THE JOURNAL OF PEDIATRICS • www.jpeds.com

Standardizing the Clinical Definition of Opioid Withdrawal in the Neonate

Shahla M. Jilani, MD[1,*], Hendrée E. Jones, PhD[2,3,*], Matthew Grossman, MD[4], Lauren M. Jansson, MD[5], Mishka Terplan, MD, MPH[6], Laura J. Faherty, MD, MPH, MSHP[7,8], Dmitry Khodyakov, PhD, MA[7], Stephen W. Patrick, MD, MPH, MS[9], and Jonathan M. Davis, MD[10]

Objective To standardize the clinical definition of opioid withdrawal in neonates to address challenges in clinical care, quality improvement, research, and public policy for this patient population.

Study design Between October and December 2020, we conducted 2 modified-Delphi panels using ExpertLens, a virtual platform for performing iterative expert engagement panels. Twenty clinical experts specializing in care for the substance-exposed mother–neonate dyad explored the necessity of key evidence-based clinical elements in defining opioid withdrawal in the neonate leading to a diagnosis of neonatal abstinence syndrome (NAS)/neonatal opioid withdrawal syndrome (NOWS). Expert consensus was assessed using descriptive statistics, the RAND/UCLA Appropriateness Method, and thematic analysis of participants' comments.

Results Expert panels concluded the following were required for diagnosis: in utero exposure (known by history, not necessarily by toxicology testing) to opioids with or without the presence of other psychotropic substances, and the presence of at least two of the most common clinical signs characteristic of withdrawal (excessive crying, fragmented sleep, tremors, increased muscle tone, gastrointestinal dysfunction).

Conclusions Results indicate that both a known history of in utero opioid exposure and a distinct set of withdrawal signs are necessary to standardize a definition of neonatal withdrawal. Implementation of a standardized definition requires both patient engagement and a mother–neonate dyadic approach mindful of program and policy implications. *(J Pediatr 2021;■:1-7)*.

The rising incidence of opioid use disorder (OUD) across the US has significantly affected pregnant people with a corresponding increase in neonatal abstinence syndrome (NAS) in their infants.[1,2] Although research indicates that NAS is attributed primarily to in utero opioid exposure, the use of other psychotropic substances also can affect the incidence and severity of withdrawal.[3-9] NAS has been described from a neurodevelopmental perspective as dysregulation in 4 dimensional and interactional neurobehavioral domains: autonomic control, attention/state control, motor/tone control, and sensory processing/modulation.[10-12]

Between 2013 and 2016, the US Food and Drug Administration introduced new terminology designating neonatal opioid withdrawal syndrome (NOWS) as the specific neonatal withdrawal from opioids.[13,14] The use of this new terminology has become more widespread and NOWS is considered a subset of NAS.[15,16] In 2018, the Department of Health and Human Services (HHS) collaborated with leading experts in maternal-child health and identified a fundamental key knowledge gap in the care of the mother–neonate dyad exposed to psychotropic substances: the lack of a standard clinical definition for withdrawal following in utero opioid exposure.[17]

The lack of a standardized definition for opioid withdrawal in the neonate impedes individualized clinical care (eg, misdiagnosis, overtreatment, undertreatment, mistimed treatment, punitive response by legal and child welfare systems) and the larger health care system approach to care for this population (eg, lack of evidence-based protocols for identification and/or treatment). Furthermore, the absence of a standardized definition hinders scientific advances in the field of understanding, preventing, and treating neonatal opioid with-

HHS	Department of Health and Human Services
NAS	Neonatal abstinence syndrome
NOWS	Neonatal opioid withdrawal syndrome
OUD	Opioid use disorder
RAM	RAND/UCLA Appropriateness Method

From the [1]Office of the Assistant Secretary for Health, US Department of Health and Human Services, Washington, DC; [2]Department of Obstetrics and Gynecology, School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD; [4]Department of Pediatrics, Yale School of Medicine, New Haven, CT; [5]Department of Pediatrics, Center for Addiction and Pregnancy, Johns Hopkins University School of Medicine, Baltimore, MD; [6]Friends Research Institute, Baltimore, MD; [7]Pardee RAND Graduate School, Santa Monica, CA; [8]Department of Pediatrics, Boston University School of Medicine, Boston, MA; [9]Division of Neonatology, Department of Pediatrics and Department of Health Policy, Vanderbilt Center for Child Health Policy, Vanderbilt University Medical Center, Nashville, TN; and [10]Division of Newborn Medicine, Tufts Children's Hospital and the Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA

*Contributed equally.

Supported by funding from the Office of the Assistant Secretary for Health at the U.S. Department of Health and Human Services (HHS Contract HHSP233201500038I_75P00120F37023). The views expressed in this article are those of the authors and not necessarily those of the Department of Health and Human Services or its divisions. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2021.12.021

drawal because of variability in clinical trial entry criteria, outcome measures, NAS incidence, prevalence and severity estimates, and assessment of short-and long-term effects.

To develop this clinical definition of neonatal opioid withdrawal, HHS partnered with national experts using modified-Delphi methodologies, such as the RAND/UCLA Appropriateness Method (RAM).[18] In the absence of consensus guidelines or evidence-based criteria, this method permits expert input in assessing clinical appropriateness and validity. The 2-step process began with a focused literature review examining how NAS has been defined in clinical studies, followed by exploring how to standardize the clinical components for the definition that is the focus of the present study.[19]

Methods

Before conducting the focused literature review and modified-Delphi approach, HHS assembled an advisory board to inform the design, development, and step-by-step evaluation of the study. The board comprised 6 experts in maternal-child health specializing in clinical care, research, and NAS policy. Board members determined the study's scope, focus, aims, intent, and content. At study completion, members systematically assessed the quantitative and qualitative findings and developed recommendations for a standard clinical definition of neonatal opioid withdrawal.

In 2020, HHS contracted with the RAND Corporation to apply the modified-Delphi methodology using a virtual platform called ExpertLens to explore expert agreement/disagreement on key clinical elements used in the literature to define NAS and NOWS.[20-23] Among other use cases, the modified-Delphi method has been used previously to develop recommendations on treatment approaches for pregnant women with OUD and their neonates.[24,25] In the present study, expert panels focused on prenatal exposure to opioids with or without other psychotropic substances, clinical signs of withdrawal, and toxicology testing. The framework centered on term neonates (>37 weeks of gestation) with no known medical conditions being evaluated for withdrawal in the first week of life. Our goal was to develop a bedside definition of opioid withdrawal distinct from other diagnoses (eg, hypoglycemia) that may have similar clinical signs. For this study, neonatal withdrawal focused on opioids with or without other substances. The RAND Human Subjects Protection Committee approved the study (study ID: 2020-0293), and the research team developed the modified-Delphi protocol before study launch; the protocol is summarized below.[26]

Twenty experts were recruited with an emphasis on clinical care of neonates with opioid withdrawal, diverse professional disciplines, and geographic diversity. Two expert panels of 10 participants (9 nonfederal) each were then constructed, with a goal of ensuring that at least 9 experts complete the modified-Delphi process, as is standard for RAM panels.[18] This panel size helped ensure participant diversity in terms of their areas of expertise as suggested by RAM guidance while allowing them to interact meaningfully during the online discussion. Moreover, this number of participants met specific requirements for the total number of participants for each panel (a maximum of 9 nonfederal participants permitted for compliance with the Paperwork Reduction Act). Panelists' backgrounds included neonatology, general pediatrics, internal medicine, nursing, and clinical pharmacology. Panel A focused on elements key to a clinical definition of NAS, and panel B focused on a clinical definition of NOWS. The principal distinction between panels A and B was the substitution of the term NOWS for NAS. Both terms were integrated into the study to explore any differences in definitions related to terminology. Stratified randomization was used to assign participants to 1 of the 2 expert panels. Balance was achieved between panels by assigning participants based on professional background and discipline, institutional location, and preferences for using NAS vs NOWS (if disclosed).

Data were collected virtually between October and December 2020 during 2 rating rounds and 1 round of moderated, anonymous, asynchronous discussion. Rating was performed by experts using a 9-point Likert-type scale to answer structured questions focusing on clinical elements used in the literature to define NAS and NOWS. In round 1, panelists provided input on the assessment of neonatal substance withdrawal, including the need for in utero opioid exposure (with or without other psychotropic substances) by clinical history and/or maternal/neonatal toxicology, the most common clinical signs of withdrawal (less common clinical signs were not included), and neurodevelopmental theory on dysregulation in neonatal functioning (**Table I**).[10-12,27] In round 2, a moderated discussion centered on areas of disagreement and clarity.[28] Panelists received feedback on how their responses compared with those of other participant responses in round 1 and if the group reached agreement for each question.[18] Round 3 offered the opportunity for the research team to modify how the questions were asked to address any inconsistencies identified during round 2 and also allowed panelists to review and revise their responses.

For enhanced clarity, 2 round 1 questions asking how "necessary" and "sufficient" experts considered the referenced clinical information were reorganized into 1 round 3 question exploring the need of information for clinical definitions of NAS and NOWS, with 1 = not at all necessary and 9 = very necessary. Scores of 1-3 indicated that the information should not be included; 4-6, that the information was helpful but not required; and 7-9, that the information should be included in the definitions.

Medians and interquartile ranges were calculated from the quantitative rating data, and the qualitative data were analyzed thematically. Consensus was determined automatically after each rating round.[18] Qualitative data were analyzed thematically to provide additional explanations of why participants considered only some information necessary for inclusion into the clinical definition of withdrawal.[26]

To elicit feedback from the broader clinical and research communities, these data and results together with a proposed

Table I. Opioid withdrawal in the neonate: Using a modified-Delphi method to assess clinical criteria to define NAS and NOWS

Round 1: Rating of 2 approaches for assessing opioid withdrawal in the neonate

Clinical signs of withdrawal (Gomez Pomar et al, 2017)[27]	Developmental domains of dysregulation (Velez et al, 2018)[12]
1. How necessary is this information to determine if the neonate has NAS or NOWS? 2. How sufficient is this information alone to determine if the neonate has NAS or NOWS? 3. How characteristic is this specified clinical sign of withdrawal?	1. How different is this approach from the way signs of withdrawal are currently assessed in clinical practice? 2. How useful is this approach for assessing opioid withdrawal in a neonate? 3. Independent of how you currently assess neonates with opioid exposure, how feasible would it be to use this approach to determine if a neonate has NAS or NOWS?

Round 2: Feedback and discussion

Clinical signs of withdrawal	Developmental domains of dysregulation
1. Panelists received reports of round 1 including: • Distribution of group responses to each question, summary of panelist comments • Group median score, interquartile range • Explanation of whether group reached agreement for each question 2. Asynchronous, threaded discussion led by clinical and modified-Delphi experts	

Round 3: Panelist reassessment of individual responses from rounds 1 and 2

Clinical signs of withdrawal	Developmental domains of dysregulation
Panelists were asked: • Modified versions of questions from round 1: 1. How necessary is this information to determine if the neonate has NAS or NOWS? 2. How characteristic is this information (specified clinical sign) of clinical manifestations of withdrawal?	Panelists were asked: • Same questions as in round 1 without modification

Illustrated here is the three-round ExpertLens process based on the modified-Delphi method used to assess clinical criteria for the definition of NAS and NOWS.

clinical definition for neonatal opioid withdrawal were shared and discussed at a national HHS convening in March 2021. Discussants included 75 experts in obstetrics/gynecology, primary care, developmental pediatrics, hospital medicine, neonatology, family medicine, psychiatry, mental/behavioral health, internal medicine, public health, social work, and bioethics.

Results

Of the 20 ExpertLens panelists, 18 completed all 3 rounds and 19 completed at least 1 round. Quantitative analysis indicated expert agreement on the need to include specific substances to which the neonate was exposed in the definition (Table II). Overall, it was apparent that exposure to opioids with or without other psychotropic substances is necessary to establish opioid withdrawal in the neonate. In contrast to exposure history, toxicology testing for the mother and neonate was not deemed essential for the diagnosis of NAS or NOWS but was considered helpful for a better understanding of the clinical presentation (Table II). Collectively, experts indicated that known history was more important than toxicology. If a comprehensive history is not available, then an alternative approach could include toxicology testing (mother following informed consent and/or neonate) that is positive for opioids (with or without other psychotropic drugs). Experts also agreed that NAS and NOWS are used inconsistently and interchangeably when in utero opioid exposure is present. Moreover, they indicated that NAS is often used when a neonate has polysubstance exposure and NOWS is often used when the predominant prenatal exposure is opioids. Several experts suggested renaming the syndrome to be more precise about the type of in utero exposure in conjunction with the development of clinical signs of withdrawal. Their answers to rating questions, open-ended comments, and proposed definitions of NAS and NOWS show varied opinions about several aspects of these clinical definitions. The terminology in current use was considered unclear even after discussing their perspectives with other expert panelists.

In addition to in utero exposures, experts agreed that the presence of clinical signs of withdrawal are necessary for a definition of NAS/NOWS (Table II). Although the NAS panel considered pharmacologic treatment an important component of the definition, the NOWS panel did not. The reasons for this disagreement were not readily apparent; the experts clearly agreed on 5 of the most common signs that are characteristic of both NAS and NOWS: excessive crying, fragmented sleep, tremors, increased muscle tone, and alterations in feeding (Table II). Three other signs were deemed characteristic of NAS only: excessive sucking, feeding intolerance, looseor watery stools. This was an unexpected distinction between the NAS and NOWS panels. Although feeding intolerance and looseor watery stools had lower median scores across both NAS and NOWS panels, they were considered clinically pertinent signs of withdrawal and were included in an overarching category created to denote gastrointestinal dysfunction (eg, altered feeding–hyperphagia or poor feeding, looseor watery stools, feeding intolerance–vomiting or spitting up). In contrast, some

Table II. Summary of ExpertLens ratings of clinical elements assessed for determining opioid withdrawal in the neonate

	NAS panel			NOWS panel		
Rating statements	**Number of responses**	**Median rating**	**Decision**	**Number of responses**	**Median rating**	**Decision**
A. In utero exposure to						
Opioids alone	8	7.5	Necessary	10	6.5	Necessary
Opioids plus other substances (eg, benzodiazepines, SSRIs, tobacco)	8	6	Potentially necessary	10	5	Disagreement
B. Maternal toxicology test results positive for						
Opioids alone	6	7	Necessary	9	4	Potentially necessary
Opioids plus other substances	8	5	Potentially necessary	9	5	Potentially necessary
Neonatal toxicology test results positive for						
Opioids alone	7	3	Unnecessary	9	3	Unnecessary
Opioids plus other substances	8	3	Unnecessary	10	3	Unnecessary
C. Neonate						
Shows signs of opioid withdrawal	8	9	Necessary	10	9	Necessary
Requires medication to treat signs of withdrawal	8	6.5	Necessary	8	3	Unnecessary
Shows dysregulation in at least 1 domain of infant development	8	6	Potentially necessary	9	5	Potentially necessary
Requires nonpharmacologic measures to manage withdrawal	8	5	Potentially necessary	9	4	Potentially necessary
D. Types of clinical signs						
Crying (excessive)	8	8	Characteristic	10	8	Characteristic
Fragmented sleep (<2-3 h after feeding)	7	8	Characteristic	9	8	Characteristic
Tremors (disturbed or undisturbed)	8	8	Characteristic	9	7	Characteristic
Increased muscle tone	7	7	Characteristic	10	8	Characteristic
Alterations in feeding (eg, hyperphagia, poor feeding)	8	7	Characteristic	10	7	Characteristic
Excessive sucking	8	7	Characteristic	9	7	Disagreement
Loose or watery stools	8	6.5	Characteristic	9	6	Potentially characteristic
Feeding intolerance	8	6.5	Characteristic	10	5	Potentially characteristic
Respiratory rate >60/min	8	5	Potentially characteristic	8	5	Potentially characteristic
Nasal stuffiness	7	5	Potentially characteristic	9	3	Uncharacteristic

SSRI, selective serotonin reuptake inhibitor.
Final ratings from the NAS and NOWS panels. Gray shading indicates agreement among experts and a group median of ≥6.5 (see text for more details).

experts indicated that individual clinical signs of withdrawal and the time they take to develop after birth should not be included, because NAS/NOWS has variable expression and these signs can be nonspecific and occur secondary to other causes. Multiple signs seen concurrently increased their confidence that NAS/NOWS had developed.

When assessing an alternative approach to evaluating neonatal withdrawal using neurobehavioral domains of dysregulation (autonomic control, attention/state control, motor/tone control, sensory processing/modulation) experts in both panels agreed that the approach is feasible and either useful or potentially useful (data not shown). In addition, both panels indicated the need for further research to evaluate this alternative approach for neonatal assessment.

At the national convening, several important themes arose from discussions of key considerations for standardizing the clinical definition of neonatal opioid withdrawal: a clear delineation of definition use case, including how it should and should not be used; requirement for 2 clinical signs vs 1 sign to balance the specificity of withdrawal with other neonatal conditions while remaining sensitive to milder presentations of withdrawal; thoughtful consideration of avoiding unintended consequences and stigmatization; and broader implications of the clinical definition on the dyad and family. Accordingly, foundational principles were created to specify uses for the definition (Table III). These principles are grounded in both evidence-based medicine and bioethics, prioritize the dyad, and avoid misuse of the clinical definition. Specifically, the definition of opioid withdrawal in the neonate is for clinical, research, and public health purposes only and should not be misconstrued as evidence of harm or used to prosecute, punish, or remove neonates from parental custody.

Taken together with the ExpertLens findings, recommended clinical criteria for the diagnosis of neonatal opioid withdrawal consists of in utero exposure (known by history, not necessarily by toxicology) to opioids with or without other psychotropic substances and the presence of at least 2 of the most common clinical signs characteristic of withdrawal: excessive crying, fragmented sleep, tremors, increased muscle tone, and gastrointestinal dysfunction (Table IV). Opioid withdrawal, recognized as a continuum of variable expression in neonates and not limited to

Table III. Foundational principles for the clinical definition of opioid withdrawal in the neonate

1. Substance use disorder is a disease requiring compassionate, ethical, equitable, and evidence-based care.
2. The maternal–neonate dyad is the appropriate subject of care; this definition is intended to identify clinical and supportive care needs of the dyad; shared interests should be prioritized.
3. A diagnosis of NAS or NOWS does not imply harm, nor should it be used to assess child social welfare risk or status. It should not be used to prosecute or punish the mother or as evidence to remove a neonate from parental custody.
4. Environmental factors, family influences, and social structures strongly influence neonatal outcome and should be recognized.

neonates who require pharmacotherapy, assumes that alternative etiologies (eg, hypoglycemia) have been eliminated. Although not intended to determine severity, the definition emphasizes the inclusion of even subtle clinical presentations of withdrawal, including those requiring only nonpharmacologic supportive therapies.

Discussion

Using modified-Delphi methodology implemented via the ExpertLens process, we have developed a standardized definition of opioid withdrawal in neonates. The overarching goal of this study focused on identifying key clinical elements considered essential to bedside diagnostic criteria, which are practical and broadly applicable to clinical practice. Findings from a focused literature review suggest that most studies used subjective NAS scoring/assessment tools and administrative coding as key elements to define opioid withdrawal in the neonate, with not all studies citing in utero opioid exposure as an inclusion criterion.[19] Inconsistencies in diagnostic criteria and in how NAS has been historically defined in clinical studies of mother–neonate dyads supports the need for a standardized definition. By examining expert agreement and disagreement on clinical elements that have typically defined NAS and NOWS, this study addresses a historical gap in the definition of opioid withdrawal in neonates.

Table IV. Recommended clinical definition of opioid withdrawal in the neonate

Substance withdrawal encompasses a continuum of variable clinical expression from neonate to neonate; the diagnosis is not limited only to neonates who require pharmacotherapy.

Purpose: to identify neonates who experience withdrawal after in utero exposure to opioids to (1) support the dyad through specific and comprehensive services to both neonates and their parents/caregivers and (2) provide an accurate and universally applied definition for clinical care and research. Alternative etiologies causing a similar presentation in neonates should first be eliminated.

Clinical criteria for diagnosis consist of the presence of clinical elements 1 and 2:

(1) **In utero exposure** to opioids with or without other psychotropic substances (recommended to be collected via confidential maternal self-report; toxicology testing also acceptable with maternal informed consent)

(2) **Clinical signs** characteristic of substance withdrawal; any 2 of the following signs qualify:
- Excessive crying (easily irritable)
- Fragmented sleep (<2-3 h after feeding)
- Tremors (disturbed or undisturbed)
- Increased muscle tone (stiff muscles)
- Gastrointestinal dysfunction (hyperphagia, poor feeding, feeding intolerance, loose or watery stools).

Principal informants in this discussion included experts caring for the substance-exposed mother–neonate dyad with findings relevant to both clinical care and clinical research. Emphasis was placed on clinical elements completely independent of scoring/assessment tools, nonpharmacologic and pharmacologic care, and administrative coding. Elements shown to be necessary in this study included in utero opioid exposure with or without other psychotropic substances and at least 2 of the 5 most common clinical signs characteristic of opioid withdrawal in the neonate. This proposed definition may be applied in the context of NAS and/or NOWS, with NAS considered exposure to opioids with or without other psychotropic substances and NOWS considered exposure to opioids alone. The emphasis on the clinical definition is important not only for clinical trials of new and existing treatments, but also for advancing needs assessments and care for the mother–neonate dyad, which is a priority for public health experts and public advocates.

Although a dedicated evaluation of current coding guidelines was beyond the scope of the current work, standardizing the definition may mitigate inconsistencies in the accuracy and reproducibility of claims, surveillance, and scientific data. Although claims data has a high positive predictive value for NAS, it requires an accurate clinical diagnosis and may miss cases of mild withdrawal.[29] Likewise, considerable variability in NAS definitions exists among states, which may be impacted by longstanding variation in the upstream clinical diagnosis and a corresponding gap in consistent bedside criteria.[30,31] Lack of consistent inclusion criteria/definitions in research limits its utility and promotes variability in clinical trial enrollment.[32]

The diagnosis of opioid withdrawal in the neonate, although necessary for clinical care and follow-up, can be of particular consequence to the mother and the mother–neonate dyad. It identifies the mother as having taken opioids during pregnancy and can initiate child welfare investigations, potentially leading to loss of parental custody. Dyadic care is potentially compromised by punitive policies such as defining substance use in pregnancy as child abuse.[33,34] Even though maternal well-being is critical to neonatal health and development, pregnant and parenting people with OUD experience discrimination, barriers to care, and criminalization.[35-38] This recommended clinical definition of opioid withdrawal in the neonate does not imply that the pregnant person has harmed the neonate, and mothers should not be blamed for any adverse outcomes. In addition, a diagnosis of NAS or NOWS should not be used to remove a child from parental custody, because this diagnosis can be due to a myriad of factors.[39] Medications for pregnant people with

OUD reduce maternal overdose deaths and preterm births but can increase the risk of NAS/NOWS.[40] We added these foundational principles to ensure that clinical definitions were not interpreted as evidence of harm or used for child welfare determinations (**Table III**).

Although considerable knowledge gaps remain, the American Academy of Pediatrics policy statement on opioid use in pregnancy notes that effective care for the dyad centers around a comprehensive focus on the needs of both the mother and neonate.[41] Similarly, the Substance Abuse and Mental Health Services Administration's 2018 guidance recommends an integrated approach to caring for the mother and neonate including timely and destigmatized access to clinical and supportive care.[24,25] In 2020, the American Academy of Pediatrics published its statement on NOWS outlining progress and deficiencies in approaches to maternal OUD, social and mental health needs assessments, connection to appropriate community resources, and postdischarge care for the dyad, including early intervention services.[42] In many instances, these comprehensive resources can be provided only once a formal diagnosis of NAS or NOWS is made. This may explain why a recent study showed that postdischarge mortality rates were significantly lower in opioid-exposed neonates with a diagnosis of NAS or NOWS compared with those without this diagnosis.[43]

This study has several limitations. Only 10 participants participated in each panel. Not all participants provided their input; 1 panelist did not complete the study, and 1 completed only 1 of the 3 rounds. Although this panel size aligned with both Paperwork Reduction Act requirements and with a standard RAM panel design, it might have been beneficial to include a broader range of clinicians' perspectives on the topic.[18] By eliciting feedback from a larger national group of stakeholders with expertise in caring for the substance-exposed mother–neonate dyad, the HHS national convening enabled more extensive expert engagement on study findings and conclusions. Although diverse professional, geographic, and clinical practice backgrounds were represented, family medicine experts were underrepresented, possibly influencing ratings and responses. Assessing the severity of opioid withdrawal was considered outside the scope of the present study. Instead, a threshold balancing sensitivity with specificity for criteria that could identify even mild cases of opioid withdrawal (which otherwise could go unrecognized) was emphasized. Although the aim was to capture a majority of withdrawal cases, an emphasis on mild signs conceivably could contribute to more diagnoses and/or false-positive cases, depending on interpretation of the criteria. The qualitative biases that may have influenced the recommended (most common) clinical criteria for a diagnosis typically with variable presentation are recognized. Differences in maternal opioid use were omitted. Coding guidelines were beyond the scope of this clinically focused study and were not addressed. Future studies should explore using the present definition to further refine *International Classification of Diseases, Tenth Revision, Clinical Modification* coding for increased accuracy.

The current recommendations are a set of clinical criteria intended for use at the bedside, distinct from state-level case surveillance definitions and implementation. Previous work by the Council of State and Territorial Epidemiologists to advance standardizing provider-level NAS reporting and coding practices led to the development of a 2-tiered approach to NAS case definitions.[44] Tier 1 relied on case reporting to public health authorities based on clinical records and provider reporting, whereas tier 2 reported administrative data from *International Classification of Diseases, Tenth Revision, Clinical Modification* codes. This recent step forward can be enhanced with the development of the presently proposed set of clinical "bedside" criteria for opioid withdrawal in neonates. Essential next steps include a focus on measures of severity and development of a strategic implementation plan using this clinical definition for clinical care at the bedside, engaging patients with lived experience; coding and real-world data; entry criteria into clinical trials; and policy decisions and public health.

To standardize a clinical definition, findings from this study indicate that clinical criteria required are a known history of in utero opioid exposure and a distinct set of signs of withdrawal. We propose this standardized clinical definition for use by clinicians, researchers, and public health advocates to improve not only scientific discovery, but also clinical needs assessment and care delivery for mother–neonate dyads and families. ■

*Acknowledgments available at www.jpeds.com (**Appendix**).*

Submitted for publication Sep 6, 2021; last revision received Nov 22, 2021; accepted Dec 5, 2021.

References

1. Hirai AH, Ko JY, Owens PL, Stocks C, Patrick SW. Neonatal abstinence syndrome and maternal opioid-related diagnoses in the US, 2010-2017. JAMA 2021;325:146-55.
2. Finnegan LP, Kron RE, Connaughton JF, Emich JP. Assessment and treatment of abstinence in the infant of the drug-dependent mother. Int J Clin Pharmacol Biopharm 1975;12:19-32.
3. Choo RE, Huestis MA, Schroeder JR, Shin AS, Jones HE. Neonatal abstinence syndrome in methadone-exposed infants is altered by level of prenatal tobacco exposure. Drug Alcohol Depend 2004;75:253-60.
4. Kaltenbach K, Holbrook AM, Coyle MG, Heil SH, Salisbury AL, Stine SM, et al. Predicting treatment for neonatal abstinence syndrome in infants born to women maintained on opioid agonist medication. Addiction 2012;107(Suppl 1_01):45-52.
5. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. JAMA 2012;307:1934-40.
6. Patrick SW, Dudley J, Martin PR, Harrell FE, Warren MD, Hartmann KE, et al. Prescription opioid epidemic and infant outcomes. Pediatrics 2015;135:842-50.
7. Sanlorenzo LA, Cooper WO, Dudley JA, Stratton S, Maalouf FI, Patrick SW. Increased severity of neonatal abstinence syndrome associated with concomitant antenatal opioid and benzodiazepine exposure. Hosp Pediatr 2019;9:569-75.
8. Huybrechts KF, Bateman BT, Desai RJ, Hernandez-Diaz S, Rough K, Mogun H, et al. Risk of neonatal drug withdrawal after intrauterine

co-exposure to opioids and psychotropic medications: cohort study. BMJ 2017;358:j3326.
9. Patrick SW, Slaughter JC, Harrell FE Jr, Martin PR, Hartmann K, Dudley J, et al. Development and validation of a model to predict neonatal abstinence syndrome. J Pediatr 2021;229:154-60.e6.
10. Velez ML, Jordan CJ, Jansson LM. Reconceptualizing non-pharmacologic approaches to Neonatal Abstinence Syndrome (NAS) and Neonatal Opioid Withdrawal Syndrome (NOWS): a theoretical and evidence-based approach. Neurotoxicol Teratol 2021;88:107020.
11. Velez ML, Jordan C, Jansson LM. Reconceptualizing non-pharmacologic approaches to Neonatal Abstinence Syndrome (NAS) and Neonatal Opioid Withdrawal Syndrome (NOWS): a theoretical and evidence-based approach. Part II: The clinical application of nonpharmacologic care for NAS/NOWS. Neurotoxicol Teratol 2021;88:107032.
12. Velez ML, McConnell K, Spencer N, Montoya L, Tuten M, Jansson LM. Prenatal buprenorphine exposure and neonatal neurobehavioral functioning. Early Hum Dev 2018;117:7-14.
13. FDA news release: FDA announces safety labeling changes and post-market study requirements for extended-release and long-acting opioid analgesics – new boxed warning to include neonatal opioid withdrawal syndrome. 2013. Accessed January 12, 2021. http://wayback.archive-it.org/7993/20170112130229/http:/www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm
14. FDA.gov. FDA announces enhanced warnings for immediate-release opioid pain medications related to risks of misuse, abuse, addiction, overdose and death. 2016. Accessed January 12, 2021. https://www.fda.gov/news-events/press-announcements/fda-announces-enhanced-warnings-immediate-release-opioid-pain-medications-related-risks-misuse-abuse
15. Schiff DM, Grossman MR. Beyond the Finnegan scoring system: novel assessment and diagnostic techniques for the opioid-exposed infant. Semin Fetal Neonatal Med 2019;24:115-20.
16. Piccotti L, Voigtman B, Vongsa R, Nellhaus EM, Rodriguez KJ, Davies TH, et al. Neonatal opioid withdrawal syndrome: a developmental care approach. Neonatal Netw 2019;38:160-9.
17. Jilani SM, Giroir BP. Neonatal abstinence syndrome: leveraging health information technology to develop a data-driven national policy approach. Public Health Rep 2020;135:173-6.
18. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, et al. The RAND/UCLA appropriateness method user's manual. Santa Monica (CA): RAND Corporation; 2001.
19. Jilani SM, Jordan CJ, Jansson LM, Davis JM. Definitions of neonatal abstinence syndrome in clinical studies of mother and infants: an expert literature review. J Perinatol 2021;41:1364-71.
20. Dalal S, Khodyakov D, Srinivasan R, Straus S, Adams J. ExpertLens: a system for eliciting opinions from a large pool of non-collocated experts with diverse knowledge. Technol Forecast Soc Change 2011;78:1426-44.
21. Zia A, Kouides P, Khodyakov D, Dao E, Lavin M, Kadir RA, et al. Standardizing care to manage bleeding disorders in adolescents with heavy menses—a joint project from the ISTH pediatric/neonatal and women's health SSCs. J Thrombos Haemost 2020;18:2759-74.
22. Barber CE, Mosher DP, Ahluwalia V, Zummer M, Marshall DA, Choquette D, et al. Development of a Canadian Core Clinical Dataset to support high-quality care for Canadian patients with rheumatoid arthritis. J Rheumatol 2017;44:1813-22.
23. Barber CE, Marshall DA, Alvarez N, Mancini GBJ, Lacaille D, Keeling S, et al. Development of cardiovascular quality indicators for rheumatoid arthritis: results from an international expert panel using a novel online process. J Rheumatol 2015;42:1548-55.
24. Substance Abuse and Mental Health Services Administration. Clinical guidance for treating pregnant and parenting women with opioid use disorder and their infants. 2018. Accessed January 12, 2021. https://store.samhsa.gov/system/files/sma18-5054.pdf
25. Klaman SL, Isaacs K, Leopold A, Perpich J, Hayashi S, Vender J, et al. Treating women who are pregnant and parenting for opioid use disorder and the concurrent care of their infants and children: literature to support national guidance. J Addict Med 2017;11:178-90.
26. Khodyakov D, Jilani SM, Dellva S, Faherty LJ. Informing the development of a standardized clinical definition of neonatal abstinence syndrome: protocol for a modified-Delphi expert panel. JMIR Res Protoc 2021;10:e25387.
27. Gomez Pomar E, Finnegan LP, Devlin L, Bada H, Concina VA, Ibonia KT, et al. Simplification of the Finnegan Neonatal Abstinence Scoring System: retrospective study of two institutions in the USA. BMJ Open 2017;7:e016176.
28. Khodyakov D, Grant S, Denger B, Kinnett K, Martin A, Peay H, et al. Practical considerations in using online modified-Delphi approaches to engage patients and other stakeholders in clinical practice guideline development. Patient 2020;13:11-21.
29. Maalouf F, Cooper WO, Stratton SM, Dudley JA, Ko J, Banerji A, et al. Positive predictive value of administrative data for neonatal abstinence syndrome. Pediatrics 2019;143:e20174183.
30. Chiang KV, Okoroh EM, Kasehagen LJ, Garcia-Saavedra LF, Ko JY. Standardization of state definitions for neonatal abstinence syndrome surveillance and the opioid crisis. Am J Public Health 2019;109:1193-7.
31. Doherty KM, Scott TA, Morad A, Crook T, McNeer E, Lovell KS, et al. Evaluating definitions for neonatal abstinence syndrome. Pediatrics 2021;147. e2020007393.
32. Wachman EM, Schiff DM, Silverstein M. Neonatal abstinence syndrome: advances in diagnosis and treatment. JAMA 2018;319:1362-74.
33. Guttmacher Institute. Substance use and pregnancy. State legislation tracker. 2021. Accessed April 27, 2021. https://www.guttmacher.org/state-policy/explore/substance-use-during-pregnancy
34. Atkins DN, Piette Durrance C. State policies that treat prenatal substance use as child abuse or neglect fail to achieve their intended goals. Health Aff (Millwood) 2020;39:756-63.
35. Terplan M, Kennedy-Hendricks A, Chisolm MS. Prenatal substance use: exploring assumptions of maternal unfitness. Subst Abuse 2015;9(Suppl 2):1-4.
36. Frazer Z, McConnell K, Jansson LM. Treatment for substance use disorders in pregnant women: motivators and barriers. Drug Alcohol Depend 2019;205:107652.
37. O'Rourke-Suchoff D, Sobel L, Holland E, Perkins R, Saia K, Bell S. The labor and birth experience of women with opioid use disorder: a qualitative study. Women Birth 2020;33:592-7.
38. Patrick SW, Richards MR, Dupont WD, McNeer E, Buntin MB, Martin PR, et al. Association of pregnancy and insurance status with treatment access for opioid use disorder. JAMA Netw Open 2020;3:e2013456.
39. Richardson SS, Daniels CR, Gillman MW, Golden J, Kukla R, Kuzawa C, et al. Society: don't blame the mothers. Nature 2014;512:131-2.
40. Schiff DM, Nielsen T, Terplan M, Hood M, Bernson D, Diop H, et al. Fatal and nonfatal overdose among pregnant and postpartum women in Massachusetts. Obstet Gynecol 2018;132:466-74.
41. Patrick SW, Schiff DM. A public health response to opioid use in pregnancy. Pediatrics 2017;139:e20164070.
42. Patrick SW, Barfield WD, Poindexter BB. Neonatal opioid withdrawal syndrome. Pediatrics 2020;146. e2020029074.
43. Leyenaar JK, Schaefer AP, Wasserman JR, Moen EL, O'Malley AJ, Goodman DC. Infant mortality associated with prenatal opioid exposure. JAMA Pediatr 2021;175:706-14.
44. Council of State and Territorial Epidemiologists (CSTE). Neonatal abstinence syndrome (NAS) standardized suveillance case definition position statement. Accessed May 22, 2021. https://kansaspqc.org/wp-content/uploads/2019/06/Slides-Kasehagen-Jackson-Coding-NAS.pdf

Appendix

We gratefully thank our Expert Panel: Walter Kraft, MD, Jefferson University Medical Center; Jodi Jackson, MD, University of Missouri-Kansas City School of Medicine; Lily Lou, MD, University of Illinois Chicago; Elisha Wachman, MD, Boston Medical Center; Corrie McDaniel, DO, University of Washington; Mark Hudak, MD, University of Florida College of Medicine; Davida Schiff, MD, MassGeneral Hospital for Children; David Golembeski, MD, Rady Children's Hospital, University of California San Diego; Lori Devlin, DO, University of Louisville School of Medicine; Renate Savich, MD, Children's of Mississippi University of Mississippi Medical Center; Lisa Cleveland, PNP, University of Texas San Antonio School of Nursing; Michele Walsh, MD, UH Rainbow Babies and Children's Hospital, Case Western Reserve University; Gerri Baer, MD, U.S. Food and Drug Administration; Anna Morad, MD, Monroe Carell Jr. Children's Hospital at Vanderbilt; Wanda Barfield, MD, MPH, Division of Reproductive Health, Center for Disease Control and Prevention; Munish Gupta, MD, Beth Israel Deaconess Medical Center; Jennifer McAllister, MD, Cincinnati Children's Hospital Medical Center; Neera Goyal, MD, Sidney Kimmel College of Medicine at Thomas Jefferson University and Nemours/AI DuPont Hospital for Children; Madge Buus-Frank, DNP, The Dartmouth Institute for Health Policy and Clinical Practice and The Children's Hospital at Dartmouth. We thank members of the RAND team, Stephanie Dellva, Emily Dao and Quiana Fulton. We also thank RADM Michael F. Iademarco, USPHS, Office of the Assistant Secretary for Health, HHS; Leith States, MD, MPH, MBA, Office of Science and Medicine, HHS Office of the Assistant Secretary for Health; and Dorothy Fink, MD, Office on Women's Health, HHS Office of the Assistant Secretary for Health for their immeasurable support of this work. Finally, the authors greatly acknowledge Anne Drapkin Lyerly, MD, Department of Social Medicine, University of North Carolina at Chapel Hill, for her thoughtful discussions and contribution to the bioethical foundational principles described in this work.