Review

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Complementary Therapies For Mild to Moderate Neonatal Opioid Withdrawal Syndrome: A Mini-review

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Abstract

Introduction: *Neonatal Opioid Withdrawal Syndrome, resulting from prenatal opioid exposure, is rising in prevalence and presents substantial health and developmental challenges for neonates. While standard treatments of opioids such as morphine have been traditionally employed for treatment, concerns about their long-term effects on neonatal development have spurred interest in alternative therapeutic strategies. This review seeks to highlight emerging non-opioid interventions for Neonatal Opioid Withdrawal Syndrome and their potential benefits.*

Methods: *Utilizing the PRISMA framework, the database PubMed was systematically searched for complementary therapies for neonatal opioid withdrawal syndrome. The search was conducted on September 27th, 2023, and employed a combination of keywords targeting the condition and the treatment modalities. Cochrane risk of bias tool was utilized to evaluate study quality and classify studies based on their risk of bias. Data captured from these studies encompassed parameters such as study design, intervention, and outcomes, including length of stay and length of pharmacotherapy.*

Results: *Among 71 identified articles, only five met the inclusion criteria. Three were randomized controlled trials, and two were quasi-experimental studies. Among the 5 included trials, 3 demonstrated potential benefits, while two revealed no differences in treatment duration or reliance on pharmacological support. The "Eat-Sleep-Console" method, acupuncture, and vibrating mattresses were associated with reduced morphine dosages and shorter hospital stays. Most trials showed moderate to high risk using the Cochrane RoB-2 tool.*

Discussion: *This review underlines the growing concern of Neonatal Opioid Withdrawal Syndrome stemming from increased opioid use during pregnancy. While severe cases necessitate pharmaceutical treatments, there's a pressing need for safer alternatives. "Eat-Sleep-Console" method and transcutaneous auricular neuromodulation might offer mild relief. Future efforts should adopt a multifaceted strategy, emphasizing further research to optimize treatments and outcomes.*

Conclusion: *Although complementary therapies show promise, with limited evidence from three RCTs, their efficacy remains uncertain. Additional studies might clarify the role while combining it with pharmacological methods could enhance outcomes. Comprehensive research is essential to optimize treatments for NOWS-affected infants. Complementary therapies in mild to moderate cases of Neonatal Opioid Withdrawal Syndrome show promising results. So far, not enough data has been obtained to support the efficacy of observed therapies.*

Introduction

Neonatal opioid withdrawal syndrome (NOWS) is a postnatal withdrawal syndrome observed in neonates who have been exposed to opioids in utero (Benninger, 2022). NOWS occurs due to sudden cessation of the opioid drug administration after birth and manifests in irritability, feeding difficulties, and respiratory complications (Vasan, 2021). In 2012, the incidence in the US was estimated at 6.0 per 1000 live births (Mangat, 2019). This trend aligns with the growing opioid crisis, resulting in an increased number of pregnant women overusing these substances (Turner, 2015).

The primary approach to treat NOWS is based on symptom severity, with opioid replacement therapies, notably morphine or methadone, being used as first-line treatment (Vasan, 2021). Other pharmacotherapy, such as phenobarbital, while effective, has demonstrated associations with neurotoxicity in animal studies (Patrick SW, 2020). They also cause neurotoxic side effects, from neural apoptosis, white matter injury, and decreased myelin maturation, leading to long-term developmental delays and social and financial implications (Vasan, 2021; Ceccanti, 2022; Farwell Jr, 1990). Due to growing concerns about the long-term effects of opioid exposure on neonatal brain development, there has been an interest in studying non-opioid therapeutic alternatives.

While the American Academy of Pediatrics recommends alternative non-pharmacologic treatments, the data supporting their efficacy is limited (Jenkins, 2021). Techniques such as laser acupuncture, acupressure, transcutaneous auricular neuromodulation (tAN), stochastic vibrotactile stimulation (SVS) using vibrating crib mattresses, and the Eat-Sleep-Console (ESC) method are among the non-opioid methods under investigation for NOWS, potentially offering a safer alternative to opioid replacement therapy. These treatments approach NOWS differently, primarily focusing on decreasing newborn irritability by activating the parasympathetic nervous system to counteract the overactivated sympathetic nervous system (Jenkins, 2021). Some smaller studies have suggested the effectiveness of auricular acupuncture in reducing opioid withdrawal in adults (Schwartz L, 2011). tAN functions by activating the vagus nerve, releasing acetylcholine, and stimulating the auriculotemporal nerve, subsequently releasing endorphins. This process inhibits proinflammatory cytokines that mediate pain (Jenkins, 2021). SVS demonstrates similar effects via a crib mattress by delivering gentle vibrotactile pulses, targeting pathophysiological instabilities in the central and autonomic nervous systems. It modulates cardiac and respiratory activity and reduces irritability (Bloch-Salisbury, 2022).

This mini-review aims to analyze the efficacy of complementary non-pharmacological adjunct treatments for NOWS, assessed by length of stay (LOS) and pharmacotherapy (LOP) in newborns.

Materials and Methods

Study Design

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PubMed was systematically searched on September 27th, 2023, to identify trials investigating the efficacy of complementary non-pharmacological treatments for NOWS by measuring the LOS and LOP (morphine or buprenorphine) in days. Hand-search methods were used to account for additional studies.

Search Strategy and Inclusion/Exclusion Criteria

The search strategy included the combination of the following keywords: ((neonatal opioid withdrawal syndrome[Title/Abstract]) OR (NOWS[Title/Abstract]) OR (prenatal opioid exposure[Title/Abstract]) OR (POE[Title/Abstract]) OR (neonatal abstinence syndrome[Title/Abstract]) OR (neonatal withdrawal syndrome[Title/Abstract])) AND ((non-invasive[Title/Abstract]) OR (neuromodulation[Title/Abstract]) OR (acupuncture[Title/Abstract]) OR (average length of stay[Title/Abstract]) OR (hospital length of stay[Title/Abstract])) with no filters.

The following criteria were included to identify the studies: (i) clinical trials with a target population of (ii) neonates (infants under 28 days of age), (iii) diagnosed with NOWS, treated with (iv) the first line treatment in addition to different complementary, nonpharmacologic treatments. The (v) LOS and LOP in days measured the efficacy of the complementary and first-line treatments. The studies that did not meet our criteria were excluded.

Screening Process

During the initial selection process of the studies, there were no date limitations or selection of studies in a different language other than English. We used the reference software manager Zotero ver.

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6.0.27, to remove repeated studies and review abstracts and content. Two authors (AA and AK) evaluated identified articles for inclusion. In case of a disagreement, a third author (ES) resolved any conflicts.

Data Extraction

All included three authors-reviewed studies. The quality of the studies was assessed using the risk of bias tools (RoB 2 Tool) from Cochrane. Three authors collected the data from the studies; the characteristics extracted from the studies include authorship, year of publication, study design, number of participants, follow-up time, intervention, control, and outcomes.

Results

The systematic search on PubMed identified 71 studies, with an additional study found through manual search. No duplicate studies were detected using Zotero. The 71 studies from PubMed were screened by analyzing their titles and abstracts, excluding 60 studies. Of the remaining 11 studies, 2 were excluded due to having a different intervention, and 5 were excluded due to having a different study design. This leaves 5 studies to be included in the review.

Study Characteristics

Figure 1 provides an overview of five studies investigating the effectiveness of complementary treatments in neonatal abstinence syndrome (NAS), published between 2009 and 2023.

All included studies explored alternative non-pharmacological treatments in neonates with neonatal abstinence syndrome (NAS) using Finnegan Neonatal Abstinence Scoring Tool (FNAST). Two studies investigated auricular stimulation. In a study involving 76 infants, auricular acupressure did not yield a significant effect on the length of hospitalization or the amount of opioid use (Schwartz, 2011). However, Jenkins et al. evaluated transauricular neurostimulation (tAN) through a device in 28 randomized neonates. Their primary outcome, assessing safety, showed that tAN therapy did not result in any adverse events, and the median duration of oral morphine therapy was reduced from a median of 9.0 days to 6.0 days (Jenkins, 2021).

In a single-center quality improvement study, neonates' behavioral strategy, "Eat, Sleep, and Console" decreased the length of stay from 10.3 days (in previous usual care) to 4.9 days. The average morphine dose also decreased from 38 to 0.3 per infant during hospitalization (Blount, 2019). Laser acupuncture as a complementary therapy to pharmacological therapy (morphine and phenobarbital) in NAS was tested in a single-blinded study. The duration of morphine therapy was significantly reduced in the laser acupuncture group compared to the control (28 days versus 39 days; $p = 0.019$), along with a reduced length of hospital stay (35 days versus 50 days in the control; $p = 0.048$) (Raith, 2015).

The use of a vibrating crib in a population of 181 randomized neonates with perinatal opioid exposure, not necessarily NAS, also exhibited favorable outcomes. There was a reduction in the administration of morphine treatment (adjusted odds ratio 0.88; 95% CI 0.81-0.93 hours per day). Among 32 infants transferred to the neonatal intensive care unit with NAS for morphine treatment, those assigned to the vibrating crib finished treatment nearly twice as fast (hazard ratio 1.96; 95% CI 1.01-3.81), resulting in 3.18 fewer treatment days and receiving a mean 1.76 mg/kg less morphine than the usual cohort (Bloch-Salisbury, 2023).

Assessment of Risk of Bias in Individual Studies

The risk of bias in individual studies was evaluated using the Cochrane RoB2 tool for randomized control trials, although two studies have different designs. This decision was made in an effort to maintain a single tool to evaluate the risk of bias and ensure that the results would be comparable. The tool evaluates studies in five domains, represented in the graph by numbers, and can rate studies in 3 categories: low risk of bias, some concerns, and high risk of bias.

Analysis of the risk of bias revealed severe concerns. Among five studies, one presented a low risk of bias (Raith, 2015), and the other four presented an overall high risk of bias.

Three studies demonstrated a high risk of bias in the randomization process (Blount, 2019; Jenkins, 2021; Schwartz, 2011). In these studies, the allocation of participants was not random, and patients and caregivers were aware of the allocation sequence. The results are probably because the study by Blount was a quality improvement, open-label, and non-randomized study, and the study by Jenkins (2021) was an open-label, non-randomized study.

Another domain that presented a high risk of bias in two studies (Block-Salisbury, 2023; Blount, 2019) and some concerns for bias in one study (Schwartz, 2011) was regarding blinding, which can lead to deviations in interventions due to the awareness of participants and carers about the allocation groups.

Four studies presented a high risk in Domain 4 (Block-Salisbury, 2023; Blount, 2019; Jenkins, 2021; Schwartz, 2011), regarding the measurement of the

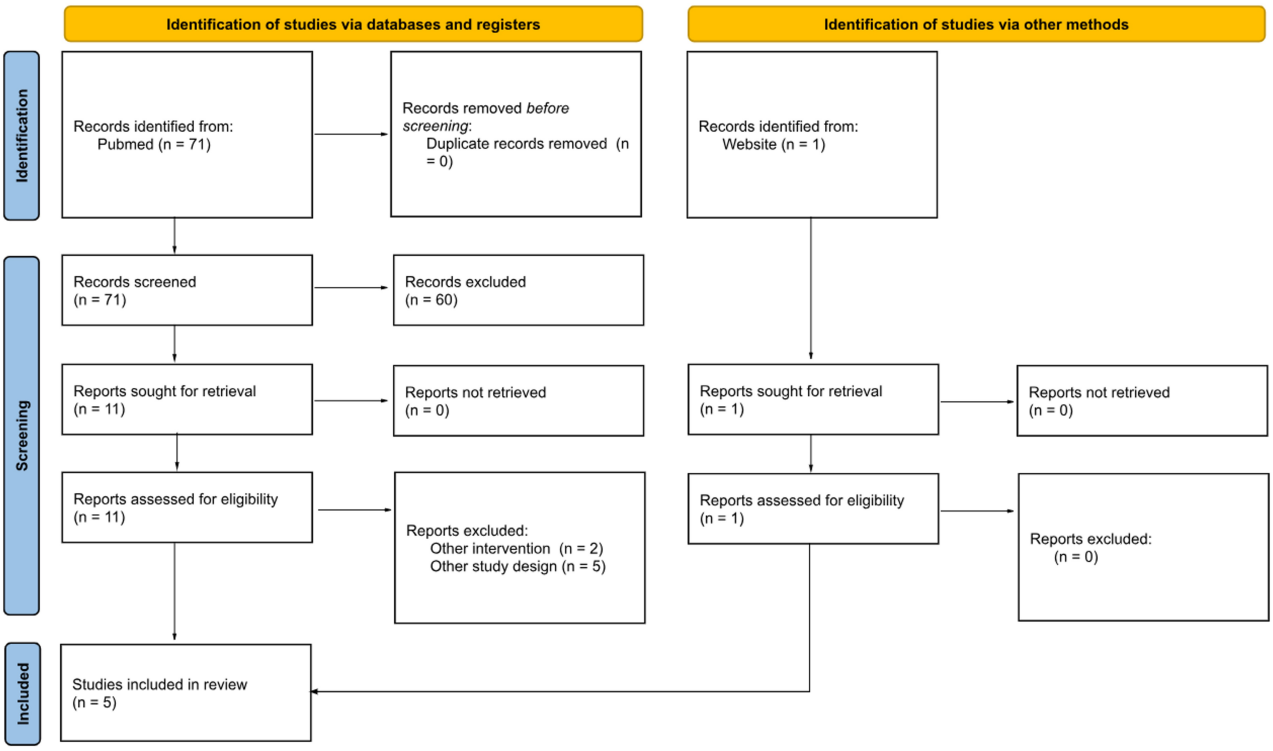

Figure 1: *PRISMA Flow Diagram.*

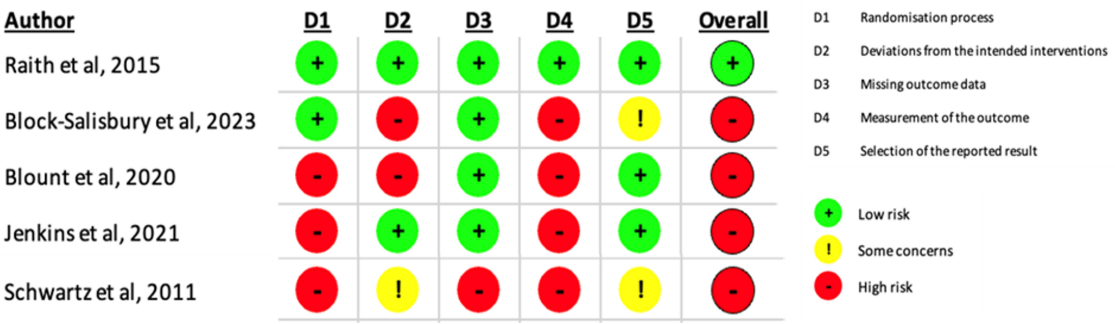

Figure 2: *Risk of bias assessment.*

Study	Study design / Population	Intervention / Control	Outcomes	Results
Schwartz, et al., 2011	Open label, randomized study N:76	Auricular acupressure / Pharmacological standard treatment	LOS[1] for NAS care Average NAS[2] score per scoring event Percentage of NAS[2] care on medications Average dose (mg/kg/day of NAS[2] care) of pharmacological support	LOS mean 25.8 days in acupressure versus 26 days in control (p=0.95) Average mean dose of diluted tincture of opium (DTO) 2.38 mg/kg/day in intervention versus 2.45 mg/kg/day in control (p=0.80).
Blount, et al., 2019	Quality improvement, open label, non randomized study N:76 (40 at baseline and 36 in the post intervention)	Eat-sleep-console (ESC) method and morphine as needed Pharmacological standard treatment	LOS[1] in infants with NAS[2] transferred to the inpatient floor Total morphine amount administered	LOS[1] decreased from 10.3 to 4.9 days Average morphine administered decreased from 38 to 0.3 doses during hospitalization
Raith, et al., 2015	Single blind, randomized controlled study N:28	Laser acupuncture/Pharmacological standard treatment	LOS[1] Duration of oral morphine therapy for NAS Highest single Finnegan score Time to reach the highest single Finnegan score Amount of oral morphine solution administered Time taken to reach the maximum amount of oral morphine solution	Duration of morphine therapy was reduced from 39 to 28 days (p = 0 .019) Reduced LOS[1] in the acupuncture group
Jenkins, et al., 2021	Open-label, non-randomized uncontrolled study N:8	Transcutaneous auricular neurostimulation (tAN) None	LOS[1] Morphine length of treatment Safety (measured by heart rate monitoring, Neonatal Infant Pain Scale, and skin irritation)	tAN therapy did not result in any unanticipated adverse events (device and non-device related) in any subject The median oral morphine LOT was 9.0 days and median LOT after tAN initiation was 6.0 days
Bloch-Salisbury, et al. 2023	Open label, Randomized study N:18 (with prenatal opioid exposure)	Low level stochastic vibrotactile stimulation (SVS) / pharmacological standard treatment	LOS[1] Total morphine amount administered	Reduction in administration of morphine treatment (adjusted OR 0.88; 95% CI 0.81-0.93 hours per day) Among 32 infants transferred to the neonatal intensive care unit for morphine treatment who completed treatment within 3 weeks, those assigned to SVS finished treatment nearly twice as fast (HR 1.96; 95% CI, 1.01-3.81), resulting in 3.18 less treatment days and receiving a mean 1.76 mg/kg less morphine than the usual cohort.

Table 1: *Baseline characteristics [MR3] of included studies.*

outcome. Results are probably due to a lack of blinding, which can bias the assessment of outcomes by assessors and the use of different methodologies to measure the outcome between the control and intervention groups.

The presence of bias in these studies underscores the need for caution when interpreting their findings.

Meta-analysis

Based on the studies, we initially tried to analyze the effect size of LOS and LOP obtained from 3 studies (Schwartz, 2011; Raith, 2015; Bloch-Salisbury, 2023) using Hedges's g. In order to analyze the effect size utilizing Hedges's g, mean (SD) was required. However, only 1 study (Schwartz, 2011) reported their result as mean, and the rest (Raith, 2015, and Bloch-Salisbury, 2023) reported the results as median. Jenkins (2021) did not have a control group, and Blount (2019) failed to report their IQR. Although the median can be transformed into mean in some cases, it is with the assumption that data was normally distributed and samples in the study were derived from the same population with the same mean and median value, which will not be the case in our analysis. Therefore, the authors decided not to report the effect size of both LOS and LOP since it would not be appropriate to transform the data.

Discussion

In this mini-review, we found 5 articles that evaluated the efficacy of complementary treatments for NOWS. Different non-pharmacologic treatments were reviewed, which included laser acupuncture using a laser pen with certain wavelengths on different parts of the body (Raith 2015), auricular acupressure using a herbal seed taped to patients' ear (Schwartz, 2011), "Eat, sleep, and console method" as a modified assessment compared to standard Finnegan Neonatal Abstinence Scoring System (FNASS) (Blount, 2019), stochastic vibrotactile stimulation (SVS) (Bloch-Salisbury 2023), and transcutaneous auricular neurostimulation (tAN) that used an earpiece electrode which will deliver low-intensity electrical pulse that targets auricular branch of vagus nerve (Jenkins, 2021). All studies compare additions of complementary treatments in addition to acceptable standard treatment compared with standard treatment alone according to each institution's protocol for managing NOWS. The studies assess outcomes with a focus on the length of hospital stay and length of pharmacotherapy.

This is the first comprehensive analysis focusing on alternative, non-pharmacological therapies in managing NOWS, filling a significant gap in the literature. The therapies reviewed pave the way for integrative health strategies, potentially transforming the care landscape for neonates affected by opioid withdrawal. The studies reviewed offer preliminary data on the potential benefits of these complementary therapies in managing NOWS. Notably, they do not present addictive risks, significant side effects, or drug interactions often associated with pharmacological treatments, thus marking a pivotal stride in this field. However, there are some important limitations in the design of the reviewed studies.

First and foremost, the small sample sizes, especially in studies like Jenkins (2021) and Raith (2015), raise concerns about the robustness and generalizability of their findings to broader populations. Small samples can lead to statistical anomalies, making it challenging to determine whether the results would remain consistent in larger, more diverse groups. The study designs themselves pose another issue.

The tAN study was single-center, open-label, with no sham control group comparison and a small sample size, which limits the interpretation of the results. The effects of tAN during early administration of morphine therapy could not either be interpreted due to infants being included at different durations of morphine therapy (Jenkins. 2021). Laser acupuncture study had the challenge of blinding patients to their treatment group due to the nature of the interventions, and long-term outcomes may not be fully addressed in a relatively short-term study. Furthermore, potential variations in the skills of acupuncturists and the choice of acupuncture points can introduce confounding factors (Raith, 2015).

The "Eat Sleep and Console" revealed a substantial decrease in the average morphine dose (from 38 to 0.3 throughout hospitalization). This important decrease drew our attention but should be interpreted with caution. The previous protocol initiated scheduled morphine doses immediately after diagnosis of NAS, while the new ESC protocol started with a non-pharmacological approach, the "eat, sleep, console," resorting to morphine only when deemed necessary. This fundamental difference alone in the first approach could substantially account for the overall decrease in morphine usage between the two groups regardless of whether or not the ESC method is effective. Furthermore, the variability in the assessment methods raised a significant concern of potential measurement bias: the subjective clinical evaluation of physicians in the ESC group to assess the need for morphine contrasts with a more objective assessment tool for the administration of morphine in the control groups, as the second used a known tool to identify the need for morphine, the FNASS score. Another critical limitation of this study is that it is

non-randomized, which introduces the potential for selection bias. Randomization is important in clinical experimental studies to minimize the impact of confounding variables and ensure that the groups are comparable at baseline. Aside from all of these potential biases, the study approach did not include statistical analysis with p-values and confidence intervals, which would allow us to determine whether the differences found were due to chance or not (Blount, 2019).

Schwartz's (2011) study's primary outcome revealed that auricular acupressure did not significantly enhance the standard medical management for NAS. The historical context of the study, conducted in the early 1990s, should be considered as clinical practices and NAS treatment guidelines may have evolved since then, potentially affecting the findings' relevance to current medical practice. Relying on maternal self-reports for maternal substance use poses challenges in establishing the precise relationship between maternal drug use and NAS severity (Schwartz, 2011). Bloch-Salisbury (2023) showed no p-value in the study. This eventually reduced the cumulative dose of morphine, the length of treatment, and the length of stay, which was significant clinically. It was well noted, however, that SVS did not show the significance for subgroups where infants did not respond to morphine treatment due to possible in-utero development disruption, polydrug exposure, and other teratogens. This study needs to be interpreted cautiously because the treatment allocation was not blinded, potentially introducing confirmation bias where effect size can be exaggerated. The treatment protocol was complex and impractical since infants need continuous monitoring to initiate SVS. SVS was a new device that had not been studied before. These may cause other variables to interfere with SVS's actual effects (Bloch-Salisbury, 2023).

Our mini-review has limitations where we focus on studying a vulnerable population of neonates. This limits the available experimental studies we can gather for analysis due to ethical reasons, the high-risk population, and the lack of studies on complementary therapies in this population. All authors agreed to include only experimental studies to gather stronger evidence to quantify the effect of non-pharmacological therapies. Unfortunately, the limited number of studies and suboptimal study designs resulted in a high risk of bias. Therefore, caution must be implemented while interpreting the results of this review. Complementary therapies in neonates also present challenges due to the lack of standardized protocol when designing some novel therapies. Variations occurred with delivery methods and measurement of the outcomes of the studies. Expanding the scope of the search to include observational studies can be another alternative to help determine whether complementary therapies are beneficial.

Conclusion

Despite these considerable limitations, the review provides foundational insights and ignites interest in the potential of these complementary therapies. The substantial reductions observed in the length of hospital stay and the length of pharmacotherapy, along with the decreased need for morphine in some cases, cannot be overlooked. These results herald a compelling direction for future research. As the field advances, investing in research with larger sample sizes, controlled environments, and more rigorous designs is paramount to validate and refine our understanding of these interventions.

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Conflicts of Interest

The authors declare no conflict of interest.

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