



## Early life opioid exposure and potential long-term effects

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### ABSTRACT

The long-term consequences of perinatal opioid exposure and subsequent development of neonatal opioid withdrawal syndrome is largely unknown and likely dependent on a multitude of factors, including co-morbid drug use, pre- and post-natal care, and individual factors including the maternal-infant relationship and home environment. This review summarizes the current literature from clinical and preclinical studies on perinatal opioid exposure, focusing on the consequences in the offspring. Although a large number of preclinical studies have been conducted examining the impact of prenatal opioid exposure, the models employed are not necessarily representative of clinical use patterns, making it challenging to translate these results to the impacted population. Use of more clinically-relevant models of perinatal opioid exposure are requisite for the development of improved pharmacological and behavioral treatment strategies to improve quality of life for this vulnerable population.

### 1. Introduction

In 2016, physicians wrote 66.5 prescriptions for opioid-based medications per 100 people in the United States (Centers for Disease Control, 2017), of which an estimated 4.7 persons misused their prescription. Although opioid prescribing rates have leveled off since 2012, due in part to increased caution on the part of healthcare providers, opioids are still prevalent drugs of abuse, and both prescription pain relievers and commonly abused drugs like heroin and fentanyl are a significant source of drug abuse and mortality. Indeed, in 2015, opioids accounted for 63.1% of all overdose deaths in the U.S. (Centers for Disease Control, 2017).

Women are prescribed opioids at a higher rate than men, with an average of 21.8 patients per 100 women in comparison to 16.4 per 100 men (Centers for Disease Control, 2017). Between 2008 and 2012, approximately 28% of privately-insured and 39% of Medicaid-insured women of childbearing age (15–44 years) filled a prescription for an opioid (Ailes et al., 2015). As half of all U.S. pregnancies are unplanned, and pregnancy is often unrecognized until the sixth gestational week (American Pregnancy Association), women of childbearing age who use opioids, either prescribed or illicit, are at risk of exposing their fetus during a critical period of development (Ailes et al., 2015).

The rate of opioid prescriptions is remarkably high for pregnant women, with an estimated 14–22% of pregnant women filling a prescription for an opioid during their pregnancy (Ailes et al., 2015). Over the past 10 years, the rate of pregnant women who are dependent on

opioids has steadily increased in the US, with an average of 0.9% of pregnant women aged 15–44 having misused opioids in the last month (Smith and Lipari, 2017). Opioid misuse during pregnancy significantly jeopardizes the health and well-being of the developing infant. Indeed, approximately 60–80% of infants exposed to opioids *in utero* will experience neonatal opioid withdrawal syndrome (NOWS) following birth (Patrick et al., 2012). In the US, the incidence rate of NOWS has increased over 400%, from 1.2 per 1000 hospital births in 2000 to 5.8 in 2012; that statistic translates to approximately one NOWS infant born every 25 min (Patrick et al., 2015).

These statistics highlight the impact of the opioid epidemic on women of child bearing years and their offspring. A 400% increase in the incidence rate of NOWS is frightening, particularly given the dearth of clinical information regarding the long-term consequences. This review will provide an overview of the recent clinical and preclinical findings on perinatal opioid exposure, and when possible, its impact on stress-responsive circuits.

### 2. Clinical studies on perinatal opioid exposure

Infants exposed to opioids during gestation are more likely to be born prematurely (< 37 weeks gestation) and at a lower birth weight (< 2500 g) (Fill et al., 2018; Hunt et al., 2008). As stated above, approximately 60–80% of these infants will experience NOWS following birth (Patrick et al., 2012). Infants undergoing NOWS will experience many, if not all, of the same symptoms experienced by adults

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undergoing opioid withdrawal. These symptoms include decreased sleep, tremors, seizures, increased muscle tone, sweating and fever, gastrointestinal dysfunction including loose/watery stools and vomiting (Ainsworth, 2014). NOWS infants are also known for their continuous high-pitched crying and inability to be consoled (Ko et al., 2016). Reduced brain volume and increased risk of sudden unexpected death have also been reported (Ko et al., 2016; Patrick et al., 2012). Secondary complications associated with NOWS include tachypnea, meconium aspiration, respiratory distress, jaundice, and sepsis (Patrick et al., 2015). Infants undergoing NOWS are more likely to be admitted into the neonatal intensive care unit (NICU) where they will spend an average of 17–23 days with an associated cost of \$66,700–\$93,000, depending on the need for pharmacological treatment (Ko et al., 2016; Patrick et al., 2012, 2015). In contrast, the average hospital stay for a full term infant is 2 days with an associated cost of \$3500 (Patrick et al., 2015).

### 2.1. Clinical outcomes

Although limited data are available regarding the impact of perinatal opioid exposure on behavioral outcomes, recent clinical studies have identified a number of cognitive, motor and sensory deficits. Children with a history of NOWS have significantly lower cognitive and motor performance scores in early childhood (Hunt et al., 2008; Baldacchino et al., 2014), and are more likely to be diagnosed with learning disabilities including developmental delays and/or speech and language disorders than age and demographic matched controls (Maguire et al., 2016; Fill et al., 2018). Although the underlying mechanisms regarding the cognitive deficits are unknown, studies in rodents have reported that *in utero* opioid exposure significantly attenuates both neural- and glial-genesis (Sanchez et al., 2008; Robinson, 2006), and decreases dendritic length and branch number in somatosensory cortical neurons (Lu et al., 2012). These preclinical findings are consistent with reports of reduced brain volumes in the basal ganglia, thalamus and cerebellar white matter in school-aged children exposed to opioids perinatally (Sirmes et al., 2017). Prenatal exposure to methadone is also associated with decreased microstructure in white matter tracts in neonates (38–39 weeks of age), indicative of less organized and more immature fiber tracts (Monnelly et al., 2018).

Very few studies have assessed for behavioral outcomes in NOWS infants. In a cohort of 5–8 month olds, Bakhireva et al. (2019) reported higher negative affect and lower self-regulation in NOWS infants versus healthy controls. NOWS infants were also more likely to be rated as ‘sensation seeking’, i.e., are more likely to search for additional sensory stimulation via oral (biting/mouthing) or physical (touching) means. Mother-child interactions are also more likely to be rated as negative for NOWS infants (Konijnenberg et al., 2016). Specifically, mothers with opioid use disorder (OUD) during pregnancy displayed lower levels of sensitivity, expressed less positive affect, and engaged in few activities with their offspring at both 12 months and 4 years of age. In parallel, children with a history of NOWS demonstrated lower positive affect, less interest in activities, and less involvement with those around them in comparison to age-matched controls (Konijnenberg et al., 2016). In addition to the reduced maternal-infant bond observed in NOWS infants, women with OUD during pregnancy are more likely to be single, have less high school education, lower family socioeconomic status, and have additional children (Bakhireva et al., 2019); these factors have been shown to contribute to the increased levels of maternal stress, which is associated with reduced maternal care.

### 2.2. ‘Causal’ factors

The studies reviewed above indicate that infants born with NOWS are at an increased risk for neurodevelopmental impairments and behavioral difficulties. The impact of perinatal opioid exposure in these infants is further compounded by the lack of pre- and postnatal

healthcare, poor maternal diet, and increased incidence of premature birth (Fill et al., 2018). Polydrug use is also common in pregnant women with an OUD, who consume, on average, 3.3 different drugs of abuse, including tobacco, alcohol, cocaine and benzodiazepines (Nygaard et al., 2016; Sirmes et al., 2017; Monnelly et al., 2018).

#### 2.2.1. Opioid pharmacokinetics

The specific mechanisms whereby perinatal opioid exposure results in changes in brain structure and/or function are not known; indeed, it is likely a combination of factors (see above) in addition to the opioids that contributes to the overall phenotype. Importantly, there are significant differences in the pharmacokinetic profile of morphine for infants in comparison to later developmental stages that may amplify the negative effects of opioid exposure. For example, in infants, the half-life of morphine is 6–12 h, compared to approximately 1 h in 1- to 6-year olds (Ainsworth, 2014). This prolonged duration of action is due to a slower elimination rate, as morphine clearance does not reach adult levels until two weeks to six months of age (Ainsworth, 2014; McRorie et al., 1992; Lynn and Slattery, 1987). Morphine also remains largely unbound during the first few weeks of life, leading to high sensitivity and increased accumulation in the brain (Bhat et al., 1990), an effect accentuated by the underdeveloped blood-brain barrier (Vathy, 2002). Morphine is metabolized via glucuronidation, which is functional at both the 3 and 6 positions in infants to produce morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), respectively (Choonara et al., 1992). However, due to an underdeveloped hepatic glucuronidation system, infants are less able to metabolize morphine to M6G, the functional metabolite of morphine, and therefore have higher levels of the M3G metabolite (Hartley et al., 1994; Bouwmeester et al., 2004). M3G has little to no affinity for the  $\mu$  opioid receptor (MOR), but rather has a high affinity for the innate pattern receptor toll-like receptor 4 (TLR4). Results from preclinical studies suggest that morphine signaling via TLR4 contributes to many of the negative side effects associated with opioid consumption, including opioid-induced hyperalgesia and tolerance (Due et al., 2012; Eidson and Murphy, 2013; Eidson et al., 2017), although this relationship remains controversial (Mattioli et al., 2014; Fukagawa et al., 2013). Regardless, the combination of long half-life, accumulation in the brain, and altered metabolism patterns suggests that infants are especially at risk for long-term developmental consequences of opioid exposure.

#### 2.2.2. Endogenous opioid levels

During pregnancy, plasma levels of  $\beta$ -endorphin increase from approximately 20 fmol/mL to > 120 fmol/mL by week 6, where they remain until parturition (Panerai et al., 1983). By postnatal day 5, endogenous opioid levels in both the infant and mother decrease to normal adult levels (Manfredi et al., 1983; Panerai et al., 1983). Infants exposed to opioids *in utero* also show elevated levels of  $\beta$ -endorphin, however, rather than decreasing to normal levels following birth,  $\beta$ -endorphin levels continue to increase to approximately 100x higher than age-matched controls (Manfredi et al., 1983; Panerai et al., 1983). Both  $\beta$ -endorphin and met-enkephalin levels remain elevated in opioid-exposed infants at postnatal day 40 (Manfredi et al., 1983; Panerai et al., 1983). Interesting, although all of the infants in the Manfredi study developed NOWS and required medication-assisted therapy, there was no effect of treatment (paregoric or phenobarbital) on endogenous opioid levels (Manfredi et al., 1983). Similarly, there was no relationship between NOWS symptom severity and endogenous opioid plasma levels.

Mu opioid receptor (MOR), the primary receptor for the exogenous opioids morphine, oxycodone, and heroin, and the endogenous opioid  $\beta$ -endorphin, is detectable in the CNS as early as 12–13 weeks’ gestation (Ray and Wadhwa, 1999). This indicates that there is functional MOR present in the CNS while the infant is exposed *in utero* to high levels of not just illicit opioids, but also  $\beta$ -endorphin. Endogenous opioids modulate CNS development by primarily inhibiting growth (Hauser

et al., 1989; Zagon et al., 1982; Zagon and MacLaughlin, 1987), providing an additional mechanism underlying the decrease in brain volume observed in NOW infants.

Previous studies in rodents have implicated endogenous opioids and their receptors in long-term cognitive deficits. In rats, early life pain (postnatal day 0), which significantly increases brain B-endorphin levels (Victoria et al., 2015) significantly impedes memory recall in rats tested as adults in the Morris Water Maze (Henderson et al., 2015). Administration of naltrexone, a non-selective opiate receptor antagonist, at the time of injury improved long-term memory on the radial arm water maze in adulthood (Nuseir et al., 2017). Together, this data suggests that elevated levels endogenous opioids in the brain may further contribute to the long-term deficits in cognition observed in NOWS infants.

### 3. Opioids and stress

As discussed above, remarkably little is known regarding the negative behavioral outcomes associated with perinatal opioid exposure in humans. In adult rodents, acute or chronic opioid exposure activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the release of corticotropin-releasing hormone (CRH), which then acts on the pituitary to stimulate adrenocorticotropic hormone (ACTH) release. ACTH stimulates the release of corticosterone in rodents or cortisol in humans (CORT) from the adrenal gland (Ignar and Kuhn, 1990), which then feeds back to the hypothalamus to turn off the further release of CRH in a negative feedback manner. Although the impact of perinatal opioid exposure on CORT release is not known, chronic morphine exposure in adults leads to tolerance of the CORT-releasing effects of morphine (Houshyar et al., 2001).

Studies in rodents have reported long-term changes in the hormonal and behavioral responses to acute and chronic stress following perinatal opioid exposure. For example, administration of morphine to rats on the day of birth results in significant anxiolytic behavior in the open field apparatus and forced swim test in adulthood (Victoria et al., 2015). Reduced basal CORT levels and blunted CORT response following 10 min of forced swim have also been reported (McPherson et al., 2007; Victoria et al., 2013, 2014). In contrast to the *hypo*-responsive profile observed following exposure to acute anxiety- and/or stress-provoking stimuli, the exact opposite behavioral response (*hyper*-responsive phenotype) was observed in P0 morphine treated rats following prolonged exposure (7 days) to mild chronic variable stress in adulthood. Similar changes in the behavioral response to stress have also been reported in adult rats born to dams who received morphine during gestation (Ahmadalipour and Rashidy-Pour, 2015; Ahmadalipour et al., 2015; Šlamberová et al., 2002; Haydari et al., 2014; Fodor et al., 2014). Together, these studies suggest that early activation of the opioid system produces long-term changes in the neurocircuitry underlying stress (LaPrairie and Murphy, 2009; Victoria et al., 2015). Interesting, enhanced morphine reward, as indicated by increased morphine preference during the two-bottle choice paradigm, was reported in adult male rats exposed to opioids *in utero* (Haydari et al., 2014), suggesting an increased propensity for drug abuse in adulthood.

### 4. Potential interventions

Researchers have now begun to identify potential, non-pharmacological interventions to mitigate the effects of prenatal opioid exposure. One promising intervention is exercise during pregnancy. Previous studies have reported that exercising dams improves outcome measures following naloxone precipitated withdrawal, and in the offspring, decreases anxiolytic behavior and morphine preference in a two-bottle choice paradigm (Haydari et al., 2014). Exercising pups from P21-P40 also attenuated responses to stress as indicated by improved time in the light compartment and open arm of the elevated plus maze

(Ahmadalipour and Rashidy-Pour, 2015). Providing environmental enrichment to pups resulted in similar improvements, and also decreased hippocampal BDNF levels (Ahmadalipour et al., 2015). Co-administration of naloxone with opioids during pregnancy attenuated most negative effects, suggesting that the impact of perinatal opioid exposure is largely mediated via MOR signaling (Vathy, 2002).

Clinically, infants successfully treated for NOWS may show better outcomes than those who experienced uncontrolled withdrawal in early life (Vathy, 2002). Maternal factors and genetic background are likely contributing factors, as opioid use disorder is highly heritable and polymorphisms in *OPRM1* and *COMT* are associated with shorter length of hospital stay and decreased the likelihood of pharmacological treatment after prenatal opioid exposure (Wachman et al., 2013; Lesage et al., 1998). Together, this suggests that early life interventions targeted to the mother or infant, along with traditional pharmacological treatment, have the potential to mitigate long-term complications due to NOWS, and that individual factors of drug use and genetic profiles should be factored in to create individualized treatment plans in the NICU.

### 5. Future concerns

Although a growing body of evidence suggests that early life opioid exposure can lead to long-term alterations in behavior and neurochemistry, the wide range of covariates in clinical data makes interpretation difficult. Particularly important for clinical translation is the observation that most preclinical models administer opioids to pregnant dams from E11-18; this development time point coincides with the emergence of androgen, estrogen, and endogenous opioid systems (Vathy et al., 1985), and is a critical period of CNS sexual differentiation (Vathy and Katay, 1992) (see Table 1). Other studies administer morphine from E5-12, which coincides with organogenesis and approximates the first trimester of human development, when infants are most sensitive to teratogens (Vathy et al., 1983, 1985; Vathy and Katay, 1992). Several studies also employ an increasing dose paradigm, where the first three doses (in these cases, on E5 and E6) were 5 mg/kg, and the remaining doses (from E6-12) were 10 mg/kg (Litto et al., 1983; Vathy et al., 1983). Importantly, these dosing paradigms do not accurately model the clinical profile of the prototypical female with OUD who typically initiates opioid consumption prior to pregnancy. As a newborn rat pup is considered neurodevelopmentally comparable to a third trimester infant, the ability to translate the results of E11-18 dosing schedule to clinical outcomes in infants born with substance use disorder is in doubt. Drug use is rarely initiated in pregnancy; rather, a pregnant woman is more likely to have initiated illicit drug use in adolescence and to actually decrease drug use over pregnancy. Indeed, only 2.4% of pregnant women report misusing drugs in the third trimester versus 9.0% in the first trimester (Creasy et al., 2014; Substance Abuse and Mental Health Services Administration, 2014). Future preclinical studies should attempt to utilize a dosing schedule that more accurately reflects actual use patterns of pregnant women, thereby improving translatability of the results.

A recent study by Byrnes and Vassoler (2018) addresses many of the concerns identified above. In this study, adult female rats were trained to self-administer oxycodone prior to and during gestation. Similar to what is observed clinically, dams who self-administered oxycodone during gestation showed reduced maternal responding (as indicated by longer latencies in the pup retrieval test), and their pups weighed significantly less at birth. In contrast to NOWS infants, pups born to oxycodone dams did not show an increase in ultrasonic vocalizations (indicative of distress), although it is not clear whether these pups displayed symptoms consistent with opioid withdrawal. Clearly, additional preclinical research needs to be conducted to delineate the long-term consequences of perinatal opioid exposure, and the study by Byrnes and Vassoler epitomizes the type of model design that should be employed in future pre-clinical studies; however, dosing should be

**Table 1**  
Summary of studies utilizing E11-18 dosing schedule.

Study Name	Morphine Dose/ Exposure Time	Pup treatment?	Age at testing?	Main effects?	Interventions?	Citation for E11-18?
Ahmadalipour and Rashidy-Pour (2015)	E11-18 2x daily. First 3 injections 5 mg/kg, remaining injections 10 mg/kg. SubQ.	Cross-fostered so each mother raised half-saline and half morphine-exposed pups. Litters reduced to 10 maximum. Sexes of pups not tested; sex not considered as a biological variable.	Tested between P41-47.	Less time in light compartment of light/dark box. Less OAT% for EPM.	Pups were exercised 30 min per day from P21-40. Improved TLC and OAT%.	Vathy et al. (1985)
Ahmadalipour et al. (2015)	E11-18 2x daily. First 3 injections 5 mg/kg, remaining injections 10 mg/kg. SubQ.	Cross-fostered so each mother raised half-saline and half morphine-exposed pups. Litters reduced to 10 maximum, with an equal sex balance. One saline-exposed and one morphine-exposed pup per sex per dam was selected for behavioral testing. Data collapsed across sexes due to high Pearson's correlation.	Tested between P51-57.	Smaller time in light compartment/entries into light compartment on L/D box. Lower OAT on EPM. Lower STL. Higher TDC. Lower BDNF levels.	Enrichment from P21-50. Improved OAT, STL, TDC, and BDNF.	Vathy et al. (1985)
Laborite et al., 2005	E11-18 2x daily 10 mg/kg. SubQ.	Litters reduced to 10 maximum. Only male rat pups tested.	Tested at 3 months age.	Decreased basal adrenal NE content. Lower basal adrenal PNMT, which did not respond to ether stress. Increased hippocampal 5HT/5HTAA after ether stress. Increased hypothalamic basal 5HT/5HTAA. Increased hypothalamic 5HTAA after stress.	Maternal adrenalectomy improves HPA axis function.	Vathy et al. (1985) and Lesage et al. (1998)
Lesage et al. (1998)	E11-18 2x daily 6 mg/ml (20 mg/kg/day). SubQ.	No differences seen between male and female pups; pups pooled. Used 2-4 pups from some of the mothers in each group for experiments.	Tested at P0.	Adrenal atrophy/hypoactivity. Reduced CRF in the hypothalamus.	Maternal adrenalectomy at E10 minimizes effects of maternal opiate exposure on the HPA axis.	N/A
Rimanóczy and Vathy, 1995	E11-18 2x daily. First 2 injections 5 mg/kg, remaining injections 10 mg/kg. SubQ.	Cross-fostered so each mother raised half saline and half morphine-exposed pups. Litters adjusted to 8-10 pups. One male and one female from each litter used. All females OVX.	OVX ~ 7-10 days before sacrifice. Tested at P75-85.	Estradiol only affects hypothalamic Bmax of mu opioid receptors in morphine exposed OVX females.	N/A	Vathy and Katay (1992) (cites Vathy et al., 1985) and Vathy et al., 1994 (cites Vathy et al., 1983; Vathy et al., 1985; Vathy and Katay, 1992)
Rimanóczy et al., 2003	E11-18 2x daily. First 3 injections 5 mg/kg, remaining injections 10 mg/kg. SubQ.	Cross-fostered so each mother raised half-saline and half morphine-exposed pups. Litters reduced to 10 maximum, with an equal sex balance. One saline-exposed and one morphine exposed male pup per litter was selected for analysis.	Tested between P60-90.	Smaller stress-induced increase in ACTH for males.	N/A	Vathy et al. (1983) and Vathy et al. (1985)
Štamberová et al., 2004	E11-18 2x daily. First 3 injections 5 mg/kg, remaining injections 10 mg/kg. SubQ.	Cross-fostered so each mother raised half-saline and half morphine-exposed pups. Litters reduced to 10 maximum. One saline-exposed and one morphine exposed female pup per litter was selected for analysis.	Tested between P60-90.	Smaller stress-induced increase in ACTH.	N/A	Vathy et al. (1985)
Štamberová et al. (2002)	E11-18 2x daily. First 3 injections 5 mg/kg, remaining injections 10 mg/kg. SubQ.	Cross-fostered so each mother raised half-saline and half morphine-exposed pups. Litters reduced to 10 maximum, with an equal sex balance. One saline and one morphine-exposed male or female used from each litter.	OVX at P60. Tested between P70-90.	Males showed more struggling and less swimming on the forced swim, as well as an increased number of squares visited along walls after cold water stress. OVX females showed less grooming on the open field.	N/A	Vathy, 1995; Vathy et al. (1985)
Vathy et al., 2000	E11-18 2x daily. First 3 injections 5 mg/kg, remaining injections 10 mg/kg. SubQ.	Cross-fostered so each mother raised half saline and half morphine-exposed pups. Litters adjusted to 10 pups. Both males and females used. All females OVX.	OVX at P60. Tested at P65-75.	Increased TH-IR in male caudal PVN/LC. Decreased TH/IR in female LC. Estradiol does not affect LC TH-IR in morphine-exposed females.	N/A	Vathy and Katay (1992) (cites Vathy et al., 1985)

refined such that clinically relevant withdrawal symptoms appear in the offspring of opioid-exposed dams.

### 5.1. Clinical relevance

The confounding factors of poor prenatal care, poor nutrition, concomitant drug use, and low maternal care make interpretation of clinical data challenging. Preclinical data show that morphine-injected dams eat approximately 25 percent less food than saline-injected controls (Kirby, 1983). When non-injected controls were pair-fed to morphine-injected dams, causing them to be food restricted, pups born to pair-fed dams were born at lower birth weights, similar to morphine-exposed pups; both cohorts reached normal weight by P6 (Kirby, 1983). Pair-fed and morphine-exposed pups also showed a reduction in spinal volume, in particular gray matter volume, suggesting that morphine's growth-retardant effects on CNS development are due, in part, to reduced maternal food consumption (Kirby, 1983). The fact that spinal volume was still decreased at P6 when body weight had returned to normal levels suggests that the spinal cord (and likely the entire CNS) is permanently impacted (Kirby, 1983). Future clinical studies may wish to include metabolic and nutritional factors in their analysis, as well as considering dietary interventions during pregnancy to improve mother and infant's quality of life.

### 5.2. Medication-assisted therapies

Although this review has thus far focused on morphine as the prototypical opioid, it is important to note that opioid-dependent mothers have often transitioned onto maintenance doses of methadone or buprenorphine when their pregnancy is discovered. Methadone has been the gold standard of treatment for pregnant women, but recent data suggests that buprenorphine may be a better choice to manage opioid dependency during pregnancy. For example, some studies report that methadone-exposed infants have an increased risk of developing NOWS as compared to buprenorphine-exposed (Lemon et al., 2017), and buprenorphine-exposed infants may require a lower dose and shorter duration of pharmacological treatment (Jones et al., 2005, 2010; Tolia et al., 2018; Hall et al., 2016), as well as a shorter length of hospital stay (Kraft et al., 2017). However, one study found more women discontinued the use of buprenorphine during their pregnancy, citing 'dissatisfaction' with the medication (Jones et al., 2010). The effect on NOWS severity is unclear, as some studies report no difference in peak NOWS scores (Jones et al., 2005) and others report higher mean severity for methadone-exposed infants versus buprenorphine (Gaalema et al., 2012). Methadone-exposed infants may also require pharmacological treatment earlier in life, with NOWS symptoms of undisturbed tremors and hyperactive Moro reflex increased in prevalence and severity (Gaalema et al., 2012). A longitudinal study on methadone- and buprenorphine-exposed infants found very little differences in developmental and behavioral outcomes at 3 years, suggesting that both drugs may serve as appropriate treatments during pregnancy (Kaltenbach et al., 2018).

## 6. Conclusions

Improving our animal models of NOWS will allow for a more clear delineation of the long-term deleterious consequences of perinatal opioid exposure, and develop new interventions to improve the quality of life of infants born with NOWS. This research can also be translated to the bedside, by informing clinical prescribing patterns and maternal interventions to prevent future deleterious consequences to their offspring.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ynstr.2019.100156>.

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