Nationwide Children's Hospital Behavioral Health Webinar Series for Primary Care

Overview and Medication Management of Common Pediatric Sleep Disorders

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&
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Wednesday, February 10, 2021

12:00 – 1:00 PM

Join by Phone: 1-415-655-0001
Conference ID: 178 672 8753

WebEx: http://bit.ly/NCH-BHWebinar-10-Feb-2021

This session is eligible for 1.0 Category 1 CME credit upon completion of the CME Evaluation Survey.

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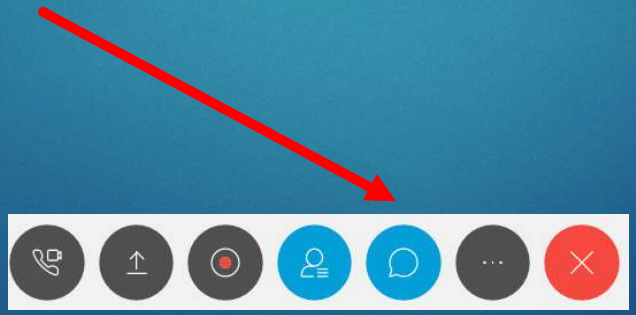
A Few Reminders

- ✓ This webinar is being recorded
- ✓ We have **muted** all participants
- ✓ **Chat with us during the webinar!** To type a question or comment for the speaker or facilitator, enter it directly into the WebEx chat box



Thanks for joining us today!

CME Objectives

- The participant will learn common sleep issues in psychiatric disorders.
- The participant will learn why we sleep.
- The participant will understand the mechanism of action of melatonin for human sleep.
- The participant will understand the limitations of sedating antidepressants for sleep.
- The participant will learn the best approach for insomnia in patients with autism spectrum disorders.

Pediatric Sleep and Psychiatry: Brief Overview

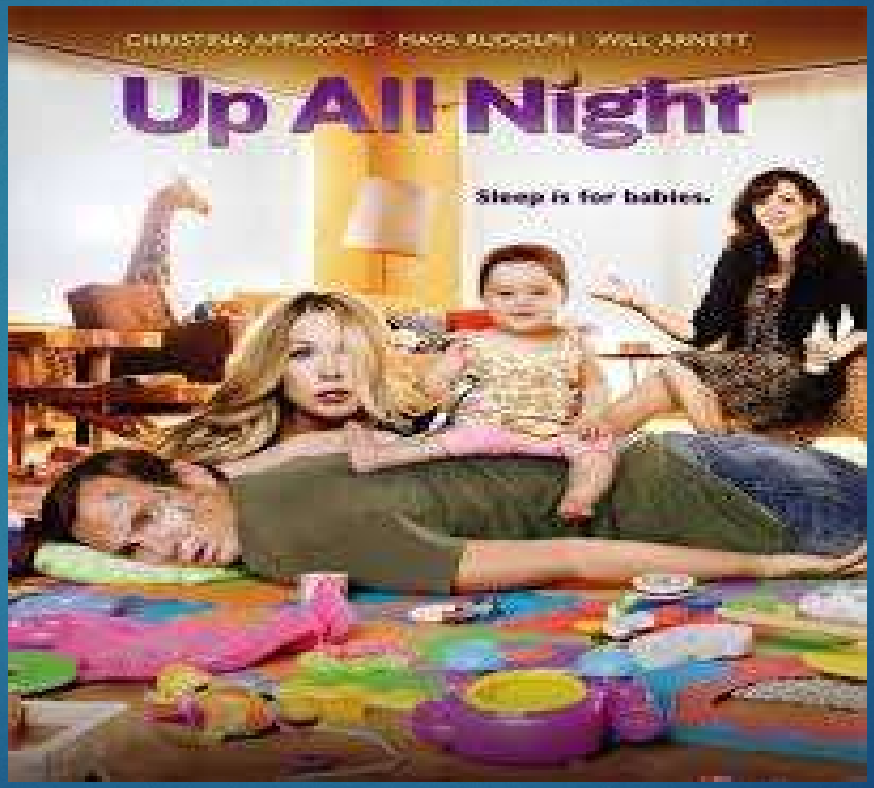
UJJWAL RAMTEKKAR, MD, MBA, MPE

CHILD AND ADOLESCENT PSYCHIATRY, PARTNERS FOR KIDS

We all Zzzzzz……

"If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process ever made."
-Allan Rechtschaffen

But it's a problem for parents only when……

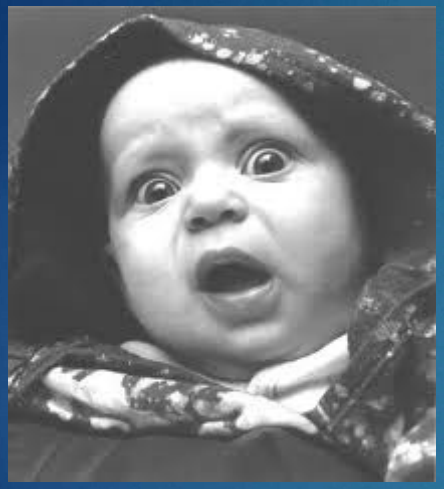


Sleep and mental health: Bidirectional relationship

Common sleep problems in psychiatric disorders

- Difficulty falling asleep (initial insomnia)
- Frequent and prolonged nighttime awakenings (intermittent insomnia
- Irregular sleep-wake cycle (circadian disturbance)
- Short sleep duration (early morning awakenings)
- Periodic limb movements (ferritin deficiency, ADHD?)
- Obstructive sleep apnea (low tone, weight gain)

Sleep in anxiety disorders



- Sleep problems at age 4 has strong correlation with anxiety and depression in adolescence
- Bedtime refusals, nightmares, night awakenings
- Recurrent nightmares: hallmark of abuse or trauma
- ↓ Slow Wave Sleep, ↑ awakenings, ↑ sleep latency
- Addressing sleep problems may be a critical step in recovery of anxiety disorders

Sleep in Depressive disorders

- Initial sleep disturbances related to development of MDD at the end of 12months
- Mainly initial and maintenance insomnia
- Differences based on gender and dev. stage
- Objective and subjective perception inconsistent
- ↑Sleep onset latency, ↓REM latency, ↑REM density - suicide and depression with psychosis
- Abnormal circadian rhythm

Sleep in bipolar disorders

- Decreased need for sleep – core symptoms in mania
- Very few studies systematically studies sleep in Pediatric Bipolar Disorder
- Sleep problems in youth were most commonly present during most severe mood symptoms
- More sleep complaints during depressive episode than manic episode
- Difficulties initiating sleep, more restless sleep, frequent nightmares, and morning headaches in young kids
- Only two studies recorded reported objective PSG data
  a. ↑ stage 1 sleep, ↓ SWS, no change REM sleep
  b. ↑ awakenings , ↓ REM sleep

Sleep in ADHD

- 5 fold more sleep complaints than general population
- Sleepiness at awakening, delayed sleep onset, frequent night awakenings, bedtime resistance
- Increased risk of intrinsic sleep problems such as periodic limb movement disorder (PLMD), increased sleep disordered breathing
- Unclear if affected by stimulants and hyperactivity
- PSG results very inconsistent
- Increased sleep propensity during the day on MSLT
- Delayed circadian pacemaker is implicated

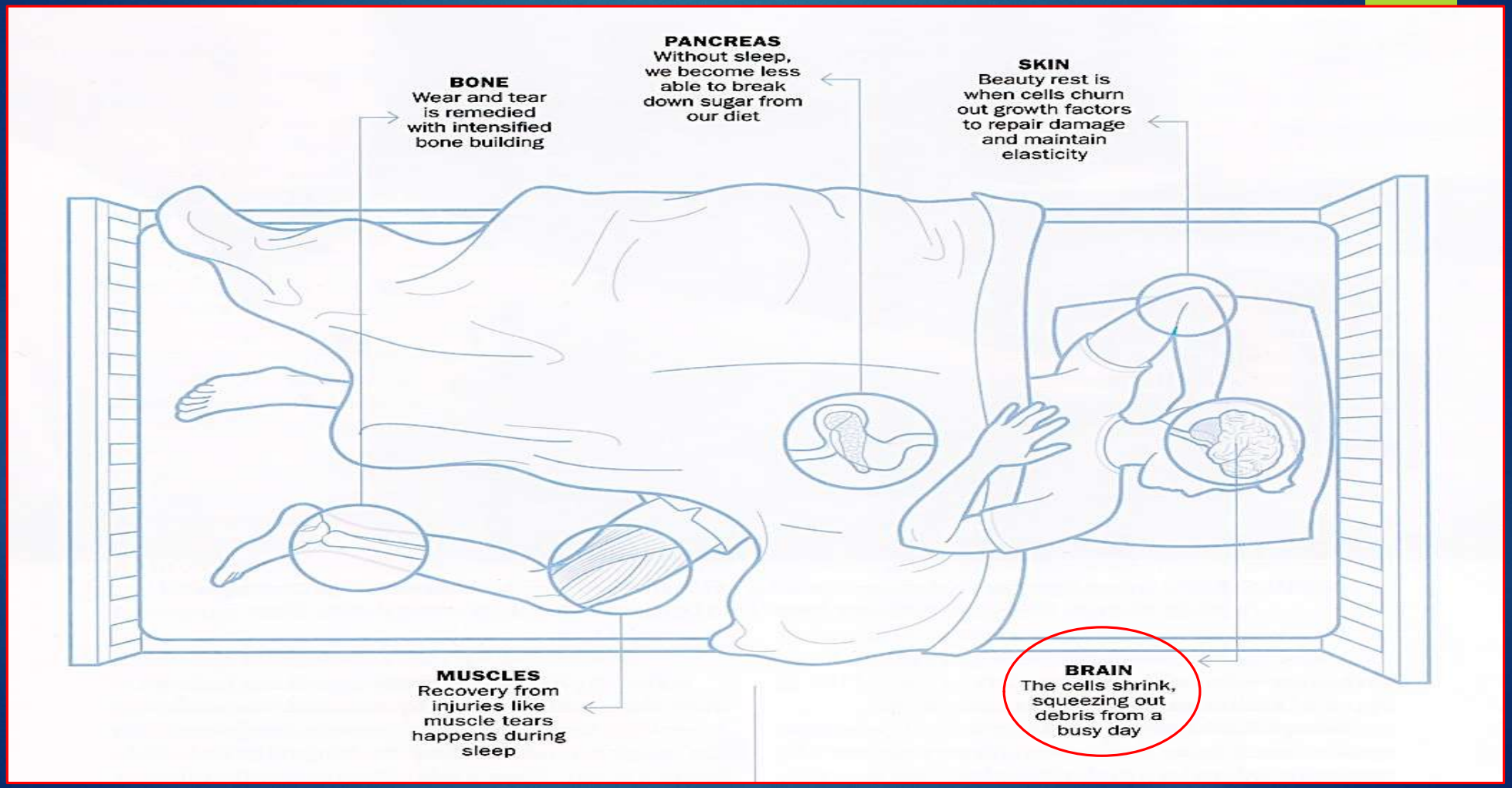
Pediatric Sleep Medications

ROBERT A. KOWATCH, MD, PHD
NCH DIVISION OF PULMONARY/SLEEP MEDICINE

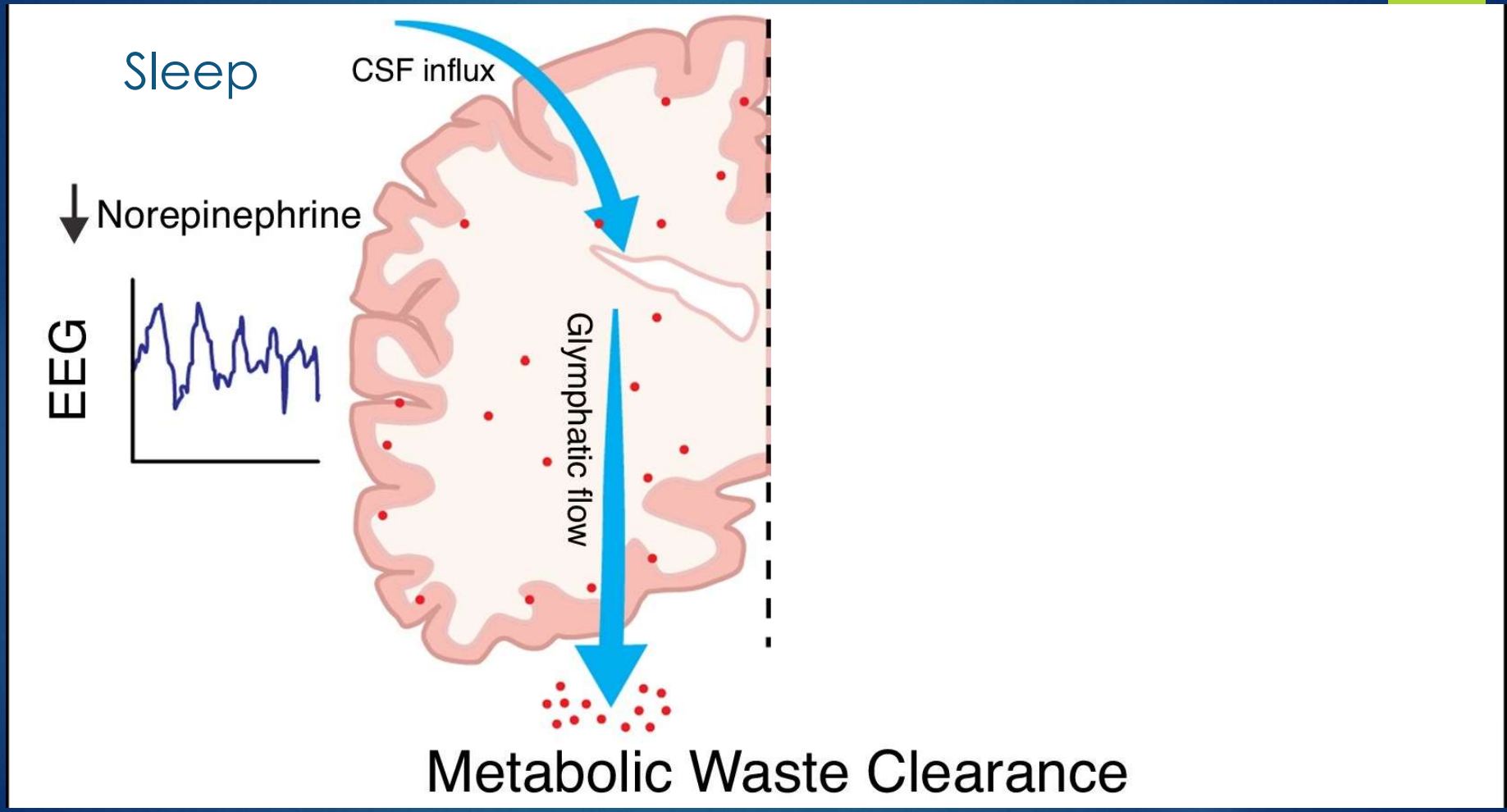
Sleep Topics

- Quick Overview of Sleep
- Pediatric Sleep Medications
  - Nonprescription Medications
  - Prescription Insomnia Drugs
    - Benzodiazepines
    - Nonbenzodiazepine receptor agonists
    - Orexin Antagonists
    - Alpha-adrenergic agonists
    - Antidepressants
- Sleep in patients with Autism Spectrum Disorder

Your Body While Sleep



Glymphatic System



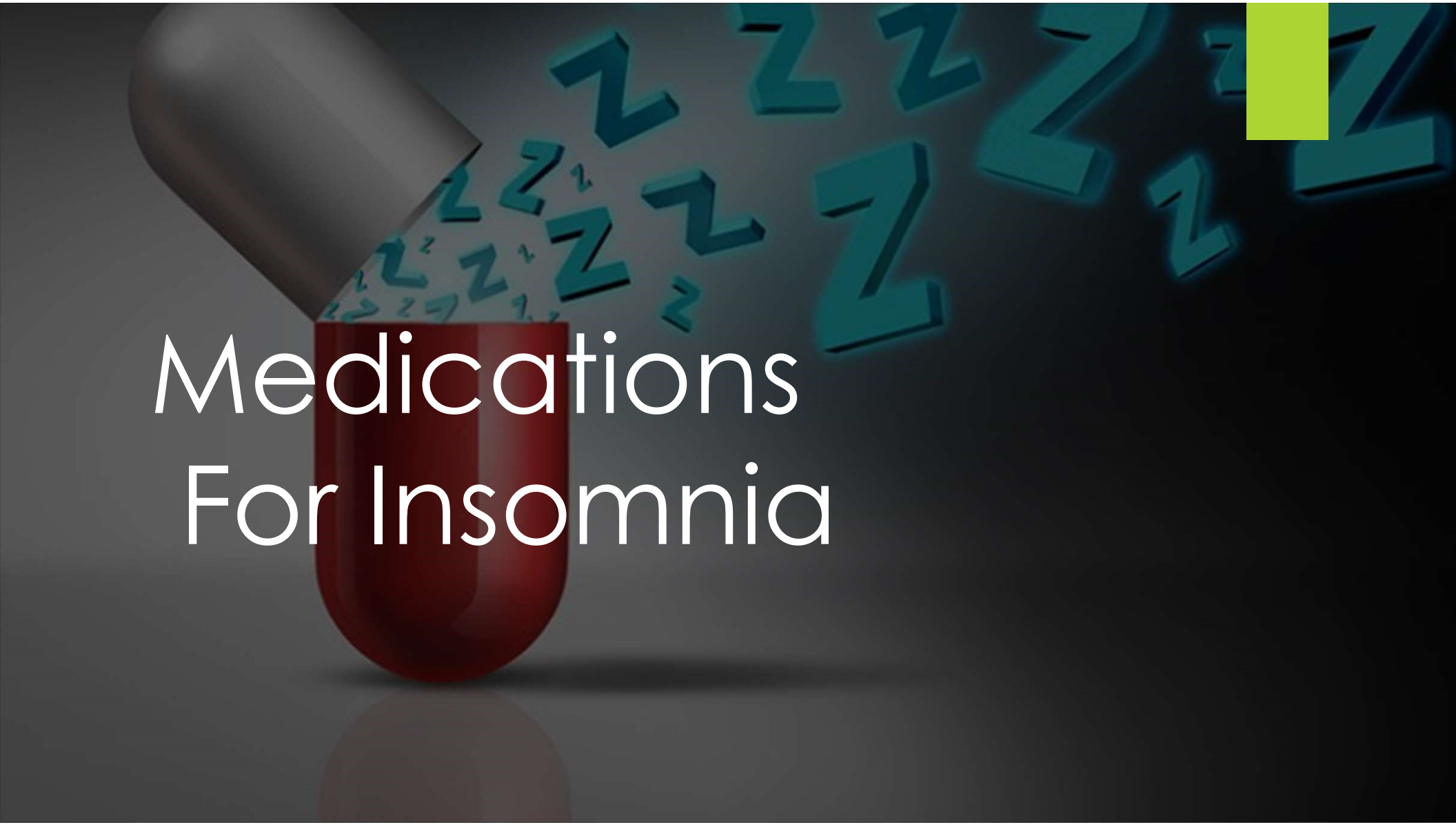
We Sleep to Perform Well the Next Day

When we sleep well, we wake up feeling refreshed and alert for our daily activities

Sleep affects how we look, feel and perform on a daily basis, and can have a major impact on our overall quality of life

To get the most out of our sleep, both quantity and quality are important

Then we wake up less prepared to concentrate, make decisions, or engage fully in work and social activities



Medications For Insomnia

Medications For Insomnia

- Nonprescription Medications
  - Antihistamines
  - Melatonin
- Prescription Insomnia Drugs
  - Benzodiazepines
    - e.g., Ativan
  - Nonbenzodiazepine receptor agonists
    - e.g. Zolpidem (Ambien)
  - Orexin Antagonists
    - Suvorexant (Belsomra)
  - Alpha-adrenergic agonists
    - Intuniv
  - Antidepressants
    - Tricyclic antidepressants
      - Doxepin (Silenor)
    - Atypical antidepressants
      - Trazodone
      - Remeron

Antihistamines

Diphenhydramine

- Peak levels 2 hours after ingestion
- Duration of action 4-6 hours
- 0.5mg/kg up to 25 mg

Considerations regarding antihistamines for sleep in children

Pros	Cons
■ Rapid onset of action and relatively short half-life ■ Caregiver acceptance high ■ Generally well tolerated ■ Widely available ■ Low cost ■ Liquid formulations available ■ Combination formulations advantageous in some situations	■ Mixed empirical evidence of efficacy ■ Adverse reactions include anticholinergic (eg, dry mouth, constipation, urinary retention, blurred vision), paradoxical excitation, residual morning sleepiness ("hangover") ■ Development of tolerance to sedation common ■ Possible interaction with other anticholinergics
Bottom line – Consider for short-term situational and/or occasional use in younger children, especially with comorbid atopic disease.	

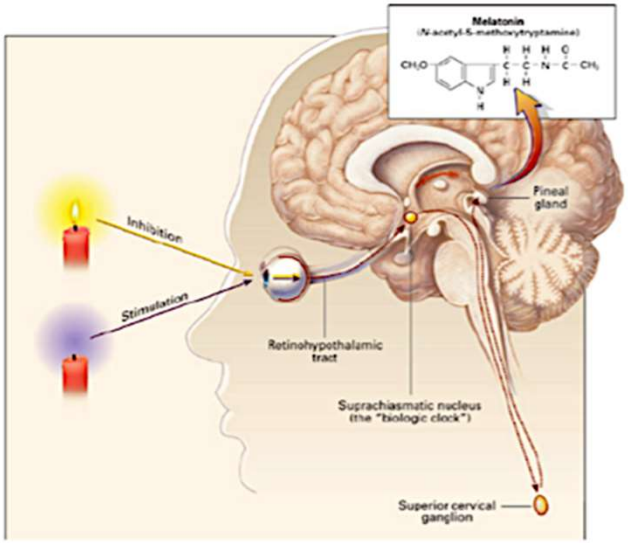
Owens et al. Up to Date 2021

Melatonin

- Produced by pineal gland; "turned on" by the SCN at night by darkness
- Melatonin on it's own will not induce sleep, it is more like a "darkness" signaler
- Dosing
  - 2.5 – 3 mg in Children
  - 5 mg Adolescents
  - Up to 10 mg in ASD

Melatonin / Circadian rythym

- Light inhibits melatonin release from the pineal gland
- the absence of light allows melatonin secretion
- Melatonin agonist for sleep



Considerations regarding melatonin for sleep in children

Pros	Cons
■ Empiric evidence for efficacy in improving sleep onset 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	■ Long-term side effects uncertain ■ Few or no studies in other psychiatric populations (eg, anxiety, mood disorders) ■ Dosing timing is important and depends on clinical use (several hours before bedtime for circadian rhythm effects or shortly before bedtime for sleep-onset insomnia) ■ Little evidence to support the use of extended-release formulation for sleep-maintenance insomnia ■ Reliability of over-the-counter preparations uncertain
Bottom line – Most appropriately used in patients with circadian phase delay. It is also a reasonable choice for children with sleep-onset insomnia who may need long-term pharmacotherapy, including those with autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD).	

Owens et al. Up to Date 2021

Ramelteon (Rozerem)

- First melatonin receptor agonist approved for treating insomnia (2005)
- 17x more potent at melatonin type I (decreased waking signal) than type II (circadian rhythms) receptors
- Primary benefit on sleep latency
- Non-scheduled medication
  - lacks potential for abuse or dependence
- Adverse effects: nausea, headache, fatigue
- Can cause prolactin increases

FDA-Indicated Sedative Hypnotics (Adults)

- **Benzodiazepines (BZs)**
  - Flurazepam (Dalmane)
  - Quazepam (Doral)
  - Temazepam (Restoril)
  - Triazolam (Halcion)
- Melatonin Receptor Agonist:
  - Ramelteon (Rozerem)
- Tricyclic Antidepressant: Doxepin (Silenor)

- **Non-Benzodiazepine Receptor Agonists** (BzRAs)
  - Eszopiclone (Lunesta)
  - Zaleplon (Sonata)
  - Zolpidem (Ambien)
  - Zolpidem Extended Release (Ambien CR)
  - Zolpidem Sublingual (Intermezzo)

Considerations regarding benzodiazepines (GABA receptor agonists) for sleep in children

Pros	Cons
■ Half-lives vary; some appropriate for sleep-maintenance insomnia ■ Anticonvulsant, anxiolytic, myorelaxant properties ■ Decrease SOL, decrease WASO; increase TST, decrease arousals (depending on drug's duration of action)	■ Effects on sleep architecture: Most suppress SWS ■ Side effects: ● Potential daytime sedation/cognitive impairment, rebound insomnia; anterograde amnesia, disinhibition ● Respiratory depression; OSA is a relative contraindication ● Ethanol use or CNS depressants may potentiate effects ■ Dependence/abuse potential
Bottom line – Limited utility in pediatric populations; other properties (eg, anxiolytic, long duration of action) may be useful in some patients.	

GABA: gamma-aminobutyric acid; SOL: sleep onset latency; WASO: wake after sleep onset; TST: total sleep time; SWS: slow-wave sleep; OSA: obstructive sleep apnea; CNS: central nervous system.

Owens et al. Up to Date 2021

Controlled Trials of Z-Drugs in Children with ADHD

Two large industry sponsored trials

- Controlled Clinical Trial of Zolpidem for the Treatment of Insomnia Associated With ADHD
  - 201 subjects aged 6–17 years with a diagnosis of ADHD and insomnia
- Eszopiclone for Insomnia Associated with ADHD
  - 371 subjects aged 6–17 years ADHD and sleep disturbances

Neither drug demonstrated efficacy

- Treatment-emergent adverse events
- 40-60%
  - dizziness, headache, and hallucinations….

Blumer et al. PEDS 2008; Sangal et al. PEDS 134, 4: 2014

Considerations regarding nonbenzodiazepine receptor agonists for sleep in children

Pros	Cons
■ Preparations available for either sleep-onset insomnia or sleep-maintenance insomnia ■ Little effect on sleep architecture: Some SWS suppression ■ Generally well tolerated (unpleasant taste, headache, anterograde amnesia, daytime drowsiness) ■ Some preparations have limitations on duration of use ■ Alternative formulations available (sublingual, oral spray)	■ Little empirical evidence of efficacy in children ■ Uncommon but significant side effects ● Hallucinations ● Complex sleep-related behaviors (eg, sleepwalking or sleep driving)* ■ Abrupt withdrawal with prolonged use (>2 weeks) may be associated with rebound
Bottom line – Lack of documented efficacy and sleep-related behavior side effects limit utility except in older adolescents.	

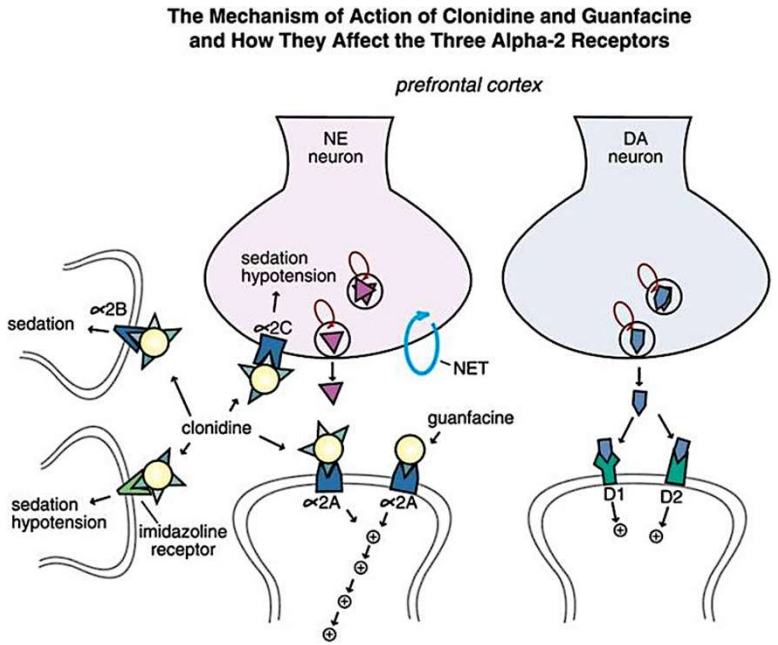
SWS: slow-wave sleep.

* These complex sleep-related behaviors may result in serious injury and, in some cases, fatalities. These medications are contraindicated for any patient who has an episode of complex sleep-related behavior, whether or not it is triggered by the medication.

Owens et al. Up to Date 2021

Alpha Agonists

- Clonidine, Kapvay, Intuniv….
  - Narrow therapeutic index
  - REM suppression
- Guanfacine, Intuniv
  - Less sedating than clonidine
- Sedating



Considerations regarding alpha agonists for sleep in children

Pros	Cons
■ Pharmacokinetics: Rapid absorption, onset action within 1 hour, peak effects 2 to 4 hours ■ Generally well tolerated ■ Widespread usage/acceptability ■ Short half-life (clonidine) creates potential for middle-of-the-night dosing	■ Little empirical evidence for efficacy, tolerability ■ Effects on sleep architecture: Increased SWS, reduced REM ■ May cause mid-sleep wakening ■ Side effects: • Hypotension • Anticholinergic • Irritability, dysphoria • Rebound hypertension on discontinuation • Exacerbation • Parasomnias ■ Tolerance often develops ■ Narrow therapeutic index; risk of overdose
Bottom line – Little data to support current level of clinician preference, but clinical experience suggests generally effective and well tolerated in ADHD.	

SWS: slow-wave sleep; REM: rapid eye movement; ADHD: attention deficit hyperactivity disorder.

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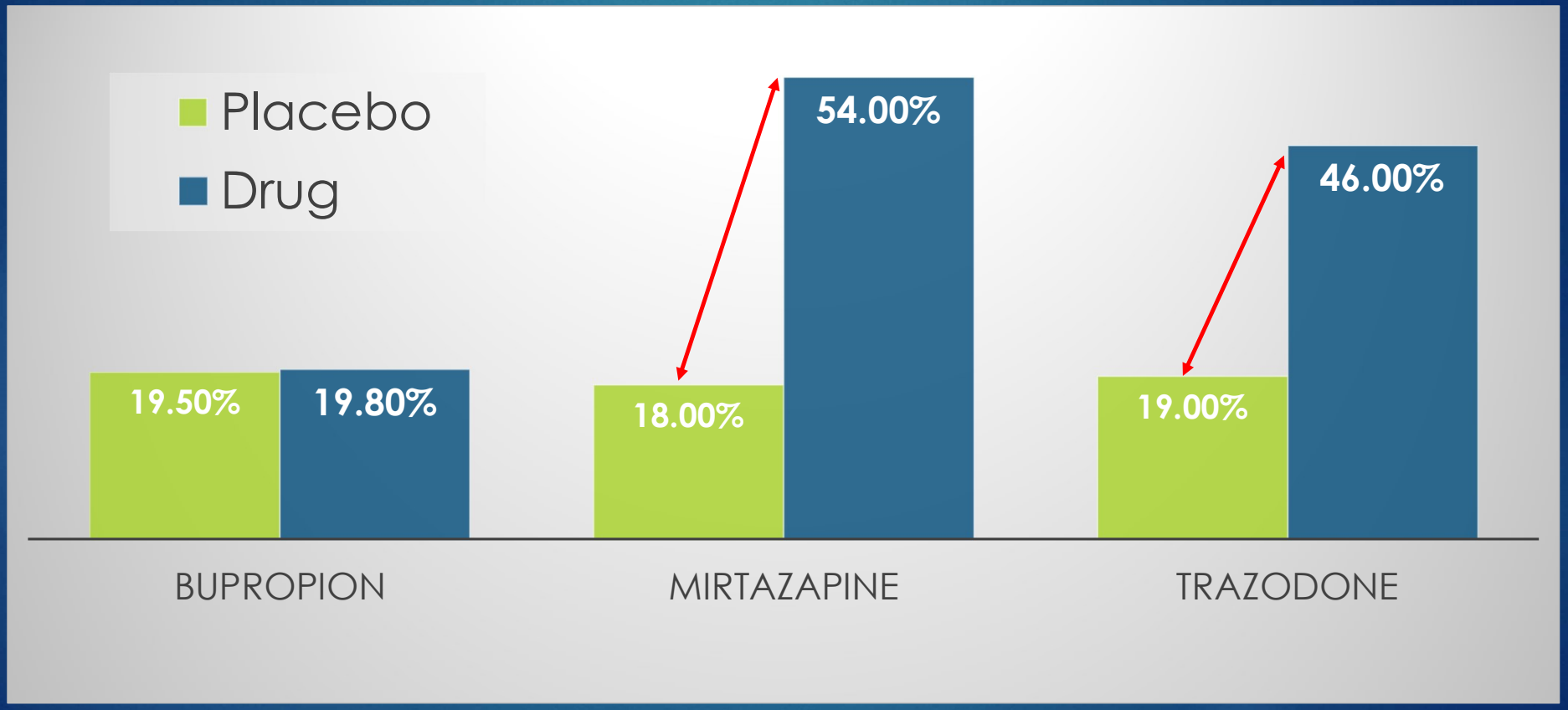
Anticonvulsants

- **Gabapentin (Neurontin)**
  - Doses of 100-900 mg for insomnia
  - FDA indications
    - Management of postherpetic neuralgia in adults
    - Adjunctive therapy in the treatment of partial onset seizures,
    - Common adverse effects include sedation, dizziness, ataxia
      - Behavioral Disinhibition
- **Pregabalin (Lyrica)**
  - Indications
    - Management of neuropathic pain associated with diabetic peripheral neuropathy
    - Management of postherpetic neuralgia
    - Adjunctive therapy for adult patients with partial onset seizures
    - Management of fibromyalgia
    - Management of neuropathic pain associated with spinal cord injury
  - Recent concerns about addiction/withdrawal

Antidepressants

- Little pediatric data on insomnia
- Trazodone
  - Blocks histamine receptors at lower doses (25-50 mg)
- Tricyclics
  - Amitriptyline, trimipramine, doxepin
  - Anticholinergic effects
  - Aggravate RLS SXs
- Mirtazapine
  - ASD
    - One, small, naturalistic study, n=25
      - Posey et al. 2001 J Child Adol Psychopharmacology

Treatment Emergent Next Day Somnolence with Antidepressants



Doghramji & Jango Sleep Med Clin 11 (2016)

Effects of Psychiatric Medications on Sleep

Medication	Sleep Quality	Sleep Architecture	Patient-Important Effects
Benzos/Non-Benzos Receptor Agonists	Decreased sleep latency	Increase stage 2 sleep Increase beta activity Reduce REM sleep	Falling asleep is improved
Stimulants	Increase sleep latency Reduce REM & SWS		Delayed sleep onset
SSRIs, eg. fluoxetine	Decreased sleep efficiency Decreased total sleep time	REM suppression Increased EOMs during NREM sleep	Increase wakefulness
SNRIs, e.g. venlafaxine		Increased wake after sleep-onset (WASO) Reduces total REM time	Insomnia, daytime somnolence, vivid dreams
Atypical Antipsychotics	Reduce sleep latency and wake time after sleep onset	Suppress REM sleep Increase slow-wave sleep	Daytime sedation

Considerations regarding antidepressants for sleep in children

Pros	Cons
■ Wide range of choices (half-life, side effects) ■ All affect non-GABA neurotransmitters (muscarinic, histaminergic, serotoninergic blockade) ■ Dosing for insomnia typically is lower than dosing as an antidepressant	■ Many have significant safety concerns; risk:benefit ratio ■ Very few data on efficacy for insomnia ■ Some have sleep-disrupting effects ■ Most suppress REM; rebound may lead to nightmares ■ May exacerbate RLS/PLMD
Bottom line – Likely most useful in the setting of comorbid mood disorders and/or anxiety; little rationale for trazadone as drug of choice*.	

GABA: gamma-aminobutyric acid; REM: rapid eye movement; RLS: restless legs syndrome; PLMD: periodic limb movement disorder; AASM: American Academy of Sleep Medicine.

* The AASM practice guideline suggests against the use of trazodone for sleep-maintenance insomnia in adults with primary insomnia, based on paucity of data and the small effect sizes observed in the single randomized trial[1].

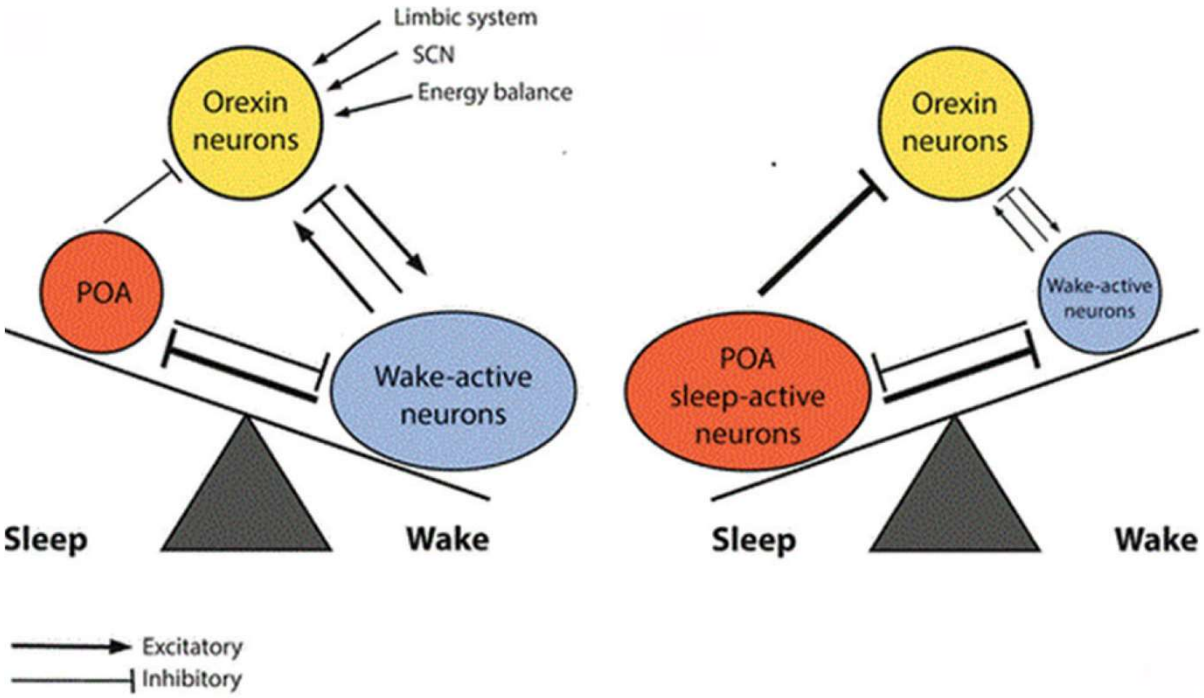
Owens et al. Up to Date 2021

Combinations of Psychiatric Medications Associated with Excessive Daytime Somnolence in Children: Clinical Experience

- LA Guanfacine + aripiprazole
- LA Guanfacine + quetiapine
- Clonidine + mirtazapine
- LA Guanfacine + valproate + mirtazapine

Orexin Antagonists

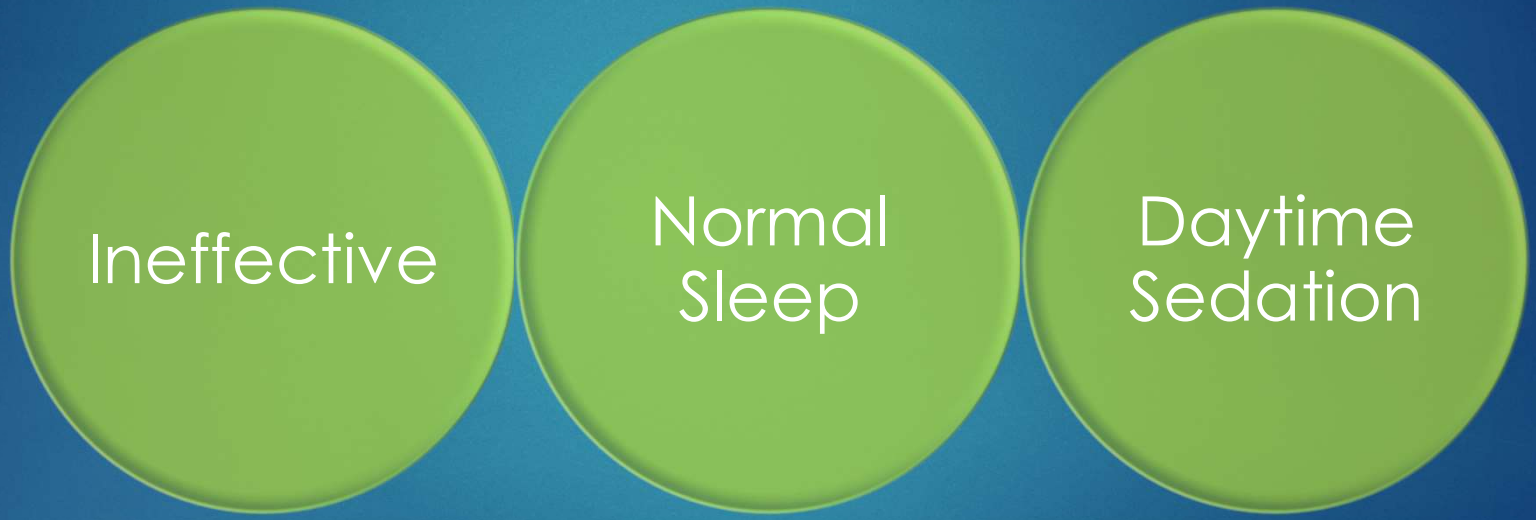
- Primary role of orexins is to control sleep and arousal, and the neurons that release orexins are most active during the day
- Dual orexin receptor antagonists (DORAs)
  - Suvorexant
  - Lemborexant
  - Daridorexant
- No pediatric indications



Clinical Use of Pediatric Sleep Medications

- Melatonin
  - 3-4 mg
    - Delayed release an option
- Clonidine
  - Patients with ADHD, 0.1-0.2 mg qHS
- Gabapentin
  - No data, sometimes works in anxious patients
    - 5 mg/kg (start)
    - 15 mg/kg (maximum)
- Doxepin (Silenor)
  - Tricyclic antidepressant
  - Dosing
    - Children: 3-6 mg as liquid/ Adolescents: 10 mg
- Trazodone
  - Adolescent: 25-50 mg

Sleep Medications



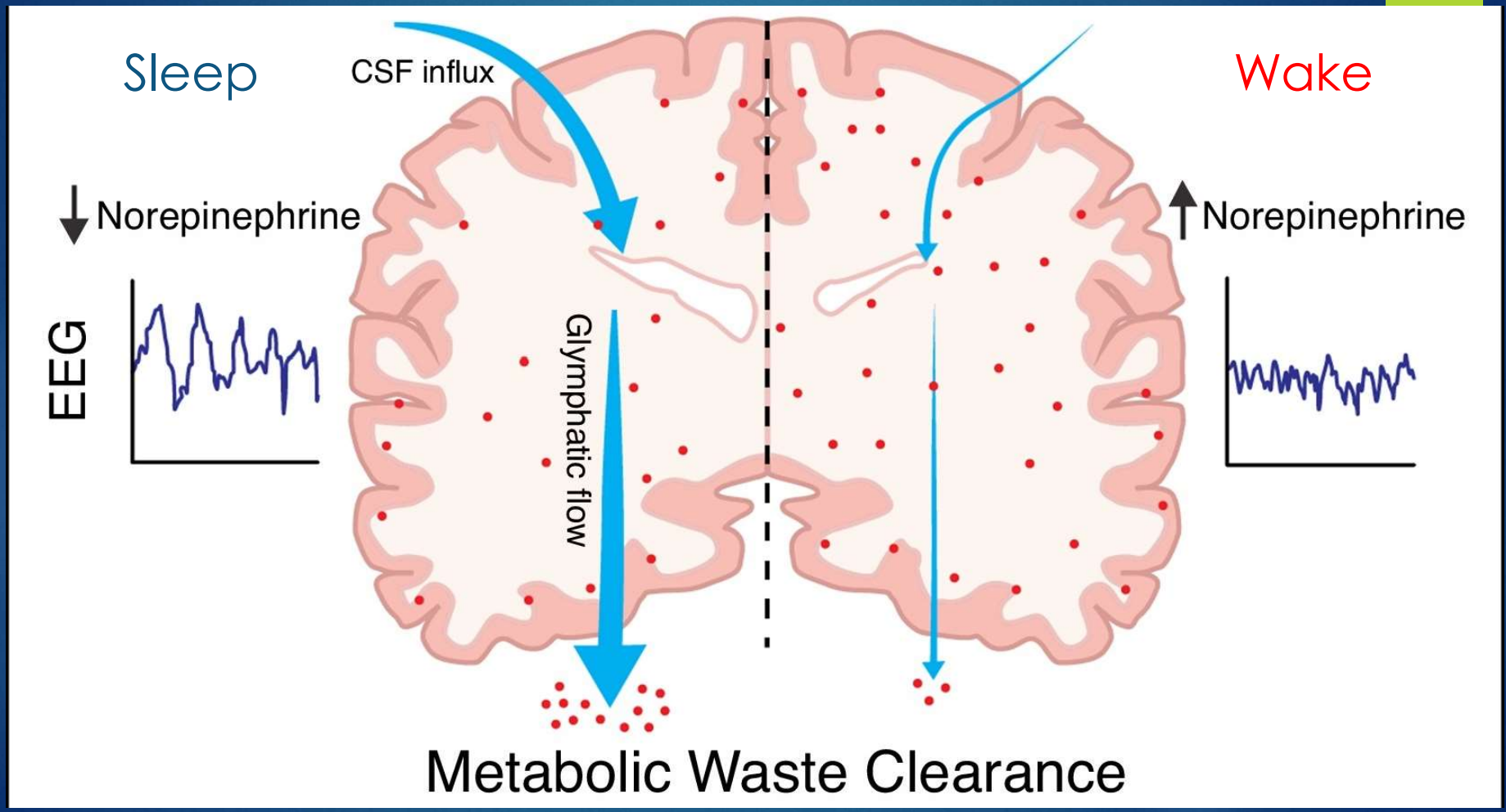
Ideal Sleep Agent

Sleep Medication Summary

There are no great sleep medication to induce sleep

- Sedating effects decrease over time
  - Increased dose
    - Next -day sedation
- Sleep is part of complex circadian system that is difficult to alter

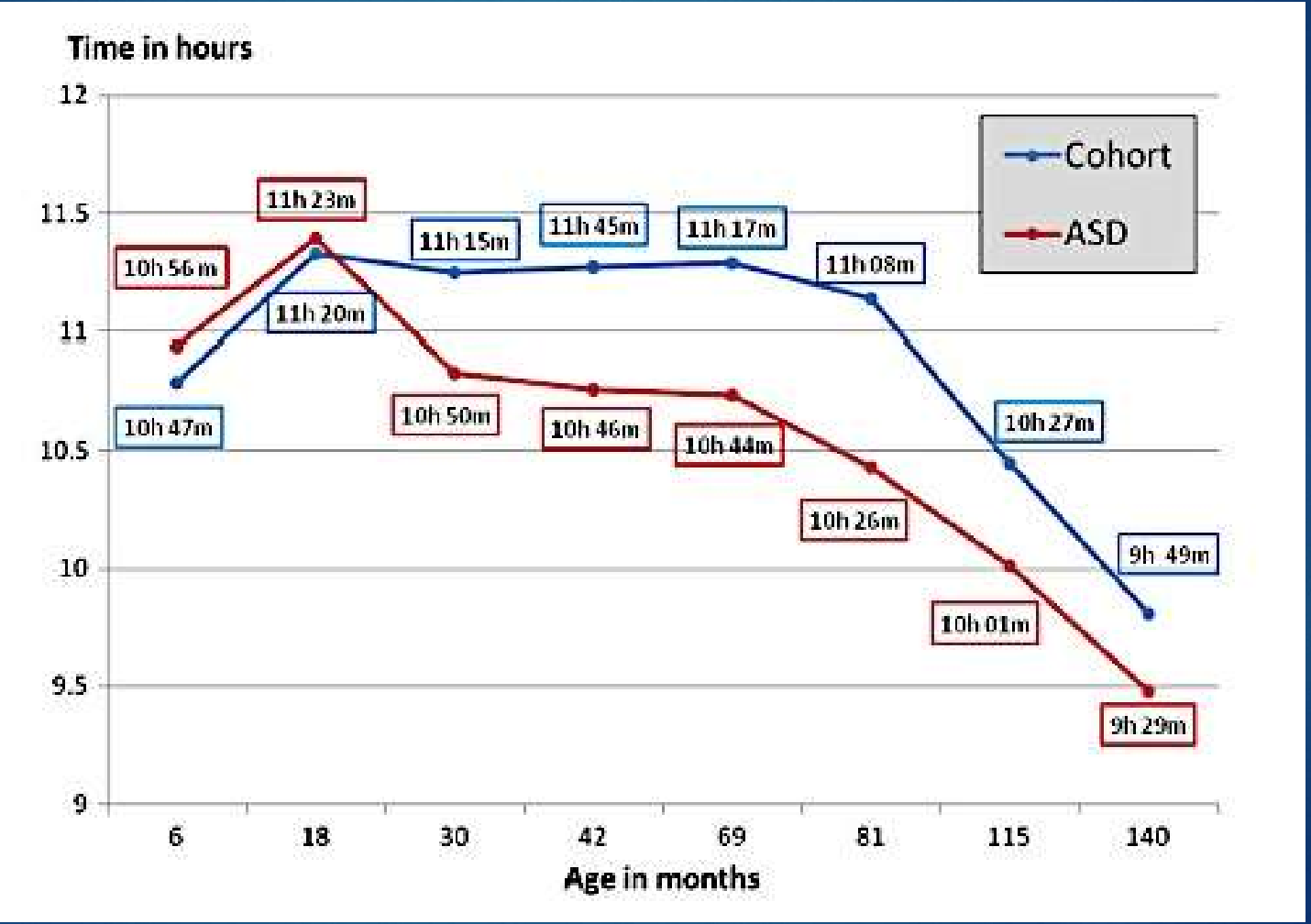
Glymphatic System



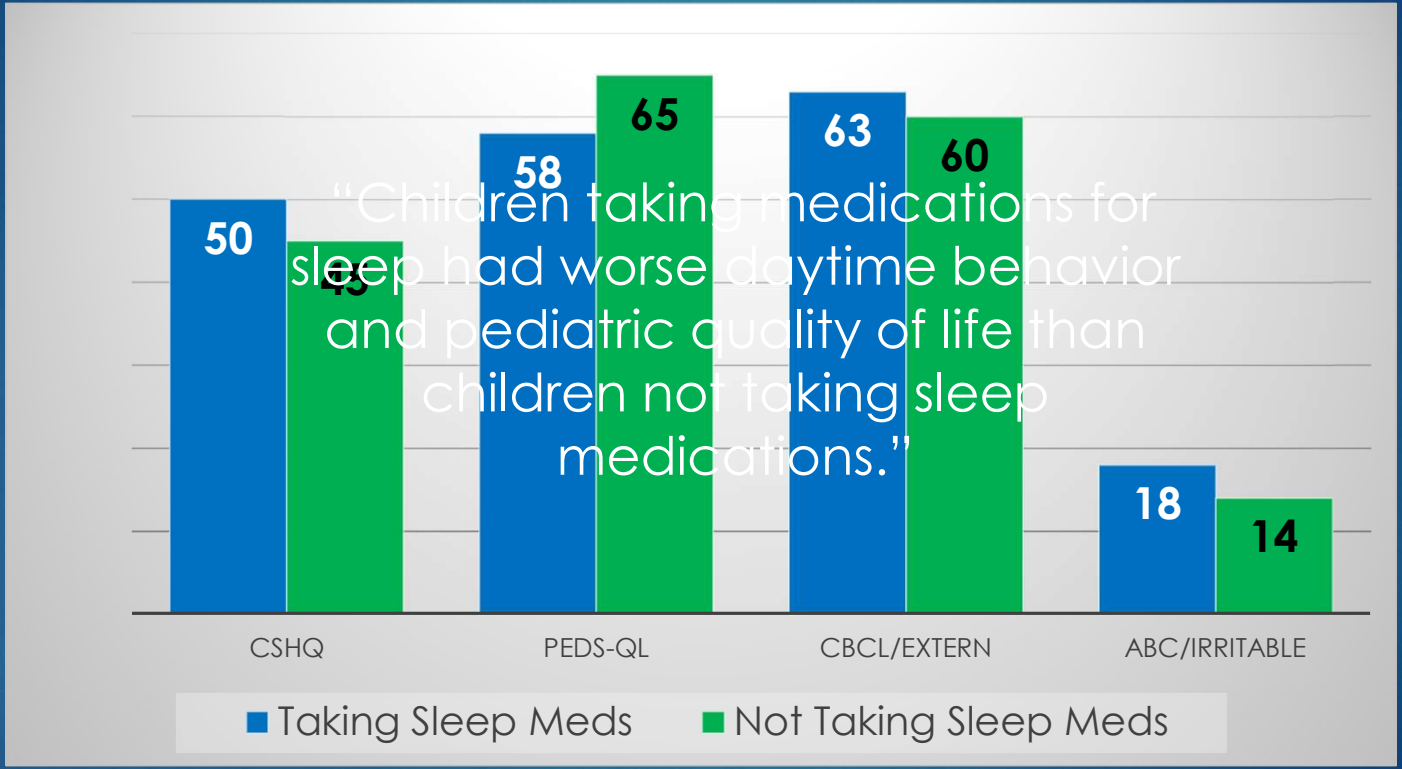
Sedation is not sleep!

Autism Spectrum Disorder (ASD)

Night-time mean sleep duration in children with autistic spectrum disorders (ASDs) compared with the rest of the cohort



Sleep Difficulties and Medications in Children With Autism Spectrum Disorders: A Registry Study



"Children taking medications for sleep had worse daytime behavior and pediatric quality of life than children not taking sleep medications."

Malow et al. Pediatrics 2016;137

SPECIAL ARTICLE LEVEL OF RECOMMENDATION

Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

- Increased risk of co-occurring conditions that contribute to sleep disturbance, such as intellectual disability, sleep apnea, epilepsy, gastrointestinal disturbances (including GERD), depression, anxiety, psychosis, bipolar disorder, and ADHD
- More likely to use medications that disrupt normal sleep patterns, such as stimulants, some antiseizure medicines, and psychotropic medications
- Environment and family factors, including child-rearing practices and bedtime routines that are not conducive to good sleep, contribute to sleep disturbance in children with ASD
- Robust evidence for parental education and behavioral strategies to improve sleep in children and adolescents with ASD is lacking
- Low to moderate confidence that melatonin improves various aspects of sleep in children and adolescents with ASD. In the studies included in the SR, pharmaceutical-grade melatonin preparations were used and the exact administration amounts ascertained

Ashura et al. Neurology 2020; 94 (9)

Slenyto / PedPRM

- "Slenyto is an age-appropriate formulation of prolonged-release melatonin indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient (EMA/CHMP opinion)."
- Slenyto is available in Germany, Finland, UK , Italy, Norway, Denmark, Iceland and Switzerland

Long-Acting Melatonin Studies in ASD

Parents are not accurate

Study	Design	Sample	Treatment	Primary Outcome Measure
Gringas et al. 2017 J Am Acad Child Adolesc Psychiatry	DB-RCT 13 Weeks	119 Ss with ASD Ages 2-17.5 yr Mean Age 8.7±4 yr	PedPRM 2, 5 10 mg	Sleep and Nap Diary (SND)
Maras et al. 2018 J Child/Adol Psychopharm	Open Study 13 Weeks	95 Ss with ASD Ages 2-17 yr Mean age 8.7±4 yr	PedPRM 2, 5, 10 mg	Sleep and Nap Diary (SND)
Schroder et al. 2019 J Autism/Dev Dis	DB-RCT 13 Weeks	119 Ss with ASD Ages 2-17 yr Mean Age 8.7±4 yr	Circadin 2-5 mg	SDQ Parent report

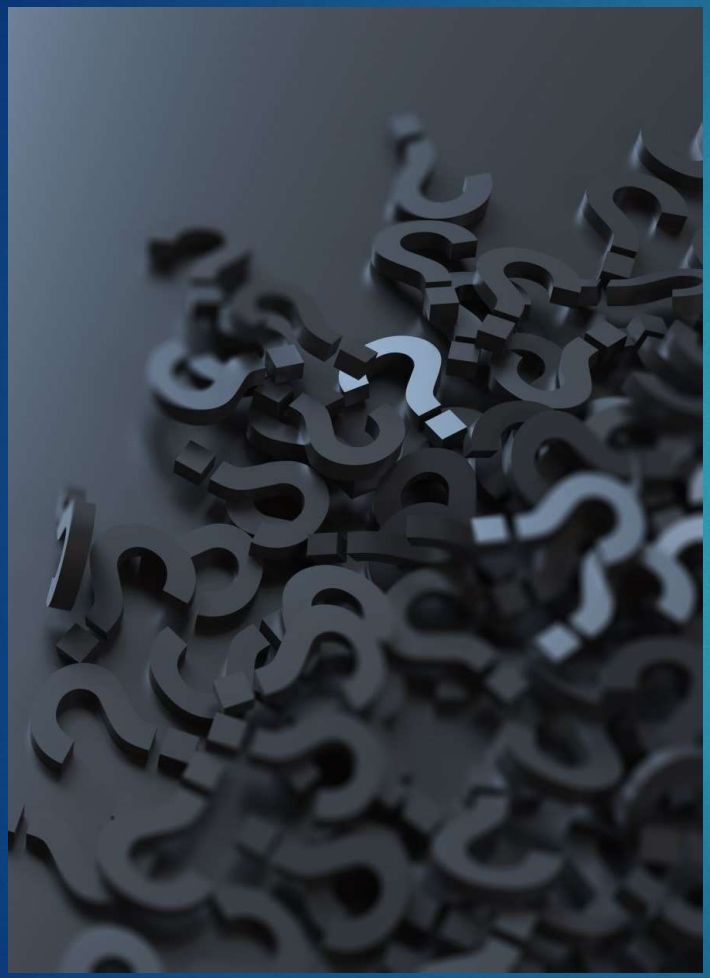
REMfresh contains 2 mg of melatonin in a continuous-release and absorption formulation

Quick release and absorption of melatonin within the first hour after dosing, to obtain a faster onset of action

No clinical trials data

Management of Disrupted Sleep in Patients with ASD

- Assess possible comorbid disorders
  - OSA, GERD, RLS/PLMS
- Review current medications that might interfere with sleep
- Assess any sleep hygiene/behavioral issues
- Develop behavioral plan
- Medications
  - Consider a trial of Short or Long-Acting Melatonin
  - Aggressiveness/Self Injurious Behavior of ASD
    - Atypical Antipsychotic




Insomnia

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  Wednesday, February 17, 2021

  - https://www.surveymonkey.com/r/BHWebinar-10Feb2021

  Please note: We are unable to provide CE credit past this deadline.

- **Visit our website to learn more!**
  - https://www.nationwidechildrens.org/specialties/
  - behavioral-health/for-providers/webinar-series

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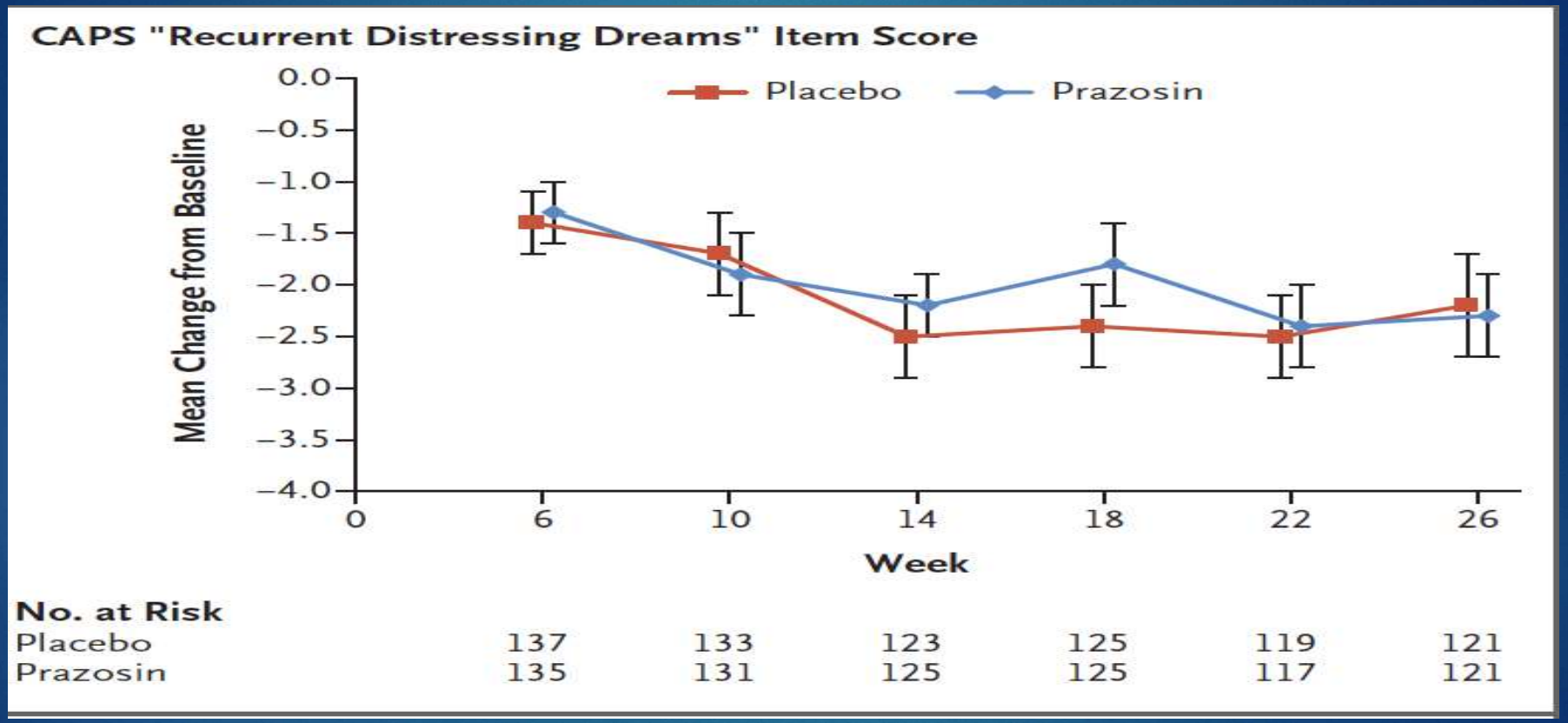
Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans

- **304 participants** were randomly assigned to receive prazosin or placebo for 26 weeks
- Drug or placebo was administered in escalating divided doses over the course of **5 weeks** to a daily maximum of **20 mg in men and 12 mg in women**.
- Three primary outcome measures
- **152 were assigned to prazosin, and 152 to placebo.**
- At 10 weeks, there were **no significant differences** between the prazosin group and the placebo group in the at 26 weeks on any of the primary or secondary outcomes.

Raskind et al. N Engl J Med 2018; 378:507-517

Primary Outcome Measure



Raskind et al. N Engl J Med 2018; 378:507-517