Understanding Sleep Health for People with Down Syndrome

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Goals

- Discuss determinants of sleep health
- Discuss current and emerging diagnostic approaches for OSA in people with Down syndrome
- Discuss current and emerging treatment options for OSA in people with Down syndrome

Sleep Health

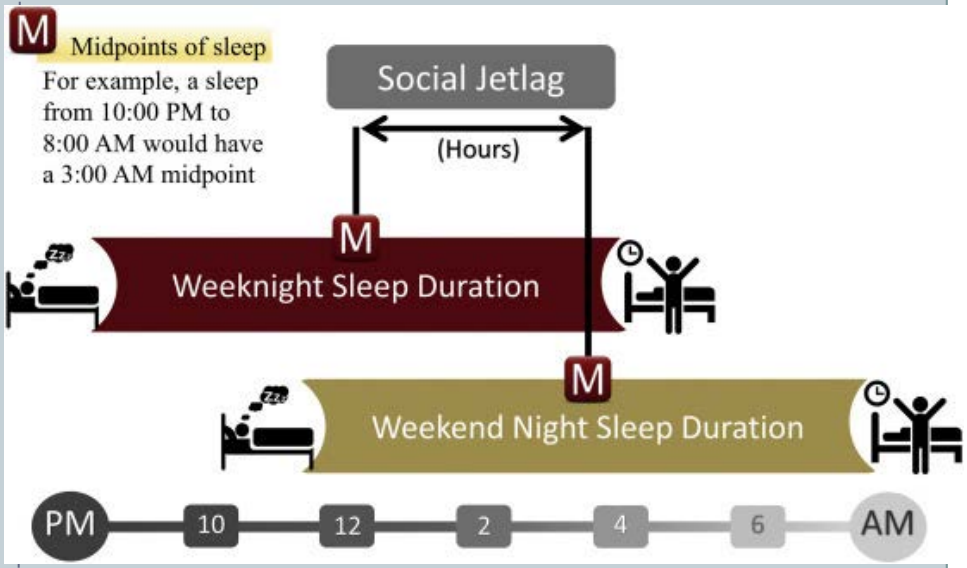
- Sleep duration
- Sleep variability
- Sleep quality

Sleep duration

- Sufficient sleep
  - Waking up refreshed
  - Not sleepy during the day
    - Sleep disorders can make this tricky
- Worrying about insufficient sleep can be a problem
  - Prolonged time in bed can lead to insomnia

Sleep variability

- Consistent sleep schedule in line with circadian rhythm
  - Varied schedule leads to social jetlag
  - Moderation matters
    - Staying up late occasionally isn't a problem



Sleep Quality

- Environment
  - Cool, dark
  - No phones in bed
- Minimize time in bed/room other than sleep
  - Need association of bed=sleep
- Sleep disorders
  - Recognize and treat

Common sleep disorders

- Obstructive sleep apnea
- Restless leg syndrome
- Parasomnias
- Insomnia

Restless legs syndrome

- 1 in 25-50 children
  - 1 in 100 moderate-severe
- Symptoms:
  - Insomnia and/or daytime sleepiness
  - Urge to move legs
  - Triggered by inactivity
  - Better with movement
  - Worse at night
- Difficult to diagnose in young children or limited verbal abilities
- Runs in families

Restless legs syndrome

- Treatment
  - Most common cause is low iron
    - Check body iron stores
    - Goal ferritin level >50
    - Treat with supplemental iron
  - Medications can be used in severe cases

- Things that aren't RLS:
  - Sleep starts
    - Jerk as child is falling asleep
  - Rhythmic movements
    - Rocking legs
    - Usually ~1x/second

Parasomnias

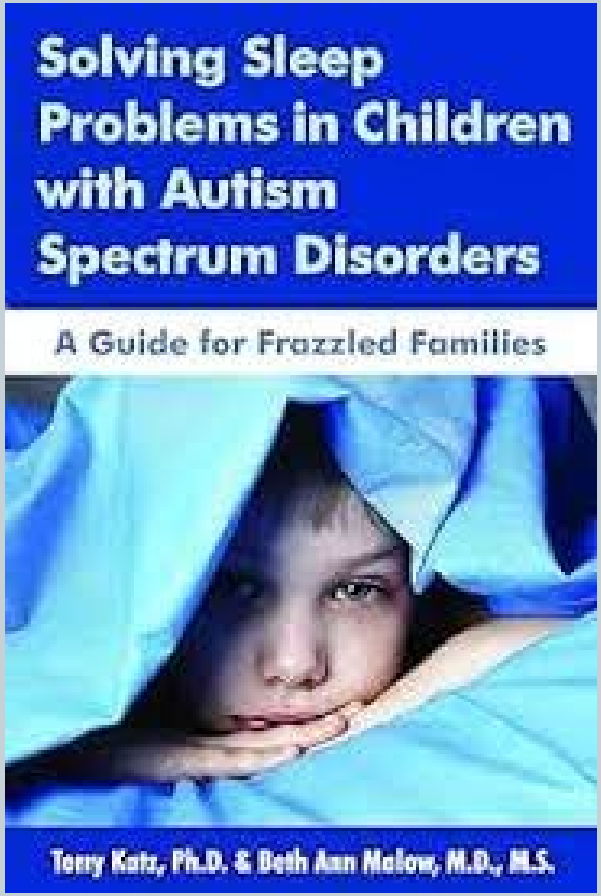
- Sleep terrors/confusional arousals
- Sleep talking
- Sleep walking
- Nightmares

Parasomnias

- Common
  - Up to 88% of kids have a parasomnia
- Treatment
  - Usually none
  - If frequent (>1-2x/week), screen for underlying disorder
  - Safety counseling for sleep walking
    - Lock doors to outside
    - 1st floor bedroom
    - Put away dangerous objects

Insomnia

- Infant/younger children



- Older children/adults
  - CBT-Insomnia
  - Sleep coach app

Obstructive Sleep Apnea in Down Syndrome

Types of sleep apnea

- Obstructive Sleep Apnea (OSA)
  - Snoring, choking, gasping
  - ~2-5% of children[1]
  - Associated with adverse cognitive, quality of life and cardiovascular effects
  - Focus of almost all literature on sleep apnea in DS
- Central Sleep Apnea
  - Silent pauses
  - Uncommon in children
    - Typically associated with neurologic or neuromuscular conditions
    - May be seen in infants
  - Some older literature suggesting common in DS[2]

1. Marcus, Brooks et al. 2012 2. Ferri, Curzi-Dascalova et al. 1997

OSA prevalence in people with DS

- Infants
  - 31% prevalence[1]
- Children
  - 50-79% prevalence[2,3,4,5]
- Adults
  - 82-100% prevalence[6,7]

- Many children with DS and OSA are not reported to have usual OSA symptoms such as snoring by parents[4]
- OSA in children with DS is severe in 50% of cases[5]
- Universal screening with polysomnography recommended by age 4 years[8]
  - 25% of children had PSG by age 4 in single center study[9]

1. Goffinski, Stanley et al. 2015 2. de Miguel-Diez, Villa-Asensi et al. 2003 3. Dyken, Lin-Dyken et al. 2003 4. Maris, Verhulst et al. 2016
5. Shott, Amin et al. 2006 6. Cornacchia, Sethness et al. 2019 7. Trois, Capone et al. 2009 8. Bull et al. 2011 9. Hsieh, Gilad et al. 2019

OSA risk factors in children with DS

- Anatomic structure[1]
  - Mid-face hypoplasia
  - Relative macroglossia
  - Adenotonsillar hypertrophy
- Hypotonia
  - Including airway hypotonia[2]
  - Worse during sleep

1. Shott 2006 2. Donnelly, Shott et al. 2004

Adverse effects of OSA in children with DS

- Cognitive/Behavioral
  - Decreased verbal IQ[1]
  - Decreased adaptive function[2]
  - Decreased verbal fluency[3]
- Decreased Quality of Life[4]
- Cardiovascular
  - Decreased left ventricular function[5]

1. Breslin, Spano et al. 2014 2. Nixon, Biggs et al. 2016 3. Chen, Spano et al. 2013 4. Churchill, Kieckhefer et al. 2015 5. Konstantinopoulou, Tapia et al. 2016

Sleep apnea diagnosis in children with DS

- In-lab Polysomnography
  - Gold standard
  - Wealth of information
    - EEG
    - Cardiac
    - Respiratory
    - Video
    - Tech
  - Challenging in children with sensory difficulties
  - Testing availability
    - 3 month + wait times
    - Lack of rural testing centers

Sleep study alternatives in DS

- Home sleep studies[1]
  - Small wearable device, monitors airflow, pulse oximetry, respiratory effort
  - HST AHI of 1: 100% sensitivity, 23% specificity compared to PSG
  - HST AHI of 3: 100% sensitivity, 83% specificity compared to PSG (PSG AHI=1)
- Overnight oximetry[2]
  - sensitivity 92%; specificity 63%
- Urinary Biomarkers[3]
  - Sensitivity 50-100%, specificity 45-95%
    - Dependent on threshold
- Combined approach[4]
  - Questionnaire, demographics, physical exam, medication review
  - Sensitivity 72-76%, specificity 51-55%

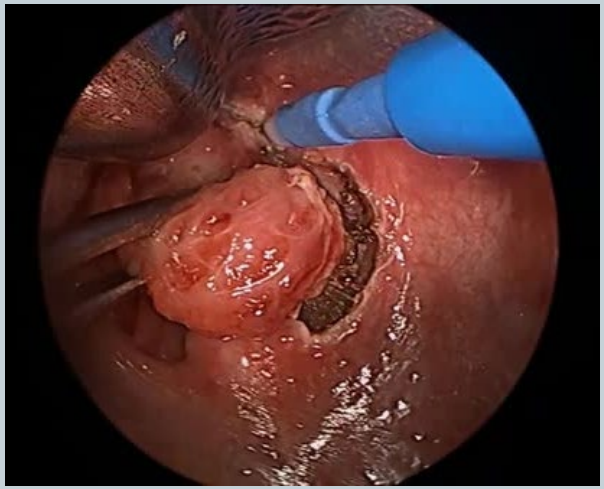
1. Ikizoglu, Kiyan et al. 2019 2. Hill, Elphick et al. 2018 3. Elsharkawi, Gozal et al. 2017 4. Skotko, Macklin et al. 2017

OSA Treatment in children with DS

- Standard
  - Adenotonsillectomy
  - Positive Airway Pressure therapy (CPAP)
- Alternative/emerging
  - Myofunctional therapy
  - Anti-inflammatory medications
  - Weight loss
  - Dental approaches
    - Palate expansion
    - Mandibular advancement device
  - Hypoglossal nerve stimulation

Adenotonsillectomy

- Typical 1st line approach for most children
- Unlikely to resolve OSA in children with DS
  - 65-73% have residual OSA after AT[1,2,3]
- Typically does decrease OSA severity in children with DS[1]
  - 44% of children showed 50% reduction of AHI[3]
  - Baseline AHI 26.6, post-AT AHI 11.6[2]
- Other ENT procedures may be considered if AT unsuccessful.



1. Shete, Stocks et al. 2010 2. Thottam, Trivedi et al. 2015 3. da Rocha, Ferraz et al. 2017

PAP therapy

- Pressurized air delivered through mask and hose from small machine
- Very efficacious (when used)
- Limited by therapy adherence
  - 46% adherence in children with DS[1]
  - 2 hours per night in prior trial[2]

1. Trucco, Chatwin et al. 2018 2. Konstantinopoulou, Tapia et al. 2016

Myofunctional Therapy

- Speech therapy-like exercises to improve airway muscle function while awake
- One DS-specific study
  - 42 children at training camp with 45-minute session 3x/daily for 1 week
  - 18 children with usable sleep study results pre and post
    - Baseline mean AHI 6.4
    - Post-treatment mean AHI 6.4

Anti-inflammatory medications

- Montelukast
  - Leukotriene receptor antagonist
- Intranasal steroids
- 2 DS-specific studies

- Study 1: Either/both medications vs observation[1]
  - Retrospective, N=45
  - Medications
    - Baseline oAHI 2.8, follow up 3.5
  - Observation
    - Baseline oAHI 2.3, follow up 2.9
- Study 2 Montelukast or steroid[2]
  - Retrospective, N=10
    - Baseline oAHI 3.5 follow up 3.6

1.Yu, Sarber et al. 2020 2. Howard, Sarber et al. 2019

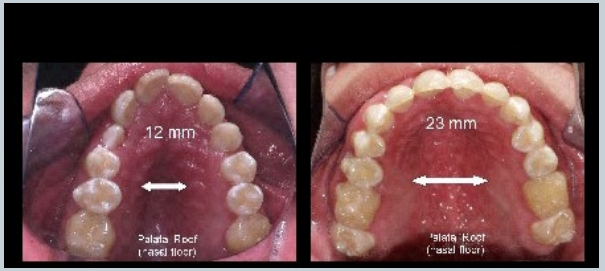
Weight Loss

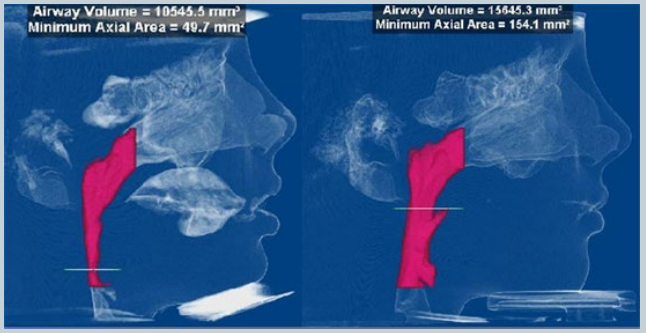
- OSA associated with obesity in children with DS[1]
  - No studies on efficacy of weight loss for OSA treatment in DS
- Easier said than done
- Typically need to lose large amount of weight

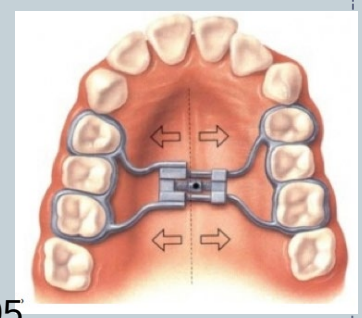
1. Bertapelli, Pitetti et al. 2016

Palate Expansion

- Useful for individuals with narrow mandibular arch
  - Common in DS
- Evidence of improved airway patency in DS[1]
- No OSA-specific studies in DS



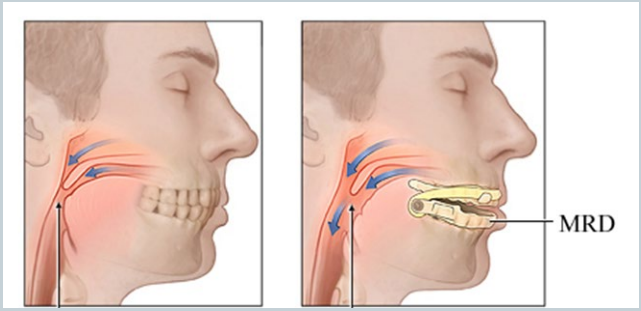




1. de Moura, Vales et al. 2005

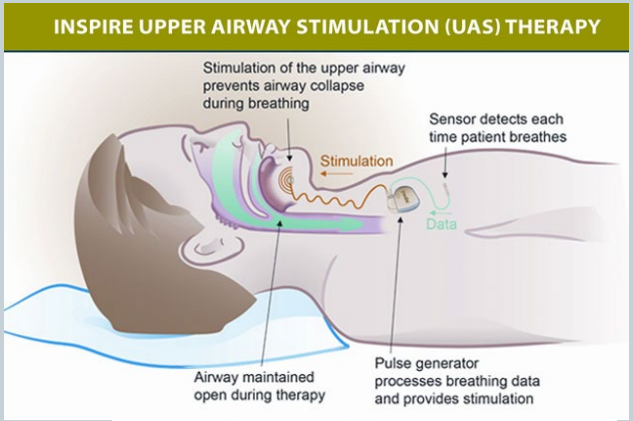
Mandibular advancement device

- Pulls forward mandible
- No DS-specific studies
- Can be used in older teenage children
  - Need to have all adult teeth in
  - ~typically age 16+



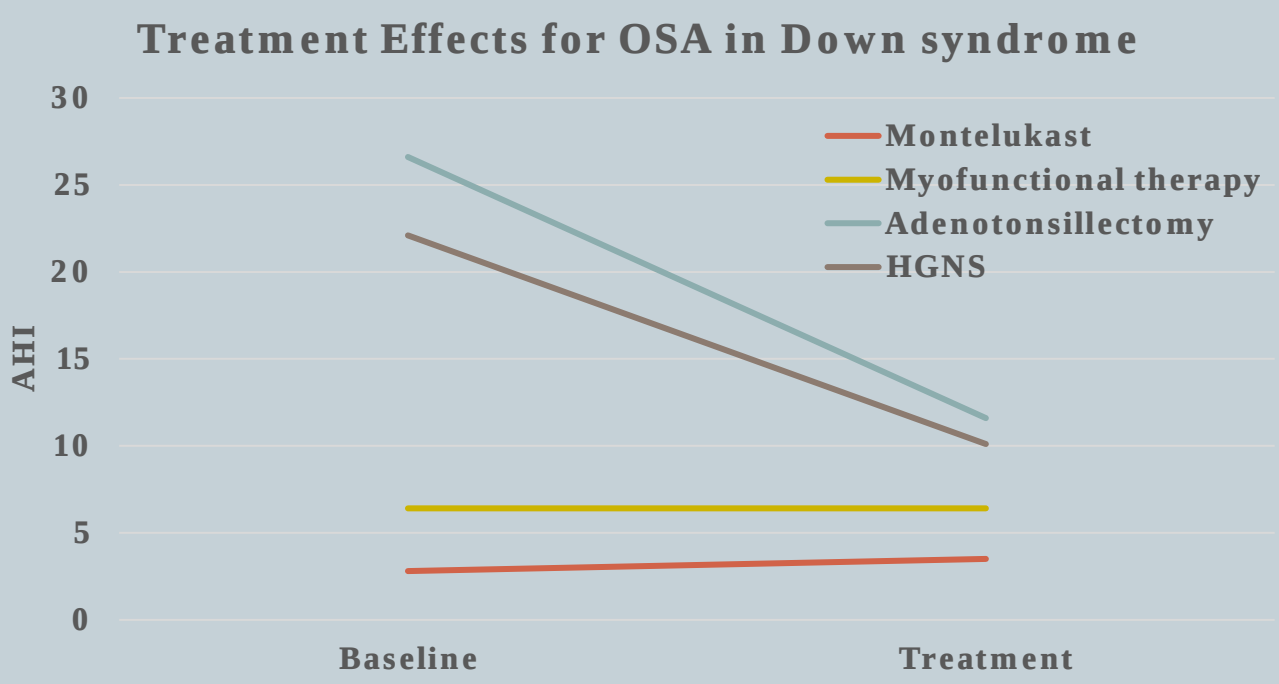
Hypoglossal nerve stimulation

- Implanted nerve stimulator
- Improves upper airway tone
- Completed trial in older children with DS[1]:
  - 42 children age 10-21
  - Baseline oAHI 22.1
  - Treatment AHI 10.1
  - Good adherence (9 hrs/night)
  - Improved OSA-related QOL



1. Yu et al. 2022

Comparative treatment efficacy for OSA

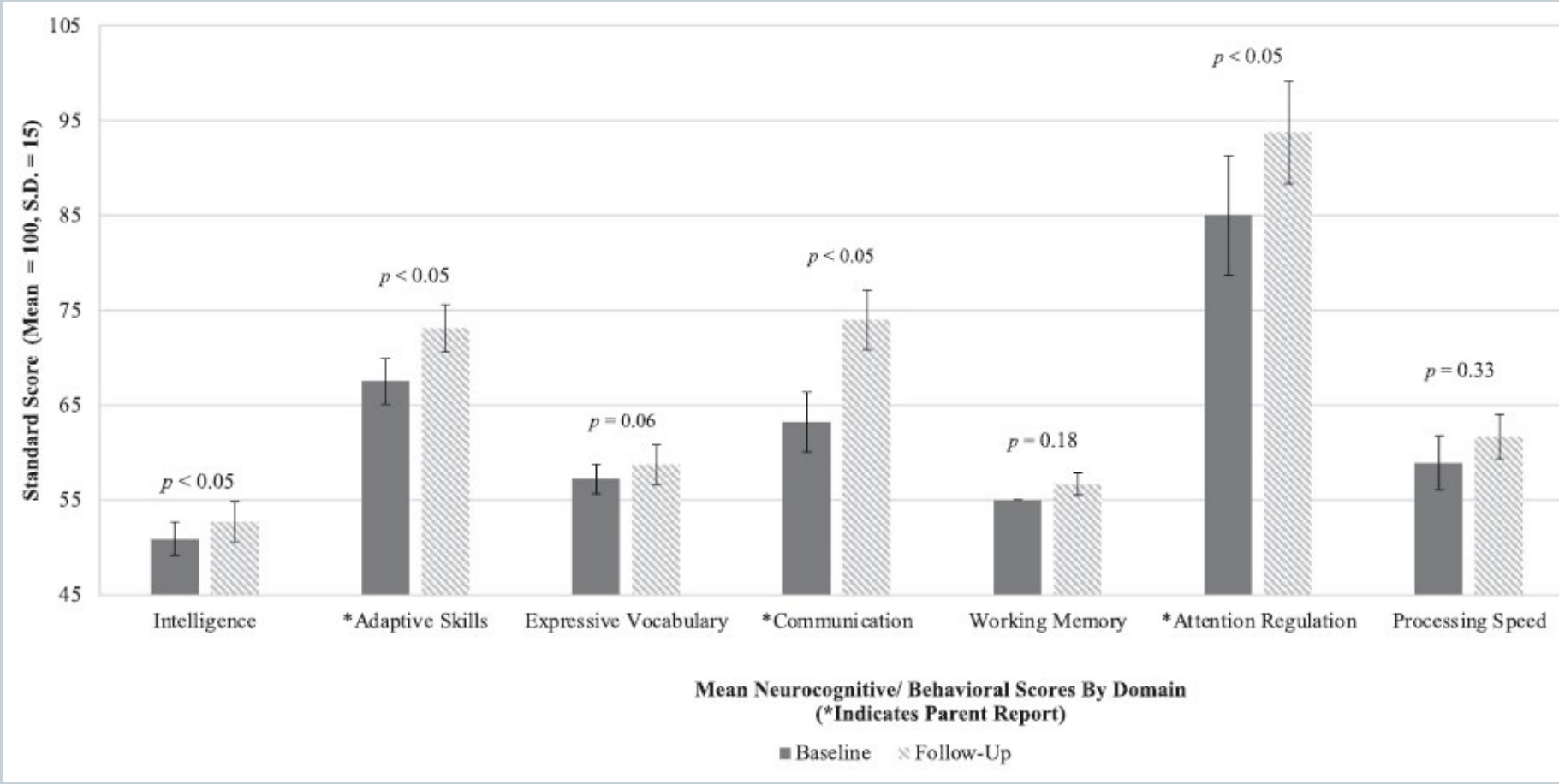


Does OSA treatment improve OSA-associated adverse effects in children with DS?

- Some studies that included children with DS:
  - Study of PAP in children with OSA, included subset (n=10) with cognitive impairment (6 with DS)[1]
    - Improved QOL and parent-reported neurobehavioral outcomes
  - Study of adenotonsillectomy in children with mucopolysaccharidoses or DS[2]
    - Improved QOL

1. Marcus, Radcliffe et al. 2012 2. Sudarsan, Paramasivan et al. 2014

Does OSA treatment improve OSA-associated adverse effects in children with DS?



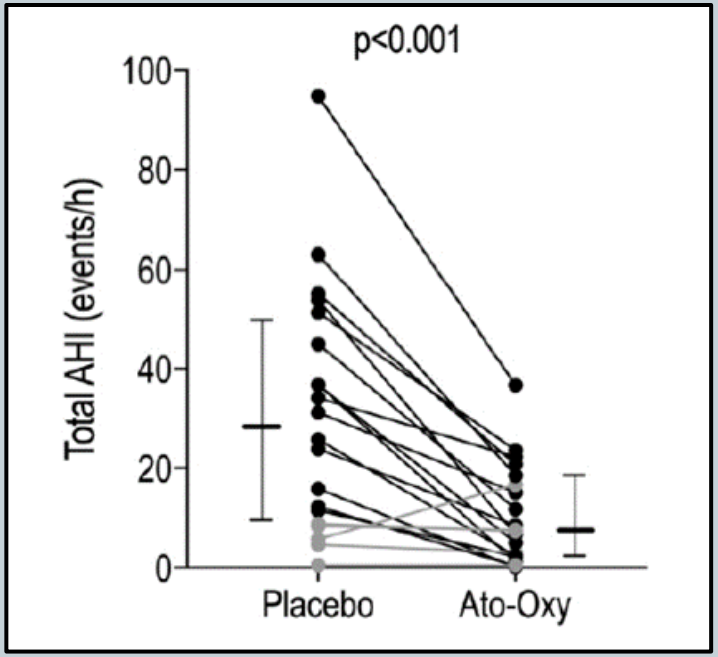
Pilot study (n=9) of DS HGNS study participants after 6 months of treatment (Grieco et al 2022).

OSA research at U of A

MEDICATIONS FOR OSA IN CHILDREN WITH DOWN SYNDROME

Ato-oxy

- Atomoxetine
  - FDA-approved to age 6 for ADHD
  - Increases norepinephrine
    - Increases airway tone in NREM
- Oxybutynin
  - FDA-approved to age 6 for overactive bladder
  - Decreased muscarinic receptor activity
    - Increases airway tone in REM
- Ato-Oxy
  - Increases upper airway muscle tone during sleep
  - ~50% improvement in AHI in adults without DS
  - In phase 3 study in adults (aroxybutynin)

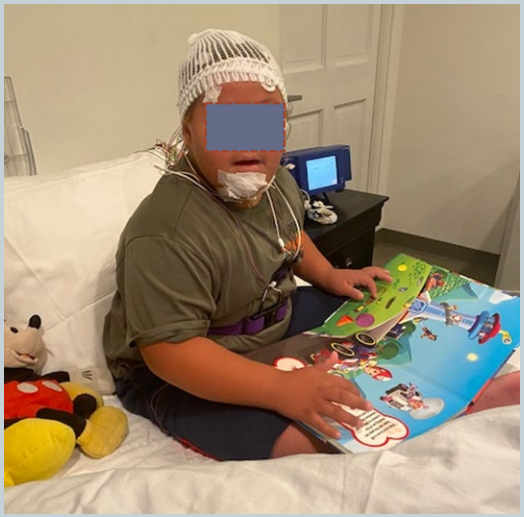


Ato-oxy significantly reduced AHI in one night study of adults without DS (Tarantino Montemuro 2019)

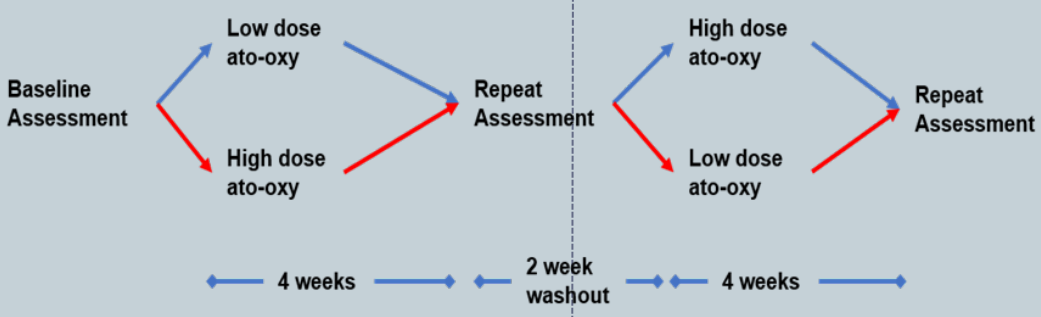
Taranto-Montemurro et al Am J Respir Crit Care Med (2019);199(10):1267-1276

Ato-Oxy in children with Down syndrome

- Ato-oxy targets airway muscle tone, key issue in DS
- HGNS effective in DS
- Ato-oxy may be non-surgical alternative to HGNS



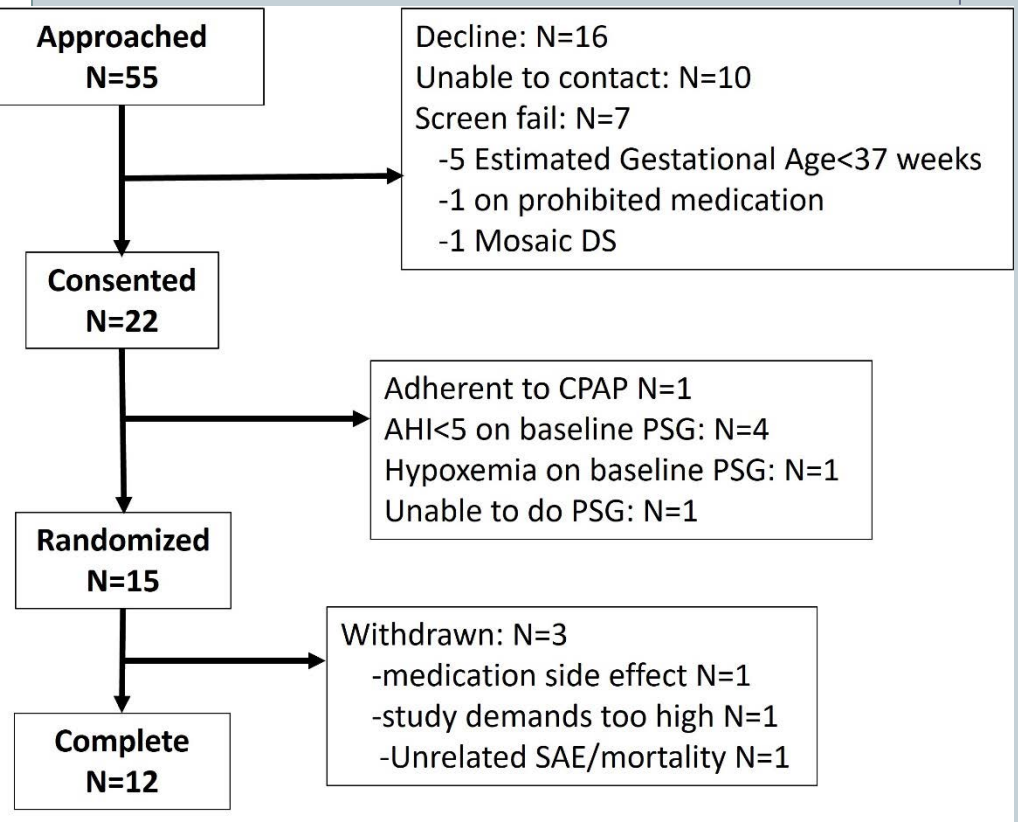
Trial Design



- Participants received high dose and low dose ato-oxy for 4 weeks
  - random order
  - 2-week washout between arms
  - High dose: 1.2 mg/kg ato (max 80 mg), 5 mg oxy
  - Low dose: 0.5 mg/kg ato (max 40 mg), 5 mg oxy

- Outcome measures
  - In-lab PSG
    - oAHI
    - sleep architecture
  - HR-QOL assessment
    - OSA-18
    - PedsQL
  - Cognitive
    - Conners

Enrollment



- One participant did not have sufficient data recorded on their third polysomnogram, therefore complete data available from 11 participants.
- AHI: apnea-hypopnea index, CPAP: Continuous Positive Airway Pressure, SAE: severe adverse event

Demographics

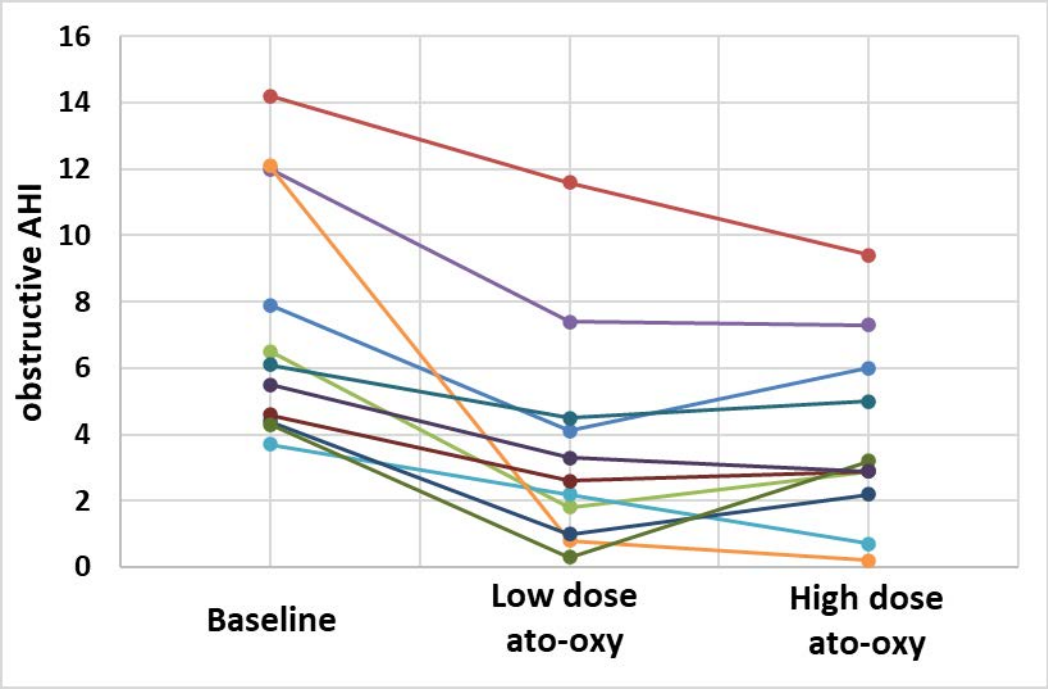
Age (years)	10.4 ± 4.1
Sex	
Female	3 (27%)
Male	8 (73%)
Race	
Black	2 (18%)
White	9 (82%)
Hispanic or Latino Ethnicity	5 (46%)
Socioeconomic status	40 ± 18
BMI percentile	79 ± 23
Congenital Heart Disease	8 (73%)
Depression	1 (9%)
Autism Spectrum Disorder	2 (18%)
ADHD	2 (18%)

Adverse Events

Adverse Event	High dose (%)	Low dose (%)	p
Fatigue	27%	13%	0.65
Mood changes	27%	20%	1.00
Diarrhea	7%	7%	1.00
Headaches	7%	0%	1.00
Abdominal pain	0%	7%	1.00
Decreased urinary frequency	7%	0%	1.00
Dry mouth	0%	7%	1.00

- AEs were generally mild.
- 1 child withdrew due to side effects, 1 child had dose reduction on high dose due to irritability and behavioral changes

Participant level changes in oAHI



Quality of life and cognitive outcomes

				p		
	Baseline	Low dose	High dose	low vs baseline	high vs. baseline	low vs. high
Health-related Quality of Life						
OSA-18 Total score	51 ± 19	45 ± 17	45 ± 16	0.09	0.37	0.85
PedsQL total score	64 ± 16	67 ± 15	66 ± 15	0.48	0.69	0.73
Conners (n=8)						
ADHD Index score	**9.1 ± 6.3**	7.9 ± 6.5	**5.6 ± 4.9**	0.47	**0.047**	0.37
Inattention	70 ± 14	67 ± 14	64 ± 11	0.45	0.15	0.23
Hyperactivity/Impulsivity	70 ± 14	67 ± 13	65 ± 11	0.49	0.29	0.59
Learning problems	78 ± 9	77 ± 9	75 ± 13	0.73	0.13	0.61
Executive Function	61 ± 14	65 ± 11	61 ± 8	0.47	0.89	0.32
Defiance/Aggression	**64 ± 10**	**53 ± 10**	58 ± 11	**0.02**	0.06	0.33
Peer relations	68 ± 21	**69 ± 17**	**62 ± 19**	0.8	0.31	**0.01**
Global Index	66 ± 16	65 ± 13	61 ± 13	0.5	0.17	0.37

- **OSA-18: OSA-specific health-related quality of life, lower scores indicate better quality of life.**
- **PedsQL: General pediatric health-related quality of life, higher scores indicate better quality of life.**
- **Conners: ADHD-oriented behavior measure, higher scores indicate worse function**

Ato-oxy in kids with DS Summary

- Low dose and high dose ato-oxy both reduced oAHI by ~50%
- Fewer side effects in the low dose group
  - If atomoxetine related, may resolve with time on therapy
- Small HRQOL improvements
  - Not significant in this small sample
  - May improve further with time on therapy

- Next steps (currently enrolling)
  - 6-month study of low dose ato-oxy
    - PSG outcomes
    - HRQOL
    - Cognitive outcomes

Study Overview

- Pilot study (completed)
  - Data on short-term efficacy of ato-oxy for OSA
    - Ato-oxy reduced OSA severity by about 50% in children with DS
  - Dose determination for next study
    - Low dose ato-oxy had similar efficacy as high dose, but fewer side effects
- Current study
  - 6-month efficacy of ato-oxy for:
    - OSA severity
    - Quality of Life
    - Cognition

Study Overview

Participants will undergo polysomnography (PSG), cognitive evaluation and (HRQOL) assessment at baseline. Polysomnography, cognitive evaluation-and health-related quality of life (HR-QOL) assessment will again be performed after 6 months of treatment.

Currently enrolling for this study, goal enrollment of 36 participants, ~8 participants either scheduled for baseline sleep study or currently in study.
Children with Down syndrome age 6-17 years may be eligible to participate

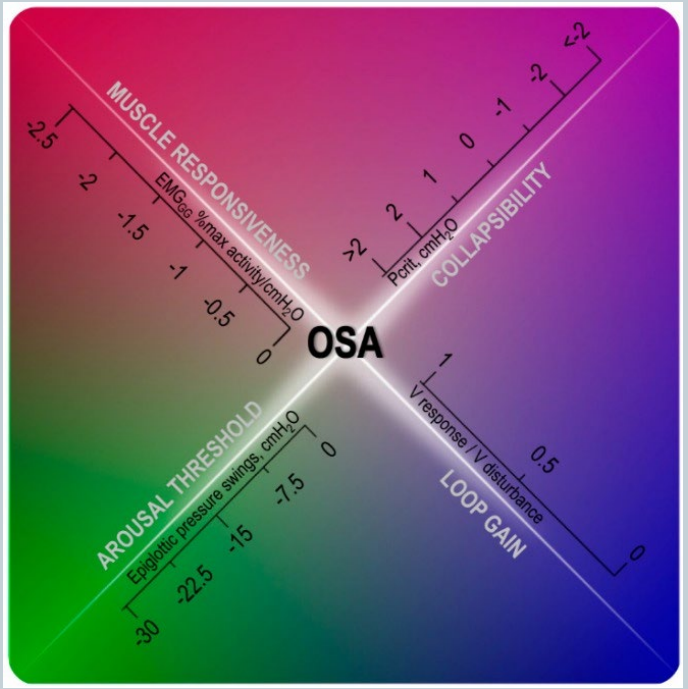
Where we hope to go

- Precision medicine therapies
  - Identify OSA features from polysomnography to determine effective treatment options

OSA Endotyping

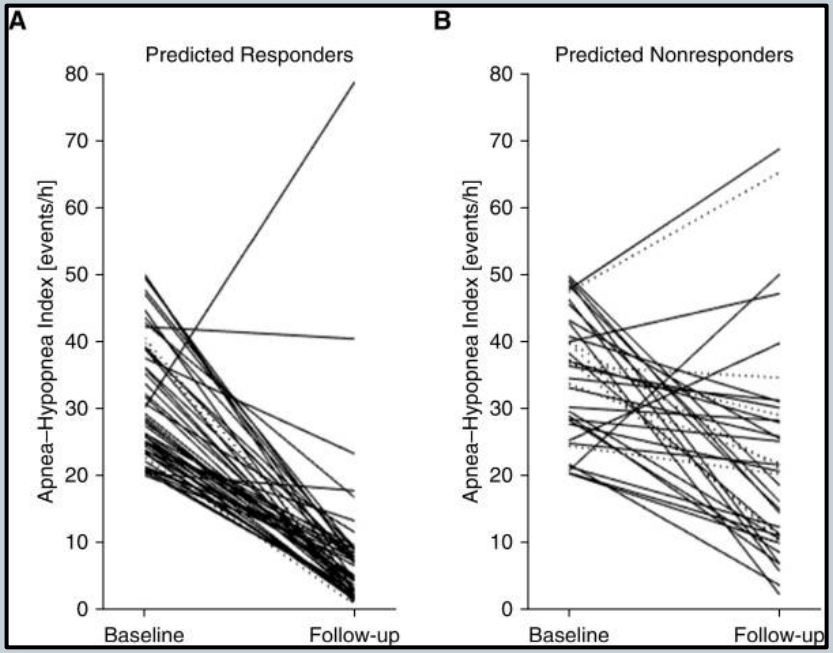
- Baseline muscle tone
- Muscle compensation
- Loop gain
  - High loop gain
- Arousal threshold
  - Low arousal threshold

- Can be derived from diagnostic PSG
  - Most data from adults

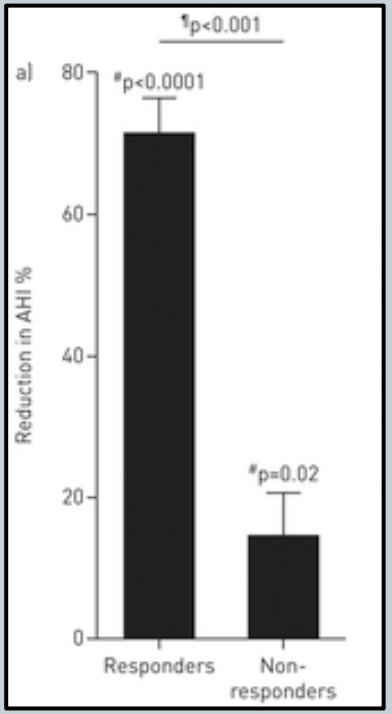


Taranto-Montemurro et al Am J Respir Crit Care Med (2019);199(10):1267-1276

OSA Endotyping predicts therapy response



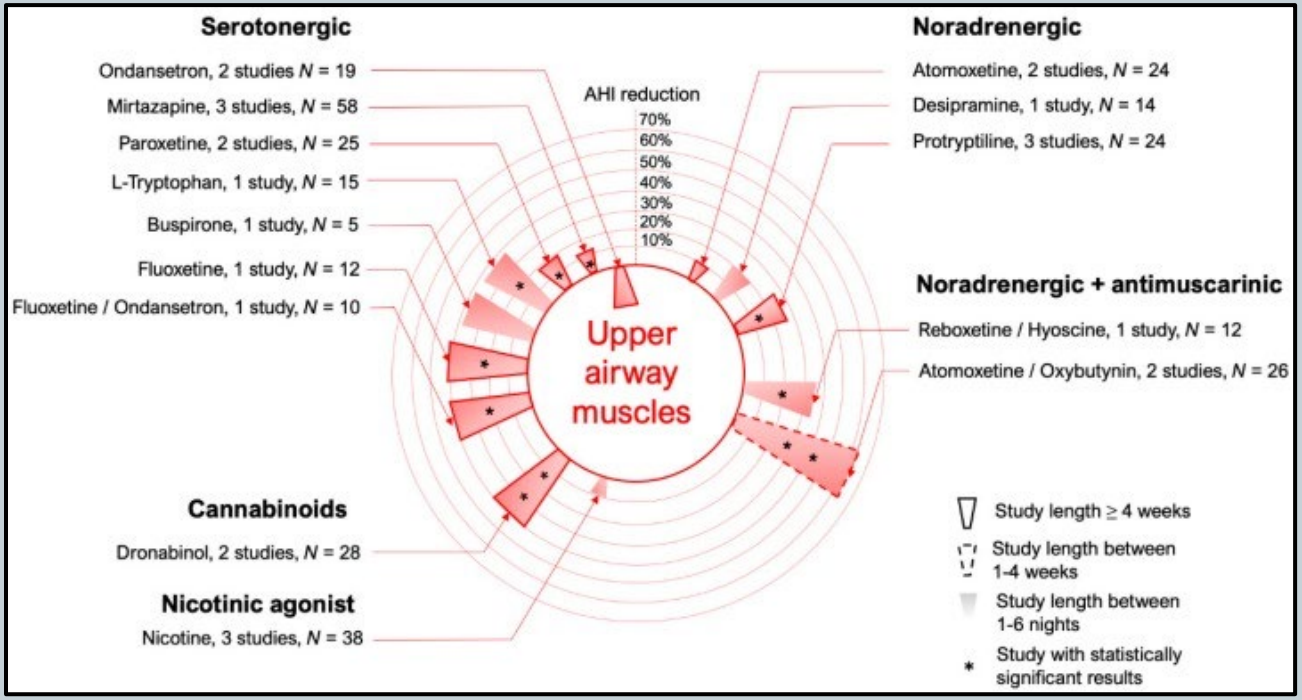
Endotype-based predicted responders vs non-responders in STAR HGNS adult study. Higher arousal threshold, lower loop gain and higher compensation predict better response



Higher loop gain and higher airway muscle tone and compensation predict response to oxygen (Sands 2019)

Op de Beeck S et al. *Am J Respir Crit Care Med* 2021;203:746-755
Sands et al. Eur Respir J. 2018 Sep 27;52(3):1800674.

Endotype-targeted drugs are coming



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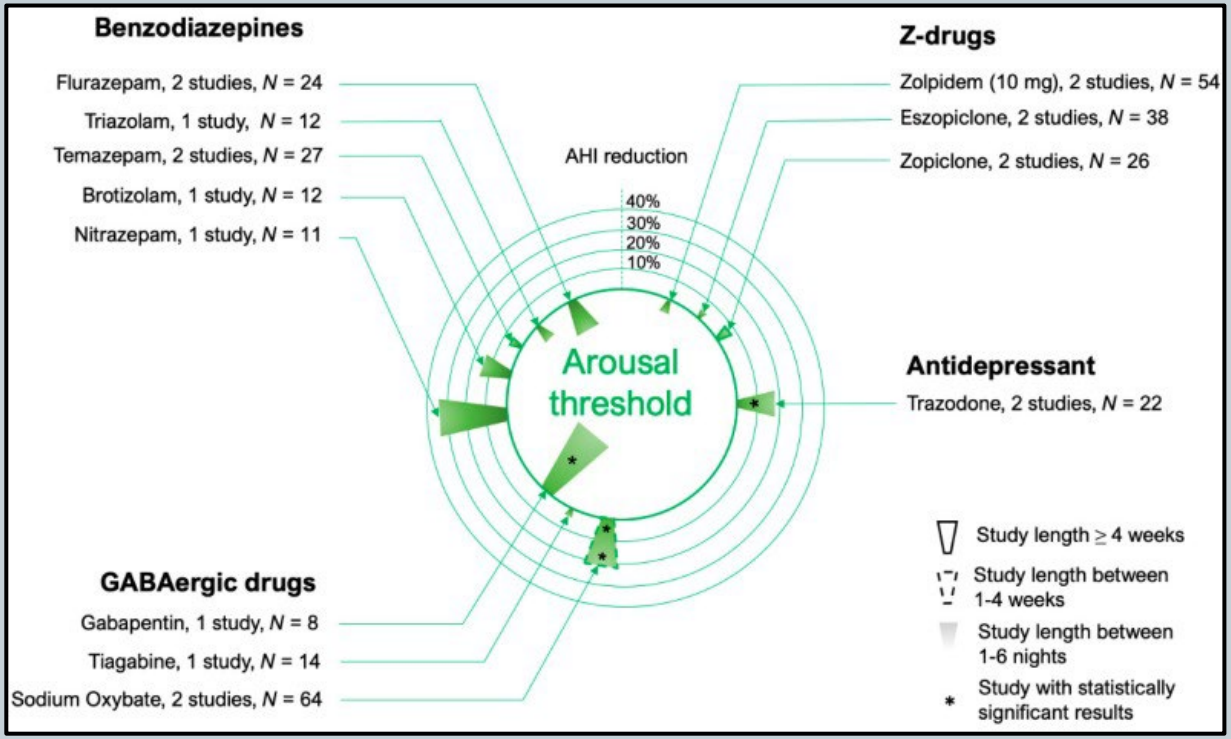

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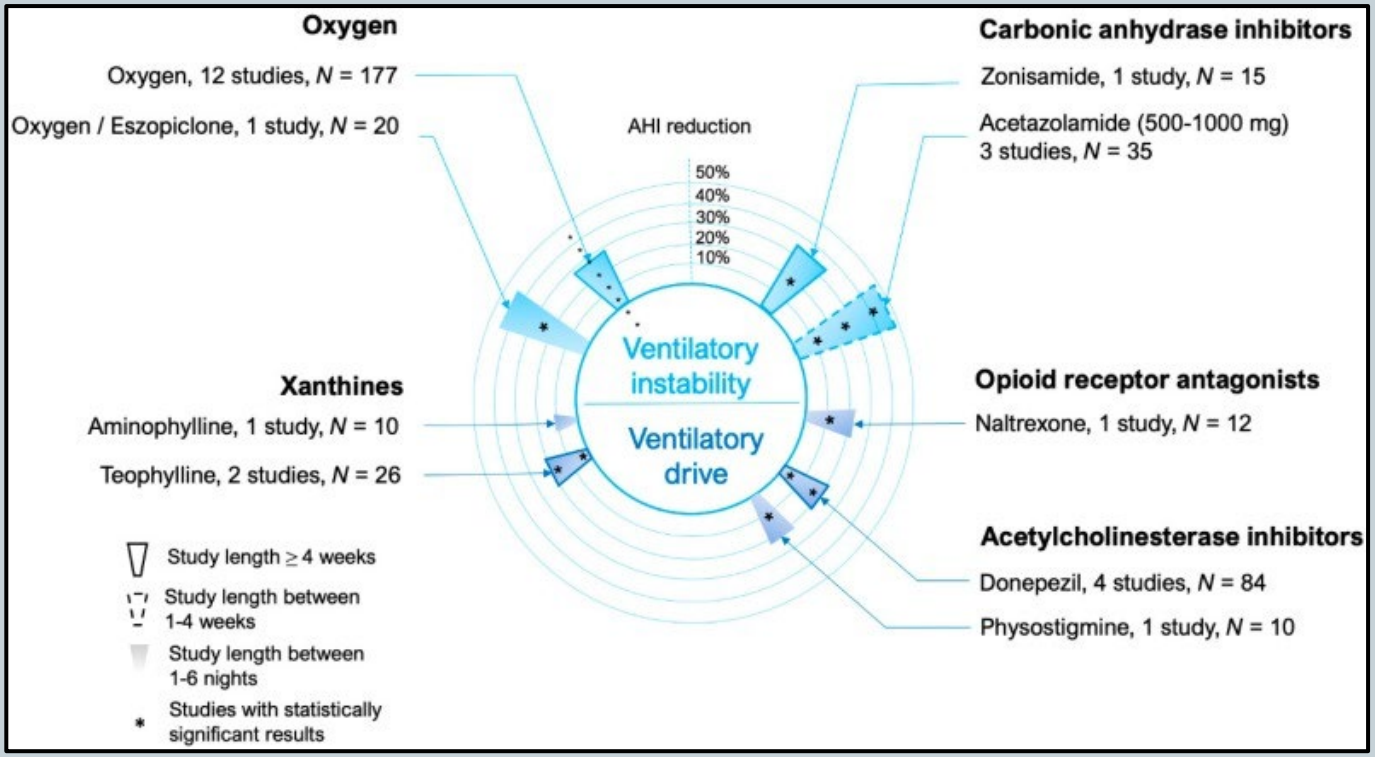

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Questions?

- Current Down syndrome research at UA
  - Clinical trial of ato-oxy for children with Down syndrome
    - Contact Lauren Melcher, Lmelcher@arizona.edu or Natalie Provencio-Dean, nataliep@arizona.edu
      - Participants will need to come to Tucson for 2 overnight study visits 6 months apart
  - Study of research participation decision-making in children and adults with Down syndrome
    - Contact Ken Bottrill, Kbottrill@arizona.edu
      - Study involves presentation and interview about example clinical trial as well as computer games
      - Single study visit for ~1.5 hours, may be done either in Tucson or Phoenix