Procedural Pain Assessments for Neonates at Risk of Neonatal Opioid Withdrawal Syndrome

A Scoping Review

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Objectives: To identify evidence for pain assessment during acute procedures in hospitalized neonates at risk of neonatal opioid withdrawal syndrome (NOWS).

Methods: This scoping review was conducted using the JBI scoping review methodology. The search strategy focused on identifying inpatient neonates undergoing acute painful procedures. Databases searched are MEDLINE, CINAHL, Embase, PsycInfo, and Scopus. The relevant data were extracted by 2 reviewers and the results were summarized in a narrative description and presented in a tabular format, including the components of participants, concept, and context.

Results: A total of 22,731 unique studies were screened, with 5 studies ultimately included. Of these studies, 2 included neonates at risk of NOWS but did not report pain responses separately. The 3 remaining studies observed procedural pain in opioid-exposed neonates compared with neonates without opioid exposure during heel lance. Pain assessment methods included physiological responses and validated composite pain scores. When using composite pain tools, 1 study showed higher pain response in opioid-exposed neonates, while the other 2 studies showed the same or lower pain response. For skin conductance, the findings from 2 studies were discrepant, with 1 study reporting higher pain response in opioid-exposed neonates and the other showing no statistically significant difference.

Discussion: There is a need for more studies designed to examine the influence of opioid exposure and withdrawal on pain responding and management in neonates. As there is currently limited evidence to guide clinical care, clinicians should continue to use validated composite pain assessment tools and pain management strategies.

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Neonatal opioid withdrawal syndrome (NOWS), which may also be referred to as neonatal abstinence syndrome (NAS), is a collection of withdrawal symptoms that arise from prenatal exposure to opioid substances (eg, morphine, heroin, and buprenorphine). Any neonate born to a birth parent who identified as having sustained opioid use during pregnancy is at risk for NOWS. With the opioid epidemic in Canada, an increasing number of neonates are born at risk of NOWS.[1] In Canada, the number of neonates born at risk of NOWS has tripled between 2003 and 2014, with Nova Scotia and New Brunswick having the highest incidences.[2] The United States has similar trends, with NOWS incidence rising over 5-fold from 2004 to 2014.[3] In addition, the incidence of NOWS is increasing disproportionately in rural areas.[4] In the United States, between 2004 and 2013, the incidence of NOWS in rural births increased from 1.2 to 7.5 per 1000 hospital births.[5] Comparatively, incidence in urban births only increased from 1.4 to 4.8 per 1000 hospital births.[5] Despite the increasing global prevalence, neonates at risk of NOWS remain a heavily under-researched population.

Neonates experiencing NOWS have longer hospital stays and are more likely to be admitted to the neonatal intensive care unit (NICU) than nonopioid-exposed neonates.[3,6] The average length of hospitalization for a healthy full-term neonate is 24 hours;[7] however, a neonate born at risk of NOWS will spend 15 to 24 days in the hospital, where they are routinely exposed to clinically required painful procedures.[2,8,9] All neonates, regardless of health status, are exposed to pain from routine procedures such as intramuscular vitamin K administration[10] and heel lances to collect blood for routine metabolic screening. In the NICU, neonates may experience up to 10 painful procedures per day.[11] Common painful procedures for hospitalized neonates include venipuncture, heel lances, intravenous line insertion, nasogastric or orogastric tube insertion, suction, and intramuscular injections.[11] Repeated exposure to pain is associated with immediate physiological instability and long-term adverse effects on neurocognitive development and pain sensitivity in neonates.[12,13] Since neonates at risk of NOWS experience more painful procedures, they are also at a greater risk of experiencing adverse effects.

Accurate pain assessment by health care practitioners is necessary for adequate pain management to decrease the adverse effects of untreated pain in neonates. Despite the development and clinical use of approximately 4 dozen pain assessment tools over the last 3 decades, there continues to be considerable diversity and no "gold standard" approach for measuring acute pain in neonates. The majority of pain assessment measures that have been developed to date are based on contextual (eg, gestational age, biological sex), behavioral (eg, crying, facial expressions, body movements), and physiological (eg, changes in vital signs) indicators.[14,15] Physiological indicators that are used to assess pain include changes in heart rate (HR), blood pressure, oxygen saturation, cortisol, skin conductance (SC), and neurophysiology.[16] However, while commonly used to quantify pain, physiological measures have limitations—most notably that they do not selectively respond to pain and vary with other contextual factors such as stress, gestational and postnatal age, and exposure to prior painful procedures. Composite biobehavioral pain scores (which combine behavioral, physiological, and contextual indicators) developed to address these limitations have the most extensive psychometric evaluation and are the most frequently used in clinical practice.[16] However, these tools also have recognized limitations, including concerns regarding lack of specificity to pain, dissociation between physiological and behavioral components, and lack of application in neonates with specific conditions.[16]

The pain assessment methods commonly used for neonates do not address the full picture of NOWS neonates. Research regarding pain assessments for procedural pain in neonates often excludes neonates at risk of NOWS, as the manifestations of NOWS may mimic pain behaviors commonly used to assess neonatal pain. Crying (behavioral) and changes in respiratory rate (physiological) are signs of withdrawal in neonates at risk of NOWS and indicators of pain used alone and as components of some composite pain scores. For example, in a study examining acute procedural pain in neonates at risk of NOWS, higher behavioral distress and more difficulty self-soothing in opioid-exposed neonates were observed compared with nonopioid-exposed neonates.[17] Accurate pain assessment is essential for guiding treatment and evaluating its effectiveness. However, due to the overlap of NOWS symptoms with common pain assessment indicators and the frequent exclusion of this population from pain assessment research; the reliability, validity, responsiveness, and clinical utility of standard tools for neonates at risk of NOWS remain unclear. There is a need for evidence syntheses examining pre-existing pain indicators, tools, and their use for neonates with different conditions to make recommendations for research and clinical practice.[18]

A preliminary search of PROSPERO, the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis was conducted, and no current or in-progress evidence syntheses regarding pain assessments for procedural pain in neonates at risk of NOWS were identified. Scoping reviews are a form of knowledge synthesis used to identify and analyze available evidence and knowledge gaps.[19–21] Given this, a scoping review method[19–21] was selected as the most appropriate review approach to map existing evidence related to pain assessments in neonates at risk of NOWS and identify gaps and opportunities for research. See Supplemental File 1 for all abbreviations in this report, Supplemental Digital Content 1, http://links.lww.com/CJP/B232.

REVIEW QUESTION

What evidence is available on pain assessments for procedural pain in hospitalized neonates at risk of NOWS?

METHODS

This scoping review was conducted in accordance with the JBI methodology for scoping reviews[19–21] and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).[22,23] This review was conducted in accordance with an a priori protocol.[24]

Inclusion Criteria

The inclusion and exclusion criteria follow the JBI *Participant*, *Content*, and *Context* (PCC) framework.[19–21]

Participants

This review considered studies that included full-term (born > 37 wk gestational age) and preterm (born < 36 6/7 wk gestational age) neonates (< 30 d of age) at risk for NOWS. Studies reporting on any neonate born to a birth parent who identified as opioid using for the whole duration of the pregnancy were considered eligible. Any study reporting on procedural pain assessment in neonates was reviewed to determine if neonates at risk of NOWS were reported separately from those not at risk.

Concept

This review considered any studies that included measurement of pain response during an invasive/pain-inducing tissue-breaking or nontissue-breaking acute procedure and/or recovery from such procedures (eg, heel lances, intramuscular injections, chest tube insertion, intubation). Measurements may use any of the following: (1) behavioral pain indicators (eg, audible cry, pain-related facial expressions, limb movements), (2) physiological pain indicators (eg, HR, RR, oxygen saturation, neurophysiologic indicators, hormonal indicators), and/or (3) validated composite pain scores (eg, Premature Infant Pain Profile-Revised [PIPP-R],[54] Neonatal Pain Agitation and Sedation Scale [N-PASS],[55,56] Douleur Aiguë du Nouveau-né [DAN],[57] Behavioral Indicators of Infant Pain [BIIP]).[58]

Context

In-patient neonates cared for in any hospital setting (including labor and delivery units, postpartum units, neonatal intensive care units, or special care nurseries) were considered eligible. In this review, the term in-patient was used broadly to capture all perinatal and neonatal hospital contexts where a neonate may undergo pain assessment.

Types of Sources

For this scoping review, we considered experimental and quasi-experimental study designs, including randomized controlled trials, nonrandomized controlled trials, before-and-after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies were considered for inclusion. We also considered descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies eligible for inclusion. Finally, evidence syntheses that meet inclusion

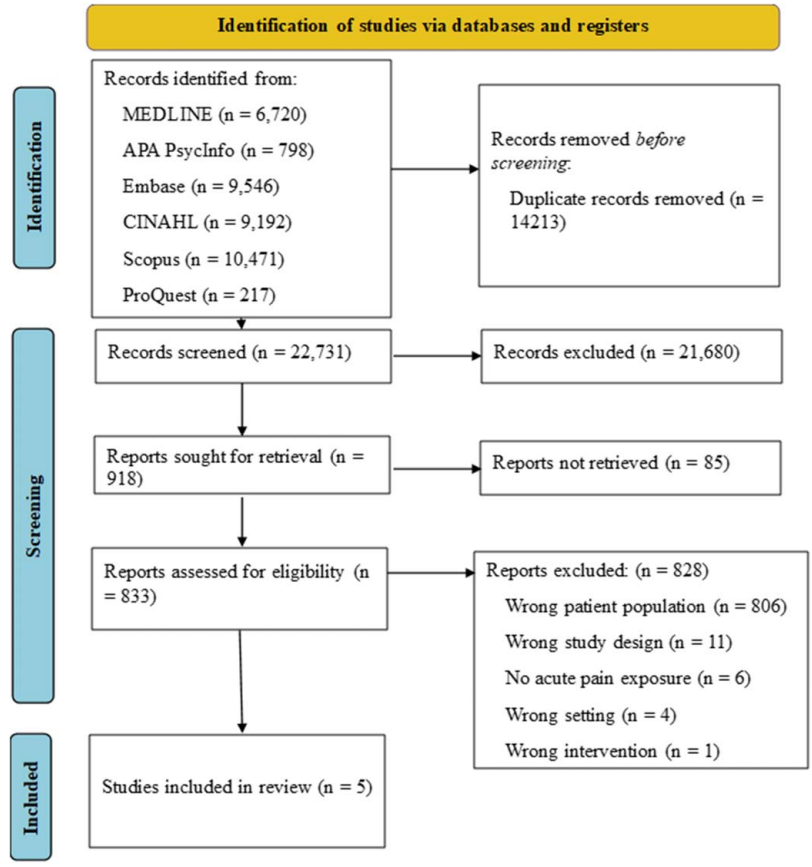

FIGURE 1. The PRISMA diagram details the search and selection process of studies included in the review.[22,23]

criteria were considered, and the reference lists were examined for additional sources reporting on procedural pain assessment in neonates at risk of NOWS.

Search Strategy

A 3-step search strategy was undertaken for this review to locate peer-reviewed published and unpublished primary studies. An initial limited search of MEDLINE (Ovid) and CINAHL (EBSCO) was conducted to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used by a health sciences librarian to develop a complete search strategy for MEDLINE (Ovid) (see Appendix I, Supplemental Digital Content 2, http://links.lww.com/CJP/B233). Text words were identified using WordFreq, the word frequency tool in Systematic Review Accelerator.[25] The initial search strategy was peer-reviewed by a second librarian using Peer Review of Electronic Search Strategies (PRESS).[26] The search strategy, including all identified keywords and index terms, was adapted for each included database or information source by a librarian using the Polyglot Search Translator, where possible.[27] The databases searched include CINAHL (EBSCO), Embase (Elsevier), PsycInfo (EBSCO), and Scopus (Elsevier). Finally, a search of ProQuest Dissertation and Theses Global was conducted to find additional sources of unpublished literature. The reference list of all included sources of evidence was screened for additional studies. Given that the first literature on infant pain was published in 1987, we considered studies published after 1985 to ensure we were inclusive of all literature on infant pain assessment.[28] We did not exclude studies based on language for inclusiveness and used translation services for the screening and data extraction process as needed. It is essential to note that titles, abstracts, or index terms of reports do not always contain or expressly state the specific demographics of the population when reporting on procedural pain assessments in neonates. When completing a trial search using an initial search strategy that included the terms "NOWS" and "NAS," a small number of papers were identified, and specific eligible target papers previously found by the team were not included. Utilizing a search strategy that did not include these terms identified specific target papers within a larger sample of potential sources. For this reason, NOWS is not included as a concept in our search to ensure we inclusively captured all literature reporting on neonatal procedural pain assessments that may include neonates at risk of NOWS. The complete search strategies for all databases are provided in Appendix I, Supplemental Digital Content 2, http://links.lww.com/CJP/B233.

Study/Source of Evidence Selection

All data management occurred in Covidence (Veritas Health Innovation, Melbourne, Australia). Following the search, all identified citations were collated and uploaded into Covidence and all duplicates were removed. A pilot test of 10% of source's titles and abstracts was screened using the

eligibility criteria by 2 reviewers (authors JL and BB).[26] Following the pilot test, titles and abstracts were screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. If the title and abstract of a report did not describe the demographics of the neonatal population included in the study but met other inclusion criteria, it was moved to full-text screening. The full-text of selected citations was assessed in detail against the inclusion criteria by 2 independent reviewers (authors JL and BB). This full-text review included a review of the sample characteristics in each report to determine if neonates at risk of NOWS were included in the study. Any disagreements between the reviewers at each stage of the selection process were resolved through discussion, or with an additional reviewer. The search results and the study inclusion process are reported in full and presented in a PRISMA-ScR flow diagram (Fig. 1).[22,23]

Data Extraction

Data were extracted from each study by 2 independent reviewers using a data extraction tool developed by the review team (see Appendix II, Supplemental Digital Content 3, http://links.lww.com/CJP/B234). The data extracted included specific details about the participants, concept, context, and key findings relevant to assessing procedural pain in neonates at risk of NOWS. Any reviewer disagreements were resolved through discussion, or with an additional reviewer.

Data Analysis and Presentation

This review aimed to map and record the number of available sources on pain assessment for procedural pain in neonates at risk of NOWS. The data are presented in tabular form to identify and summarize the evidence. This includes details of the participants (neonates at risk of NOWS), concept (measurement of pain response during or after a pain-inducing acute procedure), and context (in-patient hospitalized neonates) (Table 1). A narrative summary accompanies the tabulated results to describe the study characteristics, findings, and their relation to the research question.

RESULTS

Study Inclusion

The database searches identified 36,944 records. After removing 14,213 duplicate records, the search yielded 22,731 records for title and abstract screening. During title and abstract screening, 21,680 records were excluded leaving 918 eligible for full-text review. The team made extensive efforts to obtain full texts of all records for review at that screening stage, including accessing library networks across 3 Canadian universities. However, 85 records (representing only 0.37% of all records screened after de-duplication and 9.25% of those selected for full-text review) could not be retrieved. Most of these records were published before 2003 (before the marked rise in NOWS incidence) and appeared unlikely to meet inclusion based on detailed abstract-level review and discussion between 2 team members (JL, BB). Upon full-text review, 828 reports were excluded due to wrong patient population (n = 806), wrong study design (n = 11), no acute pain exposure (n = 6), wrong setting (n = 4), or wrong intervention (n = 1). Five studies met the eligibility criteria. The PRISMA-ScR flow diagram (Fig. 1) outlines the search process for this review.

Characteristics of Included Studies

The 5 included studies were primarily published in the 2010s, aside from 1 study published in 1993. Where the studies were conducted varied, with 2 in the United States,[17,29] 1 in the United Kingdom,[32] Germany,[31] and Australia.[30] The clinical setting also varied with studies taking place in intensive care units, special care nurseries, or postnatal wards. All 5 studies used heel lance as the pain-inducing acute procedure. The sample sizes ranged from 27 to 112 neonates, with a mean of 52.6. Various pain assessment indicators were used, including skin conductance (SC),[17,31] Premature Infant Pain Profile (PIPP),[30] Neonatal Facial Coding System (NFCS),[17] Bernese Pain Scale for Neonates (BPSN),[31] vital signs (heart rate, respiration rate, oxygen saturation),[29] and electroencephalograms (EEG).[32] The characteristics of each study are further outlined in Table 1.

Review Findings

The aim of this review was to identify available evidence for procedural pain assessments for neonates at risk of NOWS. Gonsalves et al[29] and Jones et al[32] did not separate nonopioid-exposed and opioid-exposed neonates, therefore, the data could not be analyzed further. Review findings are narratively summarized based on pain assessment indicators; specifically, physiological pain indicators and validated composite pain scores.

Physiological Pain Indicators

Gonsalves et al[29] reports on physiological indicators of HR, RR, and oxygen saturation in 35 neonates, one of whom was prenatally exposed to heroin. The study does not differentiate the results for this NOWS neonate from the rest of the sample. In terms of HR, RR, and oxygen saturation, the study found significant differences between painful and nonpainful procedures. The mean HR varied from 157.3 +/- 22.0 during nonpainful procedures to 164.8 +/- 15.4 bpm during painful procedures. The RR mean varied from 47.4 +/- 18.8 (nonpainful) to 53.9 +/- 15.6 breaths/min (painful). The mean oxygen saturation varied from 91.6 +/- 5.5% (nonpainful) to 86.9 +/- 8.8% (painful). The authors discuss that these changes appear to be indices of preterm infants' procedural pain response, but only for those infants who do not cry or change facial expressions.

Oji-Mmuo et al [17] reports on SC and the NFCS in 37 neonates, of which 22 had prenatal opioid exposure. SC was reported as electrodermal responses per second (EDR/sec, which indicates the number of changes of SC in a second), and the mean of peaks (which indicates the amplitude of rapid increases in SC). For the entire sample of neonates, EDR/sec showed a direct positive correlation with the NFCS scores in response to heel lances, suggesting that SC and behavioral responses to pain are related. In response to a heel lance, the mean of peaks and EDR/sec were both higher in the opioid-exposed group (0.05 μS and 0.25 μS) compared with the nonopioid-exposed group (0.02 μS and 0.14 μS). This study also reported that during the recovery period the mean of peaks for the opioid-exposed group was 4 times higher than that of the control group (0.08 μS compared with 0.02 μS).

Schubach et al,[31] reports on SC and the BPSN in 27 neonates, 12 of whom were at risk of NOWS. This study reports SC regarding the number of SC fluctuations per second (NSCF/s; comparable to EDR/s), the amplitude of SC fluctuations (ASCF; comparable to mean of peaks),

TABLE 1. Characteristics of Included Studies

Study	Gonsalves & Mercer [29]	Marceau et al[30]	Schubach et al[31]	Jones L et al[32]	Oji-Mmuo et al[17]
Setting	Two intensive care units (ICUs) in the United States	Special care nursery and postnatal ward in Australia	Neonatal centers and a maternity ward in Germany	Postnatal, special care, or intensive care wards in the UK	IV tertiary neonatal intensive case unit (NICU) or well-baby nursery in the United States
Study aim	To investigate the physiological responses of preterm infants to procedures that are routinely performed in NICUs	To compare the effects of oral sucrose in methadone-exposed neonates to that of unexposed neonates	To compare skin conductance (SC) in neonates with neonatal opioid withdrawal syndrome (NOWS) to that of unexposed neonates	To observe neonatal pain processing	To evaluate the utility of SC and the Neonatal Facial Coding System (NFCS) for pain assessment in opioid-exposed and unexposed neonates
Design	Clinical descriptive	Prospective observational	Not stated	Experimental dataset	Prospective, single center pilot
Sample	35 preterm infants (18 male, 17 female)	52 infants	27 newborns (12 nonsubstance exposed)	112 neonates	37 neonates
NOWS characteristics	1 neonate exposed to heroin	26 neonates were methadone-exposed in utero	Neonates were exposed to methadone (n = 11) or buprenorphine (n = 1) in utero	Some neonates included had neonatal abstinence diagnosis.	82% of neonates were exposed to methadone or buprenorphine, the other 18% were exposed to morphine or oxycodone
Pain-inducing acute procedure	Heel lance or injection	Heel lance	Heel lance	Heel lance	Heel lance
Pain assessment indicator(s) or tool(s)	Heart rate, respiration rate, oxygen saturation	Premature Infant Pain Profile (PIPP)[45]	SC and Bernese Pain Scale for Neonates (BPSN)[59]	Electroencephalogram (EEG) and PIPP	SC and NFCS
Pain assessment outcomes	For all included neonates there was a significant difference between painful and nonpainful procedures. The neonate with opioid exposure is not differentiated.	Median PIPP scores were the same for methadone-exposed neonates and nonexposed neonates.	No statistically significant changes in SC. BPSN partly indicated mild pain for both groups, with the opioid-exposed group scoring lower.	No dataset available.	Higher mean of peaks and electrodermal responses per second (EDR/sec) in response to heel lance in opioid-exposed group. NFCS scores increased in both groups during heel lance, with the opioid-exposed group having higher scores.

and mean SC levels. During a heel lance, the change in SC was not statistically significant, but there was a slight trend towards a higher mean level of SC in opioid-exposed neonates. The authors did not report the mean values, but the included p values comparing SC responses from 600 seconds before to 15 seconds after the heel lance in both groups were reported. The opioid-exposed neonate's SC parameters were NSCF/s ($P = 0.48$), ASCF ($P = 0.80$), and mean SC level ($P = 0.05$). For the nonexposed neonates: NSCF/s ($P = 0.08$), ASCF ($P = 0.08$), and mean SC level ($P = 0.45$). In addition, neonates who received opiates (n = 10) had significantly higher SC parameters than those who received only supportive treatment (n = 2); however, the compared groups were of very unequal size. The same applies to the effect of different birth parent maintenance therapies (buprenorphine [n = 1] vs. methadone [n = 11]), where no statistically significant effect was found.

Validated Composite Pain Scores

In the study by Marceau et al,[30] median PIPP scores were compared between methadone-exposed neonates and nonexposed neonates at the time of the heel lance, with both groups scoring a 2 out of 18. In the recovery period (30 s after heel lance), methadone-exposed neonates had a median score of 2, and nonexposed neonates had a median score of 1. For pain management, both groups of neonates received 0.05 mL oral sucrose 2 minutes before the heel lance, 0.05 mL at the time of the procedure, and an additional 0.05 mL every 1 to 2 minutes until completion. From the facial scoring component of the PIPP, both groups of neonates scored 0 at the time of the heel lance and 30 seconds after. HR and oxygen saturation were recorded for the PIPP. The mean HR of the methadone-exposed neonates before the heel lance was 140 +/- 20 bpm compared with 142 +/- 22 bpm in the nonexposed neonates, during the heel lance 145 +/- 15 bpm compared with 146 +/- 23 bpm, and 30 seconds after 157 +/- 15 bpm compared with 148 +/- 15 bpm. The mean oxygen saturation before the heel lance was 97 +/- 2% for the methadone-exposed neonates compared with 97 +/- 2.5% in the nonexposed neonates, during the heel lance 97 +/- 2.5% compared with 96 +/- 2.2%, and 30 seconds after 98 +/- 1.5 compared with 97 +/- 1.8%. The study also did a subanalysis to compare the median PIPP scores between methadone-exposed neonates who developed NOWS and methadone-exposed neonates who did not develop NOWS. Neonates with NOWS had a median PIPP score of 2 versus 1 in neonates without at the time of the heel lance ($P = 0.65$). Neonates with NOWS also had a higher median score 30 seconds after the heel lance when compared with neonates without (1 vs. 0; $P = 0.09$). In addition, the study compared methadone-exposed neonates who developed NOWS before the heel lance and those who developed NOWS after. The median PIPP score during the procedure in the neonates that had already developed NOWS was 2 compared with 2 ($P = 0.84$), and 30 seconds after the scores were 2 compared with 1 ($P = 0.03$).

The NFCS was used in the study by Oji-Mmuo et al[17] NFCS scores are reported in a bar graph; therefore, the graph was digitized and processed through PlotDigitizer (version 3.1.5, 2023) for approximate values. It is reported that mean NFCS scores were higher at baseline (before pain exposure) for the opioid-exposed group (38) than the control group (13, $P = 0.003$). Both groups' scores increased in response to the heel lance, with the opioid-exposed group having higher scores (58) than nonopioid-exposed (48). Brow bulge, eye squeeze, nasolabial furrowing, and opening of lips were more than 2 times higher in the opioid-exposed group during the heel lance. During the recovery period, both groups' scores decreased.

The BPSN is used in the study by Schubach et al.[31] The opioid-exposed group's mean score was 7.65, compared with the mean score of 9.45 in the control group. The study provided no statistical analysis of the BPSN outcome.

DISCUSSION

The aim of this scoping review was to identify evidence for procedural pain assessment in neonates at risk of NOWS. Using a JBI scoping review methodology,[19–21] a search strategy was developed in partnership with a health science librarian to map evidence regarding procedural pain assessment in neonates at risk of NOWS. We identified 5 studies that met our inclusion criteria. Of the 5 papers, 2 were about pain processing and included neonates at risk of NOWS; however, they did not report on opioid-exposed neonates separately from the other neonates included in the sample. The 3 remaining papers were prospective studies observing pain response in opioid-exposed neonates compared with neonates without opioid exposure during a clinically required heel lance for blood collection. These studies measure pain using SC and various composite pain scores, specifically, the BPSN, NFCS, and PIPP.

There were mixed findings across the 3 studies reporting on composite pain scores. During a clinically required heel lance, the mean BPSN score was 7.65 in opioid-exposed neonates compared with a mean score of 9.45 in neonates without opioid exposure.[31] For the BPSN, a score of 11 or more indicates pain; thus, these pain scores indicate low pain in both groups. Pain measured using the NFCS during a heel lance showed a mean score of 58 in opioid-exposed neonates compared with 48 in nonexposed neonates.[17] These pain scores indicate that all neonates were experiencing pain during the procedure, with neonates exposed to opioids having higher pain. The mean pain score measured using the NFCS was also higher at baseline (before heel lance) for opioid-exposed neonates (38 compared with 13).[17] Pain measured using the PIPP showed a median score of 2 at the time of a heel lance for both methadone-exposed and unexposed, indicating low or no pain.[30] From just the facial scoring component of the PIPP, both groups of neonates scored 0 at the time of a heel lance.[30] Within the methadone-exposed group, neonates who developed NOWS (defined as 3 consecutive Finnegan Neonatal Abstinence Scoring System[33,34] (FNASS) scores of 8 or greater) had a median PIPP score of 2 at the time of heel lance compared with a median PIPP score of 1 in neonates who did not develop NOWS.[30]

There were also mixed findings across the 2 studies that utilized SC to measure pain. During a clinically required heel lance, EDR/sec and the mean of peaks were higher in the opioid-exposed group (0.05 μS and 0.25 μS) compared with neonates without opioid exposure (0.02 μS and 0.14 μS).[17] During the recovery period following heel lance, the mean of peaks was 4 times higher for the opioid-exposed neonates compared with the nonopioid-exposed neonates.[17] In another study, pain measured using SC showed no statistically significant changes during a heel lance.[31]

The mixed findings across studies could result from different clinical characteristics of the neonatal populations. The neonates in all 3 studies had similar gestational ages at

birth, with the majority being born full-term. However, postnatal age at the time of observation varied across the studies, with researchers observing neonates at 24 to 48 hours old,[17] 48 to 72 hours old,[30] and at a median age of 72 hours.[31] The postnatal time of observation can directly influence withdrawal symptoms, which could influence SC and pain scores. Withdrawal manifestations typically reflect the half-life of the opioid involved.[4] The studies mainly looked at methadone (n = 26/26 included neonates;[30] n = 16/22 included neonates;[17] n = 11/12 included neonates[31]) as well as exposure to buprenorphine (n = 2/22 included neonates;[17] n = 1/12 included neonates[31]) and other unspecified opioids (n = 4/22 included neonates;[17] n = 7/12 included neonates[31]). Exposure to methadone and buprenorphine would typically result in withdrawal manifestations around 48 to 72 hours of age, whereas a neonate exposed to heroin would exhibit manifestations around 12 to 24 hours of age.[4] The variation in age, combined with the type of in utero opioid exposure, could account for some of the variability in the findings. A study by Esposito and colleagues observed higher risks of NOWS and severe NOWS in neonates born to birth parents who used oxycodone, methadone, morphine, or hydromorphone compared with similar cumulative exposure to hydrocodone.[35] A higher pain response, indicated by NFCS pain score, was observed in opioid-exposed neonates at 24 to 48 hours postnatal age, who were predominantly exposed to methadone.[17] Methadone-exposed neonates observed at 48 to 72 hours postnatal age had the same PIPP scores as unexposed neonates that indicated low to no pain; however, the mean PIPP score was higher in the subset of methadone-exposed neonates who developed NOWS compared with neonates who did not.[30] The BPSN scores measured low to no pain in both groups when observed at 72 hours postnatal age in predominantly methadone-exposed neonates.[31] It is important to note that the neonates, in the study using the PIPP, all received sucrose for pain management during the procedure,[30] compared with no pain management[31] or supportive care, including non-nutritive sucking and/or swaddling.[17] Sucrose is effective in reducing pain in healthy neonates[36] and this study suggests it has efficacy in neonates at risk of NOWS, as demonstrated by the low pain scores.[17] Another important note is that sucrose had been identified to blunt behavioral pain responses, but not necessarily physiological ones.[37–39] In a systematic review and meta-analysis by Stevens and colleagues, neonates receiving sucrose had similar HRs to those who received a placebo during a heel lance.[36] Non-nutritive sucking and swaddling have also shown some benefit in reducing neonatal pain, but this study still observed higher pain scores in opioid-exposed neonates.[40,41] Interactions of type of drug, withdrawal intensity, pain assessment timing, and pain management use likely underpin these mixed findings, necessitating additional research.

Exposure to other substances, such as nicotine, can increase the severity of NOWS, and this may have impacted the findings, as several birth parents in the included studies smoked during pregnancy. In 1 study, 23 of the 26 neonates were exposed to cigarette smoking and methadone.[30] In another study, 18 of 22 neonates were exposed to nicotine along with opioids.[17] Cigarette exposure was reported in 7 out of 12 neonates that were also exposed to opioids.[30] Notably, a study by Tekin et al[42] demonstrated that being born to a parent who smoked was associated with increased behavioral response to pain measured using a composite pain score, the N-PASS, during a vaccination injection procedure. In our findings, methadone-exposed neonates in the study by Marceau et al[30] had a higher frequency of smoking birth parents. While pain measured with the PIPP indicated low to no pain in this group, subgroup analyses examining the influence of nicotine exposure were not conducted.[30] Another study with similar frequency of nicotine exposure reported higher NFCS pain scores for opioid-exposed neonates.[17] The same study reported a direct positive correlation between the NFCS and SC measured.[17] Prenatal alcohol exposure can also alter the pain response of neonates and thus could have impacted the pain assessment.[43] Only 1 study reported alcohol exposure (n = 1 neonate); thus, the findings and ability to make conclusions regarding alcohol and pain intensity are limited.[31] Another cause of the conflicting findings could be a result of the differences between the composite pain scores used. Various behavioral indicators are used across the 3 composite pain scores. The PIPP and NFCS share brow bulge, eye squeeze, and nasolabial furrow indicators. The NFCS indicators brow bulge, eye squeeze, nasolabial furrowing, and opening of lips were more than 2 times higher in the opioid-exposed group during a heel lance.[17] These specific behavioral indicators are not included in the BPSN, which could account for the lower mean score during a heel lance identified in 1 study.[31] The BPSN also includes crying, posture, and breathing as indicators, but these are all manifestations of NOWS[31,32] meaning this could have affected the pain score. Grimacing is another manifestation of NOWS[31,32] that some neonates at risk would display, affecting the facial expression indicators in all 3 composite pain scores. The PIPP is the only composite pain score reported that includes contextual indicators, gestational age, and neonatal behavioral state. Withdrawal manifestations and pain processes can be affected by younger gestational age at birth, with preterm neonates typically exhibiting NOWS manifestations later than term infants (around 5 to 7 d of age).[44] However, the study reporting on PIPP scores only included full-term neonates.[30]

The BPSN and the PIPP use physiological indicators of HR and oxygen saturation. Unfortunately, the study reporting on the BPSN did not include data specific to the physiological indicators.[31] Using the PIPP, the mean HR of the methadone-exposed neonates before the heel lance was 140 +/- 20 bpm compared with 142 +/- 22 bpm in the nonexposed neonates.[30] During the heel lance, the mean HR was 145 +/- 15 bpm compared with 146 +/- 23 bpm, and 30 seconds after 157 +/- 15 bpm compared with 148 +/- 15 bpm.[30] Increase in HR results in a higher PIPP score, indicating pain.[45–47] As alterations in HR are a manifestation of NOWS, this could have affected the pain scores. While not statistically significantly different, HR was higher for opioid-exposed neonates in the recovery period.[30] Oji-Mmuo and colleagues found that during the recovery period SC mean of peaks was 4 times higher in the opioid-exposed group (0.08 μS compared with 0.02 μS).[17] Taken together, these findings suggest that physiology recovery may be slower in neonates with opioid exposure, even when receiving sucrose[30] or non-nutritive sucking and/or swaddling.[17] As NOWS manifestations reflect neurobehavioral dysregulation,[44] it is likely these neonates experience poor physiological recovery. To provide a better understanding of pain recovery in opioid-exposed neonates, future research should ensure it includes measures of physiological regulation (HR, RR, SC, hormonal indicators, etc.) and reports on these outcomes.

Variability in SC findings could result from neonatal clinical characteristics like postnatal age of observation and type of opioid exposure. SC varies within the first week of life as the sympathetic nervous system associated with arousal is still developing.[48] In one study with predominantly methadone-exposed neonates, the mean of peaks and EDR/sec were higher in the opioid-exposed neonates during a heel lance at 24 to 48 hours postnatal age.[17] Another study observed neonates at 72 hours postnatal age and during a heel lance found no statistically significant changes between the methadone-exposed neonates and those with no opioid exposure.[30] Conflicting findings could also be a result of NOWS manifestations. A study by Oji-Mmuo et al[49] examined the utility of SC in detecting sympathetic activation of neonatal withdrawal in a nonpain context. They found that neonates who required pharmacological treatment for NOWS had a higher baseline mean of peaks than those who did not require treatment.[49] One of the studies in this review, published by the same researchers, reports a higher mean of peaks in the opioid-exposed group.[17] The SC changes could reflect pain response, NOWS manifestations, or both. The study by Oji-Mmuo et al[49] also showed that SC positively correlated with the Modified Finnegan Neonatal Scoring System (MFNSS),[60] a NOWS assessment tool. Whereas a study included in this review found no correlation between measures of SC and the FNASS[61] scores, another NOWS assessment tool includes similar components.[31] Given that the MFNSS and FNASS are applied differently, it is impossible to conclude if differences in neonates or in the tools are driving the variable findings.

Implications for Research

To enhance the overall understanding of pain in this population, continued focused and funded research on the influence of withdrawal on neonatal pain response is required. As there are many other pain assessment methods (including hormonal indicators, neurophysiologic indicators, and other validated composite pain scores), we recommend that future research explore these different assessments for use in neonates at risk of NOWS. Future pain assessment research with this population needs to include physiological and behavioral indicators, and the potential differential impact of withdrawal on these indicators. Furthermore, all the studies in this review assessed procedural pain during heel lance. Given that neonates experience other pain-inducing procedures, we recommend that future research evaluate different acute procedures. Future research may also consider observing pain response in neonates at different postnatal ages, as the timing of pain exposure may impact pain symptoms. Research exploring the type of prenatal opioid exposure (eg, methadone, buprenorphine, heroin), and exposure to other substances (eg, nicotine, cannabis, and alcohol) would also be beneficial in adding to our understanding of withdrawal and pain. Finally, the studies included in this review varied concerning pain management, including no treatment,[31] swaddling combined with non-nutritive sucking,[17] or sucrose.[30] Given the demonstrated benefit of parent-infant SSC and breastfeeding for providing comfort during withdrawal in a nonpain context,[27,50] future research examining the influence of these interventions on pain intensity in neonates exposed to opioids is needed. Overall, there is a need for future experimental and observational studies with adequate sample sizes that control for confounding variables (eg, type of opioid exposure, exposure to other substances, gestational age, postnatal age, and pain treatment) designed to examine the influence of opioid exposure and withdrawal on pain responding and management in neonates.

Implications for Clinical Practice

As there is limited evidence to guide clinical care, clinicians should continue to use evidence-based composite pain scores and pain management strategies for all neonates, including those at risk of NOWS. Composite pain scores like the PIPP, although not thoroughly evaluated in neonates at risk of NOWS, are reliable and valid pain assessment tools for healthy neonates.[45–47] These tools should continue to be used during acute painful procedures to inform pain management. In terms of pain management, sucrose is one of the most extensively researched pain management interventions for procedural pain in neonates.[36] Sucrose is typically administered via a syringe on the surface of the tongue 2 minutes before the neonate undergoes a painful procedure. Many studies have been conducted evaluating the efficacy and safety of oral sucrose; showing that sucrose reduces procedural pain with minimal or no side effects.[36] Sucrose has also been tested for neonates at risk of NOWS in one study, indicating that it is an effective pain management intervention in this population.[30] Breastfeeding during a pain-inducing procedure has similar effectiveness to sucrose in regard to pain relief.[51,52] SSC promotes autonomic stability, state regulation, and bonding between parent and neonate; thus, during an acute painful procedure, SSC can be effective for reducing pain.[50] Research shows that breastfeeding and SSC are effective pain management interventions for heel lances in healthy full-term and preterm neonates.[40,41] Evidence suggests that breastfeeding and SSC also provide benefits to manage NOWS symptoms.[50,52] These nonpharmacological interventions are foundational in the "Eat, Sleep, Console" care model for neonates at risk of NOWS.[53] This approach uses nonpharmacologic interventions as first-line treatment with initiation of pharmacological interventions as needed.[53] Breastfeeding and SSC are the primary nonpharmacological interventions used, as they promote the parent-infant dyad and reduce withdrawal symptoms.[53] Further research is needed evaluating breastfeeding, SSC, and sucrose for neonates at risk of NOWS during acute painful procedures. We recommend using these interventions (breastfeeding, SSC, sucrose) during acute procedures, prioritizing parent-led nonpharmacological care.

Strengths and Limitations

Our research team had multiple authors with JBI training and designation, and we utilized rigorous JBI methodology. The PRISMA-ScR[22,23] was used to guide all phases of the study, including the literature search and inclusion process. The screening and data extraction processes were completed by 2 independent reviewers. The search strategy, created by a health sciences librarian, was comprehensive, and multiple databases were searched. However, it cannot be certain that all relevant research was included. As detailed clinical data is not necessarily reported on in all procedural pain studies, it is possible some studies including neonates at risk of NOWS could have been missed. Some of the reports (n = 85) identified from the search could not be obtained; thus, some content may be missing from the review for this reason. As only 5 studies

were included, the strength of the conclusions is limited. Although all sources included procedural pain assessment in neonates at risk of NOWS, specific pain assessment data were not always included.

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