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Review

Neonatal abstinence syndrome and neurodevelopmental health outcomes: A state of the science

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ABSTRACT

Despite the alarming increase in the numbers of infants born with neonatal abstinence syndrome (NAS), little is known about the effect on the children past the age of four. Clinical findings associated with NAS are found in the literature to have a negative effect on neurodevelopmental health outcomes. The purpose of this review is to examine the current evidence regarding NAS and neurodevelopmental outcomes, identify gaps in the literature, and discuss the possible association between NAS symptoms and neurodevelopmental disorders. A comprehensive literature review of quantitative research and review articles identified human and animal studies to clarify the current knowledge on the long-term effects of opioid exposure and NAS on neurodevelopmental outcomes. The analysis found that infants exposed to opioids *in utero* are at risk for poorer neurodevelopmental outcomes in early childhood; however, there is a lack of empirical evidence on the effect of NAS as children age.

Introduction

Neonatal abstinence syndrome (NAS), a withdrawal syndrome that occurs in infants exposed to opioids *in utero*, is a national health epidemic (Bauer and Li, 2013). Maternal use of opioids during pregnancy causes documented negative effects on neonates and is the precursor to NAS, which leads to low birth weight, neurological excitability, gastrointestinal distress, and autonomic reactivity (Lee, 2015; Maguire et al., 2016; McQueen and Murphy-Oikonen, 2016). The United States experienced a 380% increase in diagnoses of NAS from 1999 to 2013, leading to an estimated 28,000 infants diagnosed in 2013 alone (Ko et al., 2016; Patrick et al., 2015). NAS-related admissions to neonatal intensive care units (NICUs) increased from 7:1000 to 27:1000 from 2004 to 2013 (Tolia et al., 2015). Additionally, the cost of care for infants with NAS increased from $732 million in 2009 to $1.5 billion in 2012 (Patrick et al., 2015).

NAS occurs in infants following the use of opioids by the mother during pregnancy (Hudak et al., 2012; Jones et al., 2010; Lee, 2015). Opioids, both legal and illegal, including heroin, oxycodone, codeine, methadone, and buprenorphine, cross the placenta, leading to dependency in the infant (Lee, 2015). Dependence occurs when the infant functions normally only during exposure to the drug, thus they present with physical disturbances of withdrawal when the drug is removed (NIDA, 2007). Symptoms of NAS are in Table 1 and include, but are not limited to, mottled skin, inconsolable and high-pitched crying, hypertonicity, hyperreactive reflexes, difficulty eating, poor weight gain, and seizures (Lee, 2015; McQueen and Murphy-Oikonen, 2016).

Diagnosis of NAS usually occurs by the fifth day of life with onset of symptoms dependent on the type of drug taken by the mother (Maguire et al., 2016; Lee, 2015) and lasting up to six months of age (Desmond and Wilson, 1975). Although the clinical findings of NAS in the period following birth have been well documented, minimal research is available regarding the effects of NAS on neurodevelopmental health, particularly the association between NAS and incidences of neurodevelopmental disorders during childhood. Neurodevelopmental disorders emerge in childhood and affect behaviors of everyday functioning, ranging from intellectual disabilities, communication disorders, autism spectrum disorder, learning disabilities, specific learning disorder, and attention-deficit/hyperactivity disorder (ADHD) (American Psychiatric Association, 2013). Clinical findings associated with NAS can be linked to decreased neurodevelopmental health, thus a review of current empirical findings is necessary to determine the current state of knowledge. Understanding the current state of the science can assist with development of clinical interventions, such as early NAS screening, targeted to the appropriate age group and assist policy makers and advocates understand how the opioid epidemic

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Table 1
Symptoms associated with NAS.

Neurological Excitability	Gastrointestinal Distress	Autonomic Reactivity
Exaggerated moro reflex	Dehydration	Increased sweating
Frequent yawning	Diarrhea	Mottled skin
High-pitched crying	Excoriation	Nasal stuffiness
Hyperactive reflexes	Poor feeding	Temperature instability
Hypertonicity	Poor suck reflex	
Increased respiratory rate	Poor weight gain	
Irritability	Vomiting	
Seizures		
Sneezing		
Tremors		
Trouble sleeping		

Note. Adapted from "Neonatal abstinence syndrome" by K. Lee; "Neonatal abstinence syndrome" by J. McQueen & K. Murphy-Oikonen; and "Long-term outcomes of infants with neonatal abstinence syndrome" by D. McGuire et al.

affects the most vulnerable population in our society. The purpose of this review is to examine the current evidence regarding NAS and neurodevelopmental outcomes, identify gaps in the literature, and discuss the possible association between NAS symptoms and neurodevelopmental disorders.

Methods

A comprehensive literature review identified articles related to the topics of NAS and neurodevelopmental outcomes through a search of PubMed, PsychINFO, and CINAHL with multiple combinations of keywords including "Neonatal Abstinence Syndrome," OR "NAS," AND "long-term outcomes," OR "intellectual outcomes," OR "developmental outcomes," OR "developmental disabilities," OR "intellectual disabilities", OR "neurodevelopment." The search was limited to peer-reviewed journal articles and literature review articles with no limit on publication dates. Initial literature searches identified 222 articles. After reviewing titles for duplicate and non-related content, abstracts for 96 articles were reviewed further. Twenty-five articles were chosen for inclusion and extensive critique using the guidelines of Vance et al. (2013) (Fig. 1). A review matrix was organized for synthesis of the findings. The review of the literature identified human and animal studies to clarify the current knowledge on the long-term effects of opioid exposure and NAS on neurodevelopmental outcomes.

Results

Infants exposed to opioids *in utero* are at risk for poorer neurodevelopmental outcomes in early childhood; however, there is a lack of empirical evidence on the effect of NAS as children age (Bunikowski et al., 1998; Hudak et al., 2012; Hunt et al., 2008; McGlone and Mactier, 2015; Wang and Han, 2009). Current research focuses primarily on children under the age of five, often without a diagnosis of NAS, but with maternal exposure to opioids *in utero*. Research performed during early childhood indicates that children exposed to opioids during pregnancy have poorer neurodevelopmental outcomes than those who were not exposed. Neurodevelopmental outcomes are measured with specific indicators of health and development using standardized scales tested for reliability and validity (CDC, 2014). The tools used for measuring neurodevelopmental outcomes differed based on desired outcome (Table 2). Findings related to neurodevelopmental outcomes vary in the available literature.

Table 2
Developmental, behavioral and intellectual measurement tools in children exposed to opiates in-utero.

Developmental	Behavioral	Intellectual
Griffith's Developmental Quotient	ADHD medical diagnosis	Head Circumference
Bayley Scale of Psychomotor Developmental Index	Vineland Social Maturity Scale	Stanford Binet Intelligence Scale
Bayley Scale of Mental Developmental Index	Self-regulation	Reynell Expressive Language Scale
McCarthy Motor Scale		Reynell Verbal Comprehension Scale
		Standardized Testing Snijders-Oomen Nonverbal Intelligence Scale
		MRI
		Revision of the Amsterdam Children's Intelligence Scale

In the detailed review and synthesis of 25 articles, four themes emerged regarding the association between NAS and neurodevelopmental outcomes: (a) developmental outcomes, (b) intellectual outcomes, (c) behavioral outcomes, and (d) neurophysiological outcomes. We provide an overview of the findings below.

Developmental outcomes

Infants born to mothers using prescribed methadone during pregnancy scored significantly lower on the Griffith's Developmental Quotient (DQ) scale, even when taking into account smoking and alcohol consumption during pregnancy (McGlone and Mactier, 2015). The Griffith's DQ scale measures the development of infants and young children from birth to 2 years of age measuring locomotor skills, personal-social measures, hearing and language, eye and hand

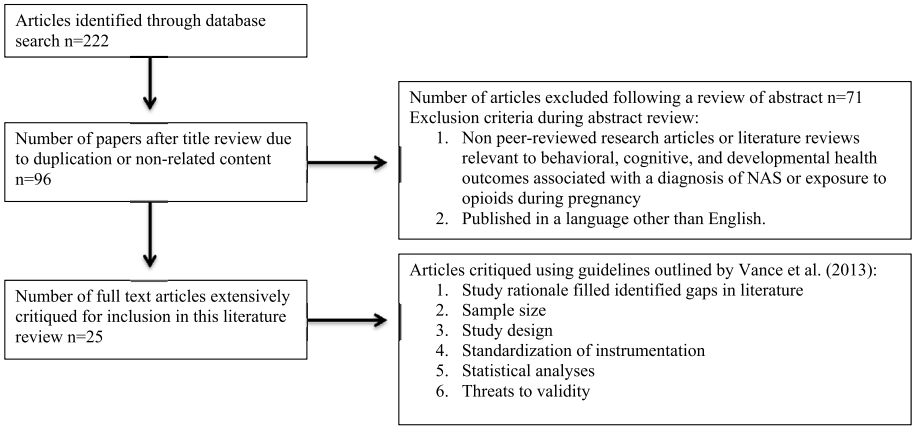

Fig. 1. Inclusion and critique criteria.