REVIEW ARTICLE

Neonatal opioid withdrawal syndrome: a review of the science and a look toward the use of buprenorphine for affected infants

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Neonates born to mothers taking opioids during pregnancy are at risk for neonatal opioid withdrawal syndrome (NOWS), for which there is no recognized standard approach to care. Nonpharmacologic treatment is typically used as a first-line approach for management, and pharmacologic treatment is added when clinical signs are not responding to nonpharmacologic measures alone. Although morphine and methadone are the most commonly used pharmacotherapies for NOWS, buprenorphine has emerged as a treatment option based on its pharmacologic profile and results from initial single site clinical trials. The objective of this report is to provide an overview of NOWS including a summary of ongoing work in the field and to review the state of the science, knowledge gaps, and practical considerations specific to the use of buprenorphine for the treatment of NOWS as discussed by a panel of experts during a virtual workshop hosted by the National Institutes of Health.

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INTRODUCTION

Opioid use disorders (OUD) and opioid overdose are part of a well documented ongoing public health crisis in the United States that results in considerable morbidity and mortality while imposing a substantial burden on families and communities [1]. In 2016, more than 11.5 million Americans reported misusing prescription opioids in the past year [2]; the self-reported incidence appeared to be decreasing in 2019 prior to the COVID-19 pandemic [3], but it is likely that the social isolation and economic stress from the pandemic will further exacerbate this problem [4]. In 2019, 1 in 5 women who used prescription opioid pain relievers during their pregnancy reported misuse of these medications, defined as receiving opioids from a non-healthcare source or using for a reason other than to relieve pain [5]. Consistent with these trends in prenatal opioid use, the incidence of neonatal abstinence syndrome (NAS) increased almost fivefold between 2004 and 2014 and has continued to escalate nationally to an estimated rate of 7.3 per 1000 neonatal hospitalizations in 2017 [6–8].

Neonates born to mothers with substance use disorders or those who require opioids to manage pain associated with medical conditions (e.g., sickle cell disease) are at risk of withdrawal syndromes. The general term for this is NAS, whereas neonatal opioid withdrawal syndrome (NOWS) refers specifically to withdrawal from opioids, thus representing a subset of NAS. While the pathophysiology of opioid withdrawal triggers similar signs and symptoms in both the mother and neonate, the physical and behavioral manifestations as well as the medical management are signficantly different [9].

Few standard, evidence-based approaches for managing NOWS have been universally adopted, resulting in significant variation in care and a general lack of high-quality data to inform clinical practice.

In August 2020, the National Institutes of Health's (NIH) Helping to End Addiction Long-term (HEAL) Initiative℠ supported a workshop—*Toward the Use of Buprenorphine in Infants: Scientific and Practical Considerations*. The workshop included 219 federal and non-federal experts in maternal-fetal medicine, neonatology, pharmacology, epidemiology, advocacy, management of maternal OUD, and management of NOWS who reviewed the current state of the field, ongoing and upcoming trials, the feasibility of a buprenorphine trial for treatment of NOWS, and next steps. The objective of this report is to provide an overview of NOWS including a summary of current work in the field and to review the state of the science, knowledge gaps, and practical considerations

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specific to the use of buprenorphine for the treatment of NOWS. We propose next steps including an assessment of the short- and long-term safety and efficacy of buprenorphine to treat neonates for NOWS.

CURRENT MANAGEMENT PRACTICES

At present there is no consistent standard approach for the management of NOWS. The Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) Collaborative, as part of the National Institutes of Health (NIH)HEAL Initiative℠, was developed to inform evidence-based practice for the clinical care of neonates with NOWS through the development and conduct of high impact research. The ACT NOW Clinical Practice Survey, a cross-sectional survey of medical centers that care for neonates with NOWS, conducted in 2017 as part of this initiative, demonstrated that a majority of centers have protocols that include the use of assessment/scoring systems, nonpharmacologic care, and pharmacologic treatment(s) [10]. However, patient-level data collected as part of the ACT NOW Current Experience (CE) Study demonstrate that clinical practice varies widely across study sites [11]. This cross-sectional study included data from 1377 neonates born at ≥36 weeks' gestation with NOWS, defined as evidence of prenatal opioid exposure and a NOWS assessment within the first 120 h of life. There was considerable site-to-site variation in the care for infants with NOWS; including the proportion of neonates having toxicology screens performed (mean 86%, range 50–100%), threshold Finnegan Neonatal Abstinence Scoring Tool (FNAST) [11] scores for initiating pharmacologic therapy (mean 10.5, range 5.6–15.3), and the proportion of neonates receiving pharmacologic therapy (mean 40%, range 7–100%) [12]. The results of ACT NOW CE have been used to plan ongoing clinical trials including the ACT NOW Weaning Clinical Trial (NCT04214834) [13] through enhanced understanding of actual clinical practices across sites.

Assessment of NOWS

Standardized assessment is a key component of the care for infants with NOWS [14, 15]. Sites participating in the ACT NOW CE study utilized protocols for the assessment of opioid withdrawal, including use of the conventional or modified FNAST. In this study population the FNAST or modification thereof represented the primary approach to assessing neonates with NOWS [11]. In contrast to the FNAST, the function based assessments utilized under the Eat, Sleep, Console (ESC) care approach have been increasingly adopted across clinical practice sites [16, 17].

Nonpharmacologic care

Nonpharmacologic interventions including but not limited to rooming-in and breastfeeding are beneficial for neonates with NOWS. Rooming-in allows primary caregivers to provide continuous nonpharmacologic care for their neonate during the initial newborn hospitalization and is associated with lower use of pharmacotherapy and a decrease in the length of hospital stay (LOS) [18]. Despite its potential benefits, rooming-in may not be feasible for all neonates with NOWS due to factors such as limitations in physical space and/or neonate specific social constraints. Breastfeeding provides multiple benefits for the mother and neonate including enhanced bonding and attachment and decreased severity of NOWS (e.g., less use of pharmacologic therapy) [19]. However, the potential to breastfeed is appropriately limited in cases with ongoing alcohol and/or illicit drug use and certain infectious diseases. National guidelines discourage breastfeeding and use of maternal breastmilk in these cases [20]. A lack of prospective clinical trials focused on nonpharmacologic care has limited the evidence to support these broadly accepted care practices.

In addition, the ESC Care Tool is only one component of the ESC care approach for NOWS, which emphasizes the optimization of nonpharmacologic care as a primary intervention (although most health systems that use the FNAST as the primary assessment tool also emphasize education, support, and empowerment of families in the care of their neonate). Quality improvement studies indicate that the ESC approach improves short-term outcomes such as LOS and use of pharmacotherapy [16, 21–24]. However, it is not clear if these findings are broadly generalizable. A formal study (ESC-NOW Clinical Trial, NCT04057820 [25]) is attempting to validate the findings of previous quality improvement work and will directly assess the safety and developmental outcomes associated with this approach compared to more traditional assessment and management strategies.

Pharmacologic care

Pharmacologic care should be considered when nonpharmacologic measures alone are not adequate to control the signs of withdrawal. The ACT NOW Clinical Practice Survey showed that morphine was the most commonly prescribed first-line pharmacologic agent for neonates with NOWS (82% of centers). First-line use of methadone (22% of centers), buprenorphine (4%), and clonidine (2%) were also reported. Clonidine and phenobarbital were the most commonly used second-line therapies [10]. Results from the ACT NOW CE study demonstrated that 86% of neonates receiving morphine, 13% methadone, <1% buprenorphine, and <1% phenobarbital as their primary medication [11].

The use of methadone as pharmacologic treatment for NOWS resulted in a significantly shorter length of treatment (LOT) than morphine in a randomized controlled trial in 31 neonates [26]. Methadone was associated with significantly shorter overall LOS, shorter LOS attributable to NAS, and shorter LOT compared to morphine in a larger multicenter randomized controlled trial ($N = 117$) [27]. However, there were no differences in neurobehavioral outcomes when infants were followed to 18 months of age [28].

More recently, symptom-triggered (i.e., "as needed") dosing regimens of morphine and methadone have been associated with significantly shorter durations of pharmacologic treatment in nonrandomized quality improvement investigations, though the safety and neurodevelopmental outcomes of this approach are unknown [24, 29]. In one study, neonates started on a symptom-triggered methadone-dosing protocol had fewer methadone treatment days (median 2.5 vs. 11.7 days, $P = 0.0001$), received a lower overall dose of methadone (0.53 vs. 4.52 mg, $P < 0.0001$), and had a shorter LOS (median 10.5 vs. 17.0 days, $P = 0.003$) than neonates started on a fixed-dosing protocol [29]. Implementation of an ESC program and provision of "as needed" opioid therapy was also associated with reductions in mean LOS (from 14.8 to 5.9 days) and in the proportion of neonates receiving pharmacotherapy (from 61 to 23%) in a Colorado hospital network [24].

In spite of the dominance of morphine and methadone for the treatment of NOWS, there is evidence to suggest that buprenorphine may be a suitable alternative medication. A meta-analysis of 18 clinical trials that included 1072 neonates receiving pharmacologic treatment for NOWS concluded that sublingual buprenorphine was the optimal medication with respect to reducing LOT [30]. However, the systematic review and meta-analysis had several important limitations: inclusion of several single-center studies, which were not blinded, thus increasing potential bias; a lack of adequate control for variations in maternal exposure, nonpharmacologic therapy, and the use of adjunctive medications and variation in the pharmacologic treatment protocols across studies, all of which must be noted when interpreting the results [31]. In addition to sublingual buprenorphine, the meta-analysis evaluated clonidine, diluted tincture of opium, morphine, methadone, and phenobarbital. Use of buprenorphine (from single-center studies) was associated with a shorter duration of treatment (−12.75 days; 95% CI, −17.97, −7.58) and LOS

(−11.43 days; 95% CI, −16.95, −5.82) compared with morphine [30]. Morphine was the lowest-ranked opioid for LOT and LOS in this analysis. Additional multicenter randomized controlled trials that take into account both pharmacologic and nonpharmacologic factors are warranted before definitive recommendations on best practice can be made [31].

POTENTIAL ROLE OF BUPRENORPHINE IN PHARMACOLOGIC MANAGEMENT OF OUD AND NOWS

Buprenorphine is a partial agonist at mu opioid receptors and an antagonist at kappa receptors that is administered once daily in nonpregnant adults because of its long elmination half-life. Since the elimination half-life of buprenorphine varies considerably and clearance is more rapid during pregnancy, more frequent dosing (e.g., 3–4 times daily) may be required in pregnant women [32]. The pharmacologic effects of buprenorphine are similar to other opioid antagonists but buprenorphine has a ceiling effect which decreases the risk for overdose. As a partial mu opioid agonist, buprenorphine has less abuse potential than full agonists and is increasingly used to treat OUD in adults [33].

The Maternal Opioid Treatment: Human Experimental Research (MOTHER) trial showed that the use of buprenorphine compared to methadone to treat maternal OUD during pregnancy yielded significant reductions in LOS, duration of treatment, and total dose of morphine in exposed neonates [34]. Follow-up of infants born to mothers in the trial to 36 months of age found that children prenatally exposed to either methadone or buprenorphine had normal physical growth, cognitive development, and language development [35]. However, it should be noted that a higher proportion of mothers randomized to buprenorphine were dissatisfied with their assigned medication, due to suboptimal control of withdrawal, and cited it as the reason for discontinuation (71% vs. 13% of mothers randomized to methadone) [34]. Much of this can be attributed to the dosing regimen for the study, which was based on time intervals rather than on clinical signs of withdrawal. Dosing based on the signs of withdrawal as assessed through a tool such as the Clinical Opoid Withdrawal Scale is the currently accepted approach to care [36]. A retrospective analysis of data from women enrolled in a perinatal treatment program demonstrated that buprenorphine was also associated with better rates of breastfeeding compared with women taking methadone [19]. This analysis also showed that fewer breastfed neonates required pharmacologic treatment for NOWS compared to formula-fed neonates, which lends support to the efficacy of breastfeeding in decreasing the severity of NOWS.

Buprenorphine is not approved for the treatment of NOWS and no pediatric formulation is commercially available. Despite these barriers, the safety and efficacy of buprenorphine for the treatment of NOWS has been evaluated in a series of single-center clinical trials [37–39]. In the largest of these trials (randomized, double-blind BBORN trial), treatment with sublingual buprenorphine was associated with a shorter median duration of treatment and LOS compared to treatment with morphine [39]. Collectively, the results of five single-center clinical studies (including BBORN) have shown that treatment of NOWS with buprenorphine is associated with consistent reductions in the LOT compared with either morphine or methadone (Table 1) [37–41]. Of note, the mean percentage decrease in LOS and LOT with buprenorphine relative to other opioids are similar to those in randomized trials, despite different populations and study sites, suggesting that the efficacy of buprenorphine over other opioids for the treatment of NOWS may not be driven solely by local dosing patterns or patient mix (Table 1) [40, 41].

Morphine, methadone and buprenorphine are all available as generic formulations and differences in the costs between drug acquisition or local compounding are negligible. The usual buprenorphine preparation contains 30% ethanol and is stable

Table 1. Buprenorphine for treatment of NOWS in infants.

Citation	Study design	Treatment, initial dose (*N*)	Length of treatment Duration in days (range)	Mean% decrease[g]	Length of stay Duration in days (range)	Mean% decrease[g]
Kraft et al. [37]	Randomized, open-label	BUP 13.2 μg/kg/d[a] (13)	22[e] (11–47)	32	27[e] (17–51)	29
		MOR 0.4 mg/kg/d[b] (13)	32[e] (14–60)		38[e] (19–66)	
Kraft et al. [38]	Randomized, open-label	BUP 15.9 μg/kg/d[a] (12)	23[e] (9–45)	39	32[e] (23–70)	24
		MOR 0.4 mg/kg/d[b] (12)	38[e] (18–67)		42[e] (15–98)	
Kraft et al. [39]	Randomized, double-blind	BUP 15.9 μg/kg/d[a] (30)	15[f] (3–67)	46	21[f] (7–71)	36
		MOR 0.4 mg/kg/d[b] (33)	28[f] (13–67)		33[f] (18–70)	
Hall et al. [40]	Retrospective cohort	BUP 13.2 μg/kg/d[a] (38)	9.4[e] (7.1–11.7)	33	16.3[e] (13.7–18.9)	21
		MET 0.2 mg/kg/d[c] (163)	14.0[e] (12.6–15.4)		20.7[e] (19.1–22.2)	
Hall et al. [41]	Retrospective cohort	BUP 13.5 μg/kg/d[a] (174)	7.4[e] (6.3–8.5)	29	12.4[e] (11.3–13.6)	8
		MOR 0.3–0.4 mg/kg/d[d] (110) or MET 0.4 mg/kg/d[c] (76)	10.4[e] (9.3–11.5)		15.2[e] (14.1–16.4)	

BUP buprenorphine, *d* day, *MET* methadone, *MOR* morphine, *NOWS* neonatal opioid withdrawal syndrome.
[a]In three divided doses (every 8 h).
[b]In six divided doses (every 4 h).
[c]In four divided doses (every 6 h).
[d]In six to eight divided doses (every 3–4 h).
[e]Mean.
[f]Median.
[g]BUP vs. comparator.

for 30 days when stored at room temperature [42]. Ideally, pediatric formulations should be free of ethanol, but when an ethanol free solution is not avaliable the American Academy of Pediatrics recommends that the blood ethanol concentrations not exceed 250 mg/L. Although this recommendation is not based on robust data from studies examining short- and long-term outcomes; just as exposure to small amounts of alcohol during pregnancy may be harmful to the fetus, exposure of neonates to low levels of ethanol may still impact neurodevelopmental and behavioral outcomes. Importantly, studies have shown that neonates with NOWS who are treated with sublingual buprenorphine, either alone or in combination with phenobarbital, had blood ethanol concentrations <70 mg/L [43, 44]. An alcohol-free formulation of buprenorphine for sublingual administration is currently under investigation in a phase 2 double-blind trial (NOWSHINE, NCT04104646 [45]). Ongoing research will better define the pharmacokinetics of buprenorphine in neonates for the purpose of optimizing dosing and weaning protocols (BPHORE, NCT03608696 [46]; NOWSHINE, NCT04104646 [45]).

CLINICAL TRIALS IN NOWS

Ongoing studies

The ACT NOW collaboration is currently conducting three multicenter studies [47]. The ACT NOW ESC Clinical Trial (ESC-NOW, NCT04057820 [25]) is evaluating the ESC approach and will examine whether this approach can shorten LOS compared with the more traditional FNAST. The ACT NOW Weaning Trial (NCT04214834 [13]) is evaluating how rapidly neonates with NOWS can safely be weaned off opioids when they require pharmacologic treatment. The ACT NOW Longitudinal Study (OBOE, NCT04149509 [48]) is using neuroimaging and neurobehavioral assessments to better understand the effects of prenatal opioid exposure and NOWS on brain structure and function throughout early childhood. This study will also examine how maternal and environmental factors interact with antenatal opioid exposure to influence neurodevelopmental and behavioral outcomes in neonates with NOWS [47]. All three studies have developed a harmonized approach to neurodevelopmental and behavioral assessments over the first 2 years of life.

The National Institute on Drug Abuse's Clinical Trials Network is conducting the Medication Treatment for OUD in Expectant Mothers trial (MOMs, NCT03918850 [49]), which is a pragmatic, randomized trial examining maternal and neonatal outcomes in 300 pregnant women given extended-release buprenorphine compared to sublingual buprenorphine [50]. Participants will be invited to join a sub-study evaluating the effects of prenatal exposure to extended-release or sublingual buprenorphine on infant neurodevelopment in which the primary measure of interest is the Bayley^{TM}-4 cognitive subscale score at the 24-month assessment. The HEALthy Brain and Child Development study, co-funded by the NIH HEAL Initiative^{SM} and several NIH institutes, will follow a cohort of pregnant women who are receiving antenatal opioids and their children for at least 10 years [51]. For this study, it has been recommended that outcomes be pragmatic (e.g., brief, with a capacity for remote administration), developmentally-sensitive and transdiagnostic with a focus on irritability as it is measurable from birth, a sign of NOWS and other adverse exposures, can be assessed via brief surveys, and has high predictive utility [52].

Research is also underway to identify biomarkers or other predictive risk factors (demographic, clinical, behavioral) associated with the development and severity of NOWS. While studies evaluating genetic and epigenetic components associated with the development and severity of NOWS have found promising results, much larger cohorts are needed to confirm these findings [53]. Such data could be used with demographic and clinical models to improve risk prediction. Validation of risk prediction models may help stratify risk and identify populations (women and neonates) for whom future precision medicine interventions might improve outcomes. Furthermore, large-scale genomic studies are needed to elucidate the contributions of genetic and epigenetic modifications related to NOWS in order to improve our understanding of the variability of NOWS-related outcomes, elucidate how maternal OUD affects the neonate's epigenetic profile, and develop more tailored personalized treatments [54].

Outcomes in NOWS. One drawback of previous clinical trials for infants with NOWS is a lack of standardization of outcome measures. In response to this issue, a core outcome set has been developed for use in clinical trials of NOWS that includes: requirement for opioid treatment; dose of opioid administered; duration of pharmacologic therapy; need for adjuvant pharmacologic therapy; feeding difficulties; consolability; time to control clinical signs; parent-neonate bonding; duration of hospitalization; breastfeeding status at discharge; weight gain at discharge; readmission for NOWS; and neurodevelopmental outcomes during early childhood [55]. The broad range of methods and instruments designed for early childhood that combine developmental sensitivity with lifespan coherence and clinical feasiblity now provides the opportunity to trace continuities and discontinuities in risk and resilience patterns to differentiate those exposed infants most likely to show persistent maladaptation from those with natural course remission [52, 56].

No large-scale studies have been published on the neurodevelopmental outcomes in early childhood for neonates with NOWS. A meta-analysis of available studies that look at neurodevelopmental outcomes showed that children born to opioid-dependent mothers had worse outcomes than children not exposed to opioids in utero [57]. Cognition and psychomotor scores were significantly lower in infants who had been exposed in utero to opioids when compared to infants without opioid exposure. Opioid-exposed children had lower mean IQ and lower expressive and receptive language scores compared to nonexposed children [57]. However, these results must be interpreted with some caution as the diverse and small studies included in this meta-analysis have significant limitations including incomplete/inadequate descriptions or confirmation of antenatal drug exposure, variability in assessor blinding and statistical approaches, differential attrition among groups, and use of comparison groups that were not well-defined or well-matched. There is also evidence that prenatal opioid exposure is associated with early emotional and behavioral dysregulation [58, 59], which presages lifespan mental health problems and disrupts the early caregiving process [60–62]. It is important to acknowledge that children with NOWS are influenced by multiple socioeconomic and home and social environmental factors that may be impossible to control for in follow-up studies. In addition, the use of a coded diagnosis of NOWS abstracted from statewide or national datasets may be inaccurate and subject to excessive variability and findings of statistical significance may not be clinically relevant. Thus, the impact of NOWS itself or the treatment for NOWS on neurodevelopmental and behavioral outcomes throughout early childhood remains unclear.

Challenges to conducting research in NOWS. The potential barriers to conducting clinical research in NOWS are numerous. In particular, patient recruitment can be problematic when concerns over confidentiality and privacy, mandatory reporting laws, and potential loss of child custody negatively impact consent rates among pregnant women with OUD. In addition, ensuring racial, ethnic, and socioeconomic diversity is a formidable challenge, not only for NOWS but for pediatric research in general [63]. There are many other gaps in knowledge and operational challenges to the conduct of studies that include but are not limited to those shown in Table 2.

Table 2. Challenges to conducting research in NOWS.

Challenge	Considerations
Defining NAS/NOWS	• Standard definitions for NAS and NOWS have been lacking
Finding and recruiting study sites	• Many potential study sites may be unwilling to change their clinical practices to align with a research protocol • As such, it is unclear how many sites remain unbiased enough to maintain equipoise and participate in an RCT
Recruiting participants	• Low consent rates for pregnant women with OUD • Optimizing diversity and inclusion is a formidable challenge
Randomization	• The ideal target for randomization remains poorly defined, including whether the pregnant mother should be screened and randomized during pregnancy, whether the infant should be randomized following birth, or whether the mother and infant should be randomized following birth as a dyad • Given the variability in clinical practice across centers, another important consideration is whether study participants are randomly assigned to an intervention as an individual (or infant/mother dyad) or by study site (i.e., cluster randomization)
Blinding and masking	• Currently available opioid formulations have different routes of administration (oral versus sublingual), dose intervals, and weaning protocols, so finding ways to reliably mask study drugs to prevent healthcare providers from knowing which one a participant is receiving is particularly challenging
Assessments	• Requiring a certain assessment tool or care approach (FNAST, modified FNAST, or ESC) as part of a study protocol may be a detriment to recruiting study sites • In general, proportion of patients requiring pharmacologic treatment will be lower among sites using the ESC approach
Interventions	• Questions remain regarding the ideal comparator for buprenorphine (morphine, methadone, or both), the use of symptom-triggered (i.e., "as needed") versus scheduled dosing, ideal tapering schedule, and use of adjunct therapies • Pharmacokinetic sampling is a key tool to optimize drug dosing, but difficult in neonatal populations
Outcomes	• Short- and long-term neurodevelopmental and non-neurodevelopmental outcomes must be clinically meaningful • The home environment following hospitalization may have a significant impact on long-term outcomes
Study design/statistical considerations	• Pragmatic assessment instruments should be sufficiently sensitive to quantify treatment effects on endpoints that are also reliable, consistent, validated, and clinically relevant • Choosing a noninferiority design (versus superiority) may have implications to the complexity of statistical considerations • Adaptive trial designs (or adaptive treatment schemas) might also be well suited for future trials

ESC Eat, Sleep, Console, *FNAST* Finnegan Neonatal Abstinence Scoring Tool, *NAS* neonatal abstinence syndrome, *NOWS* neonatal opioid withdrawal syndrome, *OUD* opioid use disorder, *RCT* randomized controlled trial.

SUMMARY AND CONCLUSIONS

NOWS is a complex disorder with many factors contributing to the incidence and severity. There is marked variability in the presentation, uncertainty in the optimal assessment of the need for pharmacologic treatment, and significant concerns about the safety and efficacy of pharmacologic therapy. To be successful and generate high-quality data that are broadly generalizable, researchers will need to embrace innovative trial designs, harness advances in neurodevelopmental science, maintain equipoise, and engage all of the essential stakeholders in public–private partnerships.

One goal of the NIH HEAL Initiative[SM] is to significantly impact public health by enhancing the outcomes for infants and children exposed to opioids. Considering the gaps in knowledge in whether buprenorphine can offer better outcomes when used to treat NOWS, a comparative effectiveness, randomized controlled trial evaluating morphine, methadone, and buprenorphine is needed to further inform clinical practice.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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