Sleep and Autism: Helping Families Get the Rest they Need

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Disclosures

- Grant support from Neurim Pharmaceuticals and Autism Speaks Autism Treatment Network
- Consultant to Neurim, Janssen, and Vanda Pharmaceuticals
- I will discuss off-label uses of medications for sleep in autism

Presentation Goals

- Identify the types of sleep problems common in individuals on the autism spectrum, along with causes and contributors
- Describe the impact of these sleep problems on the individual and family
- Provide an overview of established and emerging treatments

Autism Spectrum Disorder (ASD)

Core symptoms:

- Deficits in social communication & interaction
- Restricted interests/repetitive behaviors, sensory sensitivities

Associated symptoms:

- Seizures
- Psychiatric conditions
- Sleep

1 in 59
Half-million individuals with ASD turning 18 years old over next decade

Can we affect these core and associated symptoms by improving sleep?

Prevalence of Sleep Problems in ASD

- Multiple studies have documented sleep problems in about two-thirds of children (50-84%)
- Children with an ASD (ages 2-5 years) are twice as likely to have sleep problems than those in the general population
- Sleep disturbances are highly prevalent across spectrum diagnoses and cognitive levels

Allik, 2006; Couturier, 2005; Goodlin-Jones, 2008; Hering, 1999; Honomichl, 2002; Malow, 2006; Patzold, 1998; Reynolds, 2019; Richdale, 1995 and 1999; Souders, 2009; Stores, 1998; Krakowiak, 2008; Wiggs, 2004; Williams, 2004

Sleep Concerns in ASD

J. Sleep Res. (2004) **13,** 265–268

Sleep problems in children with autism

P. GAIL WILLIAMS, LONNIE L. SEARS and ANNAMARY ALLARD
Weisskopf Center for the Evaluation of Children, University of Louisville, Louisville, KY, USA

Parent-completed survey of 210 children, ages 2-16 years

Table 1 Amount of nighttime sleep achieved by sample of children with autism

Number of hours of sleep (h)	*Percentage of children (%)*
4–5	10
6–7	20
8–9	51
10–11	18
>11	1

Table 2 Sleep problems frequency

*Sleep problem**	*Percentage of parents reporting*
Difficulty falling asleep	53.3
Restless sleep	40
Unwillingness to fall asleep in own bed	39.5
Frequent wakenings	33.8
Difficulty arousing	31.5
Enuresis	27.7
Disoriented waking	27.1
Daytime mouth breathing	25.7
Excessive daytime sleepiness	23.3
Bruxism	21
Snoring	21
Fear of sleeping in dark	18.6
Awakens to noise	18%
Vocalizes in sleep	10.5
Breathing concerns	8.6
Headbanging	6.7
Gets up to go to bathroom during night	6.2
Wakes up screaming	5.2
Falls asleep at school	4.7
Nightmares	3.8
Apnea	3.4
Cries during night	1.9
Morning headaches	1
Sleepwalking	1

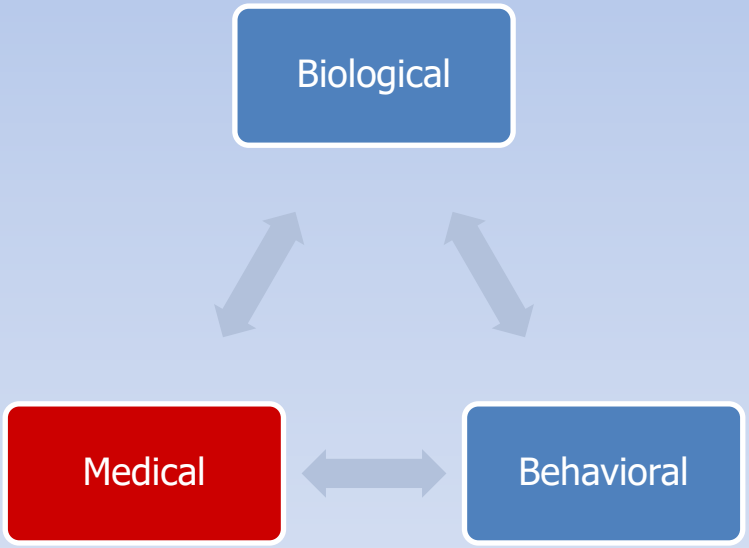
*Based on parent reports of problem occurring 'frequently' or 'almost always'.

Alex

- Alex is a 10-year-old boy with autism spectrum disorder. Bedtime is 8 pm. He takes hours to fall asleep. His parents state that "he can't shut his brain down." He takes methylphenidate (Ritalin) in the afternoon for ADHD symptoms, enjoys a glass of Mountain Dew with dinner, and plays video games after dinner. He can't settle down to go to sleep and leaves his room repeatedly to find his parents. They rub his back to help him fall asleep.
- Once asleep, he awakens multiple times during the night. Sometimes he sleepwalks and sometimes he comes to his parents' bedroom and falls asleep there (they are too exhausted to move). He snores, and is very restless with frequent leg kicks.
- It is "nearly impossible" to awaken Alex in the morning for school. Alex's teacher describes him as being sleepy as well as hyperactive and "disruptive" in class. His parents are exhausted and very overwhelmed.

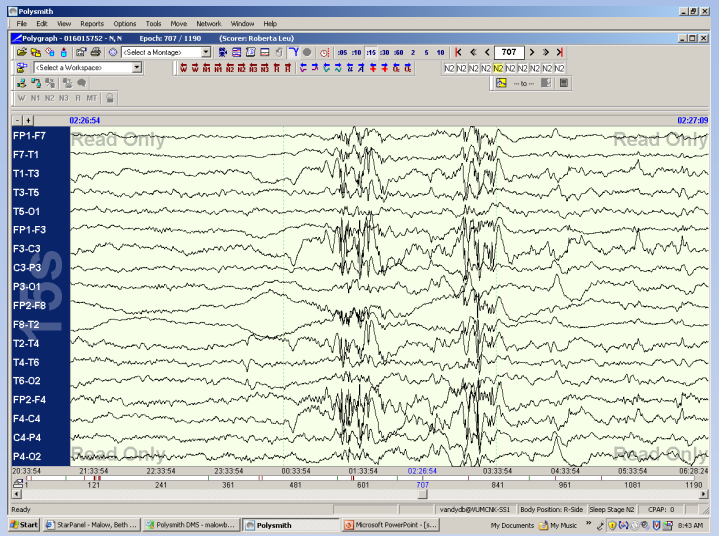
Unpacking Alex's sleep problems

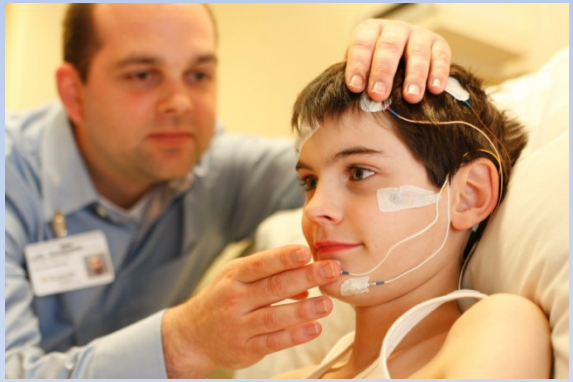
- Snoring
- Sleepwalking
- ADHD
- Methylphenidate (Ritalin)
- Leg movements (dietary?)



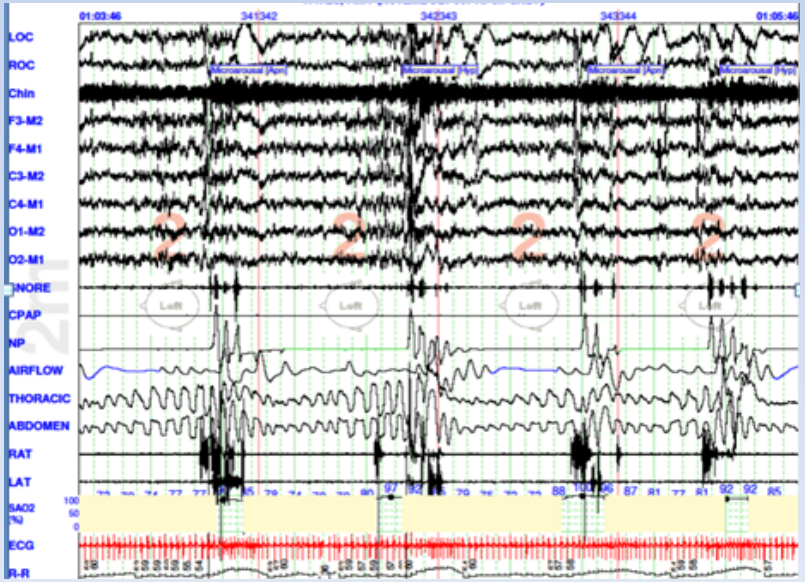
- Seizures
- GI problems
- Anxiety, Depression
- Other stimulating medications

Polysomnography





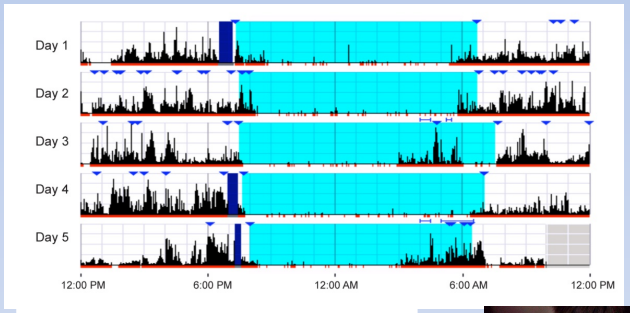
Making polysomnography more "child friendly:" a family-centered care approach. Zaremba, 2005.

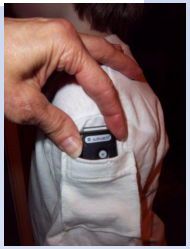


Measuring Insomnia--Actigraphy

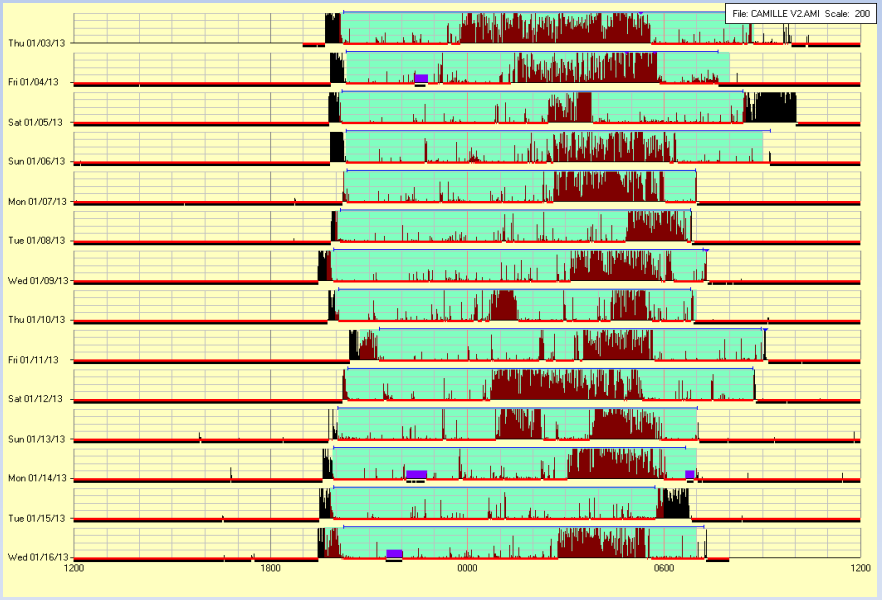
- Promising technique for measuring sleep patterns and responses to treatment in children, especially special populations (AASM, 2007)
- Commercially available, wireless, non-intrusive, relatively inexpensive, and amenable to weeks of data collection

Actiwatch (Philips Respironics)





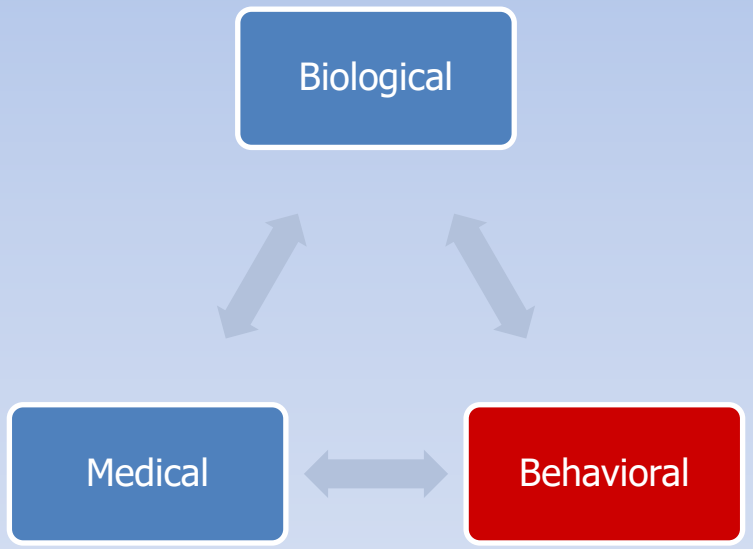
Pocket placement (Souders, 2009; Adkins, 2012)



AMI device (courtesy of Dr. Meltzer)

Unpacking Alex's sleep problems

- Tea (caffeine)
- Video Games
- Bedtime of 8 pm (too early?)
- Parent interactions (rubbing back)

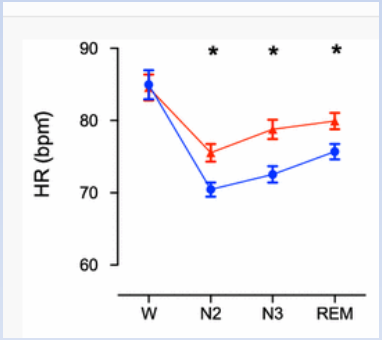


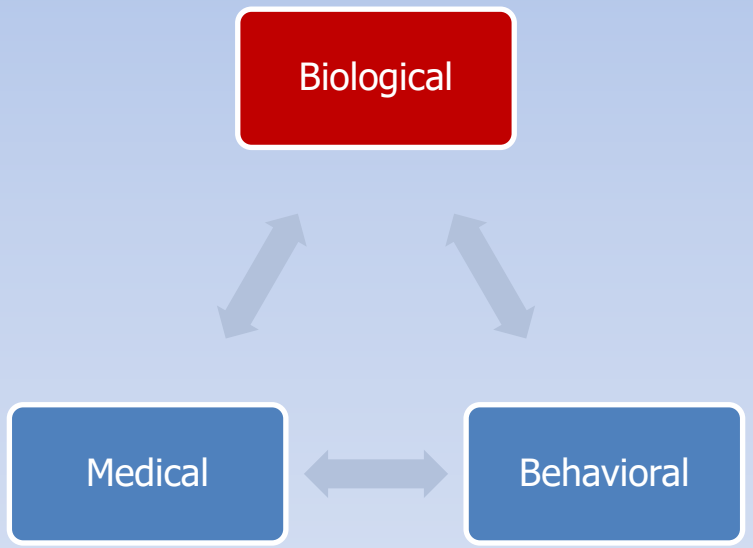
- Limited exercise
- Stimulating activities at bedtime
- Sensory sensitivities
- Restricted interests
- Difficulty with communication skills

Core symptoms

Unpacking Alex's sleep problems

- Hyperarousal
- Genetics
- Melatonin processing





Kushki, 2013, PLoS ONE; Harder, Clin Autonomic Res., 2016)

Melatonin Effects in ASD and Sleep

Endogenous Hormone
- "Hormone of darkness"
- Crosses blood brain barrier
- Ubiquitous

Hypnotic (MT1)
- Inhibits the drive for wakefulness

Circadian Clock Hormone "Chronobiotic" (MT2)
- Endogenous synchronizer: stabilizes circadian rhythm

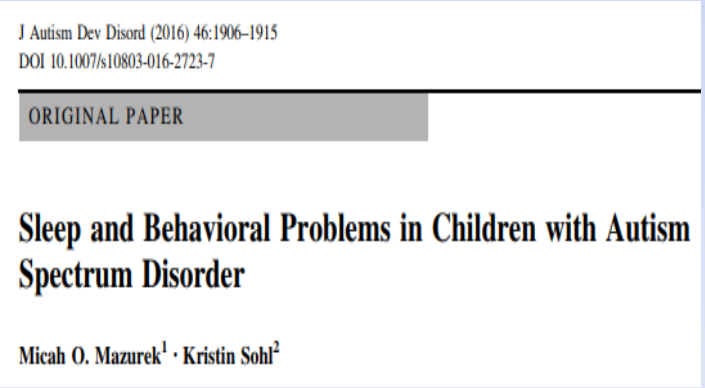
Pandi-Perumal, FEBS J, 2006

Melatonin may also act as an anxiolytic and mitigate hyperarousal

Yousaf, Anesthesiology, 2010; *Campino, Horm Metab Res, 2011*

Sleep Problems Affect Emotional Regulation, Behavior, and Core Symptoms

In > 2,714 children with ASD in the Simons Simplex collection, severity scores for core symptoms were increased for children reported to sleep ≤ 7 hours per night compared to children sleeping ≥ 11 hours per night.
(*Veatch, Autism Research, 2017*)


J Autism Dev Disord (2016) 46:1906–1915
DOI 10.1007/s10803-016-2723-7

ORIGINAL PAPER

Sleep and Behavioral Problems in Children with Autism Spectrum Disorder

Micah O. Mazurek[1] · Kristin Sohl[2]

- 81 children with autism, ages 3-19 years
- Sleep problems were significantly associated with physical aggression, irritability, inattention, and hyperactivity.

Treatment of Insomnia: Behavioral Approaches

- "Behavioral treatment of sleep problems …reduces parental stress, increases parents' satisfaction with their own sleep, their child's sleep, and heightens their sense of control and ability to cope with their child's sleep"
  (Wiggs, Br. J Health Psychology, 2001)

Parent training is feasible and effective *(Johnson, Sleep Med, 2013)*

Behavioral strategies help <u>many</u> children, if properly delivered to parents and used by parents.

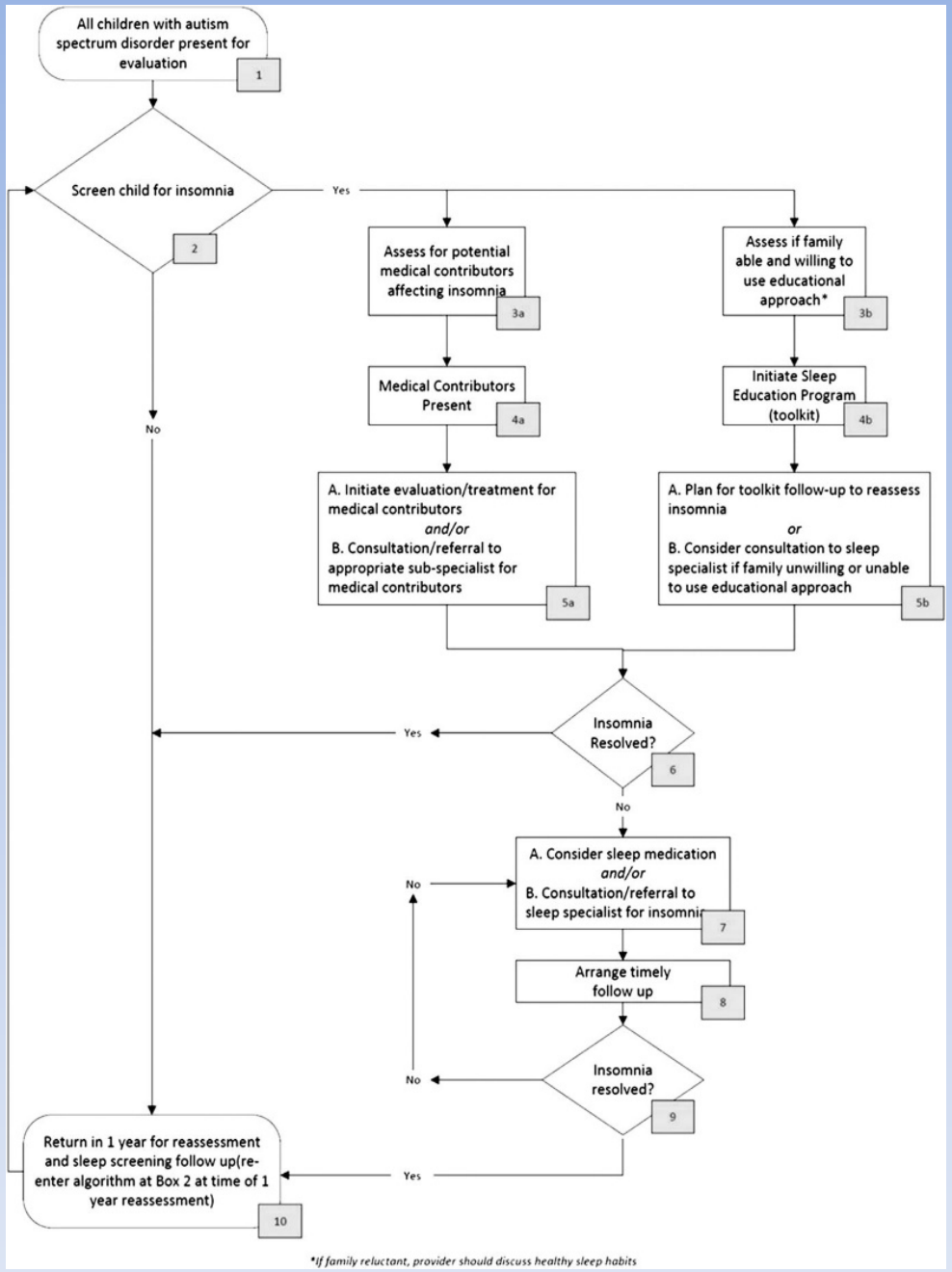
The Challenge:

How do we deliver them? How do we get parents and PCPs to use them?

And how do we identify the kids who need medications?

Practice Pathway for Insomnia in ASD

- ATN Sleep Committee pathway
- Identify and treat medical contributors
- If family is "willing and able" to use educational approach, initiate sleep education program
- Sleep medications or referral to sleep specialist if insomnia is not resolved
- Timely follow-up
- Dr. Anjalee Galion at CHOC is leading efforts to update for night wakings
- Are practice pathways followed???



Malow, Byers, Johnson, Weiss, Bernal, Goldman, Panzer, Coury, Glaze Pediatrics, 2012

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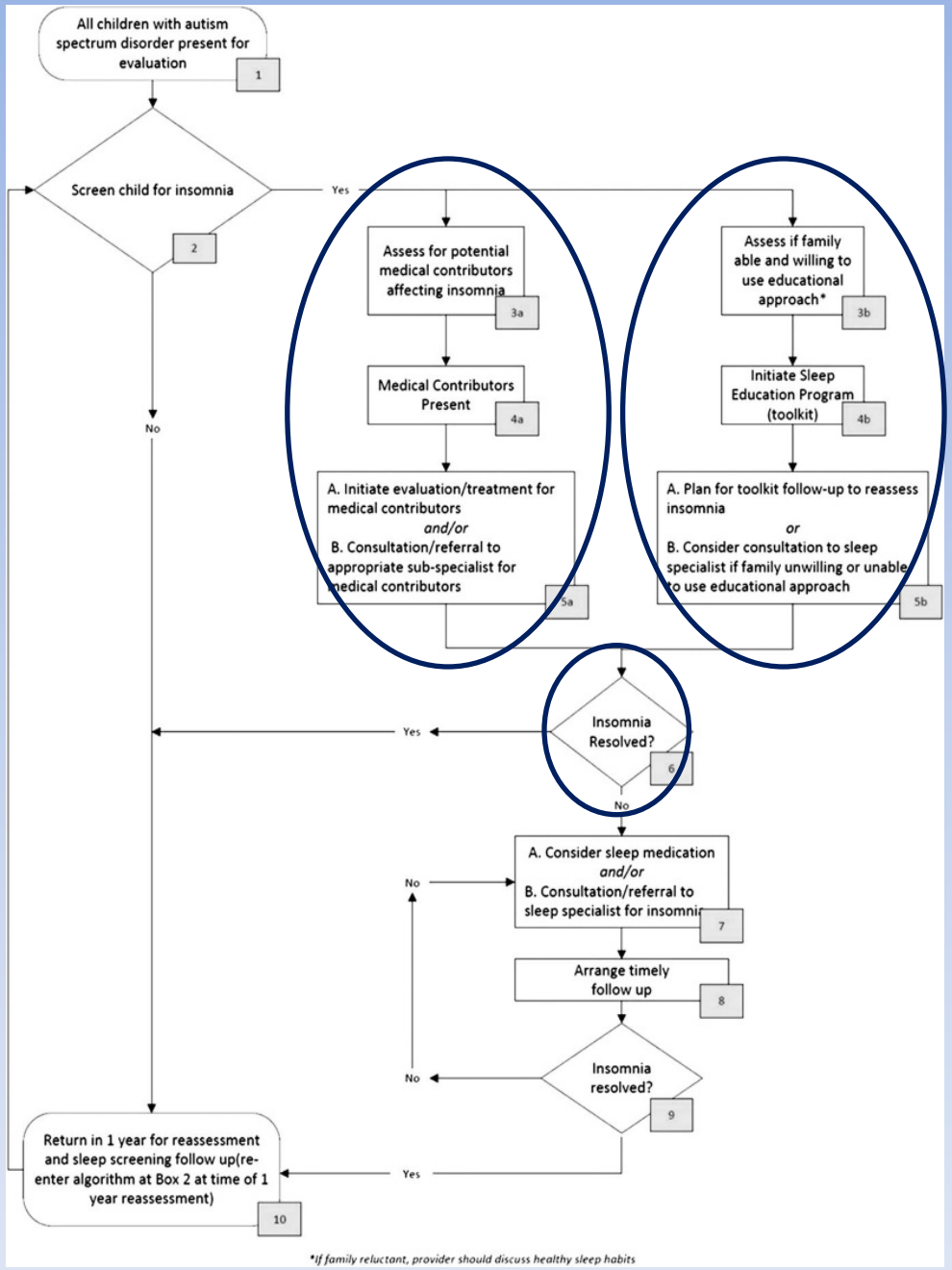
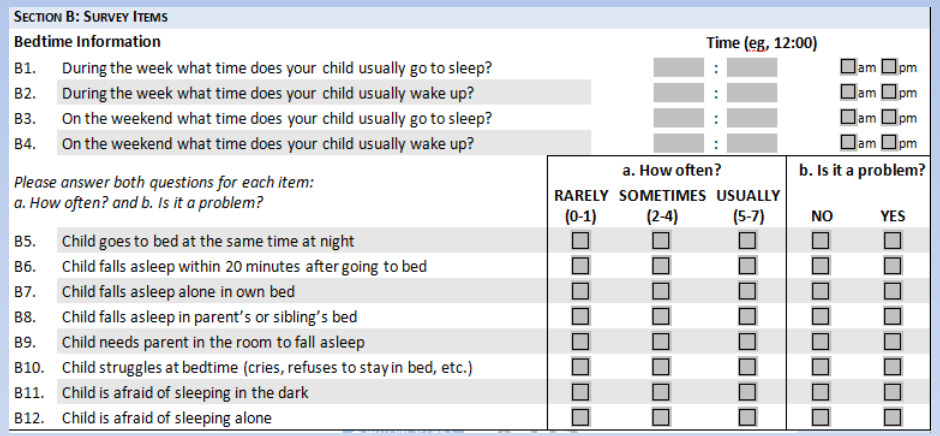


Malow, Byers, Johnson, Weiss, Bernal, Goldman, Panzer, Coury, Glaze Pediatrics, 2012

Children's Sleep Habits Questionnaire

✓Used widely in neurodevelopmental disorders
✓45-item questionnaire. 33 items retained in subscales

✓Eight Subscales:
- •Bedtime Resistance
- •Sleep Onset Delay
- •Sleep Duration
- •Sleep Anxiety
- •Night Wakings
- •Parasomnias
- •Sleep Disordered Breathing
- •Daytime Sleepiness



SECTION B: SURVEY ITEMS

Bedtime Information		Time (eg, 12:00)
B1.	During the week what time does your child usually go to sleep?	: ☐am ☐pm
B2.	During the week what time does your child usually wake up?	: ☐am ☐pm
B3.	On the weekend what time does your child usually go to sleep?	: ☐am ☐pm
B4.	On the weekend what time does your child usually wake up?	: ☐am ☐pm

Please answer both questions for each item: a. How often? and b. Is it a problem?		a. How often?			b. Is it a problem?	
		RARELY (0-1)	SOMETIMES (2-4)	USUALLY (5-7)	NO	YES
B5.	Child goes to bed at the same time at night	☐	☐	☐	☐	☐
B6.	Child falls asleep within 20 minutes after going to bed	☐	☐	☐	☐	☐
B7.	Child falls asleep alone in own bed	☐	☐	☐	☐	☐
B8.	Child falls asleep in parent's or sibling's bed	☐	☐	☐	☐	☐
B9.	Child needs parent in the room to fall asleep	☐	☐	☐	☐	☐
B10.	Child struggles at bedtime (cries, refuses to stay in bed, etc.)	☐	☐	☐	☐	☐
B11.	Child is afraid of sleeping in the dark	☐	☐	☐	☐	☐
B12.	Child is afraid of sleeping alone	☐	☐	☐	☐	☐

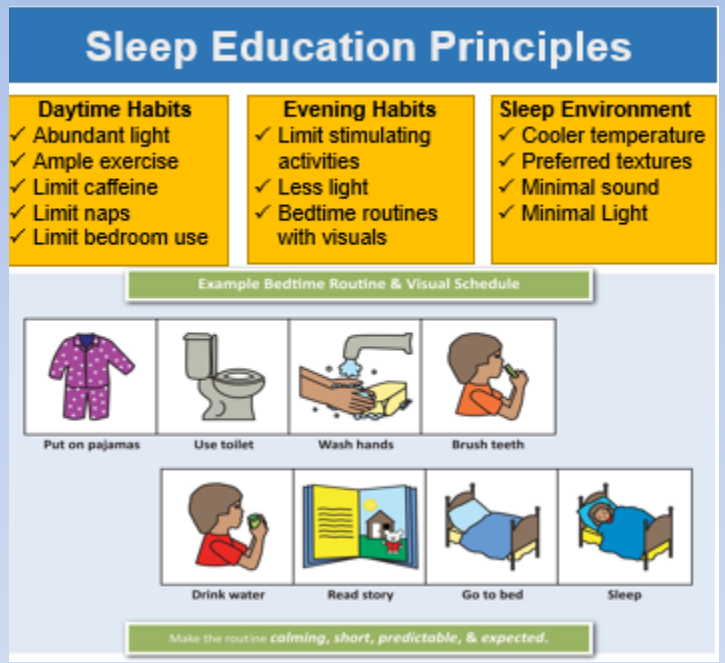
Owens, SLEEP, 2000

Modified CSHQ for ASD with 23-item, four-factor version

Sleep Initation/Duration
Sleep Anxiety/Co-sleeping
Night Waking/Parasomnias
Daytime Alertness

Katz, Shui, Johnson, Richdale, Reynolds, Scahill, Malow, JADD, 2018

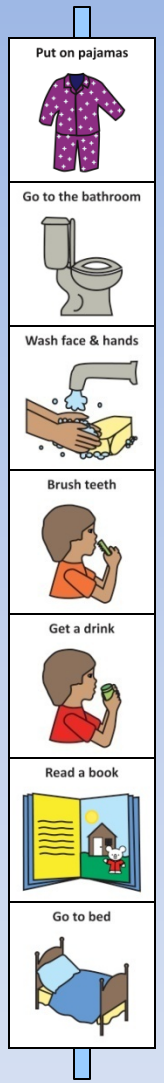
Measuring Sleep Hygiene– The Family Inventory of Sleep Habits



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 at about the same time 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 after 5 pm (examples: chocolate, Coca Cola).	1	2	3	4	5
5. In the hour before bedtime, my child engages in exciting or stimulating activities (examples: 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 stay in 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, J Child Neuro, 2009



Line Drawings

Time for bed

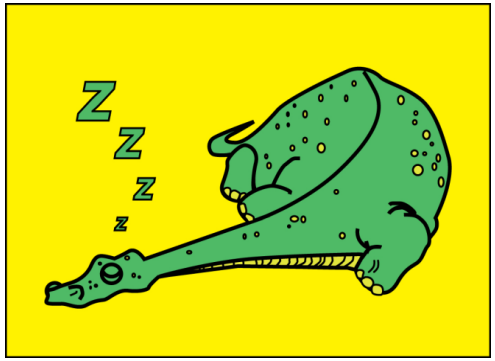
- ❑ Put on pajamas
- ❑ Use the bathroom
- ❑ Wash hands
- ❑ Brush teeth
- ❑ Get a drink
- ❑ Read a book
- ❑ Get in bed and go to sleep

Checklist

Sleep Resistance & Night Wakings

- Rocking and Swinging
- Snuggling
- Massaging
- Music
- White noise
- Night lights
- Calming scents
- Weighted blankets

Bedtime pass



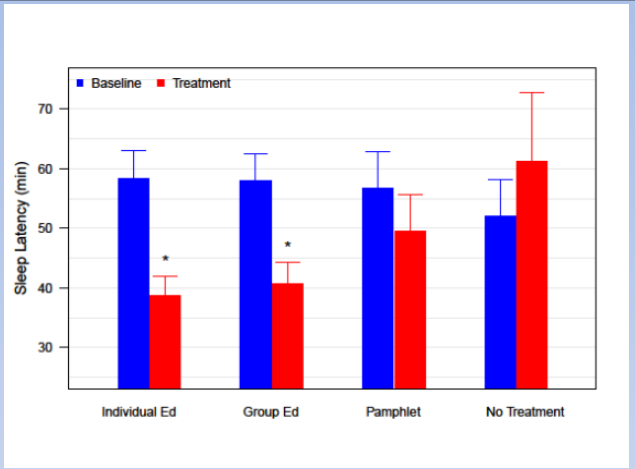
Friman, 1999

Parent Sleep Education in Autism

- ✓ We carried out a two-phase study in parents of children with autism, ages 2-10 years with sleep onset delay of 30 minutes or greater on 3 or more nights/week.
- ✓ Phase 1: 36 parents were provided either a sleep education pamphlet or no intervention. *(Adkins, Pediatrics, 2012)*
- ✓ Phase 2: 80 parents were randomized to either two 2-hour sessions in a group setting or one 1-hour session in an individual setting with a trained sleep educator with 2 follow-up calls *(Malow, JADD, 2014)*
- ✓ Sleep and behavioral measures obtained at baseline and 1 month post-treatment.

Parent Sleep Education in ASD: Results

Sleep Latency (time to fall asleep, minutes) as measured by actigraphy, significantly improved in parents receiving sleep education (vs. pamphlet). Individual vs. group education did not differ (*both p values = 0.0001).



Significant treatment improvements were also noted on:

- Children's Sleep Habits Questionnaire (insomnia domains)
- Repetitive Behavior Scale-Revised (restricted, stereotyped)
- Child Behavior Checklist (attention, anxiety)
- Pediatric Quality of Life Scale (total)
- Parenting Sense of Competence (efficacy, satisfaction)

(Malow, JADD, 2014)

Sleep Education in Community Pediatric Practices

Funding from Meharry-Vanderbilt Community Engagement Research Core, Vanderbilt CTSA, and American Sleep Medicine Foundation (now AASM Foundation) to expand to additional practices.

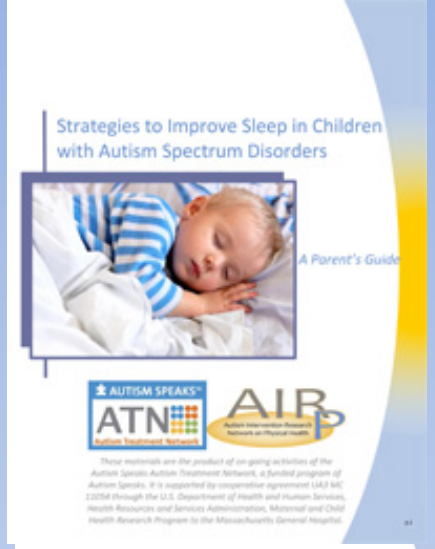
- ✓ Parents of 30 children with ASD and insomnia received sleep education (60-90 minutes with two follow-up sessions)
- ✓ Community therapists trained parents
- ✓ Pediatricians made referrals and evaluated for medical conditions

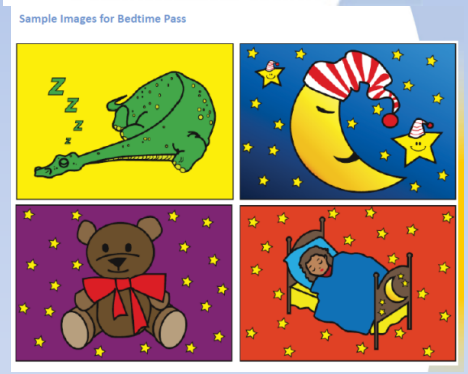
Results

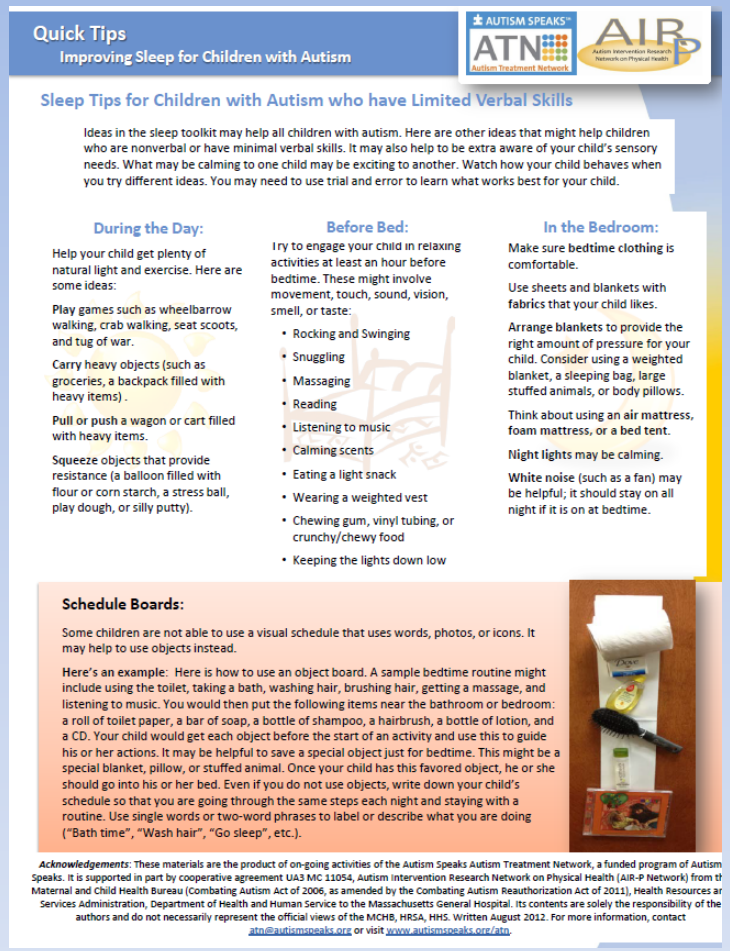
Therapists achieved fidelity goals during training and sessions

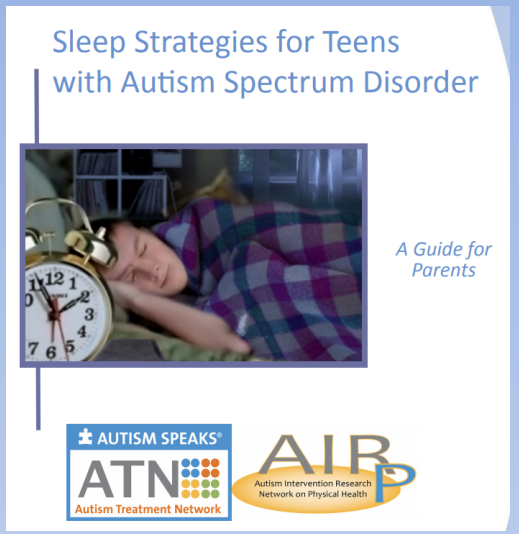
- ✓ Parents achieved scores of good to excellent understanding, comfort and implementation on the Parent Absorption Scale
- ✓ CSHQ for insomnia domains, FISH, and actigraphy (for sleep onset delay) showed improvement
- ✓ Qualitative analysis highlighted that parents were satisfied with the structure, expertise, and support provided by a trained sleep educator

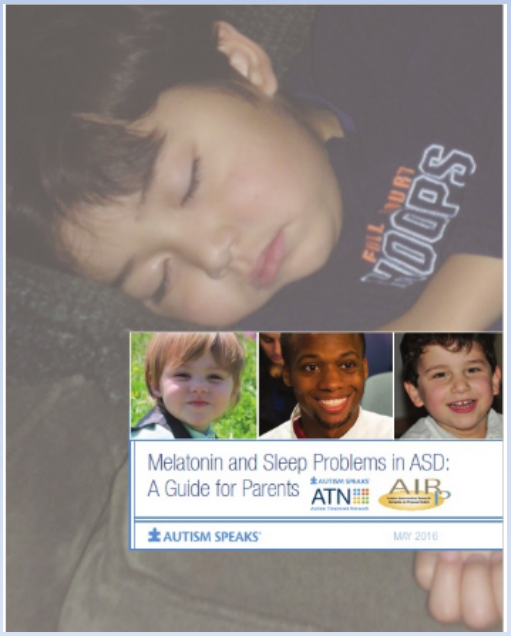
ATN/AIR-P Toolkits











Autism Speaks, online materials

Autism Speaks, Inc. is a non-profit charitable corporation with 501(c)(3) tax exempt status in the United States. Address: 1 East 33rd Street, 4th Floor, New York, NY 10016. U.S. tax-exempt number: 20-2329938.

When do we turn to medications?

- Use medications sparingly– to facilitate behavioral strategies rather than substitute for them
- Whenever possible, choose a medication that will treat a co-occurring condition 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.

Malow, Byers, Johnson, Weiss, Bernal, Goldman, Panzer, Coury, Glaze Pediatrics, 2012

Which medications work?

For which kids?

Tolerability

Patient/family collected data

Melatonin for Autism

- **Melatonin** (most studied, safe/well tolerated)

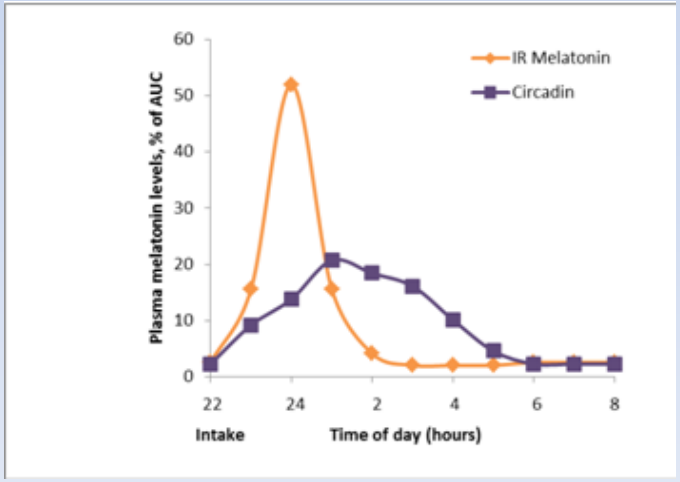
  Case series, randomized trials, and reviews– minimal side effects
  Anderson, J Child Neurology, 2008– 107 children
  Rossignol, Dev Med Child Neuro, 2011 – systematic review/meta analysis
  Malow, JADD, 2012– dose finding study– 3 mg effective in most children
  Most studies have looked at immediate release melatonin

  Melatonin (CR) + behavioral therapy most effective *(Cortesi, J Sleep Res, 2012)*

  Prolonged release mini-tablet improved sleep duration and sleep latency in 13 weeks of double-blind treatment (n = 125)
  Gringras, Am Acad Child Adol Psych 2017

  39 week open-label phase following 13 weeks
  Showed longer-term efficacy and safety
  Maras, J Child Ad. Psychpharm, 2018

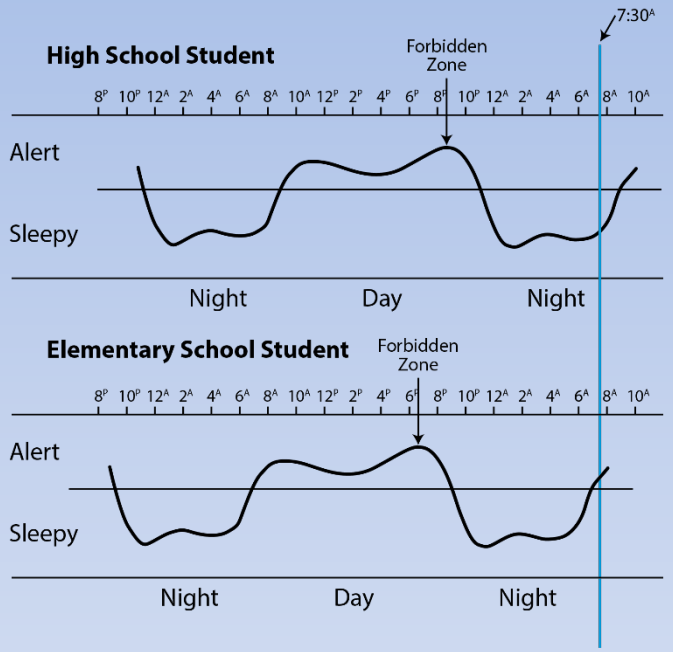
  Improvements in Child Behavior and Caregiver's QOL (in 13 week DB phase)
  Schroder, JADD, 2019



(Mostly Understudied) Medication Options for Insomnia in Autism

- Gabapentin *(Robinson and Malow, J Child Neuro, 2013)*
- Alpha-adrenergic agonists *(Ming, Brain Dev, 2008; Ingrassia, Eur Child Adol Psych, 2005)*
- Trazadone
- Hydroxyzine
- Mitazapine *(Posey, J Child Adol Psychopharm, 2001)*
- Benzodiazepines– useful in NREM arousal disorders
- Non-benzodiazepine receptor agonists (zolpidem, eszopiclone)
- Tricyclic antidepressants
- Other OTCs Diphenhydramine, Valerian, Tryptophan/5-Hydroxytryptophan

Sleep Patterns Shift in Adolescence



Resulting Pattern of Sleepiness and Alertness

Modified from Ferber R *Solving Your Child's Sleep Problems* 2006

- There is a 2 hour shift (on average) in sleep patterns with puberty.
- This shift is due to delayed release of melatonin and also to a slower buildup of sleep-promoting substances.
- Some teens have "delayed sleep phase" and are even more delayed.

Carskadon, Ann. NY Acad of Sci, 2004

- Delayed sleep phase is particularly common in adults with ASD (31%)

Baker and Richdale, JADD, 2017

Clinical Practice in Pediatric Psychology
2016, Vol. 4, No. 2, 112–124

2169-4826/16/$12.00 http://dx.doi.org/10.1037/cpp0000141

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

Whitney A. Loring, Rebecca Johnston, Laura Gray, Suzanne Goldman, and Beth Malow
Vanderbilt University Medical Center, Nashville, Tennessee

Sleep Education Program (two sessions) provided to 18 adolescents ages 11-18 years with ASD, confirmed by the ADOS, and their parents focused on behavioral strategies

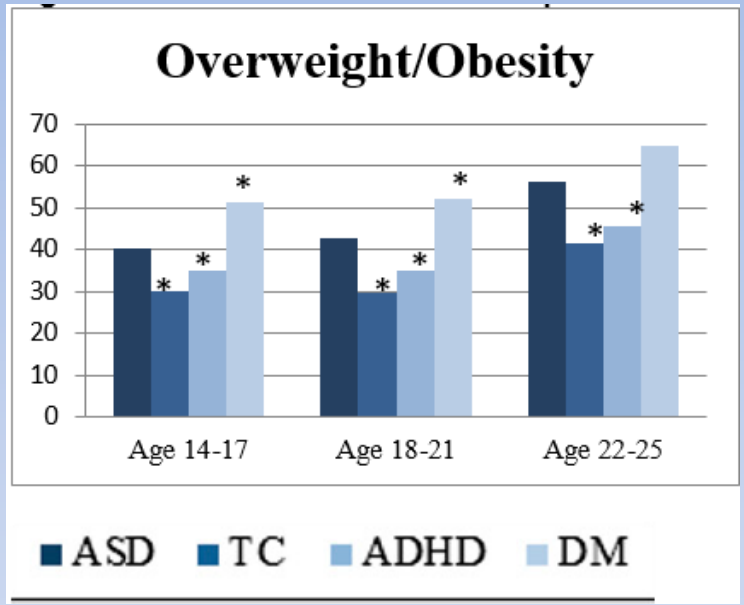
- Tailored to adolescent's cognitive level (IQ ranged from 71-124)
- Degree of parent involvement in sleep
- Individual sleep challenges
- Distraction/relaxation techniques incorporated

Improvements seen in actigraphy, sleepiness, and adolescent sleep wake scale

Sleep Treatments in Adults with ASD

- Remember co-occurring conditions
- For insomnia, incorporate cognitive/behavioral approaches – *CBTi*-- taking into account that modification in delivery may be needed

(McDonald, 2019)



Davignon, *Pediatrics,* 2018

- Similar guidelines for medication treatment apply
- Monitor closely for adverse effects

Summary and Future Directions

- Are any of the old or new medications for insomnia effective in autism and what are the side effects (across the lifespan)
- How do these medications compare in terms of effectiveness and side effects?
- Can medications and behavioral treatment work synergistically?
- How do we get overwhelmed parents of children with autism to use behavioral strategies?
- What about teens and adults with autism? How do we motivate them to improve their sleep?
- Can genetic, biomarker, or phenotyping studies guide our treatment plans?