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Potential problems and solutions of opioid-based treatment in neonatal opioid withdrawal syndrome (NOWS): a scoping review protocol

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ABSTRACT

Introduction Rates of neonatal opioid withdrawal syndrome (NOWS) have paralleled the rise of opioid use during pregnancy. While short-term phenotypic symptoms of NOWS are well defined, molecular implications and long-term effects are not well understood. Preferred and first-line of treatment for NOWS includes non-pharmacological interventions; however, more than half of the NOWS neonates will need pharmacologics, with opioids as the primary pharmacological treatment. While effective at reducing symptoms, treating NOWS with opioids is paradoxical given that molecular and long-term developmental consequences with such exposure are unknown. There is a pressing need for a synthesis of current and potential/ novel treatment options for NOWS.

Methods and analysis Following a published framework, a scoping review will be conducted to evaluate NOWS treatment, including established treatment methods and novel methods that may warrant future research and consideration. Using broad search terms, as well as Medical Subject Headings terms, a comprehensive search of PubMed, Cochrane Library, Google Scholar, CINAHL, Web of Science and Scopus, as well as references of selected literature, will take place, followed by a screening procedure to identify included and excluded articles. Included studies must address NOWS treatment, or opioid withdrawal treatment of any age group, that may or may not have been tested in preclinical or clinical models. Results will summarise the current pharmacological and non-pharmacological treatment methods for NOWS, as well as potential novel treatments with a specific interest in non-opioid pharmacological interventions.

Ethics and dissemination This scoping review aims to broadly search preclinical and clinical literature as it relates to treatment of NOWS, including potential novel treatments with a specific interest in non-opioid pharmacological interventions. Given that this study does not directly involve human subjects or animal subjects research, Institutional Review Board (IRB) or Institutional Animal Care and Use Committee (IACUC) approval is not required. Results of this scoping review will be disseminated at conferences and submitted for publication in a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first scoping review protocol exploring non-pharmacological and pharmacological treatment options for neonatal opioid withdrawal syndrome (NOWS), including treatment methods that may or may not have been tested in preclinical and/or clinical models.
⇒ The scoping review protocol will follow a specific framework to enhance methodological rigor.
⇒ A broad search strategy across six databases, as well as references of selected literature, will allow for a comprehensive exploration of NOWS treatment, including established interventions and interventions that warrant additional exploration.
⇒ Scoping reviews, in nature, often address broad questions and, as a result, findings may also be broad; however, this may also benefit the field in terms of discussing new research ideas and treatment options for NOWS.
⇒ This scoping review protocol aims to only include articles written in the English language.

INTRODUCTION

Background

Between 2010 and 2017, opioid use during pregnancy increased a staggering 131%, with rates of neonatal opioid withdrawal syndrome (NOWS) increasing by 82%.[1] Short-term symptoms of NOWS include irritability, agitation, fever, tremors, problems with feeding and sleeping, increased muscle tone and, in severe cases, respiratory problems and seizures.[2] Interestingly, emerging preclinical evidence has posited potential neuroinflammatory effects as a result of in utero opioid exposure, indicative of molecular consequences.[3] Although the aforementioned phenotypic symptoms of NOWS are well defined, molecular implications are not well understood. Even less understood are the long-term effects of in utero opioid exposure or postpartum opioid treatment for subsequent NOWS symptoms. Although

non-pharmacological treatment methods are the first line of treatment, roughly 50–80% of infants born with NOWS need pharmacological intervention.[4 5] Complicating matters further, there are no official guidelines for the treatment of NOWS and, with very few Food and Drug Administration approved drugs for neonates, many pharmacological treatments entail off-label use.[6] Drugs commonly used for NOWS treatment include low doses of morphine, methadone or buprenorphine, weaned over time, and in some cases, adjunctive therapy with clonidine or phenobarbital is also needed for symptom management.[6 7] With preclinical evidence pointing to inflammation in the brain and subsequent cognitive and memory deficits as a result of in utero opioid exposure,[3 8–10] as well as clinical observations of intellectual impairment and increased attention disorders in children previously diagnosed with NOWS,[11] it seems counterintuitive to treat NOWS infants with more opioids. However, it should be noted that such observations in clinical populations are inconclusive due to limited methodologies and sample size.[7 11 12] Moreover, opioid treatment for NOWS is of particular interest given that the studies evaluating the pharmacokinetics and pharmacodynamics of such drugs in neonates have used very small samples, employed simulation methods to generate recommended dosing strategies, reported high intra-individual variability and/or may not be generalisable due to exclusion criteria for study enrolment.[13–16] Moreover, long-term developmental effects of such treatments are unknown. However, as stated by Liu and colleagues,[17] providers are 'stuck between the devil and the deep blue sea… as there are no real alternatives to pharmacological treatment with opiates and other drugs for neonatal opiate withdrawal…' (p.3). There is a pressing need to summarise current non-pharmacological and pharmacological interventions for NOWS, as well as potential non-opioid pharmacological interventions that may warrant future consideration and research for NOWS treatment.

Long-term outcomes of NOWS

Long-term effects of early life opioid exposure, including in utero opioid exposure and subsequent opioid treatment for NOWS, are largely unknown. Preclinical studies consistently show an association between in utero opioid exposure and cognitive effects including memory deficits[18–20] and increased learning and memory errors.[3 21–23] Clinical findings, on the other hand, have been inconsistent. For example, Kaltenbach and Finnegan[24] did not find cognitive developmental differences in 4-year-olds who were or were not exposed to methadone in utero. Additionally, recent work using the Bayley Scale of Infant Development—3rd edition (BSID-III)[25] also did not find developmental differences in infants exposed to opioids in utero when compared with unexposed, healthy controls.[26] Taken together, these studies suggest environmental effects, secondary to NOWS, as the culprit for any observed cognitive deficits. Indeed, children born to mothers dependent on any substance are often exposed to other detrimental conditions including poverty, lack of resources and unstable home environments.[27]

However, as evidenced by Hunt *et al*'s[28] and Maguire *et al*'s[11] reviews, much of the literature has reported observations of neurodevelopmental deficits in children previously diagnosed with NOWS, including cognitive and social functioning deficits, as well as intellectual impairments. In a longitudinal study by Nygaard and colleagues,[29] children previously diagnosed with NOWS had lower cognitive scores when compared with healthy controls from age 1 to 8.5 years. Marked sex differences were also noted as NOWS males had significantly lower cognitive scores at all time points when compared with healthy controls, whereas NOWS females only demonstrated significantly lower cognitive scores when compared with healthy controls at the last assessment (8.5 years).[29] Additionally, recent work by Merhar *et al*[30] found significantly lower cognitive, language and motor scores as measured by the BSID-III[25] in infants previously diagnosed with NOWS when compared with normative BSID-III data. Similar results have been observed in older children previously diagnosed with NOWS. In high school students previously diagnosed with NOWS, literacy and numeracy scores were significantly lower when compared with non-NOWS matched controls, as well as when compared with those in the general population.[27] Another study by Ornoy *et al*[31] showed that children born to heroin-dependent mothers but adopted early in life had significantly improved intellectual scores on the Wechsler Intelligence Scales for Children-Revised (WISC-R)[32] when compared with children born to and raised by heroin-dependent mothers.[31] Interestingly, the intellectual scores of the same adopted children were lower than those of the healthy control children; however, with the exception of one subscale of cognitive function (WISC-R performance),[32] the difference in scores was insignificant.[31] These results suggest that environmental conditions may certainly play a role in developmental outcomes; but other factors, such as molecular implications that may or may not be driven by in utero opioid exposure and subsequent NOWS may also explain such developmental outcomes. While these studies echo the results of several other studies,[11 28] results must be interpreted with caution due to limited methodologies and small sample sizes.

Long-term development of children previously diagnosed with NOWS who also received pharmacological intervention for NOWS symptom management has also been evaluated. For instance, using the BSID-III,[25] Bakhireva and colleagues evaluated the development of infants aged 5–8 months (N=42) previously treated (n=16) or not treated (n=26) pharmacologically for NOWS and found no difference between the groups.[26] Additionally, Merhar *et al* found that type of pharmacological treatment for NOWS infants (eg, methadone, buprenorphine or morphine) did not influence BSID-III[25] development scores in children aged 18–28 months; however, sample sizes for buprenorphine and morphine were low (n=11 and n=14, respectively).[30] Moreover, Benninger

et al found that neurodevelopmental scores of infants previously diagnosed with and pharmacologically treated for NOWS were not different from normative data at 3–4 and 9–12 months; however, cognitive and language scores were significantly different from normative data at 15–18 months.[33] More recently, Benninger *et al* found that infants previously treated pharmacologically for NOWS had significantly reduced cognitive, language and motor scores at 1 year of age when compared with population means.[34] This may be of particular importance given the evidence that opioids, including those used in the postpartum period to manage NOWS symptoms, can adversely affect the developing central nervous system and may work to explain some of the long-term cognitive outcomes seen in both preclinical and clinical models.

NOWS treatment methods

The current treatment for NOWS includes both pharmacological and non-pharmacological interventions. First-line, non-pharmacological interventions that have been shown to reduce length of hospital stay and/or the use of pharmacotherapy include increased kangaroo care or skin-to-skin contact, breast feeding,[35] mom's ability to room with baby[36] and decreased environmental stimulation.[37] More recent studies have also started to evaluate acupuncture as a non-pharmacological treatment method for NOWS, with promising results.[38] Despite these non-pharmacological interventions, 50–80% of the infants with NOWS will need pharmacological treatment for symptom management.[4 5] Risk factors for NOWS severity and identifying which patients will require pharmacological treatment are not well understood but some studies have suggested neonatal genetic differences in drug-metabolising enzymes[39] or mu-opioid receptors,[40 41] as well as sex,[42] maternal polysubstance use or maternal methadone dose.[27] Pharmacological interventions primarily include opioids such as low doses of methadone, buprenorphine or morphine weaned over time, and, in extreme cases, adjunctive clonidine or phenobarbital.[6 37] Interestingly, meta-analyses have shown low efficacy of morphine for NOWS when compared with buprenorphine,[6] particularly as it relates to length of hospital stay. However, recent work has reported that 86% of the infants with NOWS receive morphine treatment, while 13% receive methadone and less than 1% receive buprenorphine.[43 44]

Nonetheless, opioids as a primary pharmacological treatment for NOWS symptom management requiring such intervention is of particular interest given the lack of knowledge regarding molecular consequences that may or may not be driving long-term outcomes. While such associations have not been made in humans, inflammation as a result of in utero opioid exposure has been associated with later cognitive and memory impairments in rat models. Therefore, it is possible that inflammatory effects may explain increased clinical implications of attention disorders and intellectual and cognitive functioning deficits observed in human children previously diagnosed with NOWS. Interestingly, other studies have suggested that an increase in exogenous opioids may affect the endogenous opioid system, which, during neurodevelopment, is responsible for regulation of brain growth. Thus, it has been postulated that an overactive endogenous opioid system, as a result of increased exogenous opioids, may restrict brain growth.[45–47] Indeed, after controlling for size, term infants exposed to opioids in utero have been found to have smaller head circumference and brain volume when compared with their peers who were not exposed to opioids in utero.[45 47] While it is unclear if these effects impact future cognitive development or other psychological conditions,[45] continuing to expose this particular patient population to opioids in the postpartum period for NOWS symptom management seems questionable. Unfortunately, there are no current pharmacological alternatives to opioids for the treatment of NOWS, and there is a pressing need to better understand potential non-opioid pharmacologics for NOWS treatment. The purpose of this scoping review is to discuss the current non-pharmacological and pharmacological interventions for NOWS, as well as potential, novel non-opioid pharmacological treatments.

Box 1 Search terms

1. Neonatal opioid withdrawal syndrome [ti, ab].
2. NOWS [(tw]).
3. Neonatal abstinence syndrome [ti, ab].
4. NAS [(tw]).
5. Antenatal opioid exposure (ti, ab, tw).
6. In utero opioid exposure (ti, ab, tw).
7. Prenatal opioid exposure (ti, ab, tw).
8. Neonatal opioid withdrawal syndrome treatment [ti, ab].
9. Neonatal abstinence syndrome treatment [ti, ab].
10. NOWS treatment [(tw]).
11. NAS treatment [(tw]).
12. Neonatal withdrawal [ti, ab].
13. Opioid withdrawal treatment [ti, ab].
14. Opioid withdrawal [(tw]).

ab, abstract; ti, title; tw, text word.

Study objectives

The objectives for this scoping review include: (1) summarize current treatment practices for NOWS including non-pharmacological and pharmacological interventions; (2) discuss potential novel, non-opioid pharmacological interventions for NOWS; and (3) establish the breadth of relevant preclinical and clinical scientific literature, including a table with study characteristics (eg, study aims; subjects; sample size; results) and discussion regarding study limitations. This will be the first study to review NOWS treatment and discuss novel pharmacological treatment options that warrant further consideration and study. Previously, neonatal abstinence syndrome (NAS) was used interchangeably with NOWS; however, in 2016, it was recommended that NOWS be the primary nomenclature for infants exposed to opioids

in utero.[48] Thus, both terms will be searched for exclusively in preclinical and clinical studies in the context of non-pharmacological interventions and pharmacological treatment.

METHODS AND ANALYSIS

Patient and public involvement

No patient/ public involvement.

Step 1: identifying the research question

Scoping reviews are intended to 'scope' the literature and ask broad questions in order to summarize the evidence. In turn, this allows for the ability to draw conclusions from such evidence, as well as identify knowledge gaps. For this scoping review, the research questions were as follows: (1) What are the current treatment methods for NOWS?; and (2) What, if any, are the potential novel, non-opioid pharmacological interventions that should be considered for future research of NOWS treatment? Given that the scoping review process is iterative and requires reflexivity,[49] these questions may evolve throughout the course of the review.

Step 2: identifying relevant studies

We have developed a search strategy to include a range of databases that incorporate clinical and preclinical studies, literature reviews, opinions and commentaries. Relevant literature will include peer-reviewed publications from PubMed, the Cochrane Library, Google Scholar, CINAHL, Web of Science and Scopus. Researchers will also search references of included studies.

Eligibility for included studies requires reporting established or novel treatment methods for NOWS including non-pharmacological and pharmacological interventions in preclinical or clinical populations. Additional studies may also include established or novel treatment methods for opioid withdrawal in adult populations including humans and animals. The search will include literature published any time in the English language. All searches will be completed in collaboration between the research team and librarians at Penn State College of Medicine. The first step will consist of an initial search of PubMed using search terms (box 1) adapted to PubMed's requirements. This will include Medical Subject Headings (MeSH) terms as generated by National Library of Medicine's 'MeSH On Demand Tool'.[50] Based on these results, the search terms will be redefined to allow for a more comprehensive search in other databases as defined above. The final step will involve searching the references of the selected literature.

Step 3: study selection

The screening process will start with a title and abstract review. Literature selected from this process will undergo full-text screening. At least two reviewers will independently screen studies by title and abstract to determine suitability for inclusion, which will require reports of pharmacological and non-pharmacological NOWS treatment, as well as opioid withdrawal treatment in neonatal and adult populations, among both preclinical and clinical models. Additional eligibility includes literature published any time and in the English language. Studies that are deemed ineligible, based on agreement of the research reviewers, will be removed. Reviewer discrepancies regarding study eligibility will be discussed among the research team for a final consensus.

Step 4: charting the data

Study characteristics will be captured using a shared Excel file. Study characteristics will include title, authors, year of publication, keywords used, aims of the study, methodology, study population, type of intervention or treatment used or discussed, key findings and future recommendations. Upon study team discussion, extracted data will be sorted into key themes using a qualitative thematic analysis approach. This will allow for an overall synthesis of the results, as well as enhanced organization as identified themes may act as headings for the scoping review.

Step 5: summarizing and reporting the results

This review will provide an overall summary of the included peer-reviewed articles. It is anticipated that this review will include a wide range of studies including pharmacological and non-pharmacological NOWS treatment in animals and humans, as well as established and novel pharmacological and non-pharmacological opioid withdrawal treatment in adult animals and humans. Any additional findings or trends will be noted, and we will include a discussion regarding identified knowledge gaps and recommendations for future research.

ETHICS AND DISSEMINATION

The purpose of this scoping review includes: (1) conducting a broad search in the preclinical and clinical literature relevant to established non-pharmacological and pharmacological treatment of NOWS; (2) conducting a broad search in the same literature to identify potential novel non-opioid pharmacological interventions for NOWS that may warrant future consideration and research; and (3) summarize results of the relevant literature. Additionally, this scoping review will follow the framework of Arksey and O'Malley,[49] employing five distinct stages as described in the methods, along with a comprehensive search using six databases and broad search terms (box 1). The results from this review will highlight current NOWS treatment, as well as identify potential novel treatments with a specific interest in non-opioid pharmacological treatments. The final manuscript will be submitted to a peer-reviewed journal and disseminated at academic conferences.

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Contributors SM-H made substantial contributions to the conception and design of the protocol, as well as drafting and revising the work. JEN made substantial

contributions to the work by drafting and revising the protocol critically for important intellectual content and provided final approval of submitted manuscript.

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Competing interests None declared.

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