UC San Diego Health

HOT TOPICS IN MEDICINE:
NOVEL THERAPIES FOR OBSTRUCTIVE SLEEP APNEA

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Disclosures

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Private consulting for Apnimed, ResMed, and Powell-Mansfield.

US Patents for drug therapy for sleep apnea pending.

Outline

- OSA 101
- Current Treatment Options
- Emerging Therapies

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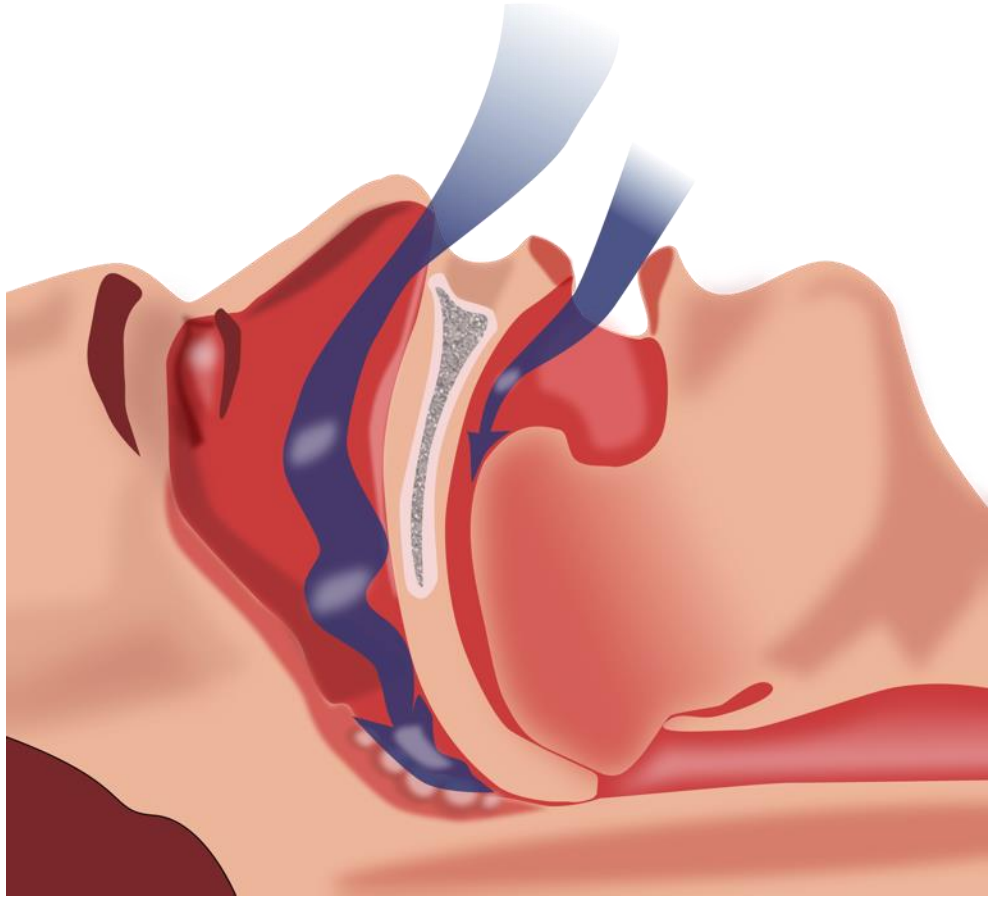
- **OSA 101**
- Current Treatment Options
- Emerging Therapies

What is OSA?

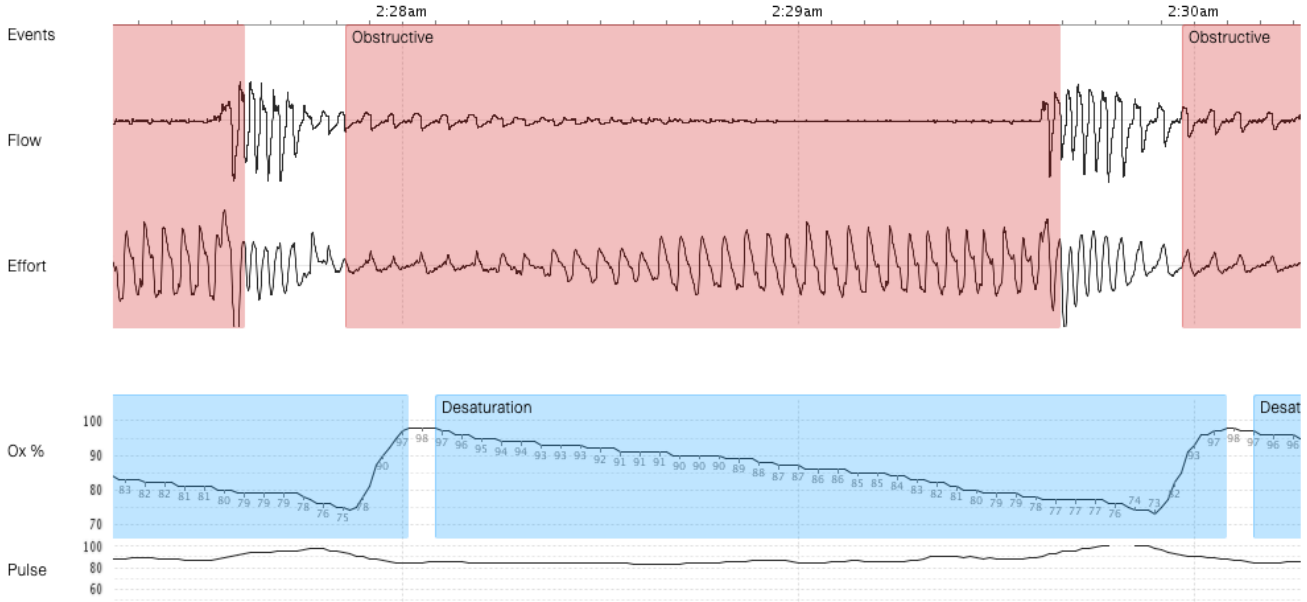


Credits to Habib M’henni / Wikimedia Commons

- Repetitive collapse of the upper airway during sleep causing
  - Arousals
  - Hypoxemia
  - Sympathetic surges

Jordan Lancet 2014

What is OSA?



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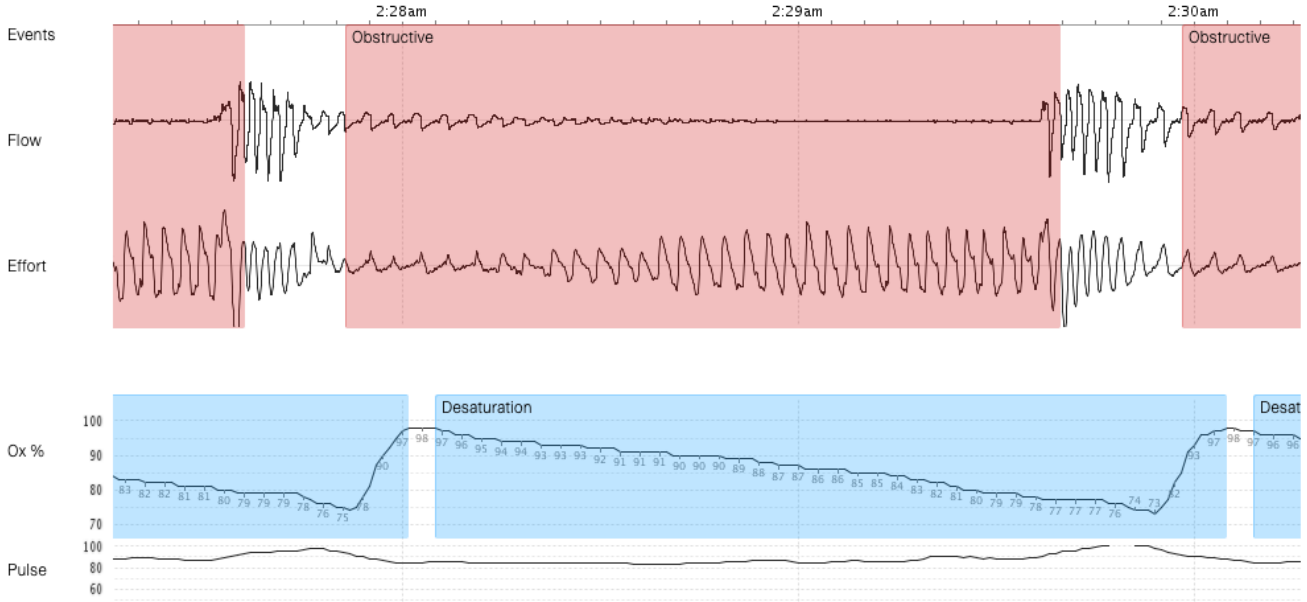


- Apnea-hypopnea index (AHI) ≥5/h
  - Mild 5-15/h
  - Moderate/Severe >15/h

Jordan Lancet 2014

Diagnosing OSA

Home Sleep Apnea Test

- Airflow Channel
- Effort Channel
- Oximetry
- Heart rate

Jordan Lancet 2014

Diagnosing OSA

Picture by Kuyohong (CC BY-SA 4.0)
https://en.wikipedia.org/wiki/Polysomnography

In-lab Polysomnography

- Respiratory Channels
- Oximetry
- Electroencephalogram (EEG)
- Electrocardiogram (ECG)
- Electromyogram (EMG)

Jordan Lancet 2014

Diagnosing OSA

Home Sleep Apnea Test

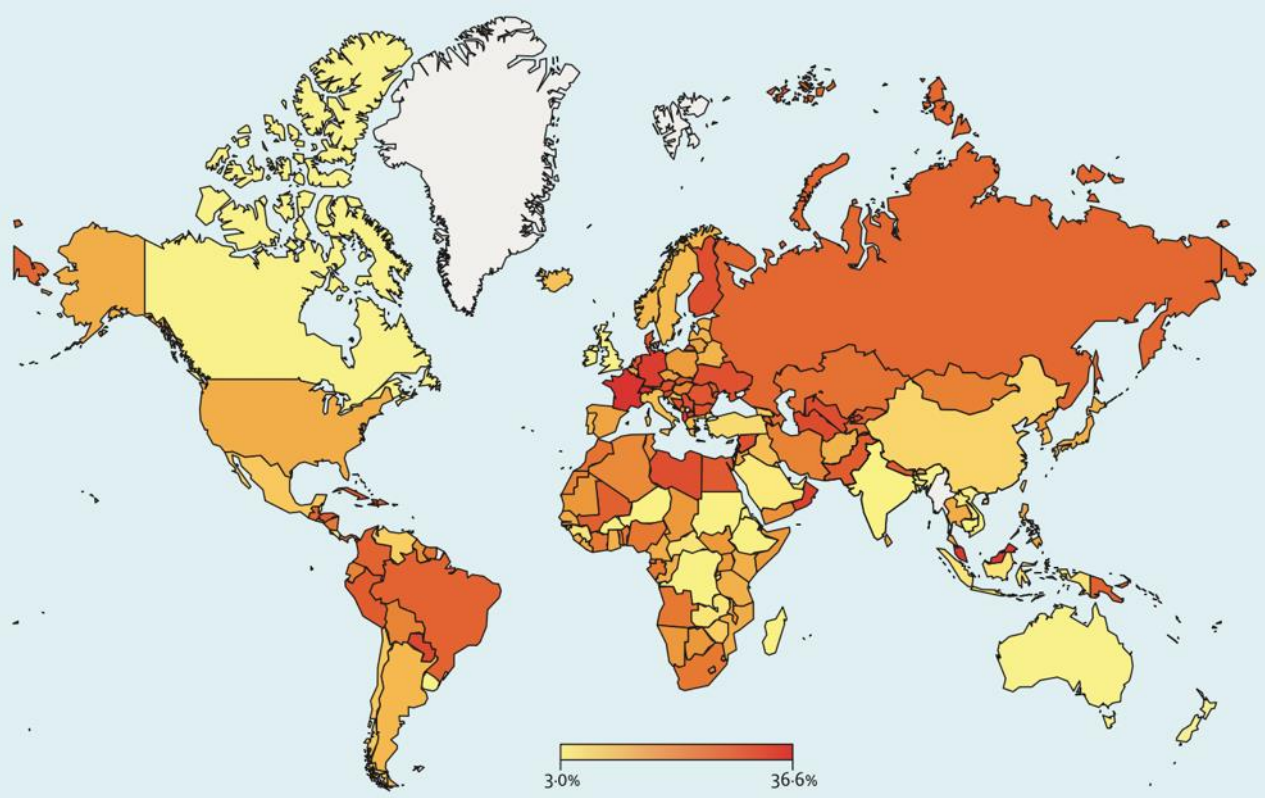
- Cheaper
- "Faster"
- More comfortable
- Tends to underestimate OSA severity
- Not validated for complex patients (e.g. heart failure, neuromuscular disease)

In-lab Polysomnography

- "Gold Standard"

Jordan Lancet 2014

Prevalence of moderate/severe OSA



- Globally >400 million
- USA: ~10%
- ~80% undiagnosed

Benjafield Lancet RM 2019, Ravesloot EAO 2012, Finkel Sleep Med 2009

Potential Consequences of OSA

- Excessive Sleepiness, Car/Work accidents, Reduced QoL
- Elevated blood pressure
- ?Cardiovascular disease (e.g., arrhythmias, heart attacks, stroke)
- ?Neurological disorders (e.g., dementia, headaches)
- ?Pulmonary disorders (e.g., asthma/COPD, pHTN)
- ?Mood disorders (e.g., depression, anxiety)
- ?Metabolic disorders (e.g., DM, NAFLD)
- ?Urologic dysfunction (e.g., nocturia, ED)
- ?Perioperative risk

Weaver Sleep 2007, Montesi JCSM 2012, McEvoy NEJM 2016, Opperer 2016, Jordan Lancet 2014

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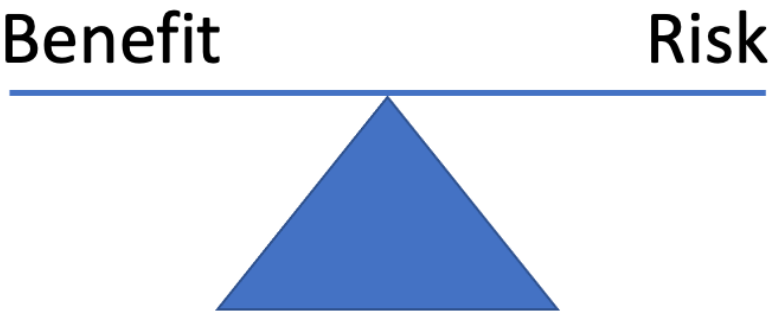
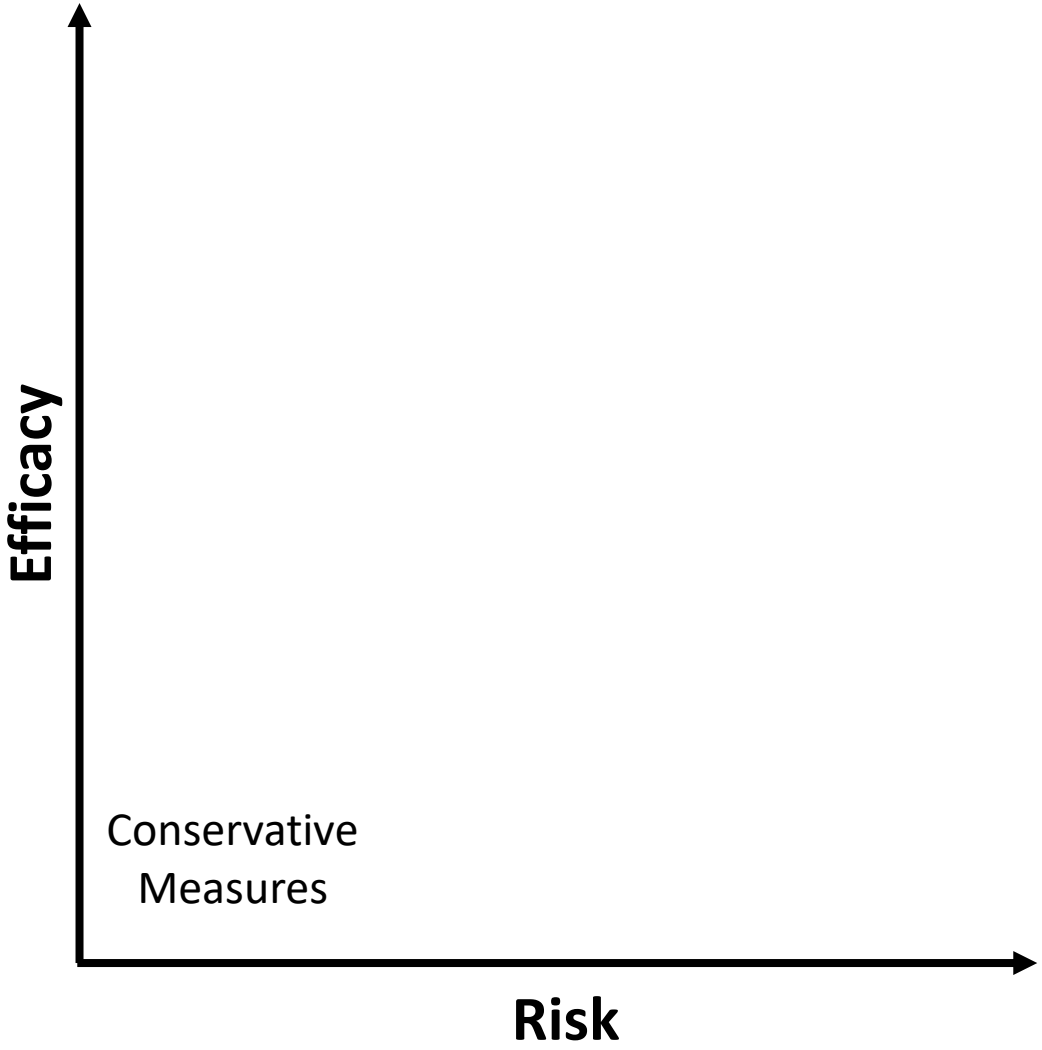
Strong evidence for treatment benefit



Weaver Sleep 2007, Montesi JCSM 2012, McEvoy NEJM 2016, Opperer 2016, Jordan Lancet 2014

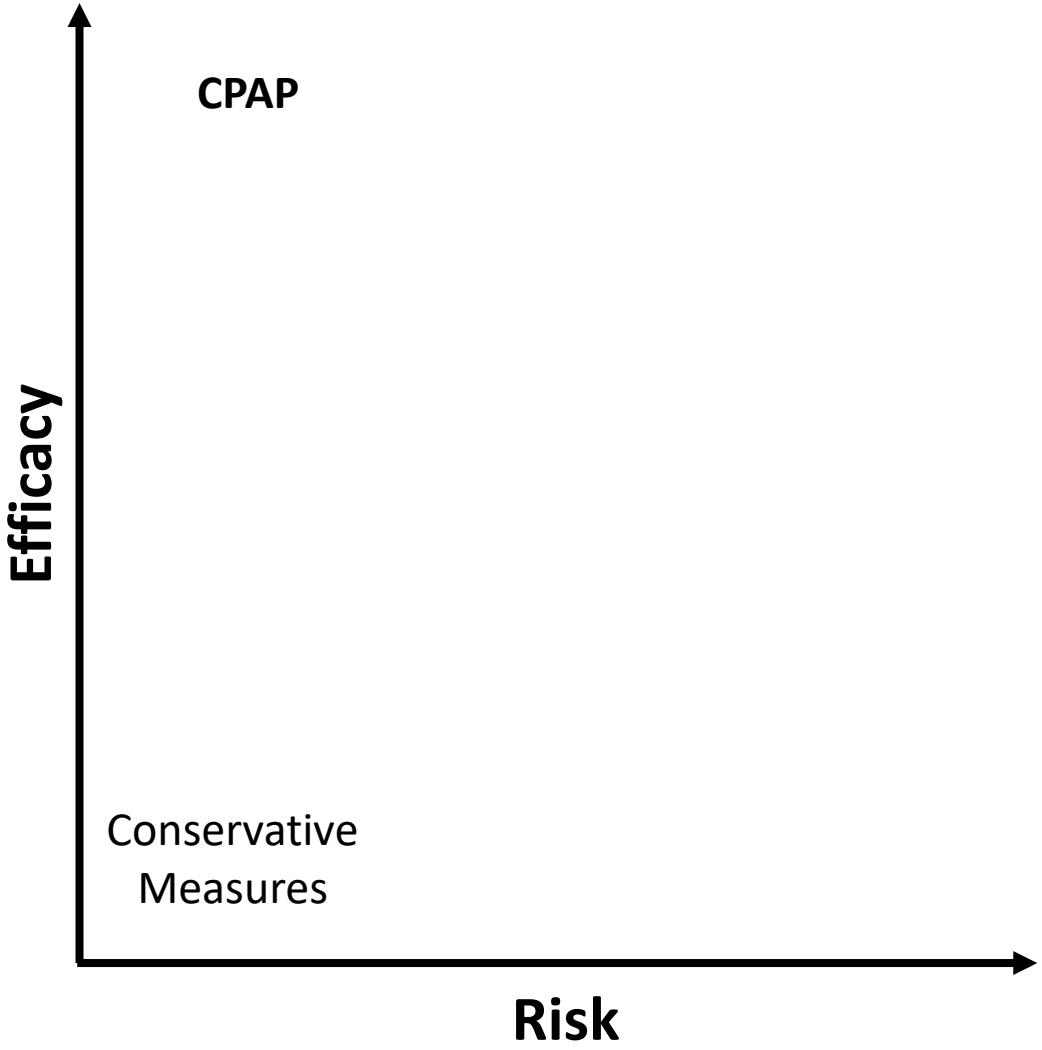
Outline

- OSA 101
- **Current Treatment Options**
- Emerging Therapies



Asymptomatic, healthy, mild OSA

- Conservative measures
  - Weight optimization (diet & exercise)
  - Treat nasal congestion and GERD
  - Avoiding sedatives (e.g., benzodiazepines) and alcohol
  - Avoiding smoking
  - Avoid supine sleep
  - Get sufficient sleep
  - Avoid drowsy driving
- Antihypertensive prn Pepin AJRCCM 2010



Continuous Positive Airway Pressure

- Improves OSA by >90% (consistently)
- Low risk
- Live monitoring
- Variable Adherence

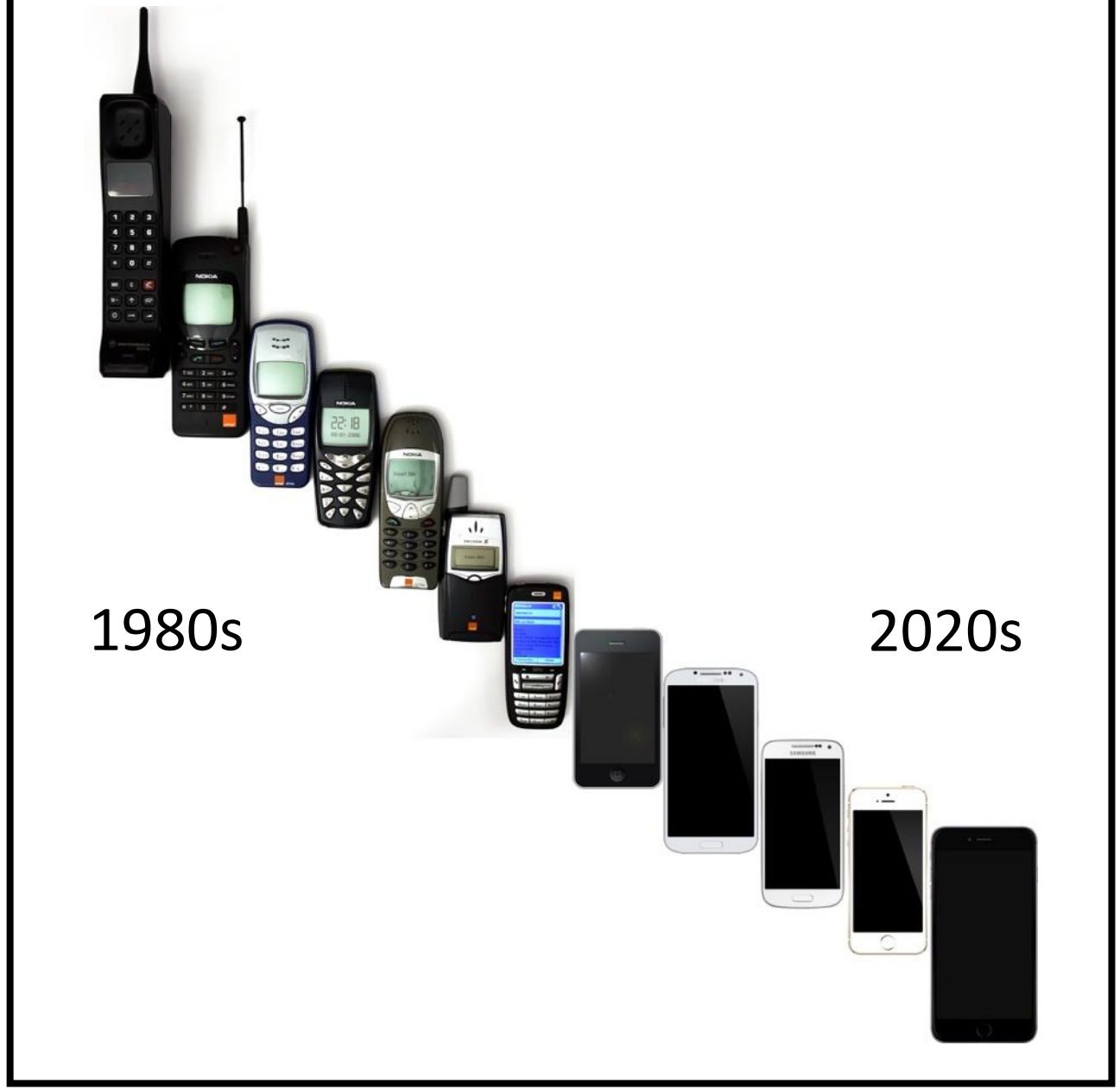
Jordan Lancet 2014, Malhotra Chest 2018, Sawyer Sleep Med 2011, Rotenberg J Oto 2016

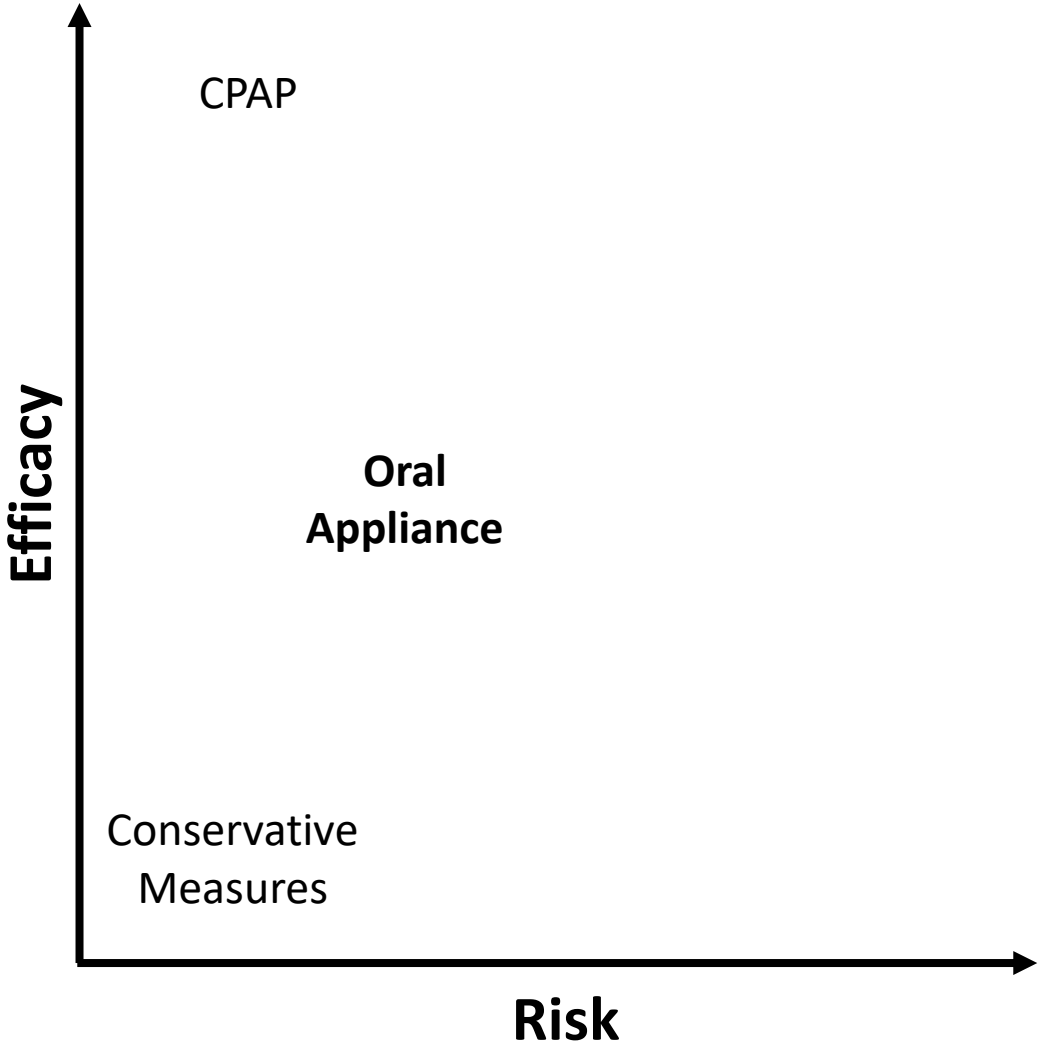
CPAP

Efficacy

Conservative Measures

Risk

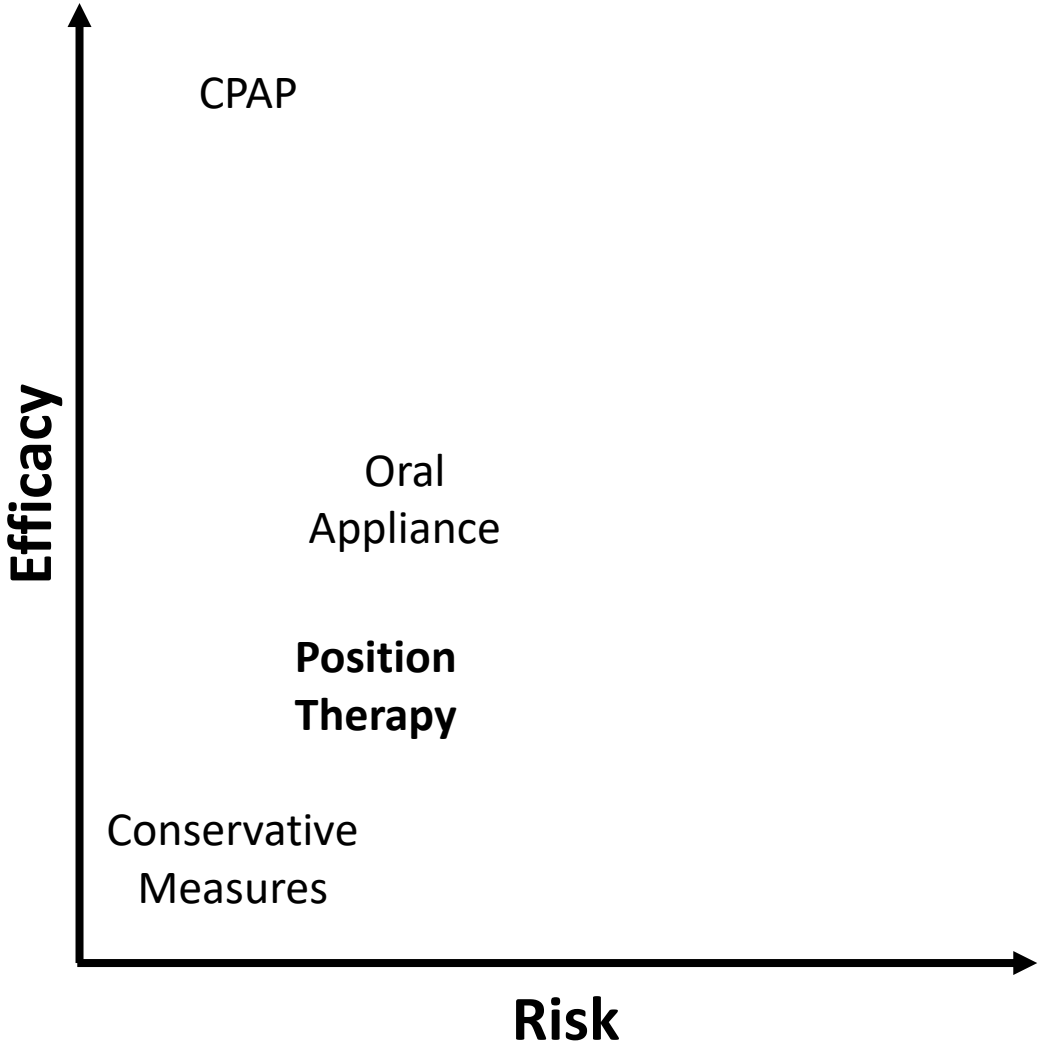




Oral Appliance Therapy (OAT)

- Improves OSA by ~50% (variable)
- Adherence/tolerance good
- Low-medium risk
- Sleep dentist (~6 months)

Ramar JCSM 2015



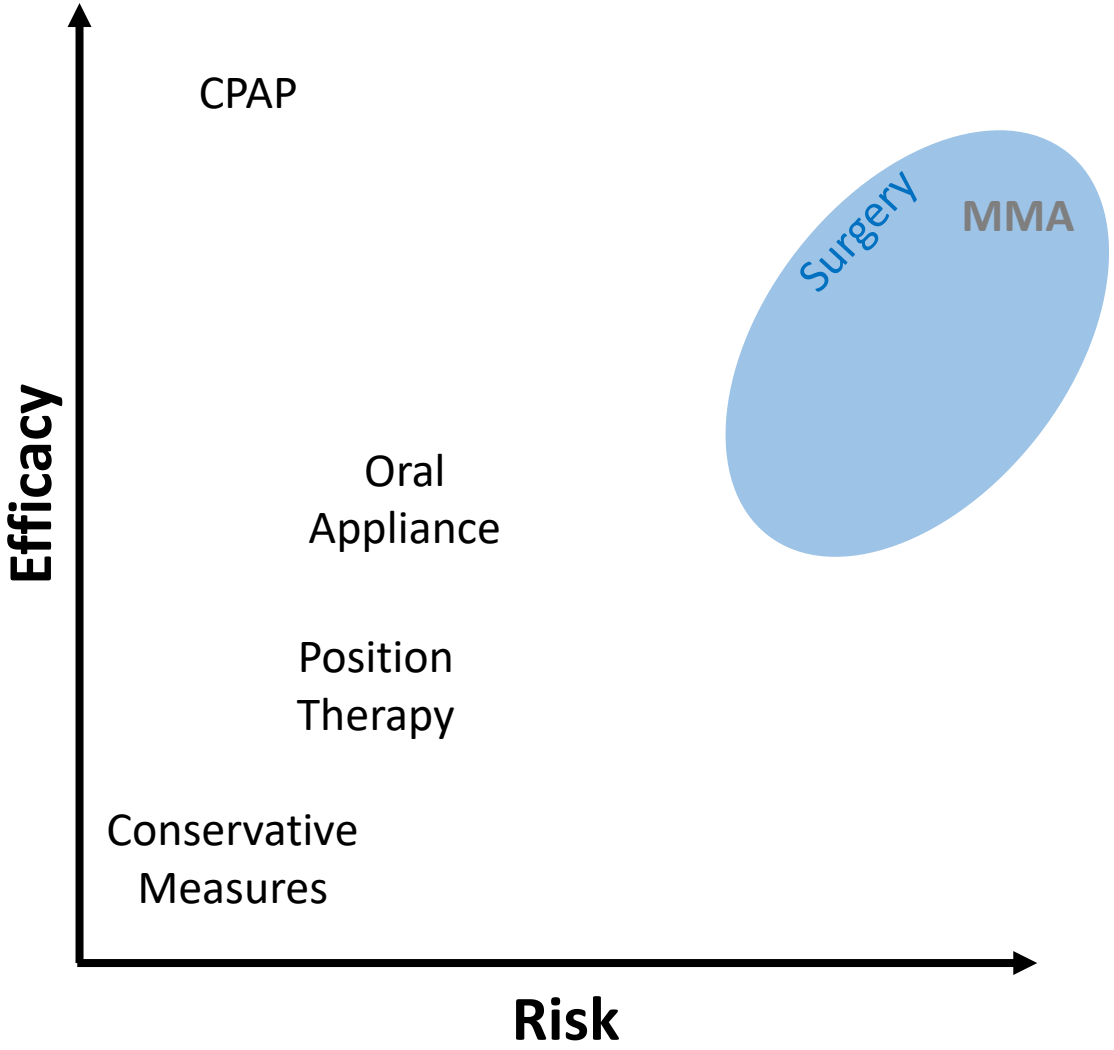
Position therapy (avoid supine sleep)

- Effect depends on positionality
- Risk low but may be costly

$0-50 Cheapest

$50-200 ?more reliable

$300-500 includes Monitoring

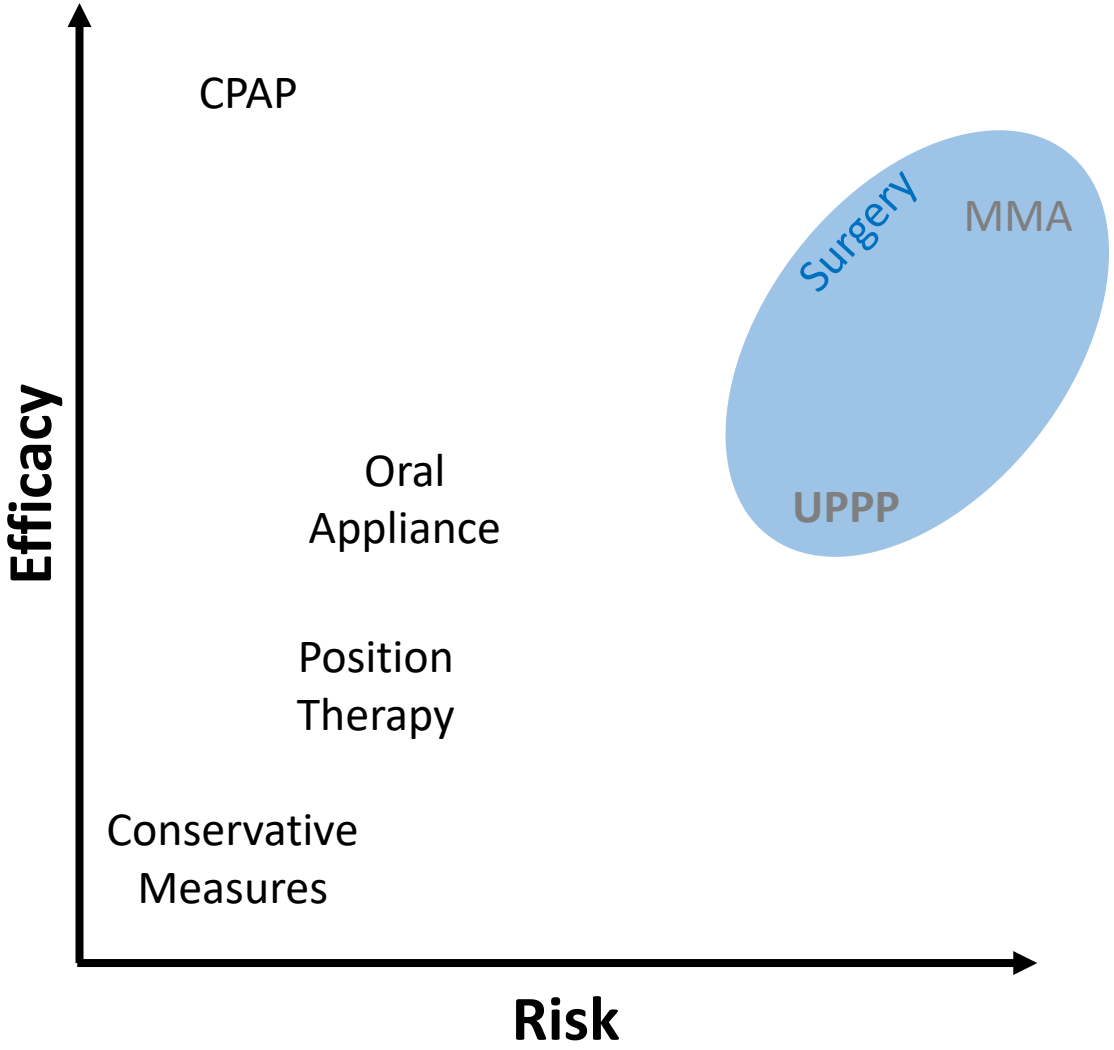


Maxillo**m**andibular **A**dvancement (MMA)

- Advance entire lower facial skeleton
- OSA improves ? 70-90%
  - adherence independent, no foreign body
- Surgical risks (major), paresthesia, cosmetic changes

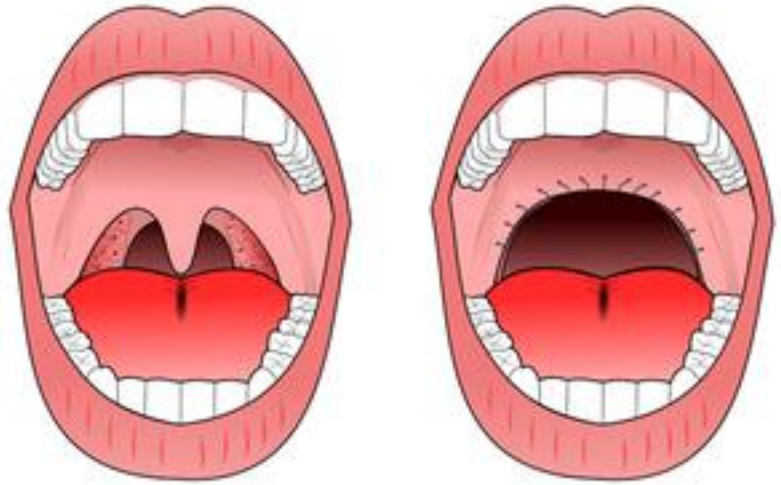
By Drcamachoent (CC BY-SA 4.0)
https://en.wikipedia.org/wiki/Maxillomandibular_advancement

Zaghi JAMA Oto 2016

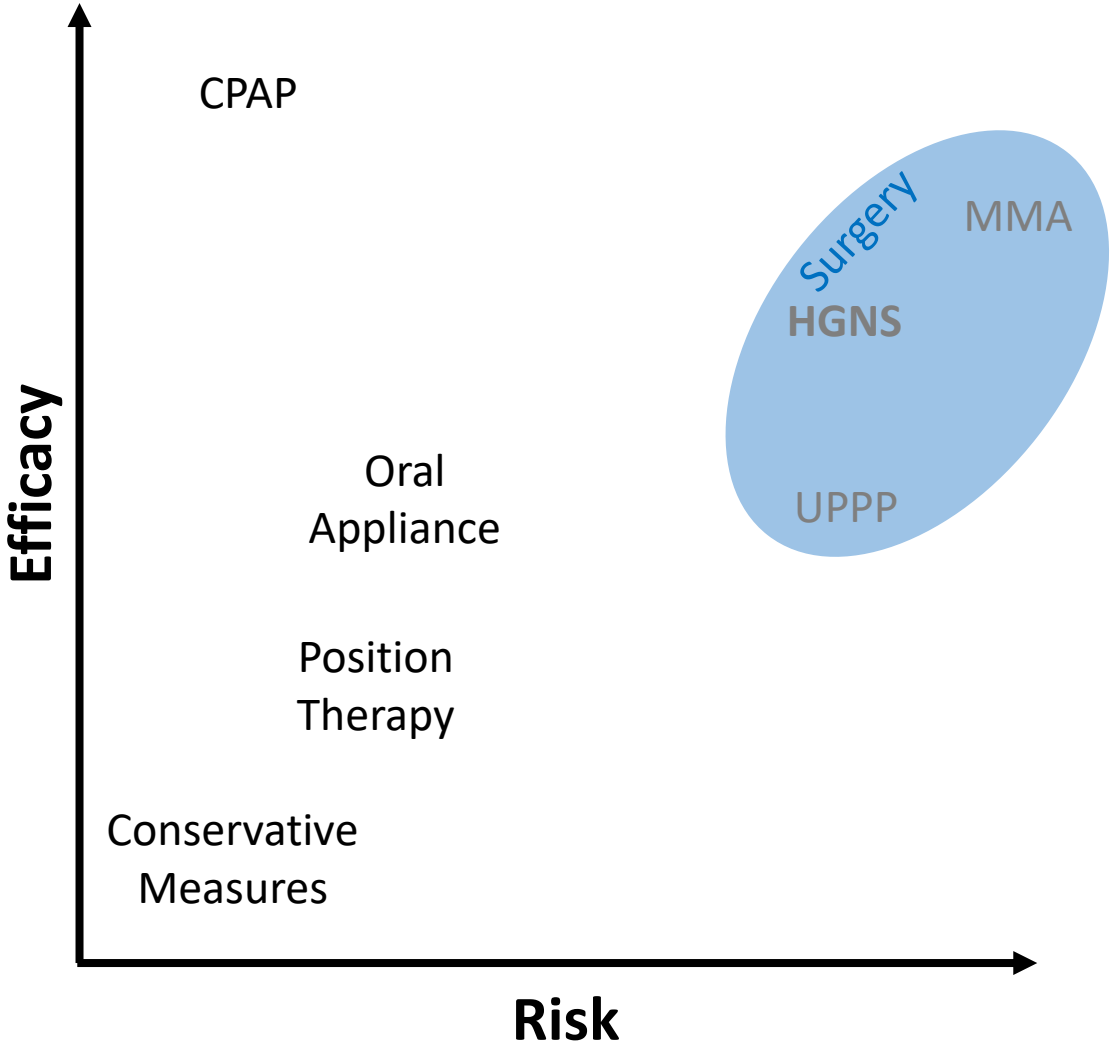


Uvulopalatopharyngeoplasty (UPPP)

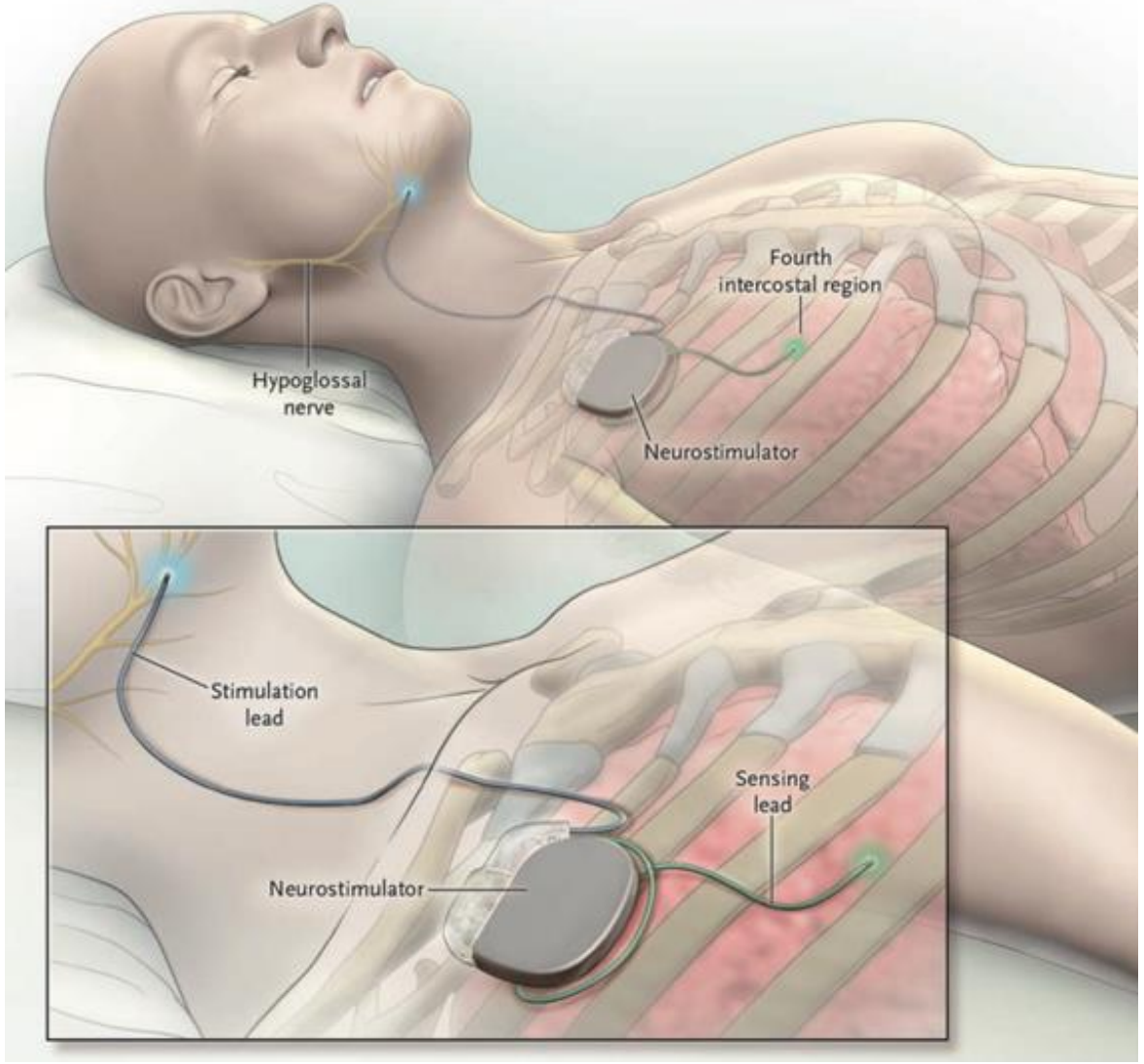
- Removal of posterior soft palate, uvula +/- tonsils
- Improves OSA by ~50% (variable)
  - adherence independent, no foreign body
- Surgical risks



Stuck Sleep Med 2017, Randerath ERJ 2011, MacKay JAMA 2020



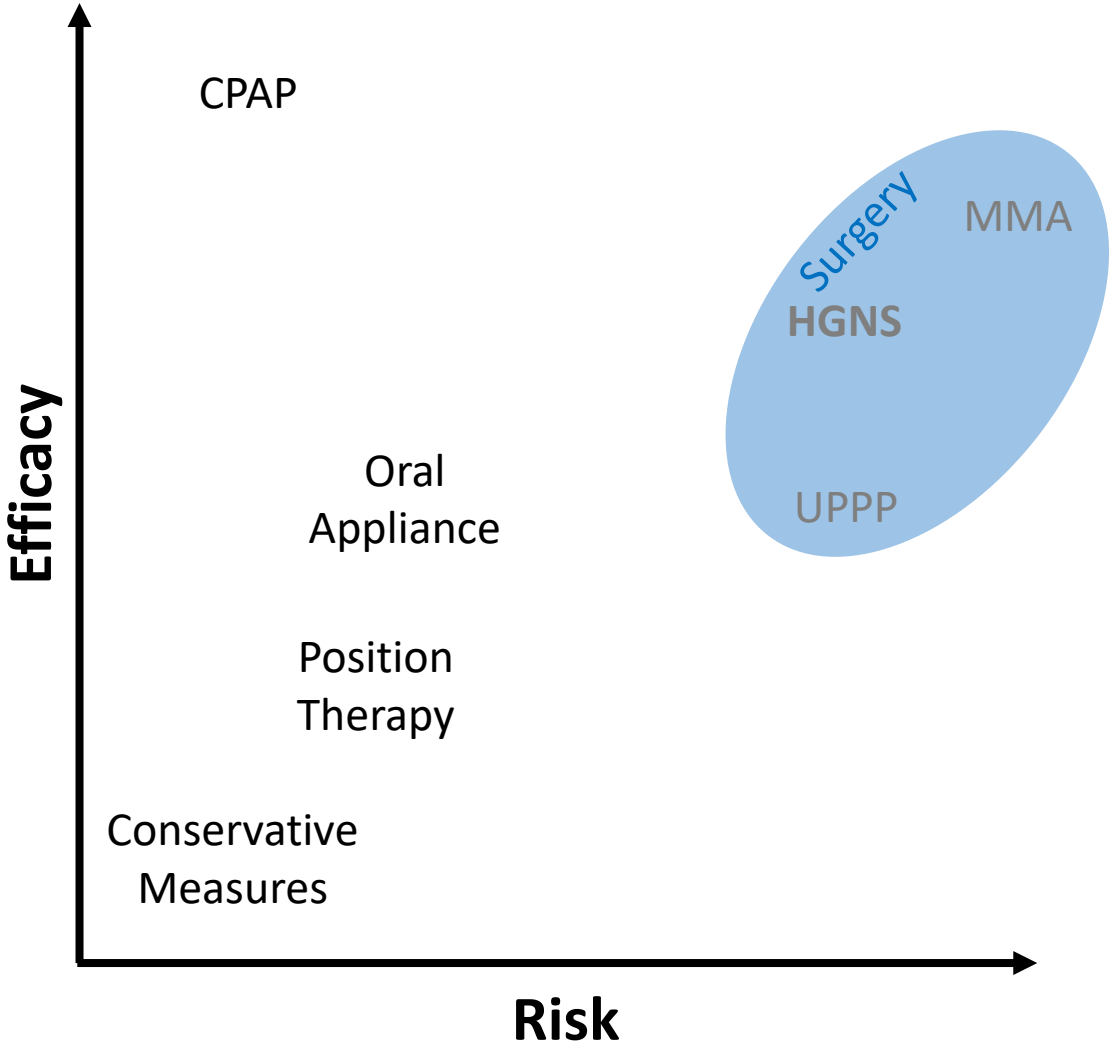
Hypoglossal Nerve Stimulation (HGNS)



Strollo NEJM 2014

Inspire HGNS – How It Works

Slide provided by Inspire Medical



Hypoglossal Nerve Stimulation (HGNS)

- For select patients with moderate-severe OSA, BMI<40 who failed CPAP

Potential Benefits:

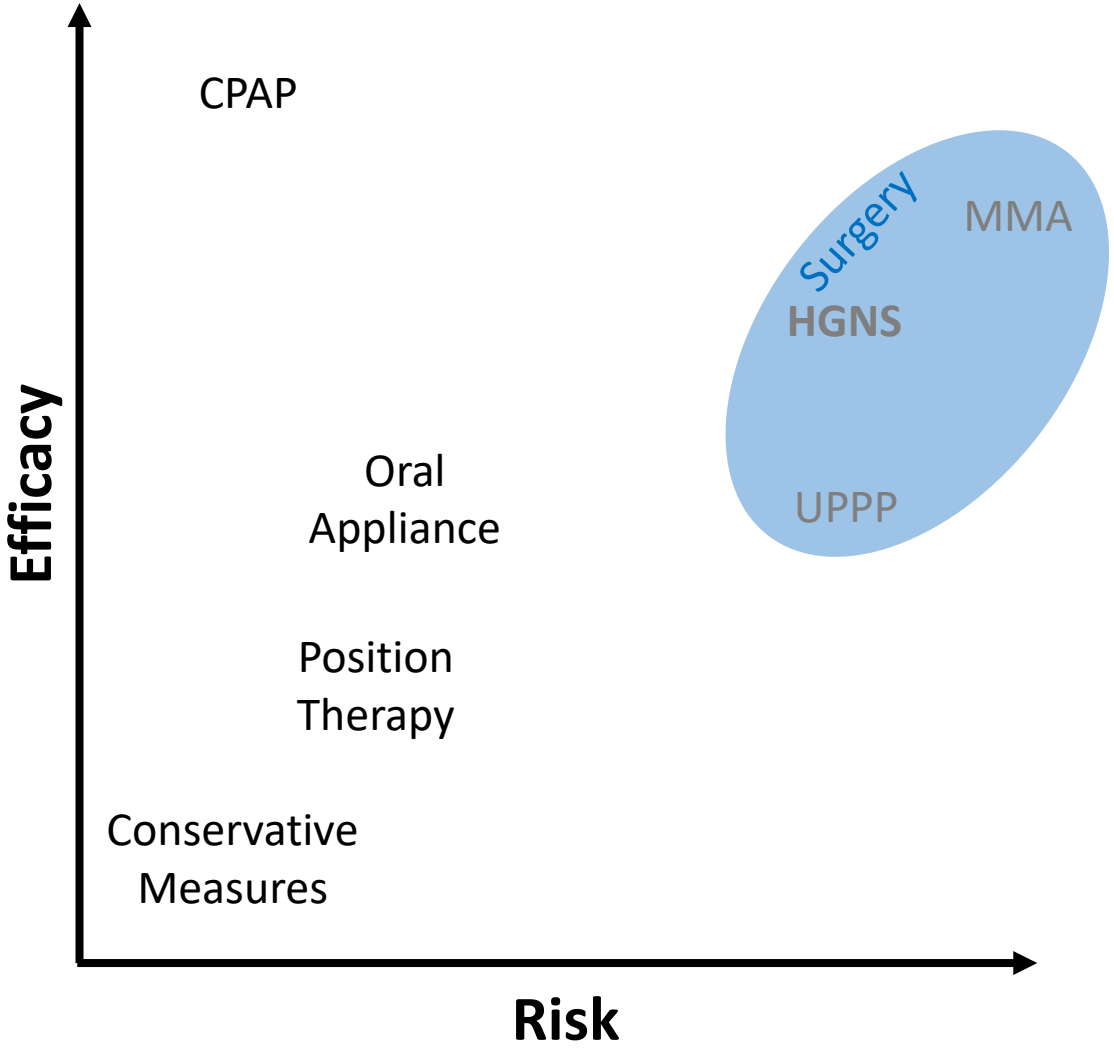
- 60-70% improvement of OSA (variable)
- Good adherence (5.7 [4-7] h/night)

Potential Risks/Downsides:

- Surgical risks; Repeat surgery ~5% over 5y
- Neuropraxia (~20%), discomfort
- Adherence-dependent (insomnia!)
- Cost, MRI, Logistics

Dr Schalch

Strollo NEJM 2014, Woodson Otolaryn 2018; Heiser ERJ 2019, Thaler Laryn 2019

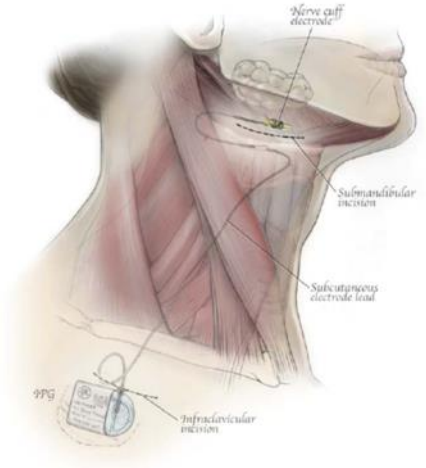


Hypoglossal Nerve Stimulation (HGNS)

- 2 new devices in the pipeline

ImThera/LivaNova (Aura6000)

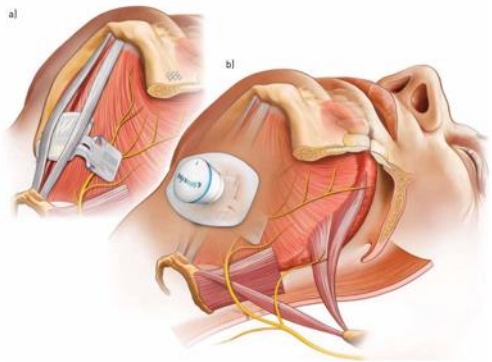
- Lateral branch, no sensing lead
- No DISE



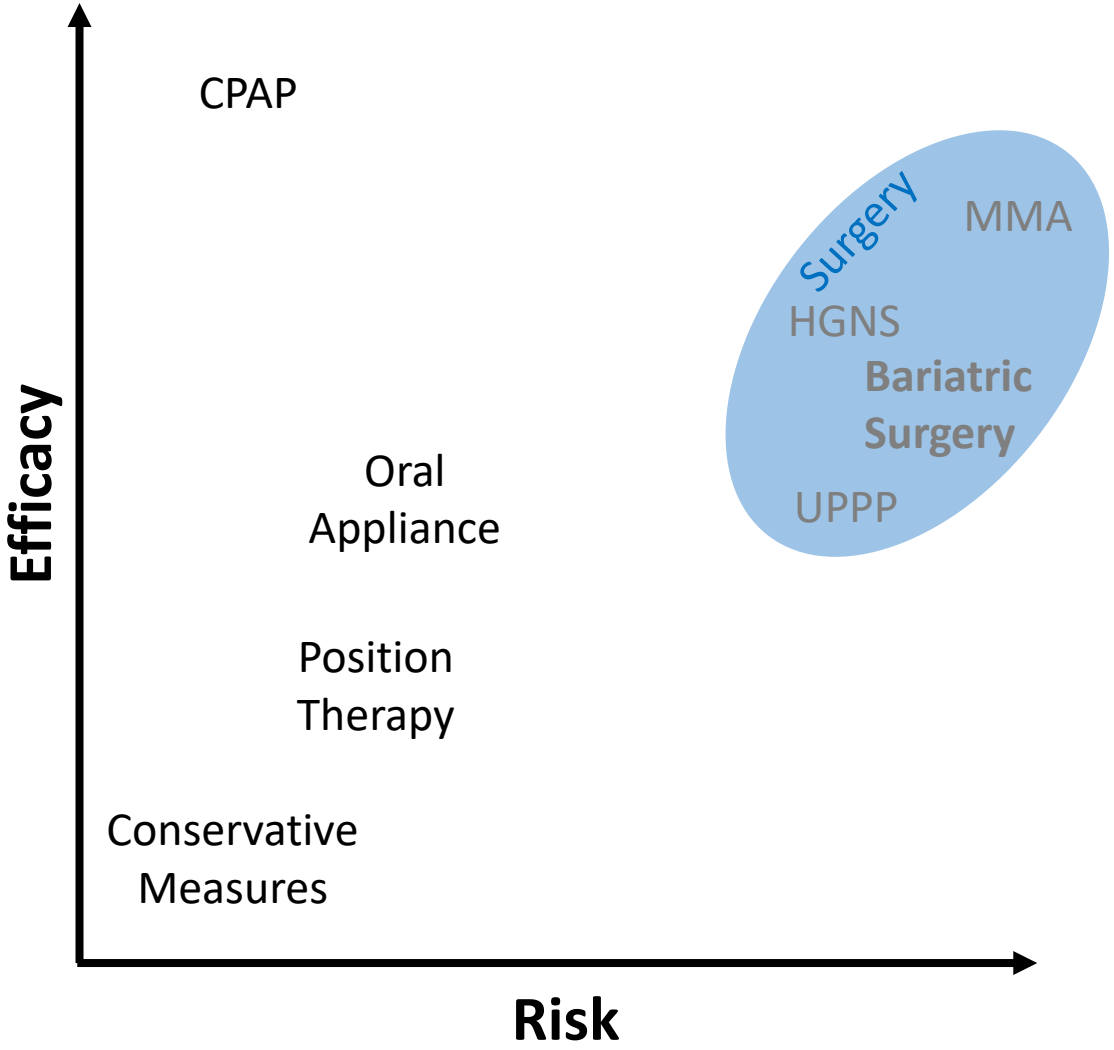
Eastwood ERJ 2020, Lewis LIO 2019, NCT03868618, NCT05592002

Nyxoah (Genio System)

- Bilateral medial branch
- External battery
- No DISE

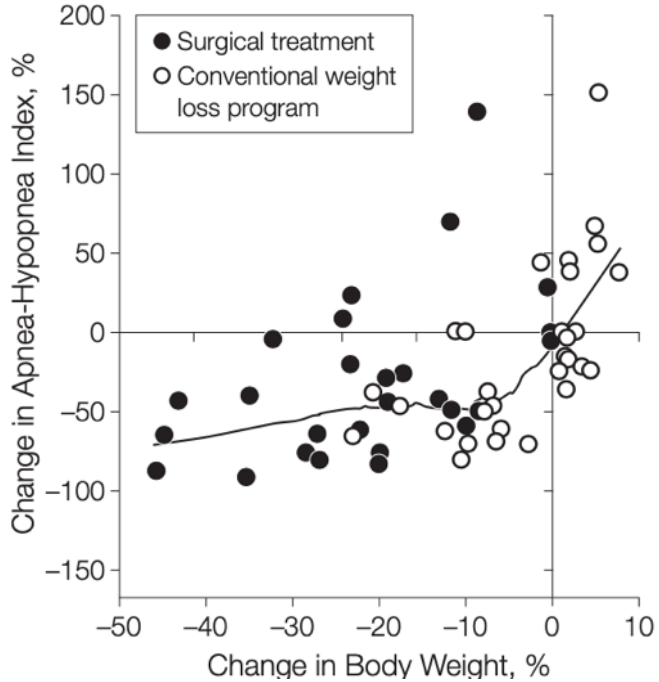


Mwenge ERJ 2013, Friedman Laryn 2016, NCT02263859

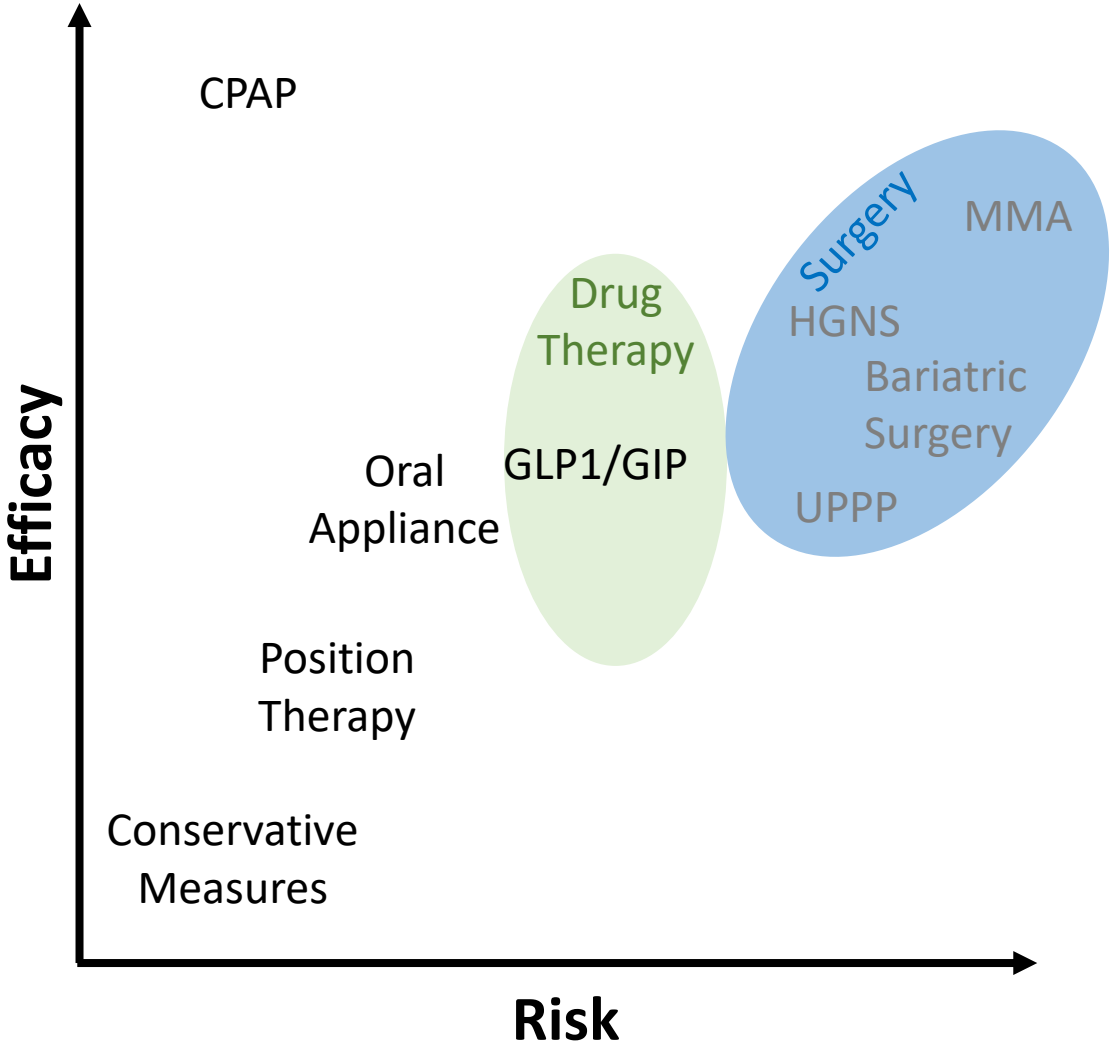


Bariatric Surgery

- ~50% of OSA attributable to overweight
- 20-30% ↓BW -> 50-60% ↓OSA (variable)



Yao NEJM Evid 2025, Dixon JAMA 2012, Peppard JAMA 2000

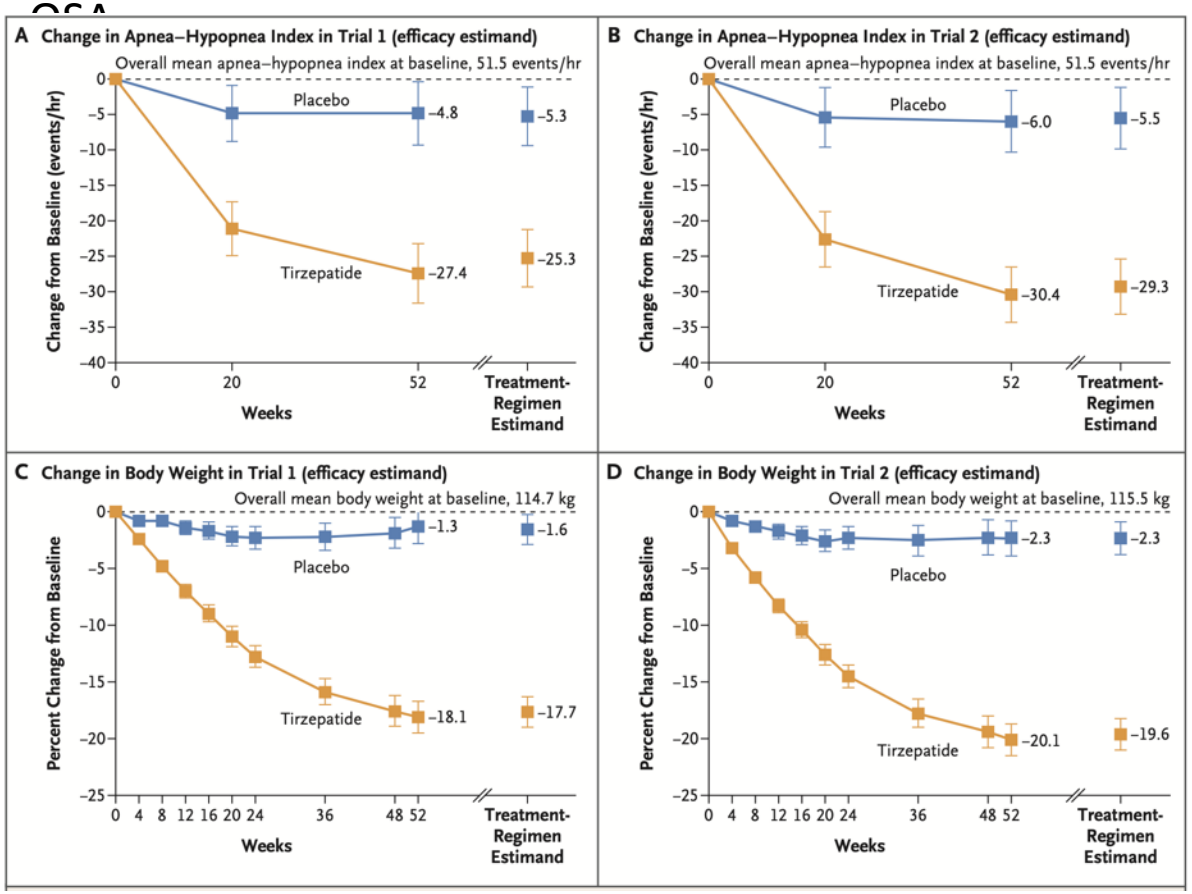


Tirzepatide

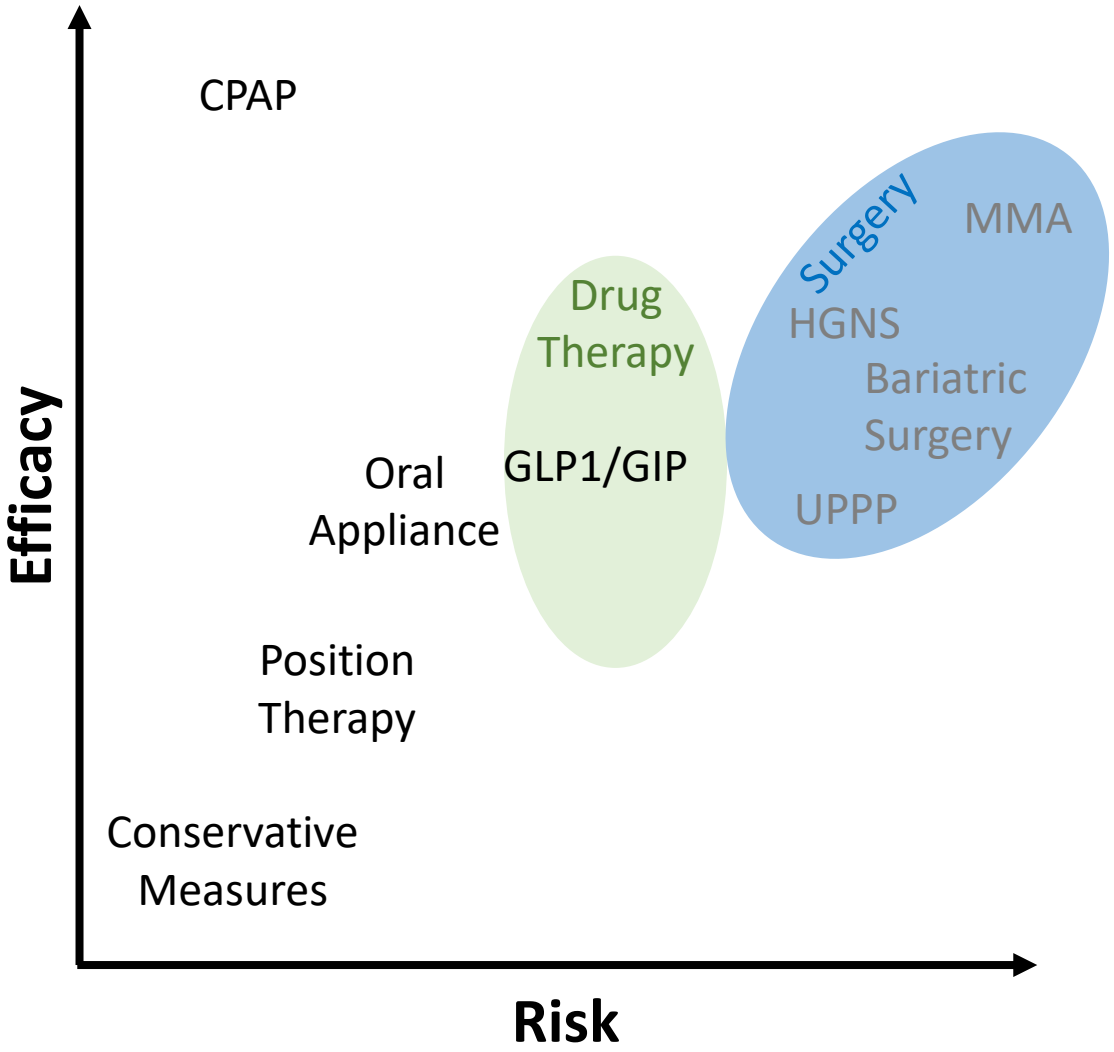
Atul Malhotra

- GLP1/GIP-RA -> ↑Satiety
- ~20% ↓BW -> ~55% ↓OSA

SURMOUNT-OSA



Jastreboff & Kushner Annu Rev Med 2023, Malhotra NEJM 2024, Schmickl NEJM Evid 2025

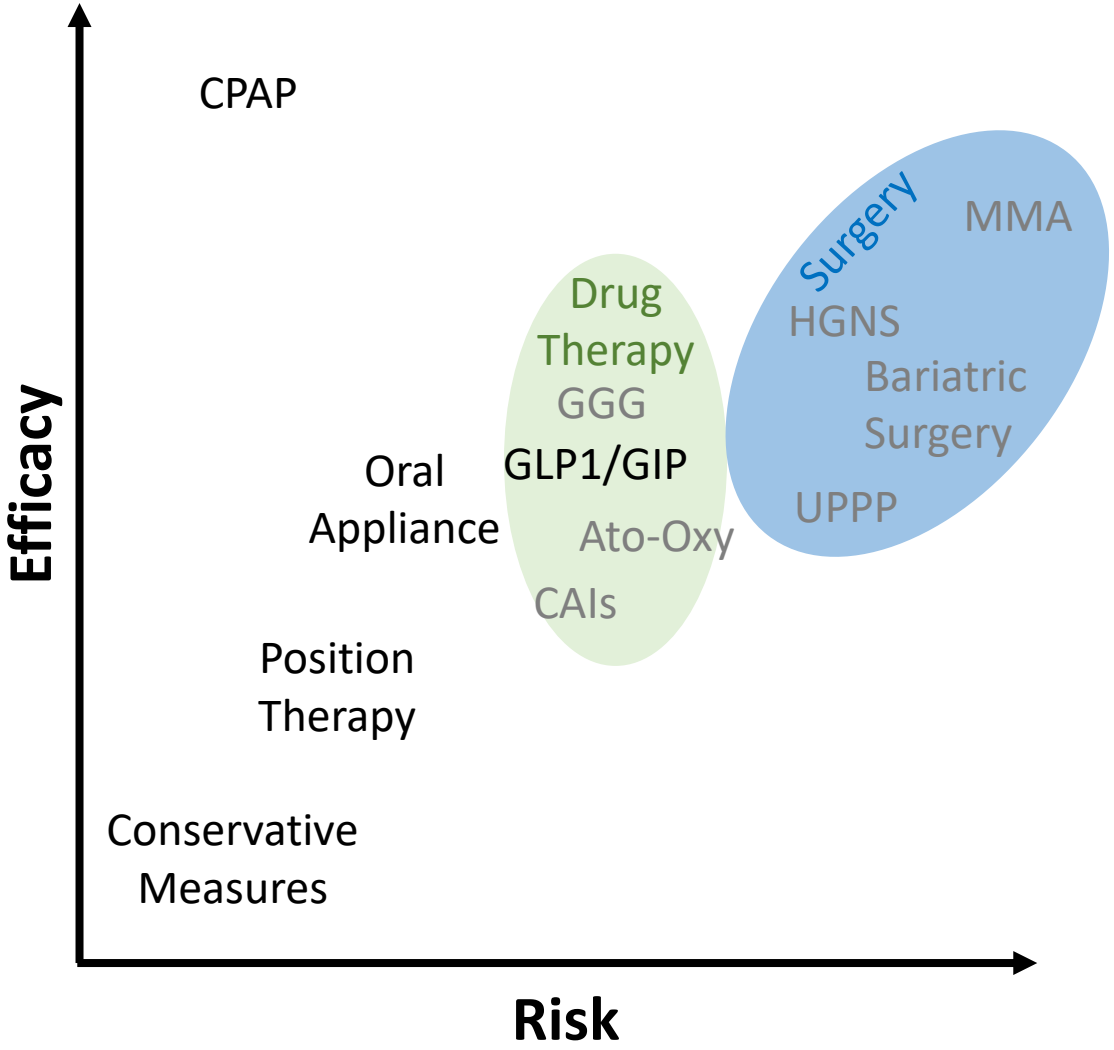


Tirzepatide

Atul Malhotra

- GLP1/GIP-RA -> ↑Satiety
- ~20% ↓BW -> ~55% ↓OSA$_{SURMOUNT-OSA}$
- "Statin" for sleep providers?

Jastreboff & Kushner Annu Rev Med 2023, Malhotra NEJM 2024, Schmickl NEJM Evid 2025



Other Drug Therapies in The Pipeline

- Next-generation weight loss drugs (e.g., GGG-agonist) -> greater weight loss, easier administration
- Drugs targeting non-anatomical factors underlying OSA
  - Atomoxetine-Oxybutynin (AD109)
  - Carbonic Anhydrase Inhibitors (CAIs)

Jastreboff & Kushner Annu Rev Med 2023, Malhotra NEJM 2024

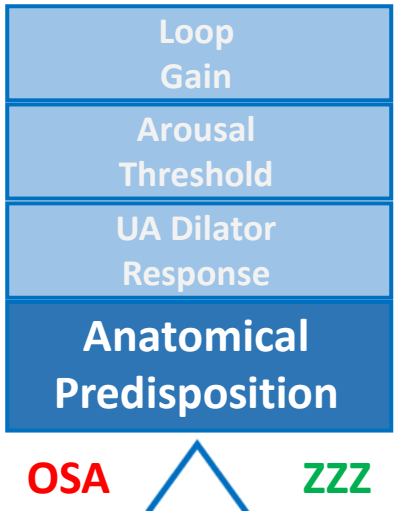
Outline

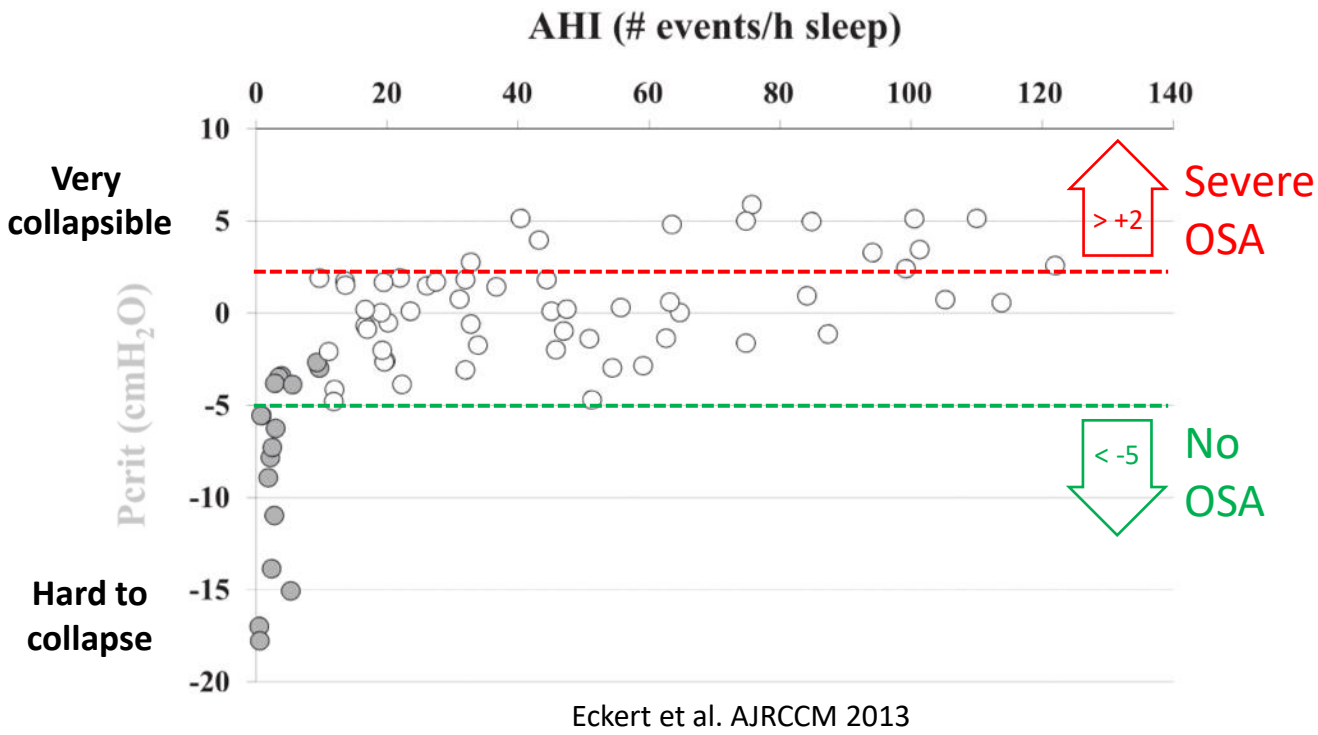
- OSA 101
- Current Treatment Options
- **Emerging Therapies**

Endotype

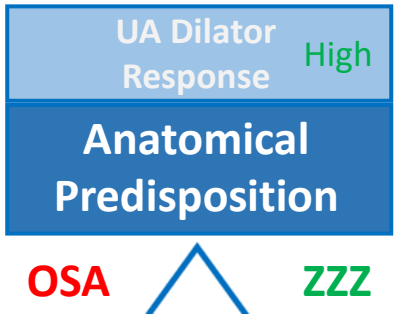
- A subgroup of patients who share a pathophysiological mechanism.

Anderson Lancet 2008, Tolbert AJRCCM 2025





Eckert et al. AJRCCM 2013


UA Dilator Response
High
Anatomical Predisposition
OSA
ZZZ


Z Z Z


ArTH
Drive


VT L
0.50
0.25
0.00
0.3635
0.2328
Flow L/s
0.5
0.0
-0.5
0.100
0.000
pMask cmH2O
5
0
5.28
0.62

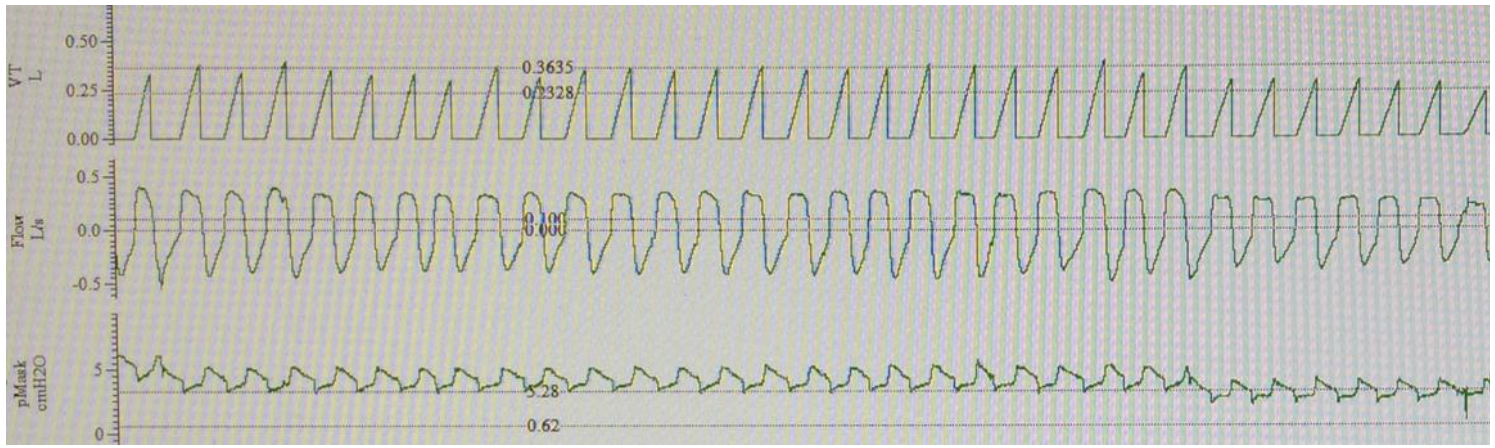
Low UA Dilator Response

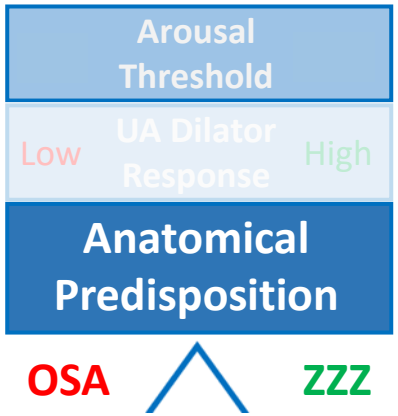
Anatomical Predisposition

OSA **ZZZ**

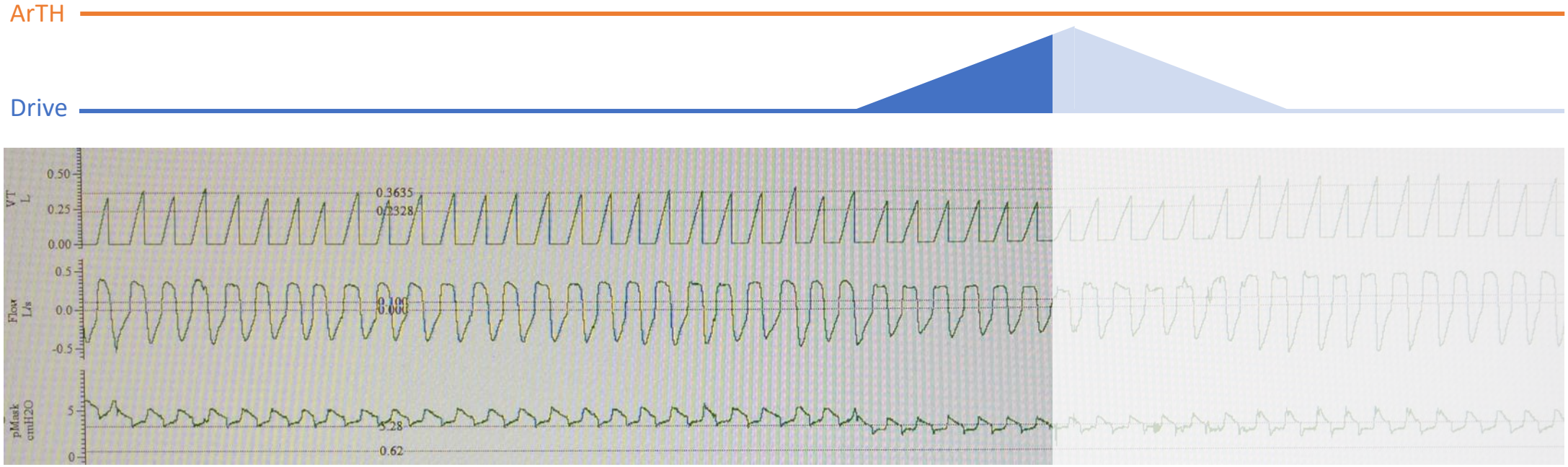
ArTH

Drive




Arousal Threshold
Low
UA Dilator Response
High
Anatomical Predisposition
OSA
ZZZ


Z Z Z


ArTH
Drive
VT L
0.50
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0.3635
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Flow L/s
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pMask cmH2O
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5.28
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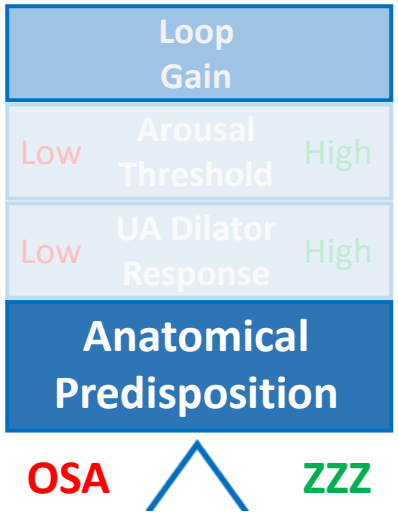
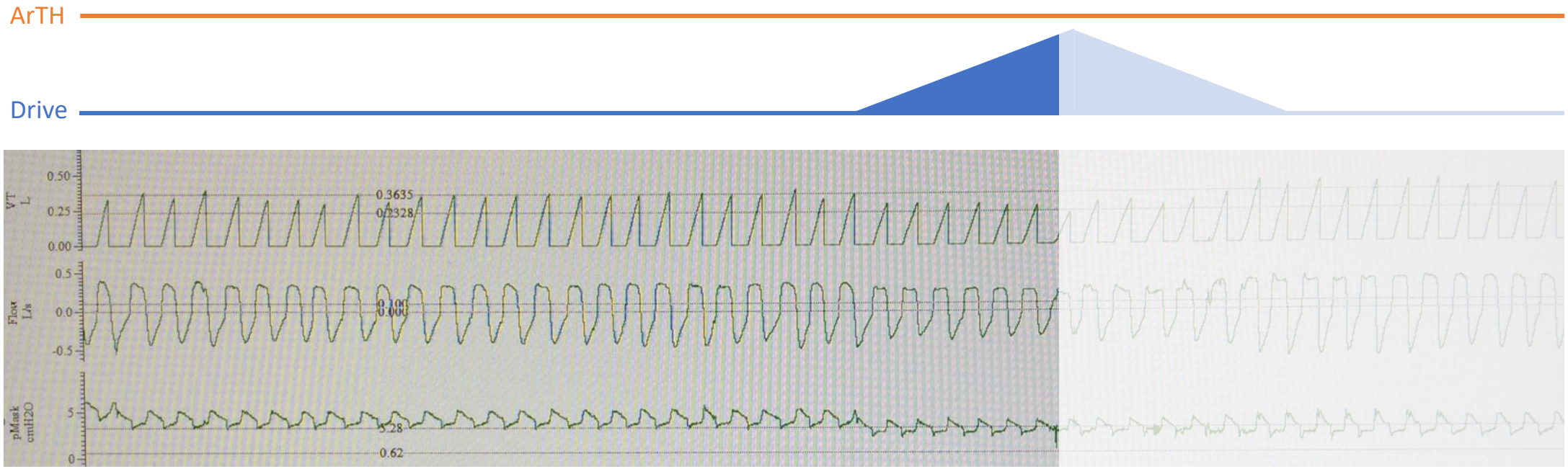
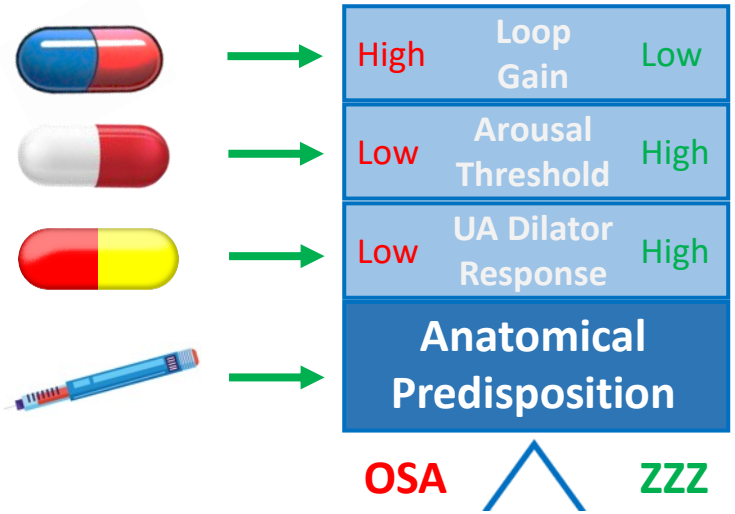


$$\frac{\Delta \text{Drive}}{\Delta \text{Ventilation}}$$

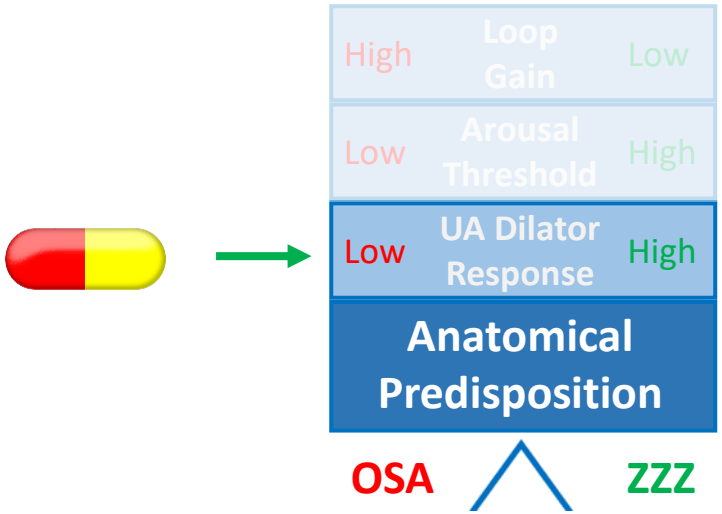




Endotype-Targeted Drug Therapy

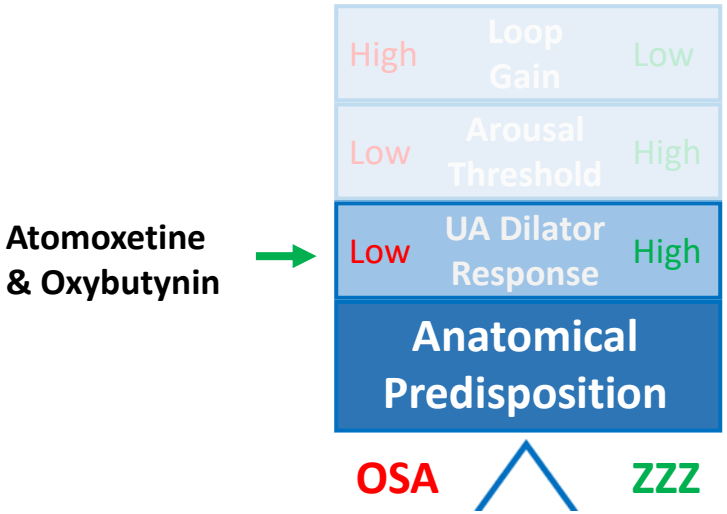
Endotypical traits can be estimated from routine PSG/HST data.

Sands AJRCCM 2018, Terrill ERJ 2015, Orr AJRCCM 2018

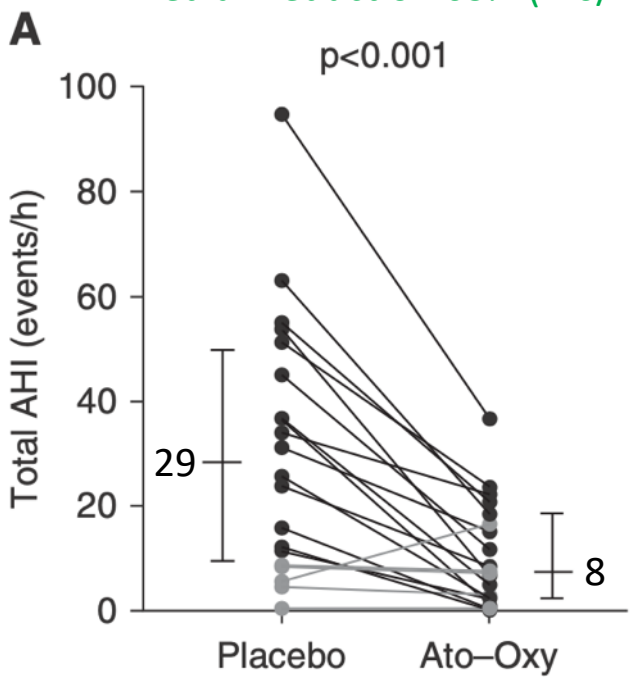


?Low UA Dilator Tone in Sleep due to:

- drop in noradrenergic tone in NREM
- cholinergic (muscarinic) inhibition in REM



median reduction 63% (-16/h)

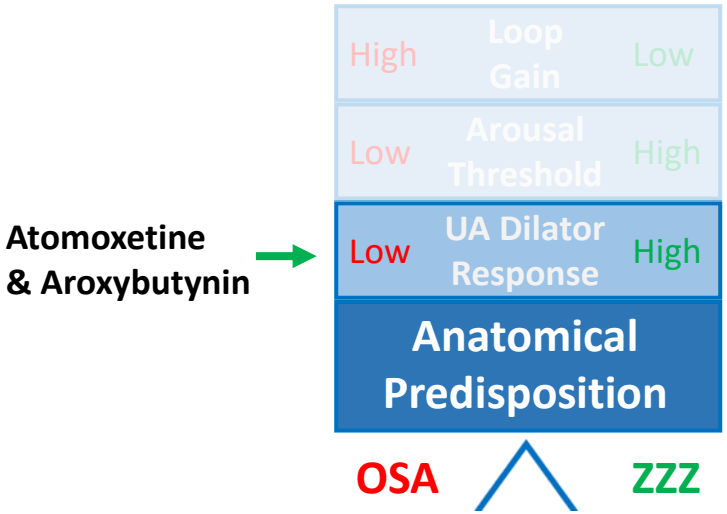


?Low UA Dilator Tone in Sleep due to:

- drop in noradrenergic tone in NREM
- cholinergic (muscarinic) inhibition in REM

- Improvement in O2 and sleep architecture
- Increase in heart rate and ?BP

Taranto-Montemurro L, et al. AJRCCM 2019



Phase IIb (MARIPOSA), N=211

Schweitzer AJRCCM 2023

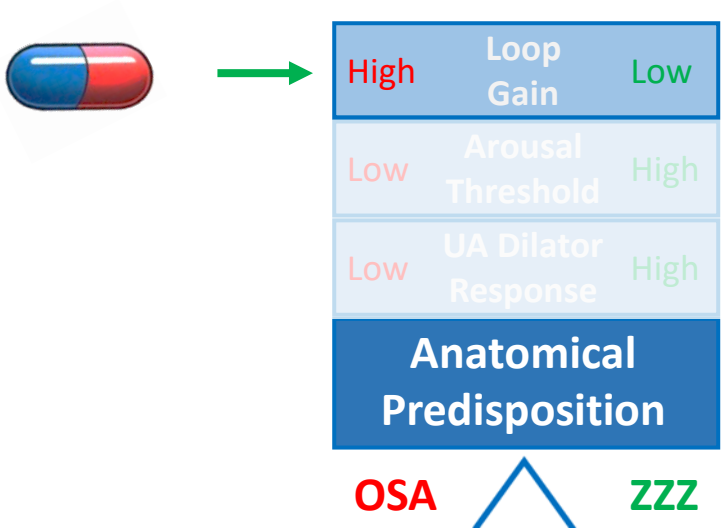
- Ato-**Ar**Oxy 75/2.5mg vs placebo x1month
- AHI: 47% reduction
- Fatigue improved, no change in other PROs
- AEs:
  - 25% Dry mouth, insomnia
  - 7% urinary hesitancy
  - HR +5bpm, DBP +4mmHg

Apnimed

COI: consulting

Phase III: Ato-ArOxy 75/2.5mg vs placebo

- SynAIRgy (NCT05813275): x6months, N=740
- LunAIRo (NCT05811247): x12month, N=660



Carbonic Anhydrase Inhibitors

↓

Bicarbonate Diuresis

↓

Metabolic Acidosis

↓

Increase in Ventilation

↓

Reduces efficiency of CO_2 excretion

↓

Dampens fluctuation in CO_2 (i.e., drive)

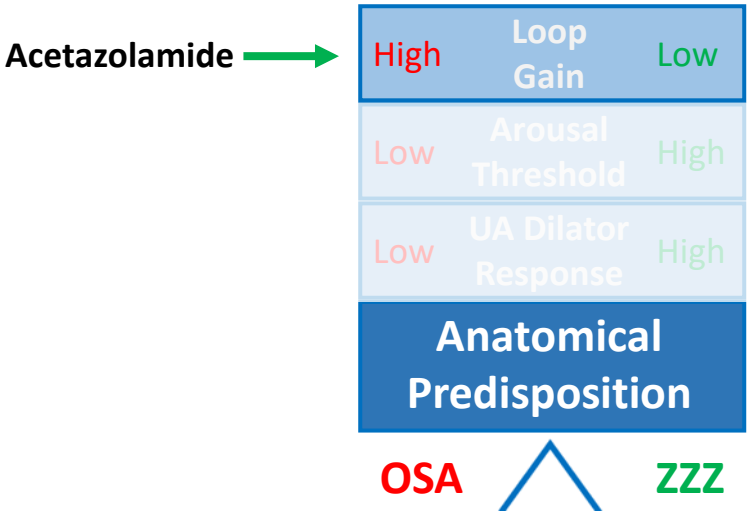
↓

Lower loop gain

Reduces UA collapsibility

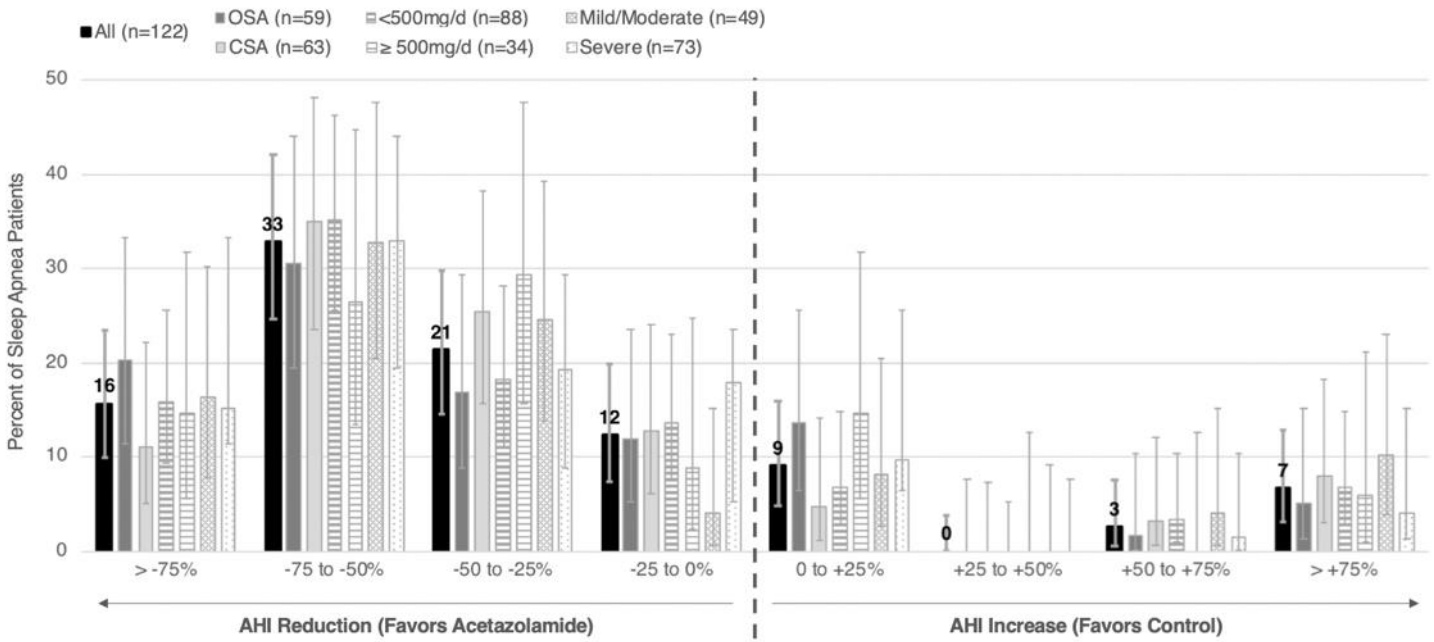
Hoff et al. Chest 2024

Schmickl et al. Phys Reports 2021

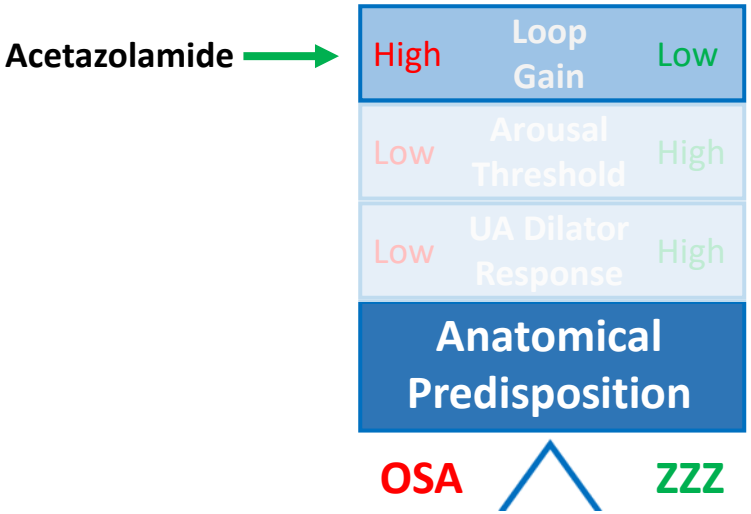


Acetazolamide ($N_{Studies}$=26)

- AHI reduction by 30-40%
  - Variable Response
  - Long-term effects unclear
  - Large effect on BP (-8/-4 mmHg) – but evidence for clinically important outcomes limited & low quality



Schmickl et al. Chest 2020, Schmickl et al. BMJ Open Resp, Schmickl et al. Phys Reports 2021



Acetazolamide ($N_{Studies}$=26)

- AHI reduction by 30-40%
  - Variable Response
  - Long-term effects unclear
  - Large effect on BP (-8/-4 mmHg) – but evidence for clinically important outcomes limited & low quality

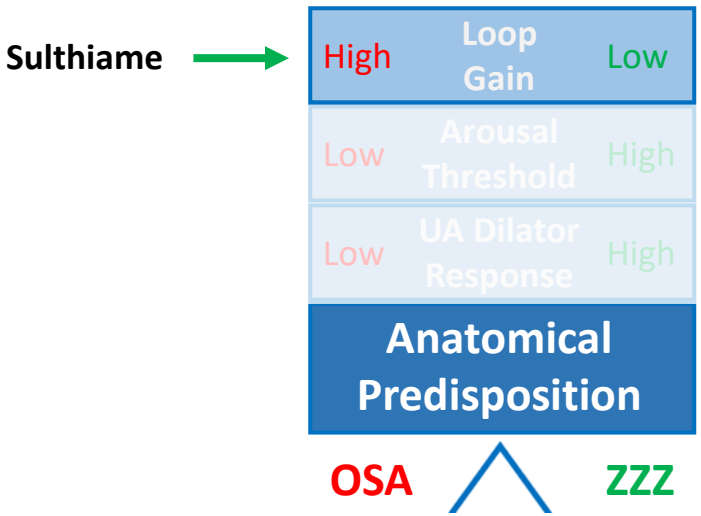
Two cross-over RCTs of acetazolamide vs placebo for OSA

Acetazolamide for Obstructive Sleep Apnea to Improve Heart Health (ACE-Of-HEARTs)

Supported by AHA Foundation
Career Development Grant (#940501; PI Schmickl)
NCT05616260 (N=46)

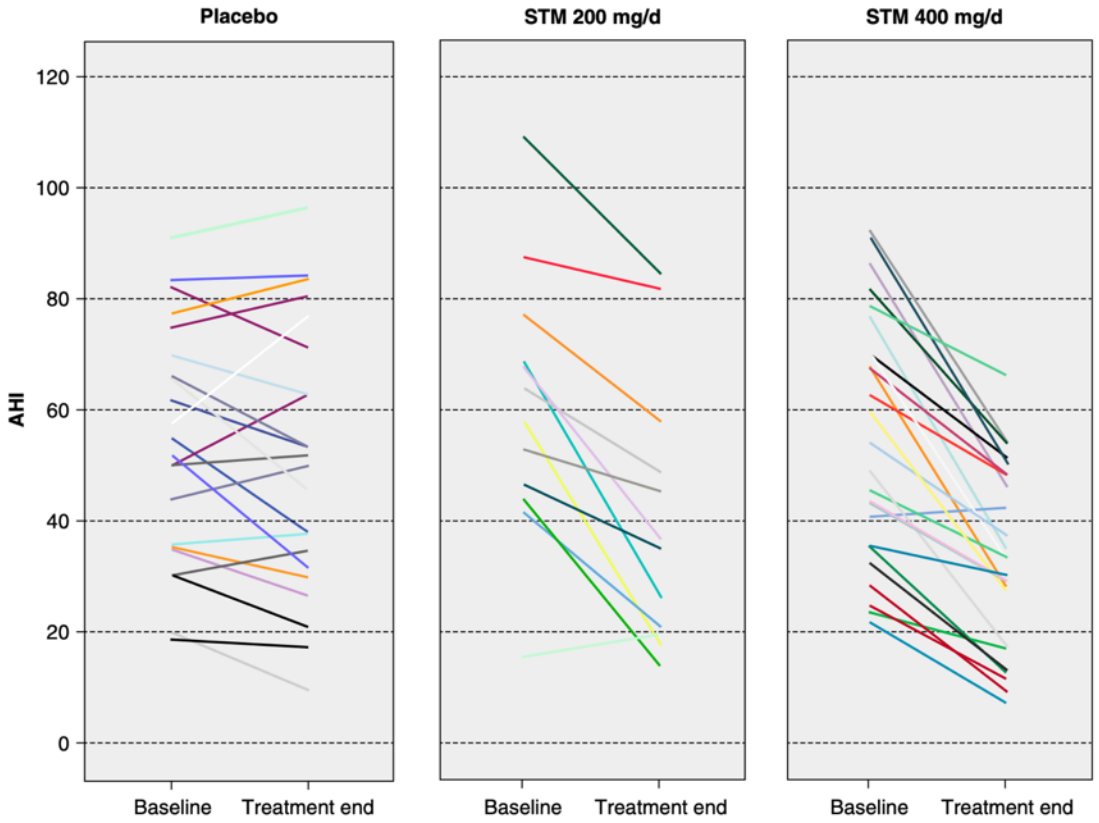
Patient-centered and Neurocognitive Outcomes with Acetazolamide for Sleep Apnea
PANACEA

Supported by NHLBI
K23HL161336 (PI Schmickl)
NCT05804084 (N=60)



Phase II RCT: Sulthiame vs Placebo x 4 weeks (n=68)

-6% (-3/h)	**-32% (-21/h)**	**-41% (-22/h)**	P<.001
n=22	n=12	n=34	



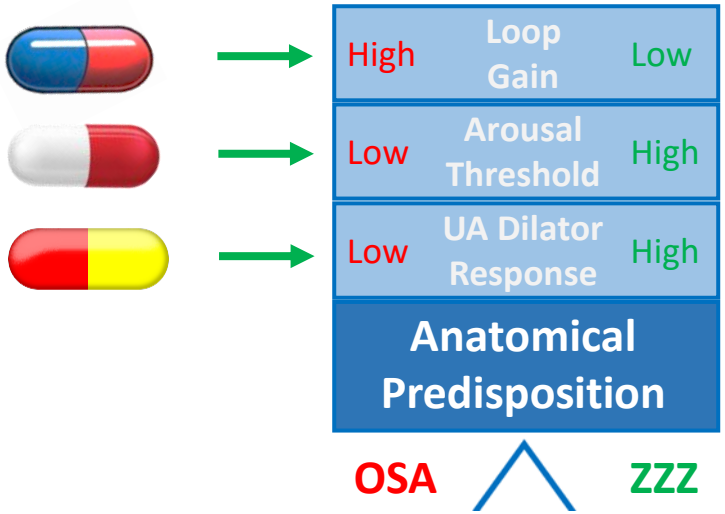
Large absolute effect, very consistent across individuals, ok tolerated

-> Large Phase 2 Trial including ~300 patients completed

(https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-002926-26/ES)

Hedner et al. AJRCCM 2022, Schmickl et al AJRCCM 2022

https://outoftheblue.transistor.fm/episodes/a-randomized-controlled-trial-exploring-safety-and-tolerability-of-sulthiame-in-sleep-apnea



Single-Trait Therapy Often only Partially Effective

The future of OSA care likely consists of combination therapy targeting 2+ mechanisms simultaneously

Take Home Messages

- OSA is very common
  - PCPs: ask about sleep problems; HSTs can be falsely negative
- There is more than just CPAP
  - For select patients, Inspire hypoglossal nerve stimulation or tirzepatide can be a good option
- Exciting time to be in sleep medicine

Thank you!

Any Questions?

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SLEEP RESEARCH GROUP

ATS American Thoracic Society

American Heart Association

NIH National Heart, Lung, and Blood Institute

AASM FOUNDATION