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The role of mother-infant bond in neonatal abstinence syndrome (NAS) management

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ABSTRACT

The opioid crisis affects pregnant women and their infants. In the past two decades, the number of infants born with neonatal abstinence syndrome (NAS) has quadrupled causing the cost of healthcare expenditures to climb sharply. Pharmacological and non-pharmacological approaches are recommended for the management of NAS. Despite the attention NAS has recently received, treatment recommendations are limited to the hospital setting with much less focus on discharge planning. Additionally, the literature on NAS management does not consider research promoting mother-infant attachment. Recently, more emphasis has been placed on taking a holistic approach to NAS management. However, scholarly writings and research in this area are scarce. This article provides a review of current literature on NAS management and attachment-based interventions. Recommendations for practice and future research focused on holistic, non-pharmacological approaches to NAS management are provided.

Problem and incidence

In 2017, the U.S. Department of Health and Human Service (HHS) declared the opioid crisis in America a public health emergency (HHS, 2018). Opioid use and misuse have experienced a staggering surge in the past two decades throughout the United States. According to the Substance Abuse and Mental Health Services Administration's (SAMHSA) National Survey on Drug Use and Health (NSDUH), in 2017 11.1 million Americans had misused prescription pain relievers in the past year (SAMHSA, 2017). Unintentional opioid overdose claimed 47,872 lives in 2017, five times more than in 1999 (Ko et al., 2017). Moreover, approximately 2.6 million Americans in 2017 had an opioid use disorder (SAMHSA, 2017). Since 2009, heroin and pain reliever use in women nearly doubled (SAMHSA, 2010). Compared to previous years, in 2014 heroin use in childbearing age women, 15–44, increased by 31% and pain reliever use increased by 5.8% (SAMHSA, 2018). Moreover, opioid use disorder, as documented in delivery hospitalization, more than quadrupled between 1999 and 2014 (Haight, Ko, Tong, Bohm, & Callaghan, 2018). As a result, the prevalence of babies born with NAS increased from 1.2 per 1000 hospital births in 2000 to 5.63 per 1000 hospital births in 2012 (Haight et al., 2018). This caused a sharp increase in health care spending due to prolonged hospital stays (an estimated $1.5 billion in 2012) (Tolia et al., 2015) hence prompting a nationwide call to address maternal opioid use and NAS beginning with The Protecting Our Infants Act of 2015 (Haight et al., 2018; Ko et al., 2017).

In utero exposure

NAS is a general clinical term used to describe a newborn's experience of withdrawal symptoms after exposure to opioids or other substances in utero. Opioid-related NAS presents with hyperirritability, high-pitched crying, tremors, increased muscle tone, seizures, fever and GI dysfunctions such as poor feeding, excessive sucking, diarrhea, etc. (Edwards, 2016; MacMullen, Dulsk, & Blobaum, 2014). Fifty to 80% of infants exposed to opioids in utero develop NAS (SAMHSA, 2018), symptoms begin 24–48 h after birth and can last up to 60 days, thus requiring lengthy stays in a neonatal intensive care unit (NICU) (Haight et al., 2018; Tolia et al., 2015). In response to this issue, various approaches are recommended for prevention and treatment (Edwards, 2016; Ko et al., 2017; MacMullen et al., 2014; Osborn, Jeffery, & Cole, 2010a; SAMHSA, 2018). Pharmacological interventions for NAS have been researched with varying results necessitating further research (Wachman, Schiff, & Silverstein, 2018); however, there are interventions presently endorsed by the American Academy of Pediatrics (AAP) (MacMullen et al., 2014; Osborn et al., 2010a). Recently, scholars have expanded research on effective NAS treatments to include non-pharmacological interventions, such as kangaroo care (KC), breastfeeding, rooming-in, positioning, acupuncture, and use of special beds to name a few (Arora, 2013; Edwards, 2016; Shannon, Blythe, & Peters, 2016). Generally, practitioners agree that NAS treatment should combine pharmacological and non-pharmacological interventions. However, due to the unknown long-term effects of pharmacological treatments on newborns, some authors argue that NAS treatment should

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shift from a traditionally biomedical model toward a holistic framework that considers social determinants of health, and supports the greater need of focusing on promoting the mother-infant bond (Maguire et al., 2016; Marcellus, 2016). The Fetus and Newborn Committee of the Canadian Pediatric Society (CPS) recently urged clinicians to adopt a more holistic approach to treating NAS, relying less on pharmacological interventions, adopting the rooming-in model of care for infants and families, and emphasizing comprehensive discharge planning (Wismark & Cardinal, 2018).

This article will first provide an overview of the mental health of infants born with NAS and provide a summary of existing pharmacological and nonpharmacological approaches in treating NAS. To support the rationale for promoting attachment in infants with NAS, an overview of the neurobiology of attachment theory will follow. Then, based on an attachment theory framework, specific interventions designed to foster the mother-child bond, as well as discuss practical implications for nurses, counselors, social workers and other professionals working with mothers with opioid use disorders and infants with NAS are considered.

Mental health of infants born with neonatal abstinence syndrome

Infant central nervous system development begins in the embryonic period (i.e., third to eighth week), with the infant brain visibly defined between three to four weeks of gestation (Sigelman & Rider, 2015). Continuing brain development proceeds through the fetal period (i.e., ninth week until birth), and for a considerable period thereafter into early adulthood (Sigelman & Rider, 2015). Thus, infants exposed to teratogens in the form of licit and illicit drugs during these critical periods, and throughout gestation, are at risk for physical, cognitive and mental health anomalies at birth and potentially throughout the lifespan (Conners et al., 2003; Sigelman & Rider, 2015).

As the recent opioid epidemic has affected more women, an increase in neonates diagnosed with NAS has occurred (Kozhimannil, Graves, Levy, & Patrick, 2017). Kraft, Stover, and Davis (2016) reported that NAS increased from seven to 27 per 1000 NICU admissions from 2004 to 2013. Recent commentators have observed that the term NAS refers to fetal withdrawal from other drugs of abuse as well (Kocherlakota, 2014; McQueen & Murphy-Oikonen, 2016). Opioid exposure results from the licit and nonmedical use of prescription opioids, or use of illicit opioids (e.g., heroin) during pregnancy including those licit opioids used in medication assisted treatments (MAT) (e.g., methadone and buprenorphine). In a nationwide 2016 study reported by Kozhimannil et al. (2017) one in five mothers (i.e., 22%) acknowledging past year nonmedical opioid use met diagnostic criteria for opioid use disorder. In all cases, NAS is a characteristic risk and estimated to involve between 55 and 94% of opioid exposed neonates (McQueen & Murphy-Oikonen, 2016). Moreover, poorer NAS outcomes are attributed to maternal use of tobacco, psychotropic substances such as benzodiazepines, and antidepressants specifically, selective serotonin reuptake inhibitors (SSRIs) (Kraft et al., 2016).

It is important to recognize that a fair number of opioid jeopardized infants are poly-drug exposed (Jansson, Velez, & Harrow, 2009). Recent findings showed that pregnant women reporting use of alcohol, tobacco and cannabis have a significantly higher predicted likelihood of nonmedical opioid use (Kozhimannil et al., 2017). Osborn, Jeffery, and Cole (2010b) reported that given the prodigious rate of poly-drug use in mothers of infants with NAS, speculated that infants included in the studies they reviewed were likely representative of drug-exposed neonates with NAS treated in conventional clinical settings.

The exact mechanism of opioid withdrawal in infants, including factors influencing severity is incompletely understood (Kocherlakota, 2014; Kraft et al., 2016). Nonetheless, several factors are considered to explain the buildup of opioids in the fetus. Opioids have low molecular weights, are water and lipid soluble, readily cross the mother's placenta, have prolonged half-lives in the fetus and, therefore, contribute to NAS in newborns (Kocherlakota, 2014). Further, Kraft et al. (2016) reported research suggesting that modified levels of neurotransmitters for example, norepinephrine, dopamine and serotonin are thought to play a crucial role in NAS (Kraft et al., 2016). NAS is a clinical entity with hyperirritability of the central nervous system regarded as the hallmark of the disorder (Kocherlakota, 2014). Other symptoms include the disruption of autonomic system functioning, tremors, irritability, undue crying, hyperthermia, diarrhea, infrequent seizures, insomnia, yawning, sweating, nasal stuffiness and sneezing (Kocherlakota, 2014; Kraft et al., 2016). In addition, Kocherlakota (2014) observed that some neonates exhibit an inconsolable high-pitched crying indicating the need for urgent attention to the infant.

Medication assisted treatments for NAS

Bagley, Wachman, Holland, and Brogly (2014) and more recently, Wachman et al. (2018) have reported that despite recent increases in NAS incidence, considerable inconsistency persists in the assessment and management of opioid-exposed infants with a number of NICUs lacking a standardized NAS treatment protocol. As Kraft et al. (2016) emphasized, a NAS diagnosis is not predicated solely on the necessity of pharmacologic treatment, but rather, by the distinctive signs of neonatal withdrawal. The most common assessment employed for measuring NAS is the Neonatal Abstinence Syndrome Score (NASS), generally referred to as the Finnegan Score (FS) and its modified versions (Bagley et al., 2014; Kraft et al., 2016; Wiles et al., 2015). Furthermore, The AAP recommends using the Finnegan assessment tool to access NAS (Bagley et al., 2014).

Pharmacologic therapy

As Kocherlakota's (2014) review described, pharmacologic therapy (PT) is essential when supportive therapy (a) fails to ameliorate NAS signs and symptoms, (b) when elevated withdrawal scores persist, (c) critical symptoms, such as seizures are observed, or (d) acute dehydration occurs as a result of vomiting and/or diarrhea.

Infants are scored using several tools, most frequently with the FS and its modified versions, every 3–4 h beginning soon after birth, and continually assessed for 5–10 days for indications of opioid withdrawal in hospital (Bagley et al., 2014). Jansson Jansson, Dipietro, Elko, and Velez (2010) advised that recorded NAS scores should demonstrate the infant's full neurobehavioral repertoire for the complete time-period since the preceding score was recorded.

PT is typically administered after a newborn receives a score of > 8 in the case of the FS, on two consecutive scorings. Osborn et al. (2010b) reviewed PT interventions and generally concluded that “opioids” be prescribed for opioid withdrawal and “phenobarbitone” (i.e., phenobarbital) prescribed in place of diazepam for sedative withdrawal. Further evidence cited suggested that infants treated with opioids might also benefit from the inclusion of phenobarbital or clonidine to mitigate withdrawal severity; however, they cautioned that efficacy and safety data required supplementary confirmation.

Nonetheless, two opioids, morphine and methadone predominate as the most frequently utilized first-line medications (Bagley et al., 2014; Jansson et al., 2009; Kocherlakota, 2014). As Kocherlakota (2014) reported (Table 4) (p.555), specified recommended doses for neonate PT are delineated. For example, dosing with morphine (a μ-receptor agonist) is as follows: 0.05–0.2 mg/kg/dose every three to 4 h, with increased increments of 0.05 mg/kg and a maximum dose of 1.3 mg mg/kg per day. Recommended dosing for methadone (a μ-receptor agonist) is 0.05–0.1 mg/kg/dose every 12 h, with increases of 0.05 mg/kg at 48 h and a maximum dose of 1 mg/kg.

Buprenorphine (a partial μ-receptor agonist, κ-receptor agonist) is administered sublingually as follows, 4–5 μg/kg/dose every 8 h with a maximum dose of 60 μg/kg/dose. As previously mentioned, two sedative medications used in specific circumstances of severe infant

withdrawal have demonstrated enhanced efficacy. Phenobarbital (γ-amino butyric acid agonist) with a loading dose of 16 mg/kg and maintenance dose of 1–4 mg/kg/dose every 12 h; and clonidine (α-adrenergic receptor agonist) with an initial dose of 0.05–1 μg/kg/dose followed by 0.5–1.25 μg/kg/dose every 4–6 h.

Although the abovementioned PT protocols are routinely applied in particular hospital settings, they have yet to be comprehensively studied. Wachman et al. (2018) reviewed 53 key studies judged exemplars of extant clinical trials, cohort studies or case series, examining infant nonpharmacologic and pharmacologic treatments for NAS. Of the five pharmacologic randomized clinical trials (RCTs) reviewed, four were specific to infants and one to mothers. Studies that explored methadone and morphine PT included a single-site randomized sample of 31 infants that found significantly fewer opioid treatment days were required for methadone treated infants versus those with morphine (14 vs 21 days). A second retrospective study of 26 infants showed contrary results, with fewer days of medication for the morphine as opposed to the methadone treated group. A third cohort study of 36 infants, found those treated with morphine scored better on a standardized measure of infant and toddler development at two months of age compared to those treated with methadone. Last, a RCT of 60 infants found no significant difference in treatment days between infants treated with morphine or phenobarbital as first line PT.

Studies comparing buprenorphine to other opioids were more consistent. Wachman et al. (2018) cited one RCT of 63 infants who received PT with buprenorphine and experienced significantly shorter hospitalization days when compared to morphine treated infants (15 vs 28 days). A multi-site study of 201 infants compared PT with buprenorphine and methadone with infants exposed to buprenorphine in utero, which resulted in significantly fewer treatment days for the buprenorphine treated group (9.4 vs 14.0).

Studies that examined clonidine as a primary or adjunctive medication showed potential promise. For instance, one RCT of 80 infants discovered that clonidine used as an adjunct, helped reduce treatment days significantly, with diluted tincture of opium when compared to placebo (11 vs 15 days) (Wachman et al., 2018). Another RCT of 68 infants found that clonidine significantly extended days of treatment when used with morphine as opposed to phenobarbital (18.2 vs 13.6) days respectively. Although results appeared promising with clonidine and phenobarbital, more research is necessary (Wachman et al., 2018).

Wachman and colleagues concluded that where PTs for managing NAS are concerned, current evidence remains inconclusive and that recommending one pharmacologic regimen over another is not warranted currently without additional studies. Buprenorphine however, was singled out as promising given that it was significantly linked with shorter length of stay across four reviewed studies (Wachman et al., 2018).

Pharmacogenetics and NAS

It is estimated that nearly one in four infants with a severe variant of the NAS phenotype require adjunctive, in addition to, first-line medications, and typically endure an extensive period of pharmacologic treatment with concurrent lengthened inpatient hospital stays (Wachman et al., 2015). Studies have shown that single nucleotide polymorphisms (SNPs) in the mu-opioid receptor OPRM1gene and COMT gene in infants influence the severity of their drug withdrawal (Devlin & Davis, 2018; Wachman et al., 2013; Wachman et al., 2014). For example, infants with the OPRM1 118 > G AG/GG genotype had significantly fewer days in hospital and no medication compared to infants with the AA genotype. Similar results were found for the COMT 158A > G AG/GG genotype, with less frequent treatment using two or more medications, when compared to infants with the AA genotype (Wachman et al., 2013).

An additional finding revealed that DNA hypermethylation of particular CpG sites in the OPRM1 gene were significantly associated with more severe infant NAS and increased need for medication-assisted treatments (Wachman et al., 2014). Although beyond the scope of this discussion, it should be conveyed that additional variations in these genes and others have been discovered, indicating future research will assuredly increase expertise at treating NAS, while concomitantly advancing comprehension of the genetic antecedents of both NAS and opioid use disorder.

Psychological, medical and environmental sequelae in neonates with NAS

Ascertaining what moderates or causes physical and psychological abnormalities in substance-exposed newborns is made difficult due to a variety of maternal factors pertaining to (a) varied substances, (b) poly-drug use, (c) differences in quantity, intensity and fetal exposure to mothers' drug(s) of use/abuse, and (d) stage of pregnancy. All can feasibly influence developmental outcomes (Carta et al., 2001).

Neonates with NAS remain at increased risk following discharge for psychological, medical and environmental risk factors besides those tied to opioid and other drug exposure in utero. The risk is potentially exacerbated if newborns are in the care of a mother and/or father with active substance use disorder (Carta et al., 2001; Ornoy, 2003; Ubel et al., 2015). As stated before, a number of opioid exposed newborns are poly-drug exposed in utero. Whether or not opioid use is solely linked to medical and psychological complications, or a combination and interaction of unknown factors, is a recognized limitation in the NAS literature (Jansson et al., 2009; Ross, Graham, Money, & Stanwood, 2015). However, studies demonstrate that NAS is necessarily a condition requiring intervention and treatment with short-term and long-term implications for the wellbeing of newborns.

Short-term implications are well documented (e.g., Ross et al., 2015). Opioid exposed newborns frequently have lower birth weight and smaller head circumference than non-NAS newborns, and most experience a characteristic withdrawal syndrome shaped by factors such as, length of in utero drug exposure, MAT therapy during pregnancy, and poly-drug use during pregnancy. If NAS is serious enough pharmacological treatment is required (Kocherlakota, 2014; Ross et al., 2015).

Long-term implications are less certain as newborn development unfolds. Ross et al. (2015) cited evidence of nystagmus and strabismus in neonates exposed to opioids and pre- and elementary school aged children showed cognitive and motor impairments, poor attention span, hyperactivity, and increased incidence of ADHD. Although based on particularly small samples, evidence of cognitive memory deficits and brain growth deficiencies, utilizing neuroimaging studies of newborn brains, have been found (e.g., Sirnes et al., 2018). Adolescent visuospatial memory related deficits have been discovered (e.g., Schweitzer, Riggins, Ross, Black, & Salmeron, 2015) and further findings that youths (17–22 years of age), opioid and poly-drug exposed in utero, exhibited smaller neuroanatomical volumes compared to controls (Nygaard, Slinning, Moe, Due-Tønnessen, Fjell, & Walhovd, 2018).

However, a meta-analysis of 200 quantitative studies published between 1995 and 2012 studying the consequences of maternal opioid use during pregnancy on the neurobehavioral functioning of children revealed no significant impairments for cognitive, psychomotor, or observed behavioral outcomes. This indicates that more longitudinal studies are needed to continue investigating the role of environmental risk factors in the care of children opioid exposed in utero (Baldacchino, Arbuckle, Petrie, & McCowan, 2014). Indeed, the most salient observation is that newborns, “later negative consequences are more related to environmental factors such as chaotic lifestyle and inadequate parental care. One of the crucial components is maternal care, which changes profoundly in addicted mothers” (Fodor, Tímár, & Zelena, 2014, p. 1).

Nonpharmacological Approaches to NAS

Recently, alternative interventions to managing NAS have been suggested. Edwards and Brown (2016) conducted a meta-analysis of studies on nonpharmacological approaches to NAS management from 1988 to present. One hundred and twelve initial articles were reduced to 14 studies that met the researchers' criteria. Five nonpharmacological approaches emerged from their review listed from greatest number of studies reviewed to least: (1) breastfeeding, (2) rooming-in, (3) acupuncture/acupressure, (4) positioning, and (5) specialized beds (Edwards & Brown, 2016).

Breastfeeding

The AAP, The American Academy of Addiction Medicine, American College of Obstetrics (ACOG) and Gynecologists and Academy of Breastfeeding Medicine all support breastfeeding in women in methadone or buprenorphine treatment provided they are HIV-negative and abstinent from all illicit drug use (ACOG Committee on Health Care for Underserved Women, 2012). Breastfeeding has been shown to significantly reduce the need for pharmacological treatment and shorten the duration of NAS, thus shortening the length of hospital stay (Abdel-Latif et al., 2006; Lefevere & Allegaert, 2015; Pritham, 2013). It is important to highlight that studies in support of breastfeeding typically compare the effectiveness of breastfeeding combined with pharmacotherapy versus pharmacotherapy alone (Edwards & Brown, 2016). For the scope of this article, the classification of breastfeeding as a nonpharmacological approach should be viewed with caution since most studies have focused on mothers in methadone-or buprenorphine-assisted treatment and their breastmilk contains opioids, albeit in small and safe amounts (Pritham, 2013).

Rooming-in

Rooming-in has received support in managing NAS in clinical trials. Rooming-in promotes having mothers and infants occupying the same hospital room while receiving NAS treatment, and is so designed to increase the mother's presence and family involvement during the treatment episode (Arora, 2013). A recent study of 86 mother-infant dyads found parental presence was associated with decreased NAS severity, a nine day decrease in hospital length of stay, and eight fewer days of opioid therapy for the infant, even when controlling for breastfeeding; showing that mothers' proximity was demonstrated as clinically significant in the management of NAS (Howard et al., 2017). These findings supported a large experimental study conducted over a 3 year period in British Columbia where 952 newborns of substance abusing mothers were compared to women who delivered in hospital with a rooming-in program, and those who received standard care only. The rooming-in group had significantly fewer days in NICU compared to the control group (Abrahams et al., 2007). However, a limitation of most rooming-in studies was that the infants were also breastfed (Edwards & Brown, 2016).

Rooming-in is not a new approach to NAS management. The rooming-in model of care for mothers and infants was introduced in Canada by Abrahams and colleagues in 2001 and has been running successfully in Vancouver for over a decade (Abrahams et al., 2007; Byrne, Foss, Clarke, Wismark, & Cardinal, 2018). In the U.S., infants with NAS are typically treated in the NICU due to risk for respiratory depression (Arora, 2013). NICU stay is the greatest contributing factor of NAS's burden on current healthcare expenditures (Ko et al., 2017; Tolia et al., 2015). Moreover, because NICUs cannot accommodate extra beds for mothers, infants are often separated shortly after delivery (Arora, 2013).

In a recent study by Holmes et al. (2016), rooming-in, combined with family and nurse education to assess NAS symptoms, significantly reduced pharmacotherapy and NICU utilization, thus reducing costs while promoting mother-infant bonding. Educating families and nurses about NAS assessment and management cannot be overstated. Holmes and colleagues' approach was unique due to its inclusion of a qualitative component asking families for their input and adjusting accordingly. The study revealed that families lacked education concerning NAS, and wanted to be involved in treatment and were therefore, included as an integral feature of assessing and managing NAS symptoms in the hospital setting (Holmes et al., 2016).

Kangaroo care (KC)

Kangaroo care (KC) is a form of skin-to-skin contact technique where the infant (ages 0–3 years), in a diaper, is held against the mother's bare chest. The method was developed in the 70s as a means to regulate low-birth-weight neonates' body temperatures in countries with no access to expensive incubators (Anderson, 1991). KC is considered a safe, cost-effective approach to caring for clinically stable low-birth-weight and preterm infants. In clinical trials involving premature infants without NAS, KC was positively associated with decreased infections and respiratory-tract illness (Charpak, Ruiz-Peláez, Zita Figueroa de, & Charpak, 1997; Sloan, et al., 1994); improved sleep, autonomic nervous system (ANS) function, arousal modulation and sustained exploration (Feldman & Eidelman, 2003; Feldman, Weller, Sirota, & Eidelman, 2002; Messmer et al., 1997); and diminished pain response (Johnston et al., 2003). Recently, studies have investigated the effectiveness of KC in managing NAS symptoms. In infants with NAS, KC was associated with improved ANS function, reduction in withdrawal symptoms and increased length of quiet sleep (Arora, Boynton-Jarrett, & Berkowitz, 2017; Eckman & Rausch, 2014).

Attachment theory and NAS

Attachment theory has been utilized to understand NAS and inform interventions for NAS symptom management, with or without the use of pharmacotherapy (Arora, 2013). Attachment theory, based on evolutionary psychology, suggests babies are born with a predisposition to form attachment to others for survival purposes, while the determinant of attachment is not food but a caregiver's responsiveness (Bowlby, 1958, 1969). Proximity and responsiveness of the caregiver during what is considered a critical period of development (age 0–3) significantly influences the emotional, psychological and behavioral development of the child later in life (Ainsworth, 1973). From the perspective of attachment theory, the mother's presence, although necessary, is only part of the equation. Various factors influence attachment, such as the mother's ability to accurately read her baby's signs of distress and need for feeding or soothing, as well as the infant's ability to communicate distress and other immediate needs to the mother. The reciprocal and nurturing nature of responding to the newborn's needs reinforces the mother-child bond (Ainsworth, 1973; Bowlby, 1958, 1969).

Attachment theory has received considerable criticism for not allowing for individual and cultural differences (Miyake, Chen, & Campos, 1985; Myers, 1984). Nonetheless, applying attachment theory to conceptualize and treat NAS is sensible as NAS infants are more vulnerable to disruption in attachment. Despite advocacy efforts from the medical community to shift public perception of addicted mothers (e.g., AAP, 1995), the criminalization of substance use in pregnant women persists. Twenty-three states and the District of Columbia consider substance use during pregnancy child abuse, and 24 states and District of Columbia require mandatory reporting to Child Protective Services. Civil proceedings are allowed in 18 states, which may result in termination of parental rights, but not result in prison sentences. In Minnesota, Wisconsin and South Dakota substance use during pregnancy is grounds for civil commitment of the mother (Guttmacher Institute, 2018). In response to the NAS crisis and staggering Medicaid costs, in 2014 Tennessee became the only state to institute a law

allowing criminal assault charges for substance abuse during pregnancy resulting in conviction and imprisonment (Springer, 2014). Thus, infants with NAS not only battle the clinical symptoms of withdrawal, but impending separation from their mothers too, which can both have devastating effects on their psychological and behavioral development (Arora, 2013). Even when the mother is not legally removed from the child, the mother-infant bond in babies with NAS is likely disrupted by multiple medical care providers caring for the child (Holmes et al., 2016).

Additionally, NAS is marked by significant dysregulation in the ANS, which plays a significant role in regulating emotional, social and behavioral systems (Porges & Furman, 2011). Therefore, mother-infant bonding in infants with NAS is disrupted by the infant's own inability to regulate distress and those innate processes that seek care and bonding with the mother.

ANS and attachment in infants with NAS

NAS severity in individual newborns varies greatly and the exact manner in which NAS develops after in utero opioid exposure requires further exploration (Arora, 2013; Stover & Davis, 2015). Because there appears to be no direct relationship between the mother's methadone dose during pregnancy and NAS severity in the infant, NAS is difficult to predict and control (Cleary et al., 2010). The most illuminating studies on individual variability in NAS expression have involved ANS measures such as heart rate and vagal tone. These studies show NAS is marked by significant ANS dysregulation. In addition, there are data associating NAS severity with SNPs in the mu-opioid receptor OPRM1 gene and COMT gene (Wachman et al., 2013). Furthermore, predictors of NAS severity in opioid-exposed infants include male gender, mother's SSRI/SNRI use, and cigarette smoking (Hambleton et al., 2013; Hickey, Suess, Newlin, Spurgeon, & Porges, 1995; Jansson et al., 2010).

ANS dysregulation leads to the infant's inability to self-regulate bodily functions, respond appropriately to internal and external stimuli, and to communicate needs to the caregiver (Arora, 2013). Researchers have proposed that ANS plays an important role in regulating social, emotional and behavioral processes, which predict attachment to caregivers and psychosocial and behavioral adjustment later in life (Gunnar, Porter, Wolf, Rigatuso, & Larson, 1995; Porges, Doussard-Roosevelt, & Maiti, 1994; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996; Porges & Furman, 2011). From this perspective, known as the polyvagal theory (Porges & Furman, 2011), infants with NAS are at greater risk for developing insecure attachment and psychosocial and emotional maladjustment later in life.

ANS dysregulation in NAS infants may be a reflection of ANS dysregulation in mothers. Although the development of ANS begins in utero, the mother is wholly responsible for regulating basic ANS functions in the fetus (Arora, 2013). While more research is needed, preliminary evidence suggests in utero exposure to opioids, particularly methadone, may similarly effect NAS expression in infants indirectly, vis-à-vis the disruption of autonomic functioning in mothers during pregnancy (Hambleton et al., 2013; Jansson et al., 2010; Ramirez-Cacho, Flores, Schrader, McKay, & Rayburn, 2006). Compared to methadone, buprenorphine therapy for pregnant women resulted in significantly less morphine for the infant (mean dose, 1.1 mg vs. 10.4 mg), significantly shorter hospital stay (10.0 days vs. 17.5 days), and significantly shorter duration of treatment for NAS (4.1 days vs. 9.9 days) (Jones et al., 2010). These studies suggest (a) in managing NAS, not all opioids are equal, and (b) non-pharmacological interventions designed to improve the ANS regulation of both infant and mother may be key for managing NAS symptoms, and additionally, promoting secure attachment in this vulnerable population as well.

Promoting secure attachment in infants with NAS: recommendations for practice

It is remarkable that few empirical studies have investigated the impact of attachment-based interventions on infants with NAS. However, a large body of literature exists on investigating ways to promote secure attachment between mother and child in a variety of at-risk populations. A review of this literature may help inform applications tailored specifically for infants with NAS and their mothers.

Direct and indirect approaches

Interventions designed to promote secure attachment in infants are divided into indirect and direct approaches. Indirect interventions target risk factors that negatively affect attachment such as mother's depression, substance use, domestic violence victimization, poor social support, etc. Most studies in the literature focus on direct interventions (e.g., Letourneau et al., 2015; Wright et al., 2017). Furthermore, direct interventions target maternal sensitivity and responsiveness to the infant's signs for needing comfort and soothing, as well as the mother's reflective function on how her thoughts, feelings and previous life experiences affect how she responds to the infant's needs.

A 2015 meta-analysis reviewed the outcomes of seven randomized controlled trials and three quasi-randomized studies investigating maternal–infant attachment security, measured by the Strange Situation Procedure (Ainsworth, Blehar, Waters, & Wall, 1978), representing a total of 965 mother–child pairs. The studies were conducted in the Netherlands, United States, United Kingdom, South Africa, Lithuania and Chile. Participants included mothers who were financially stressed, caring for adoptive or irritable infants, depressed, from intact families, yet insensitive to their infants, and in complex situations (e.g., large families, unstable marriages, maltreatment, and/or financial difficulties). All studies involved direct interventions targeting maternal sensitivity alone, or sensitivity and reflective functioning combined (Letourneau et al., 2015). The interventions included video feedback of infant and mother responses, home visits, exploring mothers' cognitive and affective responses, encouragement of sensitive responsiveness from mothers, psychoeducation on sensitive parenting and playful interaction, telephone calls with practical parenting advice, a skills-based program focusing on responsiveness to negative and positive infant cues, or a combination, to name a few (Letourneau et al., 2015). Home visits ranged from a 2–10 total, to weekly for 3–7 months. The duration of the intervention also varied; however, most studies began prenatally and lasted 6–9 months after birth. Results showed all interventions were significantly and positively associated with secure attachment in the infant. The most successful study provided skills-based training to mothers of irritable infants and showed that children involved in the intervention were six times more likely than control group participants to be securely attached (Letourneau et al., 2015). The authors concluded that interventions targeting high-risk families proved to be the most effective (Letourneau et al., 2015).

Another large meta-analysis reviewed 14 studies conducted in the U.S., Canada, U.K., Netherlands, Australia and France (Wright et al., 2017). These studies investigated the effectiveness of sensitivity/responsiveness-enhancing interventions in reducing disorganized attachment in families at greater risk due to various factors. For example, child protection issues; social and economic deprivation, maternal mental health, adolescent mothers and infant's sleep disturbance and irritability (Wright et al., 2017). Samples varied between 43 and 449 participants and included 1816 children in total, ages ranging from neonatal to a mean of 3.35 years. Most studies used Child/Infant-Parent Psychotherapy and outcome measures utilizing the Strange Situation Procedure. All but two studies showed significant reduction in numbers of children with disorganized attachment at a medium effect size ($d = 0.38$). Interventions with 16 sessions or more showed statistical significance in reduction of disorganized attachment, while

interventions with 1–4 or 5–15 sessions did not (Wright et al., 2017). This is a significant finding since, brief interventions may be effective in promoting secure attachment (van IJzendoorn, Bakermans-Kranenburg, & Juffer, 2005), longer interventions are necessary for infants with disorganized attachment.

Most studies investigating the management of NAS neglect to take into consideration the considerable amount of evidence in support of employing early interventions to improve mother and infant attachment, particularly in underserved and vulnerable populations. While none of the aforementioned studies involved infants with NAS, their findings suggest NAS management should involve prolonged and multidisciplinary interventions focused on the mother (or caregiver). Such interventions could involve nurses, social workers, and counselors and should incorporate education for mothers. For example, effective guidance about NAS symptomology and assessment, encouraging mothers' sensitivity and reflective functioning via direct feedback, skill-development, and exploration of mothers' cognitive and affective processes. In effect, preliminary evidence from NAS studies choosing a holistic approach to intervention confirm the concept that attachment-based and NAS-specific psychoeducation and caregiver skill training during hospitalization yield better outcomes in infants with NAS compared to pharmacotherapy alone (Holmes et al., 2016).

Additionally, comprehensive discharge planning may facilitate continuity of care for the mother and infant upon returning home (Holmes et al., 2016). Because infants with NAS are at increased risk for disorganized attachment, early assessment for disorganized attachment and prolonged involvement with the mother and infant (ideally > 16 weeks) is highly recommended. A review of home-based interventions for promoting secure attachment may provide insights into possible treatment options for infants with NAS and their mothers' post-hospitalization.

Home-based visiting programs

Home–based visiting programs have proven efficacy in promoting secure attachment in vulnerable parents and their children (Mountain, Cahill, & Thorpe, 2017). Home-based visiting programs are interdisciplinary, relationship-based, community-imbedded interventions designed to promote maternal sensitivity, reflectiveness and overall positive parenting through teaching, feedback and behavior modification (Mountain et al., 2017). Noteworthy outcome measures used to determine the efficacy of home-based interventions include the Ainsworth's Strange Situation procedure (Ainsworth et al., 1978), Ainsworth Maternal Sensitivity Scales (AMSS; Ainsworth, 1969), Home Observation for Measurement of the Environment (HOME; Bradley, 1993) and Nursing Child Assessment Teaching Scale (NCATS; Sumner & Spietz, 1994).

The Ainsworth's Strange Situation procedure is a 21-minute structured observation of the interactions of mother, infant, and stranger (see Ainsworth et al., 1978). The AMSS, developed by Mary Ainsworth based on her observations of interaction between mother and infant in Uganda and United States, is a single-item scale with a detailed description of levels of maternal sensitivity that range from highly insensitive (1) to highly sensitive (9). After watching a maternal-infant dyad interaction, an observer completes the scale by selecting a global rating of 1 through 9 for a measurement of the mother's sensitivity toward her infant as evidenced by her awareness of the baby's signals, an accurate interpretation of the baby's signals, an appropriate response to signals, and a prompt response (Ainsworth, 1969).

The HOME is considered the most reliable and widely used scale for measuring the effectiveness of child-rearing home-based interventions (Bakermans-Kranenburg, van IJzendoorn, & Bradley, 2005). Scoring the HOME involves a low-key, semi-structured observation and interview during a 45-to 90-minute home visit were parent and child act naturally, with minimal interference from the observer. The Infant–Toddler version of the inventory is used from birth to age three and contains 45 items divided into six subscales: Responsivity, Acceptance of Child, Involvement, Physical Environment, Learning Materials, and Variety of Experience (Bradley, 1993).

The NCATS is used to measure parent–child interactions for children from birth to 36 months old. A certified observer scores the presence or absence of 73 behaviors on a “yes/no” scale divided into four Parent subscales (Sensitivity to Cues, Response to Distress, Social-Emotional Growth Fostering, and Cognitive Growth Fostering) and two Child subscales (Clarity of Cues and Responsiveness to Caregiver) (Sumner & Spietz, 1994).

Four randomized controlled trials involving 734 parents were selected for a recent meta-analytic review. Two of the studies were conducted in the U.S., one in Canada and one in South Africa (Mountain et al., 2017). Overall, the data supported early interventions for promoting secure attachment. The authors recommended behavior modification as an integral component of attachment-based early interventions. Interventions targeting mothers' sensitivity through parent education and behavior modification showed the most promise (Mountain et al., 2017). The interventions lasted between 10 weeks to 24 months, with an average of nine months, and outcome measures administered at 6, 12 and 24 months. Interventions varied among studies, but generally were divided into parenting education, sensitivity-based and reflective function approaches.

One study utilized The Social Baby home-based visit program performed by nonprofessional women designed to improve parents' understanding of how babies communicate in a socio-economically deprived community in South Africa (Cooper et al., 2009). Mothers in the intervention group were significantly more sensitive and less intrusive toward their infants at 6 and 12 months. However, The Social Baby did not prove effective for reducing disorganized attachment and mothers' depression (Cooper et al., 2009; Mountain et al., 2017).

Another study used Minding the Baby®, a relationship-based home visit program consisting of an intensive, interdisciplinary mentalization-based procedure delivered by nurses and social workers designed to target mothers' reflective functioning (Sadler, Slade, & Mayes, 2006; Slade et al., 2005). Minding the Baby® began as an interdisciplinary collaboration between the Yale Child Study Center and Yale University School of Nursing in 2002 to help young, at-risk mothers adjust their own attachment disruption and improve reflective functioning (or mentalizing capacities) related to mother-infant attachment behaviors (Slade et al., 2005). Sadler et al. (2006) found Minding the Baby® effective in promoting secure attachment in the intervention group versus the control group; however, results were not statistically significant (Mountain et al., 2017).

The most promising study in this review utilized the Attachment and Biobehavioral Catch-up (ABC) framework developed from attachment theory and emphasizes neurobiology (Bernard et al., 2012). ABC is considered a well-established treatment for promoting secure attachment and shown to promote caregiver sensitivity and attachment security in a number of studies (Alto & Petrenko, 2017). ABC aims to (a) reduce mother's frightening or frightened behavior toward the infant, (b) shape parental behaviors that foster the child's own adaptive regulatory responses, and (c) support nurturing care, via direct observation, immediate feedback and behavior modification (Bernard et al., 2012). ABC is designed for caregivers and children from birth to 24 months, is delivered in 10 weekly individual sessions utilizing video recording and tape reviews. In infants, ABC was associated with normalizing cortisol response to stress and decreasing negative affect (Bernard, Dozier, Bick, & Gordon, 2015; Lind, Bernard, Ross, & Dozier, 2014). Infants with NAS may find ABC particularly helpful due to its effectiveness in enhancing secure attachment and improving an infant's biological functioning.

Conclusion

Infants born with NAS are at high-risk for separation from mother

and disorganized attachment. Given the impact of early-disorganized attachment on long-term social and emotional development, NAS management should include a holistic approach addressing not only symptom management, but the mother-infant bond, as well as a continuation of care following hospital discharge. Attachment-informed interventions should begin in the hospital through breastfeeding, rooming-in and kangaroo care. Discharge planning should consider ongoing assessment of attachment style, attachment-based interventions with mothers, and psychoeducation about NAS, attachment and parenting. More research is needed to investigate the effectiveness of post-hospitalization home visits and attachment-based interventions with mothers and their infants with NAS.

A limitation of this review was a primary focus on NAS management in the United States, thus inadvertently promoting a skewed picture of NAS as a stable, independent phenomenon across societies and cultures. While the authors attempted to include studies from different countries, societal and multicultural considerations pertaining to NAS presentation and treatment were not provided. Future scholarship should consider an exploration of NAS within different geographical, societal and cultural contexts. Additionally, there is a need for ongoing research and conversation regarding culturally sensitive applications of attachment-based interventions in countries outside the United States.

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