The Patterns of Sleep Disorders and Circadian Rhythm Disruptions in Children and Adolescents with Fetal Alcohol Spectrum Disorders

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
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Collaborative Program in Neuroscience
University of Toronto

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ABSTRACT

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Background: Sleep disorders have been poorly described in children and adolescents diagnosed with FASD. The objective of this study is to describe the sleep and circadian rhythm characteristics of children with FASD using overnight polysomnography, sleep questionnaires, and the Dim Light Melatonin Onset (DLMO) test. To our knowledge, no comprehensive studies of this nature have been conducted.

Methods: Children ages 6-18 years diagnosed with Fetal Alcohol Spectrum Disorder (FASD) were recruited from various FASD clinics to the Youthdale Child and Adolescent Sleep Centre. After medical consultation, each participant had one night of overnight polysomnography, as well as an additional night of DLMO. Participants completed various sleep and FASD questionnaires. Results: Significant differences were found when comparing the sleep architecture of FASD participants to normative data. There was a high prevalence of sleep disorders in this sample. Most of the melatonin profiles of the FASD participants were found to be abnormal.
ACKNOWLEDGEMENTS

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I would like to dedicate this thesis to my late grandfather, Saba Mendel Z’L, who passed away during this project. He was and continues to be an incredible source of inspiration and motivation in my life.
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Chapter 1: GENERAL INTRODUCTION

I. Study Rationale

Fetal alcohol spectrum disorders (FASD) are one of the leading preventable causes of congenital brain injuries and mental retardation. There is significant overlap in the brain structures that suffer neuropathological and functional deficits in response to prenatal alcohol exposure and those that control and regulate sleep/wake states, including circadian rhythms. Although there is strong evidence showing the neurocognitive and behavioural abnormalities caused by prenatal exposure to alcohol, there is very little work exploring the effects of prenatal alcohol exposure on sleep and circadian rhythms. At present, only two EEG studies have been conducted to study the patterns of sleep in this group of children, both replete with limitations (D’Angiulli et al, 2006; Troese et al, 2008). No reports have used overnight polysomnography. There are no studies which consider circadian rhythms in this population, such as monitoring melatonin levels to understand circadian rhythm patterns.

To obtain a clearer understanding, there is a need to investigate if prenatal alcohol exposure is associated with an increased risk of developing sleep disturbances. In particular, it is necessary to explore whether neurodevelopmental disruptions are linked to circadian rhythms disruptions. It will be important to determine whether sleep pathologies such as obstructive sleep apnea and phase-delay syndrome are more frequent in FASD and whether these disturbances are accompanied by mood disorders and difficulties in neurodevelopmental functioning in these children.
II. Study Significance

With the high prevalence of FASD in the Canadian population, the findings of this study will have important clinical implications in the care and treatment of individuals with FASD. The recognition and diagnosis of a sleep disorder or circadian rhythm disruption in an individual with FASD will lead to treatment of the disruption, and in turn this may facilitate treatment of any of the neurodevelopmental difficulties. The detection and treatment of associated sleep disorders in FASD patients could have considerable clinical impact for these patients such as improvement of daytime alertness and functioning. Currently, there has been no published research that has examined the sleep and circadian rhythms of children and adolescents with FASD. No studies have used overnight polysomnography measures to assess the sleep architecture in this cohort. Furthermore, no studies have examined the circadian rhythms in this population in general and specifically with the use of melatonin testing.

III. Research Questions

1. What are the patterns of sleep and circadian rhythms in children/adolescents with FASD?

2. What is the prevalence of sleep and circadian disorders in children/adolescents with FASD?
IV. Objectives

1. To determine the sleep patterns of circadian rhythms in children/adolescents with FASD

2. To determine the prevalence of sleep/wake disorders in children/adolescents with FASD

V. Hypotheses

This thesis is set out to investigate the following hypotheses:

1. Sleep disorders will be more prevalent in the FASD participant population compared to the general population.

2. Circadian rhythm disturbances and/or altered melatonin secretion levels will be more prevalent in the FASD participant population compared to the general population.

3. A number of factors such as FASD diagnosis, responses to self reported questionnaires, age, or gender may help predict the presence of sleep and/or circadian rhythm disorders in children/adolescents with FASD.
CHAPTER 2: LITERATURE REVIEW
CHAPTER 2: LITERATURE REVIEW

2.1 Fetal Alcohol Spectrum Disorders

2.1.1 Background on Fetal Alcohol Spectrum Disorders (FASD)

Fetal Alcohol Spectrum Disorders (FASD) represent an umbrella term used to describe the range of developmental outcomes that can occur in an individual as a consequence of maternal drinking during pregnancy (Sokol et al., 2003; Chudley et al., 2005). These developmental effects may include physical, behavioural, mental, and learning disabilities (Nullman et al., 2007). Specifically, children with FASD suffer from a vast array of co-morbidities including problems with attention, memory, learning, sensory motor skills, executive function. The FASD spectrum includes: Fetal Alcohol Syndrome (FAS), Partial Fetal Alcohol Syndrome (pFAS), and Alcohol-Related Neurodevelopmental Disorder (ARND). FAS is diagnosed when there is the characteristic pattern of facial dysmorphology, growth restriction, and central nervous system (CNS) impairment. Those with ARND do not have the characteristic facial dysmorphology or growth restriction, but CNS impairments are present and may be significant (Chudley et al., 2005) (see appendix for further details and images).

2.1.2 The Prevalence of FASD in Canada and United States

In the United States, the incidence of FASD has been estimated to be approximately 1-3 per 100 live births (1-3%) (Sampson et al., 1997; Chudley et al.,
There are no official national statistics on the rates of FASD in Canada, though epidemiological studies have described its prevalence in various communities throughout Canada to also be approximately 1 per 100 live births, making it one of the leading causes of development disabilities among Canadian children (Chudley et al., 2005). In fact, prenatal exposure to alcohol is the leading known preventable cause of mental retardation and birth defects (NOFAS, 2006). Higher incidence rates have been found in isolated Aboriginal communities in British Columbia, with about 19 FASD cases per 100 live births (Robinson et al., 1987). Current and comprehensive studies are needed to assess national figures.

2.1.3 The Diagnosis of FASD

One of the first descriptions of birth defects in children born to alcoholic parents was made in 1968 by Lemoine and colleagues (Lemoine et al, 1968). A few years later, a specific pattern of birth defects that were associated with prenatal alcohol exposure was described by Jones and Smith (1973). In the late 1990s, a diagnostic classification system was developed to categorize the various effects and symptoms of FASD (Astley and Clarren, 1999). Most recently this 4-Digit Diagnostic Code has been adapted for Canadians and published as the Canadian Guidelines for Diagnosis (Table 2.1) (Chudley et al, 2005). As there is no standardized clinical definition for FASD, these guidelines are available for clinicians to use in their assessments and are currently considered the gold standard for diagnosis. The exact characteristics for FAS, pFAS, and ARND appear in the appendix.
Table 2.1: Four-Digit Diagnostic Code Criteria for FASD

<table>
<thead>
<tr>
<th>Rank</th>
<th>Growth deficiency</th>
<th>FAS facial phenotype</th>
<th>CNS damage or dysfunction</th>
<th>Cestational exposure to alcohol</th>
</tr>
</thead>
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<tr>
<td>4</td>
<td>Significant</td>
<td>Severe</td>
<td>Definite</td>
<td>High risk</td>
</tr>
<tr>
<td></td>
<td>Height and weight below 3rd percentile</td>
<td>All 3 features: PFL 2 or more SDs below mean</td>
<td>Structural or neurologic evidence</td>
<td>Confirmed exposure to high levels</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Probable</td>
<td>Some risk</td>
</tr>
<tr>
<td></td>
<td>Height and weight below 10th percentile</td>
<td>Generally 2 of the 3 features</td>
<td>Significant dysfunction across 3 or more domains</td>
<td>Confirmed exposure. Level of exposure unknown or less than rank 4</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Mild</td>
<td>Possible</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Height or weight below 10th percentile</td>
<td>Generally 1 of the 3 features</td>
<td>Evidence of dysfunction, but less than rank 3</td>
<td>Exposure not confirmed present or absent</td>
</tr>
<tr>
<td>1</td>
<td>None</td>
<td>Absent</td>
<td>Unlikely</td>
<td>No risk</td>
</tr>
<tr>
<td></td>
<td>Height and weight at or above 10th percentile</td>
<td>None of the 3 features</td>
<td>No structural, neurologic or functional evidence of impairment</td>
<td>Confirmed absence of exposure from conception to birth</td>
</tr>
</tbody>
</table>

Note: PFL = palpebral fissure length; SD = standard deviation.


2.1.4 Risk Factors for FASD

The most important risk factors for FASD that have been consistently identified include: the frequency of maternal alcohol use, the pattern of alcohol consumption, high blood-alcohol exposure, and the timing of exposure during fetal development (Jacobson et al., 1999, Sood et al., 2001). In addition, studies have shown that older maternal age, lower education level, prenatal exposure to street drugs, custody charges, lower
socioeconomic status, reduced access to pre and postnatal care, and poor developmental environment are all additional risk factors for FASD (Bingol et al., 1987; Sood et al., 2001; Chudley et al., 2005). To date, there have been no conclusive studies regarding specifically what criteria and which exact factors are necessary for a child to develop FASD. In other words, it is unknown how much alcohol needs to be consumed, and at which point during the pregnancy that the alcohol is consumed, that the child will suffer from the neurocognitive and physical symptoms of FASD. The effects appear to vary depending on the individual, as described above; there are a variety of overlapping factors that may influence the outcome of the child.

2.1.5 CNS Impairments in Individuals with FASD

What is known from conclusive studies is that FASD cause a wide spectrum of abnormalities within the central nervous system (CNS). Using brain imaging and autopsy studies, researchers have found reductions and irregularities in the corpus callosum, cerebellum, hippocampus, and basal ganglia (Chen et al., 2003; Riley & McGee, 2005; O’Hare et al., 2005). Ethanol disrupts neurotransmitter and neuroendocrine function in the CNS as well as causing the suppression of growth hormone (GH) release, possibly accounting for the growth deficiency seen in children with FASD (Thadani & Schanberg, 1979). Furthermore, the characteristically smaller brain size may also be a result of this hormone deficiency. Archibald and colleagues (2000) have shown that white matter volume is significantly reduced compared to grey matter in the brains of individuals with FASD. The activity of the hypothalamic-pituitary-adrenal (HPA) axis is also compromised by ethanol, as it causes disruptions in the hormonal interactions between maternal and fetal systems (Weinberg et al, 2008). In turn, this alters the development of
the physiologic, metabolic, immune, and endocrine functions in the growing fetus (Zhang et al., 2005). At a molecular level, ethanol interferes with neurotransmitter mechanisms, impairs neurogenesis, and neuronal cell death (Olney, 2004).

2.1.6 The Effects of Prenatal Exposure to Alcohol on Circadian Rhythms

Features similar to those observed in human FASD are observed in rodent models of prenatal alcohol exposure, such as physical malformations, growth deficiencies, and CNS disruptions (Weinberg et al., 1982, 2008). In animal studies, prenatal exposure to alcohol has been shown to directly affect the suprachiasmatic nucleus (SCN) (Sher, 2004). There are various theories about how prenatal alcohol exposure affects the SCN. Firstly, ethanol could be interfering with the structure and/or function of cells in the SCN (Earnest et al., 2001). This may be related to the loss of specific cells or the change of expression of specific genes. More specifically, Earnest and colleagues (2001) found that prenatal exposure to alcohol in the rat, may interfere with circadian clock function due a shortened sleep-wake cycle and changes in the release of certain brain chemicals. A secondary explanation would be interference of FASD with SCN output signals, such as neuropeptides, and the circadian rhythms that these chemicals control and/or regulate, such as the sleep-wake cycle (Sher, 2004). To date, animal studies have shown that alcohol exposure during prenatal brain growth periods causes cell loss, alters information pathways between brain regions, and decreases the production of neurotransmitters. Although it is unlikely that damage induced by alcohol on the SCN would result in complete loss of circadian rhythmicity, more subtle disturbances might take place. The specific and non-specific effects of FASD on the regulation of circadian rhythmicity have
not been thoroughly explored. Moore and colleagues (1991) have shown that FASD could lead to permanent reductions in SCN rhythm amplitude and modulation of the SCN clock’s responses to light signals, therefore possibly accounting for some of the behavioural disturbances in FASD patients. Sakata-Haga and Fukui (2007) examined the effects of pre or postnatal exposure to ethanol on the circadian rhythm in adult rats. Their findings suggested that pre- and postnatal ethanol exposure impairs the development of the circadian clock response to light cues. Ethanol-exposed rats took a longer period of time than control rats to synchronize to a new light/dark cycle.

2.1.7 Prenatal Alcohol Exposure and Circadian Rhythm Disruptions

Various hypotheses suggest that prenatal alcohol exposure produces subtle abnormalities in circadian rhythms that may contribute to seasonal and non-seasonal mood disorders (Sher, 2004). Therefore, the early detection of possible circadian rhythm disruptions may aid in preventing and/or treating associated mood disorders. In mice and rat studies, researchers have shown a strong relationship between prenatal exposure to alcohol and disruption of circadian rhythms, directly through the SCN (Sei et al., 2003; Sari et al., 2004). Sei and colleagues (2003) showed that in adult rats, which were prenatally exposed to alcohol, the light sensitivity of the SCN was affected. This was thought to be a consequence of brain derived neurotrophic factor (BDNF) expression being suppressed. This resulted in a long-lasting effect on the light responsiveness of the deep body temperature circadian rhythm. In addition, Sari and Zhou (2004) found that prenatal ethanol exposure resulted in long-lasting serotonin deficit in mice. The SCN contains one of the densest serotonergic terminal plexes in the brain (Morin, 1999). Therefore, serotonergic deficit may affect the activity of the SCN, by resulting in a
melatonin deficiency and consequently, circadian rhythms (discussed below). In short, both of these studies provide direct evidence to the effects of prenatal ethanol exposure on the functioning of the master circadian pacemaker, the SCN.

2.1.8 Circadian Rhythm Disruptions and Neurocognitive Effects

If the alterations in circadian rhythms are strong enough they may contribute to the development of mood disorders, such as mild depression and seasonal affective disorder (SAD) (Sher et al., 2004). These mood disorders may aggravate any neurocognitive difficulties present in individuals with FASD already suffer from. For example, a decreased amount of deep sleep may be a marker for the onset of mild depression (Butcher et al., 2004). In addition, children with FASD who may have circadian rhythm disruptions, may be at a higher risk of developing seasonal affective disorder (SAD). SAD is a unipolar mood disorder in which patients are highly responsive to the total amount of light available in the environment (Sonis, 1992). A study in our laboratory showed that in women, nefazodone, an antidepressant, enhances sleep efficiency and sleep latency, as well as having effective anti-depressive effects (Shen et al, 2005). Therefore, diagnosis and treatment of any underlying sleep disorders may improve in the management of mental health of children with FASD. The following sections of this chapter will discuss details of sleep and its relationship to FASD.
2.2 The Sleep-Wake Cycle

2.2.1 The Evolution of Sleep

The evolutionary history of sleep has been illuminated by using a comparative approach. A phylogenetic evaluation of sleep demonstrates that all mammals, birds, and reptiles engage in sleep, and evidence for sleep in amphibians, fishes, and invertebrates is strong, if not certain, however some researchers have other theories (Lesku et al., 2006). This comparative method has revealed extensive variation in the amount and type (nocturnal, diurnal) of sleep that various animal species require. It is challenging to understand the exact evolutionary history of sleep across taxonomic groups since in many species, it is difficult to understand the function for which sleep evolved. Researchers believe that numerous adaptations became associated with sleep after its initial evolution. In other words, in animals, sleep may represent a variety of functions. Capellini and colleagues (2008) have emphasized the importance of ecology in the evolution. Predation pressure, trophic niche and energy demands contribute to our understanding of interspecific variation in mammalian sleep architecture (Capellini et al., 2008).

Although it is generally accepted that sleep evolved from a state of wakefulness, the order of the development of SWS and REM sleep in mammals and birds is less clear. There are three main hypotheses regarding the evolution of the sleep-wake cycle in mammals and birds (Lesku et al., 2006). “SWS-first”, suggesting that REM sleep evolved from SWS sleep; “REM-first”, that SWS evoled from an ancestral REM sleep state; or lastly that REM and SWS evolved at the same together. While the details of these theories are beyond the scope of this thesis, the understanding of differences in sleep architecture and physiology across species provides a better understanding of the
application of animal studies to clinical human populations, such as the FASD population.

2.2.3 The Function of Sleep

Sleep is a reversible state of reduced awareness and responsiveness to the external environment. There have been several theories proposed with regards to the function of sleep in humans. The most widely held theory about the function of sleep is that it serves as a period of physical and mental restoration in order to be able to perform daily functions (Shapiro and Flanigan, 1993). Another common theory proposes that sleep allows for the conservation of energy. More detailed research has shown that sleep is closely linked to human growth (Paxton et al., 1984), brain development (Peirano & Algarin 2007), the immune system (Zager et al., 2007), memory (Daurat et al., 2007). No single theory accounts for all of the complexities of sleep at different stages of development, and it seems that sleep serves multiple purposes (Rechtschaffen, 1998). Persistent sleep disturbances usually lead to psychological or physical disorders (Kheiandish and Gozal, 2006).

2.2.4 Developmental Progression of Sleep-Wake Cycle Patterns

Sleep architecture changes significantly across the entire lifespan, but the most significant changes occur within the first few years of life (Feinberg, 1974; Sheldon et al., 1996; Iglowstein et al., 2003). Total sleep time decreases gradually throughout childhood. For example, newborns sleep 16-20 hours per day, typically sleeping for 1-4 hr periods followed by 1-2 hrs of wakefulness. Newborn and infant sleep is broken down into active sleep (the forerunner of REM sleep) and quiet sleep (the forerunner of NREM sleep). In
the first few months of life, there is an equal balance of active and quiet sleep (Coons et al., 1982). By 3-6 months of age, NREM stages 1-4 can be identified. The proportion of REM sleep begins to decline around 3 months of age (from 50%). The changes in sleep across the lifespan are displayed in table 2.2.

Table 2.2: Changes in Sleep across the Lifespan


<table>
<thead>
<tr>
<th>Age</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Utero</td>
<td>80% “active sleep” at 30 weeks’ gestation</td>
</tr>
<tr>
<td>Newborns</td>
<td>16-20 hours of sleep every 24 hours. 5-10 hours during daytime. Active sleep = 50%. Establishment of major nocturnal sleep period by 3-4 months</td>
</tr>
<tr>
<td>One year</td>
<td>13-15 hours every 24 hours; 2-3 hours during daytime naps. 30% REM sleep</td>
</tr>
<tr>
<td>Two years</td>
<td>12-14 hours; 1.5-2.5 hours during daytime napes, 25% REM sleep</td>
</tr>
<tr>
<td>Three to five years</td>
<td>11-13 hours sleep, 0-2.5 hours during daytime naps</td>
</tr>
<tr>
<td>Five to twelve years</td>
<td>9-12 hours, usually no naps</td>
</tr>
<tr>
<td>Teenage years</td>
<td>8-9 hours, usually no naps</td>
</tr>
<tr>
<td>Second to seventh decade</td>
<td>Marked decline in the amplitude of SWS, Gradual decline in the amount of SWS</td>
</tr>
<tr>
<td>Older adults (&gt;65 years of age)</td>
<td>Decreased nocturnal sleep, increase napping, increased falling and staying asleep, lighter sleep, increase awakening, changes in melatonin secretion</td>
</tr>
</tbody>
</table>
2.2.5 Sleep Stages

Sleep is distinguishable into two main categories: REM and NREM sleep (Aserinsky and Kleitman, 1953). NREM sleep is divided into four stages: stages 1-4, where the combination of stages 3 and 4 is referred to as Slow Wave Sleep (SWS). Figure 2.1 displays a hypnogram of sleep cycle in a healthy young adult. In 2007, the American Academy of Sleep Medicine (AASM) proposed new guidelines for the classification of sleep stages. NREM is now thought to be divided into three stages: N1, N2, N3, where N3 refers to the combination of stages 3 and 4 or SWS. A typical normal night of sleep involves alternating cycles of REM and NREM sleep, beginning with stage 1 through to stage 4, followed by REM sleep. Each NREM period is typically around 80 minutes, followed by 10 minutes of REM sleep. This “sleep cycle” is repeated 3-6 times during each night (Stores, 2001). The amount of SWS tends to be greater at the beginning of the night, while the amount of REM sleep tends to be greater towards the morning hours. In REM sleep, the cortical blood flow and oxygen delivery are high, especially in the limbic regions and brainstem (Jan et al, 2010b). In addition, EEGs show the most neuronal activity in most areas of the brain, relative to NREM sleep. The duration of REM sleep is highest during early development, in all mammals (Peirano et al, 2007).
Normal sleep involves cycling through NREM and REM sleep, beginning with stage 1 through to stage 4, followed by REM sleep. (Adapted from Lin VW, Cardenas DD, Cutter NC, et al. Spinal Cord Medicine: Principles and Practice. New York: Demos Medical Publishing; 2003.)

Standardized criteria are used to classify different sleep stages according to their characteristic physiological features, by using the electroencephalography (EEG), electro-oculogram (EOG) and electromyogram (EMG) (table 2.3). Stage 1 occurs at sleep onset or following arousal from another stage of sleep. The EEG is low voltage with mixed frequencies and reduced alpha activity compared with the wake state. The EEG contains vertex sharp waves and slow eye rolling movements. This stage represents about 4-5% of the main sleep period. Stage 2 contains more slow activity, and sleep spindles and K complexes are seen. It accounts for 45-55% of overnight sleep. Stage 3 accounts for 4-6% of total sleep time and contains yet more slow EEG activity. Stage 4 is defined by the most slow activity and constitutes 12-15% of sleep. This is considered to be the deepest form of sleep from which awakening is particularly difficult. REM sleep is physiologically very different than NREM sleep. Typically, a low voltage, mixed frequency, non-alpha rhythm EEG is seen and EMG activity is virtually absent in the
skeletal musculature. Historically, REM sleep has been called “paradoxical sleep” because despite the high levels of brain activity, there is a near absence of muscle tone. Most dreaming occurs in REM sleep. This stage typically accounts for 20-25% of total sleep time.

Table 2.3: Criteria for Sleep Staging *(Adapted from: Rechtschaffen & Kales 1968).*

<table>
<thead>
<tr>
<th>Sleep Stage</th>
<th>Characteristics</th>
<th>Example EEG Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wakefulness</strong> (eyes closed)</td>
<td>- Rhythmic alpha EEG activity (8-13Hz) most prominent in occipital leads, attenuated with attention</td>
<td><img src="image" alt="Example EEG Activity for Wakefulness" /></td>
</tr>
</tbody>
</table>
| **Stage 1** | - Slow eye movement  
- Low voltage, mixed frequency EEG activity with prominence of activity in a range of 3 Hz  
- Absence of sleep spindles and K-complexes  
- EMG activity lower than wakefulness | ![Example EEG Activity for Stage 1](image) |
| **Stage 2** | - Background EEG shows low voltage, mixed frequency EEG  
- K-complex: negative sharp waves followed by a positive component which exceeds a duration of 0.5 seconds  
- Sleep spindles of at least 0.5 seconds duration | ![Example EEG Activity for Stage 2](image) |
| **Stage 3** | - 20-50% of the epoch consists of high voltage, slow wave activity  
- No eye movement  
- Low EMG tone | ![Example EEG Activity for Stage 3](image) |
| **Stage 4** | - 50% of the epoch consists of high voltage, slow wave activity  
- No eye movement  
- Low EMG tone | ![Example EEG Activity for Stage 4](image) |

*the new scoring parameters now combine stage 3 and 4 into one stage of SWS*
2.2.6 Physiology of Sleep

There are many highly complex neural networks and related physiological processes that actively control the distinct states of wakefulness, non-REM (NREM) sleep, and REM sleep. Wakefulness is promoted by ascending projections that originate in neurons located in the brainstem (reticular formation) as well as hypothalamic pathways. These largely excitatory neurons relay sensory input to the thalamus, hypothalamus, and basal forebrain (BF) and activate large areas of the cortex to increase wakefulness; their activity is suppressed during sleep (Espana, 2004). Cholinergic neurons of the dorsal midbrain and pons (pedunculopontine nucleus [PPT] and the laterodorsal tegmental nucleus [LDT]) also demonstrate increased activity during wakefulness and REM sleep and decreased activity during NREM sleep (Espana 2004).

These neurons also send excitatory projections to the thalamus, where they regulate cortical activity and allow the flow of information through the thalamus and to and from the cortex. Cholinergic neurons located in the basal forebrain (BF) also send projections throughout the cortex, hippocampus and amygdala. Their activity is high during wakefulness and REM sleep, and low during NREM sleep.
There are a number of neurotransmitters and neuropeptides that actively regulate wakefulness promotion. These include acetylcholine (increased in wakefulness and REM sleep) and a number of aminergic neurotransmitters (increased in wakefulness and very low in REM), including histamine in the tuberomammillary nucleus (posterior hypothalamus); dopamine in the ventral tegmental area, substantia nigra, posterior hypothalamus and brainstem; serotonin in the median and dorsal raphé and norepinephrine (NE) in the locus coeruleus (midbrain) (Espana 2004; Mindel and Owens, 2010). While coordinated activity across these arousal systems is necessary for complete and sustained wake states, each aminergic pathway may mediate different functions of wakefulness, such as wake onset, novel stimuli, or physical activity during periods of wakefulness (Mindel and Owens, 2010).

The ventrolateral preoptic area in the anterior hypothalamus (VLPO) is a major sleep-promoting area of the brain. The various sub-regions of the VLPO are thought to control NREM and REM sleep. During sleep, especially during slow wave sleep (SWS), VLPO neurons are active and exhibit high firing rates (Sheldon, 1996). These VLPO neurons send projections to all the major wake-promoting regions, including the tuberomammillary nucleus (TMN), locus ceruleus (LC), LDT and PPT. These inhibitory neurons are believed to induce sleep by coordinating the release of the inhibitory neurotransmitter gamma aminobutyric acid (GABA) at their sites of projections, while some utilize the inhibitory neurotransmitter galanin. The control of REM sleep involves the interaction of brainstem cholinergic and aminergic neurons in a complex feedback loop. In this loop, neurons releasing acetylcholine (LDT/PPT region) are
disinhibited by the suppression of aminergic neurons during REM (Sheldon, 1996; Espana 2004; Mindel and Owens, 2010).

2.2.7 Sleep Regulation

There are two basic, highly coupled processes that operate simultaneously and regulate sleep and wakefulness (Borbely, 1982). The homeostatic process (“process S”) and the endogenous circadian rhythm (“process C”) processes have traditionally come to represent the “two process” sleep system (figure 2.2). The homeostatic process primarily regulates the length and depth of sleep. The homeostatic drive may be related to the increase of sleep-promoting chemicals (“somnogens”), such as adenosine, cytokines, prostaglandin D2, nitric oxide, and others, which increase during prolonged periods of wakefulness (Huang et al 2007; Imeri et al, 2009). In infants and young children, this “sleep pressure” appears to build more quickly, thus requiring periods of daytime sleep, such as daytime naps. The endogenous circadian rhythm (“process C”) influences the internal organization of sleep and timing and the duration of daily sleep-wake cycles. It also governs predictable patterns of alertness throughout the 24-hour day cycle. The master circadian clock that controls sleep-wake patterns is located in the suprachiasmatic nucleus (SCN) in the ventral hypothalamus.
Figure 2.2: There are at least two factors that regulate the timing of sleep. First is the homeostatic sleep drive, which increases the longer a person is awake. The second is timing information from the suprachiasmatic nucleus (SCN). In this two-process model, the SCN promotes wakefulness by stimulating arousal networks. SCN activity appears to oppose the homeostatic sleep drive. The propensity to be awake or asleep at any time related to the homeostatic sleep drive and the opposing SCN alerting signal. At normal bedtime, both the alerting drive and the sleep drive are at their highest level. (Adapted from: Reid KJ, Zee PC, and Buxton O. Circadian Rhythms Regulation. In Atlas of Clinical Sleep Medicine, 2010 Elsevier)

The relative level of sleepiness or alertness that exists at any given time during a 24-hour period is partially determined by the duration and quality of previous sleep as well as the time awake since the last sleep period (the homeostatic drive). The 24-hour rhythm, characterized by periods of maximal sleepiness and maximum alertness, interacts with the homeostatic sleep drive. The two periods of maximal alertness generally occur mid-morning and in the evening just prior to sleep onset. Maximal sleepiness generally occurs in the late afternoon (3:00-5:00pm) and then in the later part of the night (3:00am-5:00am). Other factors, including age, sleep needs, tasks performed during the day, and environmental conditions, influence relative sleepiness and wakefulness.
Since the human circadian clock is actually slightly longer than 24 hours, intrinsic circadian rhythms are “entrained” to the 24-hour-day cycle by environmental cues, such as light, called “zeitgebers”. In the absence of zeitgebers, circadian rhythms are uncoupled from one another (known to be “free-running”). The light-dark cycle is one of the most powerful zeitgebers. Light signals are transmitted to the SCN via the circadian photoreceptor system which in the retina. In turn, this switches the body’s production of the melatonin hormone off (during light) or on (during darkness) by the pineal gland.

2.2.8 Structure and Function of the Suprachiasmatic Nuclei (SCN)

In humans, a variety of physiological processes, such as the regulation of neurotransmitters, blood hormone concentrations, and sleep-wake behaviour, undergo rhythmic fluctuations that closely parallel the time course of the daily solar cycle. However, this physiological organization occurs even in the absence of external time cues, consequently these rhythms are termed “circadian” (Earnest et al., 2001). In mammals, including humans, the internal biological clock is called the suprachiasmatic nuclei (SCN) and is localized in the brain in a pair of clusters of neurons positioned on the hypothalamus, above the optic chiasm. (Earnest et al., 2001). Through an intrinsic circadian rhythmic system, the SCN regulate diurnal behaviours such as sleep and wakefulness, drinking, eating, attention, and memory (Aloe et al., 2005; Richardson, 2005; Zee and Manthena, 2007). Its main function is to generate and synchronize all circadian rhythms. The SCN release specific neuropeptides, such as brain-derived neurotrophic factor (BDNF) and arginine vasopressin, which in turn regulate and act on other brain regions or peripheral organs to generate a variety of circadian rhythms, such as the sleep-wake cycle (Schwartz, 1993) (figure 2.3). This circadian system has cycles of
approximately 24 hours and can synchronize to the Earth’s light/dark cycles. Normal functioning of the SCN is critical for maintaining human health by allowing for the coordination of internal physiological processes with each other and with the light-dark cycle. Damage to the SCN would increase the body’s susceptibility to physiological disorders, including sleep/wake disorders (Roebuck et al., 1999).

Figure 2.3: The Basic Components of the Circadian System. Photic information to the suprachiasmatic nucleus (SCN) is transmitted from the retina via the retinohypothalamic tract (RHT). The retinal ganglion cells (RGC) of the eye, melanopsin containing photoreceptors, provide the primary photic input to the circadian clock, transmitting the signal to the neurons of the SCN. Melatonin is released from the pineal gland at night and its output is regulated by the SCN via the superior cervical ganglion (SCG). In addition to its ability to synchronize circadian rhythms, melatonin can also promote sleep. Integrated timing information from the SCN is transmitted to sleep-wake centers in the brain. (Adapted from: Reid KJ, Zee PC, and Buxton O. Circadian Rhythms Regulation. In Atlas of Clinical Sleep Medicine, 2010 Elsevier)
2.3 Melatonin

The hormone, melatonin (N-acetyl-5-methoxytryptamine), is one of the most reliable markers of SCN function (Pandi-Perumal et al., 2007). First identified by Lerner and colleagues in 1958, melatonin is known to be the primary hormone responsible for regulating sleep and circadian rhythms (Lerner et al., 1958). In humans, it is synthesized mainly in the pineal gland, but it also produced in smaller amounts in the gastrointestinal tract, ovaries, lymphocytes, platelets, bone marrow cells, skin, and in the retina (Rios et al., 2010). It is regulated by the SCN and secreted during darkness (“the hormone of darkness”), and suppressed by bright light. Melatonin is biosynthesized in a 4-step pathway from the molecule tryptophan (figure 2.4) (Hardeland, 2008). Serotonin (5-hydroxytryptamine) is formed in the biosynthesis of melatonin, and is a precursor of melatonin. It is thought that if there is a surplus of serotonin available, more melatonin may be synthesized, since it is a precursor in the pathway. Selective serotonin reuptake inhibitors (SSRI) are often prescribed for depression and act by increasing levels of serotonin in the brain (Rios et al., 2010). Therefore, the expectation is that SSRI’s would elevate levels and concentrations of melatonin in the body. Conversely, a serotonergic deficiency may contribute to lower levels and concentrations of melatonin production (Rios et al., 2010). Once formed, melatonin is immediately released into the capillaries, cerebral-spinal fluid (CSF) and then rapidly distributed into body tissues (Cardinali et al., 1998). Melatonin attains maximal plasma and CSF levels between 02:00 and 03:00am.
The secretion of melatonin is low during the day, in periods of lightness, and high during the night, during periods of darkness. These daily variations of light are transduced into electrical impulses from retinal ganglion cells and signal to the SCN, which signals to the pineal gland. During the day, noradrenaline release from postganglionic sympathetic nerve fibers is suppressed due to increased electrical activity in the SCN, and as a result melatonin production is down regulated. Where there is no light, the pineal gland is relieved of this inhibitory influence of the SCN, the release of noradrenaline is enhanced, and melatonin is produced and released into the bloodstream and CSF (Klein et al, 1992).
2.3.1 Regulation of Melatonin Secretion

During the day, the retina receives light input, which causes the reticulohypothalamic tract (RHT) to release glutamate to the SCN. This results in the depolarization and subsequent release of GABA from neurons in the SCN that project to the paraventricular nucleus of the hypothalamus (PVN). When the PVN is activated, its neurons project to the intermediolateral column of the spinal cord (IML), from which preganglionic sympathetic neurons release norepinephrine to the pineal gland (Buijs et al., 2003; Zee and Manthena, 2007). Because GABA is inhibitory, activation of the SCN by light leads to inhibition of melatonin synthesis and release. Conversely, in dim light and darkness, activity in the SCN is minimal due to lack of photic input. This causes a decrease in GABAergic input from the SCN to the PVN, which disinhibits the inhibitory effect of the SCN on melatonin secretion (Buijs et al., 2003). As a result, melatonin secretion begins with the dark period and promotion of sleep occurs.

Melatonin is a good marker of SCN function for several reasons. Firstly, melatonin is extremely sensitive to changes in environmental light, since darkness promotes the synthesis and secretion of melatonin, while light inhibits these processes (Buijs et al., 2003; Zee and Manthena 2007). Secondly, as a sleep-inducing hormone, the onset of melatonin secretion at night directly precedes sleep onset and also coincides with the fall in core body temperature, as well as alertness. Therefore, melatonin represents two of the main functions of the SCN: as a sleep-inducing hormone, it regulates sleep, and through its responses to changes in light, it represents the sensitivity of the SCN to light. As a result, measuring levels of melatonin is extremely useful to studying and understanding the function of the SCN. The most common, gold standard test to measure
levels of melatonin, as well as the onset of melatonin, is the Dim Light Melatonin Onset (DLMO) test (Rahman et al, 2009). This procedure has been useful for assessing SCN function in delayed sleep phase syndrome (DSPS) (where DLMO is delayed) and in advanced sleep phase syndrome (ASPS) (Rahman et al, 2009). Specifically, the DLMO test is a procedure in which secretion of melatonin is measured in hourly samples of saliva, beginning in the evening and until the late night. These samples are then frozen and sent to the lab for analysis, usually using the ELISA technique. The DLMO protocol is uncomplicated. Individuals are instructed to remain awake from the hours of 19:00-02:00 (wintertime) or 20:00-03:00 (summertime), in a dark room. Every hour a technician comes into the room and asks the individual to chew on a cotton swab.

2.4 Sleep Disorders in Children with FASD

In general, it appears that at least 20-30% of normally developing children, ranging from infancy to adolescence, have sleep problems that are considered significant by them or their parents (Mindell, 1993). In children with neurodevelopmental disabilities (NDD), such as FASD, the prevalence rates may be as high as 75-80% (Jan et al, 2010a). A comprehensive review by James Jan and colleagues (2010a) outlines the overwhelming need for evidence-based research regarding sleep disturbances in children with fetal alcohol spectrum disorders. It has been reported that many children diagnosed with FASD have ongoing sleep disturbances which impede the management of neurocognitive difficulties and daily activities. To date, the exact prevalence of sleep problems in children with FASD is unclear. In one survey, linked with our lab, 82 of 100 caregivers of children between the ages of 5-8 reported sleep problems such as waking up more than twice a night, sleep terrors, and daytime fatigue (Stade et al, 2008). This is the
only known study examining the prevalence of sleep problems in this population.
However, this study relied on caregiver reports, did not incorporate any objective
measures of sleep, and focused on a small range of ages. Another retrospective chart
study of 50 babies with FASD symptoms showed that 30 of these babies had disturbed
sleep (Elgen et al, 2007). The Maternal Lifestyle Study was a large-scale longitudinal
study examining associations between sleep problems and prenatal exposure to a variety
of substances, including cocaine, opiates, marijuana, alcohol, and nicotine, in children
aged 1 month to 12 years old (Stone et al, 2010). Although alcohol was included in the
list of prenatal exposures, it was not a limiting teratogen. Therefore, the results of the
study may not be applied directly to the FASD population. Nonetheless, this is one of the
only long term studies investigating sleep disturbances in a large population of children
(n = 374). Sleep data was collected based on maternal reports and compared to control
subjects. Of the 5 main substances assessed, only prenatal exposure to nicotine was found
to be a unique predictor of sleep problems. However, as with the other studies described,
the study is limited by relying on maternal reports, as well as not having any objective
measures, such as polysomnography, to assess for sleep disturbances.

It is thought that sleep difficulties in children with FASD may be secondary to
other medical problems, social, or mental difficulties. In other neurodevelopmental
disorders affecting children, numerous studies have described the high prevalence of
sleep disturbances (Jan et al, 1996, Kothare, 2011). The majority of these studies have
suggested that sleep disturbances were mainly associated with the severity of brain
disturbances. Based on this literature, the sleep disturbances reported in children and
adolescents with FASD may be a result of brain damage (Jan et al, 2010a). After
speaking with various leaders in FASD clinics, the majority of sleep disturbances fall under the category of circadian rhythm sleep disorders, and include complaints such as difficulty falling asleep, night terrors, frequent nighttime awakenings, and early morning awakenings (Jan, 2011). These complaints are in line with the research conducted in animal studies suggesting disturbances to the suprachiasmatic nucleus, which regulates circadian rhythms. The circadian rhythm complaints described may be attributed to an abnormal pineal melatonin production and/or secretion. In fact, some studies have shown that when administered at bedtime, melatonin may greatly assist in correcting the disorder in children with neurodevelopmental disorders (Wasdell et al, 2008).

2.4.1 Pediatric Sleep Disorders

As noted above, disruptions of the sleep-wake cycle and sleep disorders may have a negative impact on many aspects of daytime functioning and the overall quality of life. The most recently revised International Classification of Sleep Disorders (ICSD-R) documents 81 official sleep disorders (American Sleep Disorders Association, 2005). Although it is very comprehensive and up-to-date, the ICSD-R is essentially adult-based and needs to be modified when used for children and adolescents. Below is a list and description of some of the most common sleep disorders.

2.4.2 Insomnia

Pediatric insomnia is defined as the repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family (France & Hudson, 1993). In adults, insomnia is the most common sleep complaint, with various studies finding the prevalence to be between 5-30% of the
general population (Ohayon 1997; Morphy 2007). However, in the general pediatric and adolescent population, the most common sleep concerns are “bedtime problems” or night awakenings. Studies on insomnia in adolescents found that 9-13% experience chronic insomnia, with up to 35% experiencing insomnia at least several times a month (Morrison et al, 1992; Pollock 1994). In contrast, primary insomnia is less common in pre-pubertal children. Studies indicate that insomnia has an increased prevalence in girls post-puberty, consistent with adults (Mindell and Owens, 2010).

2.4.3 Sleep Disordered Breathing (SDB)

In children, sleep disordered breathing encompasses a broad spectrum of respiratory disorders that occur during sleep, and include apneas (Mindell and Owens, 2010). Obstructive sleep apnea (OSA) is a serious SDB condition, characterized by repeated episodes of prolonged upper airway obstruction during sleep despite continued or increased respiratory effort, resulting in complete or partial cessation of airflow at the nose and/or mouth as well as in disrupted sleep. Left untreated, these arousals and periods of hypoxia contribute to significant medical morbidities, such as increased blood pressure and insulin resistance, as well as neurocognitive and behavioural difficulties. The prevalence of pediatric OSA (as documented by overnight sleep polysomnography) is 1%-4% overall, with a reported range of 0.1%-13% (Owens, 2009). Although OSA may occur in all ages, it is most prevalent between the ages of 2-8 years, and is more in common in boys (especially after puberty) (Marcus, 2001).
2.4.4 Restless Leg Syndrome (RLS)

Restless legs syndrome (RLS) is a neurological, primarily sensory disorder characterized by uncomfortable sensations in the lower extremities that are accompanied by an almost irresistible urge to move the legs (Picchietti et al, 2007). The discomfort is temporarily relieved by increased movement of the legs. Most episodes begin or are exacerbated by rest or inactivity, such as lying in bed and/or sleeping. A common complaint by parents of children with RLS is bedtime resistance and difficulty falling asleep (Picchietti et al, 2007). Various studies have found the prevalence rates of RLS in different pediatric populations to range between 1%-6%, and there does not seem to be a gender difference (Picchietti and Stevens, 2007).

2.4.5 Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders occur when there is a misalignment of circadian cycles in relation to the subjective day and night. Two recognized sleep disorders by the American Sleep Disorders Association are advanced sleep phase syndrome (ASPS) and delayed sleep phase syndrome (DSPS) (American Sleep Disorders Association, 2005). In ASPS, individuals fall asleep early at night and wake up too early (figure 2.5b). Conversely, in DSPS individuals fall asleep too late at night and then wake up later in the morning (figure 2.5a). A summary of these phase shifts is displayed in figure 2.6.
2.4.6 Delayed Sleep Phase Syndrome (DSPS)

Delayed sleep phase disorder (DSPS), a circadian rhythm disorder, involves a significant and persistent shift in an individual’s sleep-wake schedules that interferes with environmental demands, usually resulting in significant daytime sleepiness, as well as academic and behaviour problems. (Sack et al, 2007). It is the timing, rather than the quality of sleep that is problematic. DSPS may occur at any age, but is most common in adolescents and young adults. The typical sleep-wake pattern in DSPS is a preferred bedtime or sleep onset time after midnight (usually 02:00-06:00am) and a wake-time after 10:00am (figure 2.5a). Theories into the etiology of DPSD suggest there is a problem with the synchronization of “entrainment” of the circadian clock to environmental cues, as well as a delay in the production and release of melatonin (as measured by dim light melatonin onset testing and melatonin profiles). The prevalence of DSPS is not conclusive. Various studies report different figures. According the International Classification of Sleep Disorders (ICSD) the prevalence in the general population indicates that DSPS affects approximately 7%-16% of adolescents (American Academy of Sleep Medicine 2005, Pallesen and Bjorvatn 2009). However a study from Norway showed that the prevalence amongst adolescents was much lower at 0.25% (Schrader et al, 1993). This low prevalence was also found in a study from Tokyo that reported a prevalence of 0.48% amongst school age adolescents (Hazama et al, 2008).
Figure 2.5a): An example of a 24-hour melatonin profile obtained under dim light conditions in a patient with delayed sleep phase disorder (DSPD). The arrow indicates the time of dim light melatonin onset (DLMO) at about 3a.m. which is much later than normal (DLMO in normal controls is usually between 20:00 and 22:00). Since sleep onset usually occurs about 2 hours after the DLMO, this person may not be sleepy until around 02:00, making it difficult to fall asleep earlier than 04:00, even if desired. (Adapted from Reid KJ and Zee PC. Circadian Rhythm Sleep Disorders. In Atlas of Clinical Sleep Medicine, 2010 Elsevier)

Figure 2.5b): This 24-hour profile of melatonin levels indicates that this patient has a dim light melatonin onset (DLMO) at about 14:00 (arrow), which is much earlier than normal (20:00 to 22:00). Since sleep onset usually occurs about 2 hours after the DLMO, this person will likely be very sleepy at around 4 in the afternoon. (Adapted from Reid KJ and Zee PC. Circadian Rhythm Sleep Disorders. In Atlas of Clinical Sleep Medicine, 2010 Elsevier)
2.4.7 Excessive Daytime Sleepiness (EDS)

Excessive daytime sleepiness (EDS) is defined as “the inability to stay awake during the major waking episodes of the day, resulting in unintended lapses into drowsiness or sleep” (Millman et al, 2005). EDS may be distinguished from “fatigue” by the presence of the sleep propensity. The most common causes of EDS in both adults and children are primary sleep disorders (such as OSA or RLS) that result in inadequate and/or disturbed sleep. The prevalence of daytime sleepiness in school-aged children is estimated to be between 10%-20%. Our laboratory conducted a cross-sectional survey of 2201 high school students and found that 70% of the students had less than 8.5 hours of weeknight sleep and 58-68% reported that they were “really sleepy” between 8:00am and 10:00am (Gibson et al, 2006).
2.4.8 Parasomnias

Parasomnias are defined as episodic, often undesirable, behaviours that accompany sleep. Parasomnias may be further classified as non-REM partial arousal parasomnias (such as sleepwalking) and REM-parasomnias (such as nightmares). Parasomnias also include sleep terrors, confusional arousals, and may often pose an injury risk to the child (Petit et al, 2007). Prevalence estimates in childhood for sleep terrors range from 1%-6%, for sleepwalking up to 17% with a peak at 8 to 12 years, and for confusional arousals up to 17.3% (Wills et al, 2002; Agargun et al, 2004; AASM 2010). On the basis of structured telephone interviews, Ohayon et al (1999) reported that the percentage of adolescents with sleep terrors was 2.2%, sleepwalking 2% and confusional arousals 4.2%.

2.5 Neurocognitive and Behavioural Effects of Impaired Sleep

Short-term sleep loss in children has been shown to cause difficulties in cognition, behaviour, and health. A variety of sleep difficulties, varying from fragmented sleep to sleep disordered breathing, have been closely linked to adverse daytime functioning in pediatric populations (Holmes, 2006; Kheirandish and Gozal, 2006). Based on subjective sleep criteria, infants, toddlers, and school age children who are characterized as poor sleepers show increased incidence and severity of parentally reported behavioural difficulties, compared to children without sleep problems (Ali et al, 1993; Chervin et al; 1997; Stein et al, 2001). These studies have been confirmed by objective sleep assessments which have found a high correlation between the degree of sleep disturbances and the severity of behavioural alterations (Chervin and Archbold, 2001; O’Brien et al, 2003a, b). Prolonged sleep latencies and difficulties falling asleep have
been associated to anxiety and depressive symptoms (Smedje et al., 2001; Stein et al., 2001). Sleep disturbances also have many neurocognitive consequences. Daytime sleepiness appears to be linked to attention difficulties, while sleep disordered breathing is associated with deficits in executive functions, such as planning and organizing (Bedard et al., 1991; Naegele et al., 1995). Cognitive dysfunctions associated with sleep disordered breathing have been well documented: including significantly reduced IQ scores (Blunden et al., 2000), significantly reduced memory performance on standardized psychometric tests (Rhodes et al., 1995), significantly reduced attention when compared with children (Chevrin et al., 1997, 2002), and lower level of school performance (Gozal, 1998; Richards and Ferdman, 2000) compared to children who did not have sleep disordered breathing. It is thought that sleep fragmentation and episodic hypoxia (during OSA) alter the neurochemicals substrate of several brain regions and increases neuronal cell loss, including the pre-frontal cortex (PFC) and the hippocampus, which are responsible for executive function and memory, respectively (Owens et al., 2000; Gozal et al., 2001; Lewin et al., 2002). As noted above, very few studies have examined the prevalence and patterns of sleep and circadian rhythm disturbances in the FASD population - which already suffers from an array of behavioural and neurocognitive difficulties. Furthermore, since the literature has shown how large of an impact sleep disorders can have on children’s neurocognitive functioning and behaviour, it is imperative to assess the prevalence and patterns of sleep disturbances in children with FASD. For a population with remarkably increased neurocognitive and behavioural difficulties, such as FASD, the assessment of sleep is highly warranted.
Chapter 3: METHODS
Chapter 3: METHODS

3.1 Study Design

This is a prospective, observational research study of children and adolescents who were diagnosed with FASD (by assessment at a FASD specialty clinic) and were objectively and subjectively assessed for the presence and patterns of sleep and/or circadian rhythm disorders. The study protocol was approved by the ethics board at the Independent Review Board (Aurora, Ontario) in February 2010.

3.2 Study Population

The patient population for this study was comprised of children and adolescents (between the ages of 6-18 years old) who were diagnosed with FASD. The diagnosis had to be on the FASD spectrum, either ARND, pFAS, or FAS. Patients who were in the process of obtaining an official diagnosis on the FASD spectrum, were identified with the general classification of FASD, rather than one of the three specific disorders. Study participants were referred primarily from various Fetal Alcohol Spectrum Disorder Clinics in the Greater Toronto area, as well as the surrounding area including Parry Sound, Barrie, Hamilton, Windsor, and Kitchener. All the listed FASD clinics in the Southwestern and Northern Ontario regions were contacted through mail, and followed up via phone, with regards to this study and were asked to refer patients who met the inclusion criteria (discussed below). All the referred patients were assessed for eligibility at the Youthdale Child and Adolescent Sleep Centre by Shery Goril and the sleep specialist (Dr. Shapiro). Eligibility to participate in the study was determined using the following criteria:
3.3 Inclusion Criteria

- Male and female patients 6-18 years of age
- Patients who have been diagnosed with FASD (either FAS, pFAS, ARND)
- Patients and their parents/guardians who give informed consent/assent to take part in this research study

There was no formal exclusion criteria for participation in the study, apart for the age and FASD diagnosis. This flexible and broad criteria was decided upon to ensure a realistic evaluation of sleep problems in this population. This was a naturalistic study and was representative of how patients would be seen. Excluding co-morbid conditions, such as attention-deficit hyperactivity disorder (ADHD), would not provide a realistic portrayal of this population, since so many individuals have been diagnosed with co-morbidities.

The recruitment of participants for this study was done between February 2010 and March 2011. Thirty-six patients met the inclusion criteria and provided consent to participate in this study.

3.4 General Overview of Study Procedures

The research study consisted of 4 visits to the Youthdale Child and Adolescent Sleep Centre. After potential participants were referred to the sleep centre for the study, they were scheduled to come in for an initial sleep consultation. During the consultation, study participants were given information pertaining to the research study. They were also given a consent form and any questions were answered. After providing written consent, participants were scheduled for one night of overnight polysomnography, one
night for the Dim Light Melatonin Test (DLMO), and lastly, a follow-up visit for study results. A timeline of the study components is illustrated in table 3.1.

<table>
<thead>
<tr>
<th>Table 3.1: Summary of Study Timeline Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="table.png" alt="Table" /></td>
</tr>
</tbody>
</table>

### 3.5 Outcome Measures

The research study had 4 primary outcome measures to determine the presence and patterns of sleep disorders, as well as circadian rhythm disturbances. A summary of these outcome measures has been outlined in table 3.2.

<table>
<thead>
<tr>
<th>Table 3.2: Study Outcome Measures and Method of Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="table.png" alt="Table" /></td>
</tr>
</tbody>
</table>
3.6 Study Measures

3.6.1 Patient Demographics

The sleep consultation notes as well as the patient’s chart from the Youthdale Child and Adolescent Sleep Centre were used to collect demographic information of the patients. This included: gender, age, height, weight, body mass index (BMI), medications, and any other diagnosed co-morbid conditions (physical or mental).

3.6.2 Instruments and Measures

The following is a list and a brief description of the subjective measures (questionnaires) used in this study. Caregivers and their children completed the questionnaires together. The questionnaires were completed A copy of the questionnaires is included in the appendix.

i. Centre for Epidemiological Studies Depression Scale for Children (CES-DC): is a 20-item self-report depression inventory with possible scores ranging from 0 to 60. Higher CES-DC scores indicate increasing levels of depression. The cutoff score of 15 is suggestive of depressive symptoms in children and adolescents (Weissman et al, 1980).

ii. Pediatric Daytime Sleepiness Scale (PDSS): Consisting of 13 questions (with possible ranging scores of 0 to 52, with each item ranging from a score of 0-4 points), the scale is designed as a brief measure for evaluating subjective experiences of daytime sleepiness in young students (Drake et al, 2003). Higher scores on the scale are indicative of more acute daytime sleepiness. Values above 16-17 are considered abnormal.
iii. *Epworth Sleepiness Scale (ESS)*: This scale determines trait sleepiness (Johns 1991). The ESS consists of 8 items and the scores can range from 0 to 24. A score of greater than 8-10 is indicative of high subjective sleepiness.

iv. *Fatigue Severity Scale (FSS)*: This scale determines trait fatigue (Krupp et al, 1989). The FSS consists of 9 items and the score can range from 1 to 7. An average score of greater than 4 is considered to be indicative of high subjective fatigue.

v. *Morning-Eveningness Scale for Children (MESC)*: It is recognized that morning preference increases with adulthood and aging (Carskadon et al, 1993). Teenagers tend to shift their time of day preference toward the evening. This scale was adapted from adults to children and consists of 10 questions. It evaluates the morning vs. evening preferences (Caci et al, 2005, Díaz-Morales et al, 2007). The higher the score, the higher is the morning preference. In that way a score of 10 is definitely "an evening person" and a score of 42 is "a morning person".

### 3.6.3 Objective Sleep Measures

All study participants had one overnight polysomnography (PSG) test. Overnight PSG is recognized as the “gold standard” for sleep measurement (Lacks & Morin 1992). Physiological measures were performed in a standardized manner to assess sleep architecture.

### 3.6.4 Measurements of Overnight Sleep Architecture

PSG allows the continuous collection of physiologic sleep data using a standard montage consisting of an electroencephalogram (EEG), electrooculogram (EOG) and
submental electromyogram (EMG). Standard skin electrodes are attached to the patient’s head to record and electrically document brain EEG (Guilleminault, 1982). The international 10-20 system shown in figure 3.1 was used to record the EEG. EOG is recorded by placing electrodes in specific locations near the eyes, and EMG is recorded by placing electrodes on the chin. Ancillary channels which specifically document respiratory effort, electro-cardiogram, muscle activity in the limbs, oxygen saturation and nasal airflow were also attached.

![Figure 3.1: International 10-20 System used to record EEG.](image)

The following parameters were collected from the clinical overnight PSG sleep study and were recorded for research study purposes (the cutoffs and guidelines are from the American Academy of Sleep Medicine). In children and adolescents the normative values for various sleep architecture parameters vary with different age ranges.
• **Sleep onset latency (SOL):** This is the period from lights off to first epoch of sleep. The following table displays normative limits for SOL in various age groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>SOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7 years</td>
<td>18.4 +/- 9 minutes</td>
</tr>
<tr>
<td>8-9 years</td>
<td>24.6 +/- 15.6 minutes</td>
</tr>
<tr>
<td>10-11 years</td>
<td>19.5 +/- 12.4 minutes</td>
</tr>
<tr>
<td>12-13 years</td>
<td>20.3 +/- 6 minutes</td>
</tr>
<tr>
<td>14-16 years</td>
<td>20.9 +/- 9.7 minutes</td>
</tr>
</tbody>
</table>

• **Total sleep time (TST):** This is the amount of actual sleep time in a sleep period, which is equal to the total of all REM and NREM sleep in a sleep period.

• **REM latency:** This refers to the amount of time from sleep onset to first REM episode.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>REM Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7 years</td>
<td>142.3 +/- 38.7 minutes</td>
</tr>
<tr>
<td>8-9 years</td>
<td>129.5 +/- 31.9 minutes</td>
</tr>
<tr>
<td>10-11 years</td>
<td>132.5 +/- 30.8 minutes</td>
</tr>
<tr>
<td>12-13 years</td>
<td>119.3 +/- 27.9 minutes</td>
</tr>
<tr>
<td>14-16 years</td>
<td>106.1 +/- 34.8 minutes</td>
</tr>
</tbody>
</table>

• **Sleep efficiency (SE):** This is the ratio of the total sleep time to the time spent in bed and is reported as a percentage. Normal sleep efficiency for children ages 6-15 years is 94.4% +/- 3.9%.
• **Arousal index (AI):** This refers to the number of abrupt shifts in EEG during sleep. An AI of less than 9.5/hr is considered normal.

• **Apnea hypopnea index (AHI):** This refers to the number of apnea/hypopnea episodes per hour. In children, an AHI >1 is considered significantly elevated.
  
  o  **REM AHI:** This refers to the number of apnea/hypopnea episodes per hour in REM sleep.
  
  o  **NREM AHI:** This refers to the number of apnea/hypopnea episodes per hour in NREM sleep.

• **Periodic limb movement index (PLMI):** This is the number of limb movements during each hour of sleep. A PLMI of <5/hour is considered normal in children, while value >5 are considered increased.

• **Sleep architecture measures (stages 1, 2, 3, 4 and REM):** the structure of the sleep cycle and wakefulness during sleep: 1, 2, 3, and 4: non-REM sleep- REM: REM sleep.

The following table (3.3) represents normative data (Williams and Hursch, 1974) that is used at the Youthdale Sleep Centre for evaluating overnight polysomnography. The values represent normative percentage cutoffs for each stage of sleep during one night of sleep. These normative values represent normative values for individuals not taking medications. They are organized according to age and gender.
Table 3.3: Normative Sleep Architecture Percentages for Male and Females
(Adapted from EEG of Human Sleep: Clinical Application. R.L. Williams, I. Karacan and C.J Hursch, 1974)

<table>
<thead>
<tr>
<th></th>
<th>Ages 6-9</th>
<th>Ages 10-12</th>
<th>Ages 13-15</th>
<th>Ages 16-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Wake</td>
<td>0.27</td>
<td>1.55</td>
<td>1.10</td>
<td>1.87</td>
</tr>
<tr>
<td></td>
<td>0.70</td>
<td>1.32</td>
<td>1.01</td>
<td>1.28</td>
</tr>
<tr>
<td>% Stage 1</td>
<td>2.30</td>
<td>3.65</td>
<td>4.25</td>
<td>4.02</td>
</tr>
<tr>
<td></td>
<td>2.30</td>
<td>2.28</td>
<td>3.01</td>
<td>3.74</td>
</tr>
<tr>
<td>% Stage 2</td>
<td>47.95</td>
<td>46.16</td>
<td>44.00</td>
<td>49.05</td>
</tr>
<tr>
<td></td>
<td>47.88</td>
<td>49.36</td>
<td>48.66</td>
<td>49.43</td>
</tr>
<tr>
<td>% Stage 3</td>
<td>3.60</td>
<td>5.24</td>
<td>5.53</td>
<td>5.76</td>
</tr>
<tr>
<td></td>
<td>3.13</td>
<td>2.95</td>
<td>5.20</td>
<td>5.65</td>
</tr>
<tr>
<td>% Stage 4</td>
<td>18.55</td>
<td>17.01</td>
<td>18.42</td>
<td>17.28</td>
</tr>
<tr>
<td></td>
<td>16.68</td>
<td>16.66</td>
<td>16.49</td>
<td>17.78</td>
</tr>
<tr>
<td>% REM</td>
<td>27.33</td>
<td>26.39</td>
<td>26.70</td>
<td>22.02</td>
</tr>
<tr>
<td></td>
<td>29.31</td>
<td>27.43</td>
<td>25.63</td>
<td>22.12</td>
</tr>
</tbody>
</table>

3.6.5 Scoring of Polysomnography

The polysomnography was scored by a registered sleep technologist according to standardized scoring techniques (Rechtschaffen & Kales 1968). PSG recordings were scored for every 30 second epoch of sleep. The breathing parameters were scored according to the American Academy of Sleep Medicine (AASM) most recent criteria (2010). Figure 3.2 represents the different stages of sleep as seen in the EEG.
### Figure 3.2: EEG activity in different stages of sleep

Characteristic EEG activity for wakefulness, stage 1, 2, 4 and REM sleep. K-complexes and spindles, characteristics of stage 2 sleep and rapid eye movements, characteristics of REM sleep are shown. (Adapted from *Kryge MH, Roth T, and Dement WC. Principles and Practice of Sleep Medicine (Fourth Edition)*, 2005 Elsevier Inc.)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td><img src="image" alt="Awake EEG" /></td>
</tr>
<tr>
<td>Stage 1</td>
<td><img src="image" alt="Stage 1 EEG" /></td>
</tr>
<tr>
<td>Stage 2</td>
<td><img src="image" alt="Stage 2 EEG" /></td>
</tr>
<tr>
<td>Stage 4</td>
<td><img src="image" alt="Stage 4 EEG" /></td>
</tr>
<tr>
<td>REM</td>
<td><img src="image" alt="REM EEG" /></td>
</tr>
<tr>
<td>EOG</td>
<td><img src="image" alt="EOG" /></td>
</tr>
</tbody>
</table>

#### 3.6.6 Circadian Rhythm Parameters

The Dim Light Melatonin Onset Test was used to assess melatonin levels in study participants (Pandi-Perumal *et al*, 2007). Study participants were seated in a dark room from 19:00 to 02:00h and saliva samples were collected every hour (for a total of 8
samples). Samples from each hour were refrigerated and then sent to the specialty lab at Toronto General Hospital for analysis using direct enzyme-linked immunosorbent assay (ELISA). Directions were followed from the ELISA kit from Buhlman Laboratories (Switzerland). In summary, in a direct ELISA, an unknown amount of antigen is affixed to a surface, and then a specific antibody is applied over the surface so that it can bind to the antigen. This antibody is linked to an enzyme (usually alkaline phosphatase), and in the final step, another enzyme substrate is added in order to be able to observe a detectable signal (Crowther, 1995, Lequin, 2005). The results of the DLMO test were depicted in melatonin phase response curves (PRC).

3.7 Statistical Analysis

In order to investigate the sleep architectural features, as well as the prevalence of sleep and circadian rhythm disorders in this population, the results of the sleep studies, questionnaires, and DLMO test were used for analysis. Frequency analyses were conducted to examine the demographics of the study population, as well as to investigate sleep architecture features and to determine the prevalence of sleep disorders within the population of participants with FASD. Independent t-tests were used to assess for significant differences in sleep architecture between the FASD sample and normative data, with the level significance set at p< 0.05. The normative data is displayed in table 3.3 above. Values from each stage of sleep from overnight polysomnography of each FASD study participant was age and gender matched to this normative data. For example, if there was an 8 year old FASD female, her PSG values were compared to the normative values of an 8 year old “healthy” female control. Correlation analysis was also used to
assess the relationship between sleep architecture parameters and questionnaire variables. These correlations were done to examine the relationships between the objective and subjective measures of sleepiness. In addition, correlations were conducted within objective measures, to assess if any correlations varied from those expected in a healthy, control, population. For example, a high correlation would usually be expected between a child’s BMI, AHI, and neck size. All statistical analyses were performed with IBM SPSS 19 for Windows XP.

3.8 Ethical Considerations

A. Risks and Benefits

The only negative consequence of participating in this study is the time commitment which the patient must invest to complete the study. The direct benefit of participating in the study was the possible identification of a sleep and/or circadian rhythm disorder and treatment options will be offered based on PSG and DLMO results. This may have benefited the patient in understanding and treating the sleeping disorder which in turn may help the underlying FASD.

B. Confidentiality

All data used in this study were collected from patients’ referral form, initial consultation notes, sleep study results, and DLMO results. Each patient was assigned a study code, which ensured that no personal information could be used to identify study patients. All hardcopies of study documents were kept in a locked cabinet in the office of the sleep centre, and all electronic documents were saved on one laptop with a password protected login and encrypted USB key.
Chapter 4  RESULTS
Chapter 4  
RESULTS

4.1. Demographics

For the 36 patients, there were 16 males (44.4%) and 20 females (55.6%). The mean age of the study population was $10.0 \pm 3.2$ years and the frequency distribution of the ages is displayed in figure 4.1, ranging from ages 6-18. The mean BMI was $18.1 \pm 4.1$ kg/m$^2$. The mean neck size was $29.0 \pm 3.8$ cm. The mean height was $138.7 \pm 17.8$ cm.

![Figure 4.1: Frequency distribution of participant ages (n=36).](image)
Over 70% (n=25) of the participants were taking some form of medications for various co-morbid conditions, such as attention-deficit hyperactivity disorder (ADHD) and anxiety disorder. The distribution of the type of medications that the participants were taking is illustrated in Figure 4.2. This data will have to be taken into consideration when considering the results of the polysomnography studies.

Figure 4.2: Distribution of the medications taken by study participants (NDRI = Norepinephrine-dopamine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, other = melatonin or tryptophan)

4.2 FASD Questionnaires

All study participants (and/or their guardians) were interviewed based on a FASD questionnaire (see appendix 5 for complete questionnaire). This provided more information regarding the background health history of the participant, as well as more details regarding the FASD diagnosis. Forty percent of the patients had the diagnosis of
ARND, 12% had the diagnosis of pFAS, and 1 patient (4.8%) had the diagnosis of FAS. Forty-four percent of the patients were diagnosed with the broad classification of FASD, but had not yet been sub-typed, in terms of the specific form of FASD. Some of the original questionnaire questions were eliminated from the final analysis, since the information was unavailable, such as birth APGAR score and exact patterns of alcohol consumption. Table 4.1 displays the responses to various variables from the FASD questionnaires. The complete FASD history of 11 patients was unavailable since the foster/adopted families did not have all of the complete biological and prenatal information from the birth mother.

Table 4.1: FASD Questionnaire Responses (n = 25)

<table>
<thead>
<tr>
<th>Questionnaire Variable</th>
<th>Frequency and Percentages</th>
</tr>
</thead>
</table>
| A. Diagnosis                           | ARND = 10 (40%)  
pFAS = 3 (12%)  
FAS = 1 (4%)  
FASD = 11 (44%)                      |
| B. Origin                              | Caucasian = 14 (68%)  
African American = 3 (12%)  
Aboriginal = 3 (12%)  
Biracial = 2 (8%)  
Other (Caribbean, Greek) = 3 (12%) |
| C. Confirmed Sleep Disorder Prior to Sleep Study? | Yes = 2 (8%)  
No =23 (92%)             |
| D. Confirmed Prenatal Alcohol Exposure? | Yes = 22 (88%)  
No = 3 (12%)                  |
| E. Biological Mother used Drugs during pregnancy? | Yes = 24 (67%)  
No = 0 (0%)  
Unknown = 12 (33%)         |
| F. Co-morbidities                      | None = 6 (24%)  
ADHD = 15 (60%)            |
Anxiety disorder = 1 (4%)  
Other (Oppositional Defiant Disorder (ODD) = 2 (8%)

| G. Congenital Malformations? | Yes = 13 (52%)  
No = 12 (48%) |
|-----------------------------|----------------|
| H. Did the mother receive prenatal care? | Yes = 8 (32%)  
No = 16 (64%) |
| I. Type of Birth | Vaginal = 24 (96%)  
Cesarean Section = 1 (4%)  
Forceps/Vacuum = 0 (0%) |
| J. Were there birth complications? | Yes = 7 (28%)  
No = 18 (72%) |
| K. Mean gestation week at birth (mean +/- SD) | 37.1 +/-1.9 weeks |
| L. Birth size for gestational age (GA) | Normal for GA = 18 (72%)  
Small for GA = 7 (28%)  
Large for GA = 0 (0%) |
| M. Is there a family history of sleep disorders? | Yes = 4 (16%)  
No = 7 (28%)  
Unknown = 14 (56%) |

4.3 Sleep Questionnaires

The average scores of the sleep questionnaires filled out by patients in this study are summarized in table 4.2. Nine out of the total 36 patients did not complete each of the 5 sleep questionnaires because their age was below the age criteria for some of the questionnaires. For example, some patients were 6 years old and the CES-DC is for patients over 8 years old. Due to the special needs of this population, some of the questionnaire questions were not applicable to all patients. For example, many of them are in special education classrooms, and not all of the school-related questions are applicable.
Table 4.2: Sleep Questionnaire Responses (mean ± SD) (n = 27). The last column displays normative cutoffs used to score the sleep questionnaires at the Youthdale Child and Adolescent Sleep Centre. Cutoffs are based on published references. [ESS = Epworth sleepiness scale, FSS = fatigue severity scale, MESC = Morning-Eveningness Scale for Children, PDSS = Pediatric Daytime Sleepiness Scale, CES-DC = Centre for Epidemiological Studies of Depression Scale for Children.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Mean (+/- SD)</th>
<th>Normative Values (+/- SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS</td>
<td>4.9 ± 2.9</td>
<td>Higher scores mean higher level of daytime sleepiness. “Abnormal = 8” (for adults) (Johns et al 1993, 1995)</td>
</tr>
<tr>
<td>FSS</td>
<td>3.8 ±1.5</td>
<td>Above score of 3-4 is considered “abnormal” (for adults) (Krup et al, 1989)</td>
</tr>
<tr>
<td>MESC</td>
<td>28.5 ±6.3</td>
<td>10 = “evening person” 42 = “morning person” (Diaz-Morales et al, 2007; Caci et al 2005)</td>
</tr>
<tr>
<td>PDSS</td>
<td>14.3 ±5.1</td>
<td>Values about 16 are considered abnormal (excessive sleepiness) (Drake et al, 2003)</td>
</tr>
<tr>
<td>CESD-DC</td>
<td>23.3 ±10.3</td>
<td>Cutoff score of 15 = suggestive of depressive symptoms (Weissman et al, 1980)</td>
</tr>
</tbody>
</table>

4.4 Sleep Study Results

a. Sleep Architecture

A standard polysomnography montage including electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), electrocardiography (ECG), and respiratory monitoring (oxygen saturation, nasal airflow, and breathing effort) was used to assess sleep physiology parameters and is considered the “gold standard” for objectively assessing sleep (Lacks and Morin, 1992). A blinded sleep scorer (to the
FASD diagnosis) scored the completed polysomnographs according to standardized criteria. Sleep architecture measures included: sleep onset latency (SOL), sleep efficiency (SE), total sleep time (TST), % of each sleep stage, slow wave sleep (SWS), REM latency, % REM, arousal index, % wake, arousal index (AI), average oxygen saturation, and apnea-hypopnea index (AHI).

The sleep study was analyzed in terms of the sleep architecture and physiological sleep parameters. The sleep architecture for 36 patients having 1 night of polysomnography is displayed in Table 4.3 and the physiological parameters are displayed in Table 4.4. Mean values (±SD) were determined for each parameter for 36 patients for the first night. If there were two nights of polysomnography testing for a participant, the data from the first night was used to ensure the consistency among all participants. These values were then compared to normative values for sleep parameters used by the lab according to the American Academy of Sleep Medicine (AASM, 2010).
Table 4.3: Sleep Architecture Values for One Night of Polysomnography (n = 36). The last column displays normative cutoffs (matched to the age of each study participant) used to score polysomnography studies at the Youthdale Sleep Centre. These criteria are based on guidelines from the American Academy of Sleep Medicine (AASM). [SOL = sleep onset latency, TST = total sleep time, SE = sleep efficiency, REM= rapid eye movement, SWS= slow wave]. [*] represents significant differences (p<0.001)

<table>
<thead>
<tr>
<th>Architectural Measures</th>
<th>FASD Sample (mean +/- SD)</th>
<th>Normative Values (mean +/- SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOL (min)</td>
<td>28.8 +/- 26.9</td>
<td>21.7 +/- 2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(average age matched</td>
</tr>
<tr>
<td></td>
<td></td>
<td>normative mean)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(normative limits appear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>above in the methods)</td>
</tr>
<tr>
<td>TST (min)</td>
<td>503.9 +/- 63.6</td>
<td>Varies with age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(mean range: 420 – 600min)</td>
</tr>
<tr>
<td>SE%</td>
<td>85.8 +/- 7.6</td>
<td>90.5 +/- 6.4</td>
</tr>
<tr>
<td>REM Latency (min)</td>
<td>142.7 +/- 64.1</td>
<td>124.3 ± 15.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(average age matched</td>
</tr>
<tr>
<td></td>
<td></td>
<td>normative mean)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(normative limits appear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>above in the methods)</td>
</tr>
<tr>
<td>Stage 1 %</td>
<td>4.0 +/- 2.0 *</td>
<td>2.6 +/- 0.6</td>
</tr>
<tr>
<td>Stage 2 %</td>
<td>40.4 +/- 10.2 *</td>
<td>47.8 +/- 1.4</td>
</tr>
<tr>
<td>Stage 3%</td>
<td>3.9 +/- 3.1</td>
<td>3.7 +/- 0.9</td>
</tr>
<tr>
<td>Stage 4 %</td>
<td>19.9 +/- 5.3 *</td>
<td>17.3 +/- 0.8</td>
</tr>
<tr>
<td>REM %</td>
<td>20.6 +/- 4.8 *</td>
<td>27.5 +/- 1.4</td>
</tr>
<tr>
<td>% Wake</td>
<td>9.3 +/- 8.1 *</td>
<td>0.8 +/- 0.4</td>
</tr>
</tbody>
</table>

Mean sleep architecture values for the FASD sample were compared to normative data values (table 3.3) matched for age and gender and are displayed in figure 4.3. An independent, two-tailed t-test was done. FASD participants had significantly greater
percentage of stage 1 sleep (4.02 +/- 2.09 vs. 2.6 +/- 0.66, p <0.001) and significantly
greater percentage of stage 4 sleep (19.95 +/- 5.39 vs. 17.36 +/- 0.89, p<0.05) compared
to normative data. FASD participants had a significantly smaller percentage of stage 2
sleep (10.24 +/- 1.71 vs. 1.41 +/- 0.24, p <0.001). There was no significant difference in
the percentage of stage 3 sleep, between the FASD participants and normative data.
FASD participants had a significantly less percentage of REM sleep compared to the
normative data (20.66 +/- 4.85 vs. 27.51, +/- 1.49, p <0.001). In addition, FASD
participants remained awake a significantly greater percent of time when compared to
normative data (9.38 +/- 8.14 vs. 0.86 +/- 0.44, p < 0.001).

<table>
<thead>
<tr>
<th>Sleep Stage Comparison: FASD Sample vs. Normative Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Overnight Sleep (%)</td>
</tr>
<tr>
<td>60 50 40 30 20 10 0</td>
</tr>
<tr>
<td>stage 1  stage 2  stage 3  stage 4  REM  wake</td>
</tr>
<tr>
<td>sample       control</td>
</tr>
<tr>
<td>4.025        2.64</td>
</tr>
<tr>
<td>41.769       47.865</td>
</tr>
<tr>
<td>3.933        3.788</td>
</tr>
<tr>
<td>19.95        17.359</td>
</tr>
<tr>
<td>20.661       27.505</td>
</tr>
<tr>
<td>9.383        0.8639</td>
</tr>
</tbody>
</table>

Figure 4.3: Distribution of sleep architecture percentages for FASD sample and
normative data. All (*) represent statistical significance at p<0.001, except for stage 4,
where p<0.05.
b. Physiological Sleep Measures

The mean AHI value for this patient population was 0.9 ± 1.2. Eleven out of 36 patients (31%) had an AHI >1, which is considered abnormal. The mean arousal index during REM was 9.8 +/- 5.8, and the mean arousal index during non-REM sleep was 12.5 +/- 8.5. Table 4.4 shows the physiological parameter values (means +/- SD) in this population, along with some of the known normative values used in the sleep laboratory.

Table 4.4: Physiological parameter values for one night of polysomnography (n =36). Subjects underwent standard montage polysomnography for one night. Data shown are mean ± SD. The last column displays normative cutoffs used to score polysomnography studies at the Youthdale Sleep Centre (matched to the age of each study participant). These criteria are based on guidelines from the American Academy of Sleep Medicine (AASM). [AHI = apnea-hypopnea index. AI = arousal index, RDI = respiratory disturbance index. OSAT % = oxygen saturation. TLM index = total leg movement. PLM index = periodic leg movement.]

<table>
<thead>
<tr>
<th>Physiological Parameters</th>
<th>FASD Sample (mean +/- SD)</th>
<th>Normative Limits (mean +/-SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>0.9 ±1.2</td>
<td>AHI &gt;1 = significantly elevated</td>
</tr>
<tr>
<td>Awakenings Index</td>
<td>2.7 ± 1.8</td>
<td>AI &lt; 10/hour</td>
</tr>
<tr>
<td>AI (NREM)</td>
<td>12.5 ± 8.5</td>
<td>AI (NREM) &lt; 9.5/hour</td>
</tr>
<tr>
<td>AI (REM)</td>
<td>9.8 ± 5.8</td>
<td>AI (REM) &lt; 9.5/hour</td>
</tr>
<tr>
<td>AI (TST)</td>
<td>11.7 ± 6.6</td>
<td>AI (TST) = &lt;9.5</td>
</tr>
<tr>
<td>RDI (NREM)</td>
<td>1.4 ± 1.3</td>
<td>1.3 ± 1.2</td>
</tr>
<tr>
<td>RDI(REM)</td>
<td>2.2 ± 3.7</td>
<td>1.5 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>Value 1</td>
<td>Value 2</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>RDI (TST)</td>
<td>1.6 ±1.3</td>
<td>1.2 ± 1.0</td>
</tr>
<tr>
<td>OSAT %</td>
<td>97.9 ± 0.6</td>
<td>OSAT % &gt; 92%</td>
</tr>
<tr>
<td>TLM Index</td>
<td>2.8 ±3.1</td>
<td>TLM Index &lt;5/hour</td>
</tr>
<tr>
<td>PLM index</td>
<td>0.9 ± 1.4</td>
<td>PLM Index &lt;5/hour</td>
</tr>
</tbody>
</table>

**4.5 Linear Regression Correlations**

Using regression analysis, BMI was significantly associated with AHI (r = 0.572, p<0.05) (figure 4.4a), AI (during REM) (r = 0.37, p<0.05), and RDI (during REM) (r = 0.46, p<0.05). In addition a large neck size was associated significantly with a higher AHI (r = 0.38, p<0.05) (figure 4.4b). In this population, sleep onset latency was negatively associated with stage 2 sleep (r = -0.43, p<0.05) and was positively correlated with total leg movements (TLM) (r = 0.345, p<0.05). Sleep efficiency was positively associated with total sleep time (r = 0.489, p<0.05), stage 2 sleep (r = 0.66, p<0.05) and REM sleep (r = 0.44, p<0.05).
Figure 4.4a, b: Association between neck size and Body Mass Index and AHI. There was a positive association between neck size and BMI ($r = 0.65$, $p<0.05$) and a positive correlation between neck size and AHI ($r = 0.38$, $p<0.05$). BMI= Body mass index, AHI= apnea-hypopnea index

Investigating the effect of age on sleep in this population showed that age was found to be positively associated with BMI ($r = 0.549$, $p<0.05$), and with AHI ($r = 0.445$, $p<0.05$) (figure 4.7), while is was negatively correlated with total sleep time ($r = -0.557$, $p<0.05$) (figure 4.5) percent of stage 4 sleep ($r = -0.507$, $p<0.05$) (figure 4.6), and CAI (-0.371, $p<0.05$).
Figure 4.5: Association between age and total sleep time. There was a negative association between age and total sleep time (r = -0.557, p<0.05).

Figure 4.6: Association between age and stage 4 sleep. There was a negative association between age and stage 4 sleep (r = -0.507, p<0.05).
Figure 4.7: Association between age and AHI. There was a positive association between age and stage 4 sleep ($r = 0.445$, $p<0.05$).

The association between the sleep questionnaires and objective sleep measures was also examined. There were no significant correlations found between any of the subjective sleep measures and the sleep architecture measures nor the physiological parameters.

4.6 Dim Light Melatonin Onset (DLMO) Test

The DLMO test was administered to study participants after they had completed at least one night of PSG. The test took place between the hours of 19:00 and 02:00 (or 20:00-03:00). All efforts were made to ensure 8 samples of saliva were collected to ensure for 8 measures of salivary melatonin throughout the night. In a few cases, the conditions of the test were too difficult for young children and fewer than 8 samples were collected, since it was too difficult for children to remain awake so late. Nonetheless, phase-response curves (PRC) were still generated. The phase response curves (PRC) for
24 participants are displayed in figure 2. Twelve of the 36 study patients were unable to commit to completing the DLMO test, since it required them to return to the sleep lab for a second night. For other children, particularly the ones aged 6-8 years, it was very difficult to remain awake under experimental conditions to complete the DLMO test.

**Four Main Categories of Melatonin Phase-Response Curves**

A. Normal (n=5) (21%)

B. Delayed Sleep Phase Syndrome (DSPS) (n=4) (17%)

C. Advanced Sleep Phase Syndrome (ASPA) (n=2) (8%)

D. Other Melatonin Abnormality (n=13) (54%)
Figure 4.8: Dim Light Melatonin Onset (DLMO) Analysis – Phase-Response Curves (n = 24). Saliva samples were collected hourly from 19:00 to 02:00 hours (or 20:00-03:00) and batch processed by Enzyme Linked Immunoassay Assay (ELISA) at the University Health Network - Specialty Laboratory.
<table>
<thead>
<tr>
<th>I.D.</th>
<th>Normal/Abnormal</th>
<th>Description</th>
<th>Medications Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Abnormal curve</td>
<td>Slight DSPS</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Abnormal</td>
<td>DSPS</td>
<td>Antipsychotic/NDRI</td>
</tr>
<tr>
<td>C</td>
<td>Abnormal curve</td>
<td>2nd rise of melatonin</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>Abnormal curve</td>
<td>2nd rise of melatonin</td>
<td>None</td>
</tr>
<tr>
<td>E</td>
<td>Normal curve</td>
<td>Normal curve</td>
<td>NDRI</td>
</tr>
<tr>
<td>F</td>
<td>Normal curve</td>
<td>Normal curve</td>
<td>None</td>
</tr>
<tr>
<td>G</td>
<td>Abnormal curve</td>
<td>High baseline, 2nd rise</td>
<td>NDRI</td>
</tr>
<tr>
<td>H</td>
<td>Abnormal curve</td>
<td>ASPS</td>
<td>Antipsychotic/NDRI</td>
</tr>
<tr>
<td>I</td>
<td>Abnormal curve</td>
<td>Constant melatonin secretion</td>
<td>NDRI</td>
</tr>
<tr>
<td>J</td>
<td>Normal curve</td>
<td>Normal curve</td>
<td>None</td>
</tr>
<tr>
<td>K</td>
<td>Normal curve</td>
<td>Normal curve</td>
<td>SSRI</td>
</tr>
<tr>
<td>L</td>
<td>Abnormal curve</td>
<td>2nd rise</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>M</td>
<td>Abnormal curve</td>
<td>ASPS</td>
<td>SSRI</td>
</tr>
<tr>
<td>N</td>
<td>Abnormal curve</td>
<td>Late rise of melatonin</td>
<td>Antipsychotic/NDRI</td>
</tr>
<tr>
<td>O</td>
<td>Abnormal curve</td>
<td>High baseline, late rise</td>
<td>NDRI</td>
</tr>
<tr>
<td>P</td>
<td>Abnormal curve</td>
<td>High baseline, late rise</td>
<td>NDRI</td>
</tr>
<tr>
<td>Q</td>
<td>Abnormal curve</td>
<td>Early decline</td>
<td>NDRI</td>
</tr>
<tr>
<td>R</td>
<td>Abnormal curve</td>
<td>DSPS</td>
<td>None</td>
</tr>
<tr>
<td>S</td>
<td>Abnormal curve</td>
<td>Early decline</td>
<td>SSRI</td>
</tr>
<tr>
<td>T</td>
<td>Abnormal curve</td>
<td>DSPS</td>
<td>None</td>
</tr>
<tr>
<td>U</td>
<td>Abnormal</td>
<td>Low baseline</td>
<td>Antipsychotic/NDRI</td>
</tr>
<tr>
<td>V</td>
<td>Normal</td>
<td>Normal curve</td>
<td>None</td>
</tr>
<tr>
<td>W</td>
<td>Abnormal</td>
<td>High baseline</td>
<td>None</td>
</tr>
<tr>
<td>X</td>
<td>Abnormal</td>
<td>Slow rise</td>
<td>None</td>
</tr>
</tbody>
</table>
4.7 Prevalence of Sleep Disorders in Study Population

After the completion of the polysomnography and DLMO test, participants met with the sleep consultant to receive their results. Impressions and diagnoses were recorded in patient charts. The prevalence of sleep disorders in this population was then analyzed. Of the 36 FASD participants, 78% (n = 28) has at least one identifiable sleep disorder. Eight percent (n=3) of the sample did not have a conclusive diagnosis and were to undergo further testing. Figure 5.0 displays of the distribution of the various sleep disorders in this population. In constructing figure 5.0, a hierarchical system of diagnosis was applied to assign a single, primary diagnosis of highest priority. In this system, if a patient had more than one diagnosis, only the primary diagnosis was counted. For example, if a patient was diagnosed with OSA and REM parasomnia, he/she was counted in the group that had OSA. Of the 28 patients identified as having a sleep
disorder, 19% (n= 7) were diagnosed with more than one sleep disorder. The distribution of combined primary and co-morbid sleep disorders is displayed in figure 5.1.

![Figure 5.0: Prevalence of primary sleep disorders in FASD sample (n=36).](image)

![Figure 5.1: Prevalence of primary and co-morbid sleep disorders in FASD sample (n=36).](image)
The prevalence of the various primary sleep disorders in this population was compared to the prevalence of these disorders in the general pediatric and adolescent population. This information is displayed in table 4.6.

**Table 4.6: Prevalence of sleep disorders in the FASD study population versus the general pediatric and adolescent population**

<table>
<thead>
<tr>
<th>Sleep Disorder</th>
<th>Prevalence in FASD study Population</th>
<th>Prevalence in General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insomnia</strong></td>
<td>11%</td>
<td>9-13% (Owens, 2008; Pollock, 1994; Morrison et al, 1992).</td>
</tr>
<tr>
<td><strong>Sleep Related Breathing Disorder (OSA)</strong></td>
<td>12%</td>
<td>1%-4% overall, with a reported range of 0.1%-13% (Owens, 2009)</td>
</tr>
<tr>
<td><strong>Restless Legs Syndrome (RLS)</strong></td>
<td>0%</td>
<td>1%-6% (Picchietti and Stevens, 2007)</td>
</tr>
<tr>
<td><strong>Delayed Sleep Phase Syndrome</strong></td>
<td>17%</td>
<td>7%-16% of adolescents (American Academy of Sleep Medicine 2005, Bjorvatn and Pallesen, 2009). 0.25% - 0.48% (Schrader et al, 1993; Hazama et al, 2008).</td>
</tr>
<tr>
<td><strong>Parasomnias (REM and NREM)</strong></td>
<td>27%</td>
<td>1-6% (Wills et al, 2002), 14% (Agargun et al, 2004)</td>
</tr>
<tr>
<td><strong>Sleep Fragmentation</strong></td>
<td>19%</td>
<td>18% (Sadeh et al, 2000)</td>
</tr>
</tbody>
</table>
4.8 Effect of Antidepressant Medications on Sleep

The results of prevalence of sleep disorders were further analyzed to assess for any differences based on the effects of medications, since 55% of the patients were taking some form of antidepressants (NDRI and/or SSRI). Comparison between the patients that were taking antidepressants and those that were not taking antidepressants showed some differences between the two groups and these are illustrated in figure 5.2, however these differences were not statistically significant and are displayed to highlight the varying prevalences.

![Prevalence of Sleep Disorders in Patients Taking Antidepressants vs. Patients Not Taking Antidepressants](image)

**Figure 5.2: Prevalence of sleep disorders in patients on antidepressants vs. patients not on antidepressants**

4.9 Effect of Gender on Sleep Measures

The results of the study were also analyzed to investigate any gender differences. The study included 16 males (44.4%) and 20 females (55.6%). There were no significant differences in the sleep architecture and physiological measures recorded during
polysomnography, between males and females. Although BMI did not differ significantly, the males had on average had a significantly larger neck size (30.7 ± 4.1 vs. 27.5 ± 2.8, p< 0.05). There were differences between males and females in the prevalence of various sleep disorders, which are displayed in figure 5.3, however, these differences were not statistically significant and are displayed to highlight the varying prevalences.

Figure 5.3: Comparison of the distribution of sleep disorders in males and females
Chapter 5 DISCUSSION
Chapter 5 DISCUSSION

5.1 Overview of Main Findings and Interpretation

The main objectives of this thesis were to investigate the patterns of sleep disorders and circadian rhythm disruptions in children and adolescents with FASD. The findings of this study showed that a significant proportion of FASD patients have sleep disorders and their sleep architecture is disturbed. The results further showed a remarkably high abnormality in the melatonin secretion curves in FASD patients, coinciding with a high prevalence of circadian rhythm disturbances.

5.2 Patient Demographics

All of the patients in this study were diagnosed with one of the disorders on the fetal alcohol spectrum. The majority of patients in this study were diagnosed with ARND, while a large percentage affiliated with the broad diagnosis of FASD, as they were currently awaiting final results regarding where they fit best on the FASD spectrum. The distribution of FASD diagnoses in this population was 40% ARND, 12% pFAS, 4.8% FAS, and the remaining 44% identified with the broad spectrum of FASD. This distribution is comparable to the distribution of diagnoses in the current largest sample of FASD patients recorded from the Washington State Fetal Alcohol Syndrome Diagnostic and Prevention Network (WS FAS DP), which is the longest standing FASD diagnostic program (Astley, 2010). In that study population, the diagnoses were 52% ARND, 7% pFAS, 4% FAS, and the remaining 37% was comprised of an inconclusive exact FASD.
diagnosis (Astley, 2010). This diagnosis distribution is comparable to the patients in this thesis, with ARND being far more prevalent than FAS and pFAS. This suggests that the thesis study population is a good representation of the general diagnoses distribution in the general FASD population. The vast majority of the study population (85%) was under 16 years of age, with a mean age of 10.0 +/- 3.2 years, which is comparable to the average age of 9.9 +/- 6.3 years in the WS FAS study (Astley, 2010). On average, patients in this sample were either underweight or an average weight (with a mean BMI of 18.1 +/- 4.1 kg/m², compared to an average BMI for the same mean age of 19 kg/m²), which is also consistent with previous research showing that children with FASD suffer from growth deficiencies, specifically weighing at or below the 10th percentile (1.5 standard deviations below the mean) for their age group (Sampson et al, 1994; Chudley et al, 2005, CDC 2011). In this thesis, there were more females than males (55.6% vs. 44.4%), while in the WS FAS study, males were more prevalent.

5.3 FASD and Pre-Natal History

In this study population, the distribution of races was as follows: 68% Caucasian, 12% African American, 12% Aboriginal, 8% Biracial, and 12% associated with “other” (such as Caribbean or Greek). By comparison, in the Washington State FASD study, the profile of 1,400 patients with FASD, Caucasians also comprised the largest proportion of FASD patients (48.9%), followed by African Americans (6.6%) and Aborignals (8.2%), while the remaining patients associated with Asian, Caribbean, or mixed races. Other research shows a much higher prevalence of FASD in Aboriginal communities, compared to non-Aboriginal communities, with prevalence rates recorded as high 19-46 FASD
cases per 100 live births (Asante et al, 1985; Robinson et al, 1987, Square 1997). The population in this sample had a lower representation of Aboriginal patients, which may be the result of the clinical populations of the FASD clinics from which patients were referred from.

In this study population, there was a high prevalence (72%) of co-morbid conditions, with 60% of the patients having a diagnosis of attention deficit hyperactivity disorder (ADHD). Numerous studies have reported significant attention problems among children and adolescents with FASD with a high overlap ranging between 60%-90%, however conclusive national figures do not currently exist (Nanson et al 1990; Coles et al, 2002; Mattson et al, 2006, Peadon and Elliott, 2010). It is thought that the attention impairments in FASD may share a common physiological etiology with ADHD, such as the effects of alcohol on the developing dopaminergic neurotransmitter system (O’Malley and Nanson, 2002). Accordingly, the high co-morbidity of ADHD and other neurocognitive disorders results in a high percentage of the population taking some type of medication, which is consistent with over 70% of the study population taking some type of medication (NDRI, SSRI, etc). Sleep disturbances also appear to be very common complaint in children and adolescents with ADHD, with some questionnaire studies finding 50-60% of ADHD patients having sleep complaints (Corkum et al, 1998; Owens et al, 2000). Objective findings show that children with ADHD have reduced REM sleep and a longer REM sleep latency (O’Brien et al, 2003; Gruber et al, 2009) compared to controls, suggesting that these polysomnographic features are ADHD-specific and may be a direct cause of neurochemical and structural abnormities associated with ADHD.
A report from our laboratory has shown that some sleep disorders, such as OSA and RLS, present with ADHD-like symptoms (Goll and Shapiro, 2006), yet with treatment (such as adenoidectomy or tonsillectomy), these symptoms are greatly alleviated (Chervin et al., 2002). The observation has been made that up to 20% of the fetal alcohol spectrum disorder population have seizure disorders and up to 12% have epilepsy. However, this study was not focused on detecting this co-morbidity, and furthermore, none of this sample were on anti-epileptic drugs (Hwang, 2011).

5.4 Alcohol and Other Drug Use during Pregnancy

Sixty-seven percent of the patients in this study had guardians who reported that the biological mother used illegal drugs in addition to alcohol consumption, during the pregnancy. This high percentage makes it challenging to separate out the effects of individual and/or combination of substances. Furthermore, many adoptive and/or foster families are not able to acquire complete and accurate information regarding the exact patterns of alcohol and the consumption of other illegal drugs such as marijuana and cocaine. Leonardson and Loudenburg (2003) found that 60% of women who reported drinking during pregnancy used other drugs as well. In this study, the most common drugs of abuse used by women during pregnancy included marijuana, and cocaine. In a 2008 study, Sharpe and Velasquez administered a survey to over 2000 women aged 18-44 in various low income settings in the United States. Findings showed that 75% of women reported using more than one illicit drug, and 50% of these women were more likely to report frequent drinking, drinking during pregnancy, and not using contraception.
compared to nonusers. These findings suggest that women who report using illicit drugs are at a higher risk for consuming alcohol during pregnancy. FASD continues to be most prevalent in Aboriginal communities, in which illicit drug use is also widespread (Robinson *et al*., 1987; Ahmad *et al*., 2007). This further raises the challenge of co-addiction as it remains unclear as to which substance, or a combination of which substances, may be responsible for the variety and severity of neurocognitive disruptions, as well as the sleep disturbances experienced by children with FASD. In one study, researchers surveyed sleep problems in children with prenatal substance exposure, and found that of 5 substances (cocaine, opiates, marijuana, alcohol, and nicotine) nicotine was the only unique predictor of sleep problems (Stone *et al*., 2010). This study, however, relied only on maternal self-reports, rather than formal sleep studies. Nonetheless, these findings suggest that an overlap of substances, apart from alcohol, may contribute to sleep disturbances in FASD children.

### 5.5 Responses to Self-Reported Sleep Questionnaires

The patients in this study reported high measures of depression on the CESD-DC scale (mean score of 23.3, cut-off score is 15), as well as high scores on the MESC, suggesting that more FASD patients are “morning-types”. Patients also scored higher than average on measures of fatigue, but not sleepiness. The reported high levels of depression are consistent with the findings of previous studies in both animal and human populations, showing high levels of depressive symptoms among FASD offspring (Hellemans *et al*., 2010a, b). However, these findings may be the result of co-morbid conditions such as anxiety and/or depression. These high scores on measures of fatigue
are consistent with findings from parental reports of the sleep patterns of FASD children, in which daytime fatigue was reported (Stade et al, 2008). There was a strong negative association between the Pediatric Daytime Sleepiness Scale (PDSS) and the Morning-Evening Scale for Children (MES-C). This may suggest that although the majority of patients were “morning types”, as per the MES-C, a large proportion also reported daytime sleepiness. However, no significant correlations were found between the objective and subjective measures of sleep. In other populations, the relationship between these measures is generally moderate to high (Akerstedt and Gillberg, 1990; Short et al, 2010) though in some studies, subjective questionnaires such as the Epworth Sleepiness Scale appear to be better tools than objective measures in assessing sleepiness (Sangal et al, 1999). This may suggest that in the FASD population, perhaps objective measures are required to identify any underlying sleep disturbances, since subjective measures do not seem to provide a complete picture.

5.6 Sleep Architecture

Compared to normative data, FASD patients had significantly greater percentage of stage 1 and stage 4 sleep, and significantly less stage 2 and REM sleep. In addition, FASD patients were awake significantly longer than normative data figures. In one study which using EEG, videography, and actigraphy to examine the sleep patterns of children with FASD, Troese and colleagues (2007) found that infants who had high prenatal exposure to alcohol, showed increased sleep fragmentation and decreased REM sleep. Their findings are supported by the new data that is presented in this thesis. However the age of the population is older in this thesis. Although not statistically significant, the
REM latency of the FASD sample was slightly delayed, suggesting on average, a slight delay in the circadian rhythm. However, this observation does not be apply to each participant and there is marked variability to the REM onset latency.

Using actigraphy and self report sleep questionnaires, Pesonen and colleagues (2009) also showed that prenatal alcohol exposure significantly increased the odds for having a shorter sleep duration and lower sleep efficiency. In this study, prenatal tobacco exposure did not have any effects on children’s sleep disturbances, unlike the reported findings by Stone et al (2010).

Currently there appears to be only a single sleep survey, associated with our laboratory, that examined children with FASD for sleep onset delay, sleep duration, and other sleep disturbances (Stade et al, 2008). In this study, 100 caregivers of children aged 5-8 years were surveyed about their children’s sleep difficulties. In a 7 day diary, 82% of caregivers reported sleep problems such as night terrors, sleep walking, waking more than twice a night, and day time fatigue. These findings support the notion that FASD children and their caregivers have frequent and constant sleep complaints. Furthermore, the specific sleep complaints reported in this study are consistent with the objective findings from the overnight polysomnography and sleep questionnaires. Caregivers reported an average sleep duration of 7.4 hours and a sleep onset latency of 59 minutes. These self-reported measures were also consistent with the findings of this study, with a delayed sleep onset and a slightly decreased total sleep time. Along with the previously noted studies, the results of this thesis support disturbed sleep in FASD children, specifically sleep fragmentation and decreased sleep duration.
5.7 Sleep Physiology

Very few studies have described normative polysomnography values in pediatric and adolescent populations, making it challenging to compare various populations to normative values. A recent study by Shimrit and colleagues (2004) set forth recommended limits for normal respiratory values in polysomnography. The mean AHI in the FASD population was slightly above recommended limit of 1 (0.91 +/- 1.21), though there was large variability. Eleven patients (33%) had an AHI of >1. Similarly, there was large variability in the central apnea index (CAI) values (0.71 +/- 0.89). Mean oxygen saturation was normal with value of 97% +/- 0.6%, with all patients have an oxygen saturation of over 96%. The respiratory values obtained in this population reflect the percentage of patients who have been diagnosed with mild to moderate obstructive sleep apnea (OSA). Correlation analysis showed a slight, significant correlation between neck size and AHI ($r = 0.38$, $p<0.05$), whereas in the general population, this correlation would be expected to be stronger, suggesting perhaps there is some variability in the FASD population in this domain. The high prevalence of OSA in the FASD sample suggests perhaps there is some underlying mechanism, or possible anatomical alteration, that is causing these children to experience sleep disordered breathing.

5.8 Circadian Rhythm and Melatonin Abnormalities

In this thesis, a large proportion (79%) of patients had abnormal melatonin secretion patterns, as measured by hourly saliva samples in the DLMO test. Furthermore, a subgroup has a specific circadian rhythm disruption, such as delayed sleep phase syndrome (DSPS) or advanced sleep phase syndrome (ASPS). Although no studies have
been conducted specifically investigating melatonin abnormalities in children diagnosed with FASD, a few studies have shown that a large proportion of children with neurodevelopmental disabilities (NDD) are at an increased risk of having a sleep disorder specifically DSPS and difficulties with sleep maintenance (Wasdell et al, 2008; Turk et al, 2007). The sleep disturbances of children with FASD are similar to the sleep disturbances of children with other types of bilateral brain damage and severe cognitive loss (Wasdell et al, 2008). Studies have shown that children with acute or chronic brain damage frequently have low endogenous nocturnal melatonin secretion, which may be non-specific effects of brain damage. (Tordjman et al, 2005). However no previous studies have specifically examined melatonin secretion in the FASD population.

There are virtually no studies assessing normative patterns of melatonin secretion in populations of healthy children. Touiou and colleagues (2009) studied the melatonin profiles of nine healthy prepubertal boys and found that the peak of melatonin was 03:00 am, which is consistent with the current understanding of melatonin secretion patterns in adults, as noted earlier in this thesis. Normative values for pediatric age groups do not exist, thus posing a challenge to analyze specific melatonin curves. However, the current understanding amongst clinicians and researchers is that in children melatonin begins to increase slowly increase around 1-2 hours before bedtime reaches a peak at around 03:00am, after which it quickly declines. This framework was used when analyzing the DLMO phase-response curves of the FADS participants in Youthdale Child and Adolescent Sleep Centre.

A descriptive analysis was also conducted to assess the relationship between REM latency (the time taken to enter REM sleep in each of the 4 melatonin subgroups
listed above. Four out of the 13 participants who had abnormal melatonin profiles, had a
REM latency that was more than 1 standard deviation outside the mean for that specific
group, which was categorized as abnormal. Interestingly, in the DSPS and ASPS groups,
each of the participants had an abnormal REM latency. Conversely, in the “normal”
melatonin subtype groups, only one out of the five participants had an abnormal REM
latency. Although this was not a primary study objective, it provides further evidence to
the altered patterns of melatonin secretion.

In children with NDD, a variety of randomized control trials have shown that
melatonin therapy greatly improved sleep (Dodge *et al*, 2001; Coppola *et al*, 2004). In
another randomized control trial, Wasdell and colleagues (2008) showed that melatonin
therapy increased children’s total sleep time by 30 minutes, as well as decreasing the
sleep onset latency. The FASD children in this thesis, who were diagnosed with DSPS,
have been responding well to melatonin trials as well.

5.9 Prevalence of Sleep Disorders

The results of the current study show that certain sleep disorders and circadian
rhythm disturbances are more prevalent in the FASD population than in normative
studies, based on the sample used in this study. The prevalence of fragmented sleep,
insomnia, parasomnias, OSA, and delayed sleep phase syndrome appear to be higher in
the FASD population. Restless legs syndrome appears less in this population than in the
general pediatric population. In the general population, studies have described the
average prevalence of sleep disorders to be approximately 20-30% (Mindell, 1993; Rona
*et al*, 1998; Owens *et al*, 2000). This study describes a much higher prevalence of sleep
disturbances (as well as circadian rhythm abnormalities) with about 78% having at least
one identifiable sleep problem. This figure is consistent with previous literature in children with neurodevelopmental disabilities suggesting prevalence rates of sleep disturbances to be approximately 75-80% (Jan et al, 2010a).

In spite of the high prevalence rate, it is important to consider that a large proportion of this FASD population is also diagnosed with a co-morbid condition, such as ADHD. This may be a confounding factor in understanding the sleep patterns of children with FASD. Studies have shown that up to 94% of FASD children are diagnosed with ADHD as well, suggesting that these two conditions are often overlapping (Peadon and Elliott, 2010). In independent studies of children with FASD, parents of children with attention deficit hyperactivity disorder (ADHD) reported sleep onset problems 16.5% of the time and night-time awakenings 39% of the time, on par with the prevalence figures found in this thesis (Salzarulo and Chevalier, 1983). However, another study suggests that parental sleep reports did not provide an accurate picture of objective sleep problems (Wiggs et al, 2005).

6.0 Gender Differences

Investigating the effect of gender on the prevalence of sleep disorders revealed some differences. Firstly, sleep disorders were slightly more prevalent in females (90%), than in males (80%). Secondly, in males, sleep fragmentation (31%) was the most common sleep disturbances, whereas parasomnias were the most prevalent sleep disorder (25%) in females. OSA was more prevalent in the males (19%) than in females (5%). These findings are consistent with the existing literature showing that the OSA is more in common in boys (especially after puberty) (Marcus, 2001). Insomnia was also more
prevalent in females (25%) than in males (6%), consistent with previous findings that insomnia has an increased prevalence in girls post-puberty, consistent with adults (Mindell and Owens, 2010).

6.1 Medications

Over 70% of the patients in this study were taking some form of medications. The most common medications that were taken were selective serotonin reuptake inhibitors (SSRIs) and norepinephrine-dopamine reuptake inhibitors (NDRI). It is possible that these medications may be affecting sleep in these children, and also contributing to sleep disturbances. All SSRIs can potentially alter sleep architecture and decrease sleep efficiency, and may manifest as nighttime insomnia and/or daytime sleepiness (Leonard et al., 1997). However, the sleep disturbances may be in part due to the preexisting psychiatric and/or psychological issue, rather than the medication directly. Fluoxetine, the most extensively studied SSRI, has been reported to decrease total sleep time and duration of REM sleep and to increase and stage 1 sleep, as well as the percent of being awake during the night. (Nicholson and Pascoe, 1988). Similar findings have been reported for Paroxetine (Saletu et al., 1991) and Sertraline (Winokur et al., 1991). Patients who were taking medications, continued to take medications in the weeks preceding the DLMO test, as well as the day of the DLMO test. There are no formal guidelines regarding taking medications during the DLMO test. However, there is evidence that antidepressants may increase melatonin secretion (Pandi-Perumal et al., 2009), while beta-adrenergic blockers may decrease melatonin secretion (Stoschitzky et al., 1999).
As this study was somewhat explorative, the results of the DLMO test may be influenced by the range of medications that these children take. However, as a clinical aspect, it was impractical to request that medications be stopped prior to the DLMO test, as a couple of patients experienced extreme behavioural difficulties when not taking medications. Leading experts in the field of FASD and melatonin suggested that the focus must be the patient’s needs, rather than the specifics of the test (Jan, 2011; Pandi-Perumal, 2011).

6.2 Mechanisms That May Underlie Sleep Abnormalities

The exact mechanisms that may underlie the sleep abnormalities in children with FASD are not fully understood. This is a very new and relatively unexplored research area. Therefore, a variety of studies and sources were examined to propose possible mechanisms. One potential mechanism underlying the sleep disturbances in FASD is the altered function of the hypothalamic-pituitary-adrenocortical (HPA) axis. As noted above, the developing HPA axis is affected by prenatal exposure to alcohol in various ways (Weinberg et al, 2008). Since the SCN is located in the ventral hypothalamus and is responsible for the regulation of circadian rhythms, the altered functioning of the HPA axis, and in turn the SCN may function as a potential mechanism underlying sleep dis-regulation (Weinberg et al, 2008). In general, prenatal exposure to alcohol has been linked to higher basal and post stress cortisol concentrations in FASD children (Jacobson et al, 1999), as well as in rodent studies (Weinberg, 1993). The initiation of sleep is concurrent with low HPA axis activation (Weitzman et al 1983; Born et al, 1988) while the fragmentation of sleep and nocturnal awakenings is associated with activation of the
HPA axis (Follenius et al., 1992). Thus, the high occurrence of sleep fragmentation and insomnia in this sample of children may be associated with the characteristic overly-active HPA-axis in individuals with FASD. The dysfunction of the HPA-axis may also play a causative role in sleep disorders, such as insomnia (Buckley and Schatzberg, 2005). Chronic insomnia, without depression, is associated with elevated cortisol levels, especially in the first part of the night, causing difficulties in initiating sleep (Vgontzas et al., 2001; Rodenbeck et al., 2002).

In many severe neurodevelopmental disabilities, excitatory activities may disturb the sleep/wake promoting centers of the hypothalamus and reduce the production and/or secretion of melatonin during the night, resulting in difficulties falling asleep, frequent arousals, and early morning awakenings (Jan et al., 2007). The causes of sleep difficulties in children with FASD are often multi-factorial and may be secondary to other health problems, emotional, and social issues. Nonetheless, improper or disturbed sleep may in turn exacerbate existing difficulties. As extensive literature has shown, children with sleep disorders suffer from behavioural manifestations such as hyperactivity, inattentiveness, impulsivity, depression, and other mood disorders (Archbold et al., 2002; Nash et al., 2008).

6.3 Strengths and Limitations

This thesis is the first known study to use polysomnography, combined with salivary melatonin measures and sleep questionnaires to investigate the patterns of sleep and circadian rhythms disturbances in the FASD population. Despite the comprehensive methodology, the study does contain some limitations. Firstly, there are missing data, as not all of the study patients could commit entirely to all aspects of the study. The special
needs of FASD children made data collection more challenging, especially in obtaining all previous history, which is often unavailable from birth parents. Furthermore, many study patients were unable to commit to completing the DLMO test, since it required them to return to the sleep lab for a second night. For other children, particularly those aged 6-8 years, it was very difficult to remain awake under experimental conditions to complete the DLMO test. A current study in our lab is investigating whether or not sleeping between saliva collections has an effect on the phase response curve of melatonin.

Secondly, an additional limitation in this thesis is that there was not an exact control population. The values that were used to compare sleep architecture and sleep questionnaires were taken from normative data that is used in the laboratory to score polysomnography. Future studies should incorporate gender and age-matched controls to further confirm study findings.

Thirdly, this study did not use actigraphy watches to monitor the sleep-wake cycles of study patients. Actigraphy would have provided a more long term picture of circadian rhythms, especially in DSPS and ASPS patients. However, wearing the watches may have been too cumbersome for this study population, since they are already sensitive to many things. Furthermore, the technology remains very costly and would be a large responsibility for these children.

Lastly, many mothers consumed illegal drugs during their pregnancies, along with alcohol consumption, thus it is not certain if the increased prevalence of sleep and circadian rhythm disruptions are associated solely with alcohol consumption, drug use, or a combination of both. It is challenging to tease apart these factors, as many biological
mothers do not accurately provide nor recall the exact patterns of alcohol and/or drug consumption.

6.4 Clinical Implications and Future Studies

The high prevalence of sleep disturbances and melatonin abnormalities in this population provides evidence for the need for formal sleep and melatonin assessments in FASD children and adolescents. Screening for sleep problems is necessary in the FASD diagnosis process. Having a clearer understanding of sleep may assist clinicians in their diagnosis, as well as decisions for medications. In conjunction with this thesis, one FASD clinic in the Ontario region is already implementing sleep screening, as part of their routine FASD assessments. Future studies should assess whether sleep interventions provide improvements in the neurocognitive and behavioural functioning in the FASD population. Ideally, these studies should incorporate at least 2 nights of overnight polysomnography, to negate any first night effects from sleeping in a new environment (Ahmadi et al, 2009). While we anticipate that sleep disorders such as OSA would still be found on a second night of PSG, it is uncertain if the prevalence of parasomnias and/or insomnia will be as prevalent, as the environment is more familiar. Nonetheless, we anticipate the prevalence of sleep disturbances to remain high, based on the previously discussed alterations to the various sleep control centers in the brain. Future studies in our laboratory may incorporate actigraphy to capture a more long term picture of sleep-wake patterns.

In assessing the melatonin phase response curves, there were no published studies showing normative melatonin secretion values for children and adolescents. Future studies should define normative values for melatonin secretion in children and
adolescents. These values would be very useful to obtain a better understanding of melatonin abnormalities, not only in the FASD population, but in other populations with neurodevelopmental disorders. Additionally, future studies may strive to evaluate melatonin prior to the start of a medication regimen and then compare melatonin secretion while the patient is taking the medication, to assess for any differences; as well as incorporating age and gender matched controls.

Based on the findings of this study, a few recommendations can be provided for improving the sleep of FASD children. In a landmark review, Jan and colleagues provided an excellent review of sleep health issues for children with FASD (2010a). They recommended a variety of sleep promotion techniques may help with sleep complaints. For example, they suggest establishing a comfortable sleep environment that is familiar, secure, and quiet. Preparation for sleep is also highly encouraged with calming behaviours, as well as a consistent bedtime routine. If necessary, melatonin replacement therapy may be encouraged, but only when for melatonin disturbances are formally diagnosed.
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APPENDICES

1. Normative Sleep Percentages

Normative Sleep Architecture Percentages for Male and Females
(Adapted from EEG of Human Sleep: Clinical Application. R.L. Williams, I. Karacan and C.J Hursch, 1974)

<table>
<thead>
<tr>
<th>Age</th>
<th>% Wake</th>
<th>% Stage 1</th>
<th>% Stage 2</th>
<th>% Stage 3</th>
<th>% Stage 4</th>
<th>% REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 6-9</td>
<td>0.27</td>
<td>2.30</td>
<td>47.95</td>
<td>3.60</td>
<td>18.55</td>
<td>27.33</td>
</tr>
<tr>
<td>Ages 10-12</td>
<td>1.55</td>
<td>3.65</td>
<td>46.16</td>
<td>5.24</td>
<td>17.01</td>
<td>26.39</td>
</tr>
<tr>
<td>Ages 13-15</td>
<td>1.10</td>
<td>4.25</td>
<td>44.00</td>
<td>5.53</td>
<td>18.42</td>
<td>26.70</td>
</tr>
<tr>
<td>Ages 16-19</td>
<td>1.87</td>
<td>4.02</td>
<td>49.05</td>
<td>5.76</td>
<td>17.28</td>
<td>22.02</td>
</tr>
</tbody>
</table>

2. FASD Spectrum and Diagnosis Criteria

Under the U.S Institute of Medicine (IOM) guidelines, FAS is characterized and diagnosed by: prenatal and postnatal growth deficiency (height or weight < 10th percentile when corrected for gestational age), a unique cluster of minor facial anomalies (short palpebral fissures, an elongated midface, a long and flattened philtrum, thin upper lip, and flattened maxilla) central nervous system damage (structural, neurological, and/or functional impairment) and gestational alcohol exposure. Central nervous system impairments include: neurological abnormality, developmental delay, behavioral dysfunction or deficit, intellectual impairment and/or structural abnormalities, such as microcephaly (head circumference below the 3rd percentile) or brain malformations found on imaging studies or autopsy. pFAS is characterized and diagnosed by: growth deficiency and/or facial 10 features of FAS, central nervous system damage (structural, neurological, and/or functional impairment) and gestational alcohol exposure. ARND is characterized and diagnosed by: central nervous system damage (structural, neurological, and/or functional impairment) and gestational alcohol exposure.

Figure 1: Characteristic facial features in a child with FASD

Figure 2: Assessment Scale for Upper Lip and Philtrum
3. Sleep Questionnaires

**EPWORTH SLEEPINESS SCALE**
(to be completed by adolescent 16 years and older)

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

- 0 = would *never* doze
- 1 = slight chance of dozing
- 2 = moderate chance of dozing
- 3 = high chance of dozing

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of Dozing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
</tr>
<tr>
<td>Sitting, inactive in a public place (e.g. theatre or a meeting)</td>
<td></td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td></td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in the traffic</td>
<td></td>
</tr>
</tbody>
</table>

**PEDIATRIC DAYTIME SLEEPINESS SCALE (PDSS)**
(completed by child/adolescent 11-15 years or by a parent for children aged 5-10)

Please answer the following questions as honestly as you can by circling one answer:

<table>
<thead>
<tr>
<th>Question</th>
<th>Always</th>
<th>Frequently</th>
<th>Sometimes</th>
<th>Seldom</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often do you fall asleep or get drowsy during class periods?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. How often do you get sleepy or drowsy while doing your homework?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Are you usually alert most of the day?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. How often are you ever tired and grumpy during the day?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. How often do you have trouble getting out of bed in the morning?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. How often do you fall back to sleep after being awakened in the morning?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. How often do you need someone to awaken you in the morning?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. How often do you think that you need more sleep?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MORNINGNESS/EVENINGNESS SCALE

Please circle the most appropriate response below:

1. Imagine: School is cancelled! You can get up whenever you want to. When would you get out of bed? Between...
   a. 5:00 and 6:30 am
   b. 6:30 and 7:45 am
   c. 7:45 and 9:45 am
   d. 9:45 and 11:00 am
   e. 11:00 am and noon

2. Is it easy for you to get up in the morning?
   a. No way!
   b. Sort of
   c. Pretty easy
   d. It’s a cinch

3. Gym class is set for 7:00 in the morning. How do you think you’ll do?
   f. My best
   g. Okay
   h. Worse than usual
   i. Awful

4. The bad news: You have to take a two-hour test. The good news: You can take it whenever you think you’ll do best. What time is that?
   a. 8:00 to 10:00 am
   b. 11:00 am to 1:00 pm
   c. 3:00 to 5:00 pm
   d. 7:00 to 9:00 pm

5. When do you have the most energy to do your favorite things?
   a. Morning! I’m tired in the evening
   b. More morning than evening
   c. Evening more than morning
   d. Evening! I’m tired in the morning

6. Guess what? Your parents decided to let you set your own bedtime. What time would you pick? Between...
   a. 8:00 and 9:00 pm
   b. 10:00 and 10:15 pm
   c. 10:15 pm and 12:30 am
   d. 12:30 and 1:45 am
   e. 1:45 and 3:00 am
7. How alert are you in the first half hour you’re up?
   a. Out of it
   b. A little dazed
   c. Okay
   d. Ready to take on the world

8. When does your body start to tell you it’s time for bed (even if you ignore it)?
   Between...
   a. 8:00 am and 9:00 pm
   b. 9:00 and 10:15 pm
   c. 10:15 pm and 12:30 am
   d. 12:30 and 1:45 am
   e. 1:45 and 3:00 am

9. Say you had to get up at 6:00 am every morning. What would it be like?
   a. Awful
   b. Not so great
   c. Okay (if I have to)
   d. Fine, no problem

10. When you wake up in the morning how long does it take for you to be totally ‘with it’?
    a. 0 to 10 minutes
    b. 11 to 20 minutes
    c. 20 to 40 minutes
    d. More than 40 minutes

11. Have you/your child ever become suddenly weak in the legs, or anywhere else, after laughing or being surprised by something? Yes No

12. Have you/your child ever felt unable to move for a short period, in bed, though awake and able to look around? Yes No

13. Have you/your child felt an irresistible urge to take a nap at times, forcing you to stop what you is doing in order to sleep? Yes No

14. Have you/your child ever had a sense of carrying on dreaming after waking up? Yes No
<table>
<thead>
<tr>
<th>During the past week, I have found that:</th>
<th>Completely Disagree</th>
<th>Neither Agree Nor Disagree</th>
<th>Completely Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My motivation is lower when I am fatigued.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise brings on my fatigue.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am easily fatigued.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue interferes with my physical functioning.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue causes frequent problems for me.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My fatigue prevents sustained physical functioning.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue interferes with carrying out certain duties and responsibilities.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue is among my three most disabling symptoms.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
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</tr>
<tr>
<td>Fatigue interferes with my work, family, or social life.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
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</tbody>
</table>
**CENTER FOR EPIDEMIOLOGICAL STUDIES DEPRESSION SCALE FOR CHILDREN (CES-DC)**
(completed by patients over 8 years old only)

**INSTRUCTIONS**
Below is a list of ways you might have felt or acted. Please check how much you have felt this way during the past week.

<table>
<thead>
<tr>
<th></th>
<th>0 Not at all</th>
<th>1 A little</th>
<th>2 Some</th>
<th>3 A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I was bothered by things that usually don't bother me</td>
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<tr>
<td>2. I did not feel like eating, I wasn't very hungry</td>
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<tr>
<td>3. I wasn't able to feel happy, even when my family or friends tried to make me feel better</td>
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<tr>
<td>4. I felt like I was just as good as other kids</td>
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<tr>
<td>5. I felt like I couldn't pay attention to what I was doing</td>
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<tr>
<td>6. I felt down and unhappy</td>
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<tr>
<td>7. I felt like I was too tired to do things</td>
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<tr>
<td>8. I felt like something good was going to happen</td>
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<tr>
<td>9. I felt things I did before didn’t work out right</td>
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<tr>
<td>10. I felt scared</td>
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<tr>
<td>11. I didn’t sleep as well as I usually sleep</td>
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<tr>
<td>12. I was happy</td>
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<td></td>
<td></td>
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<tr>
<td>13. I was more quiet than usual</td>
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<tr>
<td>14. I felt lonely, like I didn’t have any friends</td>
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<tr>
<td>15. I felt like kids I know were not friendly or that they didn’t want to be with me</td>
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<tr>
<td>16. I had a good time</td>
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<tr>
<td>17. I felt like crying</td>
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<tr>
<td>18. I felt sad</td>
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<tr>
<td>19. I felt people didn’t like me</td>
<td></td>
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<td></td>
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<tr>
<td>20. It was hard to get started doing things</td>
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</tr>
</tbody>
</table>
4. FASD Questionnaire

**FASD and Sleep Study: Demographics and Patient History Data Collection Form**

<table>
<thead>
<tr>
<th>PID:</th>
<th>Date of PSG #1:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date of PSG #2:</td>
</tr>
<tr>
<td></td>
<td>Date of DLMO:</td>
</tr>
</tbody>
</table>

**Demographics**

Age: __________ years  Gender: __________ (M or F)

Ht: __________ cm or __________ in  Wt: __________ kg or __________ lbs  BMI: __________

Diagnosis: ○ FASD  ○ pFASD  ○ ARND

Origin (select all that apply):

○ Aboriginal  ○ European  ○ Latin/Central/South American

○ Hawaiian/Pacific Islander  ○ Far East Asian (China, Japan, Macau, Mongolia, Korea, Taiwan)

○ South Asian (Bangladesh, Bhutan, India, Sri Lanka, Pakistan)

○ South East Asian (Vietnam, Cambodia, Malaysia, Laos, Brunei, Indonesia, Philippines, Thailand)

○ Middle Eastern/Arab/West Asian

○ African American  ○ Caribbean  ○ Caucasian  ○ Other: __________

**FASD and Sleep Study: Demographics and Patient History Data Collection Form**

<table>
<thead>
<tr>
<th>PID:</th>
</tr>
</thead>
</table>

1. Does the patient have a diagnosed sleep disorder? ○ Yes  ○ No
   • If YES, please describe: __________

2. Is there a diagnosed circadian rhythm disruption? ○ Yes  ○ No
   • If YES, please describe: __________

3. What is the prior history of prenatal alcohol exposure? ○ Confirmed  ○ Unconfirmed

4. What is the pattern of prenatal alcohol exposure?
   a) Average number of days of alcohol consumption per week: __________ (please fill in a # from 0-7)
   b) Type of alcohol consumed: ○ Beer  ○ Liquor  ○ Wine  ○ Other: __________
   c) Average amount of alcohol used per drinking occasion: __________
   d) Average # of weeks in pregnancy in which alcohol consumed? (Please indicate # of weeks)
      - In first trimester: __________  - In second trimester: __________  - In third trimester: __________

5. Are there any other prenatal substances consumed?
   ○ Crack/Cocaine  ○ Marijuana  ○ Ecstasy  ○ Other
   a) Average number of days of substance consumption per week: __________ (please fill in a # from 0-7)
   b) Average # of weeks in pregnancy in which substances were consumed? (Please indicate # of weeks)
      - In first trimester: __________  - In second trimester: __________  - In third trimester: __________
5. FASD Study Brochure

### FASD and Sleep Study: Demographics and Patient History Data Collection Form

<table>
<thead>
<tr>
<th>PID:</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

14. Is there a history of sleep or circadian rhythm disorders?
   - [ ] Yes (please specify)
   - [ ] No

15. What are the current/previous medications the child is/was taking?
   

16. Has the child ever experienced any physical or sexual abuse?
   - [ ] Yes
   - [ ] No

17. Has the birth mother ever experienced any physical or sexual abuse?
   - [ ] Yes
   - [ ] No

18. How many moves as the child endured (note: moves from one family to another family)?
   
   (Please fill # between 0-10)

19. Does the patient have any drug or alcohol abuse problems?
   - [ ] Yes
   - [ ] No

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### Dan Light Melatonin Onset Test (DLMO)

DLMO is a test to measure melatonin levels and the body’s sleep-wake cycle (i.e. biological clock). This test is especially useful for children diagnosed with FASD. Please see the brochure on DLMO for detailed information about this test.

### What Happens After the Tests:

After your sleep study, the results will be analyzed and a written report will be sent to your referring physician. This process usually takes from 2 to 4 weeks. A follow-up appointment to discuss the results of the study with your doctor will be scheduled when the report is ready to discuss treatment options.

What treatments options should you expect:
- Brief counseling with the doctor
- Several therapy sessions with a psychologist
- Medication treatment (short term or long term)
- Change in diet or food supplement
- Use of a device to improve sleep

For more copies of this and other pamphlets please visit: [www.youthdale.ca](http://www.youthdale.ca)

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### REFERRAL FORM

**Youthdale Child and Adolescent Sleep Centre**  
227 Victoria Street, Lower Level 2  
Toronto, Ontario, M5B 1L8  
Phone: (416) 703-0565  Fax: (416) 703-0567

**Patient Information:**  
Name:  
DOB:  
Contact Phone #:

**Weight:**  
[ ] Male  
[ ] Female

**Referring Doctor/Physician:**  
Name:  
Address:  
Phone #:

**Reason for Referral**  
(Please Circle All Relevant)  
Anatomical:  
- Large tonsils  
- Large adenoids  
- NAS

Nasal/Respiratory Complaints:  
- Snoring  
- Breathing problems  
- Sleep apnea  
- Other

Daytime Complaints:  
- Difficulty waking up  
- Excessive sleepiness  
- Tiredness  
- Irritability  
- Hyperactivity  
- Emotional problems in school  
- Other

History and Medical Information:

**Referring Doctor Signature:**  
Date:

---

**FASD and Sleep Disorders**

Fetal Alcohol Spectrum Disorders

[Youthdale Child and Adolescent Sleep Centre](http://www.youthdale.ca)  
227 Victoria St., Toronto, ON M5B 1L8  
Tel: 416 703-0565  Fax: 416 703-0567
What is FASD?

Fetal Alcohol Spectrum Disorders (FASD) is an umbrella term describing the range of effects that can occur in an individual whose mother drank alcohol during pregnancy.

What Are the Effects of FASD?

- Specific facial characteristics
- Growth deficits
- Mental Retardation
- Heart, lung, and kidney defects
- Hyperactivity & behavior problems
- Attention & memory problems
- Poor coordination or motor skill delays
- Difficulty with judgment and reasoning
- Learning disabilities
- Sleep and circadian rhythm disorders

The prevalence of FASD is estimated at 1 in 100 live births in Canada.

How can FASD affect Sleep?

Developmental exposure to alcohol directly affects the Suprachiasmatic Nucleus (SCN), which is a small region in the brain which is responsible for controlling the body clock.

Normal functioning of the SCN is critical for maintaining human health by allowing for the coordination of internal physiological processes with each other and with the light-dark cycle. Therefore, damage to the SCN would increase the body's susceptibility to physiological disorders, including sleep/wake disorders. With an altered SCN, light-dark entrainment is altered, resulting in altered sleep patterns. Therefore, children with FASD may experience sleep disturbances and wake up at the wrong time, as if they were permanently jet lagged.

What Does a Sleep Lab Do?

A sleep laboratory is set up to investigate and treat sleep disorders. Sleep tests are usually preceded by a clinical evaluation which would include a medical history, may require a physician examination and possibly a sleep questionnaire. The information gathered will help to determine what kinds of tests we should carry out.

Overnight Sleep Study: Polysomnogram (PSG)

The overnight polysomnogram (PSG) is used for example to help pinpoint the cause of daytime sleepiness or broken sleep and to diagnose some sleep disorders such as sleep apnea and periodic limb movements (excessive kicking) during sleep. In most cases, you will be asked to come to the lab about 8:00 p.m. The procedure includes:

- Recording brain activity during sleep (via sensors)
- Monitoring the child's breathing during sleep (via airflow sensors)
- Monitoring oxygen levels will be monitored by placing a red-lighted probe on the finger.
- Monitoring snoring with a microphone placed in the room.

All sleep consultations and studies are covered by OHIP providing a physician has referred you to the sleep lab.