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Service
Company

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Treating OSA, Mechanisms of Current Therapy

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CASE WESTERN RESERVE
UNIVERSITY
SCHOOL OF MEDICINE

Disclosures



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Inspire Medical (only FDA approved device)

- Site PI for the STAR Trial (FDA Phase III) and FDA post-approval studies

NIH and VA research Awards on Causes and Consequences of Sleep Apnea

Sommetrics LLC (Consultant)

7 Dreamers (Consultant)

Objectives

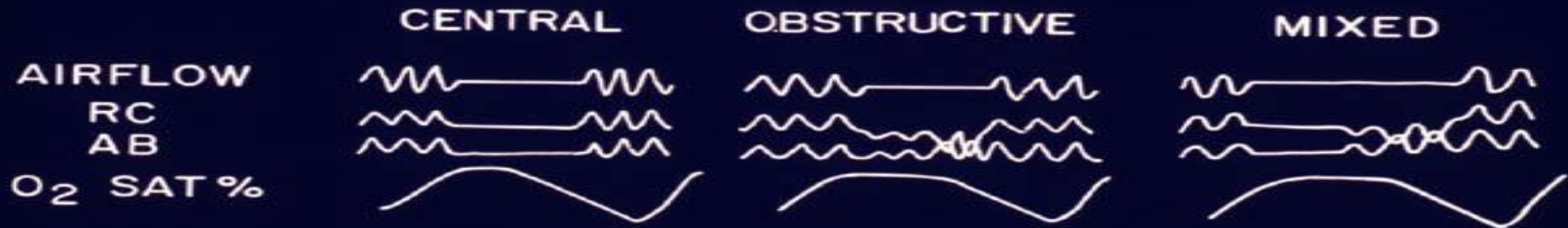


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- Compare risk factors to physiologic causes for recurrent sleep apnea
- Recount the importance of anatomy in OSA Treatment
- List other targets for therapy

Apnea Types



Non-obstructive (1978)

And... subtypes- flow limited breaths, hypopneas of all types, RERA without hypoxemia, etc.

Videotape Introduction



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29 year old with excessive daytime sleepiness, heavy snoring, snorts, restless sleep BMI 41

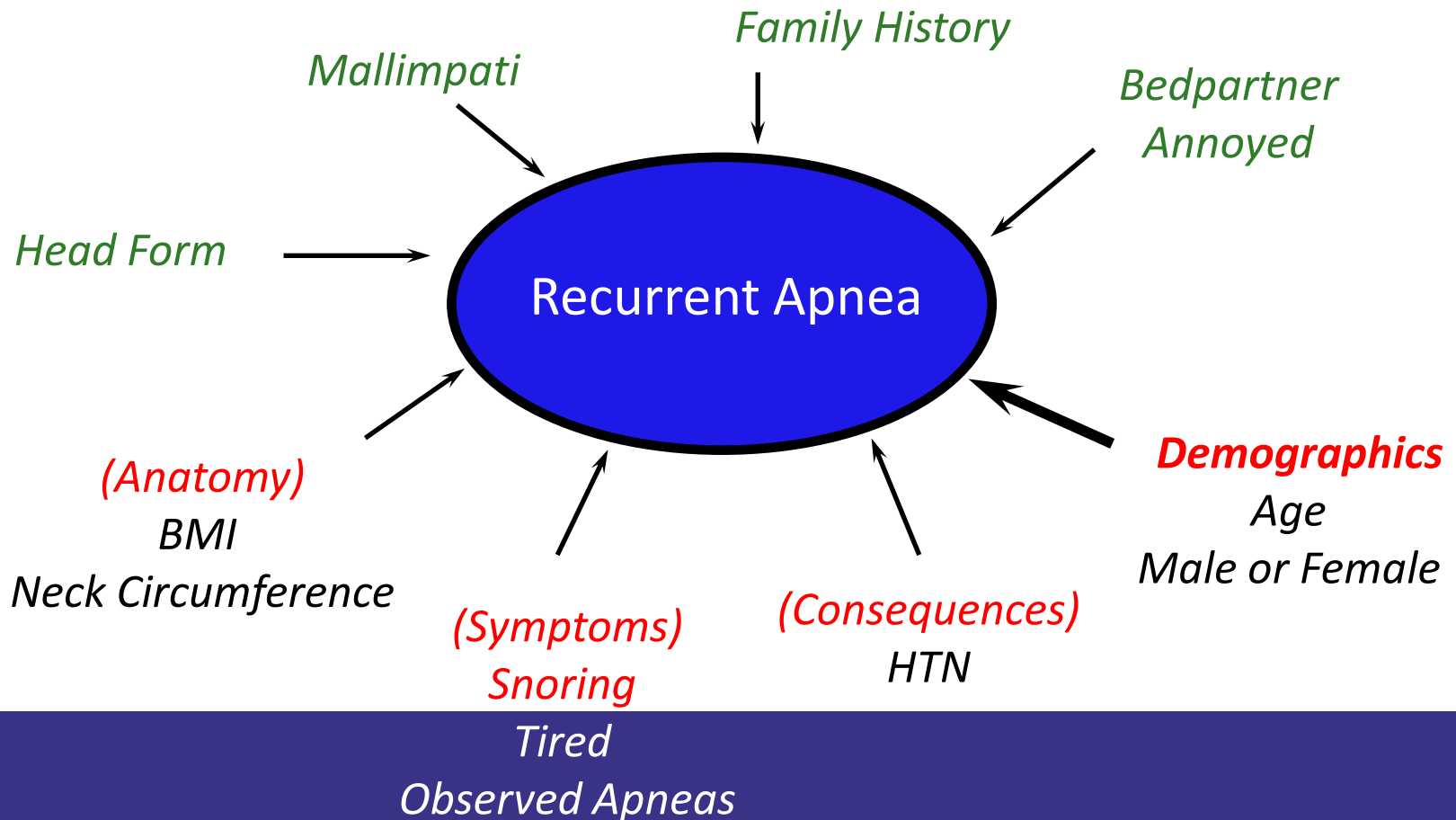
- Hx. of bipolar disorder and Hypertension



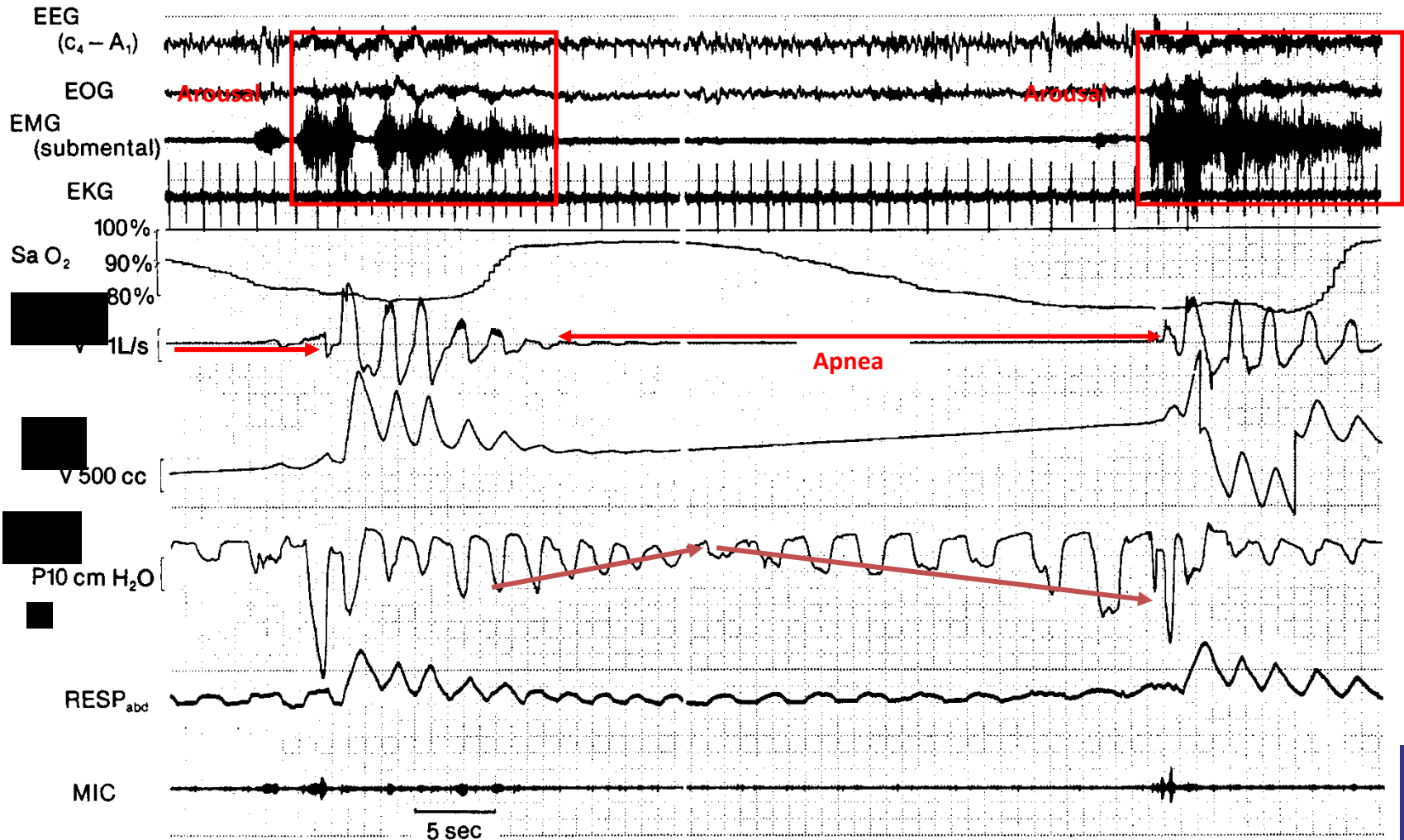
Clinical Recognition is not CAUSAL...

STOP-BANG: Snore Tired Observed (apneas)

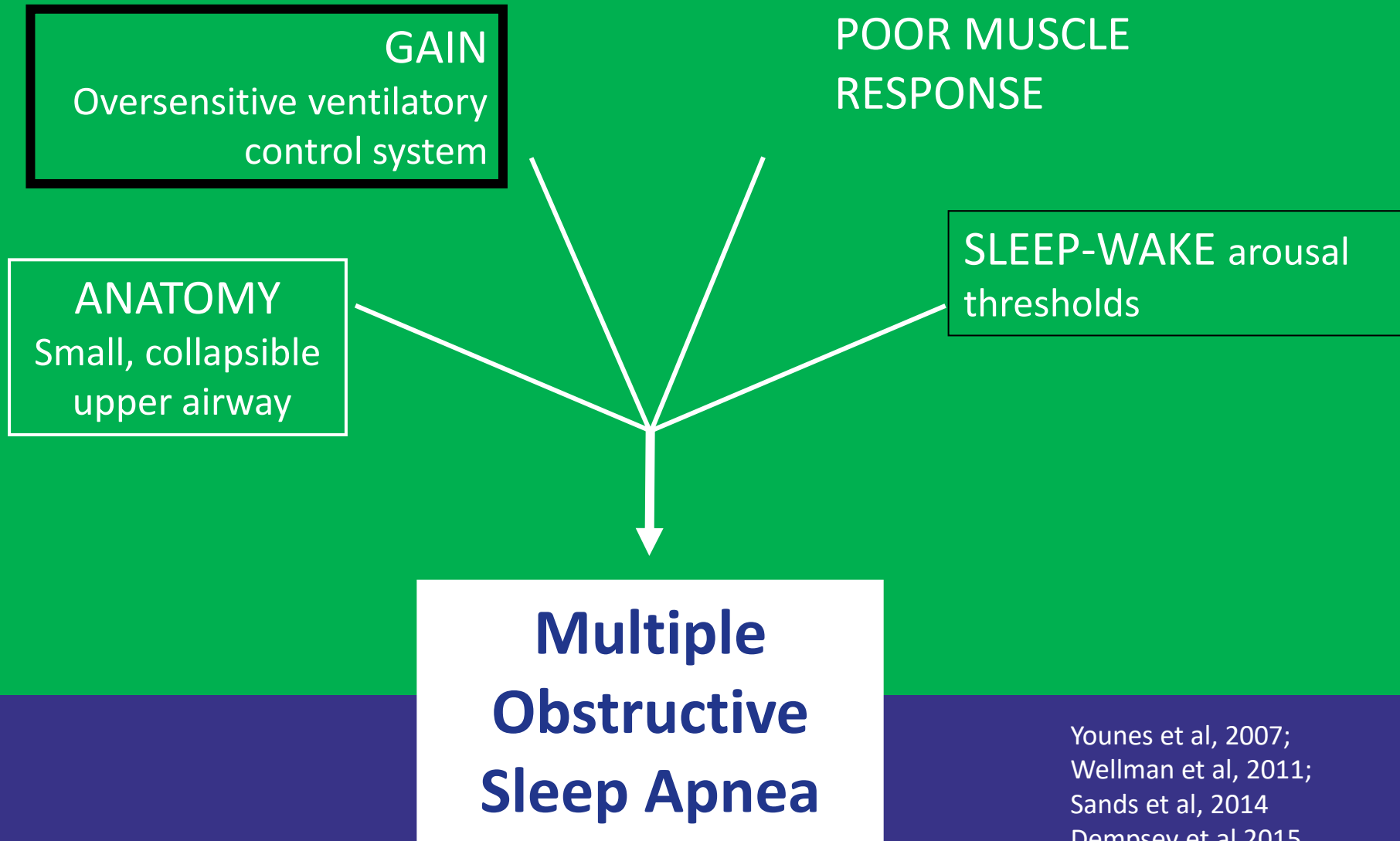
Pressure HTN)-BMI (>35) Age (>65) Neck (cm) Gender



Obstructive Sleep Apnea

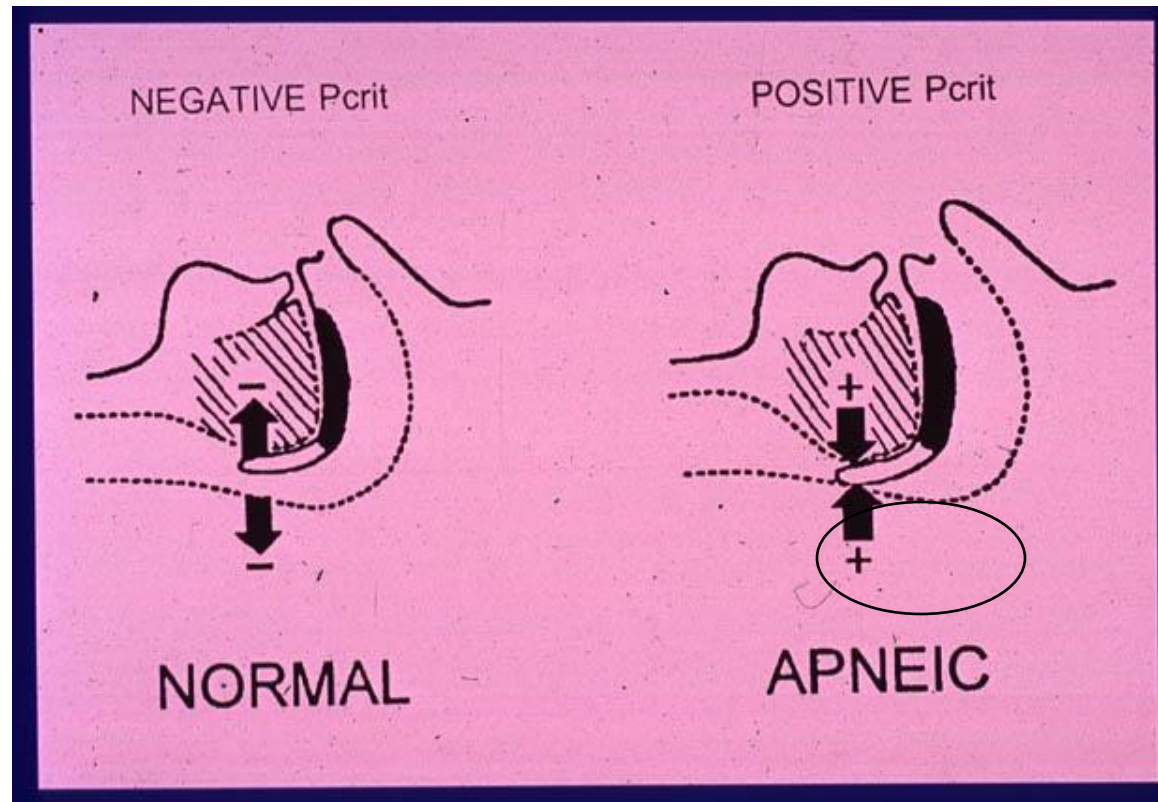


Pathways to Recurrent OSA (>15/h)



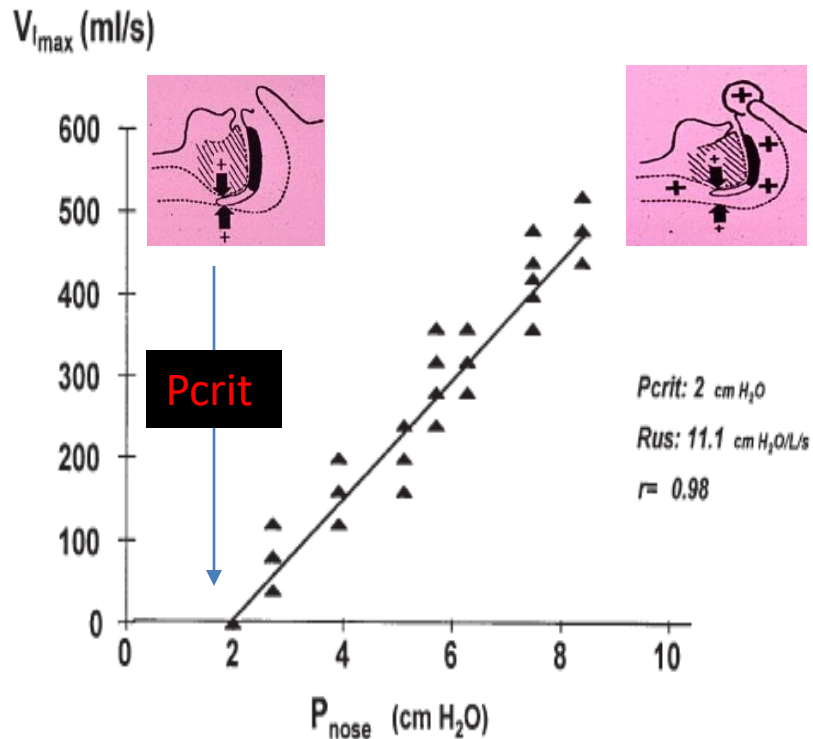
Younes et al, 2007;
Wellman et al, 2011;
Sands et al, 2014
Dempsey et al 2015

Critical Closing Pressure or Pcrit

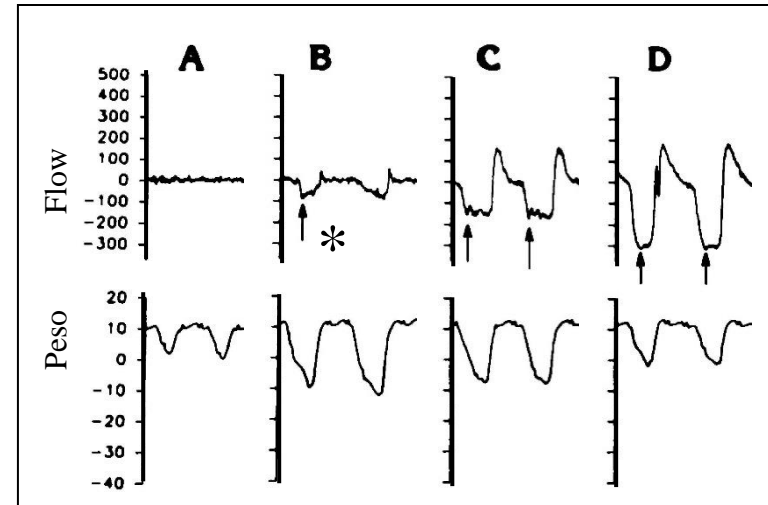


CPAP and Pressure-Flow Curves

Pcrit as calculated from an OSA patient



Summary Graph



$P_N (\text{cmH}_2\text{O}) = 1.0$

$= 3.0$

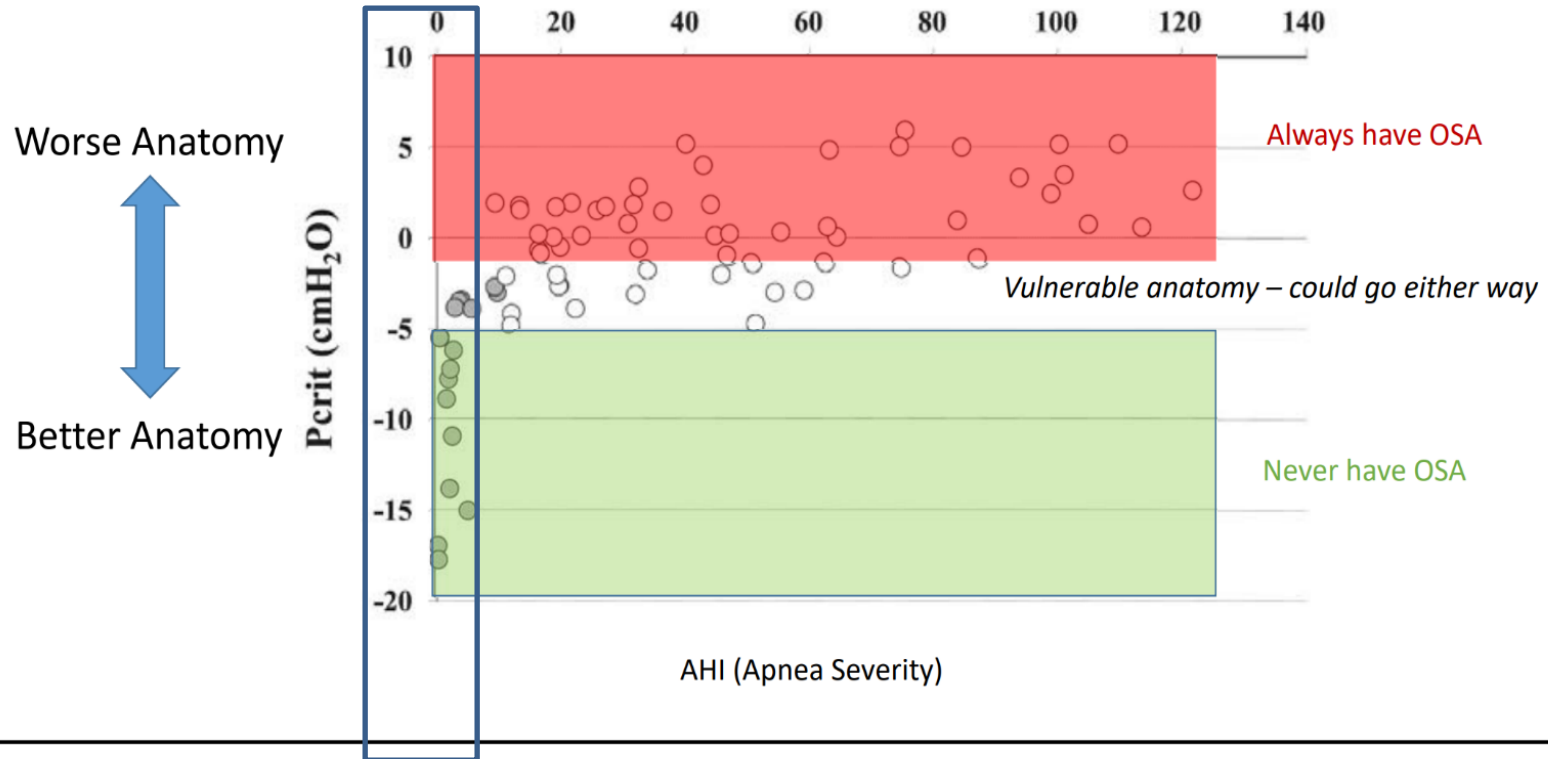
$= 5.5$

$= 8.5$

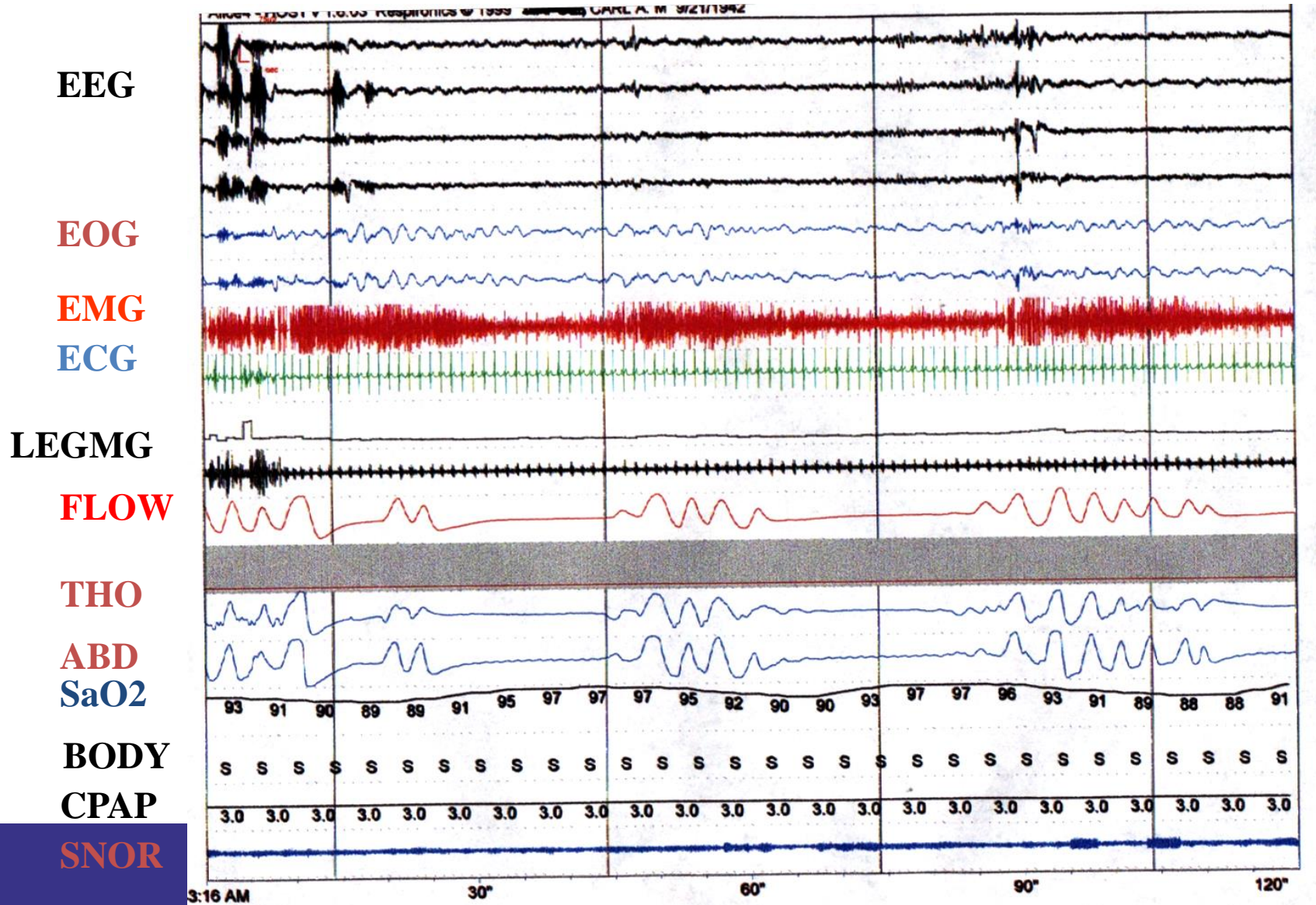
* Arrow = Point of maximal flow

Data

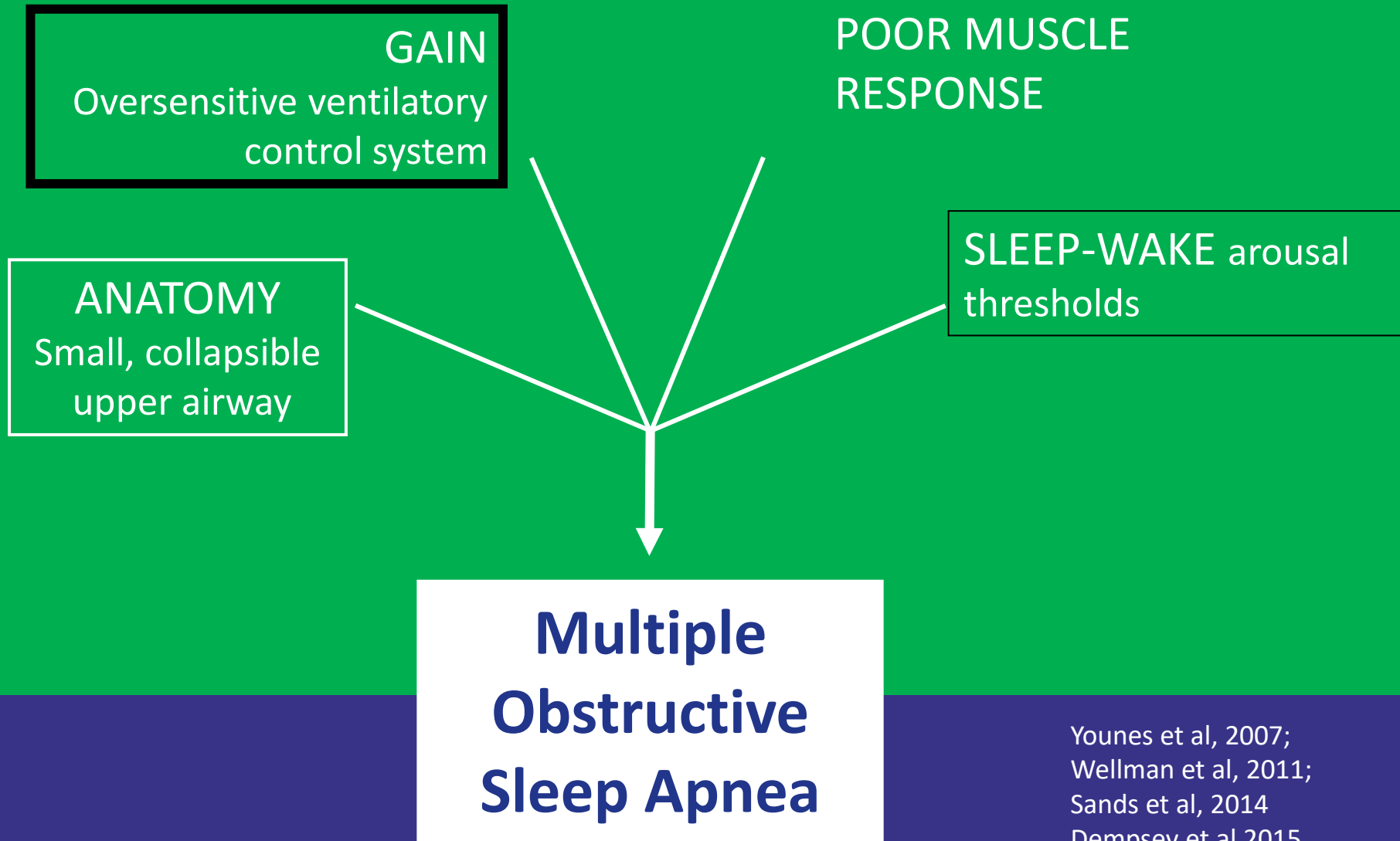
Anatomy is important in everyone



Uncovering Recurrent Central Apneas after Treatment with CPAP

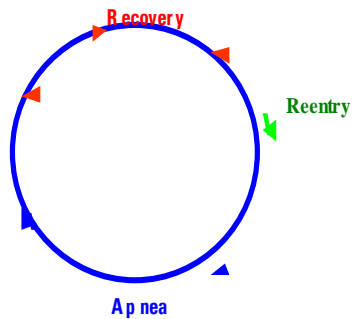


Pathways to Recurrent OSA (>15/h)

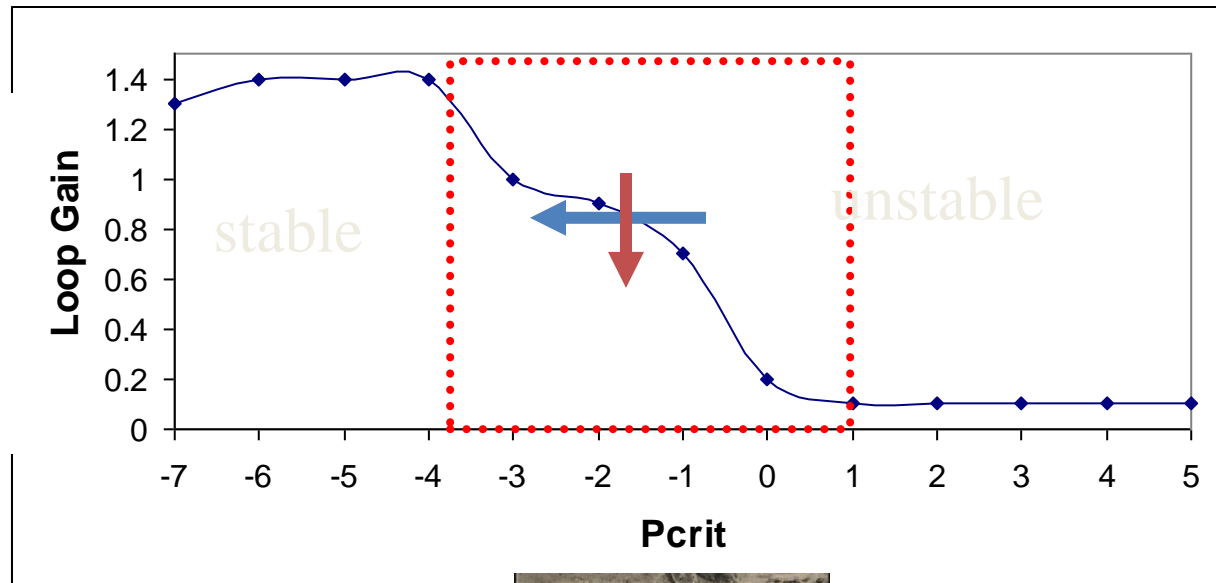


Younes et al, 2007;
Wellman et al, 2011;
Sands et al, 2014
Dempsey et al 2015

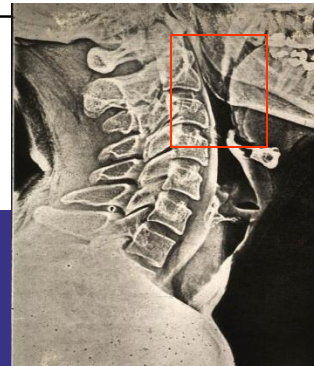
Loop Gain and Mechanical Interact



Physiology



ANATOMY
Size
Compliance



A. Wellman 2008
by permission

Optimal OSA Treatment



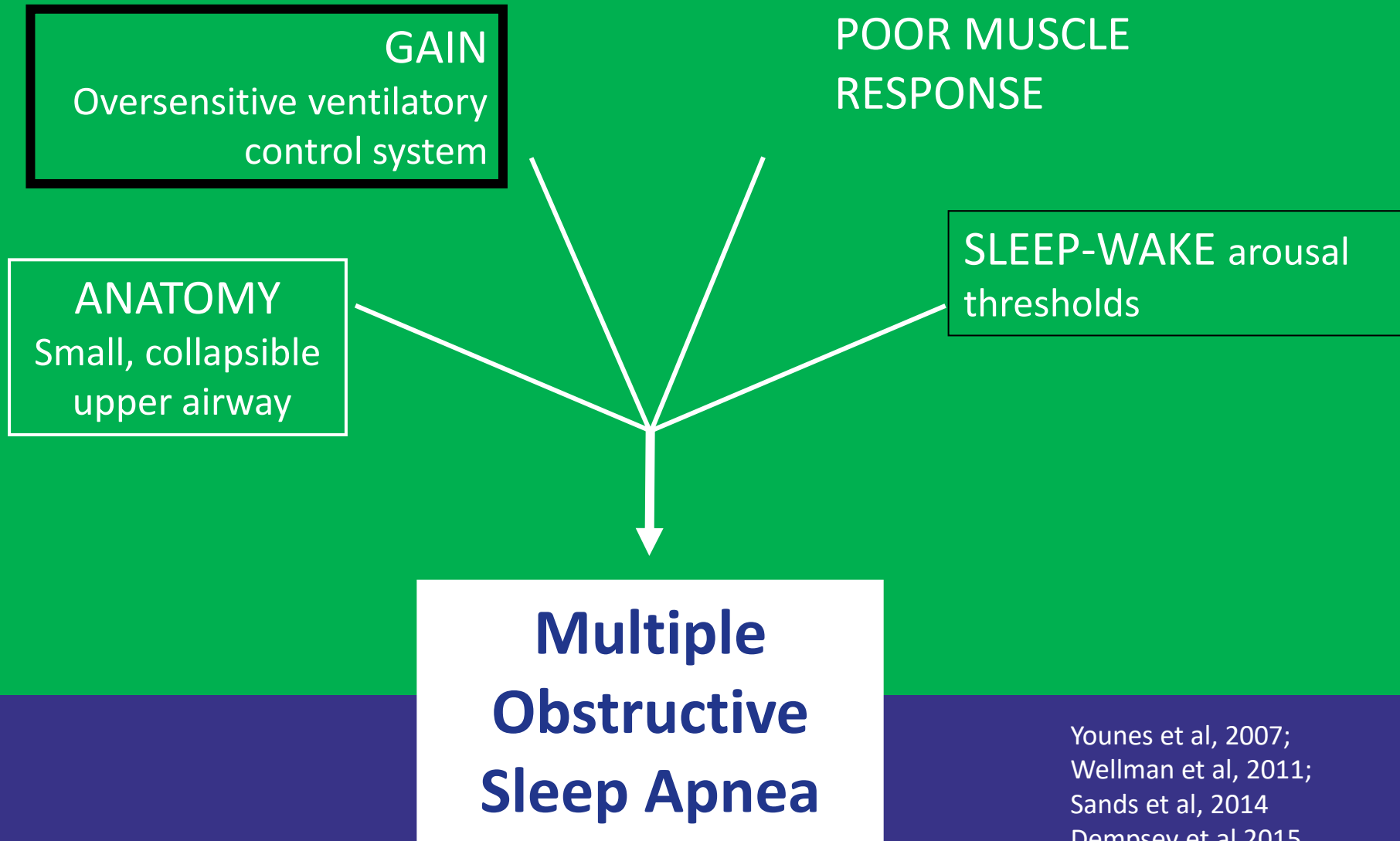
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- Maintain Upper Airway Patency during Sleep
- Restore Sleep Continuity
- Retain adequate Gas Exchange
- Improve Quality of Life
 - Sleepiness
 - Neurocognitive Function
- Lower diurnal blood pressure
- Decrease All-Cause Mortality

What is it?
How/Where
does it work?

Pathways to Recurrent OSA (>15/h)



Younes et al, 2007;
Wellman et al, 2011;
Sands et al, 2014
Dempsey et al 2015

Tracheostomy

...by-passes the problem

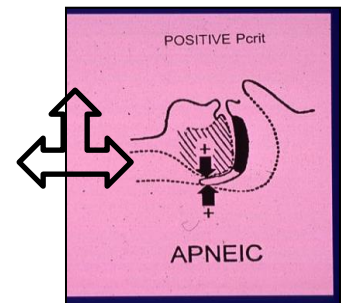


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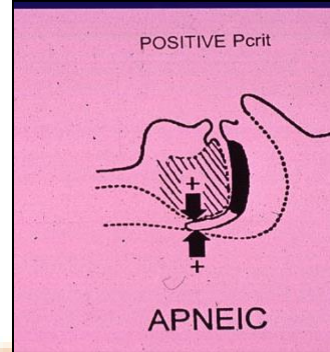
1964 Kuhlo and Doll

- Cure in 83%, with residual central apneas that resolve over time
- Significant endpoints:
 - Sleepiness resolves in 82-100% (3 studies with 98 patients)
 - Hypertension improves or resolves.
 - Hypercapnia, cor pulmonale, and cardiac arrhythmias resolve
- But.... Psychosocial problems
 - Local granulation
 - Recurrent bronchitis



(Conway W, JAMA 1981)

NAŠTENT (7 Dreamers, Japan)



Single use through one nares

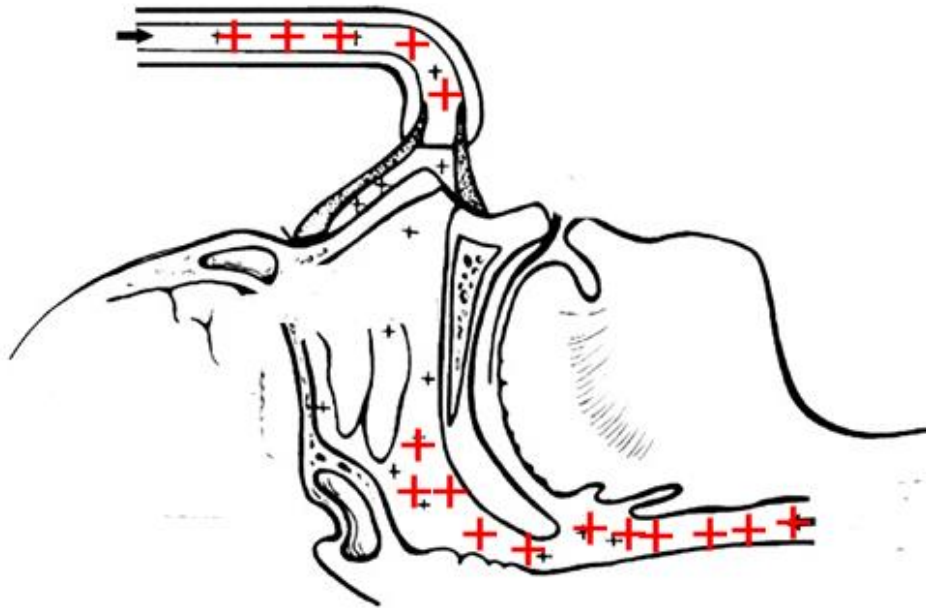
Approved/Available in Japan and Europe

Nasal CPAP “Airway Splint”



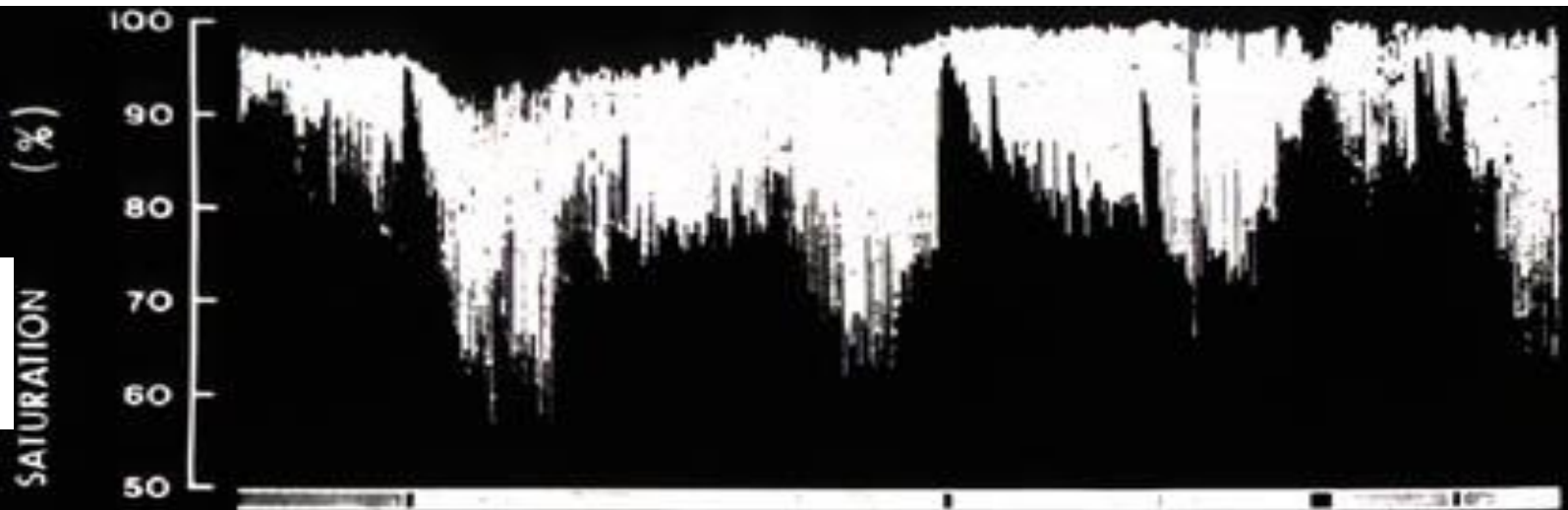
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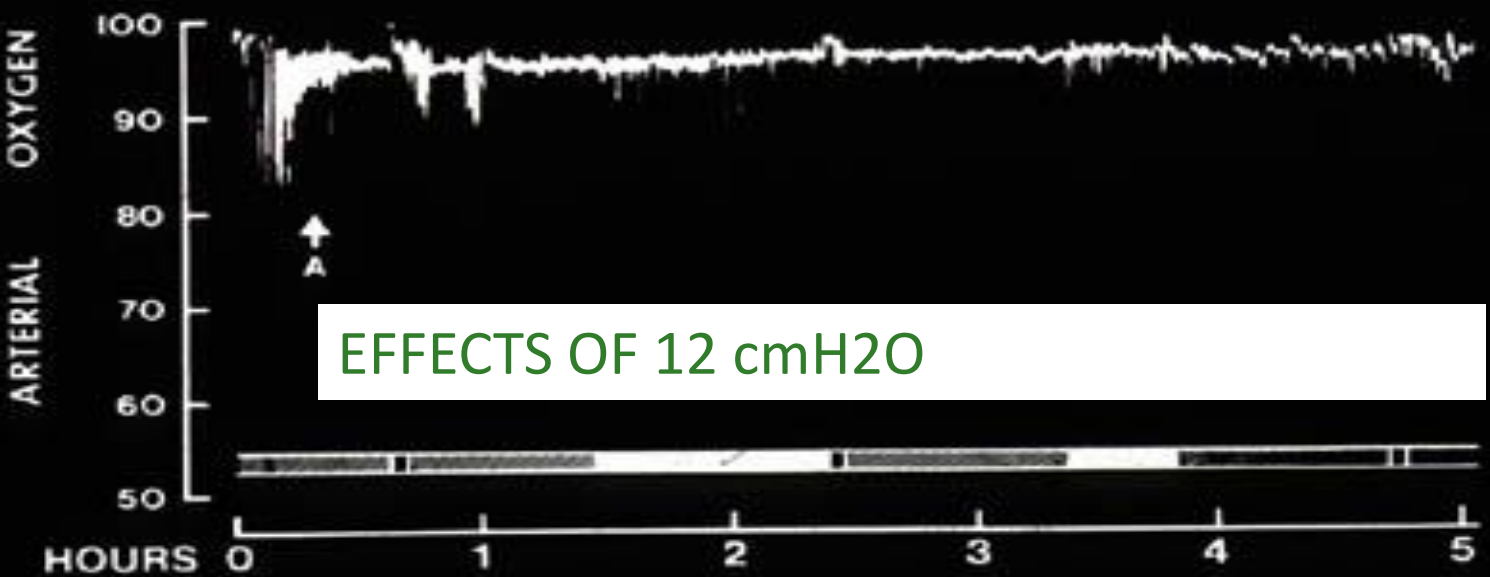


- First described by Colin Sullivan, 1979
- Doesn't care where it dilates the upper airway as a pressure splint against a $+P_{crit}$
- Increases functional residual capacity (FRC)

Baseline
Night 1



CPAP
Night 2



CPAP Mechanism: Passively opens the Airway

(no muscle activation)

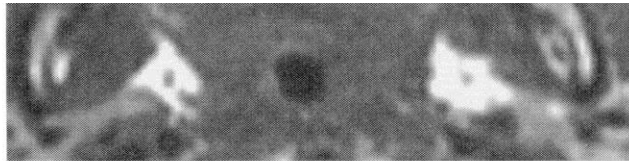


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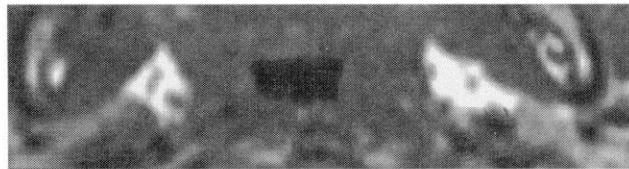
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Patient Awake

0 cm H₂O



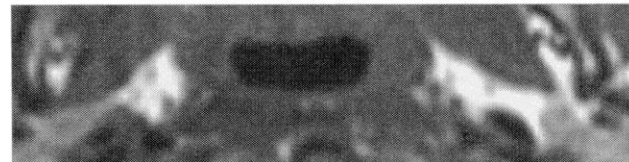
5 cm H₂O



10 cm H₂O

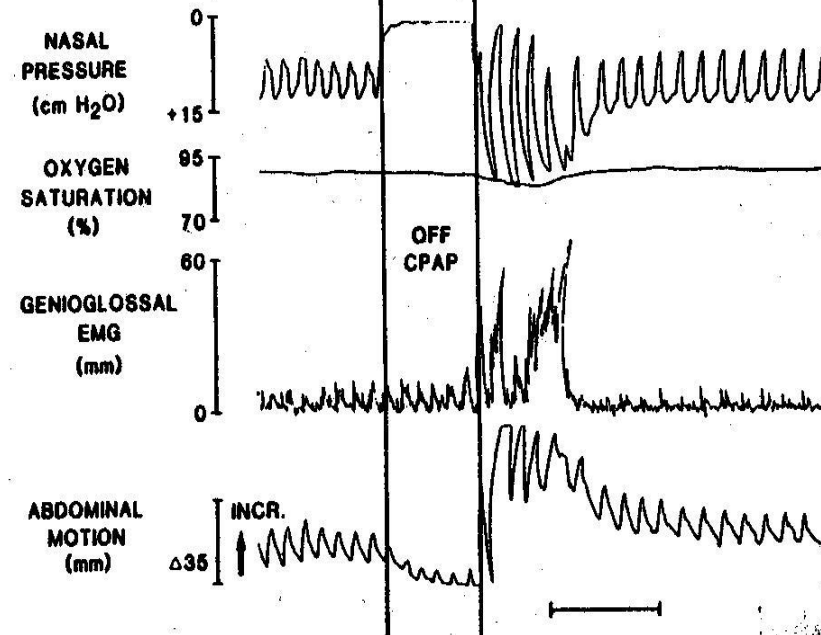


15 cm H₂O



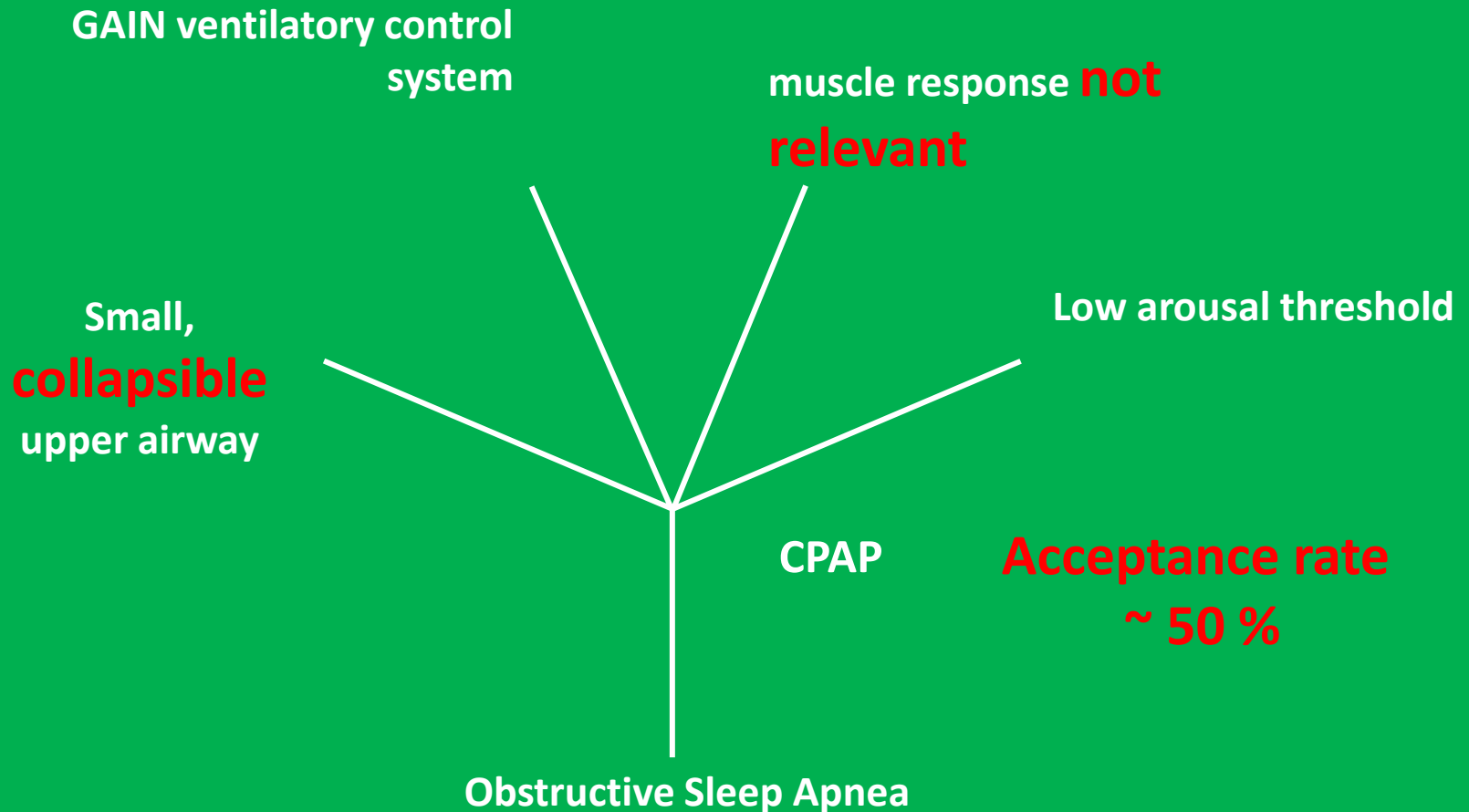
Schwab et al, 1995

Patient Asleep



Strohl and Redline, 1983

CPAP Target in OSA



(Kribbs, 1993; Engelman, 2003)

Rx with Oral Appliances

* RCTs showing effectiveness

- Tongue advancement
- Mandibular advancement
- Adjustable
- Fixed
- Customized
- Boil and bite

Advancement
↓Pcrit (-4.2 to -10.7)

Inazawa T, et al. *J Dent Res.* 2005;84:554-8.

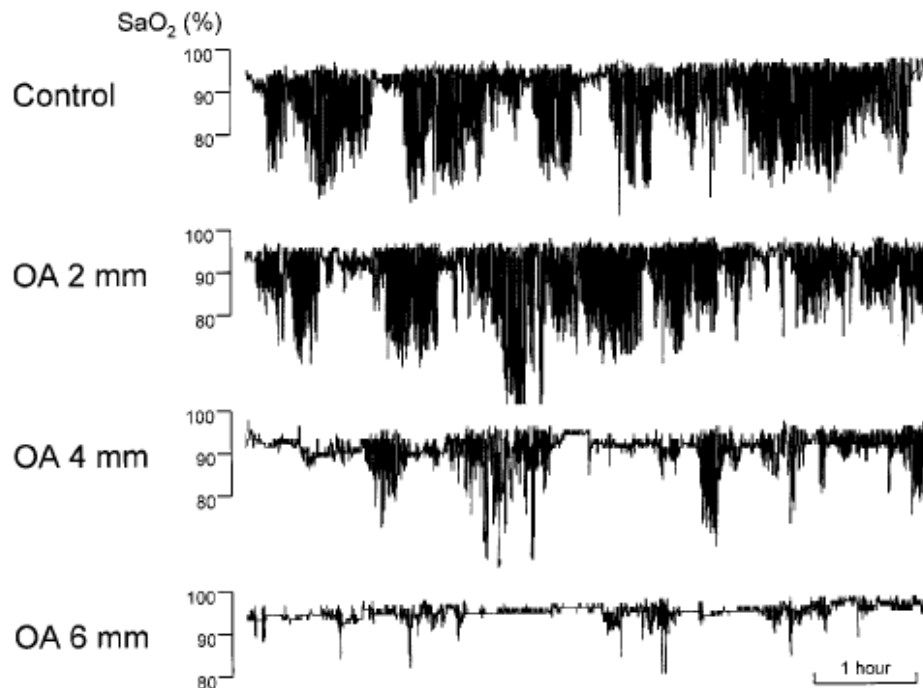


Incremental Mandibular Advancement improves Pharyngeal Mechanics and Oxygenation



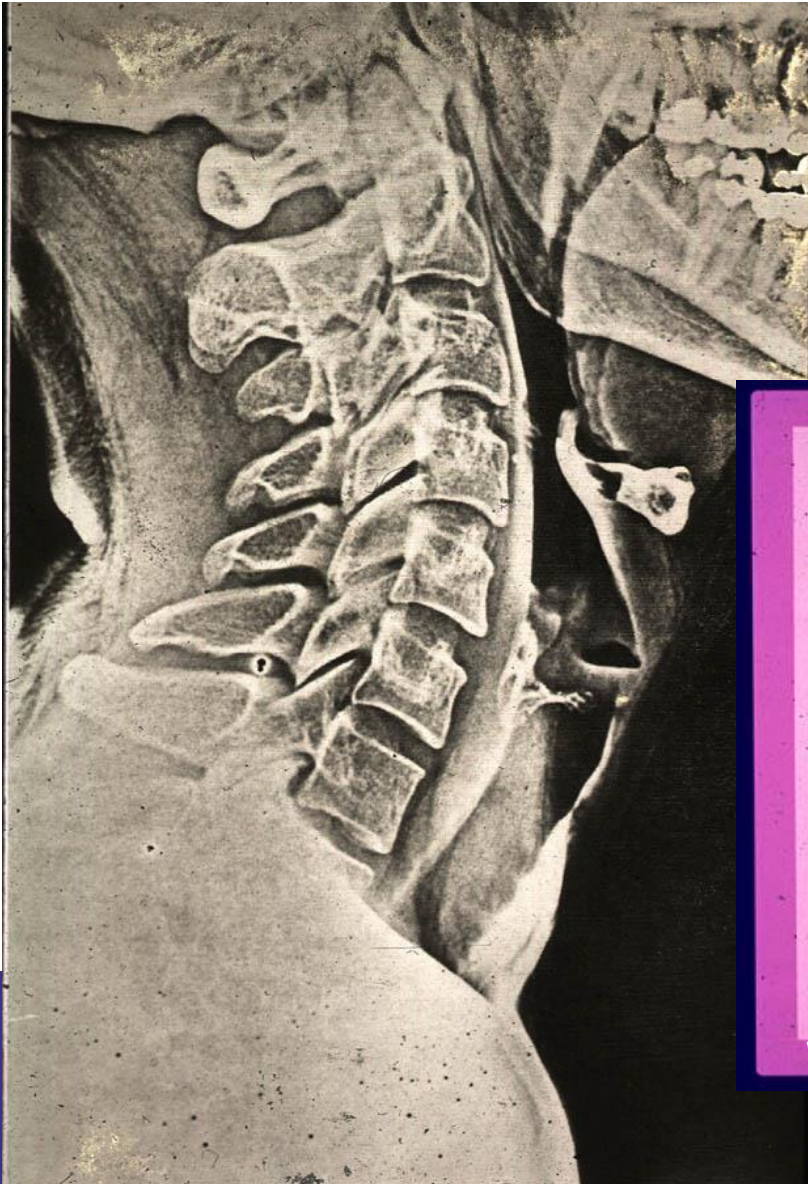
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- Each 2mm improved AHI 20%
- Obese less effective than non-obese
- Outcome not well predicted by AHI

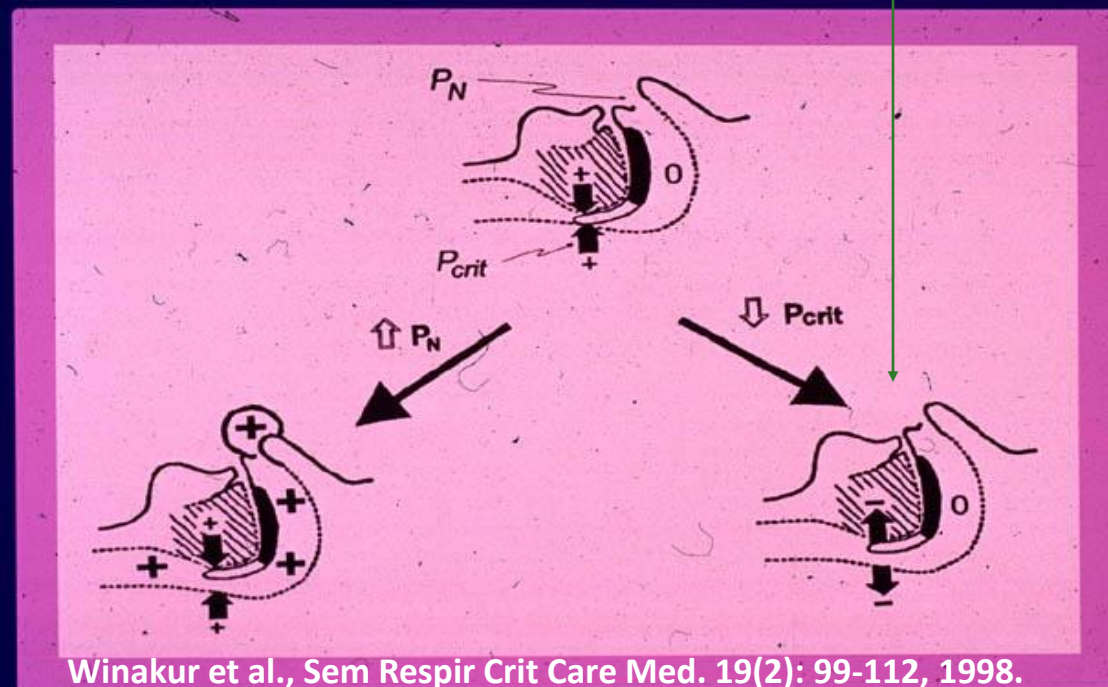


Kato J, et al. *Chest*. 2000;117:1065-72.

Treatment Principle for Surgical Therapy: Decrease P_{crit}



Size and Compliance
Surgery



Winakur et al., Sem Respir Crit Care Med. 19(2): 99-112, 1998.

One RCT showing UPPP effectiveness

Many Surgical Approaches



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- -Uvulopalatopharyngoplasty (at least 18 modifications)
- -lateral wall stabilization (v1-v6)
- -nasal surgery
- -turbinate reduction surgery
- -partial uvulectomy/ Pillar Procedure
- -Woodson Procedure (transpalatal palatopharyngoplasty)
- -Somnoplasty
 - turbinate reduction

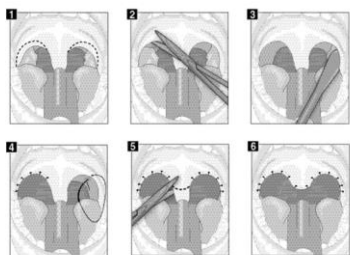
- **Epiglottis**
 - epiglottectomy
 - epiglottoplasty
- **Hyoid**
 - hyoepiglottoplasty
 - hyoid suspension and advancement to mandible
 - hyoid myotomy and suspension to thyroid cartilage
 - Expansion hyoidplasty
- -geniotubercle/genioglossus skeletal

NOT AS PREDICTABLE OR DURABLE OR GENERALIZEABLE AS ONE WOULD WANT.

- -adenoidectomy
- -Tonsillectomy (total/ partial)
- **Tongue**
 - lingual tonsillectomy
- -tongue base reduction
 - glossectomy (anterior vs. posterior)
 - linguoplasty (CO2)
 - tongue-base suspension sutures (Repose procedure)

- **Tracheostomy**

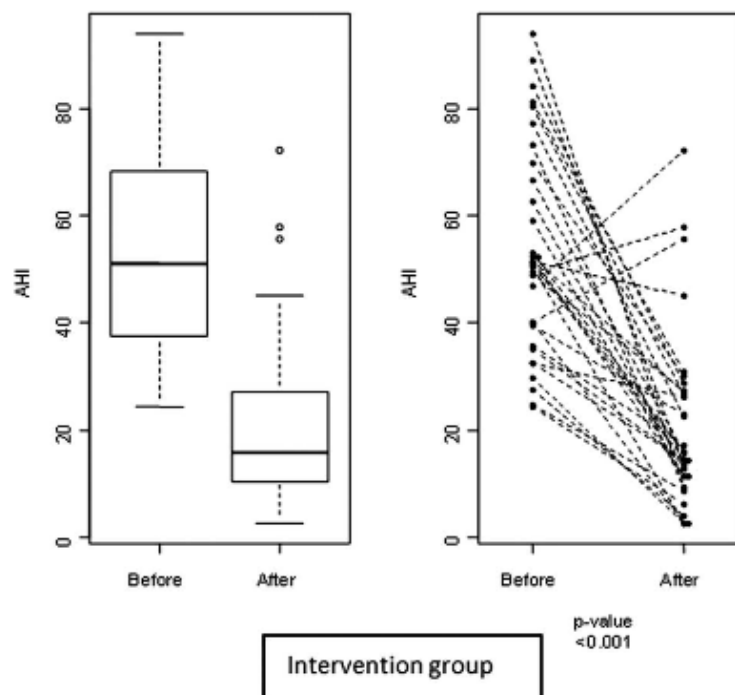
No Pcrit measures.



SKUP³ randomised controlled UPPP vs. Waiting

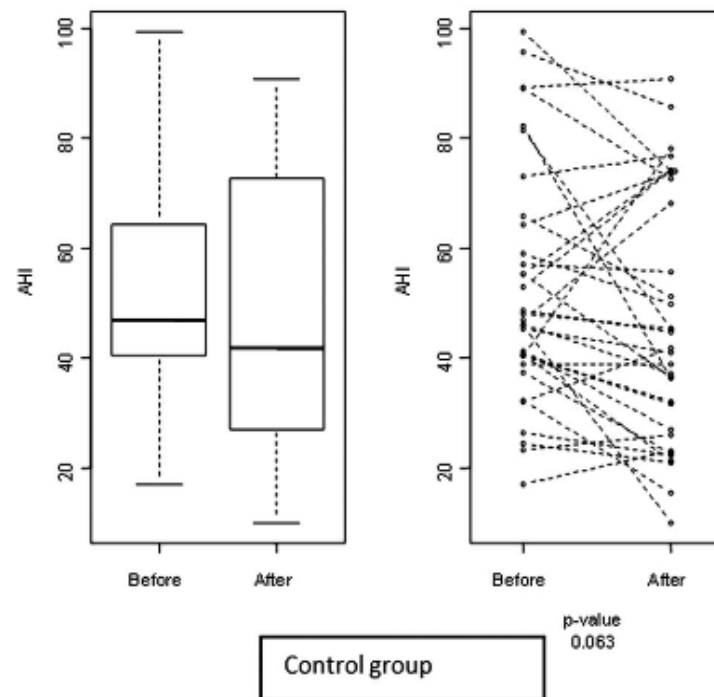
Browaldh et al Thorax 2013

Surgical Group



60% reduced

Passive Control



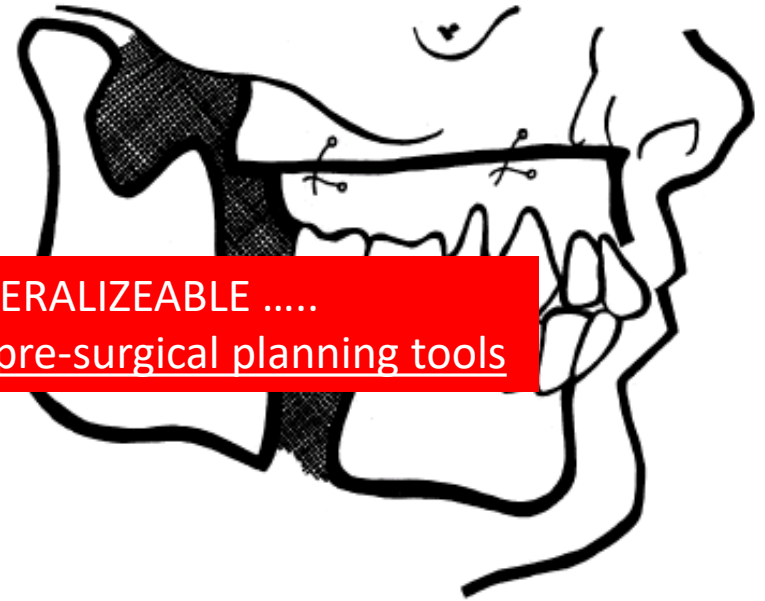
11% reduced

Maxillomandibular Advancement (MMA)

- Success rates of over 90% (Prinsell, 2002) *with very* co patients

MORE PREDICTABLE AND PERHAPS GENERALIZEABLE

in part because recent use of pre-surgical planning tools



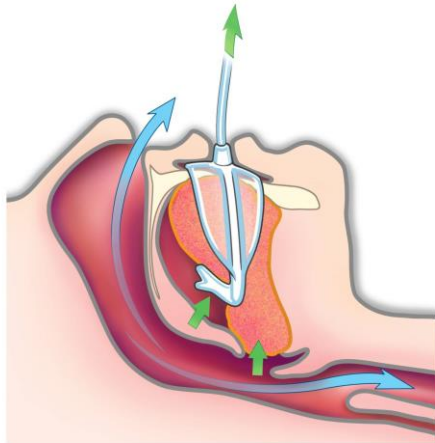
Imaging described size increases at the level of the tongue but all showed nasopharyneal enlargement.

- Best outcomes in patients with “birdlike” faces

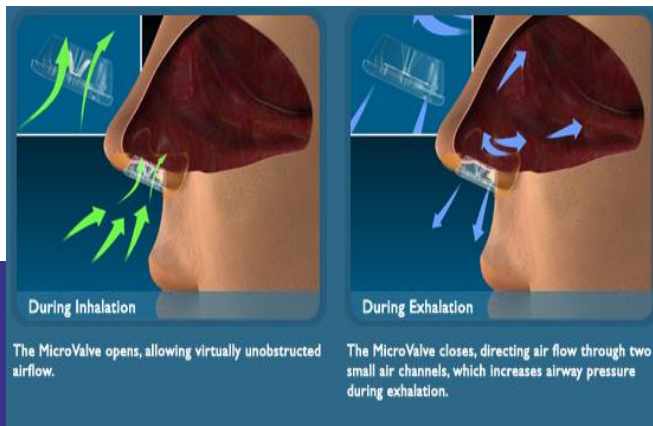
Still no measures of Pcrit in an outcome study.....

“Thingies” Lower Pcrit

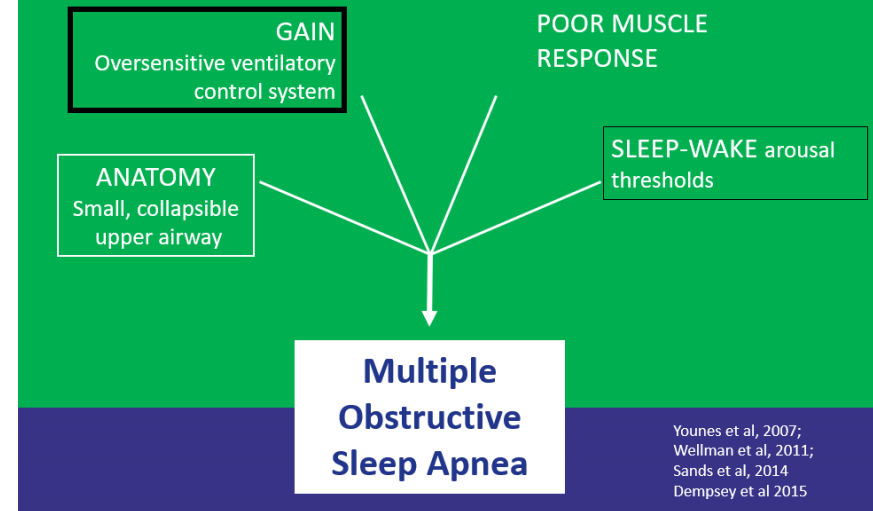
WINX: Keep Tongue forward



Provent Valves (+ pressure at end exp.)

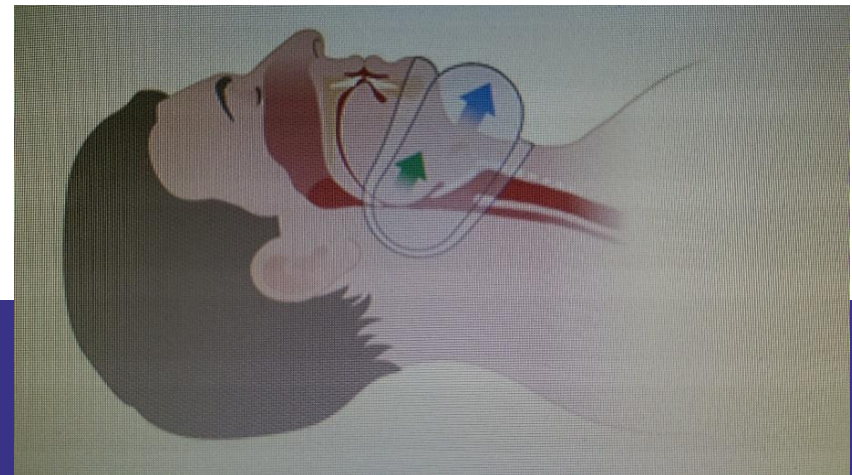


Pathways to Recurrent OSA (>15/h)

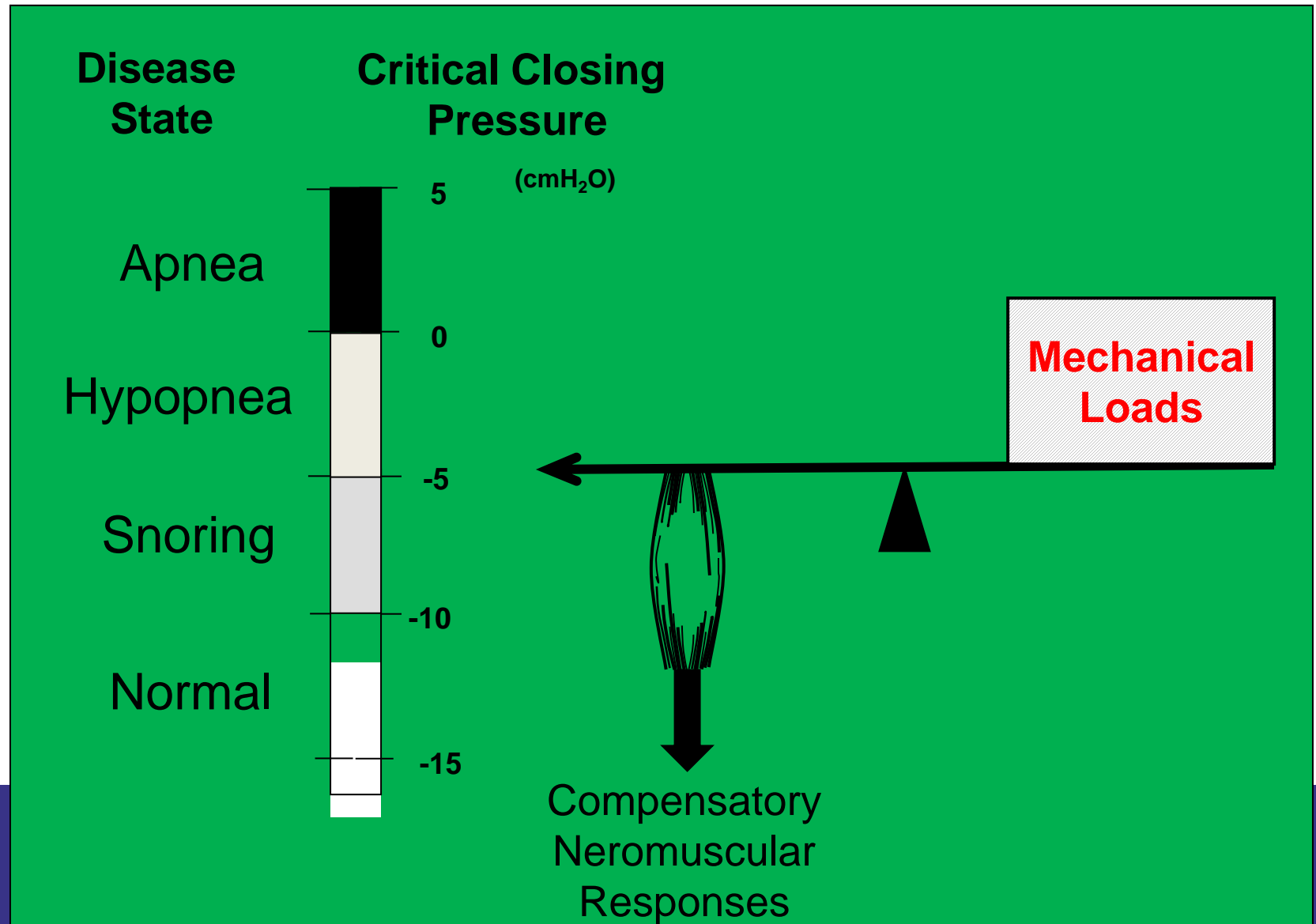


All directed at Anatomy

cNEP: Negative Pressure around neck



Loading of the system: Obesity



Weight Loss for OSA

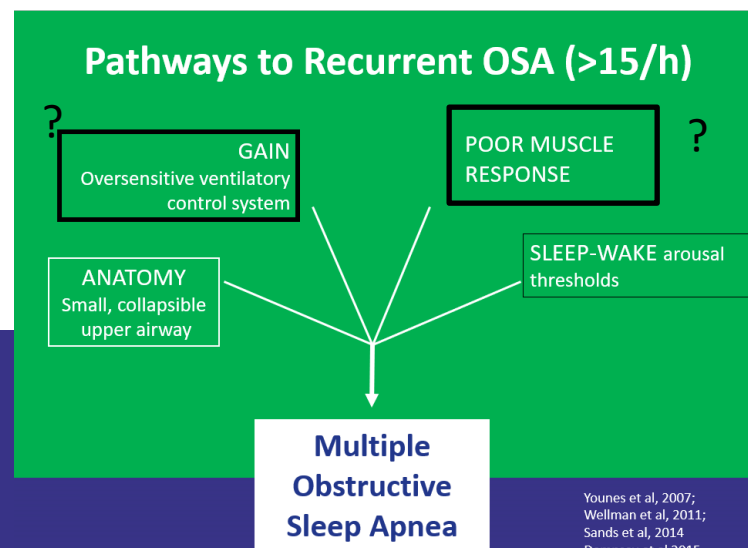
Modest (10%) weight loss results in significant (20%) improvement in AHI (Yee BJ, Int J Obes 2006)

Bariatric Surgery results in 75-88% cure rate of OSA at 1 year, independent of approach (Guardiano SA Chest 2003; Crooks, PF, Annu Rev Med 2006).

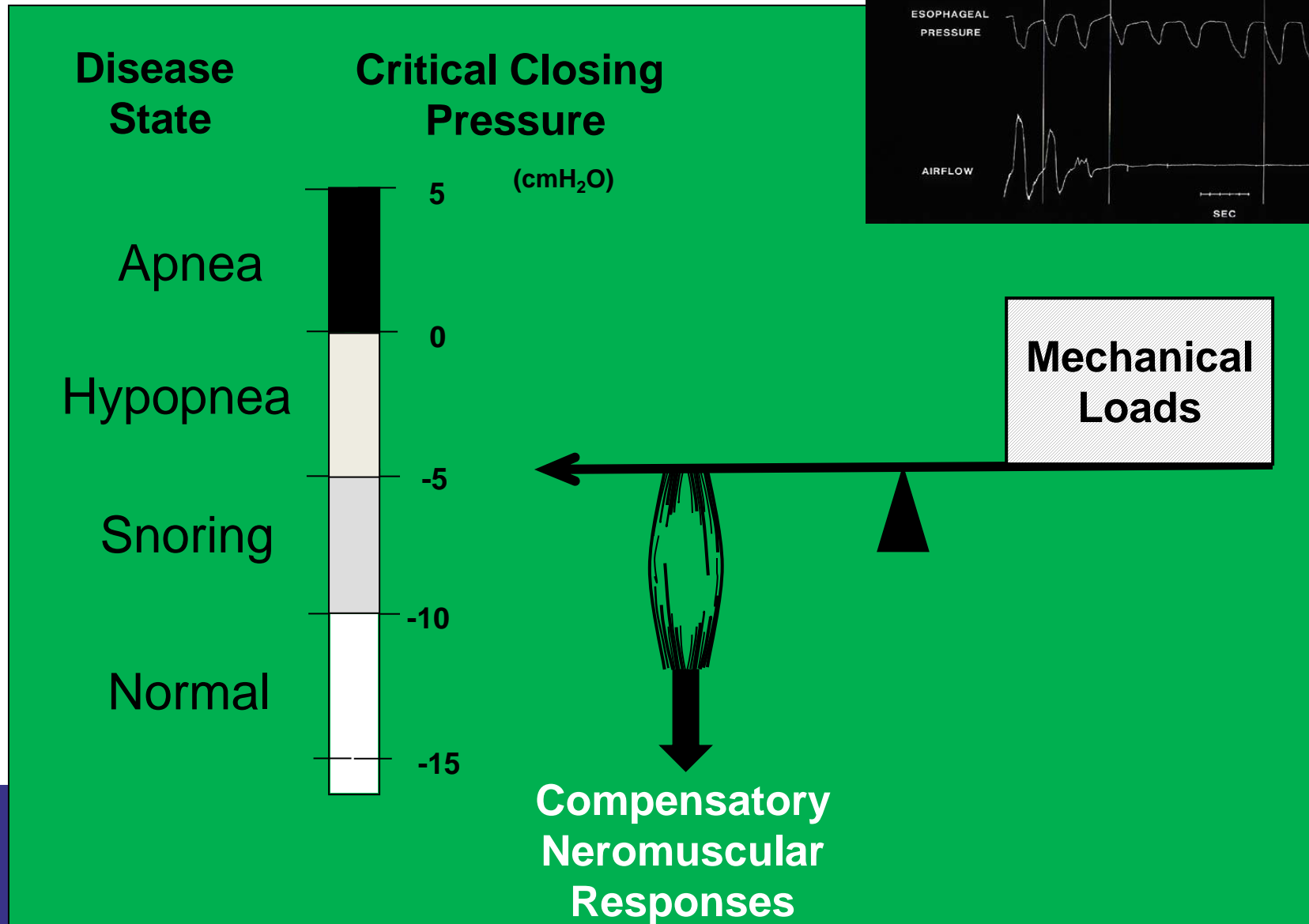
Pcrit is reduced

(medical and bariatric weight loss*).
(Schwartz review 2004)

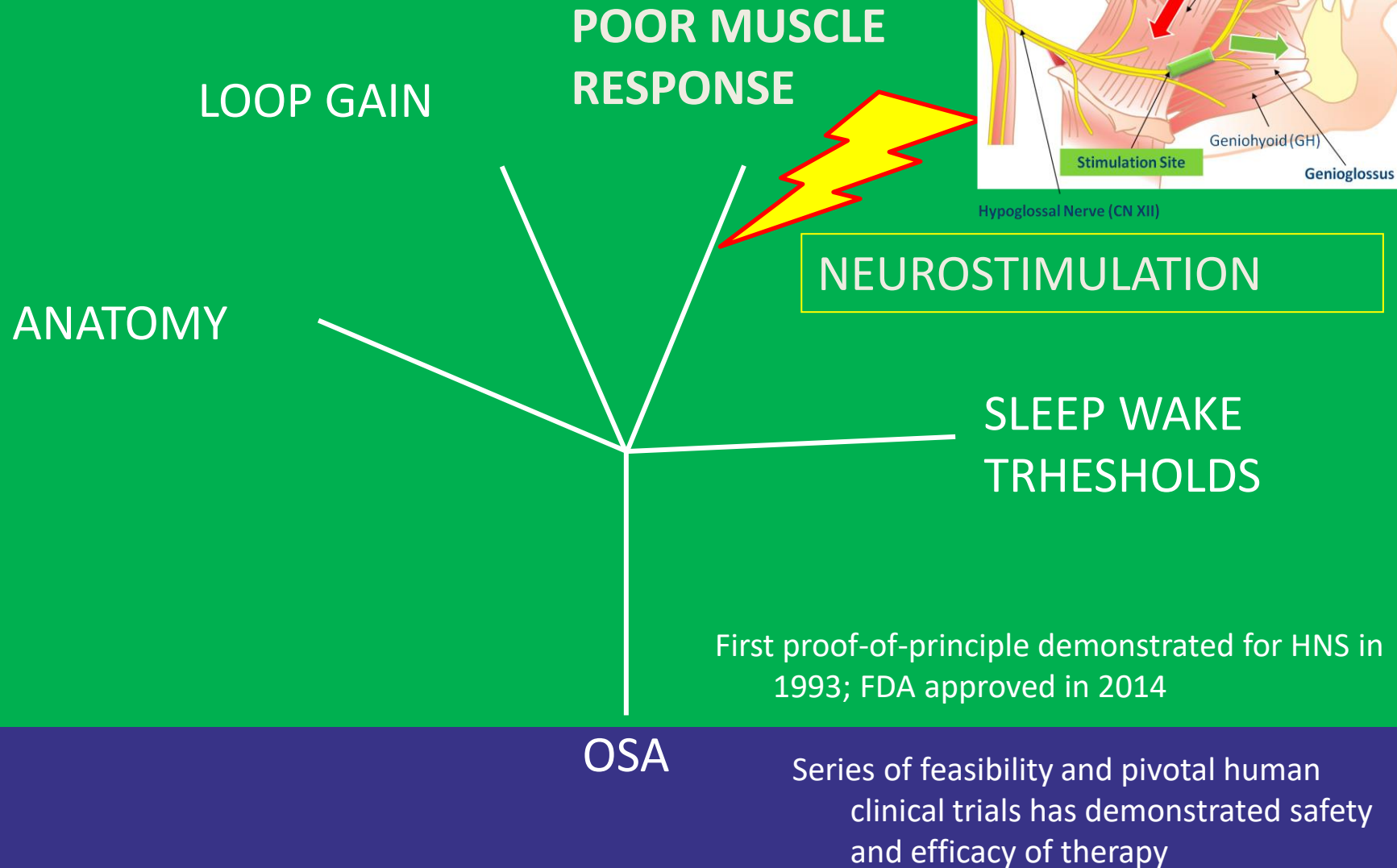
* No comparisons



Neuromuscular Therapy



Treatments for OSA



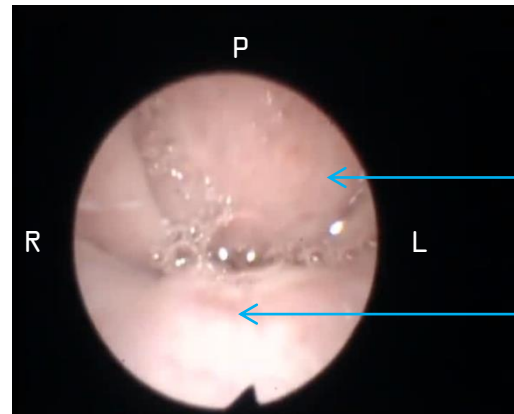
Immediately stabilizes airway...ideally leaving all other pathways alone



Stimulation

Inspire UAS effect during drug-induced sedation endoscopy (DISE)

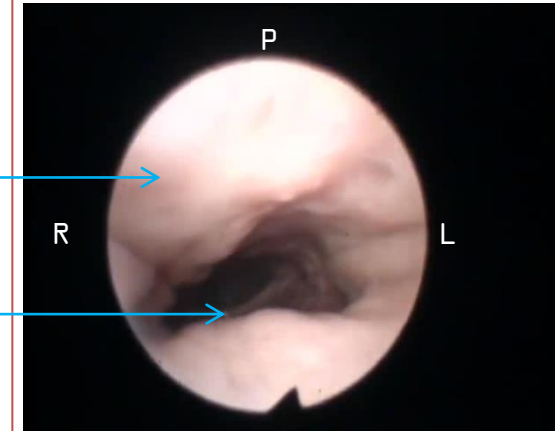
Palate - Therapy OFF



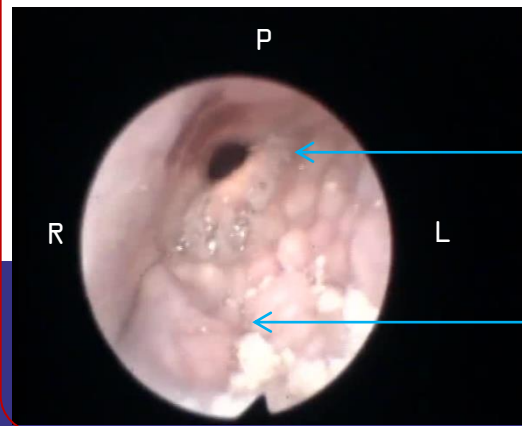
Posterior
oropharyngeal
wall

Posterior Uvula

Palate - Therapy ON



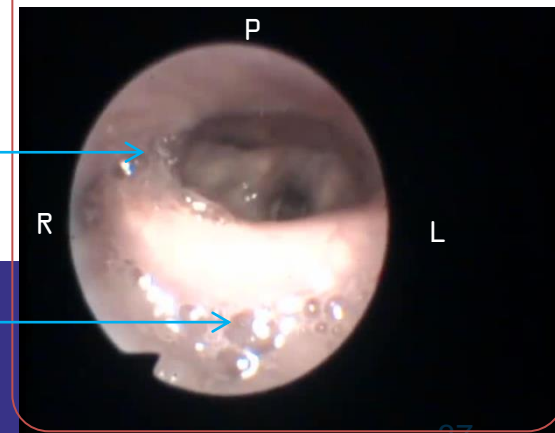
**Tongue-base, Therapy
OFF**



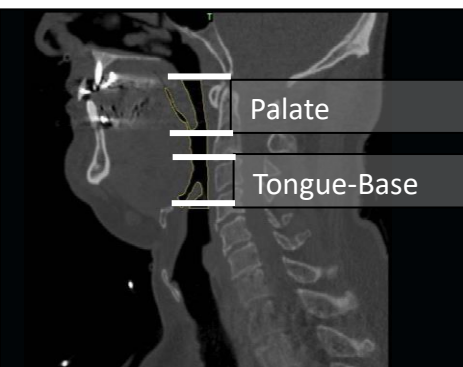
Epiglottis

Lingual Tonsils

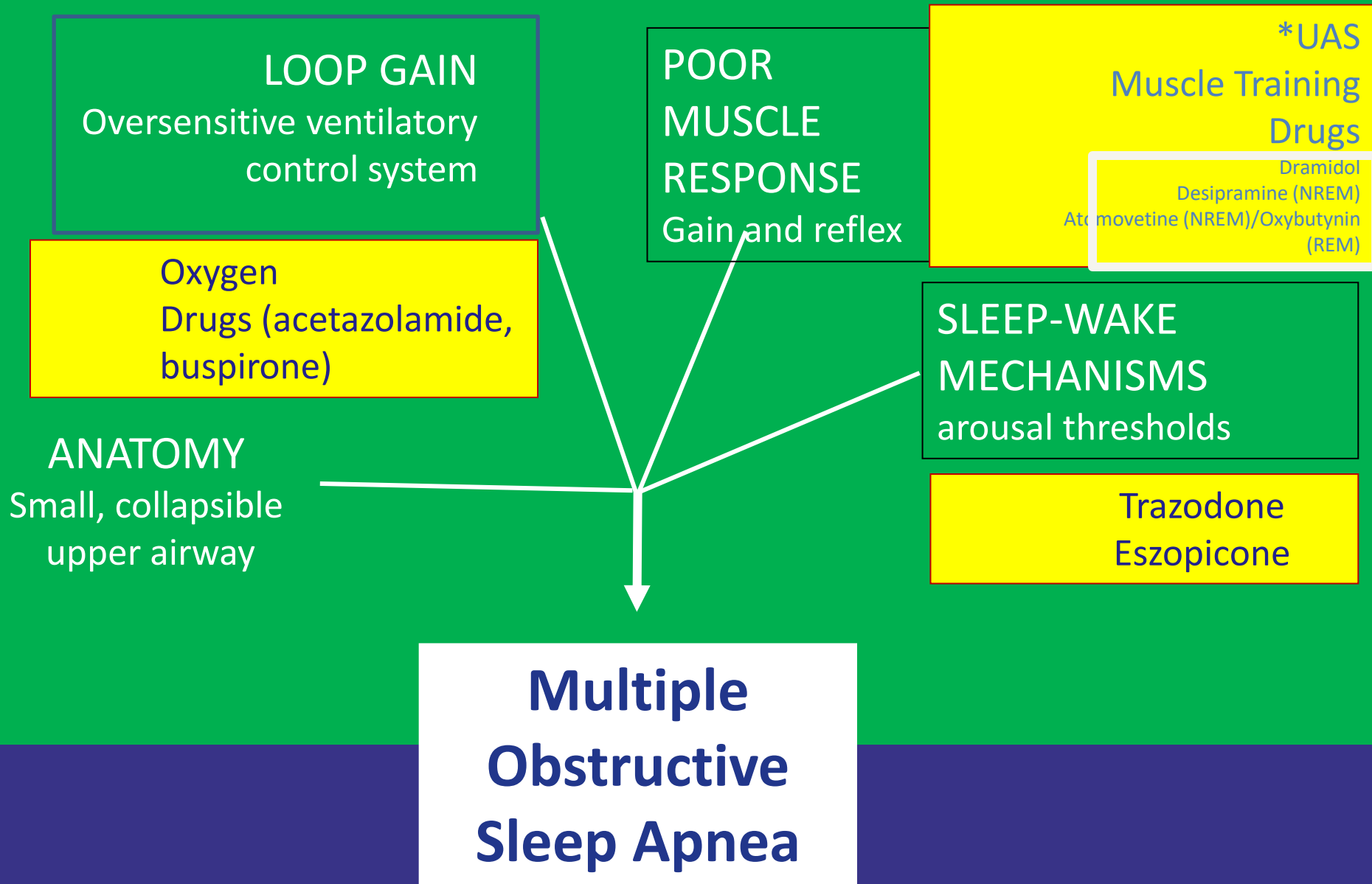
**Tongue-Base,
Therapy ON**



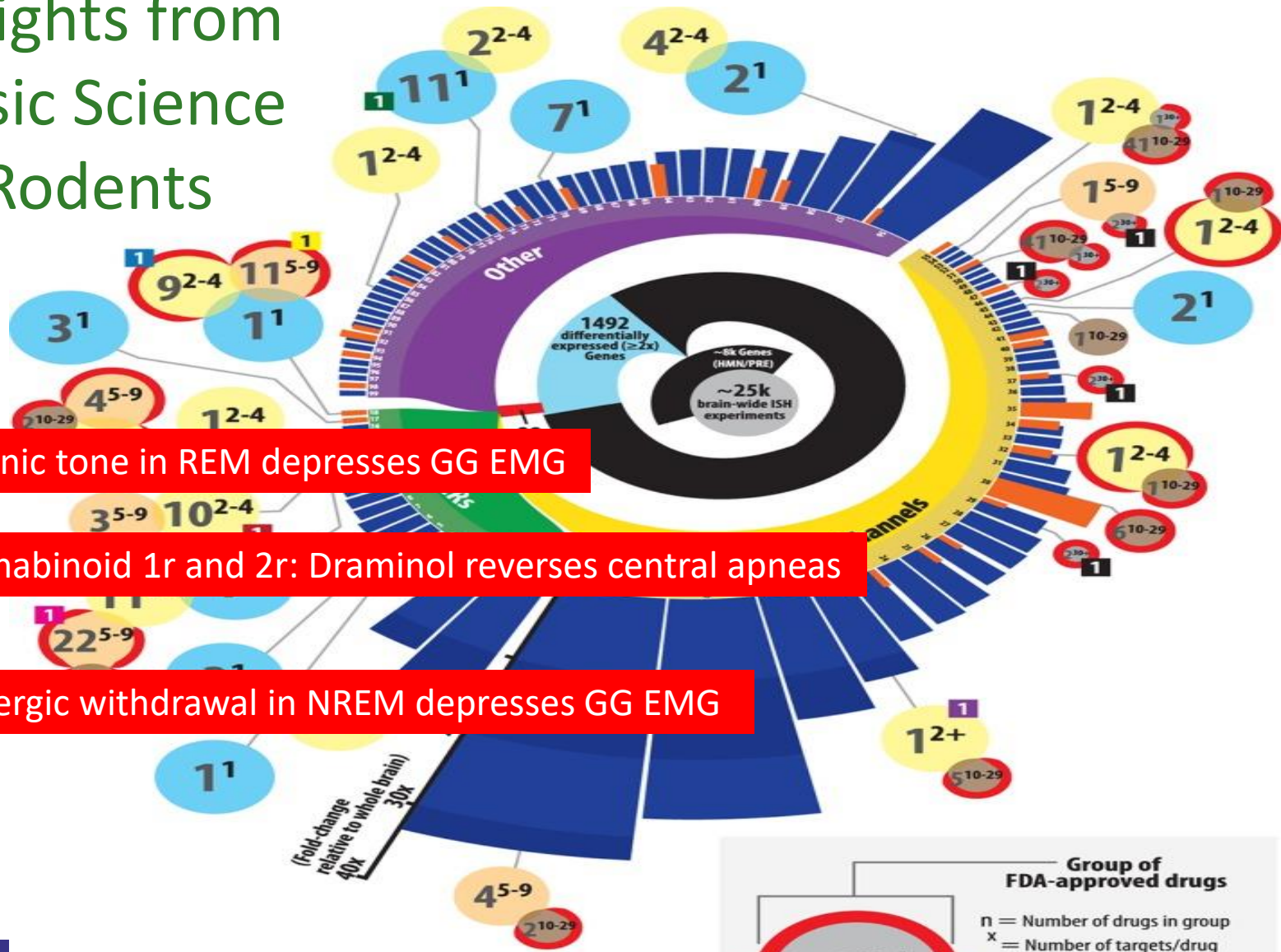
Reference: 2 slices



Druggable Pathways to Recurrent OSA



Insights from Basic Science in Rodents

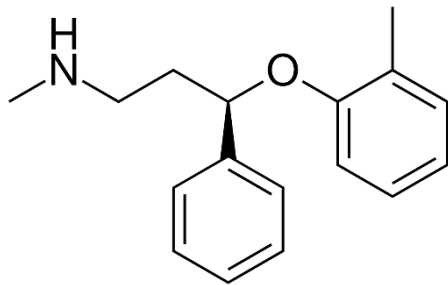


(Horner, Grace, Wellman 2017)

Activate the GG

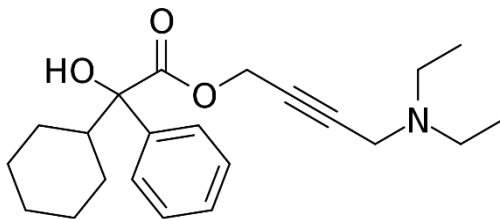
Atomoxetine (80mg) and Oxybutynin (5mg) are G-protein coupled receptors

Atomoxetine (Increase Adrenergic Tone in NREM)



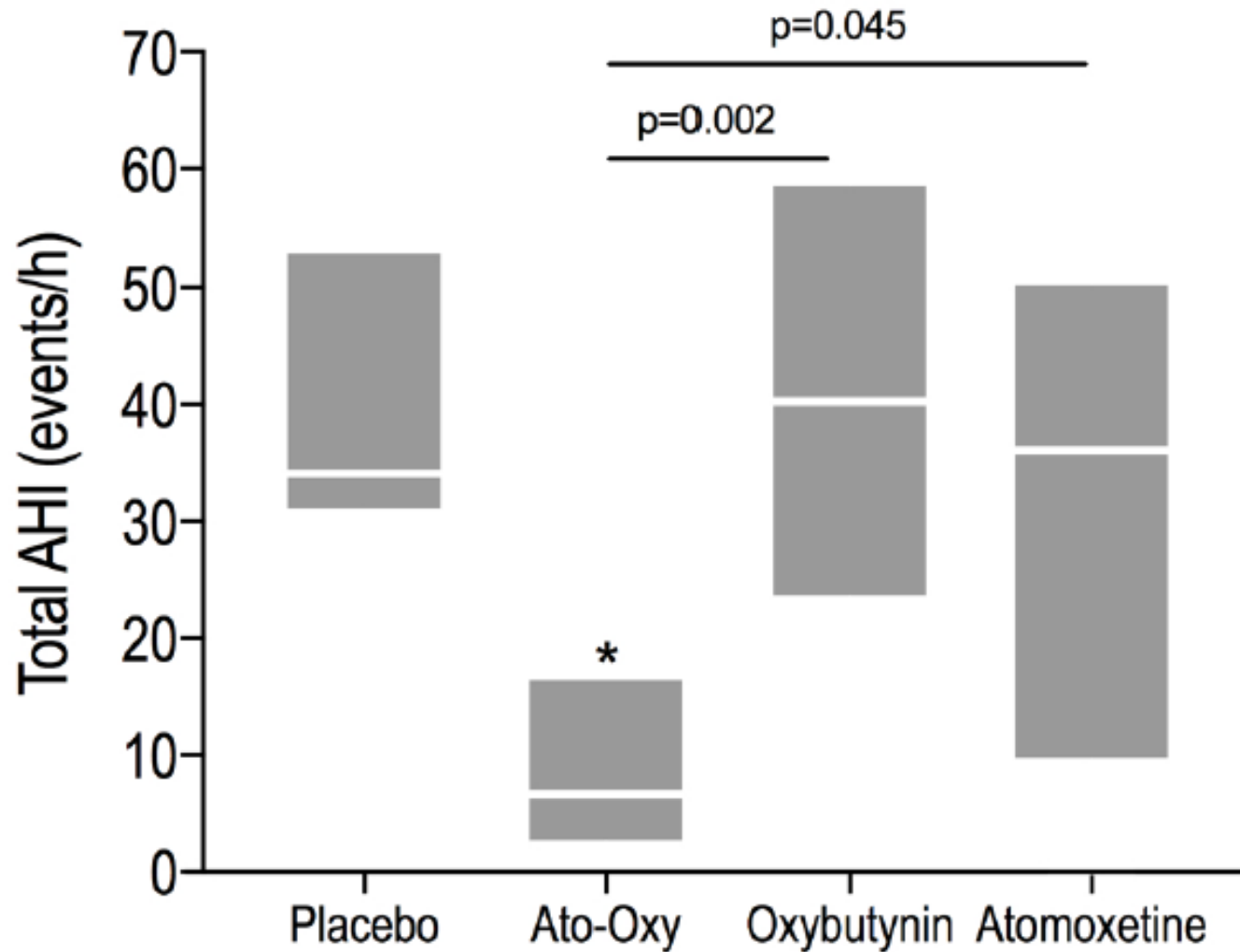
NE reuptake inhibitor used for ADHD, and off-label in 2017

Oxybutynin (Decrease Muscarinic Tone in REM)



Oxybutynin is an anticholinergic medication used in urinary and bladder difficulties, by decreasing muscle spasms of the bladder.

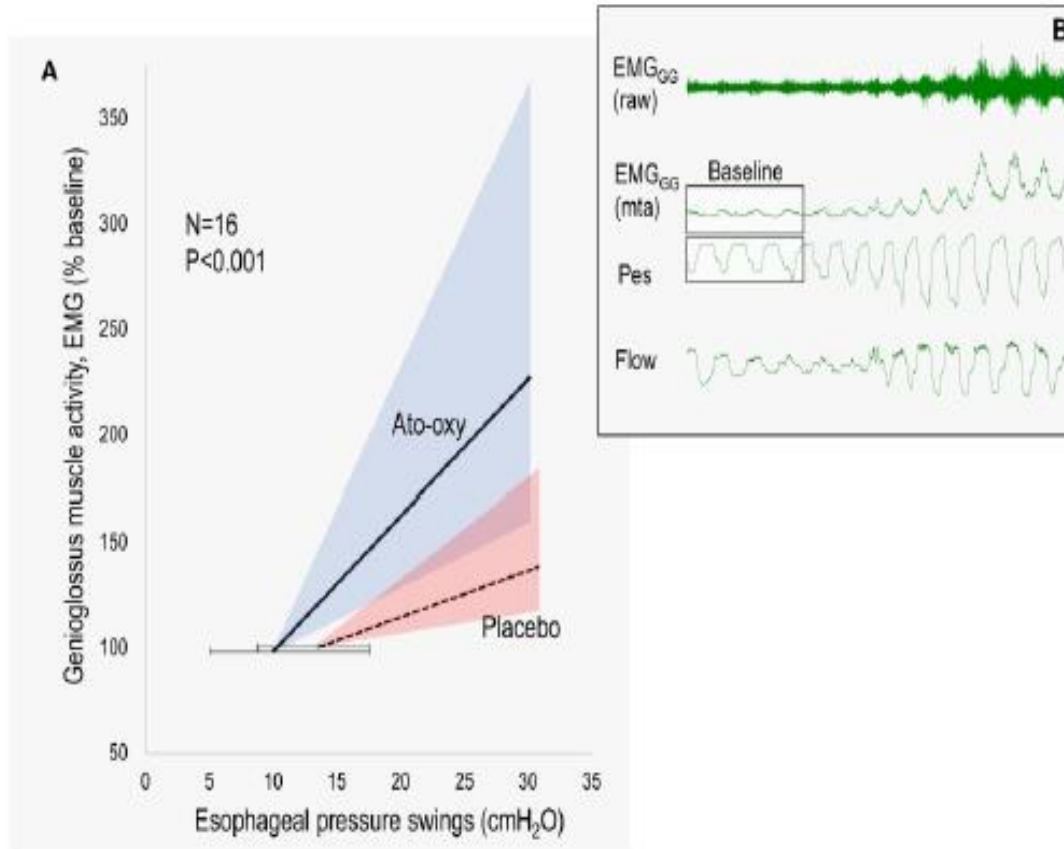
Effects of the Combination on AHI Metrics



H IS >>10 SEC REDUCTION OF >30 WITHAN AROUSAL or A DESATATURATION OF 3%

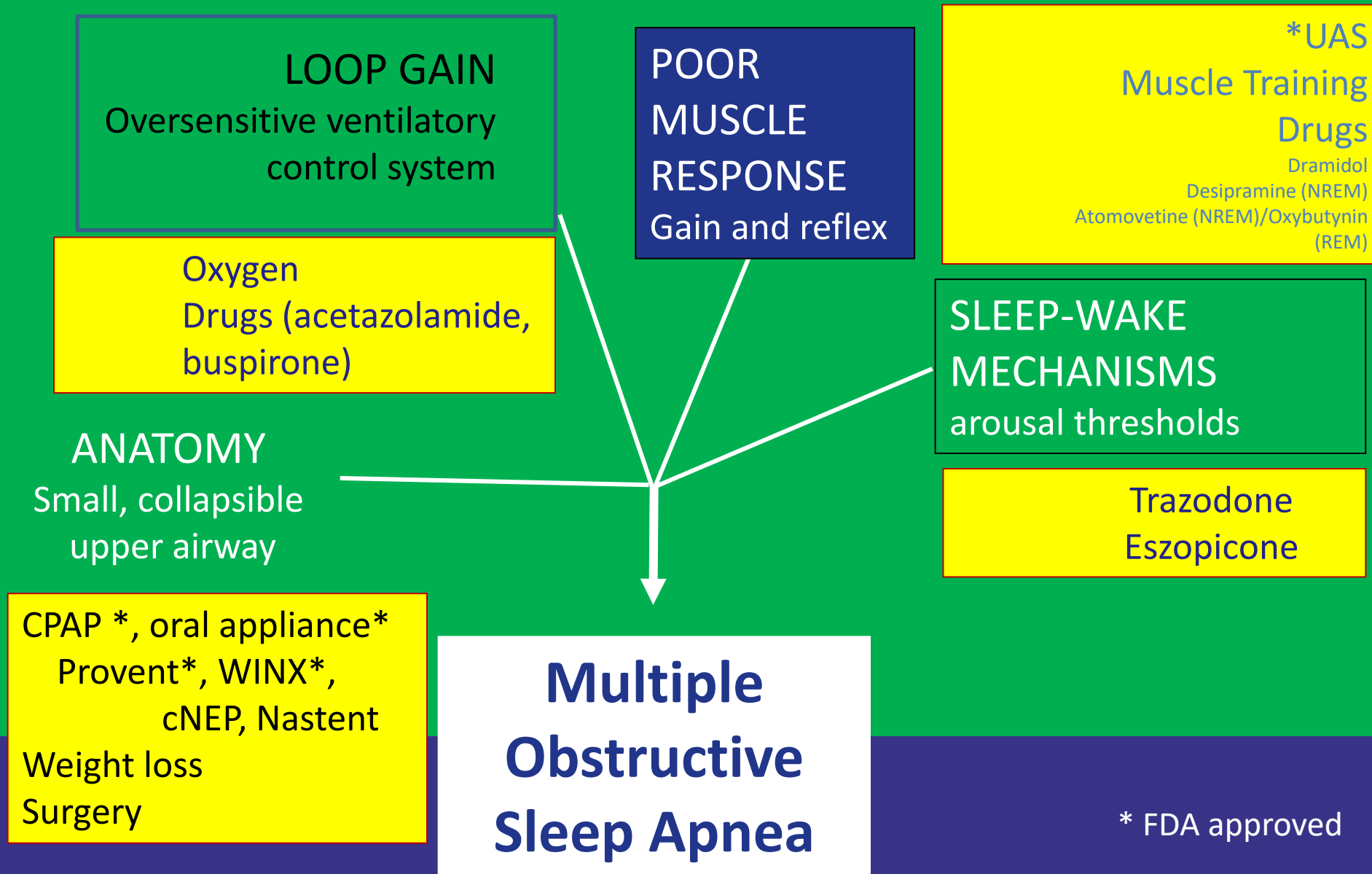
Genioglossal Measures

Indicate enhanced responsiveness



Notice that the metric is an internal standard.

Pathways to Rx. Recurrent OSA (>15/h)



Summary



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Obstructive sleep apnea hypopnea is

- state-related disorder (sleep)
- caused by an abnormal anatomy (velo- and oro-pharynx)
- a reduced muscular activation, and...
- To make a lot of apneas a high “loop gain” (sensitivity).

Current Therapy targets:

- Anatomy: CPAP, oral appliance, anatomic surgery (palatoplasty, mandibular maxillary advancement, etc.)
- Muscle activation: hypoglossal nerve stimulation
 - Aspirational: Drug therapy for activation and loop gain

Objectives



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- Compare risk factors to physiologic causes for recurrent sleep apnea
- Recount the importance of anatomy in OSA Treatment
- List other targets for therapy

