacement therapy with oral morphine or methadone is generally the first-line treatment (Hudak and Tan 2012; Jansson 2019). Morphine is a short-acting full μ opioid receptor agonist, whereas methadone is a long-acting full μ opioid receptor agonist. Buprenorphine, a partial μ opioid receptor agonist, is a newer agent and has less evidence supporting its usage. However, some studies suggest that buprenorphine may be associated with a shorter

duration of medication therapy compared to morphine and methadone for infants with NOWS (Jones et al. 2008, 2010; Hall et al. 2016; Kraft et al. 2017).

Second-line medications are used in infants with NOWS who have symptoms that are not controlled by a first-line agent. Clonidine and phenobarbital are second-line agents, which are generally used as adjunctive treatments to opioid replacement therapy, but are occasionally used as single agents (Hudak and Tan 2012; Jansson 2019). Data are limited regarding the efficacy of clonidine and phenobarbital in NOWS (Hudak and Tan 2012; Jansson 2019). Naloxone, an opioid receptor antagonist, has been used in the resuscitation of nonresponsive newborns or newborns with cardiorespiratory depression born to mothers with OUD (Moe-Byrne et al. 2018). However, naloxone must be used with caution as it could precipitate severe opioid withdrawal symptoms in the infant (Gibbs et al. 1989; Moe-Byrne et al. 2018).

Once the newborn shows no major signs of withdrawal, has stable scores using assessment tools, and is feeding well, the infant can be discharged from the hospital (Kocherlakota 2014). A multidisciplinary approach, including an assessment of maternal functioning and mental health, ongoing OUD treatment (including comorbidities) of the mother and an assessment of the home and support systems should be implemented (Jansson 2019). Regular pediatric follow-up is essential and parents must be educated on how and when to seek care. Infants with NOWS, as they develop, should be assessed for growth and behavioral milestones to identify failure to thrive. Neurodevelopmental assessments are necessary to identify cognitive and motor deficits. Psychological and behavioral assessments are indicated to identify any learning difficulties or attention-deficit/hyperactivity disorder (ADHD) symptoms when they enter school (Kocherlakota 2014). Social services may be required to assist those families affected by poverty (including housing and food instabilities), addictions, and other psychiatric conditions and domestic violence.

Treatment of pregnant women diagnosed with OUD with MAT, using methadone or buprenorphine, is currently recommended by the World Health Organization (WHO Guidelines Approved by the Guidelines Review Committee, 2014). However, there are few studies regarding the effects of MAT on neonatal outcomes at birth. One recent observational cohort study conducted in Norway and the Czech Republic compared the infants of mothers with OUD treated with buprenorphine or methadone to infants of mothers with OUD receiving no MAT, and found that treatment with MAT did not associate with worse outcomes at birth (Handal et al. 2019). Naltrexone, a full μ opioid receptor antagonist, is a common treatment for OUD among nonpregnant individuals but is not commonly used in the treatment of pregnant women. Its use in the treatment of pregnant women could result in a decrease in the incidence of NOWS infants born to these mothers, as the discontinuation of naltrexone is not associated with any known withdrawal syndrome. However, there is limited evidence for the use of naltrexone in pregnant women, so safety and efficacy are not well established. A retrospective cohort study that compared neonates exposed to naltrexone ($n = 68$) to those exposed to methadone ($n = 199$) and buprenorphine ($n = 214$) *in utero* found that naltrexone-exposed infants did not exhibit a higher rate of negative birth outcomes when compared to the buprenorphine and methadone-exposed infants (Kelty and Hulse 2017). Another retrospective cohort study compared mother–infant dyads treated with naltrexone ($n = 6$) and buprenorphine ($n = 13$) (Wachman et al. 2019). Treatment with naltrexone was associated with favorable outcomes. There were no reported cases of NOWS in the naltrexone infants as compared to 92% of the buprenorphine infants (Wachman et al. 2019). Naltrexone-exposed infants also had shorter hospital stays (Wachman et al. 2019). One recent prospective cohort study showed promising data indicating that naltrexone-exposed infants ($n = 121$) had a lower rate of NOWS when compared to a combined group of methadone and buprenorphine-exposed infants ($n = 109$), with fewer NICU admissions and a shorter length of stay in the hospital (Towers et al. 2019). Additional studies with larger sample sizes are necessary

to determine the appropriateness of naltrexone treatment in pregnant women with OUD.

GENETIC SUSCEPTIBILITY

Genetic factors play a role in OUD and its treatment and may play a role in determining which neonates are at risk for NOWS. CYP2B6 is a cytochrome P450 enzyme involved in the metabolism of drugs including methadone. Genetic variants of the *CYP2B6* gene were found to associate with the need of medication treatment for infants with NOWS born to mothers with OUD receiving methadone maintenance therapy (Mactier et al. 2017). Findings from this study suggested that infants carrying genetic variants of *CYP2B6* associated with reduced enzyme function and slower metabolism of methadone were less likely to endure abrupt withdrawal from methadone, and as a result, had less severe NOWS symptoms (Mactier et al. 2017). There is evidence that suggests single-nucleotide polymorphisms (SNPs) in *OPRM1* (the gene encoding the μ opioid receptor), *OPRK1* (the gene encoding the κ opioid receptor), *OPRD1* (the gene encoding the δ opioid receptor), *PNOC* (the gene encoding prepronociceptin, a protein that undergoes processing to produce nociceptin, a neuropeptide involved in pain sensation), and *COMT* (the gene encoding catechol-*O*-methyltransferase, an enzyme involved in the breakdown of the neurotransmitters dopamine, epinephrine, and norepinephrine) associate with NOWS severity (Wachman et al. 2013, 2015, 2017). However, some associations did not survive multiple-testing correction and these findings require replication in studies with larger sample sizes. Variation of the dopamine D2 receptor (*DRD2*) gene was found to associate with the need for NAS treatment in infants exposed to drugs *in utero*. However, three women in the drug-exposed group (n = 48) of the study presented with nonopioid drug exposure. In addition, there was a statistically significant difference in daily maternal methadone dose and in the number of mothers exposed to methadone between the infants who required NAS medication and the infants who did not require NAS medication (Oei et al. 2012). NOWS is likely a polygenic disorder. Additional research must be conducted to determine which genetic variants confer the most risk in the development of NOWS in infants. As EHRs become more common, it may be possible to obtain integrated genetic data with EHR, which will allow for larger sample sizes to be studied to conduct a more sophisticated analysis of such data to better characterize genetic risk for NOWS.

EPIGENETIC FACTORS

Epigenetic changes can occur because of age and environmental factors, and there is evidence that they can be caused by substances of abuse (Maguire et al. 2016). In humans, one study on infants with NOWS found that increased methylation of the *OPRM1* promoter, consistent with epigenetic gene silencing, was associated with worse NOWS outcomes (Wachman et al. 2014, 2018). An observational cohort study compared methadone maintained opioid-dependent mother–infant dyads to mother–infant opioid-naive dyads in which the mother was categorized as a smoker or nonsmoker. This study found that there was increased DNA methylation in DNA collected from buccal swabs of opioid-exposed newborns as compared to opioid-naive infants in three genes related to opioid function: *ABCB1* (a gene that encodes P-glycoprotein, involved in drug transport, whose substrates include morphine and methadone), *CYP2D6* (encoding a cytochrome P450 enzyme involved in the methadone metabolism), and *OPRM1* (McLaughlin et al. 2017).

LONGITUDINAL STUDIES

Long-term follow-up of infants born with NOWS is difficult because of limited retention in treatment and psychosocial stressors as experienced by the children's families. However, some studies show that NOWS affects cognitive, behavioral, and motor development, as well as academic performance (Grossman and Berkwitt 2019).

Case-control studies of early childhood development for fetal intrauterine opioid exposure

have shown cognitive, psychomotor, and behavioral deficits when the case and control groups are carefully matched for socioeconomic status, parental educational achievement, and other relevant factors (for systematic review and meta-analysis, see Baldacchino et al. 2014, 2015). There were significant impairments of cognition, psychomotor performance, and behavioral measures in this cohort among the opioid-exposed infants and children (Baldacchino et al. 2014, 2015). However, a limitation of this meta-analysis pertains to the small sample sizes (<200 participants) of the pooled studies.

Additional studies have shown the adverse long-term effects of fetal opioid exposure later in childhood. One study demonstrated that 3- to 6-year-old children with *in utero* heroin exposure were shorter, weighed less, and had smaller head circumferences than unexposed children matched for age, sex, ethnicity, and socioeconomic status (Wilson et al. 1979; Maguire et al. 2016). These children also scored lower on measures of cognitive function (Wilson et al. 1979). Maternal exposure to opioids during pregnancy is associated with reduced head circumferences and smaller brain volumes of newborn infants on magnetic resonance imaging (MRI) (Yuan et al. 2014), and these reduced brain volumes are still observed in school-aged children (Sirnes et al. 2017). Small head circumference at birth, a reflection of slow brain growth *in utero*, predicted poorer performance on measures of intelligence at 20 years of age according to the Helsinki Birth Cohort Study (Raikkonen et al. 2009; Oei 2019). Children 5–12 years of age born to heroin-dependent mothers, whether they were raised at home by their mothers or they were adopted by another family, showed lower performance IQ scores on the Wechsler Intelligence Scale for Children—Revised (WISC-R) compared to controls (Ornoy et al. 2001; Maguire et al. 2016). Children of methadone-maintained mothers followed for the first 18 months of age scored significantly lower on the Bayley Scales of Infant Development, an indicator of developmental delay (Rosen and Johnson 1982). A linked analysis of Australian children reported that those born with NOWS had lower scores on the National Assessment Program—Literacy and Numeracy (NAPLAN) standardized test starting in grade 3 as compared to age-matched controls. This difference in performance progressively worsened through grade 7 (Oei et al. 2017).

An Australian cohort study following birth, hospitalization, and death records for all children born in New South Wales between 2000 and 2011 to a maximum of 13 years of age found that children with a history of NOWS were significantly more likely to be hospitalized for "mental and behavioral disorders" when compared to children born without a NOWS diagnosis (Uebel et al. 2015; Oei 2019). This includes speech/language disorders, autism, and behavioral and emotional disorders including ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD) (Uebel et al. 2015; Oei 2019). The reason for increased risk of development of psychiatric disorders is unclear but social stressors (especially poverty), as well as the effect of opioids on the developing brain, likely play a role (Uebel et al. 2015; Oei 2019). Furthermore, there is evidence that prenatal exposure to opioids *in utero* affects maturation of cortical tracts in the brain. Higher diffusivity, as measured by diffusion tensor imaging, is correlated with reduced brain maturation and myelination (Walhovd et al. 2012). Higher mean diffusivity was observed in the superior longitudinal fasciculi of infants exposed to methadone *in utero* as compared to controls, indicative of altered development of neural tracts (Walhovd et al. 2012). At this time, longitudinal studies have inconsistent findings on the effects of fetal methadone and buprenorphine exposure on motor development in neonates (Kaltenbach and Finnegan 1987; Sundelin Wahlsten and Sarman 2013; Maguire et al. 2016). Additional research must be done to assess the long-term effects of such exposure on the development of mental disorders later in childhood and adolescence.

There have been few studies on the effects of NOWS on adult outcomes. A study in Spain was conducted in which 30 adult subjects (mean age 22.23 years) born to heroin-addicted mothers were contacted to complete an interview on their psychosocial development, socioeconomic status, and mental health issues (Herranz et al.

2014; Oei 2019). These subjects reported that they experienced a high rate of emotional and physical abuse in childhood (Herranz et al. 2014; Oei 2019). One-third of these subjects were diagnosed with a psychiatric disorder, the most common diagnoses being ADHD and major depressive disorder (MDD) (Herranz et al. 2014; Oei 2019). Social problems were common, with 30% of subjects having been arrested and 36.7% of them being unemployed (Herranz et al. 2014; Oei 2019). There was a high level of substance use in the study sample as compared to rates of substance use in the general population (Herranz et al. 2014; Oei 2019). It is unclear to what extent these issues reflect consequences of NOWS rather than psychosocial and economic factors correlated with maternal drug use.

ANIMAL MODELS

Animal models have been studied to learn more about the long-term effects of *in utero* opioid exposure on behaviors in adulthood (for review, see Byrnes and Vassoler 2018). Such exposure in rats has been shown to influence social and sexual behaviors when the rats reach adulthood (Byrnes and Vassoler 2018) as demonstrated by changes in the timing of vaginal opening in female progeny, which is an assessment of sexual maturation (Litto et al. 1983; Vathy et al. 1983, 1985). Sexual behaviors have also been affected by prenatal opioids with decreased sexual behaviors in females and an increase in sexual behaviors in males (Vathy and Katay 1992). Opioid exposure *in utero* increases pinning behavior in rats, which is a model of social behavior (Hol et al. 1996; Buisman-Pijlman et al. 2009). The presence of opioids *in utero* also shapes learning and memory processes in rats when they become adults, which may be due to the impact of opioids on neuronal activity and *in utero* neurodevelopment (Byrnes and Vassoler 2018). Furthermore, prenatal opioid exposure in rats has also been found to influence the endogenous opioid system in adulthood, including effects of opioid analgesic response and effects on reward (a model of addiction-like behaviors) (Byrnes and Vassoler 2018). Studies conducted on rats show that hyperalgesia and reduced opioid sensitivity are seen in the early postnatal period, whereas increased opioid sensitivity is seen in adulthood (Byrnes and Vassoler 2018). Studies of effects on opioid reward indicate increased behavioral sensitization and conditioned place preference (Byrnes and Vassoler 2018). A recently published study suggests that an SNP in *OPRM1* influences behavioral outcomes in mice with neonatal opioid exposure. In this study, mouse pups were treated with saline or morphine from postnatal days 1–14, which is a developmental period equivalent to the third trimester of pregnancy in humans (Robinson et al. 2019). Mice exposed to morphine during this period showed sex and genotype-specific changes in locomotor sensitization after morphine treatment as adults, a model for opioid sensitivity (Robinson et al. 2019). This study also showed that neonatal opioid exposure in mice resulted genotype-dependent changes in marble-burying behavior, a representation of anxiety (Robinson et al. 2019). In the future, it will be necessary to conduct genome-wide association studies (GWAS) of multiple outbred mice (such as the diversity outcross mice) in animal models of NOWS to determine which genetic variants confer risk for NOWS development. However, studies on animal models of opioid exposure have numerous differences in the timing, route of administration, type, and dose of opioid being used (Byrnes and Vassoler 2018). This can lead to difficulties in drawing firm conclusions about potential human outcomes from the results of animal studies. Therefore, it will also be important to determine if the genetic, epigenetic, and behavioral effects seen in animals also occur in human patients.

GAPS IN KNOWLEDGE

Although there are some data that are present with respect to psychiatric disorders that develop when NOWS infants become adults, replication of these findings is needed. Infants born with NOWS likely have an increased risk of various substance use disorders when they become adults, but there are virtually no data on this currently. Other gaps in knowledge include whether the decreased head circumferences in

infants born with NOWS leads to an increased risk of developing psychiatric or medical conditions later in life. Furthermore, there is no knowledge whether a history of NOWS causes structural abnormalities in the brain in adulthood.

CONCLUSIONS AND RELEVANCE

The infants born with NOWS during the current opioid crisis must be followed through childhood and adolescence to determine the long-term sequelae of opioid exposure *in utero*. Long-term follow-up of infants born with NOWS through adolescence is lacking. This longitudinal perspective is critical because many psychiatric conditions, such as mood disorders, anxiety disorders, psychotic disorders, and substance use disorders, commonly develop during adolescence.

Access to MAT must improve, especially in rural and impoverished areas of the United States. Genetics may play a role in determining which neonates are at risk to develop NOWS. Alleles that might convey risk for NOWS must be further characterized. Animal models may be important in this regard. Pharmacogenetics studies must be conducted to identify biomarkers of response that could be clinically useful in guiding pharmacotherapy for infants with NOWS. With an understanding of the long-term sequelae of *in utero* exposure, appropriate educational and therapeutic programs may be developed to address cognitive, developmental, and psychiatric needs of these individuals, as they progress through childhood to adolescence and young adulthood. Given the large increase in the incidence of NOWS in the past decade, psychiatrists, especially child and adolescent psychiatrists, will be increasingly called upon to evaluate individuals with a history of NOWS. Therefore, they must be well prepared to assess and treat these patients, now and into the future.

ACKNOWLEDGMENTS

The preparation of this manuscript was supported by a Tobacco Settlement Act grant from the Pennsylvania Department of Health (W.H.B. is PI) and NIH Grant No. R01 DA044015 (W.H.B. is MPI). A.E.W. was supported by T32 MH014654 (W.H.B. is PI). R.C.C. was supported by Grant No. K01 DA03 6751. B.C.R. was supported by a 2017 NARSAD Young Investigator Grant (No. 26634) from the Brain and Behavior Research Foundation as the Patrick A. Coffer Investigator, funding for which was generously provided by Ronald and Kathy Chandonais. The authors declare no competing interest. A.E.W., W.H.B., and R.C.C. conceived of the idea of the manuscript. A.E.W. drafted the manuscript. All authors provided critical feedback and revision of the manuscript for important intellectual content.

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