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Neonatal Abstinence Syndrome:

Therapeutic Interventions

Abstract

Neonatal Abstinence Syndrome (NAS) occurs in infants exposed to opiates or illicit drugs during pregnancy. It can be severe and cause long hospital stays after birth and with symptoms up to 6 months after birth. Pharmacologic interventions are commonly used as treatment for NAS; however, their safety and efficacy are not fully recognized. Pharmacologic treatments for NAS include medications such as methadone, buprenorphine, morphine, and phenobarbital. Nonpharmacologic interventions and complementary therapies have been documented in neonates. However, there are gaps in the literature regarding use of these therapies for neonatal withdrawal. This article provides an overview of the possible risks, benefits, and outcomes of pharmacologic and complementary therapies in the neonatal population, and illustrates the gaps in knowledge related to their use for neonatal withdrawal.

Keywords: Complementary alternative therapy; Neonatal Abstinence Syndrome; Pharmacology; Supportive care interventions.

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Since the 1980s, the incidence of Neonatal Abstinence Syndrome (NAS) has increased by 300% (Backes et al., 2012). NAS is a condition in which infants undergo withdrawal after exposure to prescription or nonprescription opioids such as methadone or heroin in utero. The withdrawal is due to the abrupt cessation of the opioids, which are mu receptor agonists in the central nervous system (CNS), after birth. It is characterized by a set of symptoms involving hyperirritability of the CNS and respiratory, gastrointestinal, and autonomic symptoms (Cleary et al., 2010). These symptoms usually appear within 48 to 72 hours after birth (Jansson, DiPetro, Elko, & Valez, 2010).

Hyperirritability of the CNS refers to tremors, increase in muscle tone, convulsions, and high-pitched crying. Respiratory symptoms include tachypnea and retractions. Gastrointestinal symptoms seen are usually excessive sucking with poor feeding, vomiting, and loose stools. Other symptoms are mottling, sweating, high temperature, and frequent yawning or sneezing or nasal congestion. These signs and symptoms have been well established as signs of neonatal withdrawal. These infants frequently require hospital stay in a neonatal intensive care unit (NICU) with hospital stays of varying lengths (Zimmermann-Baer, Notzli, Rentsch, & Bucher, 2010). The average hospital stay is 25 days for an infant with NAS (Backes et al., 2012). Typically, NAS infants are treated with standard nonpharmacologic approaches and pharmacologic approaches. Complementary therapies also present further options for management of these infants. This article explores varied therapy options for infants with NAS and the risks, benefits, and outcomes of the therapies.


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Guidelines for Treatment

Most infants exposed to opioids in utero will exhibit some form of NAS withdrawal. However, the degree of withdrawal is variable from infant to infant (Jansson et al., 2010). According to Pizarro et al. (2011), for mothers in methadone maintenance therapy programs during pregnancy, recent research shows no correlation with the dose of maternal methadone and severity of NAS for the infant. It has also been postulated that gender may play a role in the need for NAS treatment. The male sex has been documented to be more vulnerable in infancy and childhood. In one study males were not more likely to be treated, but once treatment was initiated for NAS, male infants had longer hospital stays and treatments were more intensive (Jansson et al., 2010). Hou et al. (2004) suggests that the male brain has a higher affinity for methadone than that of the female brain after their work in animal research. However, Holbrook and Kaltenbach (2010) refute the idea of gender difference in their research. They state that NAS severity or the need for treatment is not associated with the sex of the infant after performing a large retrospective chart review of 308 NAS infants.

Monitoring Neonatal Abstinence Syndrome

Diagnostic testing associated with detecting opioids in the infant is typically that of blood and urine drug screens from the mother and baby. However, if the drug exposure was not recent, these tests are not the most sensitive. Meconium testing is quite sensitive (Bio, Siu, & Poon, 2011). Meconium accumulates drugs in utero for approximately the last 5 months of pregnancy (Zimmermann-Baer et al., 2010) and is a good option for diagnostic testing. The American Academy of Pediatrics (AAP) Committee on Drugs guidelines recommends that an assessment tool should be used, maternal history and urine drug testing should be done, and drug testing of urine and meconium from the infant should also be performed (Hudak & Tan, 2012).

In order to monitor NAS symptoms in the hospital, various tools such as the Lipsitz tool, Finnegan scoring system, Neonatal Withdrawal Inventory, and the Neonatal Narcotic Withdrawal Index, or Ostrea System can be used (Bio et al., 2011). The AAP Committee on Drugs recommends scoring NAS symptoms using an appropriate tool (Hudak & Tan, 2012). The Lipsitz tool has a sensitivity of 77% and uses a value above four to indicate significant withdrawal (Sarkar & Donn, 2006). The Finnegan scoring system was designed by Loretta Finnegan to assess neonatal withdrawal. This tool gives a number rating to symptoms in four areas of classification: CNS irritation, respiratory distress, gastrointestinal distress, and vegetative symptoms. A Finnegan score higher than 8 is typically clinically significant for withdrawal from narcotics (Zimmermann-Baer et al., 2010). Zimmermann-Baer et al. (2010) sought to test the tool's reliability and validity and determined a Finnegan score done every 8 hours is sufficient to monitor signs of withdrawal; they also concurred that a score over 8 was suggestive of withdrawal.

Current monitoring and treatment of NAS vary depending on the institution and the philosophy of the physicians. Approximately half of the infants born to opioid-dependent women will require some form of pharmacotherapy. There are several pharmacologic approaches used. However, once pharmacologic treatment is initiated, there will be a hospital stay of varying lengths, most likely in an NICU. Methadone therapy is frequently used in many institutions. Isemann, Meinzen-Derr, and

Akinbi (2011) provide an example of a hospital protocol used by the University Hospital of Cincinnati NICU. Infants of mothers with known opiate dependency determined by a positive urine drug screen are monitored using the Finnegan scoring tool. Nonpharmacologic methods are attempted first when monitoring the infant. Any infant with two Finnegan scores above 8 is started on methadone therapy. There is an eight-step taper once methadone therapy is initiated, based on keeping the Finnegan score below 8. If methadone therapy is not sufficient, phenobarbital therapy is concurrently added. The infant may be discharged home on phenobarbital once off methadone for 48 hours based on appropriate Finnegan scores (Isemann et al., 2011). In addition to methadone, other pharmacologic therapies are used such as morphine, buprenorphine, clonidine, tincture of opium, and, as already stated, phenobarbital.

Pharmacologic Therapy

Management of NAS usually involves treatment with an opiate derivative such as morphine. Methadone and buprenorphine are classified as synthetic opiates. Diluted tincture of opium is a diluted morphine solution. Other treatments, such as phenobarbital, are used more for sedation than treatment of symptoms. In addition to opioid and sedating medications, clonidine has also been trialed for use in withdrawal for the neonate (Bio et al., 2011). According to Sarkar and Donn (2006), the treatment of NAS using pharmacologic methods varies greatly. Only one-half of the NICUs responding to their survey had clinical guidelines for withdrawal using an appropriate tool to identify severity for withdrawal (Sarkar & Donn, 2006).

AAP guidelines illustrate oral morphine and methadone as first-line therapies based on current evidence and practice in the United States. Clonidine is also suggested as a first-line therapy or adjunctive therapy based on new literature illustrating its efficacy (Hudak & Tan, 2012). This is a change from AAP (1998) recommendations, which included tincture of opium as the preferred choice of treatment for opiate withdrawal.

Phenobarbital is the preferred choice for sedative/hypnotic withdrawal. Other sedating medications, such as benzodiazepines such as diazepam, have been recommended in the past. However, AAP does not currently recommend their use due to their sedating effects and decreased ability to metabolize the drug with an immature liver (Hudak & Tan, 2012). Phenobarbital continues to be a better adjunct than benzodiazepines (Bio et al., 2011). Naloxone is also a contraindicated medication for infants with known opioid-dependent mothers due to the risk for seizure per the AAP (Hudak & Tan, 2012). However, despite the recent research, there is still no clear answer to standardized therapy for NAS. Table 1 compares drugs available for NAS treatment.

Nonpharmacologic Therapy

There is extensive research on pharmacologic therapy for NAS. However, nonpharmacologic therapy is thought to be supportive care, and there is little research in this area of treatment for the infant. Although one may not be able to forego pharmacologic therapy, nonpharmacologic therapies have equal importance in caring for an infant with NAS. Infants undergoing NAS are in a state of dysfunctional regulation of its CNS stimulation and responses to stimulation. A small amount of stimulation may cause them to experience a hyperactive response or an underactive response. In addition, these infants also have difficulty regulating their sleep and wake states and have increased tone, among other responses, which can contribute to increasing Finnegan scores and need for titration of pharmacotherapy (Velez & Jansson, 2008).

Environmental stimuli are important to infants in withdrawal. They need an environment that is quiet and dark. In addition, handling of these infants should be slow and gentle to reduce stimuli. Tight swaddling of the infants may be effective as well in containing the infant from hypertonic and erratic movements. Infants may be positioned on their back or side mimicking a fetal position. Pressure applied over the infant's head and body has a calming effect. Care should be clustered to promote sleeping states. Pacifiers are also a useful tool to help infants soothe themselves. Non-nutritive sucking helps to decrease the stress in the infant and have less erratic, uncoordinated movements. The positioning and use of non-nutritive sucking may also assist in preventing excoriation of skin due to erratic movements, which is scored on a NAS scale (Velez & Jansson, 2008).

Gastrointestinal upset is commonly seen in infants with NAS. Small frequent feedings are encouraged. Sometimes, a higher calorie formula may be used to facilitate weight gain when experiencing withdrawal symptoms. Even rubbing instead of patting an infant with burping may decrease stimulation and avoid stress (Velez & Jansson, 2008).

Holding and rocking an infant also have been shown to be effective supportive care treatments. Use of water beds and rocking chairs has shown to be effective in soothing infants (Velez & Jannson, 2008). In addition, Kangaroo care or skin-to-skin with the infant's mother is also an effective therapy. According to Hiles (2011), infants in withdrawal demonstrated decreased pain scores and had improved sleep patterns when skin-to-skin therapy was initiated.

Breastfeeding is often overlooked in NAS therapy. However, it is not contraindicated for mothers to breastfeed or provide breast milk for their infant. If the mother is on methadone or buprenorphine, both medications are compatible to take while breastfeeding. Methadone is transmitted through breast milk but in low doses. Buprenorphine has poor availability through the oral route, thus is also compatible. Breastfeeding rates are still low among this population despite lack of contraindications. Breastfeeding offers benefits to both mother and baby despite opioid addiction. It also assists with bonding under difficult circumstances (Wachman, Byun, & Phillip, 2010). Breastfeeding can actually decrease the stress response of the mother and lead to a calm interaction with the infant. This could potentially increase loving behaviors from the mother and perhaps decrease the risk of abuse, which is

higher in this population (Jambert-Gray, Lucas, & Hall, 2009). According to Isemann et al. (2011), using maternal breast milk can decrease length of stay. They also suggested that infants receiving maternal breast milk could be weaned more aggressively from methadone and discharged to the infant's home at an earlier rate. Thus, breastfeeding can also be an integral part of care for NAS protocol.

Complementary Alternative Medicine in the NAS Population

Although various complementary alternative medicine (CAM) therapies are used in the NICU, there is minimal research to support their use in the NAS population. Color and light therapy are used with infants. Traditionally, phototherapy has been used as a treatment for hyperbilirubin states in infants. Procianoy, Silveira, Fonseca, Heidemann, and Neto (2010) found that phototherapy produces some anti-inflammatory effects by reducing interleukin-6, an inflammatory cytokine, on newborn infants. However, further research is necessary to determine if this is a positive clinical finding as a phototherapy effect. Light therapy separate from phototherapy is used to help infants establish a normal circadian rhythm. Velez and Jansson (2008) suggest that light therapy with a dark environment and avoidance of bright colors prevents visual overstimulation in NAS infant. Black and white colors are more soothing for these infants, and it is also known to be a common practice to dim the lights in the NICU to decrease visual stimuli. Music therapy, such as classical music, helps decrease agitation and assists with sleep (Jones et al., 2001).

Table 1. **Pharmacologic Intervention Comparison for Neonatal Abstinence Syndrome**

Drug Attributes	Morphine[a]	Methadone[b]	Clonidine[c]	Buprenorphine[d]	Diluted Tincture of Opium[e]	Phenobarbital[f]
Class	Opiate	Synthetic opiate	Centrally acting adrenergic	Synthetic opiate	Opiate	Barbiturate
Action	Mu agonist	Mu agonist	Alpha 2 adrenergic agonist	Partial mu agonist	Mu agonist	Decrease hyperactivity in the CNS
Duration of action	Shorter half life 8 hours	Long-acting half life 26 hours	Long acting	Long acting	Variable	Long acting
Adverse effects	Respiratory depression	Prolonged Q-T interval	Rebound symptoms of increased BP and HR with abrupt cessation	Respiratory depression	CNS depression, respiratory distress, seizures, and hypotension	Oversedation Impaired sucking reflex
Special considerations	First-line therapy Frequent dosing	First-line therapy	Less sedative effects or respiratory depression	Able to titrate to high doses Needs more research on efficacy	Diluted oral morphine solution. No standard formulation: high morphine and opioid concentrations	Adjunctive therapy Outpatient monitoring and weaning Periodic blood level monitoring
Efficacy	More effective than phenobarbital	Trials inconclusive compared to morphine	↓ Finnegan scores with primary or adjunctive therapy	Decrease in duration of therapy when compared to morphine.	No difference between diluted tincture of opium and oral morphine	Improved outcomes as an adjunctive agent

CNS = central nervous system; DTO.
[a] Hudak & Tan (2012), Langenfeld et al. (2005), Ebner et al. (2007), Jackson et al. (2004).
[b] Bio et al. (2011), Jones et al. (2010).
[c] AAP (2012), Agthe et al. (2009), Leikin et al. (2009).
[d] Jones et al. (2010), Kraft et al. (2011).
[e] Langenfeld et al. (2005).
[f] Bio et al. (2011), Coyle, Ferguson, LaGasse, Liu, and Lester (2005), Isemann et al. (2011), Langenfeld et al. (2005).

Aromatherapy therapy can also be used in the NICU. This can be in the form of oils such as lavender or the mother's scent. Field et al. (2007) conducted a randomized controlled trial comparing behavior, sleep, and cortisol patterns in infants bathed by their mothers with and without a lavender-scented bath. The infants exposed to lavender had a decrease in crying, cortisol levels, and time to fall asleep. The mothers also had a decrease in cortisol and were more attentive to their infant in the group with the lavender-scented bath. This research, though, was not done in NICU. In addition to scents such as lavender, familiar scents of the mother are also beneficial. Goubet, Rattaz, Pierrat, Bullinger, and Lequien (2003) found that premature infants exposed to a familiar scent, in this case, vanillin, had decreased crying when exposed to a moderately painful procedure such as a heelstick. Marlier, Gaugler, and Messer (2004) also found that premature infants exposed to vanillin in the incubator had a decrease in frequency of apneic episodes. The study was small and consisted of infants already on standard drug therapy of caffeine and doxapram for apnea. Mothers are encouraged to leave clothing or items that have their scent in the child's bed to help decrease agitation and assist with bonding. Nishitani et al. (2009) found in a randomized controlled trial comparing infant response during a painful procedure when exposed to their mother's breast milk, another mother's breast milk, and formula that the infants were soothed by the scent of their mother's breast milk.

Massage therapy is a technique that is used in the neonatal population in the hospital (Jones, Kassity, & Duncan, 2001). In a study by Massaro, Hammad, Jazzo, and Aly (2009), massage therapy improved weight gain in preterm infants. There are various types of massage such as gentle touch, stroking, kinesthetic stimulation, and others. The level of massage should be adjusted based on the infant's age and needs (Jones et al., 2001).

One therapy that is currently being investigated is auricular acupuncture in the NAS infant. It has had some effectiveness in the adult population with opioid abuse. Raith, Kutscher, Muller, and Urlesberger (2011) reported that there were active ear acupuncture points in six NAS infants. Although acupuncture was not performed on the infants, the acupuncture points were detected using a sensor device that responds at acupuncture points. It was noted the infants had significantly fewer active acupuncture points than an adult. Given that there has been some effectiveness of auricular acupuncture in adults, it is a possibility for therapy for NAS infants. Other than acupuncture, few other results for CAM therapies in the NAS population have been studied.

The therapies discussed previously have been implemented successfully with term and preterm infants. However, their efficacy in the NAS population is not known. Given further research in this area, many of the therapies have potential to be successful in the NAS population.

Expected Course for the NAS Infant

The hospital course for the NAS infant is varied. Withdrawal is seen in approximately 80% of infants exposed to opioids in utero (Raith et al., 2011). However, the severity of their withdrawal is unknown and, while still debated, not thought to be related to maternal drug dosing (Pizarro et al., 2011). Jambert-Gray et al. (2009) suggested that treatment of the NAS infant should be with his or her mother in the room. This assists with attachment and may allow mother and baby to be discharged home at the same time. Saiki, Lee, Hannam, and Greenough (2010), in a cohort study, compared postnatal unit monitoring to monitoring in the NICU and found shorter lengths of stay in the hospital with postnatal unit monitoring and even reduced need for treatment, than with NICU monitoring.

New research suggests outpatient management for infants with NAS may be a possibility. Backes et al. (2012) completed a retrospective review from a 2-year period comparing a combined inpatient and outpatient approach to strictly inpatient for treatment of NAS. Outpatient management was only offered to mothers already enrolled in a methadone treatment clinic. The outpatient office was also able to provide primary care for the infant long term. The combined approach showed a decrease in cost and hospital stay as well as a higher incidence of breastfeeding. The researchers were encouraged by the higher incidence of breastfeeding because of its association with maternal infant attachment. Further research, however, is needed.

Clinical Implications

Decrease environmental stimuli
Cluster care activities with gentle handling
Use tight swaddling, supine, or side-lying positioning
Apply pressure over infant's head and body for calming effects
Encourage breastfeeding and Kangaroo care
Encourage mother's scent aromatherapy
Encourage non-nutritive sucking
Use small, frequent feedings

Conclusion

The incidence of NAS is increasing for infants exposed to opioids or recreational drugs in the prenatal period. Although there is no standardized treatment for NAS infants, most regimens rely heavily on pharmacologic resources. Nonpharmacologic and alternative therapies, while being used, have not received much emphasis in the literature. Newer treatment approaches using CAM therapies and alternative approaches to standard inpatient therapies are being investigated. Although clinical implications are suggested in the literature, further research is needed to incorporate CAM into the nursing care of the NAS population. ✣

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