Outline

1) definitions, terminology & basics of the sleep/ wake cycle
2) type of sleep problems/disorders in ASD
3) working theories about why people with ASD sleep differently
4) current approaches to treatment
5) where to go from here
Sleep is a reversible behavioral state of perception disengagement from and unresponsiveness to the environment.

Sleep is dynamic.

Sleep both reflects the state of and contributes to the health of your body and brain.
Sleep Terminology

Sleep architecture: structure/stages of sleep: REM, non-REM (stages 1-3), wake

Ultradian rhythms: the nocturnal cycle of sleep stages

Circadian rhythms: the 24-hour rhythm of sleep/wakefulness and many physiologic systems (e.g., body temperature, hormones)

Sleep regulation: determinants of sleepiness and alertness levels

Sleep patterns: a combination of biology, learning, maturation, culture and environment
Circadian Timing System

- Wake-promoting
- ~24.3 h: Synchronized or “entrained” to 24 hour day by environmental cues
- Governs many body systems
- **Light** most powerful cue; leads to suppression of melatonin secretion by the pineal gland
- Predictable 24 h peaks and troughs of alertness
Circadian Regulation

Body temperature lowers

Hormone levels rise and fall
“Two Process” Model of Sleep Regulation

Sleep Regulation Conceptual Framework

- Homeostatic Sleep Drive
- Circadian Rhythm Sleep-Wake Cycle

Sleep Facilitators-Inhibitors
- Physiologic
- Behavioral
- Environmental
- Genetic
Optimal Sleep

Sleep Practices
(Schedules, Feeding, Napping, Co-Sleeping)

Macro Sleep Environment
(Temperature, Noise, Light, Toxins, Safety)

Micro Sleep Environment
(Sleep Surface, Bedding, Position)

Social/Emotional Context
(Attachment, Temperament, Maternal Mental Health/Stress)

Socio-Cultural Context
(Values, Parenting Practices)

Health Issues
(Illness, Medication, Nutrition)

Developmental Context
(ID?)

Optimal Sleep
States of Being

AWAKE

REM SLEEP

NREM SLEEP
Neurobiology of Sleep and Wake

Thalamus
- Cortical Activation
- Sleep Spindles
- EEG Synchronization

Cortex

Brainstem
- Ascending Cortical Activation
- REM/SWS Switch

Hypothalamus
- Sleep/Wake Switch

Suprachiasmatic Nucleus (SCN)
- Circadian Clock

SWS = slow-wave sleep

SWS = slow-wave sleep
Brain waves represent different stages of sleep.

**NREM Sleep**
- Stage 1
- Stage 2
- Stage 3/4

**REM Sleep**

![REM Sleep waveforms](image)

![Sleep cycle graph](image)
<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Wakefulness</th>
<th>NREM sleep</th>
<th>REM sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>↑↑↑</td>
<td>—</td>
<td>↑↑</td>
</tr>
<tr>
<td>Monoamines</td>
<td>↑↑↑</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>Orexin/Hypocretin</td>
<td>↑↑↑</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MCH</td>
<td>—</td>
<td>—</td>
<td>↑↑</td>
</tr>
<tr>
<td>GABA/galanin</td>
<td>—</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>
Major gaps exist in understanding processes underlying links between sleep and neurodevelopment.
Sleep In Early Childhood

• Newborns spend 16-17/24h asleep

• By age 2y, average child has spent 9500h (~13mths) asleep vs 8000h awake

• Between 2-5y, time asleep = time awake

• In school-age children, sleep occupies 40% of the 24h day

• **Sleep is the primary activity of the brain during early development**
**CONSENSUS STATEMENT**

**Recommended Amount of Sleep for Pediatric Populations:**
A Consensus Statement of the American Academy of Sleep Medicine

Shalini Paruthi, MD<sup>1</sup>; Lee J. Brooks, MD<sup>2,3</sup>; Carolyn D’Ambrosio, MD<sup>4</sup>; Wendy A. Hall, PhD, RN<sup>5</sup>; Suresh Kotagal, MD<sup>6</sup>; Robin M. Lloyd, MD<sup>6</sup>; Beth A. Malow, MD, MS<sup>7</sup>; Kiran Maski, MD<sup>8</sup>; Cynthia Nichols, PhD<sup>9</sup>; Stuart F. Quan, MD<sup>10</sup>; Carol L. Rosen, MD<sup>11</sup>; Matthew M. Troester, DO<sup>12</sup>; Merrill S. Wise, MD<sup>13</sup>

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<table>
<thead>
<tr>
<th>Age Group</th>
<th>Age Range</th>
<th>Recommended Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns/Infants</td>
<td>4 - 12 months</td>
<td>12-16 hours</td>
</tr>
<tr>
<td>Toddlers/Children</td>
<td>12 - 24 months</td>
<td>11-14 hours</td>
</tr>
<tr>
<td></td>
<td>3 - 5 years</td>
<td>10-13 hours</td>
</tr>
<tr>
<td></td>
<td>6 – 12 years</td>
<td>9-12 hours</td>
</tr>
<tr>
<td>Adolescents</td>
<td>13-18 years:</td>
<td>8-10 hours</td>
</tr>
</tbody>
</table>
Hypnogram
When sleep is fragmented by frequent arousals, the amounts of both deep sleep and REM sleep are severely compromised.

The very high arousal threshold in deep sleep in children may be protective in terms of neurodevelopment.
sleep disruption.... characterize the disturbance

• Fragmentation

• Restriction

• Misalignment
Insomnia

Insomnia is defined as a **persistent difficulty with sleep initiation, duration, consolidation or quality** that occurs despite **adequate opportunity** and circumstances for sleep and results in some form of **daytime impairment**
CAUSES OF INSOMNIA IN ASD

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/periodic limb movement disorder (nutritional link to low iron in ASD)

Behavioral: Children with ASD may have difficulty with emotional regulation, transitions, and understanding parental expectations regarding sleep. Parents may have difficulty effectively conveying these expectations given other priorities and stressors.

Other causes related to ASD: neurotransmitter abnormalities, including melatonin pathways, possibly GABA and serotonin.

Multiple causes may exist in the same child
Theories of Insomnia in ASD

Different organization (intrinsic abnormalities in GABA, glutamate, aminergic)

Circadian gene abnormalities (Veatch 2016)

Abnormal melatonin production (Kulman, 2000, Melke 2008, Tordjman 2005)

Medical co-occurring conditions

Lack of entrainment to social cues
The relationship between sleep and behavior in autism spectrum disorder (ASD): a review

Simonne Cohen, Russell Conduit, Steven W Lockley, Shantha MW Rajaratnam and Kim M Cornish
http://www.autismspeaks.org/science/resources-programs/autism-treatment-network/tools-you-can-use/sleep-tool-kit OR search for Autism Speaks Sleep Toolkit
Medications for Insomnia

**OTC**

- Antihistamines**
- Melatonin**
- Herbals/Supplements**

**Rx**

- BZDs
- Non-BzRAs**
- Melatonin receptor agonist*
- Histamine receptor agonist*
- Orexin receptor antagonist*
- Alpha agonists**
- Antidepressants
- Antipsychotics**
- Anticonvulsants
- Other

*FDA approved in adults
**Pediatric data available

NONE APPROVED IN CHILDREN
Melatonin

Most commonly dispensed hypnotic drug, especially in young children (1-2yo)

Supplementation affects endogenous pineal hormone
Has both hypnotic (MT1) and chronobiotic (MT2) properties
As chronobiotic, timing of dose dependent on DLMO (3-5 hrs prior)
Pharmacokinetics: plasma levels peak 1 hr

(Hartz et al, 2012)
Melatonin

Additional indications
• Possible anti-seizure effect; no evidence exacerbation
• Headaches
• Neuroprotective effects animal models; hypoxic-ischemic injury neonates?

Adverse events
• Long-term side effects unknown - potential suppression hypothalamic-gonadal axis (trigger precocious puberty upon discontinuation) but little evidence
• Lowered BP, glucose reduction
• Increased immune system reactivity
• Most frequently reported side effects: morning sedation, increased enuresis, headache, dizziness, mood changes, GI symptoms
• Inhibitors of CYP1A2 (TCAs, fluvoxamine) may increase melatonin concentration; OCPs also decrease metabolism
• Increase melatonin metabolism: carbamazepine, omeprazole
Melatonin: Pediatric Studies (ADHD/ASD)

Premise: Children with NDD may have a delayed endogenous circadian clock

- ADHD patients with sleep onset insomnia vs typical controls have significantly later sleep onset, morning wake time, melatonin onset
- 5 published trials suggest 3-6 mg bedtime melatonin significantly shortens SOL in children with ADHD

Premise: Studies suggest alterations of melatonin secretion in children with ASD, daytime elevation, lack of or later nighttime elevation, decreased amplitude
- Growing evidence melatonin effective in treating sleep-onset and possibly maintenance insomnia (CR) in ASD
- Usual dose 1-3mg 30 min before BT; dose range 1-6mg

(*Tjon et al 2003; Weiss et al 2006; Van der Heijden et al 2007; Mohammedi et al 2012; Hoebert et al 2009; Rossignol 2011; Cortesi 2012)
Melatonin: Clinical Guidelines*

Consider for prolonged sleep onset latency (SOL)

Minimum age 6 months

**Chronobiotic**
– Recommend salivary melatonin levels before starting; administer 2-3hrs before DLMO (if unavailable, administer 3-4h before actual SO)
– Start with 0.2-0.5mg; increase as needed by 0.2-0.5mg/wk to max 3 mg

**Hypnotic**
– Start with 1-3mg 30min before BT; increase as needed by 1mg/wk to max 3mg (<40kg) or 5mg (>40kg)
Treatment duration >1mth; consider D/C annually

Melatonin

**PROS**
- Empirical evidence for efficacy in typically-developing children and those with neurodevelopmental disorders
- Minimal effects on sleep architecture
- Acceptability to caregivers
- Low side effect profile
- Widely available
- Low cost
- Low dose and liquid preparations available

**CONS**
- Long-term side effects uncertain
- Few or no studies in other psychiatric populations (eg, anxiety, mood disorders)
- Dosing timing critical and should be based on DLMO
- Little evidence to support use of extended-release for maintenance insomnia
- Reliability of OTC preparations uncertain
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**Bottom Line:** Most appropriate used in patients with circadian phase delay; reasonable choice in general and special pediatric populations (ASD, ADHD) with sleep onset insomnia who may need longer term medication.
SUMMARY: SLEEP & ASD

• Sleep is complex, finely orchestrated
• Homeostatic, Circadian and External Factors Influence Pattern
• Insomnia most prevalent disturbance, reasons not clear
• Behavioral Modification May Work
• Melatonin best studied with best profile
• FUTURE DIRECTION: NEURODEVELOPMENTAL SLEEP RESEARCH
Dysregulation of neurotransmitter systems

Clock gene polymorphisms and dysregulation

Brain structure abnormalities

Severity and functioning

Sleep-wake cycle disturbances

Neurocognitive/neuropsychiatric impairment

Stages

Ultradian Rhythms

Neural Oscillations

Circadian Rhythms

NT profiles

Homeostasis
A consortium is established to *create and initiate standardized protocols* for collecting longitudinal, prospectively ascertained electrophysiologic sleep data with contemporaneous behavioral phenotyping to identify normal and abnormal developmental trajectories amenable for potential therapeutic intervention.

**Summary on NIH website:**