NRC Research Press

INVITED REVIEW

Understanding and managing sleep disruption in children with fetal alcohol spectrum disorder[1]

Ana Hanlon-Dearman, Maida Lynn Chen, and Heather Carmichael Olson

Biochem. Cell Biol. Downloaded from www.nrcresearchpress.com by UNIV MANITOBA on 07/02/19
For personal use only.

Abstract: Accumulating evidence has revealed high rates of sleep disruption among children with fetal alcohol spectrum disorder (FASD). Multiple animal and clinical studies have found a clear association between sleep problems and prenatal alcohol exposure, and recent research is beginning to characterize the types and extent of sleep disruption in FASD. Nevertheless, sleep disruption in children with FASD often goes unrecognized or is treated without referring to an evidence base. Children's disrupted sleep interferes with parental sleep and increases caregiver burden, which is of particular importance for families raising children with FASD, a group with very high levels of caregiving stress. The literature supporting an association between sleep problems and deficits in emotional, behavioral, and cognitive function in children is compelling, but needs further investigation in children with FASD. This paper will review the current state of knowledge on sleep in FASD and recommend a rational approach to sleep interventions for affected children and their families.

Key words: FASD, sleep, pediatrics, prenatal alcohol exposure, maternal alcohol use.

Résumé : De plus en plus de données révèlent une haute incidence de troubles du sommeil chez les enfants atteints d'un trouble du spectre de l'alcoolisation fœtale (TSAF). Plusieurs études cliniques et chez l'animal ont trouvé une claire association entre les troubles du sommeil et l'exposition prénatale à l'alcool, et les recherches récentes commencent à caractériser les types et l'ampleur des perturbations du sommeil dans les TSAF. Néanmoins, les troubles du sommeil chez les enfants atteints de TSAF sont souvent mal ou peu reconnus et sont traités sans références aux données probantes. Le sommeil perturbé des enfants interfère avec le sommeil des parents et accroit le fardeau des aidants naturels, ce qui est d'une importance particulière pour les familles qui élèvent les enfants atteints de TSAF, un groupe à hauts niveaux de stress liés aux soins. La littérature qui appuie une association entre les problèmes de sommeil et les déficits des fonctions émotionnelles, comportementales et cognitives chez les enfants est irréfutable, mais elle nécessite une recherche plus approfondie chez les enfants atteints de TSAF. Cette synthèse passera en revue l'état des connaissances actuelles sur le sommeil dans les TSAF et recommandera une approche rationnelle d'interventions sur le sommeil pour les enfants affectés et leurs familles. [Traduit par la Rédaction]

Mots-clés : TSAF, sommeil, pédiatrie, exposition prénatale à l'alcool, consommation maternelle d'alcool.

Introduction

Fetal alcohol spectrum disorder (FASD) is characterized by lifelong neurodevelopmental disabilities arising from prenatal exposure to alcohol (PAE) (Stratton et al. 1996; Bertrand et al. 2004; Chudley et al. 2005;; Olson et al. 2009*a*). The prevalence of FASD has generally been estimated to be 9 or 10 cases per 1000 live births in the United States (Sampson et al. 1997; May and Gossage 2001), although there are more recent estimates using active case ascertainment in school studies that range as high as 2%–5% of younger school children in the United States (May et al. 2009, 2014), with much higher estimates in high-risk subgroups such as children in care (Lange et al. 2013). FASD is considered a major public health problem (Riley and McGee 2005; Warren et al. 2005) that is global in extent (Warren et al. 2005; Calhoun et al. 2006); May et al. 2009). FASD is known to have frequent sequelae, including social adaptive dysfunction (Streissguth et al. 2004), adverse impact on caregiver and family function (Olson et al. 2009*b*), and high societal costs (Lupton et al. 2004; Riley and McGee 2005; Popova et al. 2012, 2013, 2014*b*, 2015). There is also increasing concern about elevated rates of physical health problems in this clinical population and their long-term impact (Popova et al. 2012, 2016). Opportunities to maximize functioning and reduce morbidity in FASD are, therefore, critical for affected individuals, their families, and communities.

In children with FASD, sleep problems from infancy through the school years are commonly experienced by families, yet are poorly understood by health care providers (Wengel et al. 2011; Ipsiroglu et al. 2013; Honaker and Meltzer 2016). While the frequency of sleep problems in developmentally typical children is often quoted as about 25%, the frequency of sleep problems in children with FASD has been observed as high as 85% in keeping with other children with developmental disabilities (Chen et al. 2012; Robinson-Shelton and Malow 2016). For example, sleep problems are reported to occur in 50%–80% of children with autism spectrum disorder (Kotagal and Broomall 2012) and up to 70% of those with attention-deficit/hyperactivity disorder (ADHD) (Cortese

Received 3 April 2017. Revision received 31 July 2017. Accepted 11 August 2017.

A. Hanlon-Dearman. Pediatrics and Child Health, College of Medicine, Faculty of Health Sciences, University of Manitoba, Winnipeg, MB R3T 2N2, Canada; Manitoba FASD Centre, Winnipeg, MB R3E 3G1, Canada.
M.L. Chen. Department of Pediatrics, Pulmonary and Sleep Medicine Division, University of Washington School of Medicine, Seattle, WA 98195, USA.
H.C. Olson. Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA 98195, USA; Center for Child Health, Behavior and Development, Seattle Children's Research Institute, Seattle, WA 98101, USA.
Corresponding author: Ana Hanlon-Dearman (email: ahdearman@rccinc.ca).

[1]This Invited Review is one of a selection of papers covering various aspects of fetal alcohol spectrum disorder (FASD).

Copyright remains with the author(s) or their institution(s). Permission for reuse (free in most cases) can be obtained from RightsLink.

Biochem. Cell Biol. Downloaded from www.nrcresearchpress.com by UNIV MANITOBA on 07/02/19
For personal use only.

et al. 2013). Various characterizations of the sleep disturbances seen in children with FASD have included sleep onset delays, shorter sleep, and more frequent night wakings as well as atypical features including elevated rates of parasomnias and sleep anxiety (Wengel et al. 2011; Chen et al. 2012), The complexity of both the sleep disturbance and resultant impact on daytime behavior and learning is significant for both children and their caregivers (Blackmer and Feinstein 2016). With a high rate of FASD represented in children in care, and a high level of documented caregiver stress, the further impact of night dysregulation on family functioning and the risk for potential destabilization of a care placement is significant (Bobbitt et al. 2016). Recognizing these sleep disorders in this high-risk group and offering effective treatment strategies offers an opportunity to improve child behavior, reduce caregiver stress, stabilize social placement, and increase child and caregiver resilience.

Contributors to sleep difficulties in children with FASD are multifactorial, including (1) hypothesized physiologic changes resulting from the neurotoxic effects of PAE on sleep architecture, circadian physiology, and respiratory control, (2) lasting sequelae in health and daytime function for chronically sleep-disrupted/sleep-deprived parents and affected children, and (3) impact on interpersonal relationships restructured by emotional, behavioral, and cognitive perceptions of a "difficult" sleeper. Sleep difficulties are potentially modifiable when attempting to maximize neurodevelopmental potential and health in each individual with FASD. However, addressing these sleep difficulties must consider the many factors influencing sleep, the sleep environment, and the child/individual experiencing these difficulties within their family. A management approach that integrates current scientific understanding of the impact of PAE on sleep, neurobehavioral patterns, and the needs of the child and family offers the strongest opportunity for effectively addressing these complex difficulties.

The purposes of this review are to characterize what is known about sleep challenges in children with FASD, explore pathophysiologic mechanisms, discuss the impact of sleep problems within this population, and recommend a rational approach to sleep treatment and support for these children and their families. This review will present the most current research on sleep mechanisms in FASD and will contextualize this research with established knowledge and expert clinical experience.

Mechanisms of sleep disruption related to prenatal alcohol exposure

Preschool or school-aged children with PAE, including those who are not yet diagnosed with FASD, may experience sleep difficulties related to PAE. These may be further compounded by post-birth events, including trauma. Co-occurring prenatal exposures may also have an effect (Rosett et al. 1979; Chernick et al. 1983; Scher et al. 1988). The mechanisms underlying the teratogenic effects of PAE on sleep are complex. Descriptive studies using animal models or humans have explored the connection between PAE and sleep disruption to delineate possible underlying physiologic mechanisms. An understanding of the impact of PAE including altered sleep architecture, fragmentation, and shorter sleep duration has emerged from such research.

Correlational data from studies of infants with a history of PAE, who may or may not be diagnosed with FASD, have described the impact of PAE on physiologic mechanisms of self-regulation. Early electroencephalographic (EEG) studies of these infants, assessed both prospectively in pregnancy and via retrospective maternal report of gestational alcohol use, showed adverse changes in neonatal state regulation including problems in sleep, sleep cycling, and arousal (Havlicek et al. 1977; Rosett et al. 1979; Chernick et al. 1983; Loffe et al. 1984; Ioffe and Chernick 1988; Scher et al. 1988). Work published in *The Lancet* (1976) was the first to describe disorganized and hypersynchronous voltage patterns in the EEGs of infants of alcoholic mothers (Havlicek and Childaeva 1976). Later work continued to describe a characteristic EEG pattern across all stages of sleep, with significantly higher voltage than the patterns seen in healthy nonexposed infants (Havlicek et al. 1977). Followup work demonstrated that the EEG differences were prolonged, independent of gestational age, and not related to neonatal withdrawal from alcohol (Loffe et al. 1984). More recent work correlated the early presence of these EEG differences in infants with PAE with subsequent motor and cognitive development later in childhood (Ioffe and Chernick 1988, 1990).

Newer research has revealed altered arousal responses during sleep in alcohol-exposed infants (Troese et al. 2008). A recent large, well-designed longitudinal study in Finland has extended the study of sleep and PAE into childhood, where associations between low birth weight, prenatal exposure to alcohol and tobacco, and sleep duration and efficiency (based on actigraphy, or measurement of sleep movement) were examined in 8 year olds (N = 289) (Pesonen et al. 2009). PAE was associated with shorter sleep duration and poorer sleep efficiency, even after controlling for birth weight and tobacco exposure. In this study, no assessments of daytime function or diagnosis of conditions in the category of FASD were undertaken (Pesonen et al. 2009).

Data from experimental animal models of PAE have demonstrated possible mechanisms of alcohol's teratogenic effect on sleep processes and allowed consideration of these issues apart from the impact of other prenatal or postnatal influences. These data suggest that sleep compromise is under both neurological and genetic control and is impacted by PAE and that problems persist across the lifespan. These data have also characterized the sleep disturbance seen with PAE. Comparing alcohol-exposed rat pups with controls, disturbances in sleep–wake patterns have been found including shorter sleep and sleep fragmentation (Hilakivi 1986; Hilakivi et al. 1987). Rat models of the full fetal alcohol syndrome (FAS) have demonstrated changes in sleep architecture with significant reductions in REM sleep. Studies using alcohol-exposed rats have shown a shortened circadian sleep–wake cycle as well as abnormal circadian neurotrophin expression in the suprachiasmatic nucleus, which regulates circadian rhythmicity (Earnest et al. 2001; Allen et al. 2005; Sakata-Haga et al. 2006; Dubois et al. 2008; Fukui and Sakata-Haga 2009). Subsequent work has suggested that impacts on circadian rhythmicity may be long term and that PAE may exert a metabolic effect on clock regulatory genes in the hypothalamus (Allen et al. 2005; Dikranian et al. 2005; Farnell et al. 2008; Agapito et al. 2014), which may predispose exposed individuals to nocturnal sleep fragmentation (Allen et al. 2005; Dikranian et al. 2005; Farnell et al. 2008; Agapito et al. 2014). In a 2016 study of binge pattern PAE on adult rats, impaired slow-wave sleep with increased slow-wave/fast-wave transitions were demonstrated; furthermore, this sustained sleep fragmentation was associated with memory impairments in these adult mice (Wilson et al. 2016). Of importance, previous work has suggested the selective sleep deficits found in young adult rats with concurrent deficits in spatial memory could be attenuated with treatment, although human implications are less clear (Stone et al. 1996). Finally, blunted ventilatory responses to hypoxia in juvenile rats with PAE have also been demonstrated, suggesting that increased risk for significant sleep-disordered breathing (SDB) could occur (Dubois et al. 2008, 2013; Kervern et al. 2009).

There are data from animal and human studies that provide potential mechanisms of the links between the teratogenic effects of PAE with clinical findings of SDB and disrupted sleep among children with FASD. Both SDB and sleep disruption encompass a broad range of disorders with varying etiologies, but a few potential pathophysiologic possibilities warrant further discussion, as they specifically pertain to children with PAE.

First, central respiratory modulation and respiratory muscle coordination may be impacted in those with PAE via abnormali-

Biochem. Cell Biol. Downloaded from www.nrcresearchpress.com by UNIV MANITOBA on 07/02/19
For personal use only.

ties in the midline cerebellum (Verrier et al. 2005). Animal models and neuroimaging studies have demonstrated the effect of PAE on in utero development of the cerebellar vermis (Dikranian et al. 2005; Riley and McGee 2005; Spadoni et al. 2007). Cerebellar anomalies have been described among individuals with FAS and those with conditions on the broader fetal alcohol spectrum (Rasmussen et al. 2006). Mechanisms by which cerebellar compromise may play a role have been illustrated by examining children with lesions in the cerebellar vermis who show a markedly higher incidence of apneas and increased risk of sudden death from presumed SDB (Chen et al. 2005). Abnormalities in those same areas of the cerebellum may thus predispose children with PAE to challenges with central respiratory control and coordination.

Second, SBD among those with FASD could also be related to airway obstruction due to a combination of anatomic and neuromuscular differences in the upper airway. Airway patency is challenged during sleep due to inherently decreased neuromuscular tone in the upper airway muscles, predisposing them to collapse (Wills et al. 2006). When coupled with midface anomalies, which are known to occur in those with classically described FAS, repeated episodes of airway obstruction are at high risk of leading to SDB (Stratton et al. 1996; Chudley et al. 2005; Riley and McGee 2005). Taken together, these studies suggest the possibility that those with FASD experience respiratory abnormalities during sleep arising from cerebellar abnormalities and (or) upper airway obstruction. Respiratory abnormalities, from central nervous system impairment and (or) SDB, may additionally result in repeated cortical arousals during sleep, which also leads to sleep fragmentation (Katz and Marcus, 2005).

Third, neuroimaging and animal research suggest that children with FASD may also be predisposed to teratogenic damage to the suprachiasmatic nucleus, presumed to play a critical role in "the circadian clock" (Earnest et al. 2001). PAE in mice has also been shown to decrease levels of γ-aminobutyric acid, an important neurotransmitter in sleep–wake stability (Godin et al. 2011). A dysfunctional circadian system and (or) disrupted γ-aminobutyric acid circuits may lead to frequent nighttime arousals (clinical and subclinical) as well as to insomnia, perhaps because awake and sleep states are not appropriately recognized at a neurological level.

In summary, sleep can be fragmented by the impact of PAE through a variety of potential mechanisms, the effects of which may be compounded if these teratogenic insults are combined.

Characterizing sleep problems in children with FASD

Several research groups in the 1990s identified sleep problems among children with FASD as part of an initial characterization of a neurobehavioral profile for this set of neurodevelopmental disabilities. An early longitudinal study in Germany (1998) examined a clinical sample of individuals with FAS (N = 158) at preschool, school age, and adolescence (Steinhausen and Spohr 1998). Using questionnaires and clinical interviews, "sleep disorders" were generally noted as a common clinical problem and, importantly, many participants showed newly manifested sleep disorders at school age. No details were given about types and exact frequency of sleep disorders, nor were validated measures used. The same year, a US study (N = 472) found that just over 50% of informants identified "sleeping problems" in the clinical phenotype of alcohol-affected children, identifying these to be of greater importance than the "hyperkinetic disorders" (Streissguth et al. 1998). A later 2006 US chart review of youth referred for FASD diagnosis (N = 2231) found "sleep disorder" rates ranging from 9.7% (no confirmed PAE) to 52.3% (high risk alcohol exposure) (Bhatara et al. 2006). A 2009 survey of children with FASD in Canada (N = 89), aged 8–15 years, found 62% with "sleeping disorders" gathered from clinical interview compared with 11% of controls, making sleep disorders the most prevalent comorbidity in children with FASD occurring at a similar rate to that of ADHD/ADD (Green et al. 2009). All of these studies have established a consistent and significant prevalence of reported sleep problems among children with PAE and (or) FASD.

There is emerging research that more precisely describes sleep difficulties in children with FASD. Cross-sectional findings for young children with FASD (N = 100) aged 5–8 years, using sleep diaries and caregiver questionnaires, reported reduced sleep duration and frequent night wakings (Stade et al. 2008). Studies have consistently described high rates of clinically significant sleep problems in several samples of children with FASD, suggesting that primary difficulties with sleep initiation and maintenance are common (Chen et al. 2006, 2012; Wengel et al. 2011; Goril et al. 2016). Furthermore, research is describing abnormalities in sleep architecture and efficiency impacting circadian regulation (Chen et al. 2012; Goril et al. 2016).

Three recent studies are of note. In 2011, a Canadian study by Wengel et al. used actigraphy, as well as sleep scores from the validated children's sleep habits questionnaire (CSHQ), and compared these with sensory processing characteristics in a group of young children (ages 3–6 years) with FASD compared with controls (Wengel et al. 2011). This study showed a significantly increased rate of sleep disruption and parasomnias in young children with FASD compared with controls and showed that patterns of sleep disruption also correlated with differences in sensory processing (Wengel et al. 2011). In 2012, Chen et al. compared a representative group of 4–10 year old children with FASD with an age-matched typically developing community sample (N = 418) (Chen et al. 2012). They also used the CSHQ (Owens et al. 2000) and, in addition, obtained parent norm-referenced questionnaire reports of concerning daytime behaviors. Both studies found large differences between groups, with high rates of clinically significant sleep problems in the children with FASD compared with controls. Chen et al. reported that a striking 85% of children with FASD fell above the cutoff for clinically significant sleep problems (CSHQ total score ≥41), significantly more than the 35% seen in community matched controls ($p < 0.001$). In addition, subscales concerning for pediatric insomnia were also elevated among children with FASD compared with controls (Havlicek et al. 1977; Loffe et al. 1984; Popova et al. 2014).

Chen et al. also performed a full overnight sleep study for a small group of these children with FASD and significant sleep problems, all of whom had CSHQ scores >41 (Chen et al. 2012). Polysomnography in this study was the first to show objective evidence of fragmented sleep among children with FASD as well as mildly elevated carbon dioxide levels, suggesting SDB. These pilot polysomnography data, coupled with CSHQ parent report data from both studies, suggest two broad areas in which children with FASD may commonly have sleep problems: (1) difficulties with sleep initiation/maintenance and (2) respiratory disturbances.

Most recently in 2016, Goril et al. characterized the sleep and circadian rhythm of 36 children and adolescents with FASD, age 6–18 years, using both gold standard assessments of polysomnography and evaluation of dim light melatonin onset (Goril et al. 2016). Consistent with prior work, this study described significant sleep disruption in children and adolescents diagnosed with FASD (Hanlon-Dearman 2003; Wengel et al. 2011; Chen et al. 2012). Goril et al. (2016) also described a high rate of parasomnias in children with FASD (which Hanlon-Dearman's much earlier work had suggested) and a variable pattern of melatonin secretion (Hanlon-Dearman 2003). Previous work has reported an increased rate of atypical nocturnal behaviors among young children with PAE compared with age-matched controls, including talking, kicking, or picking and sniffing of bedclothes (Hanlon-Dearman 2003; Ipsiroglu et al. 2013). Given the variable presentation of alcohol toxicity on neurodevelopment, dependent on factors such as dose, timing, and maternal health, this variable pattern of sleep problems and underlying hormonal mechanisms may be a predictable conse-

Biochem. Cell Biol. Downloaded from www.nrcresearchpress.com by UNIV MANITOBA on 07/02/19
For personal use only.

quence and is certainly consistent with previous animal literature investigating the effects of alcohol on other hormonal systems (Lan et al. 2017).

Impact of sleep difficulties on daytime function and treatment possibilities

Growing data associating difficulties in sleep and daytime function suggest that disrupted childhood sleep is associated with significant deficits in emotional, behavioral, cognitive, and academic functioning and that these impact child health and quality of life among both typically and atypically developing children. Sleep problems are particularly prevalent in atypically developing children, with reported prevalence rates of up to 80% (Wiggs and Stores 1999; Wiggs 2001; Berkman 2006). Associations between sleep and daytime function are reported in many pediatric clinical populations and particularly among those with developmental disabilities. Frequent night wakings among children with developmental disabilities have been associated with self-injurious behavior, hyperactivity, and aggressive and disruptive behavior (Wiggs and Stores 1996; Wiggs 2001, 2009). These disturbances have a significant impact on parent and child quality of life. For example, the association between sleep problems and reduced child quality of life in ADHD has been described, independent of severity of ADHD symptoms (Sung et al. 2008). In autism spectrum disorder, parent reports have revealed an association between ratings of poor sleep and less optimal child daytime behavior, with moderately strong associations between sleep latency from polysomnography and ratings of affective problems and aggressive behavior (Wiggs and Stores 2004; Malow et al. 2006; Sikora et al. 2012). Significantly, sleep problems are related to child behavioral dysregulation, such as externalizing problems and executive dysfunction. These also represent the most challenging areas of daytime function for children with FASD (Mattson and Riley 2000; Astley et al. 2009).

Data on restricted sleep and SDB (the latter of which includes obstructive sleep apnea) shed further light on the connection between sleep and daytime function at school and at home. There is evidence that obstructive sleep apnea, currently the best studied model of sleep fragmentation in children, is associated with poor school performance, neurocognitive deficits such as deficits in self-regulation, daytime inattention and hyperactivity, behavior problems, mood instability, and decreased growth (Chervin and Archbold 2001; Rosen et al. 2002; Gottlieb et al. 2003; Beebe 2006). For children with obstructive sleep apnea, lower scores have been found in measures of phonological processing, executive functioning, and visual attention (O'Brien et al. 2004). Of interest, as many studies have shown, individuals with FASD commonly have problems in these areas of function (Stratton et al. 1996; Mattson and Riley 2000; Bertrand et al. 2004; Riley and McGee 2005; Astley et al. 2009; O'Connor and Paley 2009; Chen et al. 2012). Surprisingly, however, there has only been one study so far using polysomnography in children with FASD to examine the possibility of SDB and other clinically significant objective sleep study parameters (Chen et al. 2012). This is unfortunate because treatment of SDB leads to notable decreases in health care utilization and likely improves child quality of life (Mansfield and Naughton 2004). It is important to note that there is a promising and significant treatment opportunity for children with FASD who also show SDB.

Many studies have documented challenges in daytime learning and behavior among children with FASD, but none, to our knowledge, have examined difficulties in daytime function in relation to sleep problems. This is a critical gap in research on FASD. In other clinical populations, sleep fragmentation has been linked to deficits in attention, response inhibition, and working memory (Dahl 1996; Gozal and Kheirandish-Gozal 2007; Sadeh 2007; Anderson et al. 2009), all areas of neuropsychological impairment well documented among children with FASD (Green et al. 2009, 2014; Kodituwakku 2009). For this paper, new exploratory findings from the Chen et al. (2012) sample revealed that daytime behavioral deficits in children with FASD, particularly in inhibition and working memory as assessed with the behavior rating inventory of executive function (BRIEF) questionnaire (Gioia et al. 2000), were moderately and significantly correlated with sleep problems as measured by CSHQ total score. Strikingly, these new exploratory analyses suggest that children with FASD and more severe sleep complaints tend to have greater impairment in executive function as revealed in an objective parent report. Although studies have not yet clearly linked daytime behavior with sleep in children with FASD, integrating treatment for sleep disorders in an attempt to optimize daytime behaviors should be considered for most children with FASD. Treatments for various sleep problems span the gamut of low to high risk and should not be taken lightly given the current lack of an empirical evidence base for this clinical population. However, the strength of the association between improved sleep and improved behavior in typically developing children makes it quite plausible that successful sleep treatments for those with FASD could result in improvements in daytime behavior.

Sleep problems in FASD and associations with psychosocial risk and caregiver impact

The association between prenatal adversity and poor-quality sleep among offspring has become increasingly recognized and described (Pesonen et al. 2009). The "developmental origins" hypothesis relates adverse changes in the intrauterine environment (such as PAE, poor nutrition, or multiple stressors) to later outcomes of mental health or other chronic disorders (Pesonen et al. 2009). Dysregulation of the hypothalamic–pituitary–adrenocortical axis related to these changes is suggested as a final common pathway between early experiences of adversity (including PAE) and poor sleep quality and diurnal regulation (McLachlan et al. 2016). High rates of cumulative risk and adverse caregiving experiences have been well described in children with FASD, who often experience multiple home placements and other types of psychosocial disruption (Streissguth et al. 2004; Olson et al. 2007). In the broader literature on sleep, children's cultural/racial background and increased psychosocial risk have been associated with differences in sleep patterns and parental sleep expectations (Jenni and O'Connor 2005). Proximal measures of risk, such as chaotic living conditions, are salient to sleep problems (Brown and Low 2008). The more distal factor of socioeconomic status may moderate the impact of sleep disruption on daytime functioning, with those experiencing higher socioeconomic status somewhat protected from negative impact and those with lower socioeconomic status more affected (Moore et al. 2002; Buckhalt et al. 2007; El-Sheikh et al. 2007).

Disrupted sleep in children increases caregiving burden and negatively impacts parental sleep in both typically (Meltzer and Mindell 2007; White et al. 2009) and atypically developing populations (Doo and Wing 2006; Meltzer and Mindell 2006; Sung et al. 2008; Hoffman et al. 2008). Fortunately, treatment of children's sleep disturbance helps improve family quality of life. Outcome studies of sleep interventions used with younger children resulted in improved caregiver sleep as well as improved mood and marital satisfaction after treatment (Mindell and Durand 1993). Improvement in caregiving stress and adult distress is especially important for families raising children with FASD, as there are very high levels of stress and psychological distress among parents of children in this clinical population (Olson et al. 2009*b*; Leenaars et al. 2012). In FASD, caregiving stress appears to be directly related to the child's functional impairments (Paley et al. 2006). Sleep problems are an important area of functional impairment in FASD. Interventions targeting sleep problems clearly have potential to improve the lives of both parents and children.

Biochem. Cell Biol. Downloaded from www.nrcresearchpress.com by UNIV MANITOBA on 07/02/19
For personal use only.

Treatment recommendations for pediatric sleep care in FASD: a rational approach

Families are frequently overwhelmed by the complex neurobehavioral and medical challenges of FASD, including the impact of sleep difficulties (Stade et al. 2008; Leenaars et al. 2012). Families may be further frustrated because children's sleep difficulties are not thoroughly assessed by primary care providers. In turn, providers may not know how to respond to pediatric sleep difficulties and particularly behavioral sleep difficulties (Honaker and Meltzer 2016). A rational approach to treating pediatric sleep problems is recommended here.

In the opinion of the authors, the ideal model in pediatric sleep care for children with FASD would be anchored in a multidisciplinary approach with opportunity for screening, evidence-based sleep-related intervention (e.g., caregiver sleep education, counseling regarding sleep hygiene), referral to therapies, and specialty referral for further behavioral or medical assessment. This approach also supports long-term health care by using a layered, flexible, and individualized approach. A multidisciplinary approach that recognizes the neurodevelopmental complexity of sleep issues in children with FASD and the unique stressors on their family and caregivers has the best potential to optimize sleep management for these children. However, in full recognition of limited resources, many recommendations offered here can still be implemented by providers who do not have the benefit of a multidisciplinary team.

Evidence supporting management of sleep-related difficulties for children with PAE is linked to the developmental origins of these difficulties. Comprehensive management must consider several important issues. First is consideration of the "fetal programming" of the child's biological system. Second is the need to address the child's sleep difficulties in context of his or her neurodevelopmental profile of strengths and weaknesses. Third is the need to address the past and current child care environment. Addressing these three areas will result in an integrated care plan.

While it is beyond the scope of this paper to explore each of these issues exhaustively, the following core ideas and related recommendations are made.

Core Idea No. 1

It is critical to understand the impact of prenatal adversity and the priming impact of PAE on the child's biology ("fetal programming"). Prenatal adversity reflects the maternal environment as well as the child's biological responses. Early dysregulation of the hypothalamic–pituitary–adrenocortical stress system through the impacts of maternal substance use (which can include PAE and (or) undernutrition and early disrupted caregiving experiences) can lead to altered diurnal cortisol secretion patterns influencing both daytime and nighttime self-regulation(McLachlan et al. 2016). Related to this core idea, it has been long observed that early FASD diagnostic assessment is a key protective factor.

Recommendation 1: Access early FASD assessment and diagnosis. Individuals with confirmed PAE should receive early assessment and diagnosis — ideally by an experienced multidisciplinary team (or appropriate mental health or health care providers, depending on available resources) — followed by recommendations for appropriate interventions, deployed early in life or during the school years. Early intervention can help to positively modulate physiologic self-regulatory systems, including altered diurnal rhythms. However, if diagnosis in infancy or early childhood is not possible, diagnosis and appropriate recommendations should still be pursued at any age.

Recommendation 2: Advocate for healthy families. Public health interventions and policies supporting pregnant women and families through optimizing nutrition and food security, screening for substance exposure, supporting both harm reduction and addiction treatment, income and housing support, addressing intimate partner violence, and supporting positive parenting have cumulative effects on the physiologic health of the infant, child, and adolescent within their community.

Core Idea No. 2

Addressing sleep difficulties in FASD must combine an understanding of the neurodevelopmental consequences of FASD with a comprehensive understanding of developmental processes of sleep regulation. The neurobiology seen in FASD has developmental origins with consequences for behavioral and diurnal regulation. Rational treatment of disordered sleep in FASD must address day/night regulation, behavioral regulation, and biochemical regulation. Sleep is regulated by both circadian systems (regulated externally) and sleep/wake homeostatic systems (regulated internally). Sleep is also a developmental process for all, and principles of sleep training and support are equally important considerations for those with and without developmental disabilities (Wiggs and France 2000; Wiggs 2001).

Recommendation 3: Apply principles of sleep hygiene in the sleep management plan. Classical principles of sleep hygiene are evidence-based principles and address the circadian and regulatory problems seen in individuals with FASD. These principles include stressing regular day and night routines and schedules, control of light exposure during the day and darkness at night, appropriately timed physical activity, and support for self-regulation of arousal and sleep (Bathory and Tomopoulos 2017). External schedules should support the coordination of biological light and temperature rhythms relating to sleep–wake patterns of hormonal secretion and regulation including melatonin and cortisol (Bathory and Tomopoulos 2017).

Recommendation 4: Use melatonin appropriately with input of an experienced clinician. Treatment with exogenous melatonin may be a rational part of a comprehensively developed sleep management plan for those with FASD (Jan et al. 2010; Goril et al. 2016). Use of melatonin should be under the guidance of a clinician experienced in appropriate management and use.

Recommendation 5: Consider sensory needs of the individual with FASD. Atypical responses to sensory stimuli may need to be assessed and the environment appropriately modified for the needs of the child or older individual with FASD (Jan et al. 2010; Wengel et al. 2011). For children, consultation with occupational therapists experienced in assessment and management of a child's sensory needs will contribute to a comprehensive understanding of the child's behavior and sleep. Strategies to support sensory needs may include appropriate changes to an affected individual's environment, modifying sensory stimuli, and self-regulation, in childhood and beyond (Wengel et al. 2011; Vasak et al. 2015).

Core Idea No. 3: Supporting the parent–child system

In infancy and the early childhood and school age years, quality of the parent–child relationship and certain parent characteristics, especially attachment disorders and affect disorders in the parent (depression and anxiety), have significant and persisting influences on sleep (O'Connor et al. 2007). Maternal depression mediates maternal–infant attachment, and attachment insecurity has been strongly linked to disordered sleep in young children (O'Connor et al. 1987; Benoit et al. 1992). It has been elegantly observed by Charuvastra and Cloitre (2009) that "the capacity to self-regulate affect and to allow affect regulation by environmental cues and caregivers will contribute directly to a child's ability to initiate and maintain sleep, and reciprocally one of the functions of sleep is to restore the capacity for affective and behavioral self-regulation". Postnatal risk factors such as instability in the caregiving environment, often seen among those with FASD, can further challenge the parent–child system.

Recommendation 6: Screen for parental mood disorders. Especially for infants and young children with FASD, screening for parental mood disorders both prenatally and postnatally offers

Biochem. Cell Biol. Downloaded from www.nrcresearchpress.com by UNIV MANITOBA on 07/02/19
For personal use only.

the opportunity for positive intervention that may eventually have a long-term impact on the child's sleep (Pearson et al. 2013).

Core Idea No. 4: Working with the family/caregiving environment and professional team

There is significantly increased prevalence of FASD among children in care (Popova et al. 2014*a*), and stressors associated with raising individuals with FASD can be significant (Bobbitt et al. 2016). For individuals who have experienced trauma, particularly those with FASD whose biology may be adversely primed, standard behavioral sleep programs that assume typical capacity to self-regulate in response to treatment may require modification (Charuvastra and Cloitre 2009).

Recommendation 7: Screen for attachment insecurity and advocate for safe environments. Recognizing risk factors for attachment insecurity, such as multiple caregiver placements for children in care, and histories of trauma and attachment disorder offers further opportunity for intervention to improve sleep problems. This is especially true among those with FASD, who often have histories characterized by high levels of postnatal psychosocial risk. Advocacy for stable and safe environments for the affected individual and family will support emotional and behavioral sleep needs.

Recommendation 8: Advocate for appropriate caregiver support. There is a significant need for caregiver support for sleep-deprived parents caring for individuals with FASD, particularly in the early years (Jan et al. 2010; Bobbitt et al. 2016). Given the often complex behavioral and medical needs of those with FASD, sleep management plans are often more complex and take longer to implement. Ensuring that parents are receiving support and respite to address their needs is critical for them to effectively meet the needs of their individual with FASD.

Conclusions

An adequate amount of good-quality sleep is fundamental to maximizing an individual's neurodevelopmental potential and overall well-being, and this is especially crucial in childhood. Youth with FASD experience high rates of often underrecognized sleep difficulties that likely impact their daytime functioning — and certainly adversely affect family function. For these youth and their families, sleep difficulties have commonly been a chronic, debilitating problem leading to caregiving burden and stress. Treatment of pediatric sleep disorders for those with FASD can be complex, so a multifaceted, evidence-informed, and integrated clinical care plan is needed. Ultimately, identification and treatment of sleep disorders in those with FASD provides a feasible intervention target with high utility, given the possibility to improve functional outcomes, overall health, and quality of life of both the affected individual and the family (Jan et al. 2010).

Conflict of interest statement

The authors have no conflicts of interests in the manuscript including financial, consultant, institutional, and other relationships that might lead to bias.

References

Agapito, M.A., Zhang, C., Murugan, S., and Sarkar, D.K. 2014. Fetal alcohol exposure disrupts metabolic signaling in hypothalamic proopiomelanocortin neurons via a circadian mechanism in male mice. Endocrinology, **155**(7): 2578–2588. doi:10.1210/en.2013-2030. PMID:24797626.

Allen, G.C., West, J.R., Chen, W.J., and Earnest, D.J. 2005. Neonatal alcohol exposure permanently disrupts the circadian properties and photic entrainment of the activity rhythm in adult rats. Alcohol. Clin. Exp. Res. **29**(10): 1845–1852. doi:10.1097/01.alc.0000183014.12359.9f. PMID:16269914.

Anderson, B., Storfer-Isser, A., Taylor, H.G., Rosen, C.L., and Redline, S. 2009. Associations of executive function with sleepiness and sleep duration in adolescents. Pediatrics, **123**(4): e701–e707. doi:10.1542/peds.2008-1182. PMID:19336360.

Astley, S.J., Olson, H.C., Kerns, K., Brooks, A., Aylward, E.H., Coggins, T.E., et al. 2009. Neuropyschological and behavioral outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. Can. J. Clin. Pharmacol. **16**(1): e178–e201. PMID:19329824.

Bathory, E., and Tomopoulos, S. 2017. Sleep regulation, physiology and development, sleep duration and patterns, and sleep hygiene in infants, toddlers, and preschool-age children. Curr. Probl. Pediatr. Adolesc. Health Care, **47**(2): 29–42. doi:10.1016/j.cppeds.2016.12.001. PMID:28117135.

Beebe, D.W. 2006. Neurobehavioral morbidity associated with disordered breathing during sleep in children: a comprehensive review. Sleep, **29**(9): 1115–1134. doi:10.1093/sleep/29.9.1115. PMID:17040000.

Benoit, D., Zeanah, C.H., Boucher, C., and Minde, K.K. 1992. Sleep disorders in early childhood: association with insecure maternal attachment. J. Am. Acad. Child. Adolesc. Psychiatry, **31**(1): 86–93. doi:10.1097/00004583-199201000-00013. PMID:1537786.

Berkman, J.M. 2006. Sleep in children with developmental disabilities. Med. Health R.I. **89**(3): 94–96. PMID:16596931.

Bertrand, J., Floyd, R.L., Weber, M.K., O'Connor, M., Riley, E.P., Johnson, K.A., and Cohen, D.E.; National Task Force on FAS/FAE. 2004. Fetal alcohol syndrome: guidelines for referral and diagnosis. Centers for Disease Control and Prevention, Atlanta, Ga.

Bhatara, V., Loudenberg, R., and Ellis, R. 2006. Association of attention deficit hyperactivity disorder and gestational alcohol exposure: an exploratory study. J. Atten. Disord. **9**(3): 515–522. doi:10.1177/1087054705283880. PMID:16481668.

Blackmer, A.B., and Feinstein, J.A. 2016. Management of sleep disorders in children with neurodevelopmental disorders: a review. Pharmacotherapy, **36**(1): 84–98. doi:10.1002/phar.1686. PMID:26799351.

Bobbitt, S.A., Baugh, L.A., Andrew, G.H., Cook, J.L., Green, C.R., Pei, J.R., and Rasmussen, C.R. 2016. Caregiver needs and stress in caring for individuals with fetal alcohol spectrum disorder. Res. Dev. Disabil. **55**: 100–113. doi:10.1016/j.ridd.2016.03.002. PMID:27058320.

Brown, E.D., and Low, C.M. 2008. Chaotic living conditions and sleep problems associated with children's responses to academic challenge. J. Fam. Psychol. **22**(6): 920–923. doi:10.1037/a0013652. PMID:19102613.

Buckhalt, J.A., El-Sheikh, M., and Keller, P. 2007. Children's sleep and cognitive functioning: race and socioeconomic status as moderators of effects. Child. Dev. **78**(1): 213–231. doi:10.1111/j.1467-8624.2007.00993.x. PMID:17328701.

Calhoun, F., Attilia, M.L., Spagnolo, P.A., Rotondo, C., Mancinelli, R., and Ceccanti, M. 2006. National Institute on Alcohol Abuse and Alcoholism and the study of fetal alcohol spectrum disorders. The International Consortium. Ann. Ist. Super. Sanita, **42**(1): 4–7. PMID:16801719.

Charuvastra, A., and Cloitre, M. 2009. Safe enough to sleep: sleep disruptions associated with trauma, posttraumatic stress, and anxiety in children and adolescents. Child Adolesc. Psychiatr. Clin. N. Am. **18**(4): 877–891. doi:10.1016/j.chc.2009.04.002. PMID:19836694.

Chen, M.L., Witmans, M.B., Tablizo, M.A., Jubran, R.F., Turkel, S.B., Tavare, C.J., and Keens, T.G. 2005. Disordered respiratory control in children with partial cerebellar resections. Pediatr. Pulmonol. **40**(1): 88–91. doi:10.1002/ppul.20225. PMID:15880401.

Chen, M., Olson, H., and Astley, S. 2006. Sleepless in Seattle: preliminary data suggesting sleep disorders in those with FASD. Research Society for Alcoholism, Fetal Alcohol Spectrum Disorders Study Group.

Chen, M.L., Olson, H.C., Picciano, J.F., Starr, J.R., and Owens, J. 2012. Sleep problems in children with fetal alcohol spectrum disorders. J. Clin. Sleep Med. **8**(4): 421–429. doi:10.5664/jcsm.2038. PMID:22893773.

Chernick, V., Childiaeva, R., and Ioffe, S. 1983. Effects of maternal alcohol intake and smoking on neonatal electroencephalogram and anthropometric measurements. Am. J. Obstet. Gynecol. **146**(1): 41–47. doi:10.1016/0002-9378(83)90924-9. PMID:6846423.

Chervin, R.D., and Archbold, K.H. 2001. Hyperactivity and polysomnographic findings in children evaluated for sleep-disordered breathing. Sleep, **24**(3): 313–320. doi:10.1093/sleep/24.3.313. PMID:11322714.

Chudley, A.E., Conry, J., Cook, J.L., Loock, C., Rosales, T., LeBlanc, N., and Public Health Agency of Canada's National Advisory Committee on Fetal Alcohol Spectrum Disorder. 2005. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. CMAJ, **172**(5 Suppl.): S1–S21. doi:10.1503/cmaj.1040302. PMID:15738468.

Cortese, S., Brown, T.E., Corkum, P., Gruber, R., O'Brien, L.M., Stein, M., et al. 2013. Assessment and management of sleep problems in youths with attention-deficit/hyperactivity disorder. J. Am. Acad. Child Adolesc. Psychiatry, **52**(8): 784–796. doi:10.1016/j.jaac.2013.06.001. PMID:23880489.

Dahl, R.E. 1996. The impact of inadequate sleep on children's daytime cognitive function. Semin. Pediatr. Neurol. **3**(1): 44–50. doi:10.1016/S1071-9091(96)80028-3. PMID:8795841.

Dikranian, K., Qin, Y.Q., Labruyere, J., Nemmers, B., and Olney, J.W. 2005. Ethanol-induced neuroapoptosis in the developing rodent cerebellum and related brain stem structures. Brain Res. Dev. Brain Res. **155**(1): 1–13. doi:10.1016/j.devbrainres.2004.11.005. PMID:15763270.

Doo, S., and Wing, Y.K. 2006. Sleep problems of children with pervasive developmental disorders: correlation with parental stress. Dev. Med. Child Neurol. **48**(8): 650–655. doi:10.1017/S001216220600137X. PMID:16836776.

Dubois, C., Houchi, H., Naassila, M., Daoust, M., and Pierrefiche, O. 2008. Blunted response to low oxygen of rat respiratory network after perinatal ethanol

Biochem. Cell Biol. Downloaded from www.nrcresearchpress.com by UNIV MANITOBA on 07/02/19
For personal use only.

exposure: involvement of inhibitory control. J. Physiol. **586**(5): 1413–1427. doi:10.1113/jphysiol.2007.147165. PMID:18096598.

Dubois, C.J., Kervern, M., Naassila, M., and Pierrefiche, O. 2013. Chronic ethanol exposure during development: disturbances of breathing and adaptation. Respir. Physiol. Neurobiol. **189**(2): 250–260. doi:10.1016/j.resp.2013.06.015. PMID:23811193.

Earnest, D.J., Chen, W.J., and West, J.R. 2001. Developmental alcohol and circadian clock function. Alcohol Res. Health, **25**(2): 136–140. PMID:11584552.

El-Sheikh, M., Buckhalt, J.A., Keller, P.S., Cummings, E.M., and Acebo, C. 2007. Child emotional insecurity and academic achievement: the role of sleep disruptions. J. Fam. Psychol. **21**(1): 29–38. doi:10.1037/0893-3200.21.1.29. PMID: 17371107.

Farnell, Y.Z., Allen, G.C., Nahm, S.S., Neuendorff, N., West, J.R., Chen, W.J., and Earnest, D.J. 2008. Neonatal alcohol exposure differentially alters clock gene oscillations within the suprachiasmatic nucleus, cerebellum, and liver of adult rats. Alcohol. Clin. Exp. Res. **32**(3): 544–552. doi:10.1111/j.1530-0277.2007.00598.x. PMID:18215209.

Fukui, Y., and Sakata-Haga, H. 2009. Intrauterine environment–genome interaction and children's development (1): Ethanol: a teratogen in developing brain. J. Toxicol. Sci. **34**(Suppl. 2): SP273–SP278. PMID:19571480.

Gioia, G., IIsquith, P., Guy, S., and Kenworthy, L. 2000. Behavior rating inventory of executive function. Psychological Assessment Resources, Inc., Odessa, Fla.

Godin, E.A., Dehart, D.B., Parnell, S.E., O'Leary-Moore, S.K., and Sulik, K.K. 2011. Ventromedian forebrain dysgenesis follows early prenatal ethanol exposure in mice. Neurotoxicol. Teratol. **33**(2): 231–239. doi:10.1016/j.ntt.2010.11.001. PMID:21074610.

Goril, S., Zalai, D., Scott, L., and Shapiro, C.M. 2016. Sleep and melatonin secretion abnormalities in children and adolescents with fetal alcohol spectrum disorders. Sleep Med. **23**: 59–64. doi:10.1016/j.sleep.2016.06.002. PMID: 27692277.

Gottlieb, D.J., Vezina, R.M., Chase, C., Lesko, S.M., Heeren, T.C., Weese-Mayer, D.E., et al. 2003. Symptoms of sleep-disordered breathing in 5-year-old children are associated with sleepiness and problem behaviors. Pediatrics, **112**(4): 870–877. doi:10.1542/peds.112.4.870. PMID:14523179.

Gozal, D., and Kheirandish-Gozal, L. 2007. Neurocognitive and behavioral morbidity in children with sleep disorders. Curr. Opin. Pulm. Med. **13**(6): 505–509. doi:10.1097/MCP.0b013e3282ef6880. PMID:17901756.

Green, C.R., Mihic, A.M., Nikkel, S.M., Stade, B.C., Rasmussen, C., Munoz, D.P., and Reynolds, J.N. 2009. Executive function deficits in children with fetal alcohol spectrum disorders (FASD) measured using the Cambridge Neuropsychological Tests Automated Battery (CANTAB). J. Child Psychol. Psychiatry, **50**(6): 688–697. doi:10.1111/j.1469-7610.2008.01990.x. PMID:19175817.

Green, C.R., Roane, J., Hewitt, A., Muhajarine, N., Mushquash, C., Sourander, A., et al. 2014. Frequent behavioural challenges in children with fetal alcohol spectrum disorder: a needs-based assessment reported by caregivers and clinicians. J. Popul. Ther. Clin. Pharmacol. **21**(3): e405–e420. PMID:25658693.

Hanlon-Dearman, A. 2003. Sleep characteristics of young alcohol affected children: a quantitative and qualitative analysis. M.Sc., Community Health Sciences, University of Manitoba, Winnipeg, Man.

Havlicek, V., and Childaeva, R. 1976. E.E.G. component of fetal alcohol syndrome. Lancet, **2**(7983): 477. doi:10.1016/S0140-6736(76)92579-4. PMID:73786.

Havlicek, V., Childiaeva, R., and Chernick, V. 1977. EEG frequency spectrum characteristics of sleep states in infants of alcoholic mothers. Neuropadiatrie, **8**(4): 360–373. doi:10.1055/s-0028-1091532. PMID:201887.

Hilakivi, L. 1986. Effects of prenatal alcohol exposure on neonatal sleep–wake behaviour and adult alcohol consumption in rats. Acta Pharmacol. Toxicol. (Copenh.), **59**(1): 36–42. doi:10.1111/j.1600-0773.1986.tb00131.x. PMID:3766148.

Hilakivi, L., Tuomisto, L., Hilakivi, I., Kiianmaa, K., Hellevuo, K., and Hyytia, P. 1987. Effect of prenatal alcohol exposure on neonatal sleep–wake behaviour and adult alcohol consumption in the AA and ANA rat lines. Alcohol Alcohol, **22**(3): 231–240. PMID:3619998.

Hoffman, C., Sweeney, D., Lopez-Wagner, M., Hodge, D., Nam, C., and Botts, B. 2008. Children with autism: sleep problems and mothers' stress. Focus Autism Other Dev. Disabl. **23**(3): 155–165. doi:10.1177/1088357608316271.

Honaker, S.M., and Meltzer, L.J. 2016. Sleep in pediatric primary care: a review of the literature. Sleep Med. Rev. **25**: 31–39. doi:10.1016/j.smrv.2015.01.004. PMID:26163054.

Ioffe, S., and Chernick, V. 1988. Development of the EEG between 30 and 40 weeks gestation in normal and alcohol-exposed infants. Dev. Med. Child Neurol. **30**(6): 797–807. doi:10.1111/j.1469-8749.1988.tb14642.x. PMID:3234608.

Ioffe, S., and Chernick, V. 1990. Prediction of subsequent motor and mental retardation in newborn infants exposed to alcohol in utero by computerized EEG analysis. Neuropediatrics, **21**(1): 11–17. doi:10.1055/s-2008-1071450. PMID: 2314553.

Ipsiroglu, O.S., McKellin, W.H., Carey, N., and Loock, C. 2013. "They silently live in terror…" why sleep problems and night-time related quality-of-life are missed in children with a fetal alcohol spectrum disorder. Soc. Sci. Med. **79**: 76–83. doi:10.1016/j.socscimed.2012.10.027. PMID:23305724.

Jan, J.E., Asante, K.O., Conry, J.L., Fast, D.K., Bax, M.C., Ipsiroglu, O.S., et al. 2010. Sleep health issues for children with FASD: clinical considerations. Int. J. Pediatr. **2010**: 639048. doi:10.1155/2010/639048. PMID:20706655.

Jenni, O.G., and O'Connor, B.B. 2005. Children's sleep: an interplay between culture and biology. Pediatrics, **115**(1 Suppl.): 204–216. doi:10.1542/peds.2004-0815B. PMID:15866854.

Katz, E., and Marcus, C. 2005. Diagnosis of obstructive sleep apnea syndrome in infants and children. *In* Principles and practice of pediatric sleep medicine. *Edited by* S. Sheldon, R. Ferber, and M. Kryger. Elsevier Saunders, Maryland Heights, Mo. pp. 197–210.

Kervern, M., Dubois, C., Naassila, M., Daoust, M., and Pierrefiche, O. 2009. Perinatal alcohol exposure in rat induces long-term depression of respiration after episodic hypoxia. Am. J. Respir. Crit. Care Med. **179**(7): 608–614. doi:10.1164/rccm.200703-434OC. PMID:19106308.

Kodituwakku, P.W. 2009. Neurocognitive profile in children with fetal alcohol spectrum disorders. Dev. Disabil. Res. Rev. **15**(3): 218–224. doi:10.1002/ddrr.73. PMID:19731385.

Kotagal, S., and Broomall, E. 2012. Sleep in children with autism spectrum disorder. Pediatr. Neurol. **47**(4): 242–251. doi:10.1016/j.pediatrneurol.2012.05.007. PMID:22964437.

Lan, N., Chiu, M.P., Ellis, L., and Weinberg, J. 2017. Prenatal alcohol exposure and prenatal stress differentially alter glucocorticoid signaling in the placenta and fetal brain. Neuroscience, **342**: 167–179. doi:10.1016/j.neuroscience.2015.08.058. PMID:26342748.

Lange, S., Shield, K., Rehm, J., and Popova, S. 2013. Prevalence of fetal alcohol spectrum disorders in child care settings: a meta-analysis. Pediatrics, **132**(4): e980–e995. doi:10.1542/peds.2013-0066. PMID:24019412.

Leenaars, L.S., Denys, K., Henneveld, D., and Rasmussen, C. 2012. The impact of fetal alcohol spectrum disorders on families: evaluation of a family intervention program. Community Ment. Health J. **48**(4): 431–435. doi:10.1007/s10597-011-9425-6. PMID:21687984.

Loffe, S., Childiaeva, R., and Chernick, V. 1984. Prolonged effects of maternal alcohol ingestion on the neonatal electroencephalogram. Pediatrics, **74**(3): 330–335. PMID:6472963.

Lupton, C., Burd, L., and Harwood, R. 2004. Cost of fetal alcohol spectrum disorders. Am. J. Med. Genet. C Semin. Med. Genet. **127C**(1): 42–50. doi:10.1002/ajmg.c.30015. PMID:15095471.

Malow, B.A., Marzec, M.L., McGrew, S.G., Wang, L., Henderson, L.M., and Stone, W.L. 2006. Characterizing sleep in children with autism spectrum disorders: a multidimensional approach. Sleep, **29**(12): 1563–1571. doi:10.1093/sleep/29.12.1563. PMID:17252887.

Mansfield, D.R., and Naughton, M.T. 2004. Sleep apnea and congestive heart failure. Minerva Med. **95**(4): 257–280. PMID:15334041.

Mattson, S.N., and Riley, E.P. 2000. Parent ratings of behavior in children with heavy prenatal alcohol exposure and IQ-matched controls. Alcohol. Clin. Exp. Res. **24**(2): 226–231. doi:10.1111/j.1530-0277.2000.tb04595.x. PMID:10698376.

May, P.A., and Gossage, J.P. 2001. Estimating the prevalence of fetal alcohol syndrome: a summary. Alcohol Res. Health, **25**(3): 159–167. PMID:11810953.

May, P.A., Gossage, J.P., Kalberg, W.O., Robinson, L.K., Buckley, D., Manning, M., and Hoyme, H.E. 2009. Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. Dev. Disabil. Res. Rev. **15**(3): 176–192. doi:10.1002/ddrr.68. PMID:19731384.

May, P.A., Baete, A., Russo, J., Elliott, A.J., Blankenship, J., Kalberg, W.O., et al. 2014. Prevalence and characteristics of fetal alcohol spectrum disorders. Pediatrics, **134**(5): 855–866. doi:10.1542/peds.2013-3319. PMID:25349310.

McLachlan, K., Rasmussen, C., Oberlander, T.F., Loock, C., Pei, J., Andrew, G., et al. 2016. Dysregulation of the cortisol diurnal rhythm following prenatal alcohol exposure and early life adversity. Alcohol, **53**: 9–18. doi:10.1016/j.alcohol.2016.03.003. PMID:27286932.

Meltzer, L.J., and Mindell, J.A. 2006. Impact of a child's chronic illness on maternal sleep and daytime functioning. Arch. Intern. Med. **166**(16): 1749–1755. doi:10.1001/archinte.166.16.1749. PMID:16983054.

Meltzer, L.J., and Mindell, J.A. 2007. Relationship between child sleep disturbances and maternal sleep, mood, and parenting stress: a pilot study. J. Fam. Psychol. **21**(1): 67–73. doi:10.1037/0893-3200.21.1.67. PMID:17371111.

Mindell, J.A., and Durand, V.M. 1993. Treatment of childhood sleep disorders: generalization across disorders and effects on family members. J. Pediatr. Psychol. **18**(6): 731–750. doi:10.1093/jpepsy/18.6.731. PMID:8138867.

Moore, P.J., Adler, N.E., Williams, D.R., and Jackson, J.S. 2002. Socioeconomic status and health: the role of sleep. Psychosom. Med. **64**(2): 337–344. doi:10.1097/00006842-200203000-00018. PMID:11914451.

O'Brien, L.M., Mervis, C.B., Holbrook, C.R., Bruner, J.L., Smith, N.H., McNally, N., et al. 2004. Neurobehavioral correlates of sleep-disordered breathing in children. J. Sleep Res. **13**(2): 165–172. doi:10.1111/j.1365-2869.2004.00395.x. PMID: 15175097.

O'Connor, M.J., and Paley, B. 2009. Psychiatric conditions associated with prenatal alcohol exposure. Dev. Disabil. Res. Rev. **15**(3): 225–234. doi:10.1002/ddrr.74. PMID:19731386.

O'Connor, M.J., Sigman, M., and Brill, N. 1987. Disorganization of attachment in relation to maternal alcohol consumption. J. Consult. Clin. Psychol. **55**(6): 831–836. doi:10.1037/0022-006X.55.6.831. PMID:3693649.

O'Connor, T.G., Caprariello, P., Blackmore, E.R., Gregory, A.M., Glover, V., Fleming, P., and ALSPAC Study Team. 2007. Prenatal mood disturbance predicts sleep problems in infancy and toddlerhood. Early Hum. Dev. **83**(7): 451–458. doi:10.1016/j.earlhumdev.2006.08.006. PMID:17008033.

Olson, H.C., Jirikowic, T., Kartin, D., and Astley, S. 2007. Responding to the

Biochem. Cell Biol. Downloaded from www.nrcresearchpress.com by UNIV MANITOBA on 07/02/19
For personal use only.

challenge of early intervention for fetal alcohol spectrum disorders. Infants & Young Children, **20**(2): 172–189. doi:10.1097/01.IYC.0000264484.73688.4a.

Olson, H.C., Ohlemiller, M.M., O'Connor, M.J., Brown, C.W., Morris, C.A., and Damus, K.; U.S. Department of Health and Human Services. 2009*a*. A call to action: advancing essential services and research on fetal alcohol spectrum disorders: a report of the national task force on fetal alcohol syndrome and fetal alcohol effect.

Olson, H.C., Oti, R., Gelo, J., and Beck, S. 2009*b*. "Family matters:" fetal alcohol spectrum disorders and the family. Dev. Disabil. Res. Rev. **15**(3): 235–249. doi:10.1002/ddrr.65. PMID:19731388.

Owens, J.A., Spirito, A., and McGuinn, M. 2000. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep, **23**(8): 1043–1051. PMID:11145319.

Paley, B., O'Connor, M.J., Frankel, F., and Marquardt, R. 2006. Predictors of stress in parents of children with fetal alcohol spectrum disorders. J. Dev. Behav. Pediatr. **27**(5): 396–404. doi:10.1097/00004703-200610000-00005. PMID:17041276.

Pearson, R.M., Evans, J., Kounali, D., Lewis, G., Heron, J., Ramchandani, P.G., et al. 2013. Maternal depression during pregnancy and the postnatal period: risks and possible mechanisms for offspring depression at age 18 years. JAMA Psychiatry, **70**(12): 1312–1319. doi:10.1001/jamapsychiatry.2013.2163. PMID:24108418.

Pesonen, A.K., Raikkonen, K., Matthews, K., Heinonen, K., Paavonen, J.E., Lahti, J., et al. 2009. Prenatal origins of poor sleep in children. Sleep, **32**(8): 1086–1092. doi:10.1093/sleep/32.8.1086. PMID:19725260.

Popova, S., Lange, S., Burd, L., and Rehm, J. 2012. Health care burden and cost associated with fetal alcohol syndrome: based on official Canadian data. PLoS One, **7**(8): e43024. doi:10.1371/journal.pone.0043024. PMID:22900084.

Popova, S., Lange, S., Burd, L., Chudley, A.E., Clarren, S.K., and Rehm, J. 2013. Cost of fetal alcohol spectrum disorder diagnosis in Canada. PLoS One, **8**(4): e60434. doi:10.1371/journal.pone.0060434. PMID:23593216.

Popova, S., Lange, S., Burd, L., and Rehm, J. 2014*a*. Canadian children and youth in care: the cost of fetal alcohol spectrum disorder. Child Youth Care Forum, **43**: 83–96. doi:10.1007/s10566-013-9226-x. PMID:24489454.

Popova, S., Yaltonskaya, A., Yaltonsky, V., Kolpakov, Y., Abrosimov, I., Pervakov, K., et al. 2014*b*. What research is being done on prenatal alcohol exposure and fetal alcohol spectrum disorders in the Russian research community? Alcohol Alcohol. **49**(1): 84–95. doi:10.1093/alcalc/agt156. PMID:24158024.

Popova, S., Lange, S., Burd, L., and Rehm, J. 2015. Cost attributable to fetal alcohol spectrum disorder in the Canadian correctional system. Int. J. Law Psychiatry, **41**: 76–81. doi:10.1016/j.ijlp.2015.03.010. PMID:25846557.

Popova, S., Lange, S., Shield, K., Mihic, A., Chudley, A.E., Mukherjee, R.A., et al. 2016. Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis. Lancet, **387**(10022): 978–987. doi:10.1016/S0140-6736(15)01345-8. PMID:26777270.

Rasmussen, C., Horne, K., and Witol, A. 2006. Neurobehavioral functioning in children with fetal alcohol spectrum disorder. Child Neuropsychol. **12**(6): 453–468. doi:10.1080/09297040600646854. PMID:16952890.

Riley, E.P., and McGee, C.L. 2005. Fetal alcohol spectrum disorders: an overview with emphasis on changes in brain and behavior. Exp. Biol. Med. (Maywood), **230**(6): 357–365. doi:10.1177/15353702-0323006-03. PMID:15956765.

Robinson-Shelton, A., and Malow, B.A. 2016. Sleep disturbances in neurodevelopmental disorders. Curr. Psychiatry Rep. **18**(1): 6. doi:10.1007/s11920-015-0638-1. PMID:26719309.

Rosen, C.L., Palermo, T.M., Larkin, E.K., and Redline, S. 2002. Health-related quality of life and sleep-disordered breathing in children. Sleep, **25**(6): 657–666. doi:10.1093/sleep/25.6.648. PMID:12224844.

Rosett, H.L., Snyder, P., Sander, L.W., Lee, A., Cook, P., Weiner, L., and Gould, J. 1979. Effects of maternal drinking on neonate state regulation. Dev. Med. Child Neurol. **21**(4): 464–473. doi:10.1111/j.1469-8749.1979.tb01650.x. PMID:520694.

Sadeh, A. 2007. Consequences of sleep loss or sleep disruption in children. Sleep Medicine Clinics, **2**(3): 513–520. doi:10.1016/j.jsmc.2007.05.012.

Sakata-Haga, H., Dominguez, H.D., Sei, H., Fukui, Y., Riley, E.P., and Thomas, J.D. 2006. Alterations in circadian rhythm phase shifting ability in rats following ethanol exposure during the third trimester brain growth spurt. Alcohol. Clin. Exp. Res. **30**(5): 899–907. doi:10.1111/j.1530-0277.2006.00105.x. PMID:16634860.

Sampson, P.D., Streissguth, A.P., Bookstein, F.L., Little, R.E., Clarren, S.K., Dehaene, P., et al. 1997. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. Teratology, **56**(5): 317–326. doi:10.1002/(SICI)1096-9926(199711)56:5<317::AID-TERA5>3.0.CO;2-U. PMID:9451756.

Scher, M.S., Richardson, G.A., Coble, P.A., Day, N.L., and Stoffer, D.S. 1988. The effects of prenatal alcohol and marijuana exposure: disturbances in neonatal sleep cycling and arousal. Pediatr. Res. **24**(1): 101–105. doi:10.1203/00006450-198807000-00023. PMID:3412843.

Sikora, D.M., Johnson, K., Clemons, T., and Katz, T. 2012. The relationship between sleep problems and daytime behavior in children of different ages with autism spectrum disorders. Pediatrics, **130**(Suppl. 2): S83–S90. doi:10.1542/peds.2012-0900F. PMID:23118258.

Spadoni, A.D., McGee, C.L., Fryer, S.L., and Riley, E.P. 2007. Neuroimaging and fetal alcohol spectrum disorders. Neurosci. Biobehav. Rev. **31**(2): 239–245. doi:10.1016/j.neubiorev.2006.09.006. PMID:17097730.

Stade, B., Khuu, M., Bennett, D., Sandor, P., Stephens, R., and Lanceta, M. 2008. Sleep disturbances in children with fetal alcohol spectrum disorder (FASD). *In* Proceedings of the Canadian Pediatric Society 85th Annual Conference, Victoria, B.C.

Steinhausen, H.C., and Spohr, H.L. 1998. Long-term outcome of children with fetal alcohol syndrome: psychopathology, behavior, and intelligence. Alcohol. Clin. Exp. Res. **22**(2): 334–338. doi:10.1111/j.1530-0277.1998.tb03657.x. PMID:9581637.

Stone, W.S., Altman, H.J., Hall, J., Arankowsky-Sandoval, G., Parekh, P., and Gold, P.E. 1996. Prenatal exposure to alcohol in adult rats: relationships between sleep and memory deficits, and effects of glucose administration on memory. Brain Res. **742**(1–2): 98–106. doi:10.1016/S0006-8993(96)00976-6. PMID:9117426.

Stratton, K., Howe, C., and Battaglia, F. 1996. Fetal alcohol syndrome: diagnosis, epidemology, prevention and treatment. National Academy Press, Washington, D.C.

Streissguth, A.P., Bookstein, F.L., Barr, H.M., Press, S., and Sampson, P.D. 1998. A fetal alcohol behavior scale. Alcohol. Clin. Exp. Res. **22**(2): 325–333. doi:10.1111/j.1530-0277.1998.tb03656.x. PMID:9581636.

Streissguth, A.P., Bookstein, F.L., Barr, H.M., Sampson, P.D., O'Malley, K., and Young, J.K. 2004. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J. Dev. Behav. Pediatr. **25**(4): 228–238. doi:10.1097/00004703-200408000-00002. PMID:15308923.

Sung, V., Hiscock, H., Sciberras, E., and Efron, D. 2008. Sleep problems in children with attention-deficit/hyperactivity disorder: prevalence and the effect on the child and family. Arch. Pediatr. Adolesc. Med. **162**(4): 336–342. doi:10.1001/archpedi.162.4.336. PMID:18391142.

Troese, M., Fukumizu, M., Sallinen, B.J., Gilles, A.A., Wellman, J.D., Paul, J.A., et al. 2008. Sleep fragmentation and evidence for sleep debt in alcohol-exposed infants. Early Hum. Dev. **84**(9): 577–585. doi:10.1016/j.earlhumdev.2008.02.001. PMID:18400423.

Vasak, M., Williamson, J., Garden, J., and Zwicker, J.G. 2015. Sensory processing and sleep in typically developing infants and toddlers. Am. J. Occup. Ther. **69**(4): 6904220040. doi:10.5014/ajot.2015.015891. PMID:26114460.

Verrier, V., Harper, R. and Hobson, J. 2005. Cardiovascular physiology: central and autonomic regulation. *In* Principles and practice of sleep medicine. *Edited by* M.H. Kryger, T. Roth, and W.C. Dement. Elsevier Saunders, Maryland Heights, Mo. pp. 192–202.

Warren, K., Floyd, L., Calhoun, F., Stone, D., Bertrand, J., and Streissguth, A. 2005. Consensus statement on FASD. International statistical classification of diseases and related health problems. 2nd ed. World Health Organization, Geneva.

Wengel, T., Hanlon-Dearman, A.C., and Fjeldsted, B. 2011. Sleep and sensory characteristics in young children with fetal alcohol spectrum disorder. J. Dev. Behav. Pediatr. **32**(5): 384–392. doi:10.1097/DBP.0b013e3182199694. PMID:21654404.

White, C.P., White, M.B., and Fox, M.A. 2009. Maternal fatigue and its relationship to the caregiving environment. Fam. Syst. Health, **27**(4): 325–345. doi:10.1037/a0018284. PMID:20047356.

Wiggs, L. 2001. Sleep problems in children with developmental disorders. J. R. Soc. Med. **94**(4): 177–179. PMID:11317619.

Wiggs, L. 2009. Behavioural aspects of children's sleep. Arch. Dis. Child. **94**(1): 59–62. doi:10.1136/adc.2007.125278. PMID:18977784.

Wiggs, L., and France, K. 2000. Behavioural treatments for sleep problems in children and adolescents with physical illness, psychological problems or intellectual disabilities. Sleep Med. Rev. **4**(3): 299–314. doi:10.1053/smrv.1999.0094. PMID:12531171.

Wiggs, L., and Stores, G. 1996. Severe sleep disturbance and daytime challenging behaviour in children with severe learning disabilities. J. Intellect. Disabil. Res. **40**(6): 518–528. doi:10.1111/j.1365-2788.1996.tb00662.x. PMID:9004112.

Wiggs, L., and Stores, G. 1999. Behavioural treatment for sleep problems in children with severe learning disabilities and challenging daytime behaviour: effect on daytime behavior. J. Child Psychol. Psychiatry, **40**(4): 627–635. doi:10.1111/1469-7610.00479. PMID:10357168.

Wiggs, L., and Stores, G. 2004. Sleep patterns and sleep disorders in children with autistic spectrum disorders: insights using parent report and actigraphy. Dev. Med. Child Neurol. **46**(6): 372–380. doi:10.1017/S0012162204000611. PMID:15174528.

Wills, L., Swift, J., and Moller, K. 2006. Craniofacial syndrome and sleep disorders. *In* Sleep: a comprehensive handbook. *Edited by* T. Lee-Chiong. John Wiley and Sons.

Wilson, D.A., Masiello, K., Lewin, M.P., Hui, M., Smiley, J.F., and Saito, M. 2016. Developmental ethanol exposure-induced sleep fragmentation predicts adult cognitive impairment. Neuroscience, **322**: 18–27. doi:10.1016/j.neuroscience.2016.02.020. PMID:26892295.