

Sleep and Autism Update

Beth A. Malow, M.D., M.S.
 Burry Chair in Cognitive Childhood Development
 Professor of Neurology and Pediatrics
 PI, Vanderbilt Autism Treatment Network
 Director, Vanderbilt Sleep Disorders Division

Disclosures

- I have received grant support from Neurim Pharmaceuticals to study Circadin® (prolonged-release melatonin)
- I have consulted for Janssen and Vanda Pharmaceuticals
- I will discuss off-label uses of medications for pediatric sleep disorders

Causes of Insomnia in ASD/NDD (or any child)

The diagram consists of three overlapping circles labeled Biological, Medical, and Behavioral. The Biological circle is at the top, the Medical circle is at the bottom left, and the Behavioral circle is at the bottom right. The intersections between all three circles are shaded.

- Circadian Clock Factors
- Neurochemical
- Overarousal
- Sensory Oversensitivity
- Anxiety, BP, OCD, ADHD

Biological

- Limited Exercise
- Caffeine
- Screen Time
- Parenting Stress
- Early Bedtimes
- Early Wake Times (for school)

Medical

- Sleep Apnea
- Seizures
- GI reflux
- RLS/PLMs
- Medications

Behavioral

The Possible Interplay of Synaptic and Clock Genes in Autism Spectrum Disorders

T. BOUVEREON
Human Genetics and Cognitive Function Unit, Department of Neuroscience, Institut Pasteur, Paris, France, and Université Denis Diderot Paris 7, Paris, France

Cold Spring Harbor Symposia on Quantitative Biology, 2007

Social timing, clock genes and autism: a new hypothesis

International Journal of Molecular Sciences

Article
Clock Genes and Altered Sleep-Wake Rhythms: Their Role in the Development of Psychiatric Disorders 2017

Annaïlle Charrier ^{1,*}, Bertrand Olliac ^{2,3}, Pierre Roubertoux ¹ and Sylvie Teodjman ^{1,3}

Table 5
Clock genes and autism spectrum disorder (ASD).

Studies	Measure	Individuals with Psychiatric Disorder (n)	Controls (n)	Results
Nicholas et al. [10]	Screening of eleven clock clock-related genes	High-functioning ASD individuals (n = 120)	Healthy parents (n = 220)	Significant associations for two single-nucleotide polymorphisms in Per1 and in Npas2
Yang et al. [11]	Divergent sequencing analysis of the coding regions of 18 canonical clock genes and clock-associated genes	with sleep disorders (n = 14), ASD individuals without sleep disorders (n = 14)	Healthy individuals (n = 21)	Mutations in circadian-related genes (specifically Per1, Per2, Per3, Clock, Npas2, Bmal1, Dax, Cry1, Cry2, Dsp and Chl3) affecting gene function are more frequent in individuals with ASD than in controls.

Causes of Insomnia in ASD (or any child)

- Biological**
- Medical**
 - Sleep Apnea
 - Seizures
 - GI reflux
 - RLS/PLMs
 - Medications
- Behavioral**
 - Limited Exercise
 - Caffeine
 - Screen Time
 - Parenting Stress
 - Early Bedtimes
 - Early Wake Times (for school)

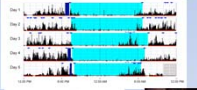
Polysomnography

Making polysomnography more "child friendly": a family-centered care approach. Zaremba, 2005.

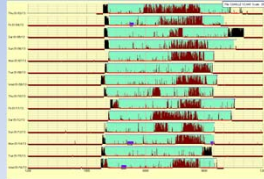
Measuring Insomnia--Actigraphy

- Promising technique for measuring sleep patterns and responses to treatment in children, especially special populations (AASM, 2007)
- Commercially available, wireless, non-intrusive, relatively inexpensive, and amenable to weeks of data collection

Actiwatch (Philips Respironics)



Pocket placement (Souders, 2009; Adkins, 2012)

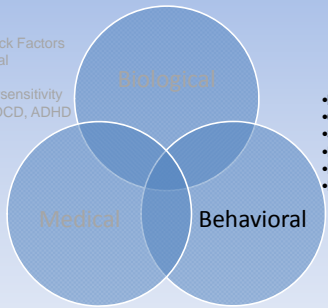


AMI device (courtesy of Dr. Meltzer)

Causes of Insomnia in ASD

- Circadian Clock Factors
- Neurochemical
- Overarousal
- Sensory Oversensitivity
- Anxiety, BP, OCD, ADHD

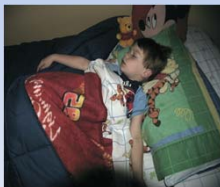
- Sleep Apnea
- Seizures
- GI reflux
- RLS/PLMs
- Medications



- Limited Exercise
- Caffeine
- Screen Time
- Parenting Stress
- Early Bedtimes
- Early Wake Times (for school)

Treatment of Insomnia: Behavioral Approaches

- Daytime habits
- Evening habits
- Sleep environment
- Bedtime routines



Measuring Sleep Hygiene– The Family Inventory of Sleep Habits (FISH)

•We developed the FISH as a sleep habits questionnaire for children with ASD

•The FISH contains 12 questions that ask about sleep habits in the child and family

•Excellent test-retest reliability and external validity with the Children's Sleep Habits Questionnaire (CSHQ)

DIRECTIONS: For each item below, please indicate how often it was true within the last month.

	Never	Occasionally	Sometimes	Usually	Always
1. My child gets exercise during the day.	1	2	3	4	5
2. My child wakes up or shows the same mood each morning.	1	2	3	4	5
3. In the hour before bedtime, my child engages in relaxing activities.	1	2	3	4	5
4. My child has drinks or foods containing caffeine other than tea/coffee, chocolate, Coca Cola.	1	2	3	4	5
5. In the hour before bedtime, my child engages in exciting or stimulating activities (excitement: rough play, video games, sports).	1	2	3	4	5
6. My child's room is dark or dimly lit at bedtime.	1	2	3	4	5
7. My child's room is quiet at bedtime.	1	2	3	4	5
8. My child goes to bed at the same time each night.	1	2	3	4	5
9. My child follows a regular bedtime routine that lasts between 15 and 30 minutes.	1	2	3	4	5
10. I enter my child's room until he/she falls asleep.	1	2	3	4	5
11. After my child is tucked in, I check on him/her before he/she falls asleep.	1	2	3	4	5
12. My child watches TV, videos, or DVDs to help him/her fall asleep.	1	2	3	4	5

Malow, 2009



Line Drawings

Time for bed

- Put on pajamas
- Use the bathroom
- Wash hands
- Brush teeth
- Get a drink
- Read a book
- Get in bed and go to sleep

Checklist

Children with Limited Verbal Skills

- Schedules with photos
- Object schedules
- Cues in the environment

Schedule Boards:

Some children are not able to use a visual schedule that uses words, photos, or icons. It may help to use objects instead.

Here's an example: If your child's bedtime routine consists of using the toilet, taking a bath, washing hair, brushing hair, having a massage, and listening to music, you might have a place near the bathroom or bedroom with the following items: a roll of toilet paper, a bar of soap, a bottle of shampoo, a hairbrush, a bottle of lotion, and a CD. Your child would get each object before the start of an activity and use this to guide his or her actions. Save a special object just for bedtime. This might be a special blanket, pillow, or stuffed animal. Once your child has this object, he or she should go into his or her bed. Even if you do not use objects, write down your child's schedule so that you are going through the same steps each night. Use single words or two-word phrases to label what you are doing.



AS ATN Toolkits

Strategies to Improve Sleep in Children with Autism Spectrum Disorders

Visual Supports and Autism Spectrum Disorders

Autism Speaks, on line materials

<http://www.autismspeaks.org/science/resources-programs/autism-treatment-network/tools-you-can-use/sleep-tool-kit>

A Brief Behavioral Intervention for Insomnia in Adolescents With Autism Spectrum Disorders

Whitney A. Loring, Rebecca Johnston, Laura Gray, Suzanne Goldman, and Beth Malow

Sleep Education Program provided to 18 adolescents ages 11-18 years with ASD, confirmed by the ADOS, and their parents

Table 1. **Demographics/Pre-treatment**

Sleep parameter	Baseline		Treatment		F value	p value
	Mean (SD)	SD	Mean (SD)	SD		
Sleep latency (min)	20.26 (10.07)	10.07	13.14 (11.41)	11.24	2.163	.152
Waking after sleep onset (WASO) (min)	10.28 (10.07)	10.07	4.08 (7.70)	7.70	2.276	.139
Total sleep time (min)	414.29 (146.41)	146.41	329.29 (146.41)	146.41	1.107	.292

Table 2. **Autism Spectrum Sleep Wake Scale (ASWSL)**

Sleep parameter	Baseline		Treatment		F value	p value
	Mean (SD)	SD	Mean (SD)	SD		
ASWSL total score	10.28 (10.07)	10.07	13.14 (11.41)	11.24	2.163	.152
ASWSL sleep latency	10.28 (10.07)	10.07	4.08 (7.70)	7.70	2.276	.139
ASWSL WASO	10.28 (10.07)	10.07	4.08 (7.70)	7.70	2.276	.139
ASWSL total sleep time	10.28 (10.07)	10.07	13.14 (11.41)	11.24	2.163	.152

Table 3. **Parental Sleep Questionnaire (PSQ)**

Sleep parameter	Baseline		Treatment		F value	p value
	Mean (SD)	SD	Mean (SD)	SD		
PSQ total score	10.28 (10.07)	10.07	13.14 (11.41)	11.24	2.163	.152
PSQ sleep latency	10.28 (10.07)	10.07	4.08 (7.70)	7.70	2.276	.139
PSQ WASO	10.28 (10.07)	10.07	4.08 (7.70)	7.70	2.276	.139
PSQ total sleep time	10.28 (10.07)	10.07	13.14 (11.41)	11.24	2.163	.152

Table 4. **Parental Sleep Questionnaire (PSQ)**

Sleep parameter	Baseline		Treatment		F value	p value
	Mean (SD)	SD	Mean (SD)	SD		
PSQ total score	10.28 (10.07)	10.07	13.14 (11.41)	11.24	2.163	.152
PSQ sleep latency	10.28 (10.07)	10.07	4.08 (7.70)	7.70	2.276	.139
PSQ WASO	10.28 (10.07)	10.07	4.08 (7.70)	7.70	2.276	.139
PSQ total sleep time	10.28 (10.07)	10.07	13.14 (11.41)	11.24	2.163	.152

When Use Pharmacological Treatment?

- Best used after behavioral treatments have been tried unsuccessfully, and in combination with behavioral therapies
- In ASD...
 - We published a practice pathway for children with insomnia and ASD applicable to other special populations.¹
 - ✓ Identify co-occurring conditions (OSA, seizures, sleep terrors)
 - ✓ Offer behavioral therapies first when family is willing and able
 - Whenever possible, choose a medication that will treat a comorbidity such as epilepsy, anxiety, or a mood disorder
 - Start at low doses, to avoid excess sedation and adverse effects
 - For primary insomnia, no FDA-approved drugs. Agent that has been most studied is melatonin.

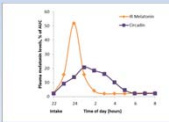
¹Malow, 2012

Treatment Options for ASD and DD

- Melatonin and melatonin agonists
- Alpha-adrenergic agonists (clonidine, guanfacine)
- Gabapentin
- Trazadone
- Mirtazapine
- Benzodiazepines
- Non-benzodiazepine receptor agonists (zolpidem, eszopiclone)
- Tricyclic antidepressants
- Other OTCs besides melatonin
 - ✓ Valerian
 - ✓ Tryptophan/5-Hydroxytryptophan
 - ✓ Cereal enriched with tryptophan, adenosine, and uridine
 - ✓ Omega-3, Omega-6

Prolonged Release Melatonin

- ✓ Prolonged release melatonin has shown promise in reducing night wakings in ASD.¹⁻²
- ✓ Prolonged release melatonin may be more efficacious for night wakings given its longer duration of action³ and showed efficacy in an open label trial of 6-12 year olds (n = 88; mostly SMS, some ASD, Angelman, Rett syndrome patients)⁴
- ✓ A novel 3 mm mini-tablet (easier to swallow) has been studied in a 13-week double-blind placebo controlled trial in ASD and SMS (Neurim Pharmaceuticals, Circadin®)⁵



- ✓ 125 children, ages 2-17.5 yrs
- ✓ Improved sleep latency (25 min)
- ✓ Longer sleep time (32 min)

¹Giannotti, 2006; ²Cortesi, 2012; ³Zisapel, 2010; ⁴Leersnyder, 2011; ⁵Gringras, 2017

Alpha-2 Agonists

- Clonidine is a centrally-acting alpha-2 adrenergic agonist that acts presynaptically to inhibit sympathetic outflow, and also has sedative effects.
- In ASD, open-label study of 17 children (ages 4-16 years) prescribed clonidine for sleep onset insomnia or night wakings (0.05 to 0.1 mg). All with sleep onset delay improved and 16/17 with night wakings improved.¹
- In a separate study in 6 children (ages 4-15 years) with neurodevelopmental disorders, fewer night wakings and longer sleep duration were noted with 0.15-0.225 mg/24 hours, in two divided doses.
- Side effects include pallor, tachycardia, hypotension, irritability and increased night wakings.

¹ Ming, 2008; ²Ingrassia, 2005

Gabapentin

- Gabapentin inhibits voltage-gated calcium channels containing the alpha-2-delta-1 subunit
- Dosing: 5 mg/kg, to increase to 10 mg/kg to 15 mg/kg. May see paradoxical insomnia/agitation which resolves with discontinuation.
- In our series of 23 children, ages 1-15 years, the majority improved in both sleep-onset and sleep-maintenance insomnia (including those who had not responded to melatonin).
- Co-occurring conditions included ASD, epilepsy, OCD, ADHD, and bipolar disorder

Robinson and Malow, 2013

Summary

- Sleep problems are common in children with ASD
- There are many causes and contributors, most of which are treatable
- Identification of sleep problems in this population, beyond improving sleep, can contribute to improved daytime functioning

Future Directions

- Large treatment studies, including randomized controlled trials using objective measurements (such as actigraphy)
- More studies that incorporate behavioral interventions in combination with medications
- More adolescent studies; more non-ASD studies
- Comparative effectiveness studies
- Assessment of long-term efficacy and side effects
- Understanding of genetic contributors
- Attention to co-occurring conditions
- Result would be a practice guideline for treating insomnia in children with ASD and related NDD
