

The Time is NOW: Filling the Gaps in Treatment of Opioid-Exposed Infants: A Prospective, Pragmatic, Randomized Control Drug Trial

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ABSTRACT

The opioid epidemic has reached into all aspects of life in the United States. The epidemic has crossed racial, economic, social, and generational barriers. This epidemic also impacts infants. Fetal exposure to opioids can produce a withdrawal effect in newborns, referred to as Neonatal Opioid Withdrawal Syndrome (NOWS). NOWS treatment lacks a standard approach, with prominent variation across the United States. Furthermore, many treatment strategies for NOWS are not evidence-based but reflect anecdotal experience. Variable approaches to NOWS treatment contribute to more extended hospital stays and greater postnatal opioid exposure. The most prolonged period of NOWS treatment occurs during the weaning phase. This paper describes the first prospective randomized control trial to address systematized weaning of opioids for infants with NOWS.

KEYWORDS: Neonatal Opioid Withdrawal Syndrome, Neonatal Abstinence Syndrome, Substance Use Disorder, Opioids

INTRODUCTION

The opioid epidemic in the United States has affected all aspects of our society, including pregnant patients and their newborns. The incidence of maternal opioid use in the United States has increased substantially since 2000,¹ affecting both rural and urban communities.² The rise in opioid use is not just in illicit substances, but in prescription opioids, and a subsequent surge in medication-assisted treatment.³ The increased incidence of opioid use in pregnancy has contributed to an increase in Neonatal Opioid Withdrawal Syndrome (NOWS), the clinical syndrome that reflects the signs of opioid withdrawal in newborns. The National Institutes of Health (NIH) has developed an aggressive research strategy to make headway in the epidemic under the initiative's umbrella, Helping to End Addiction Long-Term (HEAL).⁴ HEAL is a trans-agency national initiative to address the opioid public health crisis. In 2019, the Health Care Cost and Utilization Project by the Agency for Healthcare Research and Quality (AHRQ)^{5,6} reported rates of NOWS from < 3.2 to > 10.9 newborns per 1000 births. NOWS

rates vary by region within the United States.² The rates are particularly high across the Northeast and the Appalachian states. The states most affected are West Virginia, Vermont, and Kentucky, where rates are 48.1, 28.0, and 22.9 per 1000 live births.² While NOWS initial focus was on newborn hospitalization, there is now growing recognition that NOWS effects extend beyond the neonatal period and impact developmental outcomes.^{7,8} Also, infants with NOWS have increased hospital readmission rates than infants without opioid exposure (46.3/1000 vs. 25.6/1000 live births in 2016.⁹ Hospital readmission reflects higher rates of failure to thrive, seizures, and child abuse. This article will focus on the neonatal aspects of opioid withdrawal to identify gaps in treatment approaches and a recently initiated clinical trial to fill these gaps.

BACKGROUND

A recent Journal of Pediatrics editorial emphasized the rapid rise of NOWS in the United States. It provided a framework to target research initiatives and care delivery innovations for these infants.¹⁰ Research and quality improvement initiatives should be safe, effective, patient-centered, equitable, and achieve the goals of limiting ongoing infant opioid exposure, minimizing family separation, and reducing healthcare expenditures. To date, there is a lack of randomized clinical trials that rigorously evaluate aspects of NOWS treatment.¹¹

Quality improvement (QI) methods to standardize NOWS treatment have been successful in reducing the length of therapy (LOT) and hospital stays among affected infants.^{12,13} There is the acceptance that initial care should be individualized, supportive and non-pharmacologic. This has been the focus of many QI initiatives.³ These measures include minimizing environmental stimuli,¹⁴ encouraging breastfeeding, and providing on-demand nutrition. If non-pharmacologic strategies cannot control NOWS signs, pharmacological therapy is indicated. The pharmacological treatment uses opioid replacement to control NOWS signs to avoid severe central nervous system dysfunction. In contrast to QI initiatives addressing non-pharmacologic strategies, limited randomized clinical trials guide NOWS pharmacologic treatment.

Pharmacologic treatment traditionally begins once an infant has reached a predetermined threshold using a NOWS

assessment tool. There are many different NOWS assessment tools; the original and gold standard is the Finnegan Neonatal Abstinence Scoring System (FNASS).¹⁵ Irrespective of the assessment tool, once a child crosses the treatment threshold, opioid replacement therapy (ORT) occurs in three phases: initiation, stabilization, and weaning. Initiation is the start of ORT, stabilization is the interval of time where no further escalations in dose are needed, and weaning consists of serial reductions in ORT and/or lengthening the time interval between doses.

Medical professionals generally agree on ORT phases, but they do not agree on a standard of care for pharmacologic treatment of NOWS.¹⁶ Clinical teams may use different drugs as first-line agents (morphine, methadone, or buprenorphine) and second-line agents (phenobarbital or clonidine), with limited data to guide either. To date, there have been five trials that have enrolled a total of 345 infants.¹²⁻¹⁶ Three trials were terminated early due to slow recruitment.¹⁷⁻¹⁹ These trials compared morphine to another medication for NOWS treatment (phenobarbital, methadone, or buprenorphine). The inclusion of morphine in each arm reflects that morphine has been used most widely for ORT. This was further supported by data from the ACT NOWS Current Experience, a retrospective chart review conducted among the IDEa States Pediatric Clinical Trials Network (ISPCTN) and Neonatal Research Network (NRN) indicated that morphine was the first-line drug for ORT in 86% of NOWS infants and represented one of the few aspects of care without variation.²⁰ The ACT NOWS Current experience data affirms the historical use of morphine and reflects limited high-quality data to effect change in treatment.

Of the three phases of opioid replacement therapy, the weaning phase is the longest and contributes to the greatest variation on length of hospitalization. Like other aspects of NOWS care, there is no standardized approach to weaning ORT. A review of practice guidelines from over 20 centers in the ISPCTN and NRN affirm the weaning decrements' variability. Centers most often wean ORT by a percentage reduction of the stabilization dose, varying from 10% to 15%; some centers even reduce by 20%. Although a standard of care for weaning morphine does not exist, the plurality of existing clinical trials used 10% reductions of the stabilizing dose.^{17-19,21,22} The interval between dosage weans also varies by center and ranges from every 12 to 48 hours. This facet of weaning was absent from the prior trials and remained a significant gap in previous studies' interpretation.

The weaning phase of ORT has the greatest variation and thus shortening the weaning phase has the greatest potential to impact healthcare costs. Based on data from the ACT NOWS Current Experience, the average LOS for pharmacologically treated infants is 14.6 days. A treatment reduction of 2.0 days represents a 14% reduction in treatment duration and has the potential to reduce healthcare costs by more than \$15.7 million per year. Potential cost savings would

be even greater for hospitals that care for NOWS infants in NICUs or special care nurseries. Unfortunately, there are no randomized trials to inform clinicians of potentially better regimens to wean morphine or methadone.

OPPORTUNITY FOR AN INTERVENTION

The absence of a well-studied weaning strategy contributes to wide practice variation adding to LOS and costs. Since clinical teams want to minimize NOWS signs' recurrence as drug treatment is reduced, and a state of inertia is often perpetuated whereby clinical consensus drives decisions rather than an evidence-based protocol. It is easy for clinical teams to adopt a "let's wait another day" mentality. Given the potential to reduce healthcare costs with a systematic weaning strategy, investigators at Women & Infants Hospital of Rhode Island are leading a large multicenter randomized trial to develop an evidence-based weaning strategy. The trial's hypothesis is that among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for NOWS, a rapid-wean intervention (15% reduction from stabilization dose) will reduce the days of opioid therapy from the first weaning dose to the cessation of opioid, compared to a slow-wean intervention (10% reduction from stabilization dose). This trial will be a pragmatic, randomized, blinded trial. It will compare what is used by most centers (10% decrements from the stabilization dose) with an emerging practice of faster weaning (15% decrements from the stabilization dose). The following is an overview of this clinical trial's essential elements, which began recruitment in September of 2020.

INCLUSION CRITERIA

The study has both site-level and patient-level inclusion and exclusion criteria. Site- inclusion criteria are that the hospital provides pharmacologic treatment to at least 12 opioid-exposed infants each year, uses a scoring system to assess for signs of NOWS, and the primary opioid replacement therapy is either morphine or methadone. Site-level exclusion criteria are discharging more than 10% of infants from the hospital on opioid replacement therapy.

Infant-level inclusion criteria are gestational age \geq 36 weeks, receiving scheduled pharmacological therapy with morphine or methadone as the primary drug treatment for NOWS secondary to maternal opioid use, and tolerating enteral feeds and medications by mouth. Infant-level exclusion criteria are major birth defects, surgery, hypoxic-ischemic encephalopathy, seizures, treatment with opioids for reasons other than NOWS, respiratory support greater than 72 hours, use of other opioids for NOWS, and/or weaning before randomization.

PRAGMATIC FEATURES

This is a pragmatic, randomized, blinded trial of opioid weaning; **Figure 1** illustrates when the study interventions will occur during the hospitalization.

The treatment of NOWS has regional, state, and center differences. With such variation, this trial purposely incorporated pragmatic components into the design. A practical design’s benefits are to gain acceptance among participating centers and allow center-specific management practices for NOWS treatment after birth and before randomization. The protocol-directed elements are limited to direct care management after randomization during the weaning phase. Pragmatic features may include the following practices:

- Location of care for the infant (mother-baby unit, Neonatal Intensive Care Unit (NICU) or Pediatric floor, etc.).
- Monitoring frequency of vital signs and the use of cardiopulmonary monitors.
- Agreement to optimize non-pharmacologic treatment based on choice from a protocol-provided standardized bundle.
- Use of breast milk and breastfeeding.
- Scoring assessments of NOWS signs.
- Scoring criteria to initiate ORT and thresholds for weaning vs. escalation of study drug.
- Choice of opioid (morphine or methadone) as the primary treatment and dosing to initiate pharmacological therapy.
- Initiation and dosing adjustment of the second- and third-line drugs for NOWS signs (e.g., phenobarbital, clonidine) if NOWS signs are not adequately controlled with ORT.
- Duration of stabilization whereby the clinical team determines the interval over which no further drug dosage changes are needed to control NOWS signs before weaning is initiated.

The pragmatic components will hopefully bolster recruitment and center engagement. To account for the pragmatic elements in the data analysis, randomization will be stratified by center.

STUDY INTERVENTION

Infants will be randomized to either a rapid-wean intervention arm (15% reduction from stabilization) or a slow-wean intervention arm (10% reduction from stabilization) whenever the clinical team weans the opioid (**Figure 2; Table 1**). The clinical team will discontinue ORT when the infant can tolerate 25% or 20% of the stabilization dose without NOWS signs in the rapid- and slow-wean arms, respectively.

There are eight weans or dose levels for the rapid- and slow-wean intervention arms, each representing the amount of opioid the clinical team will administer. Infants in the rapid-wean intervention arm will undergo 5 study drug weans followed by three placebo levels. Infants in the slow-wean

Figure 1. Timing of Study Intervention in Relationship to Hospital Stay

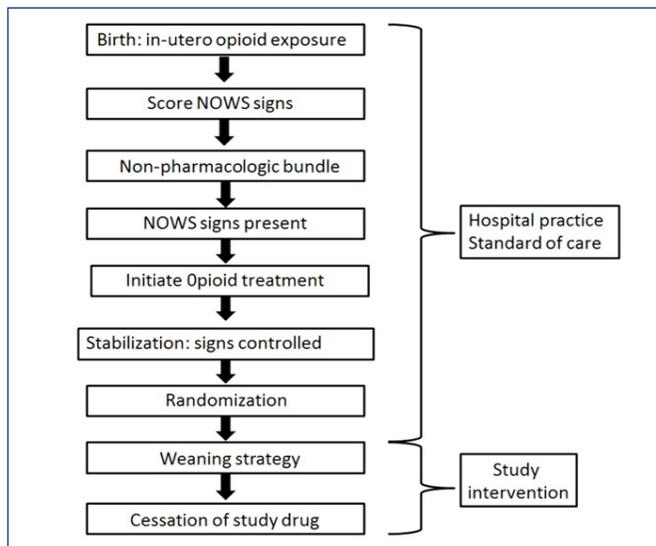


Figure 2. Overview of the Study Intervention

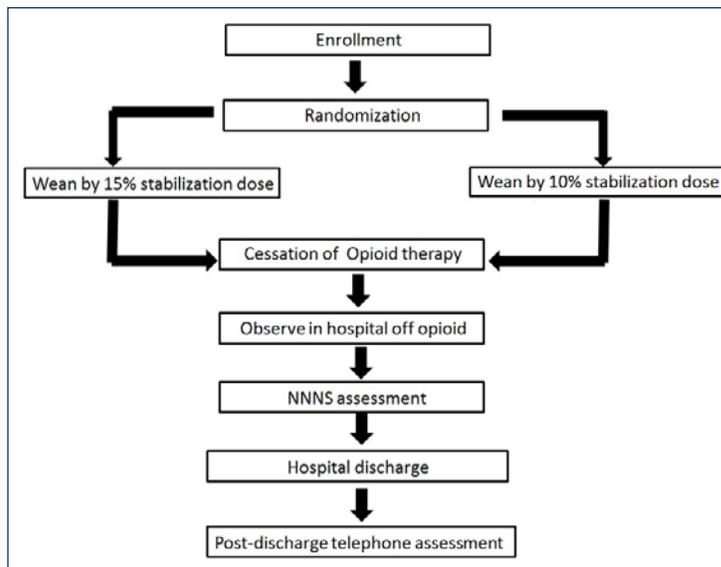


Table 1. Dose Levels of the Rapid-Wean and Slow-Wean Interventions

| Dose | Rapid wean: 15% of stabilization dose | Slow wean: 10% of stabilization dose |
|--------------------|---------------------------------------|--------------------------------------|
| Stabilization Dose | 100% | 100% |
| Dose Level A | 85% | 90% |
| Dose Level B | 70% | 80% |
| Dose Level C | 55% | 70% |
| Dose Level D | 40% | 60% |
| Dose Level E | 25% | 50% |
| Dose Level F | Placebo | 40% |
| Dose Level G | Placebo | 30% |
| Dose Level H | Placebo | 20% |

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