SLEEP AND MELATONIN SECRETION ABNORMALITIES IN CHILDREN & ADOLESCENTS WITH FASD

DR. S. GORIL

DR. D. ZALAI

DR. C. SHAPIRO

DR. L. A. SCOTT

SLEEP

- Pivotal role in brain development during maturation
- Sleep problems in neurodevelopmental disorders (NDD) is high
- Exacerbate the symptoms of NDD and decrease effectiveness of other interventions
- Treatment of sleep disorders improves daytime functioning (e.g.: cognition, reactive behaviour, academic performance)
- Also reduce caregiver burden

LITERATURE REVIEW

- Parents report 85% of children with chronic sleep disturbance in Prenatal Alcohol Exposure (PAE))
- Usually data obtained via questionnaire
- Small sample sizes when PSG used
- EEG studies of PAE infants detected differences in sleep/wake patterns, increased arousal, fragmentation, generalized hypersynchrony,
- Prospective PAE studies: increased EEG power predicted poor cognitive and motor over first year of life

OBJECTIVES

- High parental report of sleep disturbances
- Little objective data in PAE
- Animal model indicates PAE can disrupt melatonin secretion via changes in suprachiasmatic nuclei (SCN)

Table 1. Participant Characteristics

Demographics	
Age (years) (mean ±SD)	10±3.2
Age groups (percent)	36
6-9 years old	18 (50.0)
10-12 years old	11 (30.6)
13-18 years old	7 (19.4)
Gender (female %)	55.6
Ethnicity (%)	
Caucasian	68
African American	12
Aboriginal	12
Biracial	8
Confirmed sleep disorder prior to this study (%)	
Yes	8
No	92
Medications (%)	
Norepinephrine reuptake inhibitors (NDRI)	50
Antipsychotics	25
Selective serotonin reuptake inhibitors (SSRI)	8.3
Melatonin	5.6
None	11.1

HYPOTHESES

- Sleep abnormalities more common in PAE
- High rate of melatonin secretion abnormalities

METHOD

METHOD

- Youthdale Sleep Centre
- Recruited participants aged 6 to 18y from FASD Diagnostic Clinics in Ontario
- Overnight PSG & Dim Light Melatonin Onset (DLMO) test
- Expert Interviews
- Four visits to Sleep Clinic for Consult, Overnight PSG, Nighttime DLMO, & Follow-up

PERCENTAGE OF FASD DIAGNOSES

	FAS	pFAS	ARND	FASD
STUDY	4.8%	12%	40%	44%
WASHINGTON	4%	7%	52%	37%

DLMO TEST

- In the sleep lab from before 7pm until 2am
- Sit in dim light (<30lux) with hourly saliva samples gathered.
- No eating or drinking for 30 min before sample taken, no use of electronic devices, some meds discontinued from 2 -6 weeks before test (e.g.: melatonin, fluoxetine)
- Melatonin concentrations measured and then analyzed (ELISA) with results graphed

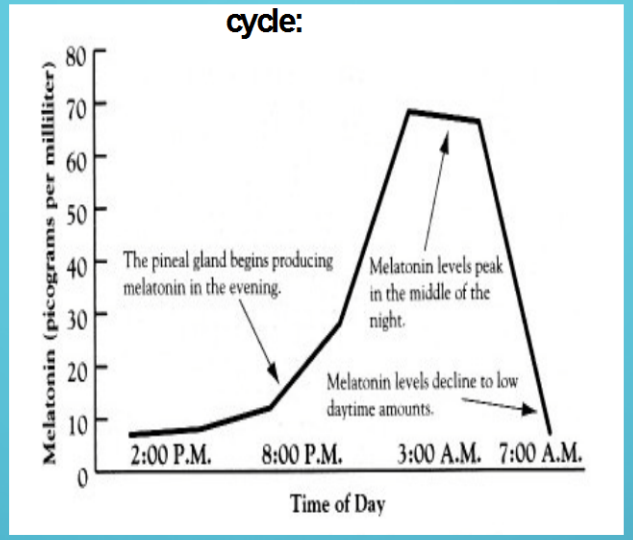
What is Melatonin?

Melatonin is a hormone found in all living creatures from algae to humans. In higher animals melatonin is produced by pinealocytes in the pineal gland in the brain which is about the size of a pea and is located in the centre of the brain:

Melatonin helps regulate the circadian rhythm. It is naturally synthesized from the amino acid tryptophan . Production of melatonin by the pineal gland is under the influence of the suprachiasmatic nucleus of the hypothalamus (SCN) which receives information from the retina about the daily pattern of light and darkness.

Melatonin is also synthesized by various plants, such as rice.

The Melatonin levels in a normal person go through this 24-hour cycle:



Normally, the production of melatonin is inhibited by light and permitted by darkness. For this reason melatonin has been called: the hormone of darkness. The secretion of melatonin peaks in the middle of the night and gradually falls during the second half of the night. Even low light levels can diminish melatonin production to some extent.

Ingested melatonin has almost similar effect as the melatonin produced in the body.

Dim Light Melatonin Onset (DLMO):

The human body produces its own melatonin starting two hours before bedtime, provided the lighting is dim. This natural action is known as "dim light melatonin onset" (DLMO) and helps keep the body on a regular sleep-wake schedule. Today, DLMO is considered the best test available, a "gold standard", for measuring Melatonin levels and Circadian Rhythm Disorders.

Therefore, taking the DLMO test is very helpful for discovering and understanding disturbances in the human biological clock.

DLMO is useful for determining whether an individual is entrained (synchronized) to a 24-h light/dark cycle or is in a free-running state. DLMO is also useful for assessing phase delays or advances of rhythms in entrained individuals. DLMO marker is also useful for identifying optimal application times for therapies such as bright light or external melatonin treatment.

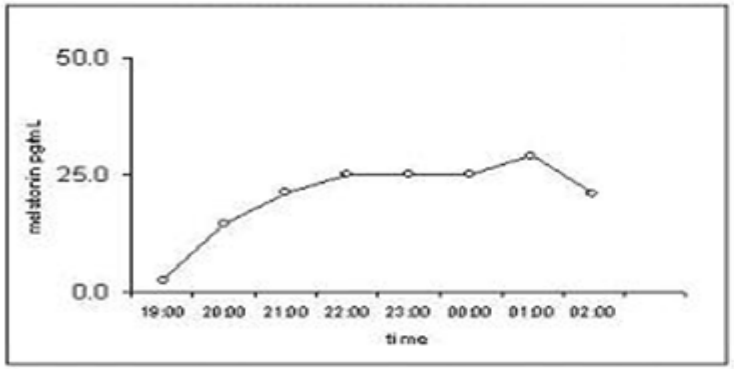
RESULTS

MELATONIN

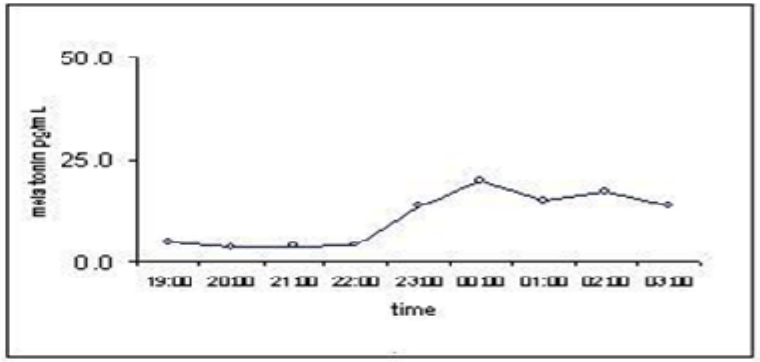
- 24/36 completed DLMO test
- 79% had abnormal melatonin secretion curve
- Suggests some underlying change to melatonin regulation
- May suggest abnormal circadian rhythm function even if not phenotypically obvious

Four Main Categories of Melatonin Phase-Response Curves

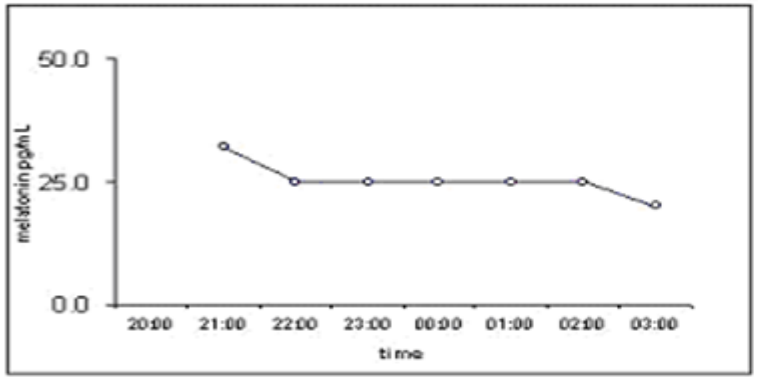
A. Normal (n=5) (21%)



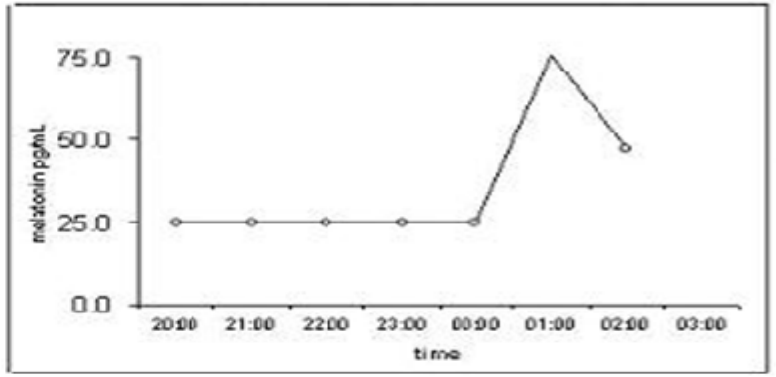
B. Delayed Sleep Phase Syndrome (DSPS) (n=4) (17%)



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



D. Other Melatonin Abnormality (n=13) (54%)



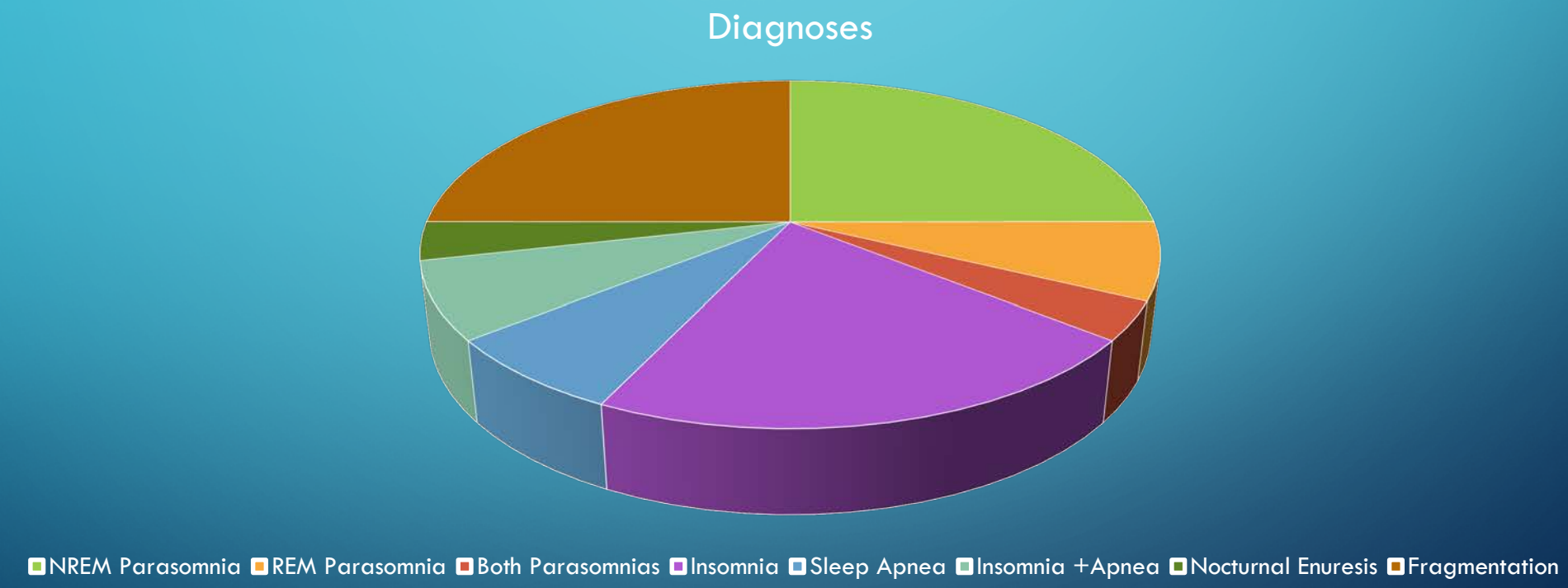
Note: Each figure shows a single example from the group type that the figure represents.

DLMO	Participant's age (years)
21 hours 16 minutes	6
20 hours 56 minutes	9
19 hours 11 minutes	9
22 hours 3 minutes	12
22 hours 7 minutes	13
19 hours 8 minutes	15
22 hours 6 minutes	18
21 hours 27 minutes	18

DLMO

Note: The Table shows Dim Light Melatonin Onset (DLMO) in 33 % of the group that underwent melatonin assessment. The DLMO could not be determined in the remainder of the sample. Reference values (mean DLMO): ages 6-12 years: 20 hours 43 minutes; 13-15 years: 21 hours 32 minutes; 16-50 years: 22 hours 11 minutes

DIAGNOSIS OF SLEEP DISORDERS



SLEEP ARCHITECTURE

	Age 6-9 years	Age 10-12 years	Age 13-18 years
TST (min)	528.00 (12.5)	489.6 (19.5)	468.4 (25.5)
SOL (min)	34.7 (7.7)	29.0 (7.8)	16.5 (2.3)
WASO (min)	25.3	69.0	29.7 (2.3)
SE (% TST)	81.3	84.0 (2.8)	88.9 (2.7)
N 1 (% TST)	3.6 (.40)	3.5 (.42)	5.4 (1.1)
N 2 (% TST)	42.3 (1.8)	38.2 (2.5)	48.8 (1.9)
N 3 (% TST)	25.3 (1.2)	25.25 (2.5)	20.7 (.76)
REM (% TST)	18.1	21.6 (1.7)	23.5 (1.7)
AI	9.8 (.89) (88.9% of the age group above the cut-off)	8 (9% of the age group above the cut-off)	13.0 (2.8) (85.71% of the age group above the cut-off)
AHI	2 (16.6 % of the age group above the cut-off)	.65 (9% of the age group above the cut-off)	.30 (0% of the age group is above the cut-off)

Note: The table shows the mean/median values of the respective sleep parameters for each age group (the median is presented for the non-normally distributed variables). The numbers in brackets next to the mean values are the standard deviations.
TST = total sleep time; SOL = sleep onset latency; WASO = wakefulness after sleep onset; SE = sleep efficiency; N1 = stage 1 sleep; N2 = stage 2 sleep; N3 = slow wave sleep; REM = rapid eye movement sleep; AI = arousal index; AHI = apnea hypopnea index

FINDINGS

- Majority of those diagnosed under FASD demonstrate abnormal sleep patterns and circadian system
- Population studies suggest 20-30% sleep problems in same aged children compared to 78% of our sample
- Our sample consistent with neurodevelopmental disorders (58%)
- This study revealed high rate of parasomnias not reported elsewhere in literature; we report a high rate of sleep fragmentation
- Objective evidence that FASD children are more sleepy and similar to parental reports

FINDINGS

- Variable patterns in melatonin secretion
- Extrapolating from animal model might indicate PAE impacts SCN justifies using melatonin in children where there is a detected hormonal abnormality
- Large number of children in sample had previous depression diagnoses with medication prescribed, hypothesize if treat sleep problems in children = potential to reduce such diagnoses later

LIMITATIONS

- Over representation of children with sleep problems although recruitment was open
- Comorbidities, as 15 had previous ADHD Dx and beyond current study but previously we found that sleep disorders present in FASD regardless of whether demonstrated ADHD symptoms
- Did not change current meds of participants
- No imposition of standardized schedule before DLMO test
- Limited normative DLMO test data for children

NEXT STEPS

- Review data on treating both sleep and circadian as suggest that treated together significant improvement in sleep and behaviour
- Suggest that Fragmented sleep be considered a diagnosis for NDDs

THANK YOU FOR LISTENING (AND STAYING AWAKE)

- Reference: Goril,S., Zalai,D., Scott,L., Shapiro, C. (2016))Sleep and melatonin secretion abnormalities in children and adolescents with fetal alcohol spectrum disorders. *Sleep Medicine* pp. 59-64.

- For a copy of this presentation please contact: drscottassociates@execulink.com