Sleep in Autism

IACC Workshop on Under-Recognized Co-Occurring Conditions

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Have you seen this child?

- Alex is a 6-year-old boy with autism spectrum disorder (ASD). He takes hours to fall asleep. His parents state that “he can’t shut his brain down.” He drinks 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.
- Once asleep, he awakens multiple times during the night. Sometimes he awakens his parents. Other times he wanders around the house, goes to the kitchen to eat, and falls asleep in a different room.
- It is “nearly impossible” to awaken Alex in the morning for school. His parents are exhausted and very overwhelmed. Alex’s teacher describes him as being hyperactive and disruptive in class.

Framing Questions

- What do we know about sleep in autism?
- What is the evidence linking biological causes of sleep disturbance with features of ASD?
- What do we need to learn in order to treat sleep disturbance in ASD? What are the gaps? What are the opportunities?
- What autism-specific features affect proper diagnosis and treatment?

What Have We Learned?

- High prevalence of parent–reported sleep concerns in ASD, across cognitive levels.
  - Courturier (2005): **78% ASD** (TD 26%)
  - Krakowiak (2008): **53% ASD** (DD 46%, TD 32%)
  - Souders (2009): **66% ASD** (TD 45%)
- Sleep disturbance associated with child behavior/family functioning
- Insomnia is the most prevalent sleep disturbance
  - ✓ Prolonged time to fall asleep
  - ✓ Preference for delayed bedtime (older children)
  - ✓ Bedtime resistance (younger children)
  - ✓ Increased arousals and awakenings
  - ✓ Decreased sleep duration

Reynolds AM & Malow BA. (2011), Richdale AL & Schreck KA. (2009)

What Have We Learned?

- ✓ Multiple causes of insomnia; many are treatable.
- ✓ Medical (GI) & Neurological (epilepsy)
- ✓ Psychiatric: Anxiety, bipolar disorder, depression, obsessive compulsive or ADHD symptomatology
- ✓ Medications: Serotonin reuptake inhibitors, stimulants, some antiepileptic drugs
- ✓ Other Sleep Disorders: Obstructive sleep apnea, parasomnias, restless legs syndrome
- ✓ Behavioral: poor sleep habits...and also features related to ASD such as difficulty with transitions and sensory sensitivities. Exhausted parents may think poor sleep is part of autism and be unaware that behavioral approaches can help.
- ✓ Other causes related to ASD: Neurotransmitter abnormalities, including in melatonin pathway, possibly GABA and serotonin

Framing Questions

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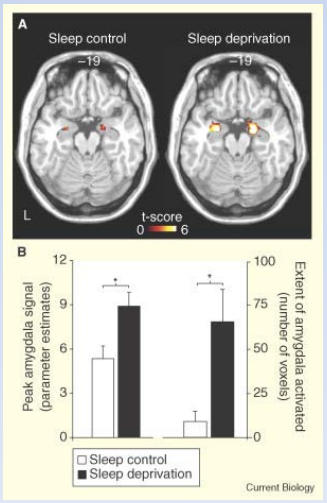
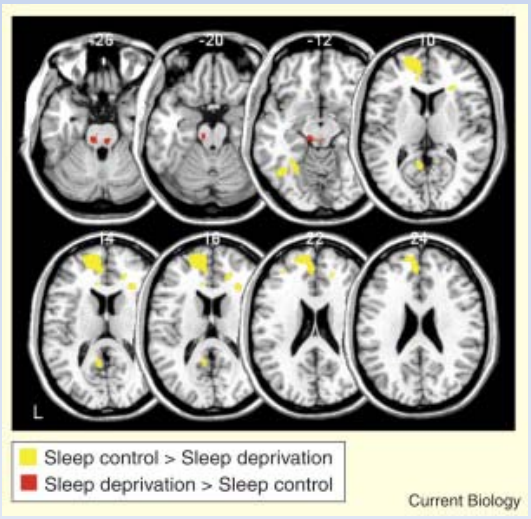
Biology of Sleep Disturbance and ASD: Emotional Regulation

Sleep deprivation affects the neural circuitry underlying emotional regulation, including connectivity of the amygdala and prefrontal cortex. (reviewed in Maski, 2013). This abnormal connectivity also exists in ASD.

- ✓An fMRI study in which sleep-deprived healthy adult participants were compared with those who had slept showed increased amygdala activation after viewing images that were emotionally adversive. (Yoo, 2007)
- ✓In addition, the functional connectivity was stronger between the medial-prefrontal cortex and the amygdala in the sleep control group, and the autonomic brainstem regions and the amygdala in the sleep deprived group.

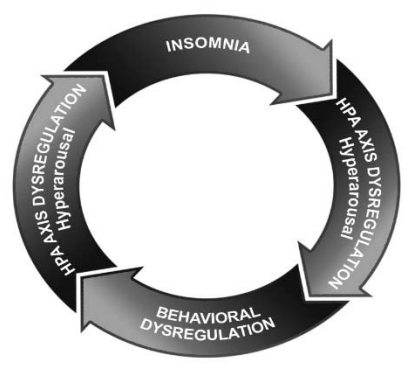




Biology of Sleep Disturbance and ASD: Arousal Dysregulation

- Arousal dysregulation (hyperarousal) may tie together several features of ASD (Mazurek, 2013)
  - ✓Anxiety
  - ✓Sensory over-responsivity
  - ✓Functional GI problems

  Insomnia?



- Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis occurs in both insomnia and ASD, in association with daytime stressors (Buckley, 2005 and Corbett, 2008 and 2009).
- Studies of autonomic function provide additional evidence for hyperarousal (elevated baseline heart rate; Kushki, 2013)
- Insomnia treatment studies designed to target hyperarousal provide an opportunity to measure biological markers of autonomic and HPA dysfunction

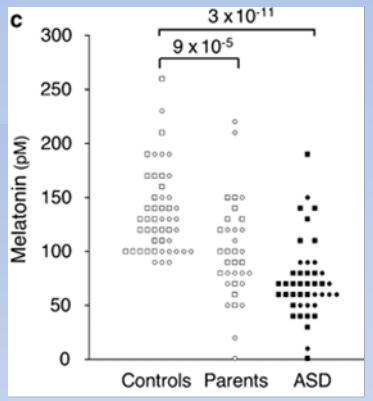
Biology of Sleep Disturbance and ASD: Melatonin

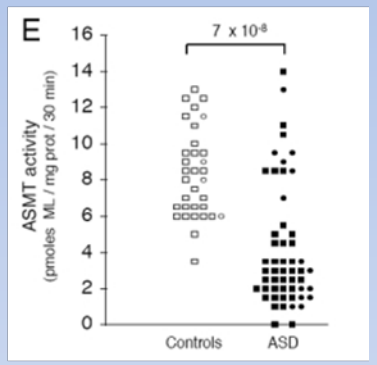
- Endogenous melatonin, produced by the pineal gland, promotes sleep and stabilizes circadian rhythms through actions on receptors of the SCN. (Pandi-Perumal, 2006)
- Apart from hypnotic and circadian properties, melatonin inhibits ACTH responses in the human adrenal gland. (Campino, 2011)
- Melatonin processing appears to be altered in ASD.

Biology of Sleep Disturbance and ASD: Melatonin

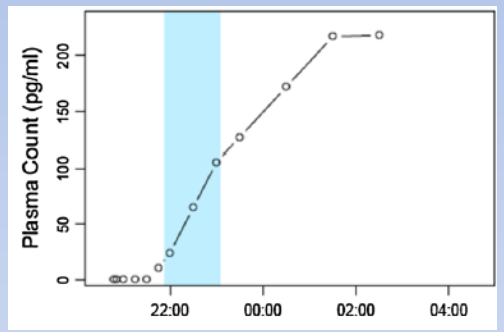
Examine melatonin synthesis and degradation pathways with both biochemical and molecular approaches

Tryptophan
↓
serotonin
↓ **AA-NAT**
N-acetylserotonin
↓ **ASMT**
Melatonin
↓ **CYP1A2**
6-sulfoxymelatonin
(major metabolite)

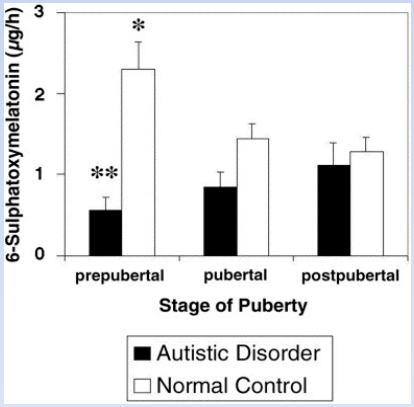




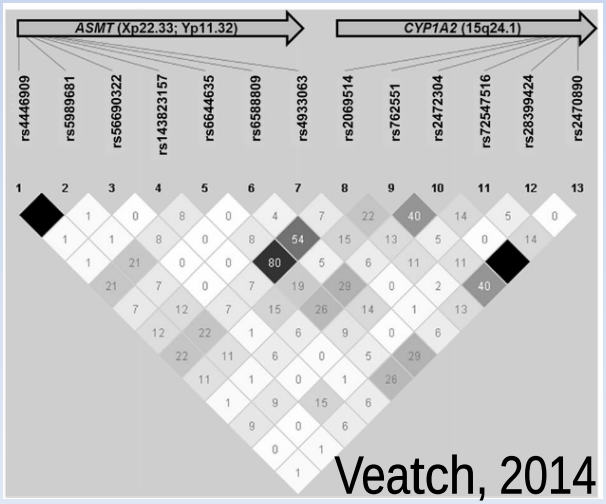
Melke, 2008



Goldman, 2014



Tordjman, 2005



Veatch, 2014

Framing Questions

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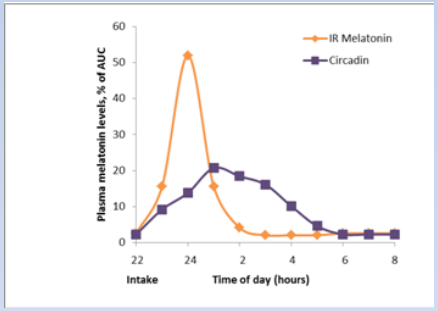
Gaps and Opportunities in Treatment

Autism Speaks Autism Treatment Network (AS ATN) Practice Pathway for Management of Insomnia– Supplement in *Pediatrics* (Malow, 2012)

- ✓ Clinicians need to ask about sleep.
- ✓ Medical co-occurring conditions need to be identified and treated.
- ✓ Behavioral sleep education works (Vriend, 2011; Malow, 2014) (and also improves child behavior and family functioning)
- ✓ Limited studies of sleep medications for ASD; none FDA-approved.

Under study:

- ✓ Melatonin agonists (Tasimelteon®, Vanda Pharmaceuticals)
- ✓ Prolonged release melatonin minitablet preparations that children can easily swallow (Circadin®, Neurim Pharmaceuticals)

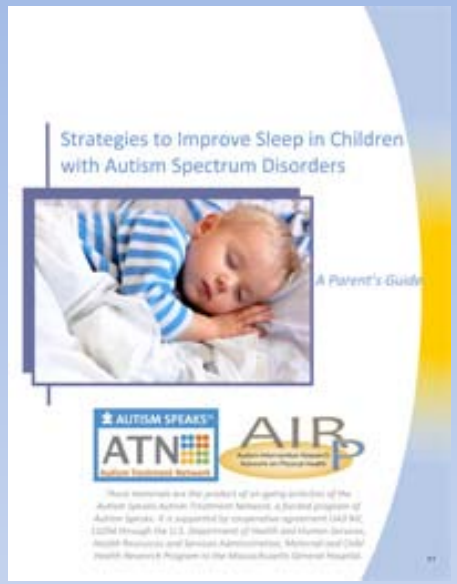


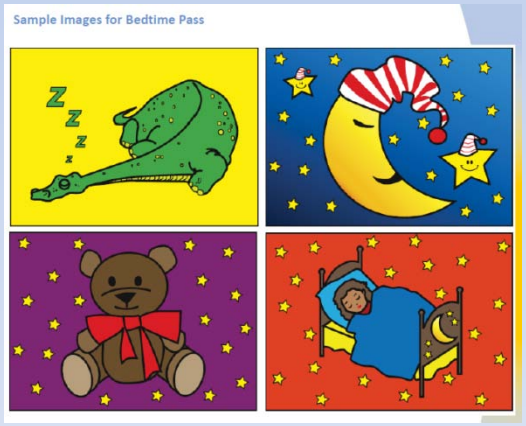
Zisapel, 2010

Measures of baseline sleep status and treatment response

- ✓ Polysomnography
- ✓ Actigraphy
- ✓ Sleep Questionnaires and Diaries

Autism Speaks Autism Treatment Network Toolkits





http://www.autismspeaks.org/science/resources-programs/autism-treatment-network/tools-you-can-use/sleep-tool-kit
Or search for Autism Speaks Sleep Toolkit

Summary and Future Directions

What we know:

- ✓ Sleep disturbance, especially insomnia, is common in ASD (50-80%)
- ✓ Sleep disturbance associated with child behavior/family functioning
- ✓ There are many treatable causes of insomnia

What we think we know (more data are needed):

- ✓ Improving sleep impacts favorably on children and families

What we still need to know:

- ✓ How do we best measure sleep and improvements in sleep?
- ✓ What treatments are effective? And in which children?
- ✓ Which children need medications for sleep? (vs. sleep education alone)
- ✓ Whether biological markers of sleep disturbance (e.g., cortisol, melatonin, genetic variability) predict treatment response.