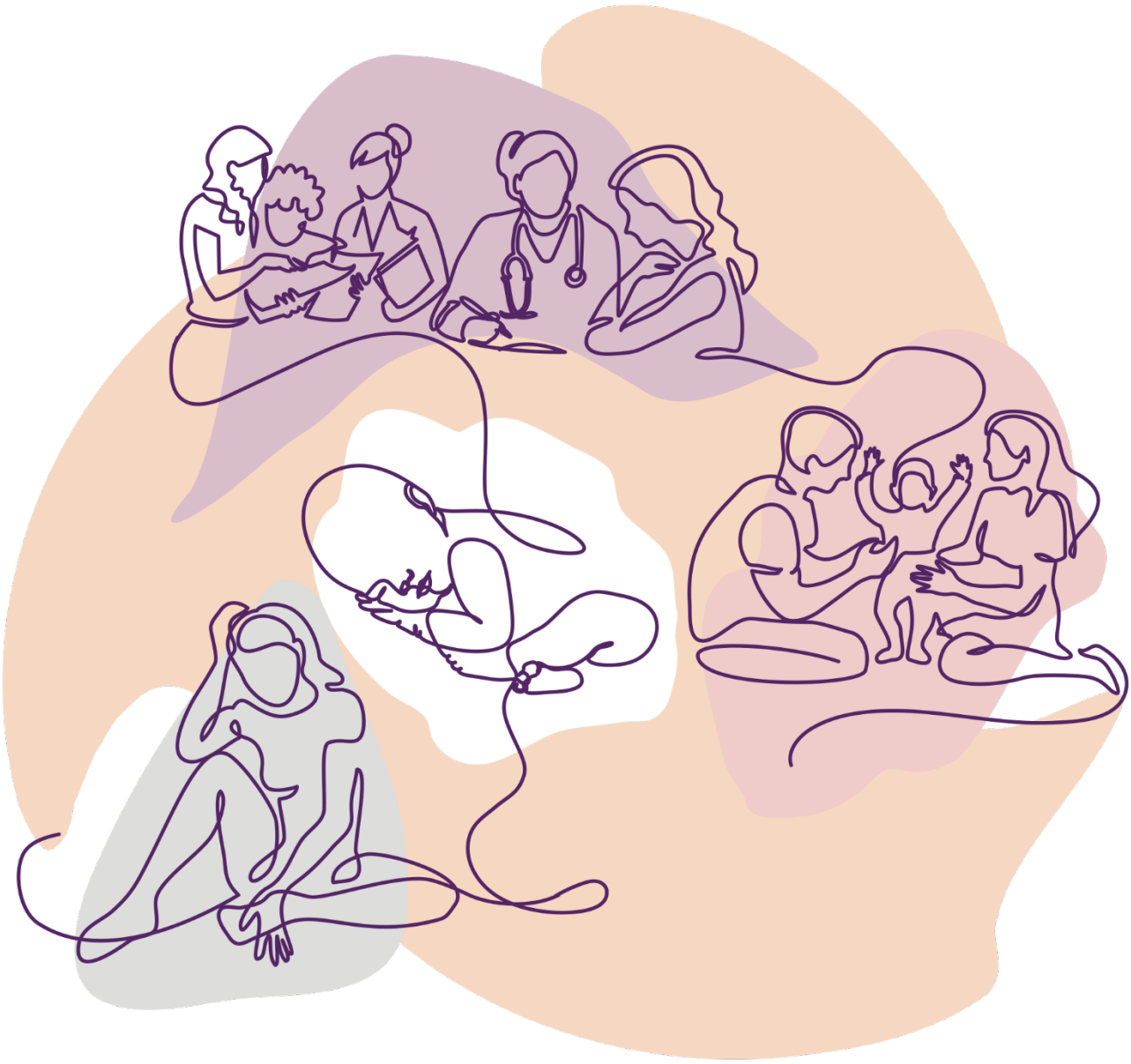
Toward the Use of Buprenorphine in Infants: Scientific and Practical Considerations



WORKSHOP EXECUTIVE SUMMARY

NIH HEAL INITIATIVE

Live Virtual Workshop
August 24-25, 2020
Bethesda, MD 20817

Workshop

In August 2020, the National Institutes of Health's Helping to End Addiction Long-term (HEAL)℠ Initiative supported a workshop – *Toward the Use of Buprenorphine in Infants: Scientific and Practical Considerations* – to review the state of the science, knowledge gaps, and practical considerations regarding use of buprenorphine for the treatment of neonatal opioid withdrawal syndrome (NOWS).[*] The workshop included 221 federal and non-federal experts in maternal-fetal medicine, management of maternal opioid use disorder (OUD), and NOWS who reviewed the current state of the field, ongoing and upcoming trials, the feasibility of a buprenorphine trial, and next steps.

The workshop was structured with 4 specific topic sessions:

- Session 1: State of the Science and Practice – What Has Been Done So Far?
- Session 2: Ongoing/Upcoming Trials – Where Are We Going?
- Session 3: Feasibility – Operational Lessons from Known Studies
- Session 4: Next Step – How Do We Get There?

The workshop was moderated by Andrew Bremer, MD, PhD, MAS, Chief, Pediatric Growth and Nutrition Branch with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Introductory remarks on Day 1 of the workshop were provided by the leadership of both the NICHD (Diana Bianchi, MD, Director) and the National Institute on Drug Abuse (NIDA; Nora Volkow, MD, Director). During her opening remarks, Dr. Bianchi highlighted the current findings from the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) Program – a research program conducted through a collaboration between NICHD's Neonatal Research Network (NRN) and the National Institutes of Health's Institutional Development Award States Pediatric Clinical Trials Network (ISPCTN). Dr. Volkow emphasized the disadvantaged nature of infants affected by NOWS and highlighted the opportunities to improve short- and long-term outcomes in this population through better management of OUD in pregnant women and better management of NOWS in infants.

[*] Video recordings of the workshop are available at:
- Day 1: https://videocast.nih.gov/watch=38354 (as of November 3, 2020: 324 total views)
- Day 2: https://videocast.nih.gov/watch=38356 (as of November 3, 2020: 267 total views)

State of the Science and Practice—What Has Been Done So Far?

The incidence of NOWS in the United States has been increasing, driven by increasing rates of opioid use (illicit and prescription), and likely augmented by the COVID-19 pandemic. The ACT NOW Current Experience study of 1808 infants with NOWS conducted at 30 U.S. sites found considerable variability in what drugs infants were exposed to – illicit drugs, maternal medication for addiction treatment (MAT), and polysubstance exposures (e.g., tobacco, methamphetamine) – and how the mothers and infants are clinically managed (Young LW et al. Pediatrics 2020; *in press*).

The ACT NOW Current Experience study also highlighted considerable site-to-site variation and the lack of a national standard of care for infants with NOWS, suggesting that not all infants are receiving efficient and effective care for NOWS. Many clinical centers are moving toward models of care that emphasize non-pharmacologic approaches (e.g., rooming in, breastfeeding, cuddling), including the Eat, Sleep, and Console (ESC) care model. Alternatively, other clinical centers use care models that, while not exclusive of non-pharmacologic approaches, tend to result in higher rates of pharmacologic therapy for NOWS. Morphine is the most widely used opioid replacement therapy for NOWS, with methadone being a distant second. Adjunctive non-opioid pharmacologic treatments (clonidine and phenobarbital) are added when symptoms persist; however, the risks and benefits of each of these on outcomes is not well understood.

Buprenorphine is a partial agonist at the μ(*mu*)-opioid receptor and is currently used in only a small fraction of NOWS cases. The current sublingual formulation of buprenorphine also contains 30% ethanol, which may be one reason why it has not been widely adopted for use in infants. Much of what is known about its use in infants has been extrapolated from experience in adults. Sublingual buprenorphine has low bioavailability overall and high variability in individual clearance rates. It seems to have a favorable safety profile with less respiratory effects, a lower abuse potential, and longer half-life. A physiologic-based pharmacokinetic model exists; potential refinements of the model may help identify optimal weaning or dosing.

Smaller studies suggest that buprenorphine may be associated with better NOWS outcomes than methadone, which, in turn, is associated with better outcomes than morphine. However, buprenorphine has not been compared directly against morphine. Moreover, no large trials have compared buprenorphine to other medications for the treatment of NOWS.

Ongoing/Upcoming Trials—Where Are We Going?

The ACT NOW Program is currently conducting three large studies evaluating: (1) how rapidly it is safe to wean NOWS infants off of morphine or methadone; (2) whether the ESC approach

can shorten hospital stay more than an approach using the Finnegan Neonatal Abstinence Scoring Tool (FNAST or modified FNAST); and (3) what changes may occur in brain development and associated neurodevelopment and behavioral outcomes in infants with NOWS. All three studies will be assessing neurodevelopment at approximately 24 months of age.

In addition, NIDA's Clinical Trials Network (CTN) is conducting the Medication Treatment for Opioid Use Disorder in Expectant Mothers (MOMs) trial. This pragmatic, randomized trial is comparing mother and infant outcomes in 300 pregnant women given extended-release, subcutaneous versus daily sublingual formulations of buprenorphine.

Beyond these studies, research is underway to identify biomarkers or other predictive risk factors (demographic, clinical, and behavioral) associated with NOWS development and/or severity. Genomic studies are evaluating genetic components affecting NOWS development and severity; however, much larger cohorts are needed to confirm the results. 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 newborns) for whom future interventions might improve outcomes.

Feasibility—What Have We Learned from Existing Studies?

Numerous operational challenges exist for clinical trials addressing NOWS:

Optimizing study design: outcomes for NOWS infants may differ based on the medication used to treat the mother's OUD, when and how long she was treated during pregnancy, whether she received comprehensive treatment versus medication only, and if she used multiple substances. Matching prenatal opioid exposure to the NOWS study drug as a potential way to improve outcomes may also need to be tested.

Finding a sufficient number of study sites for future trials: many potential study sites may be unwilling to change their current clinical practices. As such, it is unclear how many sites remain unbiased enough to maintain equipoise and participate in a randomized clinical trial.

Recruiting participants: consent rates for OUD pregnant women are typically very low because of concerns about privacy, mandatory reporting laws, and potential loss of child custody. How can diversity and inclusion be optimized in future clinical trials?

Randomizing participants: who is randomized – the pregnant mother, the newborn(s), or the combined dyad? Would the participants be randomized by intervention or by hospital?

Blinding and masking: because current morphine, methadone, and buprenorphine formulations have much different routes of administration (intravenous versus sublingual), dose intervals, and weaning protocols, it is particularly challenging to find ways to reliably mask study drugs so that the healthcare providers do not know which one a participant is receiving.

Accessing study drugs 24/7: because many of the study drugs are controlled substances and may require changing dosages at any time during treatment, trial research pharmacies need to be available outside of normal hours of operation or have procedures in place to handle this.

Additional study design and implementation issues: (1) choosing reliable, but easy-to-use assessment tools (some with higher interrater reliability may require extensive training); and (2) managing confounding factors (NICU vs. special-care nurseries; varying non-pharmacologic approaches, and polysubstance use).

Finally, selecting clinically meaningful outcomes and a long- versus short-term primary endpoint has implications for trial length, cost, and implementation. Non-neurodevelopmental outcomes for NOWS include sleep, respiration, and gastrointestinal function. Meaningful neuro-developmental outcomes could include emotion dysregulation (e.g., irritability) throughout the first year of life, which has an increased risk for internalizing and externalizing issues later in life. For long-term outcomes, having a study population in unstable living situations, where the infants may end up in foster care, makes it especially important for research staff to develop relationships with families, guardians, and stakeholders (e.g., foster care organizations) to maintain contact, establish trust, and ensure adherence with long-term follow-up requirements.

Next Step—How Do We Get There?

Statistical considerations for a buprenorphine trial include: (1) selecting pragmatic assessment instruments sensitive enough to quantify treatment effects that are also reliable, consistent, validated, and clinically relevant; (2) carefully calculating statistical power and effect sizes (continuous measures provide more statistical power than categorical); and (3) accounting for the complexity of randomizing mother-infant dyad and confounding factors, such as exposures *in utero* combined with post-natal NOWS treatments and clinical management practices. For the overall trial framework, a non-inferiority design would be more complex. An adaptive trial design (or an adaptive treatment schema) might also be well suited for future trials.

Summary

Considering the gaps of knowledge of whether and when to use buprenorphine to treat NOWS and the potential for better outcomes, a comparative-effectiveness, randomized controlled trial evaluating morphine, methadone, and buprenorphine is needed to inform clinical practice.

Organizing Committee:

Kathryn Adams (NICHD)	Petra Jacobs (NIDA)	Alan E. Simon (OD)
Andrew A. Bremer (NICHD)	Chloe Jordan (NIDA)	Betty Tai (NIDA)
Michelle Freund (NIDA)	Carmen Rosa (NIDA)	Stephanie Wilson Archer (NICHD)

NICHD: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA: National Institute on Drug Abuse
OD: Office of the Director, National Institutes of Health

Acknowledgements:

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NIH HEAL INITIATIVE

MEETING AGENDA

Toward the Use of Buprenorphine in Infants: Scientific and Practical Considerations

August 24-25,
2020 Digital Meeting
Bethesda, Maryland 20817

WORKSHOP OBJECTIVES

- Review the state of the science, knowledge gaps, and practical considerations regarding use of buprenorphine in infants for treatment of neonatal opioid withdrawal syndrome (NOWS)

- Propose next steps to test the safety and efficacy of buprenorphine for treating NOWS

AUGUST 24, 2020 DAY 1

10:30 AM **Welcome and Outline of the Day**
Dr. Andrew Bremer, MD, PhD, NICHD

10:35 AM **Introductory remarks**
Dr. Diana Bianchi, MD, NICHD
Dr. Nora Volkow, MD, NIDA

SESSION 1: STATE OF THE SCIENCE AND PRACTICE – WHAT HAS BEEN DONE SO FAR?

11:00 AM **What Does Practice Currently Look Like?**
Dr. Lori Devlin, DO, MHA, University of Louisville, and
Dr. Leslie Young, MD, University of Vermont

11:30 AM **State of the Science of Buprenorphine in NOWS**
Dr. Walter Kraft, MD, Thomas Jefferson University

12:10 AM **State of the Science of Methadone and Morphine for NOWS**
Dr. Elisha Wachman, MD, Boston University

12:30 PM **Lunch and CONTINUED Discussion**

1:00 PM **SESSION 1: State of the Science Discussion**
Speaker panel and audience discussion
Drs. Leslie Young, Lori Devlin, Walter Kraft, and Elisha Wachman
Moderated by Dr. Andrew Bremer, MD, PhD, NICHD

SESSION 2: ONGOING/UPCOMING TRIALS – WHERE ARE WE GOING?

1:20 PM **ACT NOW Trials**
Weaning, Dr. Adam Czynski, DO, Brown University
Eat/Sleep/Console, Dr. Leslie Young, MD, University of Vermont
OBOE, Dr. Stephanie Merhar, MD, MS, Cincinnati Children's Medical Center

1:40 PM **Networks Available for Participation**
Dr. Betty Tai, PhD, Director CCTN

2:00 PM **MOMs Study -Trial Structure and Associated CTN Trials**
Dr. Theresa Winhusen, PhD, University of Cincinnati

2:20 PM **SESSION 2: Ongoing Trials Discussion**
Speaker panel and audience discussion
Drs. Adam Czynski, Leslie Young, Stephanie Merhar, Theresa Winhusen, and Betty Tai
Moderated by Dr. Robert Lindblad, MD, Emmes

SESSION 3: FEASIBILITY - OPERATIONAL LESSONS FROM KNOWN STUDIES

2:40 PM **Identifying the Research Questions**
Dr. Andrew Bremer, MD, PhD, NICHD

3:00 PM **SUMMARY OF DAY**

AUGUST 25, 2020 DAY 2

10:30 AM **Outline of the Day**
Dr. Andrew Bremer, MD, PhD, NICHD

SESSION 3: FEASIBILITY - OPERATIONAL LESSONS FROM KNOWN STUDIES

10:40 AM **Gaps in Knowledge – Known Operational Challenges**
Dr. Jonathan Davis, MD, Tufts University

11:00 AM **Do The Outcomes for the Baby Differ With the Medication To Treat Opioid Use Disorder In the Mother?**
Dr. Hendrée Jones, PhD, University of North Carolina

11:20 AM **Feasibility for Buprenorphine in Neonates**
Dr. Stephanie Merhar, University of Cincinnati
Dr. Brenda Poindexter, MD, MS, Emory University

11:40 AM **Regulatory Considerations**
Dr. Gioia Guerrieri, DO, FDA

12:00 PM **Where do we need to go?**
Dr. Alan Simon, MD, NIH ECHO

12:20 PM **SESSION 3: Feasibility**
Panel and audience discussion
Drs. Jonathan Davis, Hendrée Jones, Stephanie Merhar, Brenda Poindexter, Gioia Guerrieri, and Alan Simon
Moderated by Dr. Andrew Bremer, MD, PhD, NICHD

12:40 PM **Lunch and CONTINUED Discussion**

SESSION 4: NEXT STEP – HOW DO WE GET THERE

1:10 PM **What Are Clinically Meaningful Neurodevelopmental Outcomes to Measure in Infancy?**
Dr. Lauren S. Wakschlag, PhD, Northwestern University

1:30 PM	**Non-Neurodevelopmental Outcomes in the Care of NOWS Infants** Dr. Amy Salisbury, PhD, Virginia Commonwealth University
1:50 PM	**Treatment Groups and Subgroups – What Should We Be Testing?** Dr. Jonathan Davis, MD, Tufts University
2:10 PM	**Statistical Considerations** Dr. Abby Matthews, PhD, Emmes
2:30 PM	**SESSION 4: Next Steps Discussion** Speaker panel and audience discussion Drs. Lauren S. Wakschlag, Amy Salisbury, Jonathan Davis, and Abby Matthews Moderated by Dr. Andrew Bremer, MD, PhD, NICHD
2:50 PM	**MEETING SUMMARY** Dr. Andrew Bremer, MD, PhD, NICHD
3:00 PM	**Comments from Attendees**
3:45 PM	**ADJOURN**