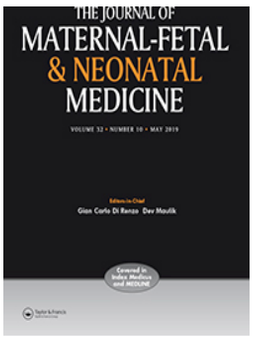

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REVIEW ARTICLE

Nonpharmacological management of neonatal abstinence syndrome: a review of the literature

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ABSTRACT

Background: Infants with neonatal abstinence syndrome (NAS) experience withdrawal that occurs as a result of termination of placental opioid supply following delivery. Common symptoms include restlessness, tremors, agitation and gastrointestinal disturbances. Severe NAS is often treated using opioids and/or sedatives. Although commonly employed effectively in neonatal care, there is a lack of published information regarding nonpharmacological management of the NAS infant.

Objective: The purpose of this review was to summarize the current literature on nonpharmacological management of NAS.

Methods: A literature search of Medline and EMBASE was performed for articles published between 2000 and June 2107.

Results: Nonpharmacological management encompasses "environmental control", "feeding methods", "social integration", "soothing techniques" and "therapeutic modalities". Several interventions, including: breastfeeding, swaddling, rooming-in, environmental control and skin to skin contact have proven to be effective in managing NAS and should be incorporated into standard of care for this population (Level I–III Evidence). These interventions can be effective when offered in combination with pharmacological therapy, or as stand-alone therapy for less severe cases of NAS (Finnegan score <8).

Conclusions: Given the increasing body of evidence on its efficacy and ease of implementation, nonpharmacological treatment should universally be incorporated into standard of care for NAS.

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Neonatal abstinence syndrome; nonpharmacological; opioid-related disorders; therapeutics

Introduction

Neonatal abstinence syndrome (NAS) is a withdrawal condition that can develop in infants exposed to opioids *in-utero* upon the sudden discontinuation of placental opioid supply at birth. NAS can occur following exposure to a variety of prescription and illicit natural and synthetic opioids, including: methadone, buprenorphine, heroin, oxycodone, codeine and morphine. A diagnosis of NAS is made based on the presence of a cluster of neurological, gastrointestinal and cardiorespiratory symptoms following *in-utero* opioid exposure, including hypertonicity, excessive, high-pitched crying, loose stools, disturbed feeding and sleep, tremors and convulsions [1].

NAS severity can be assessed using multiple methods, however, the Finnegan and modified Finnegan scores are the most common, used in 65–95.5% of neonatal units [2,3]. The Finnegan score assesses central nervous system, metabolic, vasomotor, respiratory and gastrointestinal symptoms, using the overall score to determine treatment, with most centers initiating pharmacological treatment following three consecutive scores ≥ 8 [4]. A diagnosis of NAS does not require the presence of all the above symptoms, potentially resulting in neonates with identical NAS scores presenting with different symptoms. Infants may, therefore, respond to treatment differently and require specifically tailored supportive care strategies [5,6]. The variability in NAS presentation makes researching nonpharmacological management difficult and requires practitioners to rely on clinical experience and a certain amount of trial and error to determine the most appropriate course of treatment for each case. Symptom onset depends largely on the opioid's metabolic half-life. Synthetic and semisynthetic opioids, such as methadone and buprenorphine, have longer half-lives and typically result in a later onset of symptoms compared to natural opioids with shorter

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half-lives such as morphine. Symptoms most commonly present 24–72 hours after birth, but have been reported to occur as early as 6 hours and as late as 7 days after birth [7–9].

As global rates of opioid use during pregnancy continue to rise, so too will the frequency with which clinicians encounter NAS. Although high-quality evidence supports pharmacological treatments, there are currently limited data regarding nonpharmacological options. The nonpharmacological management of NAS has been discussed in previous review articles, but often as a side note, overshadowed by pharmacological care. The purpose of this review is to highlight the potential benefits of nonpharmacological management of NAS and to describe the existing literature.

Materials and methods

A search of Medline and EMBASE was performed, with results restricted to peer-reviewed English literature published from 2000 to June 2017. In Medline, "NAS" was combined with ["Therapeutics" OR "Treatment"] to produce 329 hits. In EMBASE, "withdrawal syndrome" AND ["Therapy" OR "Therapeutic"] were combined with ["Infant" OR "Newborn"] to produce 74 hits. Additional articles were found in references of relevant papers. Abstracts of the resultant papers were read and all relevant papers underwent full review. Quality of evidence for each study was graded using the Canadian Task Force on Preventative Health Care guidelines.

Results

Nonpharmacological management of NAS is becoming more common. A survey by Mehta reported that 26.1% of institutions relied primarily on nonpharmacological therapy with adjunctive pharmacotherapy, while 54.1% relied equally on pharmacological and nonpharmacological therapy [3]. In an earlier study, Mehta found that 95% of NICUs offered some aspect of nonpharmacological care [10]. Despite widespread use, little research on its efficacy has been conducted. Since many NAS symptoms involve infant overstimulation, nonpharmacological care largely focuses on controlling environmental factors to maximize infant comfort. Common methods of nonpharmacological care include: swaddling, quiet and dimly lit rooms, rooming-in, skin-to-skin contact, breastfeeding and infant positioning. Despite the availability of nonpharmacological care, there is little empirical support, with most clinical recommendations stemming from anecdotal evidence. Levels of evidence for each of the interventions discussed below are summarized in Table 1.

Table 1. Levels of evidence for nonpharmacological management of NAS.

Intervention in NAS	Level of evidence
Breastfeeding	I
Rooming-in	II
Swaddling	III
Quiet, low light rooms	III
"Skin to skin" contact	III

Levels of evidence grade based on the Canadian Task Force on Preventive Health Guidelines.

Mild cases of NAS (Finnegan Score <8) can often be managed solely using nonpharmacological treatment, while more severe cases are treated with adjunctive medication. Below, we describe the existing research regarding nonpharmacological management of NAS, classified according to five novel categories: "environmental control", "feeding methods", "social integration", "soothing techniques" and "therapeutic modalities".

Environmental control

Environmental control including quiet and dimly lit rooms, swaddling and bed type are perhaps the most commonly employed. Several authors suggest that an understanding of NAS symptoms and neonatal physiology is sufficient to support the practice [11,12]. Managing environmental stimuli, such as sound and light, is important for hyper-aroused infants who are going through withdrawal, in order to ensure they are not over stimulated [7,13].

Swaddling is common practice and involves tightly wrapping the infant in a blanket with the intention of decreasing arousal and prolonging sleep [12]. A 2007 systematic review validated this practice in healthy infants, reporting decreased arousal, longer sleep, better selfregulation, decreased distress and improved pain tolerance (Level I Evidence); however, their findings have not been reproduced in NAS infants [14].

Different bed types have also been studied in NAS populations. In a sample of 30 opioid-exposed neonates, Oro reported that infants on waterbeds were treated with up to 2 mg/kg less phenobarbital, had lower NAS scores and began gaining weight one day earlier than infants on conventional beds (Level I Evidence) [15]. In contrast, D'Apolito found that infants kept on rocking beds exhibited increased withdrawal symptoms, decreased neurobehavioral functioning and poorer sleep patterns compared to conventional beds [16].

Feeding methods

Of all the nonpharmacological treatments for NAS, feeding methods have been examined the most. Although not contraindicated, there is often confusion surrounding the safety of breastfeeding while on opioid substitution therapy [17]. This stems partly from previous (pre 2001) clinical guidelines suggesting a harmful effect on the infant with maternal methadone doses >20 mg/day and partly from the possibility of continued concomitant illicit drug use, as this is still a contraindication to breastfeeding [18].

As a result, some healthcare providers are overly cautious regarding promoting breastfeeding in this population. If implemented, routine urine drug screening can resolve most concerns regarding potential illicit use. Although opioids are present in the breast milk of mothers on substitution therapy, the concentration is low enough not to have a detrimental effect on the infant. Nikolaou et al. analyzed the breast milk of three mothers taking 40–70 mg of methadone per day and found that concentrations ranged from 16–32 ng/mL, only a portion of which would be absorbed by the fetus due to its low oral bioavailability [19]. A study by Bogen analyzed methadone concentration in the breast milk of 20 mothers taking 40–200 mg daily, and found that the maternal dose did not affect the safety of breastfeeding [20]. Total infant dose did not exceed 0.1 mg/kg/day, amounting to only 2% of maternal dose. Furthermore, other authors found breast milk methadone concentration is unrelated to maternal dose [21]. Opioid substitution therapy is, therefore, not a contraindication to breastfeeding and most mothers on substitution therapy should be encouraged to breastfeed [19,21,22].

In healthy populations, breastfeeding is known to have a variety of positive effects on the neonate. In an NAS population, Abdel-Latif compared the effects of breast milk, expressed breast milk and formula in 190 infants exposed to opioids *in-utero* [22]. Breastfed infants had lower mean Finnegan scores for the first 9 days of life, a 26% reduction in pharmacological treatment requirements and a 20-day decrease in pharmacological treatment duration versus formula-fed infants (Level II Evidence). Formula-fed infants were three times more likely to end up in foster care and were in hospital an average of 5-day longer than their breastfed counterparts. Interestingly, there was no difference between infants who fed at the breast and those who received expressed breast milk, suggesting that milk content may play an important role. In contrast, other authors suggest the benefits of breastfeeding may primarily be due to the bonding and maternal–infant contact rather than the content of the milk itself [23]. More research is needed to determine the exact mechanism through which breastfeeding reduces NAS severity.

Breastfeeding is consistently associated with a decrease in severity of NAS. Hodgson examined 295 infants with NAS and found that 12% of breastfed neonates received morphine therapy, compared to 37% of those not breastfed (Level II Evidence) [24]. Similarly, McQueen noted a reduction in mean NAS scores and decreased frequency of NAS scoring in breastfed infants ($n = 28$) (Level II Evidence) [25]. In a retrospective review of 128 NAS cases, Isemann reported an inverse relationship between breast milk consumption and duration of opioid treatment and length of hospital stay (Level II Evidence) [26]. Interestingly, Welle-Strand found that breastfeeding reduced pharmacological treatment doses in methadone-exposed infants by 27%, but had no effect in those exposed to buprenorphine ($n = 124$) (Level II Evidence), perhaps due to different bioavailability in breast milk [27].

In a 2011 survey of 383 American NICUs, 74.1% of respondents recommended breastfeeding for mothers on methadone therapy [3]. Despite the apparent benefits and hospital support for breastfeeding infants with NAS, rates remain relatively low. Of 276 opioid-exposed mother–infant pairs treated in a "baby-friendly" hospital, Wachman reported that 90% of women on buprenorphine and 52% on methadone were eligible to breastfeed [28]. Of those eligible, only 24% breastfed to any extent during their hospital stay, 60% of whom stopped after an average of 5.9 days. O'Connor examined 85 mother–infant pairs maintained on buprenorphine at an integrated-care center, 76% of whom decided to breastfeed [29]. Of those, 66% were still breastfeeding 6–8 weeks after discharge. Similarly, Welle-Strand found that 74% of women on methadone and 78% of those on buprenorphine initiated breastfeeding, albeit with a high-dropout rate and a median duration of 7 and 12 weeks for buprenorphine and methadone, respectively [27]. Across the three studies, the only negative predictors of breastfeeding were incidence of illicit drug use and number of previous preterm births [27,29]. All three hospitals employed comprehensive care models: one with a standard integrative program, one based on the 10 steps to encourage breastfeeding developed by Baby-Friendly USA, Inc. and the other focusing on reducing barriers to breastfeeding by providing access to all aspects of maternal–infant care in one setting [27–29]. Since promoting breastfeeding appeared to be a main objective

of all three centers, it is difficult to determine the factors affecting the varying success of each program.

Several authors have suggested that small frequent feedings are beneficial for NAS infants, as they better establish a circadian rhythm and are more tolerable for infants with gastrointestinal symptoms [11,13,22]. For infants unable to feed due to an attenuated suck response, gavage feeding of breast milk is recommended [11].

Given the documented benefit, attempts should be made to minimize potential barriers and increase breastfeeding rates in opioid-exposed neonates. Future research should focus on the factors affecting the decision of mothers on opioid substitution therapy or illicit opioids whether or not to breastfeed their infants.

Social integration

Rooming-in and skin-to-skin contact are the two main "social" methods of managing NAS. Rooming-in can facilitate mother–infant bonding and maternal comforting of the infant. Abrahams examined the effects of rooming-in in infants exposed to methadone or heroin *in-utero* [30]. Thirty-two infants roomed-in with their mothers and were compared to two control groups of 38 and 36 infants treated in a level II NICU. In the rooming-in cohort, 63% of mothers breastfed, compared to 8 and 11% in the other cohorts. Rooming-in also reduced morphine treatment, vomiting, length of hospital stay and admission to level-two nurseries and increased the likelihood of retaining child custody (Level II Evidence). Since a large proportion of rooming-in mothers breastfed, it is difficult to separate the effects of breastfeeding from those of rooming-in in this study.

Hodgson also examined the effects of rooming-in on morphine dosing in a hospital in which rooming-in was standard care for NAS [24]. Of the 295 infants exposed to a variety of opioids and other substances, 21% ultimately were treated with morphine therapy. Of infants exposed only to methadone *in-utero*, 37% received morphine. In contrast, in a nonrooming-in hospital, Lim found that 77% of infants exposed to methadone received morphine therapy [31]. Since maternal methadone dose was similar between the studies, Hodgson attributed their observed reduction in morphine requirements to their rooming-in protocol [24].

Davies compared morphine treatment and length of stay before and after implementation of a rooming-in protocol as standard of care for NAS [32]. The two cohorts consisted of 24 NAS infants admitted to the NICU prior to the policy change and 21 who roomed-in with their mothers after the change. Morphine therapy was used in 14% of rooming-in infants compared to 83% of those in the NICU. Mean length of stay also decreased from 25 to 8 days, respectively (Level II Evidence). In a follow-up study of maternal satisfaction, mothers were highly satisfied with the experience [33]. Perhaps related to maternal satisfaction, 86% of mothers were still breastfeeding two and a half months after discharge. As evidenced by the high rate of breastfeeding postdischarge, adopting a rooming-in protocol likely promotes long-term mother–infant bonding and a nurturing relationship. Further studies by Newman et al. (2015) [34] and Hünseler et al. (2013) [35] similarly identified rooming-in lowered LOS and the need for pharmacological NAS treatment.

Skin-to-skin contact or "kangaroo care" is another intervention that goes hand-in-hand with rooming-in. Several studies of healthy infants have shown that placing a naked infant on the mother's bare chest can decrease restlessness and respiratory distress and improve engagement and nursing, while simultaneously stimulating maternal–infant bonding [36–39]. In NAS infants, Hiles [40] reported that skin-to-skin contact reduced infant pain scores and improved sleep patterns (Level III Evidence). A skin to skin/cuddling initiative, part of a coordinated rooming-in model and environmental controls of care described by Holmes in 2016 found a 41% reduction in the proportion of opioid-exposed infants treated pharmacologically [41]. A similar, multifaceted model of supportive care initiated with a cohort 283 NAS neonates described by Grossman in 2015, also resulted in a decrease in length of stay, and need for pharmacological treatment [42]. Interestingly, nonpharmacological interventions were viewed as equivalent to medications; when increased intervention was required, parental involvement was increased [42]. Skin-to-skin contact is common practice in hospital settings, especially where rooming-in is offered.

Soothing techniques

Despite a lack of empirical evidence, soothing techniques including pacifier use, hand-to-mouth, selfclinging and infant positioning are common practice in NAS management. Non-nutritive sucking has anecdotally been shown to be helpful in organizing dysregulated hypersensitive infants [5]. Pacifier use has also been associated with decreased agitation and improved movement coordination, as well as increased mother–infant eye contact [5,7,12,43]. Infant positioning has also been proposed as an effective means of

managing NAS. Gentle pressure over the infant's head or body, pressing the infant's hands into its chest and positioning infants in a fetal position is thought to have a calming effect [12,44].

Therapeutic modalities

Therapeutic modalities such as scented relaxation baths and massage have been used in NAS populations, however, there is no empirical evidence to support their use. Acupuncture is currently the only modality with supporting evidence in this population. Acupuncture is used to treat opioid withdrawal in adults, but has not been evaluated thoroughly for NAS. Janssen examined the effect of maternal auricular acupuncture before delivery, as an adjunct to methadone and found no significant differences between groups in NAS rates or neonatal opioid-treatment after delivery [45]. Raith evaluated the effects of laser acupuncture adjunct to phenobarbital and morphine in 14 NAS neonates versus 14 treated solely pharmacologically [46]. Mean duration of morphine therapy was significantly reduced from 39 days in the controls to 28 in the acupuncture group. Furthermore, length of stay was reduced from 50 days in the controls to 35 in the acupuncture group. Although a significant difference was noted between the groups in this study, length of stay for both the groups was unusually long, almost double the length of stay of control groups reported by other authors [22,26,30]. In 2012 Fillipelli reported on the use of manual acupressure on acupuncture points in 92 NAS affected neonates [47]. Descriptive, nonstatistical analysis identified improved sleep and feeding and decreased agitation [47]. These findings may suggest an adjunctive role for neonatal acupuncture therapy in NAS management.

Conclusions

Nonpharmacological interventions such as breastfeeding, rooming-in and skin-to-skin care have shown great promise in NAS management. Given the increasing body of evidence on its efficacy, formalized, multidisciplinary supportive/nonpharmacological treatment for NAS should be universally and formally incorporated into standard care for NAS infants. Future research might focus on specific nonpharmacological interventions with less empirical support, such as swaddling and quiet/dim rooms, as well as other soothing techniques in NAS populations. Formalized, multidisciplinary supportive/nonpharmacological treatment for NAS shows much promise and developing evidence.

Disclosure statement

No potential conflict of interest was reported by the authors.

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