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Rest Easy: Understanding Sleep Challenges and Solutions in Williams Syndrome

This webinar is sponsored by the Williams Syndrome Clinc at Nationwide Children's Hospital in partnership with the Williams Syndrome Association

Williams Syndrome Clinic

Nationwide Children's Hospital – Columbus, Ohio

About the Clinic

Multidisciplinary care for children and adults with Williams syndrome

Personalized treatment plans from a team of specialists

Nationally recognized center and member of the U.S. Williams Syndrome Clinical Consortium

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Why Families Choose Us

Comprehensive evaluations in a single visit

Access to cutting-edge research and therapies

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Learning Objectives

1. **Recognize Common Sleep Disturbances in Williams Syndrome**
   Identify prevalent sleep issues such as prolonged sleep latency, frequent night awakenings, restless sleep, and excessive daytime sleepiness commonly observed in individuals with Williams Syndrome.
2. **Understand the Impact of Sleep on Development and Behavior**
   Explain how sleep disturbances can affect cognitive development, behavioral regulation, and overall health in children with Williams Syndrome.
3. **Explore Underlying Medical Conditions Contributing to Sleep Disorders**
   Discuss medical factors such as sleep-disordered breathing, periodic limb movements, and anxiety that may exacerbate sleep problems in individuals with Williams Syndrome.
4. **Review Current Research and Evidence-Based Interventions**
   Summarize recent studies on sleep patterns in Williams Syndrome and evaluate the effectiveness of various interventions, including behavioral strategies and medical treatments.
5. **Develop Practical Strategies for Managing Sleep Issues at Home**
   Provide caregivers with actionable tips and resources to address sleep challenges, aiming to improve sleep quality and overall well-being for their children.

Agenda

1. Dr. Barnhardt – Overview of sleep challenges in Williams syndrome

2. Dr. Lyren – Behavioral interventions for sleep difficulties

3. Dr. Drees – Medical causes of sleep disruption and approach to management

4. Dr. Kozel – Research updates on sleep in Williams syndrome

5. Interactive Q&A

Please send questions to Dasha throughout presentation

Sleep Difficulties

Are common!

Mott Children's Hospital recently conducted a national survey of parents of children aged 1-6 (https://mottpoll.org/reports/getting-young-children-bed-sweet-dreams-or-nightmare)

- 1 in 4 parents say their young child can’t go to sleep because of being worried or anxious.
- 1 in 5 parents give their young child melatonin to help with sleep.
- 1 in 3 parents stay in the room until their child goes to sleep.

Types of Sleep Disorders

Insomnia
- Behavioral
- Conditional
- Transient

Sleep Apnea (Obstructive, Central)

Somnabulism (Sleepwalking)

Bedwetting/Nocturnal Enuresis

Night Terrors

Nightmares

Excessive Daytime Sleepiness

Bruxism (Grinding Teeth)

Restless Leg Syndrome

Types of Sleep Disorders

- Insomnia
  - Behavioral
  - Conditional
  - Transient
- Sleep Apnea (Obstructive, Central)
- Somnabulism (Sleepwalking)
- Bedwetting/Nocturnal Enuresis
- Night Terrors
- Nightmares
- Excessive Daytime Sleepiness
- Bruxism
- Restless Leg Syndrome

Sleep and Child Development

Sleep problems have been shown to have negative impact on language development for both typically developing children and children with neurodevelopmental disorders

Sleep problems can also predict maternal mood, stress, fatigue, and family functioning, including maternal depression and familial stress (Meltzer & Mindell, 2007)

Who can help if your child has sleep difficulties?

Sleep and Child Development

Sleep problems have also been linked to immune system dysfunction (Franck et al, 1999)

Sleep disturbances in general can impact children's attention, mood/anxiety in typically developing peers (already a concern in WS)

Sleep and Development in Children with WS

Negative impacts on language development and cognitive skills such as auditory and visual memory have been demonstrated (Santoro et al, 2016)

- Greiner de Magalhaes et al (2020) found significant relations between nighttime sleep duration and both expressive and receptive language when controlling for nonverbal reasoning ability

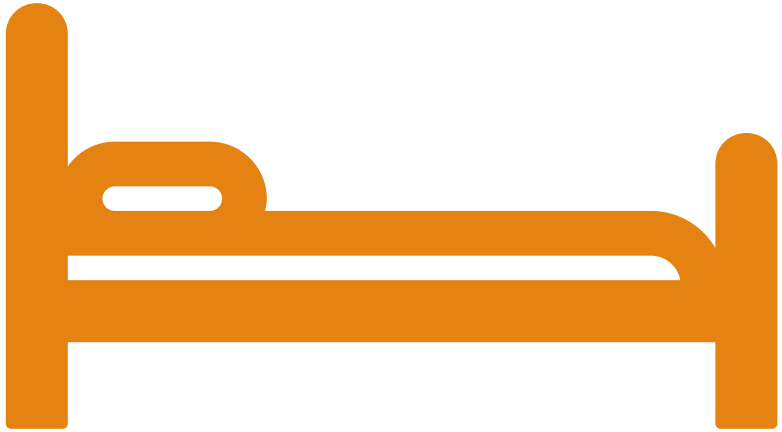
Sleep Difficulties in Children with WS

Sleep difficulties are very common

- In survey of 64 parents of children with WS ages 6-12, 97% reported sleep problems (Annaz et al, 2010)

Types of sleep problems

- Sleep-related breathing disorders
- Sleep anxiety
- Bedtime resistansce
- Sleep onset delay
- Frequent nightwaking
- Restlesness/Periodic Limb Movement
- Excessive daytime Sleepiness



Sleep across the lifespan

In survey of 96 parents of 2 year-olds with WS, children slept an average of 10.36 hours per night, not different from typically developing toddlers

Beyond infancy children have more sleep problems

Some literature supports differences in total time slept in older children

Studies with adolescents and adults report higher rates of daytime sleepiness, nocturnal leg discomfort, and fragmented sleep as measured on sleep studies

Causes of sleeping difficulties in children with WS

Increased bedtime cortisol levels

- Persists into adolescence

Less pronounced rise in melatonin levels

Higher rate of Obstructive Sleep Apnea

Sleep studies have identified decreased sleep efficiency, increased respiratory-related arousals, increased slow wave sleep, increased non-rapid eye movement percentage, decreased REM percentage, irregular sleep cycles

Sleep Medications in Williams

Research is limited

In a study involving children and adults with WS, 25% reported a family member had taken medications to help with sleep (Martens et al, 2017)

- 40% of medication use was in the 0-5 age group, youngest 6 months of age

What medications are being used?

Martens et al (2017) found the following:

- 67% (n=87) reported using melatonin
  - 91% reported helpful or somewhat helpful
  - Very few side effects reported
- 29% reported trying Diphenhydramine (n=38)
  - Behavioral and neurological side effects in 18%
- 6% (n=8) reported use of Clonidine
- 5% (n=6) reported use of Guanfacine
- 10% (n=10) reported use of Quetiapine

Behavioral Strategies to Support Sleep

Before I start, **an** acknowledgment—making changes with sleep can be difficult!

Think about when might be a good time to try to implement some new strategies

Behavioral Strategies

Help your child learn association between bed and sleep (e.g., try to avoid down time in bed, phone time in bed., etc.)

Try to have a consistent routine (going to bed and waking up around the same time)

Can also use a visual schedule for bedtime routine!

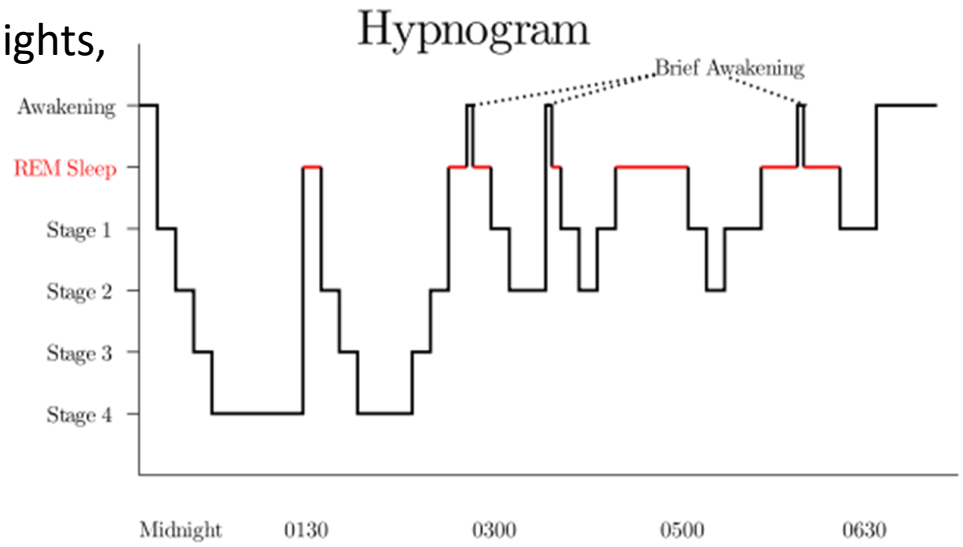
Try to limit screen time before bed (screens limit our body's production of melatonin)

Behavioral Strategies

We all have times that we briefly wake throughout the night

Some children may be sensitive to the environment they fall asleep in (want the environment to match exactly when they wake throughout the night)

- So, what does this mean?
  - Consider where your child falls asleep, and what is on (e.g., lights, music?)
  - Put your child to sleep drowsy, but awake



Strategies for Frequent Awakenings/Constantly Getting Out of Bed

Parent attention is very motivating!

Try to provide limited attention if your child wakes up in the night and comes to get you (e.g., if they want to play, talk about something, get a glass of water, etc.)

Some children benefit from visual aids (e.g., color changing alarm clock)

[Bedtime Battles: Going to and Staying in Bed - The Kids Mental Health Foundation]

Fading Parental Support During Bedtime

Gradual Fading: Try to slowly remove yourself from the environment (e.g., sit by their bed, sit in a chair, sit outside the door, etc.)

- Steps can be as big or small as you would like!

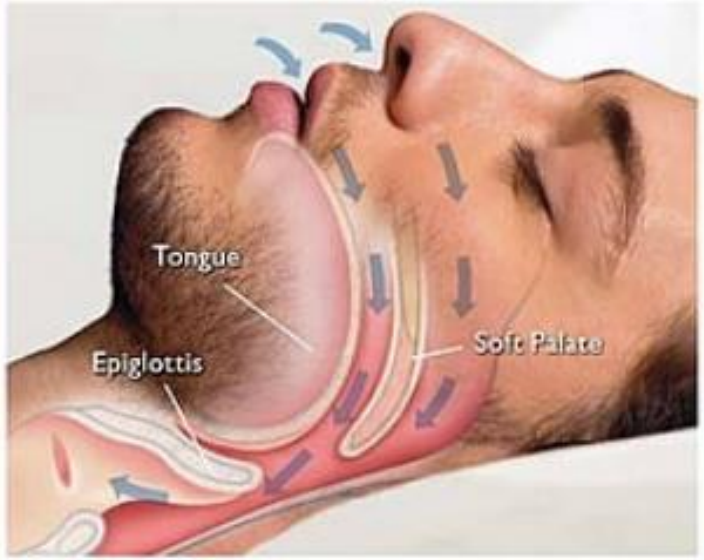
Parent Check In: Leave the room after putting child to bed and then come back in shortly after to "check in". Try not to provide a lot of attention—goal is a quick check in. Then, gradually increase the amount of time between check ins (e.g., 30 seconds, 1 minute, 5 minutes, etc.)

- Can also stay in the room with your child and briefly leave and come back
- Again, steps can be as big or small as you would like!

Signs of Obstructive Sleep Apnea

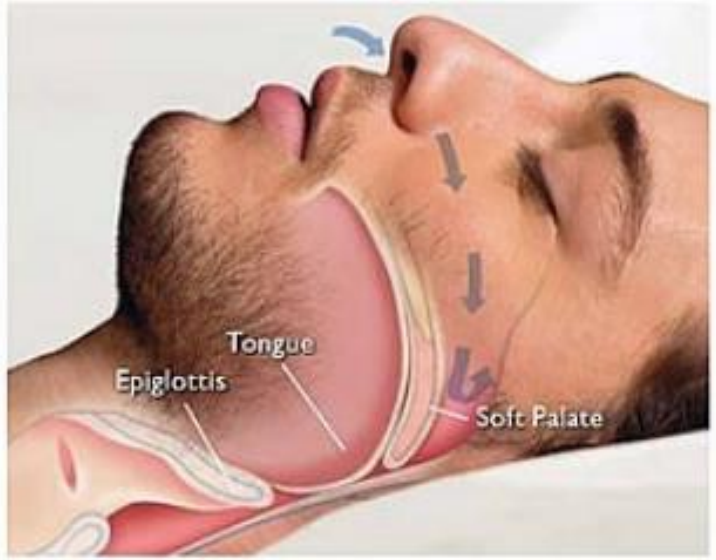
- Snoring!
- Pauses in Breathing
- Waking up frequently at night
- Difficult to rise in the morning
- Gasping/Choking episodes
- Mouth breathing/Dry Mouth

What is Obstructive Sleep Apnea?



Normal breathing

During sleep, air can travel freely to and from your lungs through your airways.

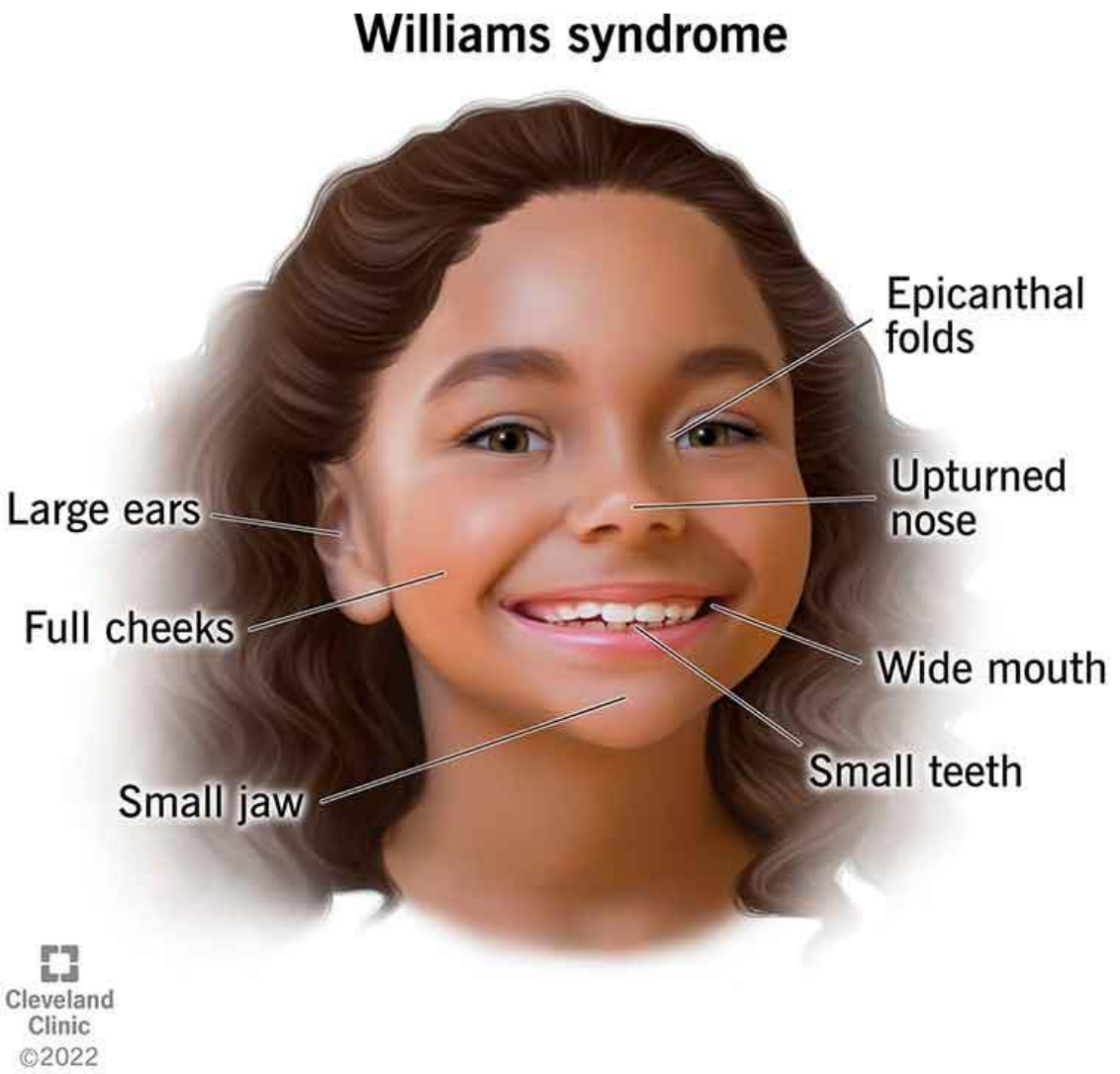


Obstructive Sleep Apnoea

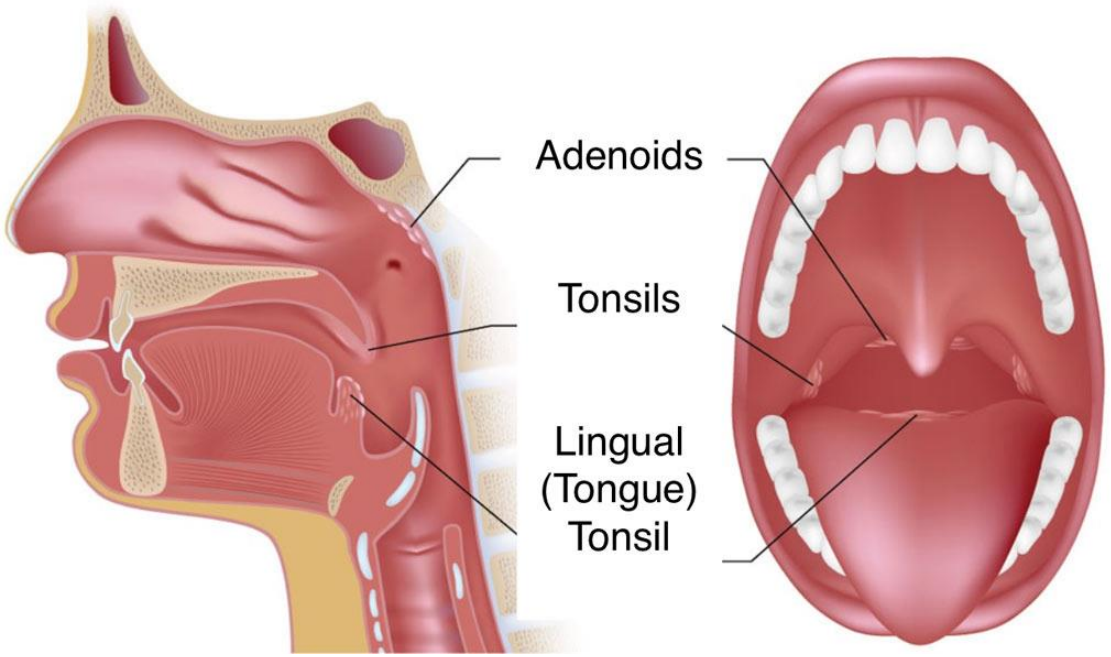
Your airway collapses, stopping air from traveling freely to and from your lungs and disturbing your sleep.

Obstructive Sleep Apnea

- Large Tonsils and Adenoids
- Obesity
- Poor muscle tone
- Craniofacial anatomy


Williams syndrome
Epicanthal folds
Upturned nose
Large ears
Full cheeks
Wide mouth
Small teeth
Small jaw
Cleveland Clinic
©2022

Tonsils and Adenoids

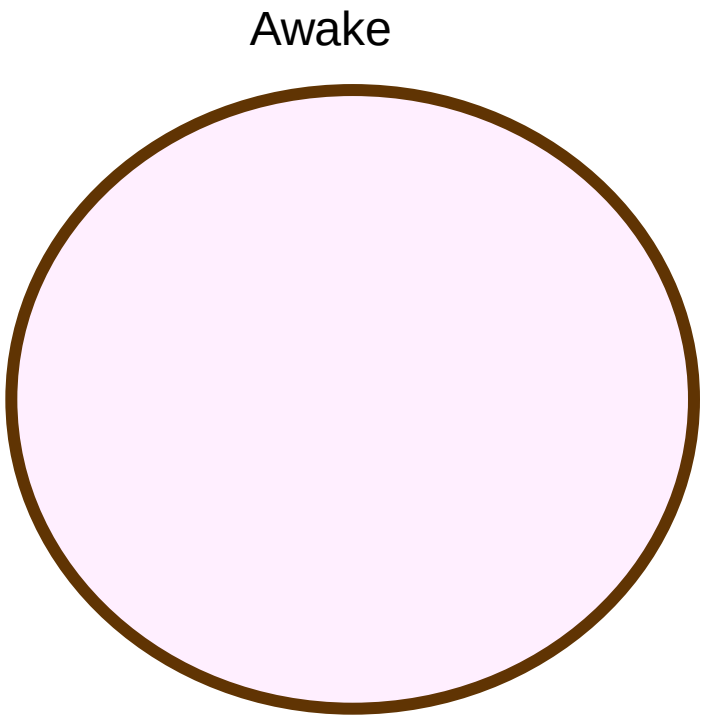


Grow faster than airway between ages 2-7

Tend to shrink after 7 years old

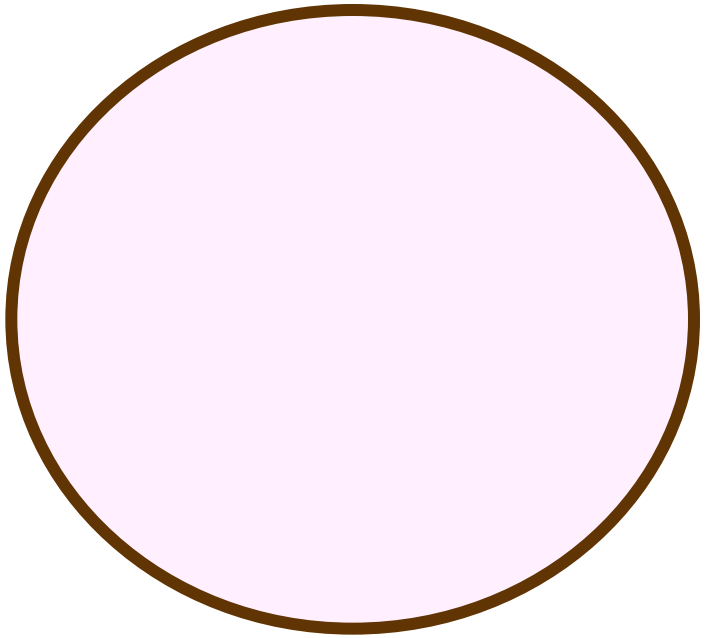
Adenoids cannot be seen on physical exam

Obstructive Sleep Apnea

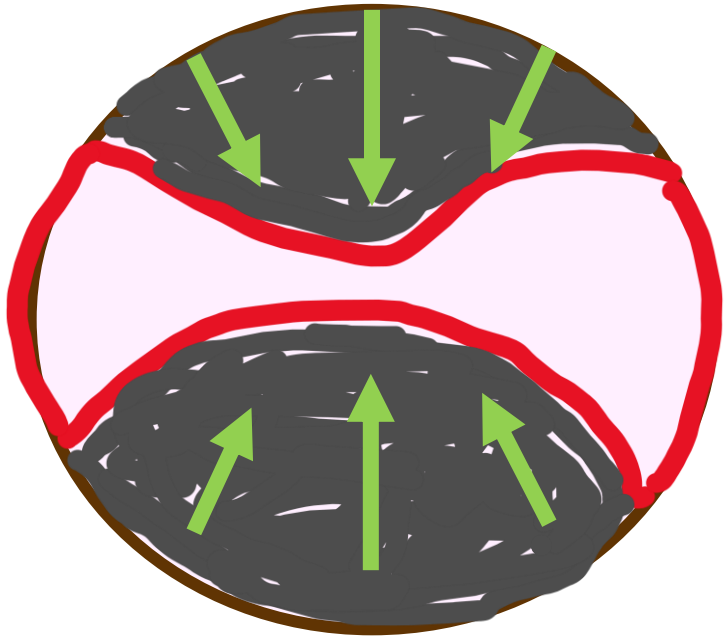


Obstructive Sleep Apnea

Awake

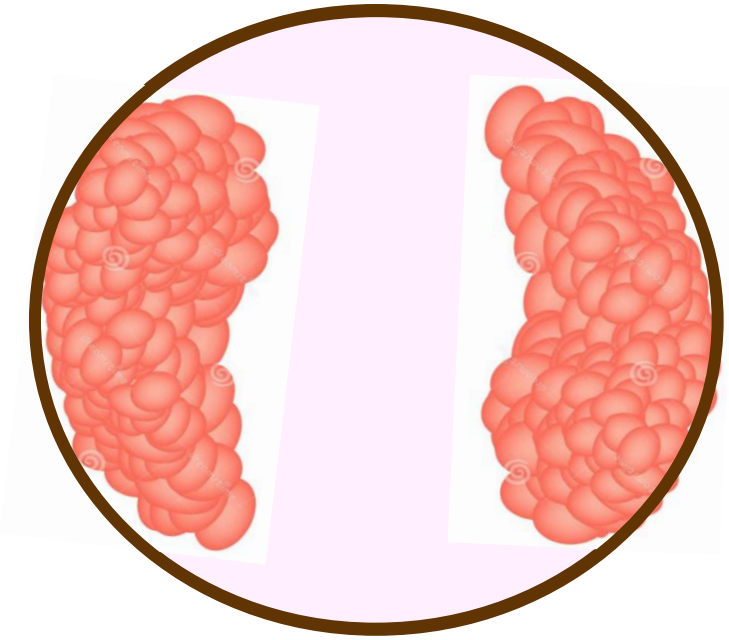


Asleep

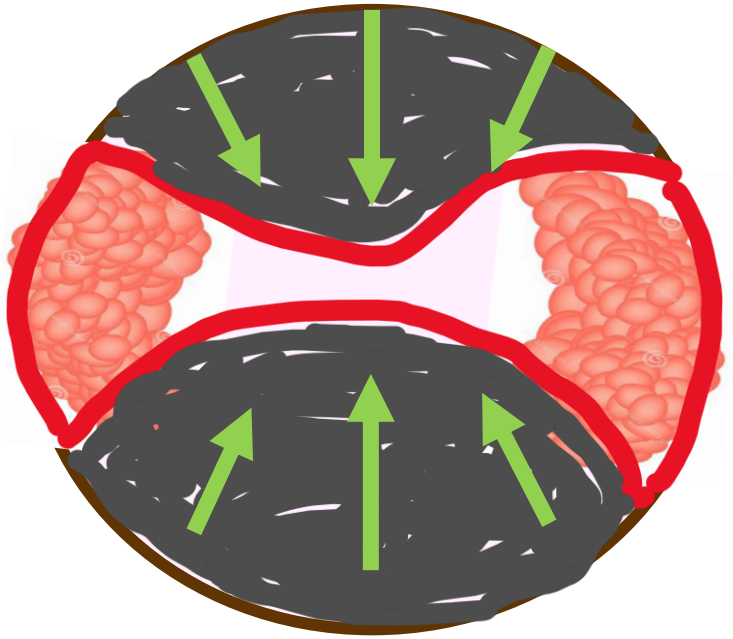


Obstructive Sleep Apnea with Tonsils

Awake

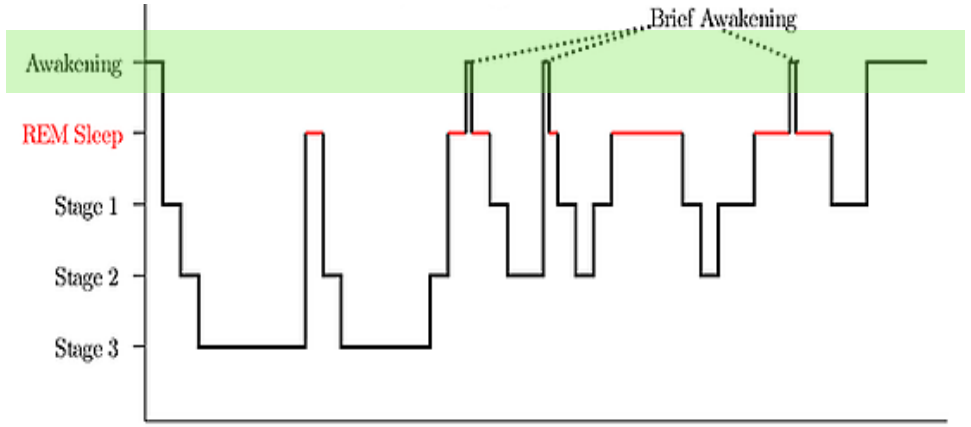


Asleep

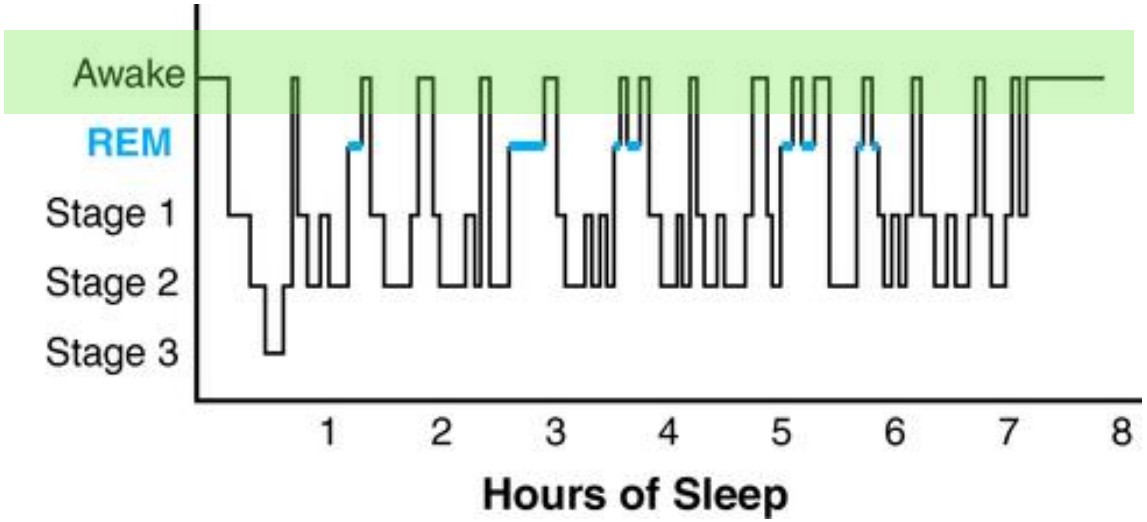


Poking the Bear

Normal



Obstructive Sleep Apnea



Obstructive Sleep Apnea

- Daytime Sleepiness
- Hyperactivity/Impulsivity
- Poor Academic Performance
- Mood disturbances
- High Blood Pressure
- Bedwetting
- Cardiovascular Risk

Treatment for OSA in Children

Adenotonsillectomy

Medical Management

- Fluticasone (Nasal Steroid Spray)
- Montelukast (Rx Allergy/Asthma Pill)

CPAP

Other surgical options

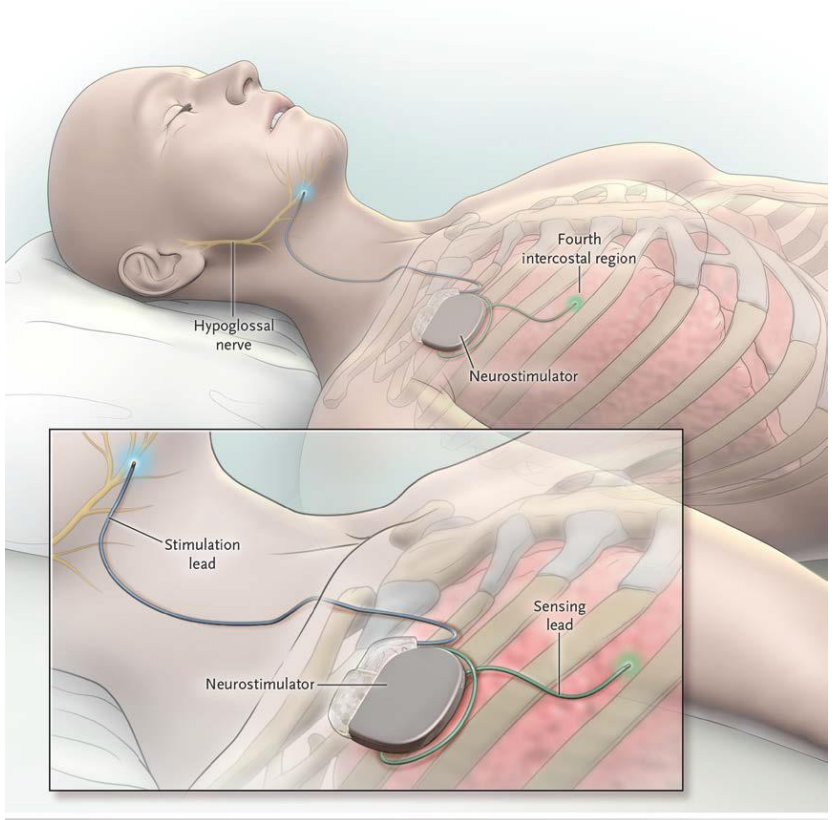
Treatment for OSA in Adults

- CPAP
- Mandibular Advancement Device (Dental Device)
- Hypoglossal Nerve Stimulator (Inspire)
- Other surgical options

Mandibular Advance Device

Somnomed

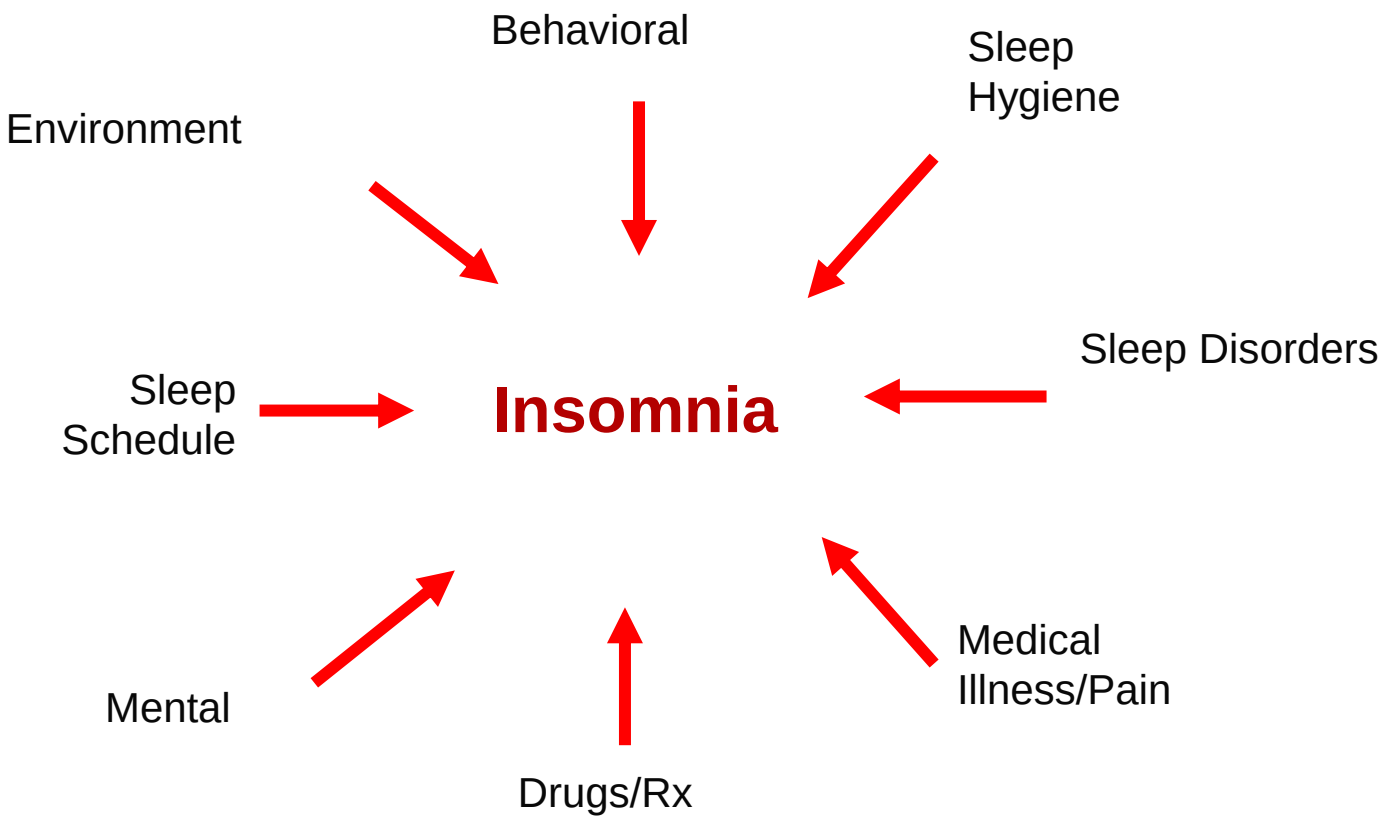
Hypoglossal Nerve Stimulator



Strict Criteria

- **Mod-Severe OSA (AHI >15)**
- **Failed CPAP**
- **BMI<35**
- **DISE**

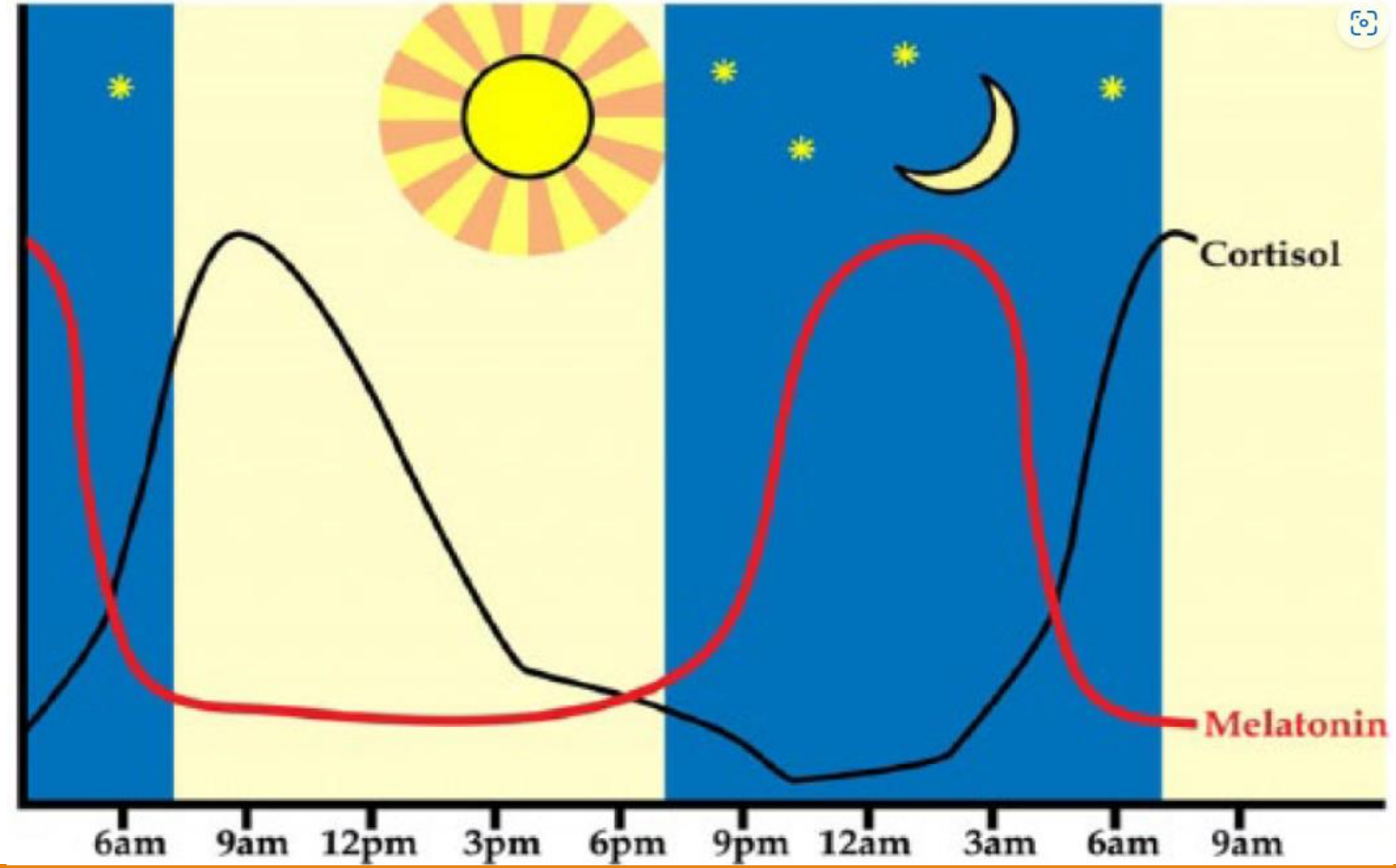
****Battery lasts for 10 years****



Insomnia is often Multifactorial

Melatonin Supplements

- Not FDA regulated
- Jump starts natural production
- Generally, very safe
- Poorly absorbed and quickly metabolized
- No increased benefit from higher doses
- Be cautious about “Sleep” Supplements with multiple ingredients



Manganaro et al. (2017). Journal of Central Nervous System Disease.

Supplemental Melatonin

- Jump starts endogenous melatonin positive feedback loop
- No tolerance, no withdrawal, etc!
- Very poor bioavailability ~15% (first pass effect)
- Quickly metabolized 15-45 minutes
  - XR formulation ~1.5-2 hours
- Parasomnias, nightmares, hangover effect, irritability, very low risk of seizure, headaches
- Questionable long term puberty risk

When to start pharmacologic therapy

QoL Burden

Ability to implement non-pharmacologic interventions

Adjunctive to non-pharmacologic intervention

Why should we avoid sleep medicines?

- No pediatric FDA approved sleep aid for insomnia
  - Only doxepin, benzos, Z-drugs, melatonin agonists, new orexin antagonists
- Band-aid, not building skills
- Side Effects
- Nearly all sleep aids cause habituation/tolerance
- Withdrawal

Irritability with Sleep Medications

Disinhibition of frontal lobe and executive functioning skills

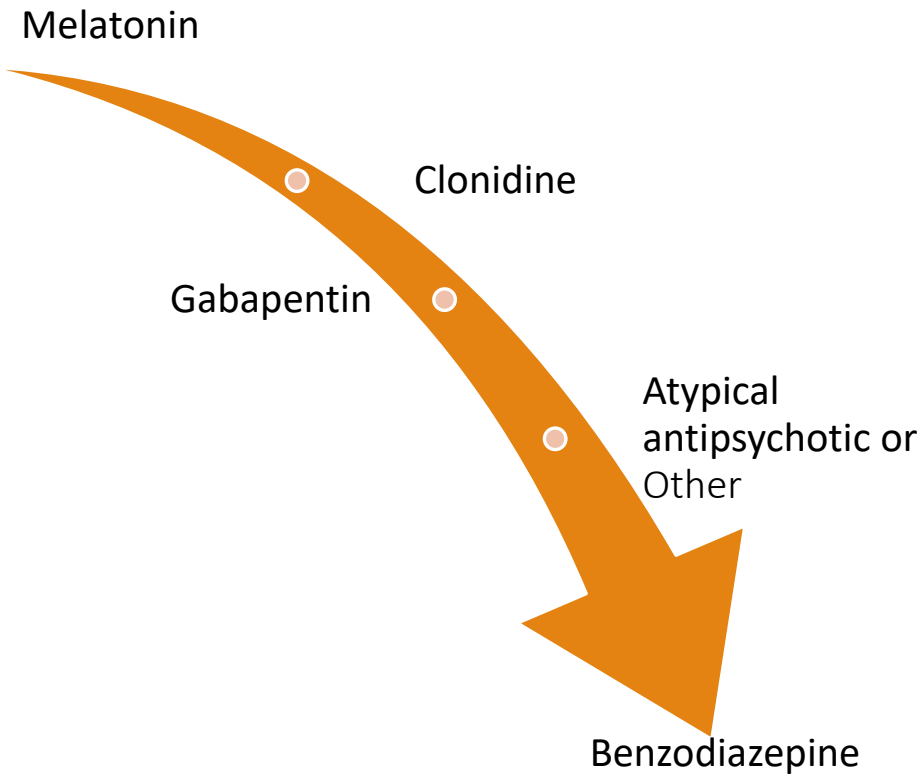
- “Tipsy but not passed out”
- Increased sleep fighting/negative behaviors

Often due to patient brain’s receptor profile and reaction to medication

Sleep Medications

Sleep Onset	Sleep Maintenance	Both!
Clonidine	Clonidine XR	Mirtazapine
Melatonin	Doxepin	Quetiapine
Hydroxyzine	Eszopiclone	Clonazepam
Zaleplon		Gabapentin
Diphenhydramine		Zolpidem
		Trazodone

Anecdotal Order



Monitoring

1

ALWAYS track changes over time

- One option: CSHQ

2

Monitor closely for side effects

3

Re-evaluate periodically about possibility of decreasing/stopping medication if clinically indicated

Restless Leg Syndrome

Urge to move legs, unpleasant sensation in legs

Begins or worsens during periods of rest

Partially or totally relieved by movement

Only during periods of rest or inactivity, worse in the evening

Diagnosis strengthened by first degree relative with RLS or Periodic Limb Movements of Sleep on sleep study

Associated with Dopamine!

Allen RP, Picchietti DL, et al; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. Sleep Med. 2014 Aug;15(8):860-73.

Periodic Limb Movements of Sleep

- Restless Movements during Sleep
- Associated with RLS
- Treated the same as RLS
- Sleep Quality Disrupter
- Kicks at night, sheets and blankets messed up in morning

Iron Therapy

Iron co-factor for tyrosine hydroxylase (rate limiting step of release of dopamine)

For Restlessness, Goal Ferritin > 75 ng/ml

Avoid dairy, best on empty stomach

May consider IV iron infusion

Closely regulated by body

GI issues!

Khan FH, Ahlberg CD, Chow CA, Shah DR, Koo BB. Iron, dopamine, genetics, and hormones in the pathophysiology of restless legs syndrome. J Neurol. 2017 Aug;264(8):1634-1641.
Simakajornboon N, Kheirandish-Gozal L, Gozal D. Diagnosis and management of restless legs syndrome in children. Sleep Med Rev. 2009 Apr;13(2):149-56.

Sleep Clinic or Sleep Study

Sleep study for Sleep Apnea or Restless Sleep

- Snoring + 1
  - Witnessed apneas
  - Hypersomnia
  - Sleep disruption
  - Large Tonsils
  - Obese
- “Wild” Sleeper, Sheets/Blankets tossed about in AM

Sleep Clinic or Sleep Study

Insomnia
Circadian Rhythm Disorders
PAP management
Parasomnias
Hypersomnia/Excessive Daytime Sleepiness
Sleep Training

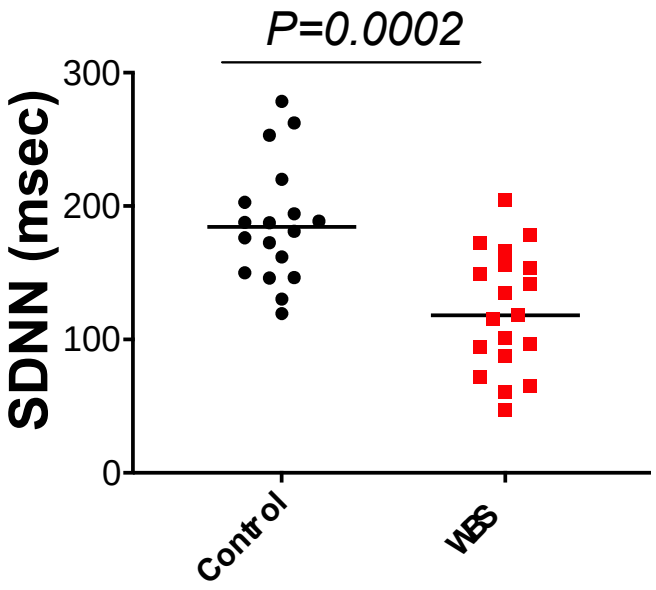
Sleep & autonomic programming in WS:

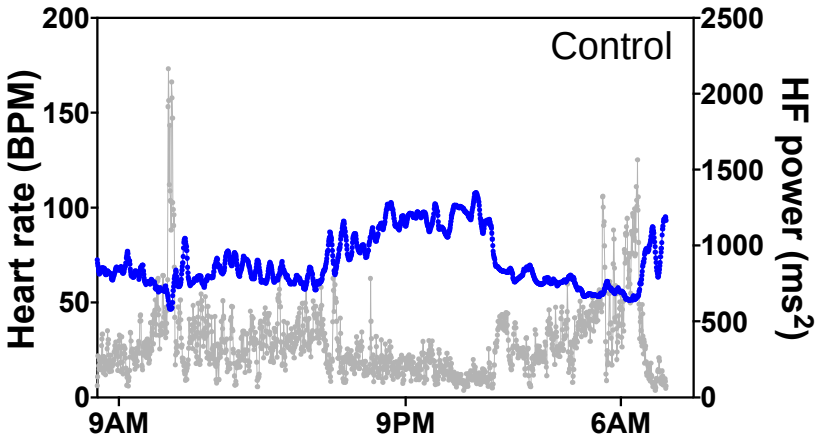
a wearable device study

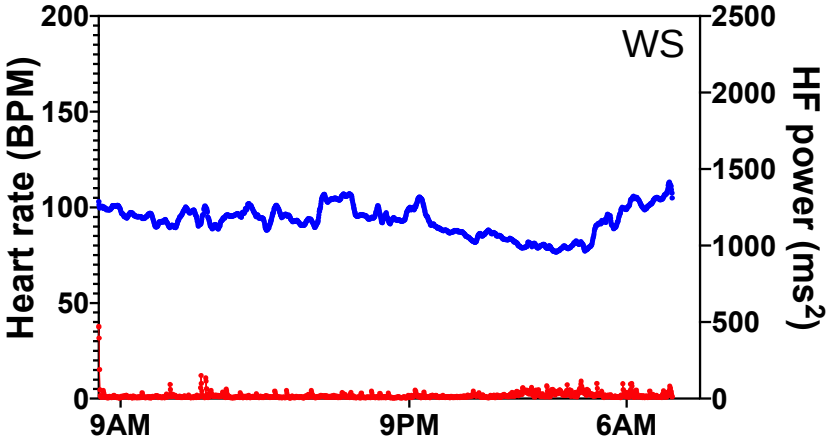
BETH A. KOZEL, MD, PHD

NATIONWIDE CHILDREN'S HOSPITAL

Individuals with WS exhibit decreased heart rate variability



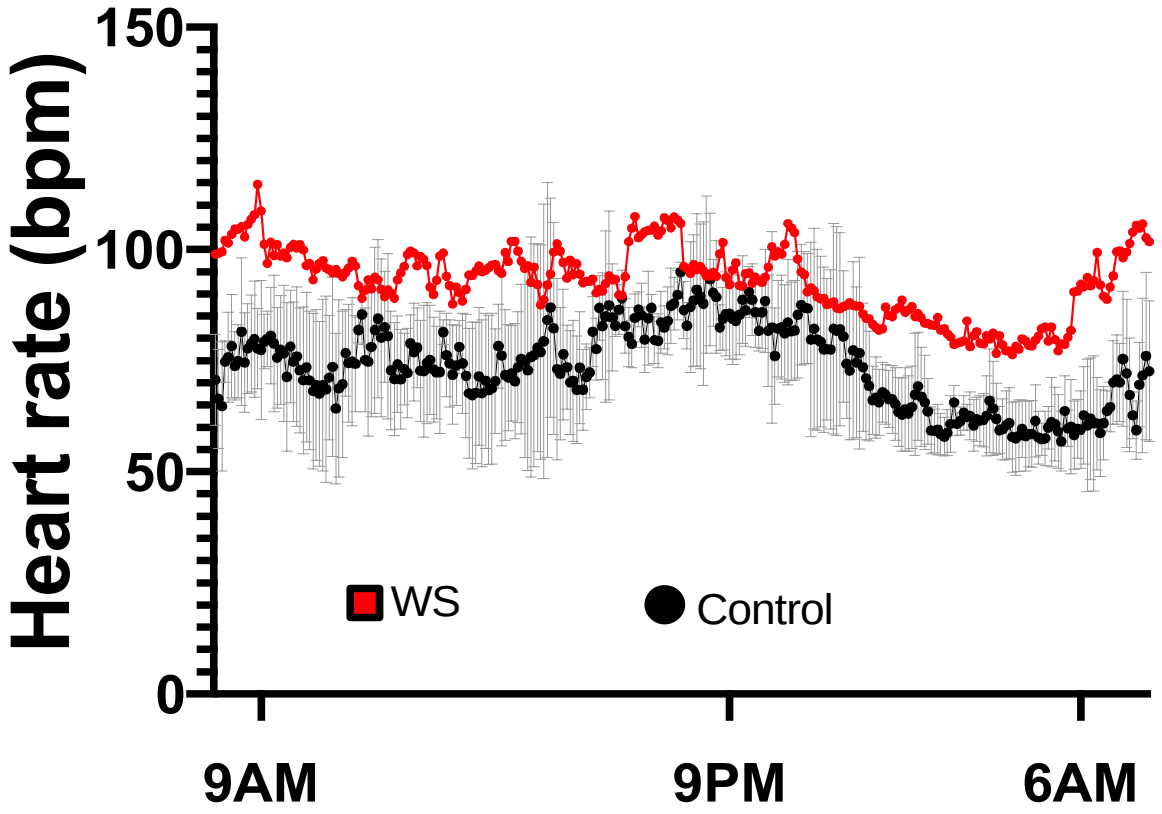




Decreased parasympathetic tone

Levin et al, *JACC Clin Electrophysiol*. 2022

Elevated heart rate (sympathetic tone) throughout the day and night in people with WS

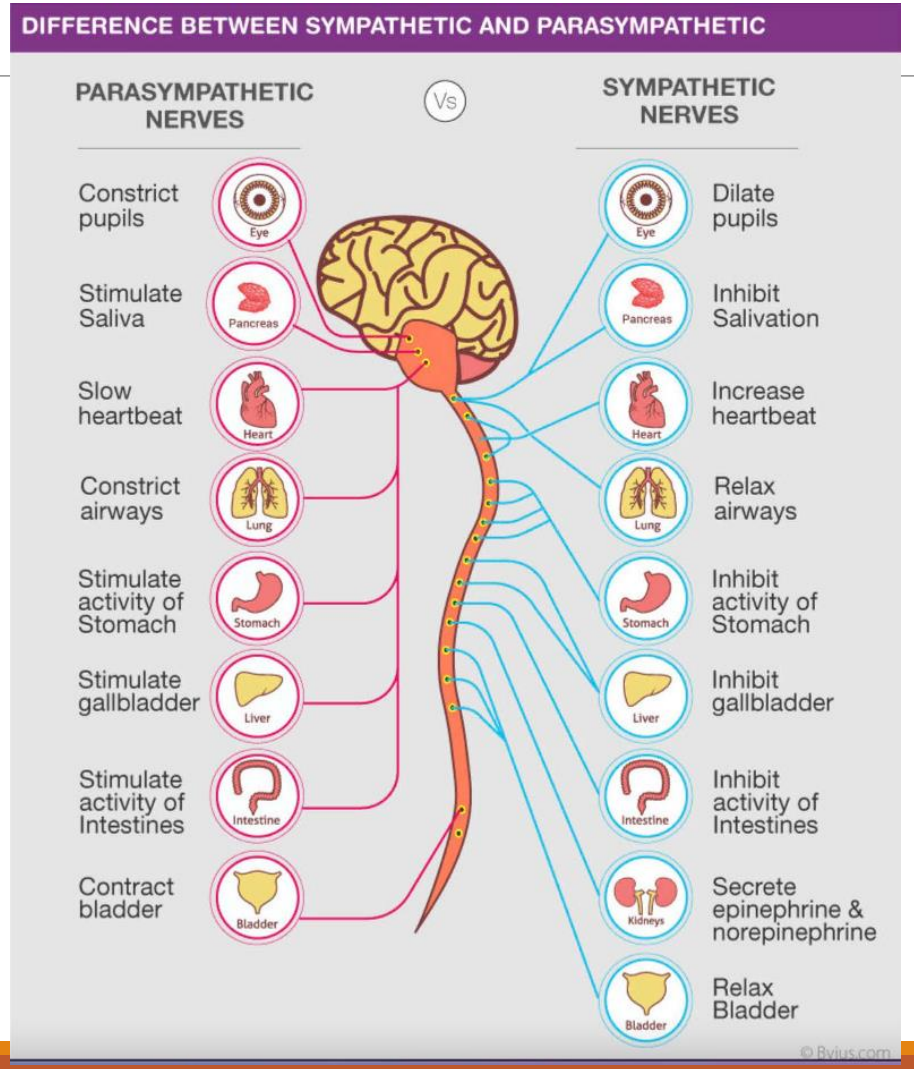


Levin et al, *JACC Clin Electrophysiol*. 2022

Differences in autonomic function may impact a variety of body functions

"fight or flight" (sympathetic)

"rest and digest" (parasympathetic)



Implications for:

- Anxiety
- Executive processing
- Abdominal pain
- Sleep

Study Participant Information

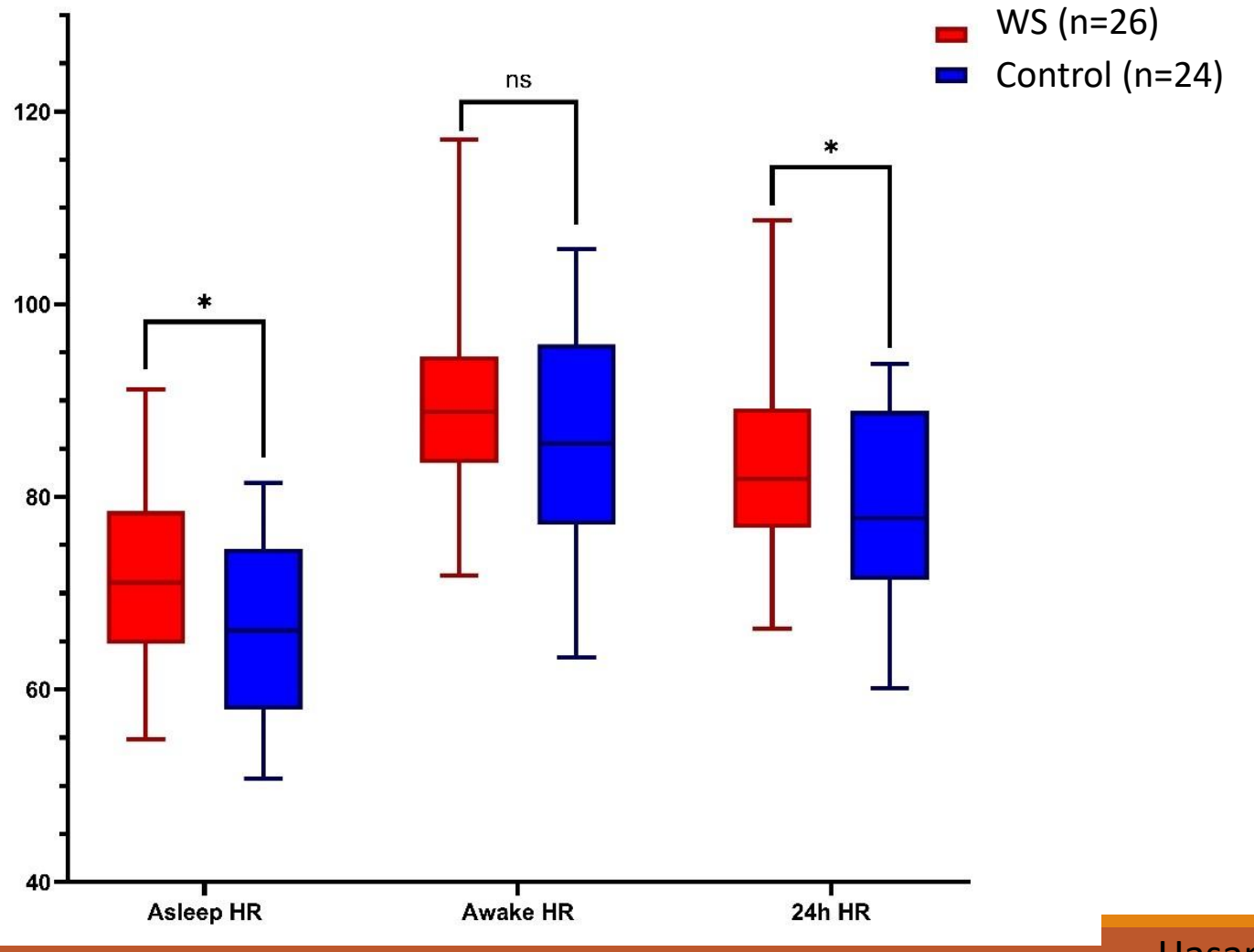
	WS (N=26)	Control (N=24)	P Value
Sex			0.65[1]
Female	10	10	
Male	16	14	
Age (years)**		21.4 (9.9)	0.33[2]
7-18	9	10	
18-30	10	9	
30-44	7	5	
BMI (kg/m^2) **	23.0 (5.0)	22.2 (5.0)	0.57[2]
<18.5	4	6	
18.5-24.9	15	13	
25-29.9	3	2	
>30	4	3	

No beta blockers; No sleep medications other than melatonin (n=4); must wear device most of the day for >5 days

Hasanzadeh et al, In preparation

Real world testing: Increased sympathetic tone

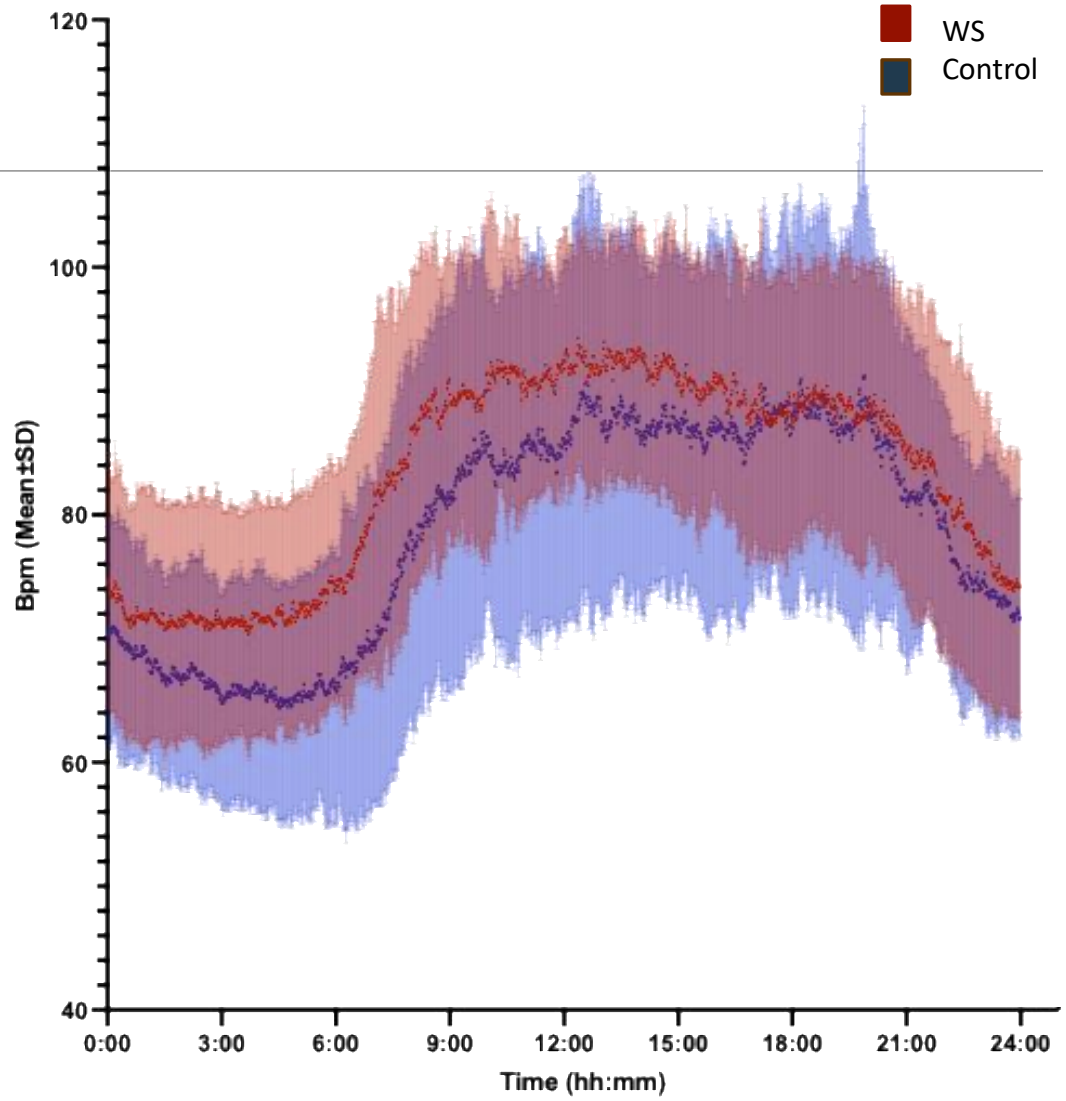
(Increased HR night>day)



No differences in measured step count

Hasanzadeh et al, in preparation

HR is generally higher in people with WS, but the difference varies by time



Hasanzadeh et al, in preparation

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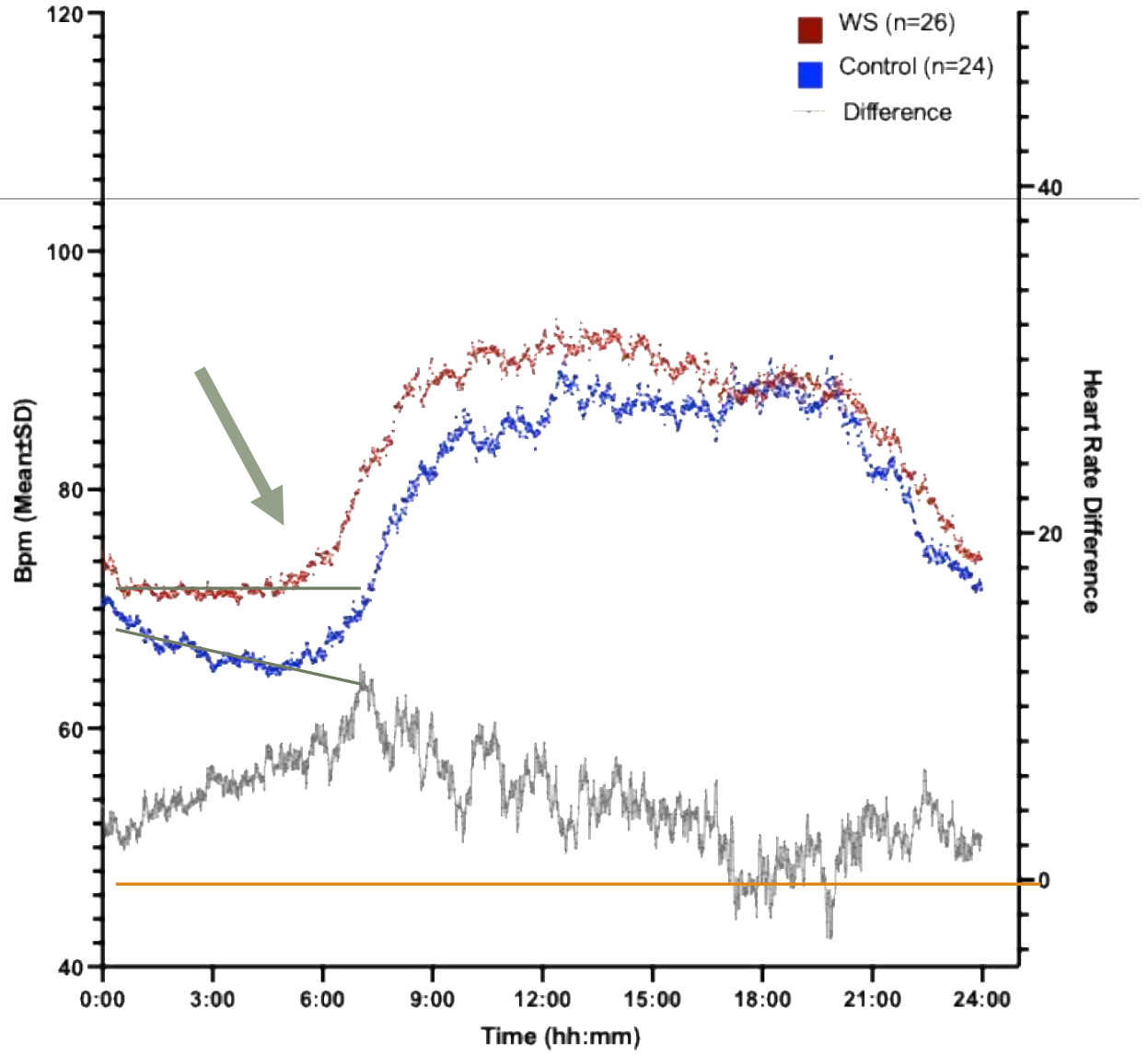
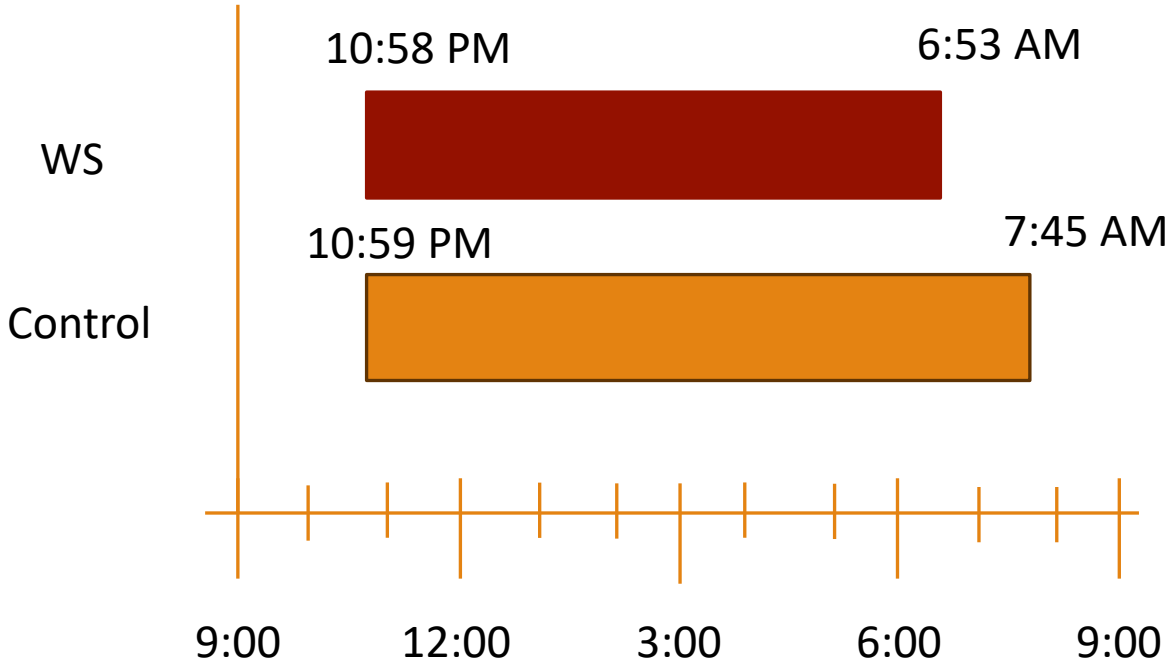


Hasanzadeh et al, in preparation

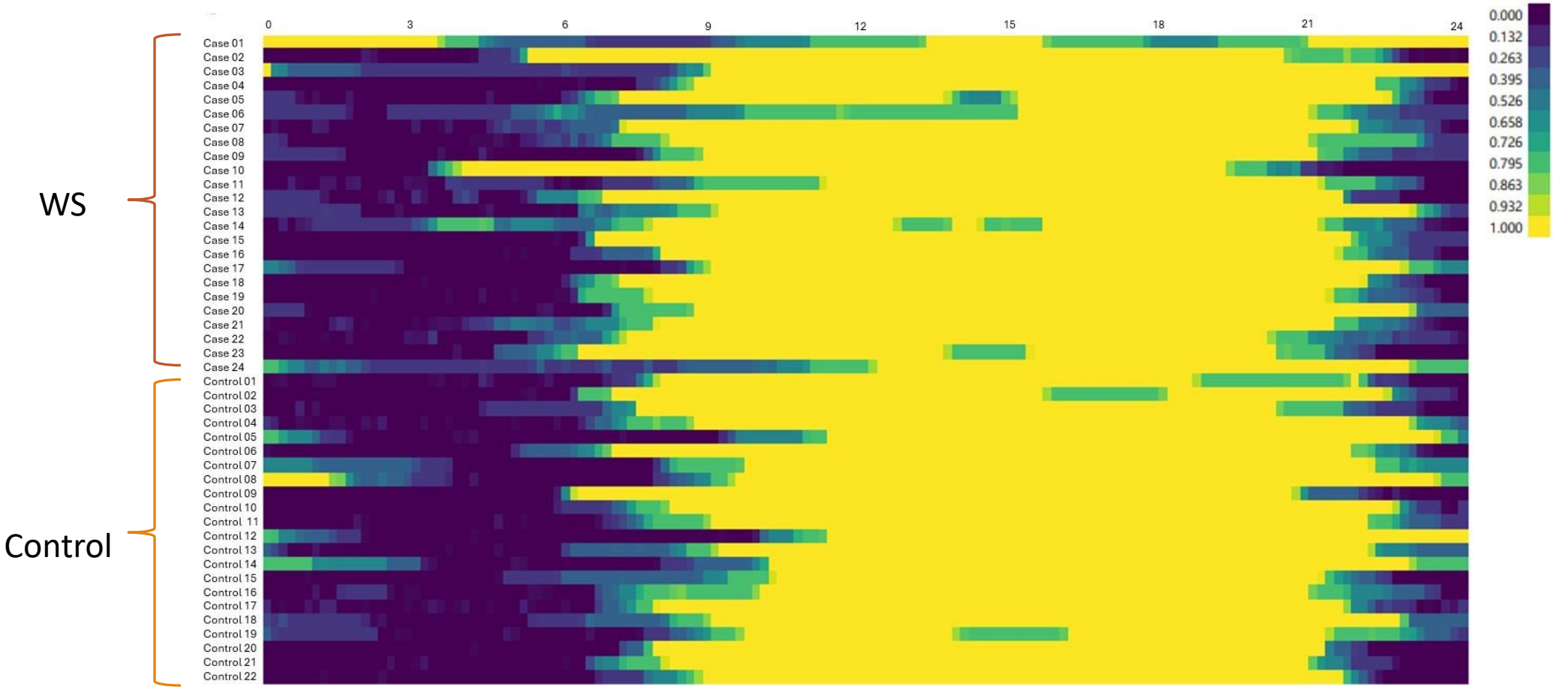
Reduced sleep duration in older children and adults with WS is primarily due to early awakening



	WS N=26 Mean (SD)	Control N=24 Mean (SD)	Difference in means:	P-value
Sleep duration (min)	415.84 (60.73)	456.62 (42.57)	40.78	**0.008**
Time in Bed (min)	475.37 (65.16)	525.53 (48.83)	50.16	**0.004**
Sleep onset time (hr)	22.96 (1.513)	22.99 (1.38)	0.03	0.079
Awakening time (hr)	6.88 (1.36)	7.75 (1.19)	0.87	**0.028**

Hasanzadeh et al, in preparation

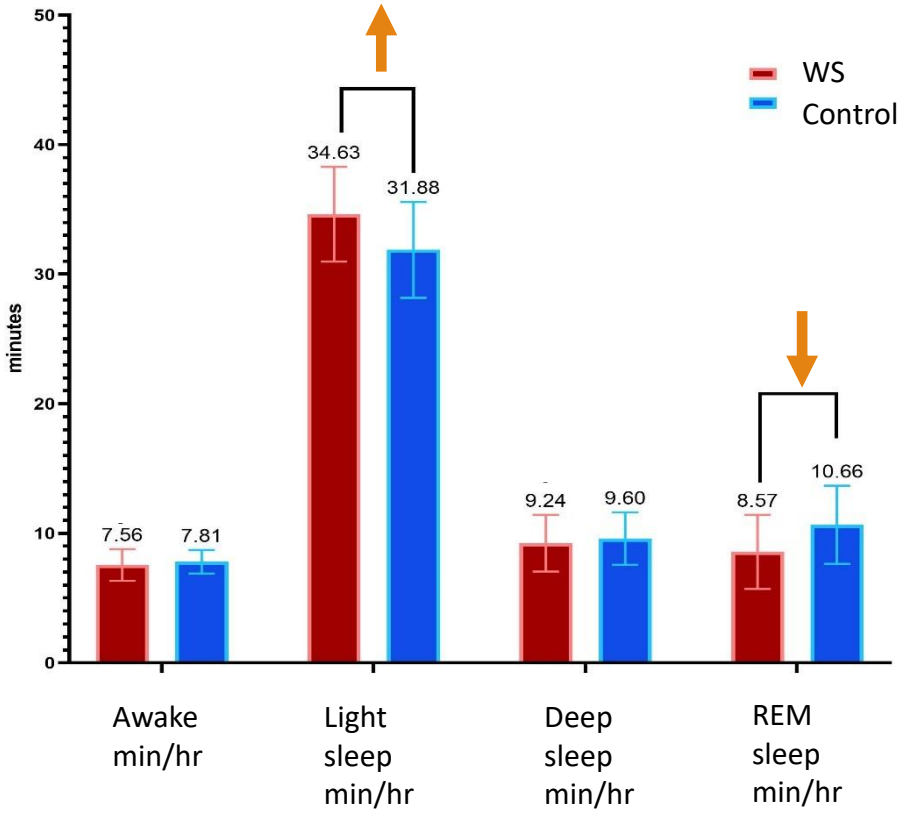
WS sleep regularity is not different from control



SRI trended lower in WS (76.5% vs. 82.1%, p = 0.094)

Hasanzadeh et al, in preparation

Sleep is lighter in people with WS, with reduced REM sleep



No difference from control in:

- nighttime oxygen saturation
- number of apneas

Hasanzadeh et al, in preparation

Wearables in WS (Conclusions)

- Heart rate trends from holter monitors largely reproduced in wearable device worn “in the wild”
- Heart rate is higher in people with WS, but the degree varies throughout the day
- Sleep is reduced in people with WS with largest effect being earlier awakening
- No overnight HR slowing
- No change in awakenings but sleep stages are lighter with less REM sleep
- Findings suggest altered autonomic response in WS that might be targetable with medications
- Future studies

Questions?

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