Potential Pharmacotherapies for OSA and CSA

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UPMC
LIFE CHANGING MEDICINE

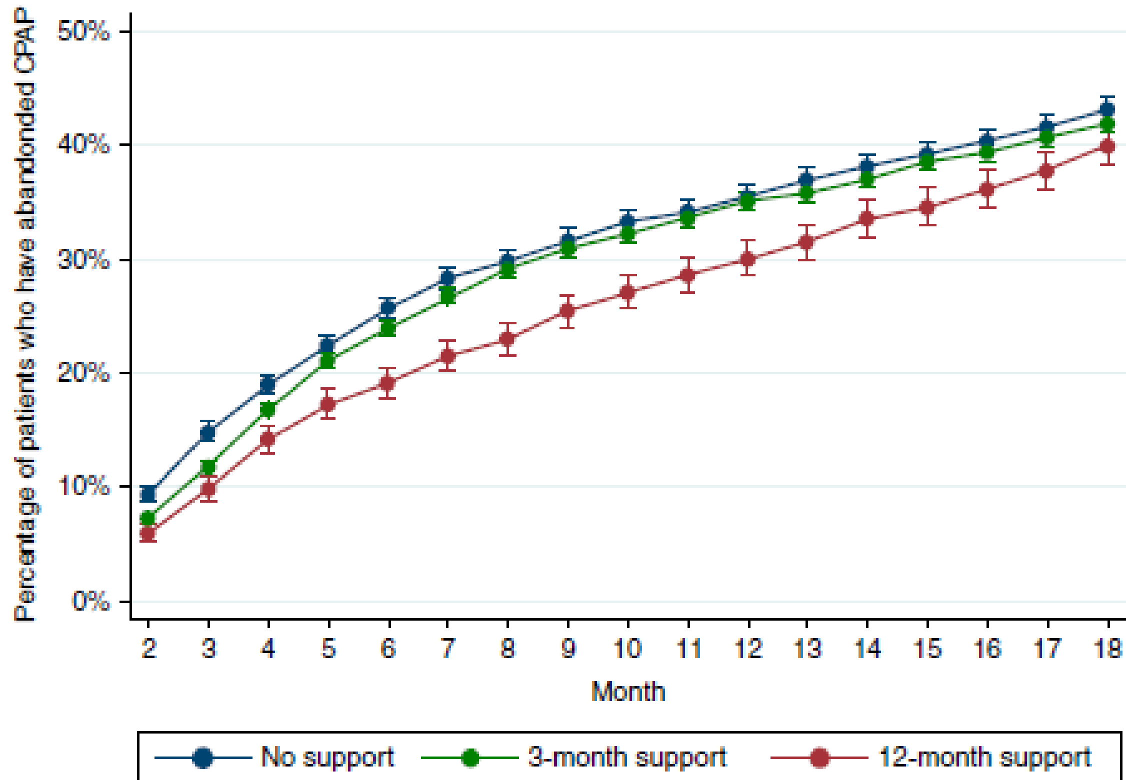
Disclosures:

I have received grant funding in the past through the University of Pittsburgh from Bayer Pharmaceuticals, Philips Respironics, Respicardia, and Sommetrics.

I have received consulting fees in the past from Bayer Pharmaceuticals, NovaResp Technologies, Philips Respironics, and Powell Mansfield.

I am currently consulting for Apnimed Inc.

Why is there a need for pharmacology?



PAP therapy is not well tolerated long-term.

Patel SR et al. Annals ATS 2022; 19(12):2070-6.

Pharmacologic approaches for OSA

1. Treat risk factors for developing OSA
   - Obesity
   - Nasal congestion
   - Menopause

2. Treat OSA directly and prevent consequences

3. Treat OSA symptoms
   - Excessive daytime sleepiness
   - Nocturnal awakenings

4. Treat/prevent long term OSA consequences
   - Lower blood pressure
   - Decrease cardiovascular risk
   - Preserve cognitive function

Challenges for OSA pharmacotherapy

1. No validated marker to define success.

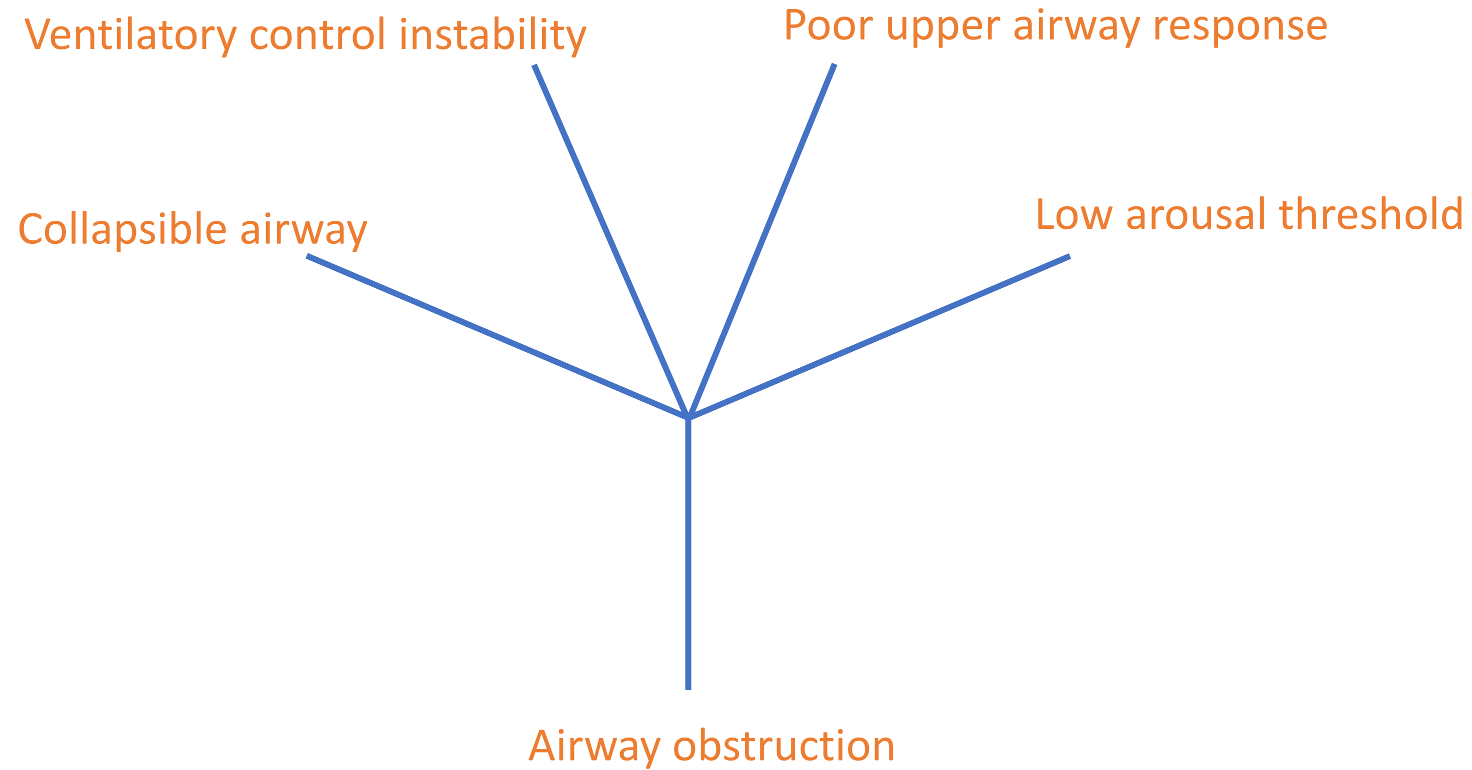
"Insufficient evidence exists to assess the validity of change in AHI as a surrogate or intermediate measure for long-term health outcomes."

2. Most candidate drugs act on CNS and so may have off-label CNS effects.

3. Potential long-term benefits of treating OSA unproven.

AHRQ. CPAP Technology Assessment Program. Dec 1, 2022.

OSA risk factors



Pharmacologic approaches

- Decrease collapsibility
  - Incretins (GLP1/GIP agonists)
  - SGLT2 inhibitors
- Decrease loop gain
  - Carbonic anhydrase inhibitors
- Increase UA dilator tone
  - Adrenergic agonist/Muscarinic inhibitor
  - SNRI
  - Dronabinol
  - TASK1/3 channel inhibitors
- Increase arousal threshold
  - BZRAs
  - Trazodone

Decreasing collapsibility

- Weight loss
- Mandibular advancement
- Diuresis

Incretin therapy

- GLP1 and GIP are secreted by gut in response to food and increase insulin sensitivity, reduce gut motility, reduce appetite and increase satiety.
- Agonists were developed as T2DM therapies but found to produce substantial weight loss.

Incretin	Year	Duration	Weight Loss w/ Drug	Weight Loss w/Placebo	% Losing 10% w/Drug	% Losng 10% w/Placebo
Liraglutide 3.0 mg qd	2015	56 wks	19 lbs	6 lbs	33%	11%
Semaglutide 2.4 mg qwk	2021	68 wks	34 kg	6 lbs	69%	12%
Tirzepatide 15 mg qwk	2022	72 wks	52 kg	5 lbs	90%	13%
Retatrutide 12 mg qwk	2023	48 wks	58 kg	4 lbs	93%	9%

Pi-Sunyer X et al. NEJM 2015; Wilding JPH et al. NEJM 2021; Jastreboff AM et al NEJM 2022; Jastreboff AM et al. NEJM 2023.

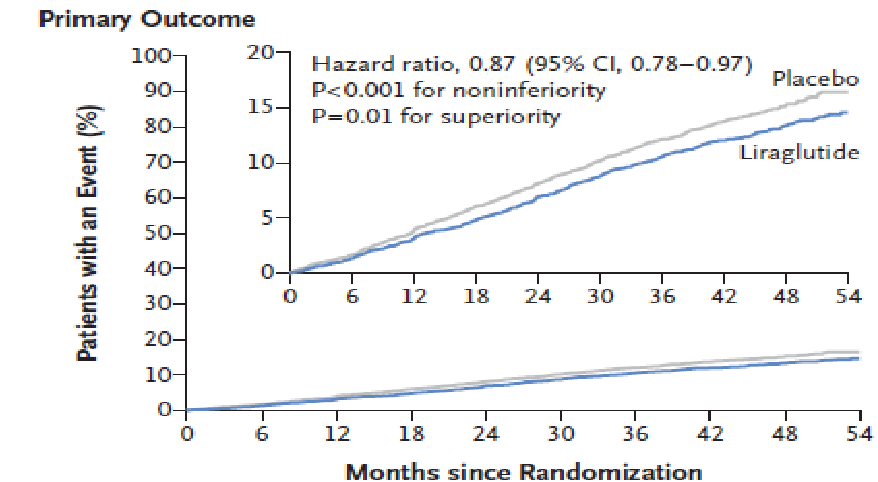
Long term effects of incretin therapies

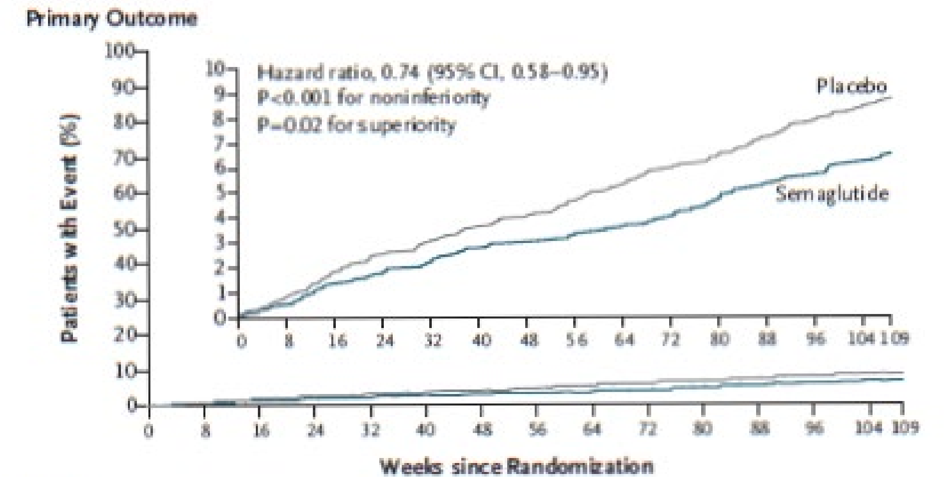
Side effects:

- Most common: nausea, diarrhea – are dose related and improve with time
- More serious: gall bladder disease, pancreatitis

Benefits:

- Improve glucose control
- Lower cardiovascular risk





Marso SP et al. NEJM 2016; Marso SP et al. NEJM 2016.

Incretins and OSA

- 359 pts with obesity and moderate-severe OSA who were CPAP intolerant randomized 1:1 to liraglutide or placebo for 32 weeks across 40 sites in US and Canada.

	Liraglutide Baseline	Placebo Baseline	Liraglutide Change	Placebo Change	P-value
BMI	38.9	39.4	-2.2	-0.6	<0.0001
AHI	49.0	49.3	-12.2	-6.1	0.015
ESS	9.2	10.3	-2.5	-2.3	0.15
FOSQ	17.1	17.2	1.3	1.1	0.16

Additional pending studies:

- ROMANCE – Liraglutide and/or CPAP in OSA+T2DM (completed in 2020)
- SURMOUNT OSA – Tirzepatide in OSA (expected completion April 2024)

Blackman A et al. Int J Obes 2016; 40:1310-9.

SGLT2 inhibitors

- 36 Chinese patients with T2DM and OSA who failed metformin alone randomized to 6 months of dapaglifozin vs. glimepiride.

AHI reduction 29% vs. 5%

	Dapagliflozin Baseline	Dapagliflozin Post-tx	Glimepiride Baseline	Glimepiride Post-tx	P-value
BMI	28.2	25.9	28.0	27.0	0.004
AHI	37.5	26.7	38.1	36.1	<0.001
Min SpO2	84%	87%	84%	84%	0.02
ESS	11.8	9.0	12.5	12.1	0.004

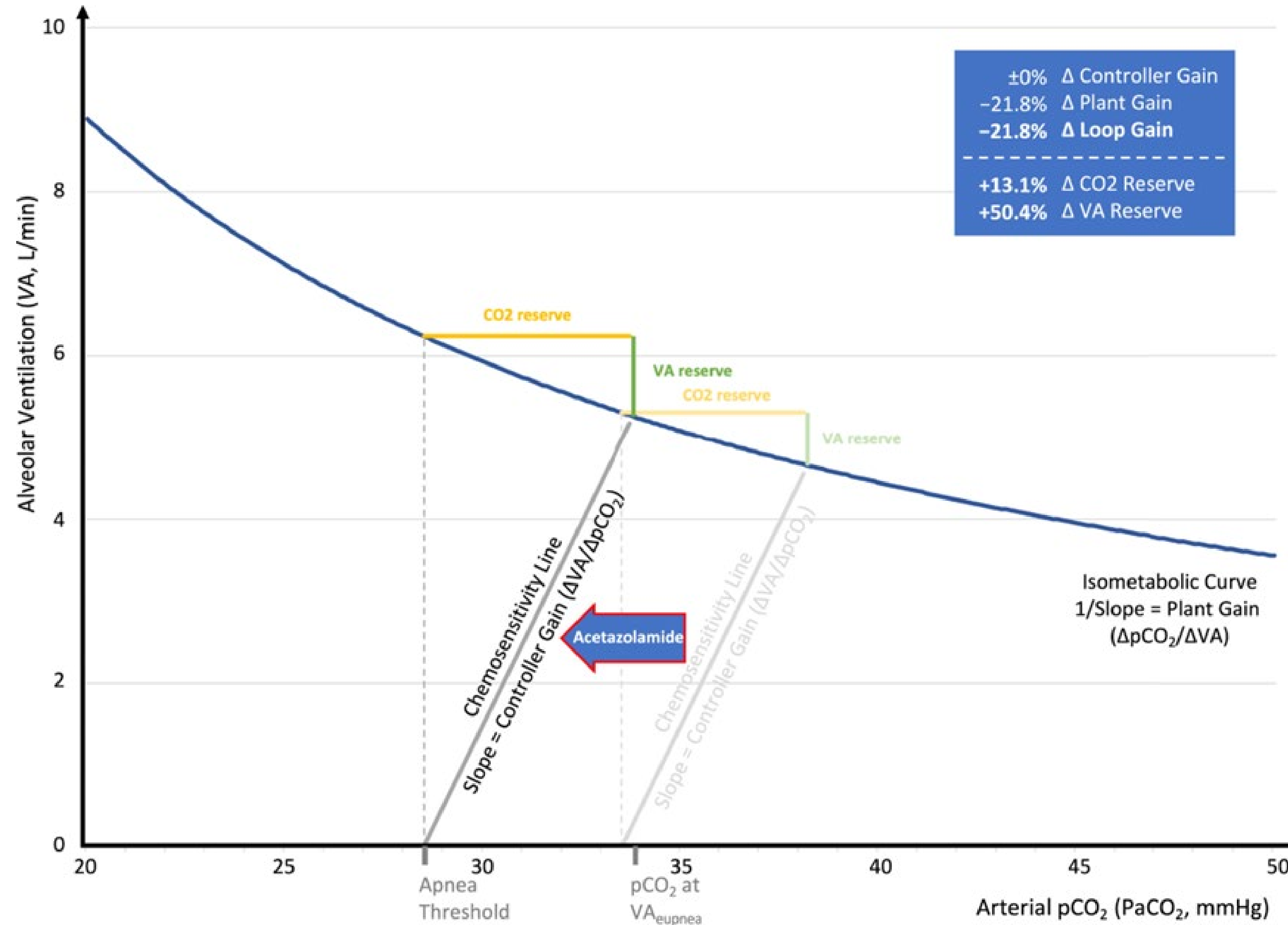
Tang Y et al. Nutr Diab 2019; 9(1):32.

Decreasing loop gain

- Carbonic anhydrase inhibitors
  - Acetazolamide
  - Sulthiame

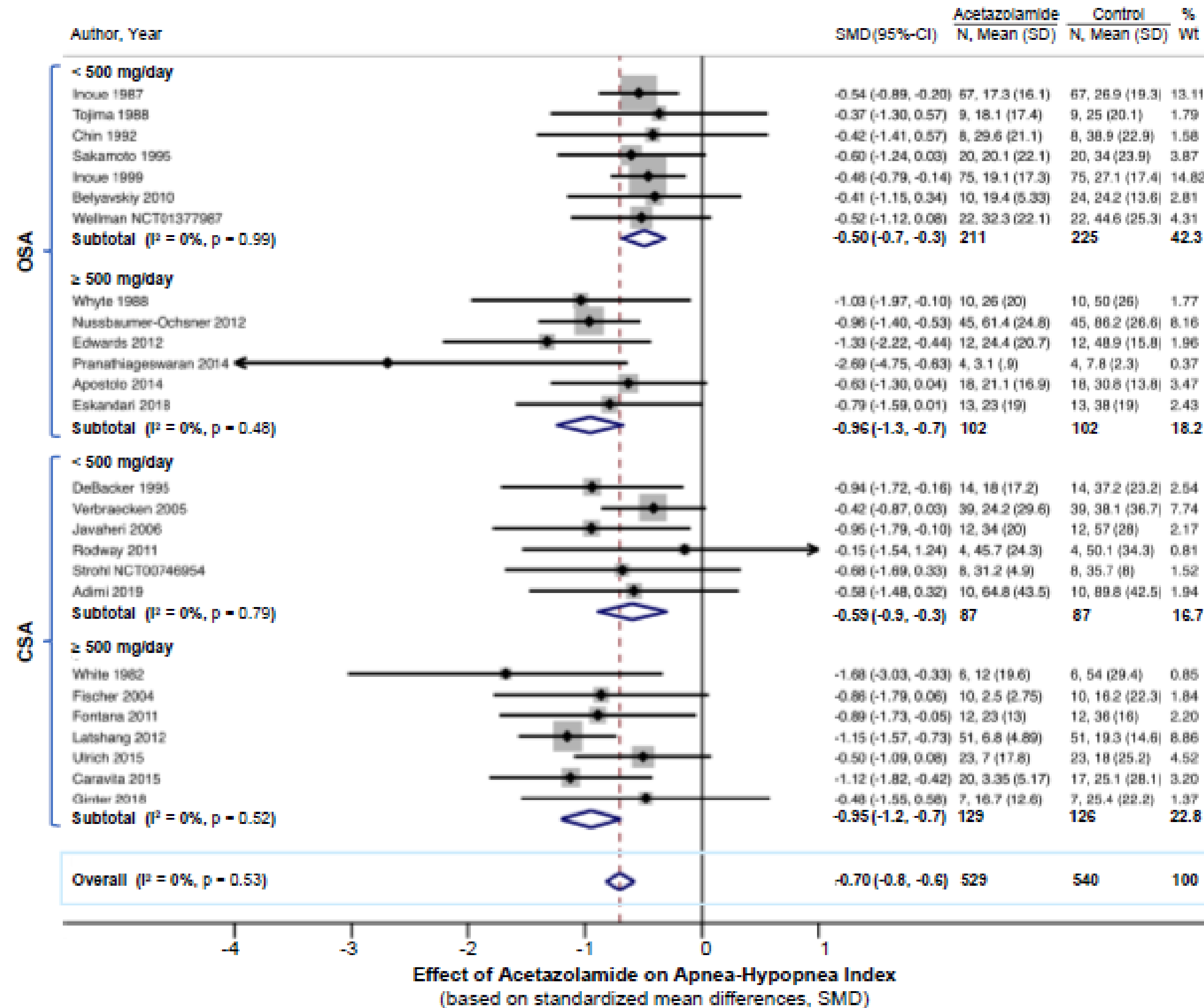
- Oxygen

Acetazolamide and ventilatory stability



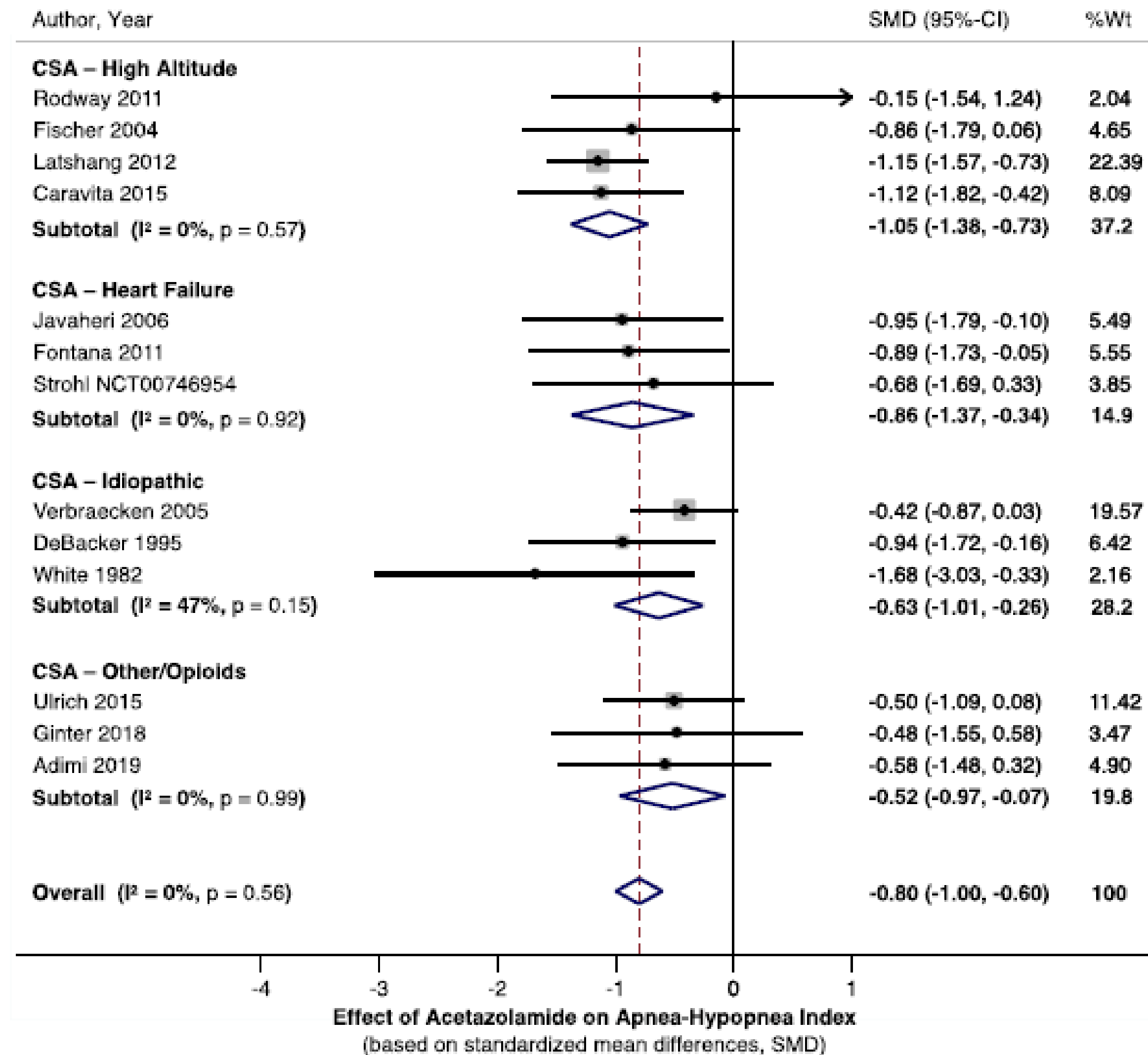
Schmickl CN et al. Physiol Rep 2021; 9(20):e15071.

Meta-analysis of acetazolamide



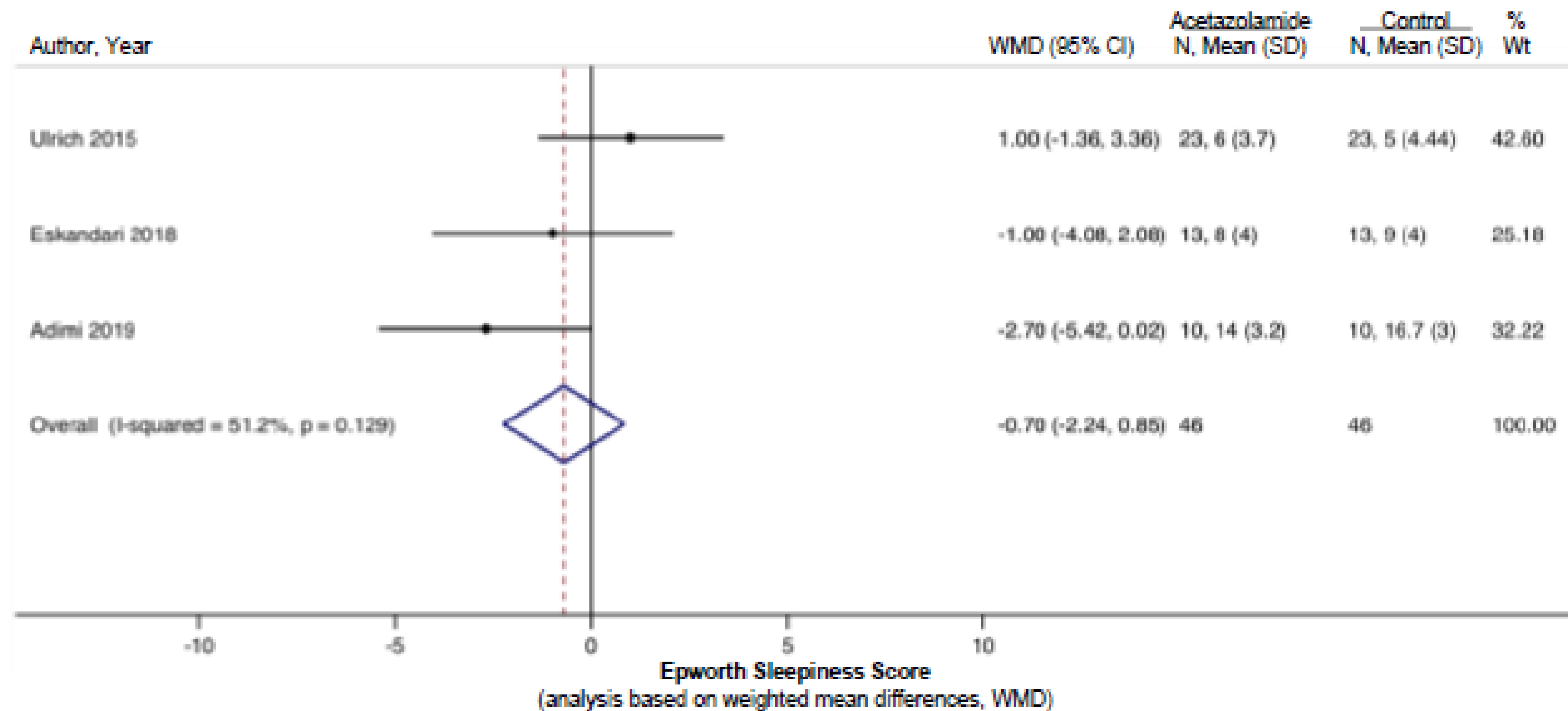
Schmickl CN et al. Chest 2020; 158(6):2632-45.

Acetazolamide in CSA



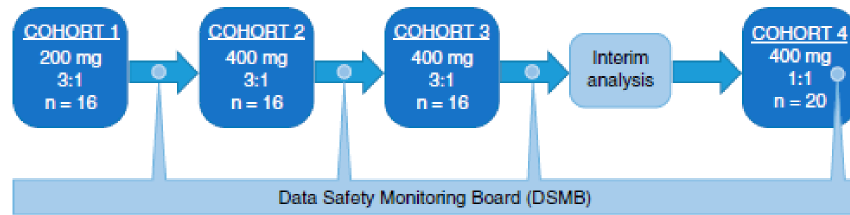
Schmickl CN et al. Chest 2020; 158(6):2632-45.

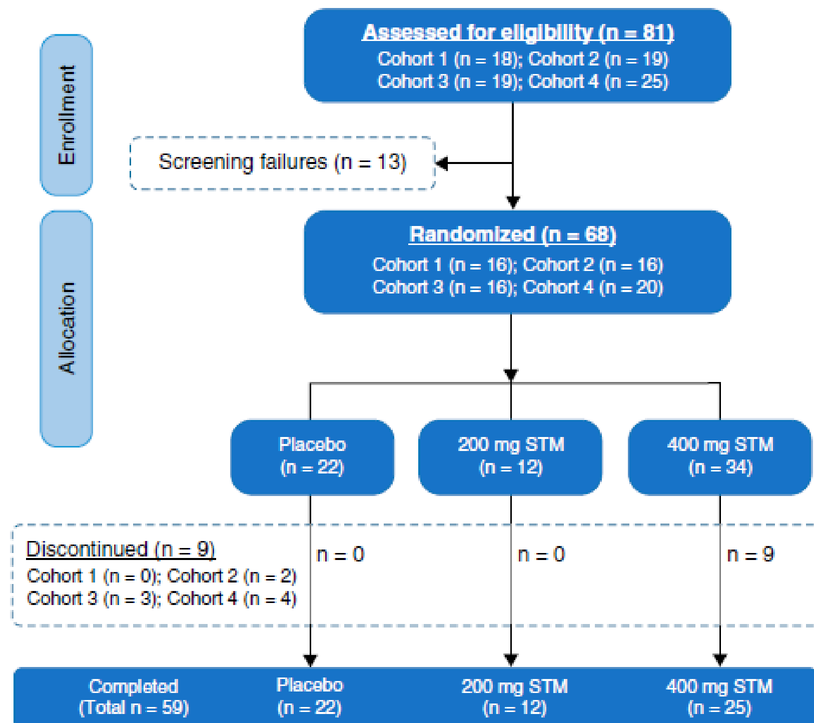
Effect on sleepiness



Schmickl CN et al. Chest 2020; 158(6):2632-45.

Sulthiame for OSA

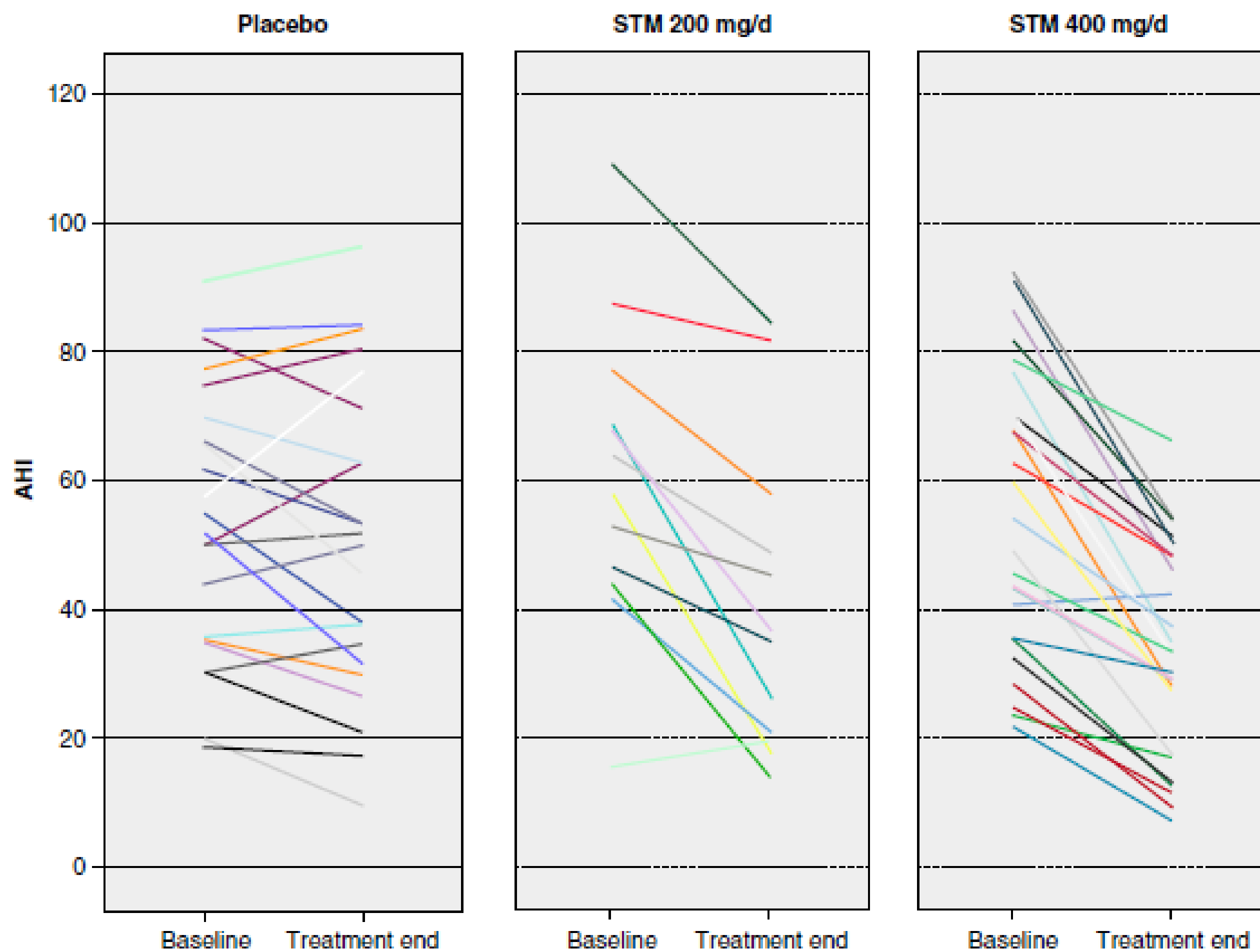




- Phase 2 RCT of sulthiame vs. placebo for 4 weeks in moderate to severe OSA who had failed CPAP.
- Dosing planned to increase from 200 mg to 1000 mg but DSMB stopped dose escalation at 400 mg.

Hedner J et al. AJRCCM 2022; 205(12):1461-9.

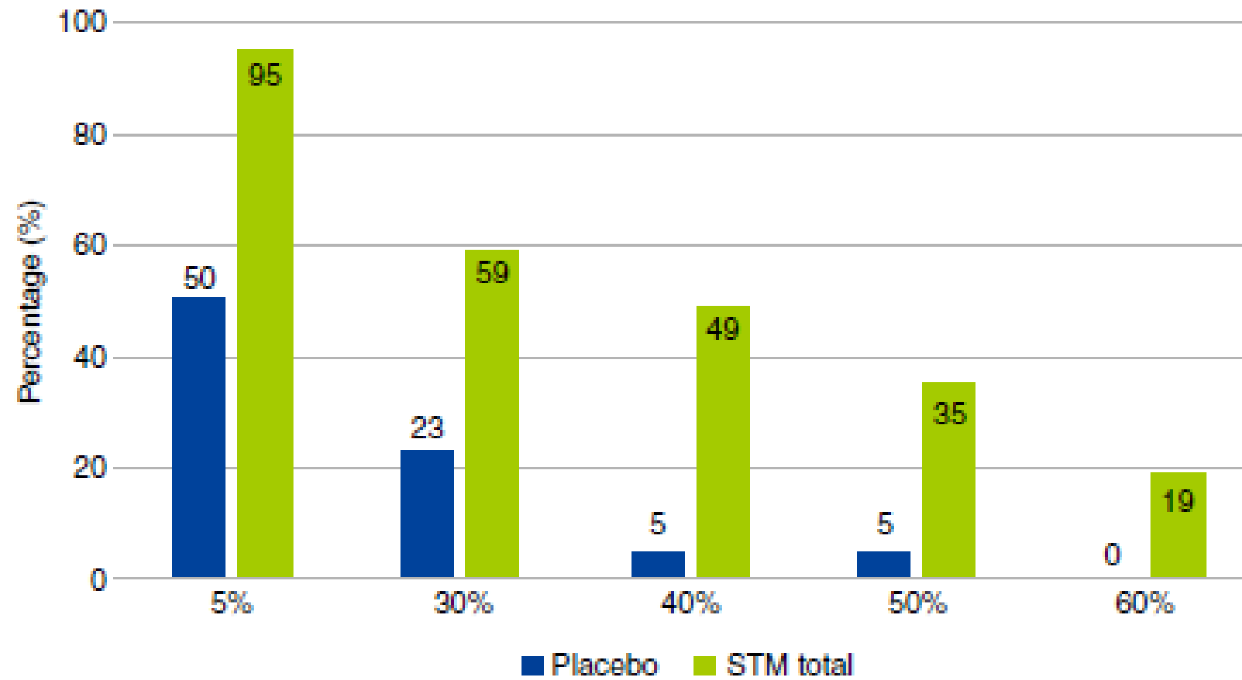
Effect of sulthiame on AHI



Mean AHI reduction:
STM 400: -39.8%
STM 200: -33.4%
Placebo: -5.4%

Hedner J et al. AJRCCM 2022; 205(12):1461-9.

Effect of sulthiame on OSA



Hedner J et al. AJRCCM 2022; 205(12):1461-9.

Effect of sulthiame on OSA symptoms

	STM 400	STM 200	Placebo	P-value (STM 400 vs. Placebo)
ESS	-0.8	-1.7	-1.3	0.73
FOSQ	0.4	1.4	0.9	0.97

Hedner J et al. AJRCCM 2022; 205(12):1461-9.

Side effects of sulthiame

	Sulthiame	Placebo
Paresthesia	76%	18%
Headache	17%	0%
Dyspnea	13%	0%
Nausea	7%	0%
Anorexia	4%	0%
Fatigue	4%	9%

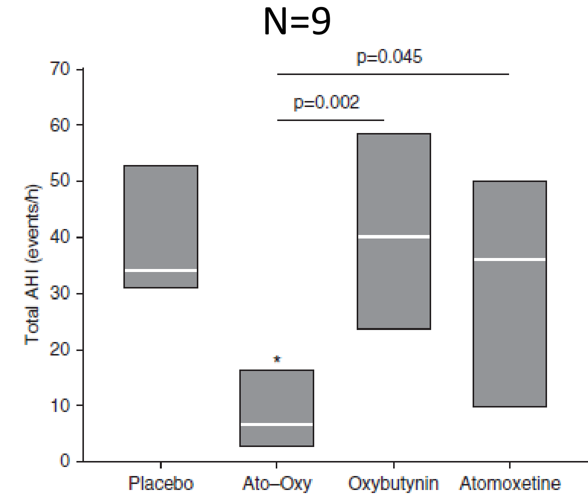
Hedner J et al. AJRCCM 2022; 205(12):1461-9.

Increasing upper airway muscle function

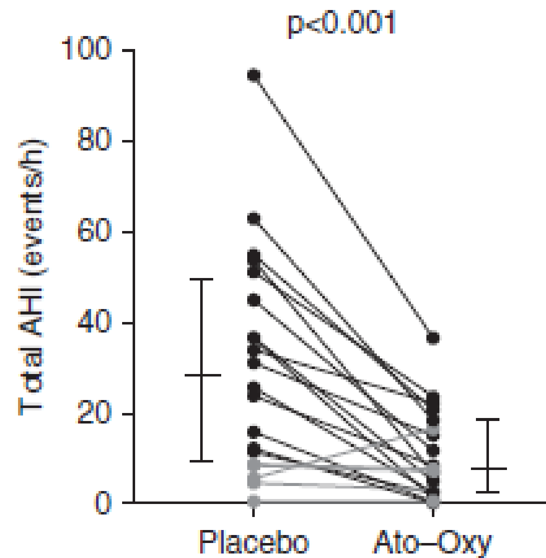
- Noradrenergic agonists
- Serotonergic agonists
- Muscarinic inhibition
- Cannabinoid agonists
- TASK 1/3 channel inhibition

Atomoxetine - Oxybutynin

- Rationale for combination drug
  - Reduced upper airway dilator muscle tone due to:
    - Decreased noradrenergic tone in NREM sleep
    - Muscarinic cholinergic inhibition in REM sleep
  - Oxybutynin counters alerting effects of atomoxetine



Median reduction in AHI 63%

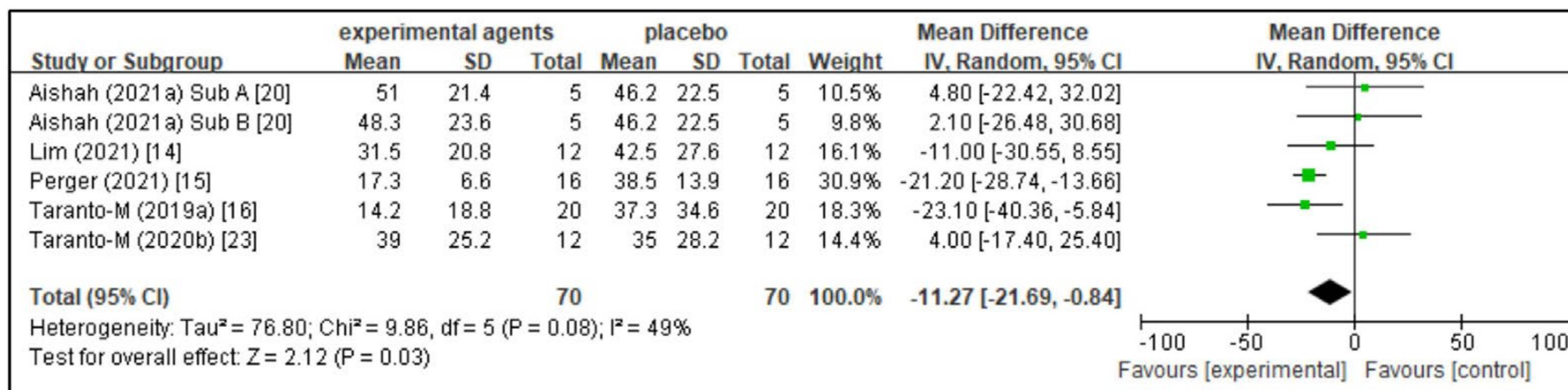


1 night cross-over trial of 80mg ato/ 5mg oxy (N=20)

Taranto-Montemurro L et al. AJRCCM 2019; 199(10):1267-76.

Adrenergic/Antimuscarinic therapy

Meta-analysis of 5 studies (N=70) of 1 night cross-over RCTs



Study or Subgroup	experimental agents Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Aishah (2021a) Sub A [20]	51	21.4	5	46.2	22.5	5	10.5%	4.80 [-22.42, 32.02]
Aishah (2021a) Sub B [20]	48.3	23.6	5	46.2	22.5	5	9.8%	2.10 [-26.48, 30.68]
Lim (2021) [14]	31.5	20.8	12	42.5	27.6	12	16.1%	-11.00 [-30.55, 8.55]
Perger (2021) [15]	17.3	6.6	16	38.5	13.9	16	30.9%	-21.20 [-28.74, -13.66]
Taranto-M (2019a) [16]	14.2	18.8	20	37.3	34.6	20	18.3%	-23.10 [-40.36, -5.84]
Taranto-M (2020b) [23]	39	25.2	12	35	28.2	12	14.4%	4.00 [-17.40, 25.40]
Total (95% CI)			**70**			**70**	**100.0%**	**-11.27 [-21.69, -0.84]**

Heterogeneity: $Tau^2 = 76.80$; $Chi^2 = 9.86$, df = 5 (P = 0.08); $I^2 = 49\%$

Test for overall effect: Z = 2.12 (P = 0.03)

Drug combinations studied:

- atomoxetine plus oxybutynin
- atomoxetine plus fesoterodine
- atomoxetine plus biperiden
- atomoxetine plus solifenacin
- reboxetine plus oxybutynin
- reboxetine plus hyoscine

Zha S et al. Sleep Med Rev 2022; 64:101649.

Adrenergic/Antimuscarinic side effects

- Urinary retention
- Dry mouth
- Insomnia
- Sexual dysfunction
- Headache
- Palpitations

Zha S et al. Sleep Med Rev 2022; 64:101649.

Mariposa – Phase II trial of atomoxetine/aroxybutynin

- 211 patients with AHI_4 10-45 randomized to 4 weeks therapy in one of four arms:
  - AD109 75 mg atomoxetine/5 mg aroxybutynin
  - AD109 75 mg atomoxetine/2.5 mg aroxybutynin
  - 75 mg atomoxetine
  - placebo
- Atomoxetine alone decreased TST.
- PROMIS Fatigue improved with AD109 75/2.5.
- Most common side effects:

  Dry mouth, insomnia, nausea

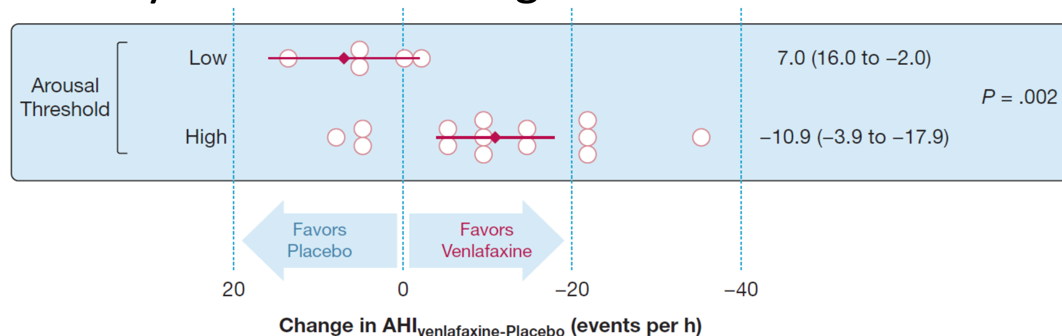
	Baseline AHI	Final AHI	% Change	P-value vs. placebo
AD109 75/5	19.4	9.5	-51%	<0.0001
AD109 75/2.5	20.5	10.8	-47%	<0.0001
Atomox 75	19.8	11.8	-40%	<0.01
Placebo	20.1	16.3	-19%	

Schweitzer P et al. ATS 2023 presentation.

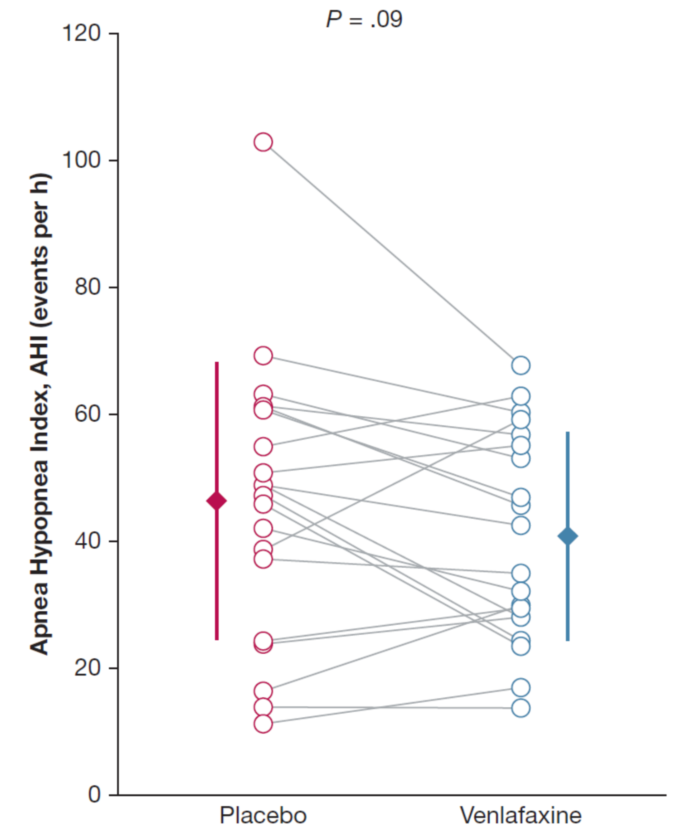
Venlafaxine

- Increase noradrenergic and serotonergic tone to UA dilator muscles.
- Cross-over RCT of 1 night venlafaxine 50 mg in 20 patients with OSA.
- TST, Sleep Efficiency, N1 time all significantly worse with venlafaxine.
- No significant improvement in AHI.

- Post-hoc analysis suggests possible greater efficacy in those with high arousal threshold.



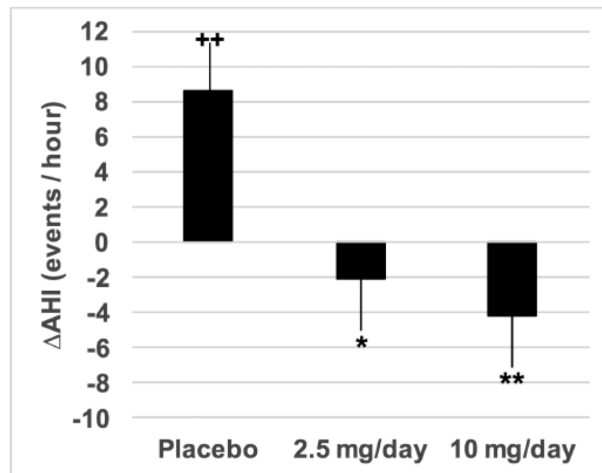
Mean AHI change -12% (-6/hr)



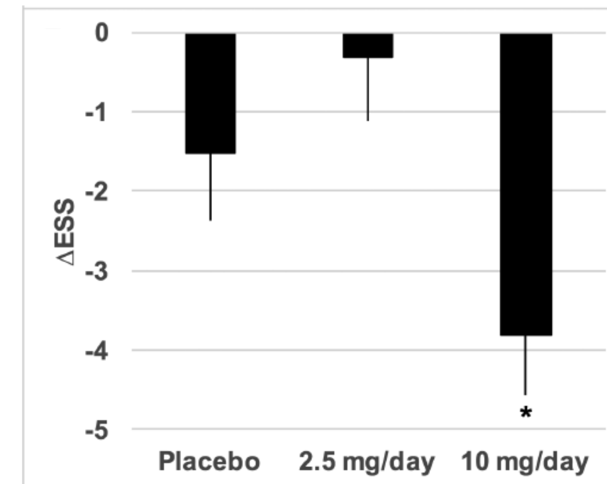
Schmickl CN et al. Chest 2020; 158(2):765-75.

Dronabinol

- CB_1 and CB_2 receptor agonist that might lower loop gain and increase UA muscle tone.
- 73 moderate to severe OSA patients randomized to placebo, dronabinol 2.5 mg or dronabinol 10 mg at bedtime for 6 weeks.
- 56 patients (77%) completed the study.
- Compared to placebo, AHI improved by 11 and 13 events/hr in dronabinol arms.



Difference in AHI across three arms (p=0.05)



ESS 2.3 pts lower with dronabinol 10 mg vs. placebo (p=0.05)

Carley DW et al. Sleep 2018; 41(1):zsx184.

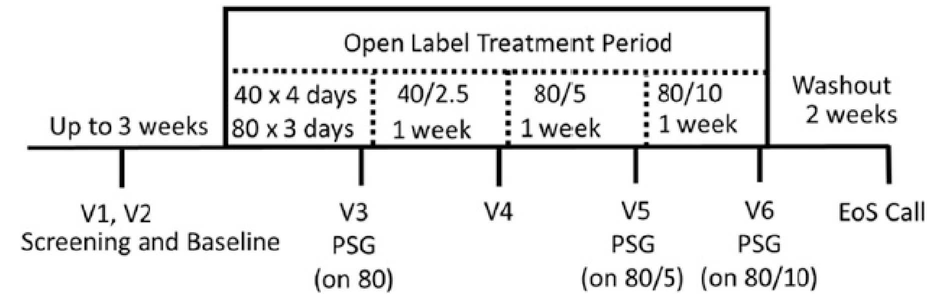
Dronabinol side effects

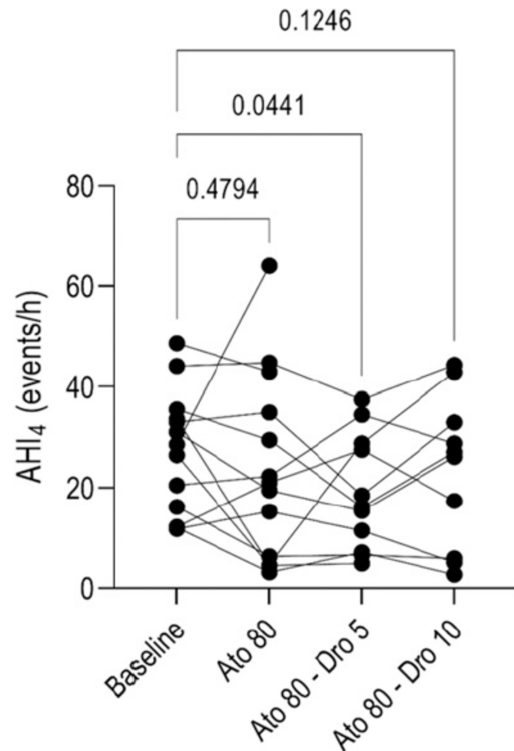
- Sleepiness
- Headache
- Nausea/vomiting
- Dizziness/lightheadedness

Carley DW et al. Sleep 2018; 41(1):zsx184.

Atomoxetine - Dronabinol

- 15 pts with AHI 10-50 enrolled in open label dose escalation.
- No changes in loop gain or arousal threshold noted.
- Collapsibility and muscle activation did improve.





PROMIS scale	Baseline	Ato 80	Ato 80 Dro 5	Ato 80 Dro 10
Sleep disturbance	12 (3)	13 (2)	11 (2)	11 (1)
Sleep-related impairment	13 (9)	10 (9)	8 (8)*	8 (7)*
Fatigue	14 (9)	11 (12)	8 (4)*	7 (7)*

Messineo L et al. JCSM 2023; 19(7):1183-90.

Acetazolamide - Dronabinol

- 11 pts with moderate to severe OSA enrolled in randomized cross-over trial of placebo vs. three doses of drug – each for 1 week – with 1 week washout.
- Significant reductions in AHI with all three doses of acetazolamide - dronabinol.
- No improvements in sleepiness or mood.

	Placebo	Low Dose	Medium Dose	High Dose
Change in AHI	-2.8 ± 21.0	-19.7 ± 27.1	-17.5 ± 23.2	-16.4 ± 23.8

- Phase 2/3 trial planned of dronabinol vs. acetazolamide vs. acetazolamide - dronabinol vs. placebo.

Walsh J et al. SLEEP Adv 2022; 3(S1):A11.

TASK 1/3 channel inhibition

- TASK1/3 channels are inwardly rectifying and voltage-gated potassium channels.
- Blockade at the hypoglossal motor pool results in increased tonic and phasic pharyngeal muscle activity.

- 34 patients with AHI 15-50 and prior CPAP use randomized to 100 ug BAY2253651 or placebo.

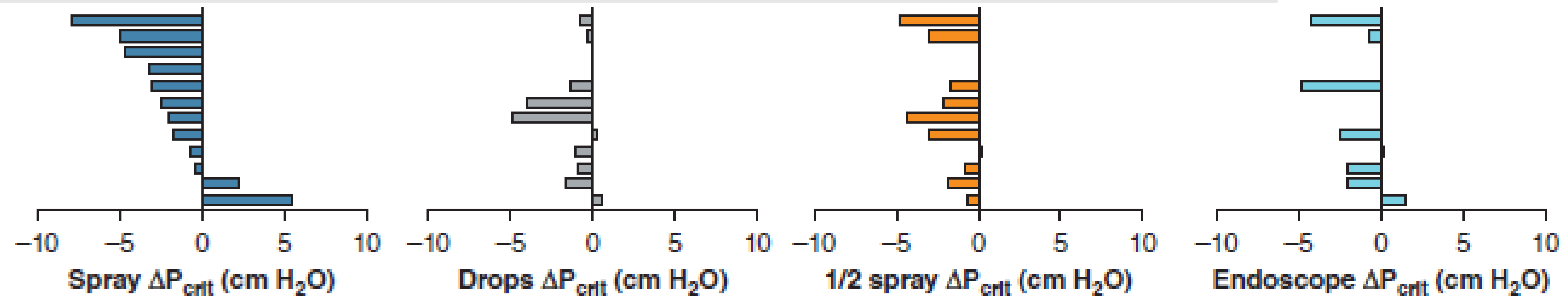
	AHI Night 1	AHI Night 2	AHI Change
BAY2253651	30.5	32.9	2.4
Placebo	27.8	29.8	2.0

- AHI improved by 50% in 6.3% of BAY2253651 vs. 6.7% of placebo.
- 9 patients followed for 5 nights with no improvement in ODI.
- Study terminated early due to futility.

Gaisl T et al. ERJ 2021; 58(5):2101937.

BAY2586116

- BAY2586116 is another TASK1/3 channel inhibitor that can be topically administered.



- Subsequent Phase 2 trial completed in November 2021 without any reporting of results.

Osman AM et al. Chest 2023; 163(4):953-65.

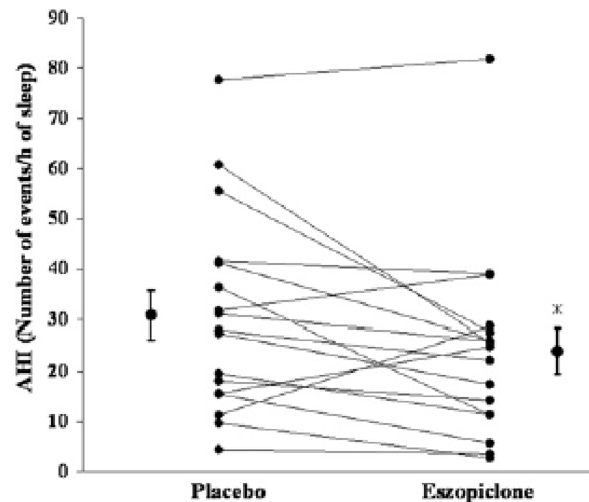
Increase arousal threshold

- Benzodiazepine receptor agonists
- Trazodone
- CBTi

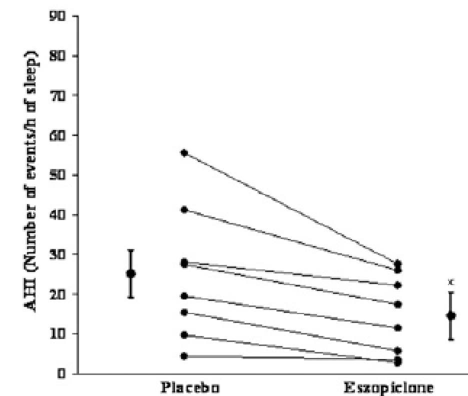
Increasing arousal threshold

- Single night cross-over RCT of eszopiclone 3 mg in 17 untreated OSA patients.
- Arousal threshold assessed by mean P_{epi} prior to arousal over 20 respiratory events in N2 sleep.

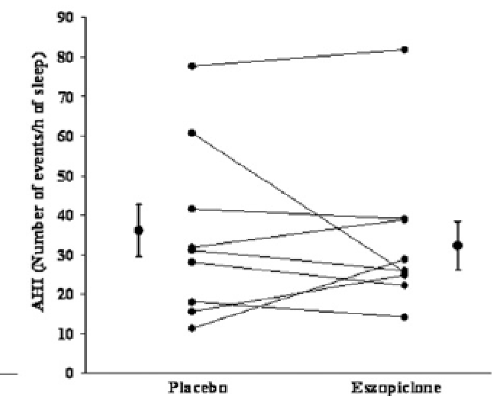
Mean 23% reduction in AHI (7/hr)



Low N2 ArTh: 43% reduction (N=8; p<0.05)



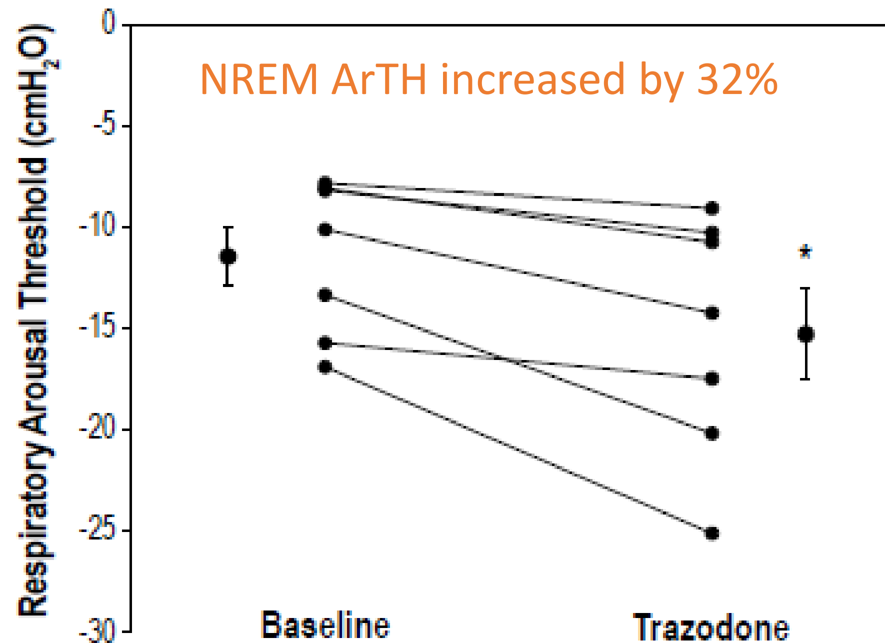
High N2 ArTh: (N=9; p=0.52)



Eckert DJ et al. Clin Sci 2011; 120(12):505-14.

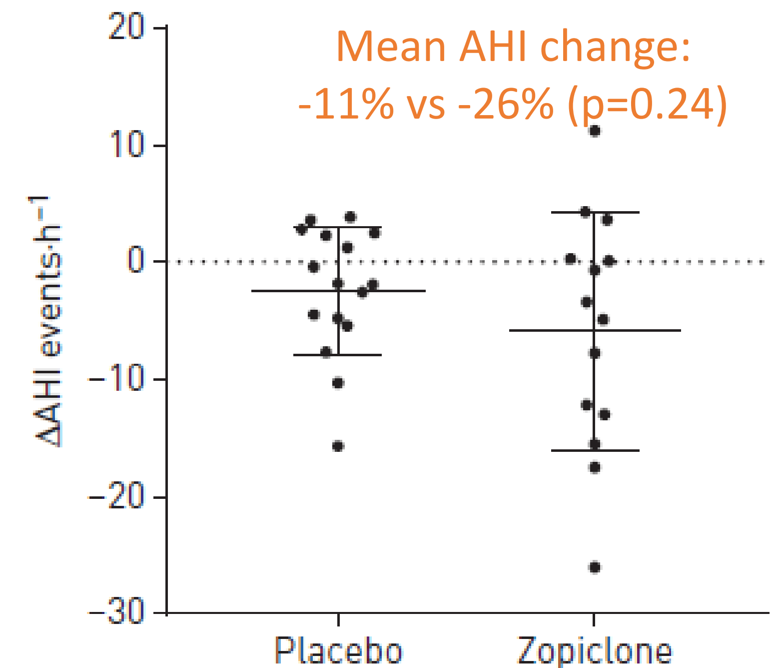
Effect of increasing arousal threshold

7 OSA patients with low arousal threshold treated with 1 night of trazodone 100mg



Mean AHI changed by 0%
(39 vs. 39)

69 OSA patients screened and 30 with low-mod arousal threshold randomized to 30 days of zopiclone 7.5 mg vs. placebo.



Eckert DJ et al. Sleep 2014; 37(4):811-9;
Carter SG et al. ERJ 2018; 52(1):1800149.

Where are we right now?

- There is growing interest in developing novel pharmaceuticals for treating OSA.
- Larger studies with longer follow-up and assessment of downstream effects including symptoms and cardiovascular risk are sorely needed.
- Such trials are underway or beginning soon for sulthiame, ertugliflozin, and combination acetazolamide/dronabinol.
- A patent was recently filed for lipid formulation of dronabinol for OSA.
- Industry-sponsored Phase 3 trials are underway for tirzepatide and atomoxetine/aroxybutynin.

SURMOUNT-OSA

- 52-week trial of patients with moderate to severe OSA and obesity.
- 63 sites across 9 countries and 5 continents.
- 469 patients recruited and randomized in 1:1 fashion to tirzepatide vs. placebo.
- Aim for 50% of patients otherwise untreated and 50% on CPAP.
- All patients receive lifestyle weight loss intervention.
- Outcomes include AHI, weight loss, FOSQ and ESS.
- Study began on 6/21/2022 and completion estimated on 3/29/2024.

Malhotra A et al. Sleep 2023; 46(S1):A249-50.

LunAIRo

- 52-week trial of patients with OSA and fatigue with BMI<40-42 who refuse/failed CPAP to receive atomoxetine/aroxybutynin.
- Plan to recruit 640 patients and randomized in 1:1 fashion to drug vs. placebo.
- Outcomes include AHI and PROMIS Fatigue score.
- Study began 8/2023 and completion estimated in 6/2025.
- SynAIRgy to begin late 2023 as an independent, similarly designed trial with 6-month follow-up.

How will pharmaceuticals impact clinical practice?

- Most novel OSA devices have set desired price points based on CMS coverage of CPAP.

- Pharmaceutical companies have a much higher price expectation that may lead to increased cost of caring for OSA.

- Recycling of old drugs – e.g., atomoxetine/aroxybutynin – may limit ability to raise prices due to off-label use of generic equivalents (e.g. Silenor)

How will pharmaceuticals impact clinical practice?

- Most drugs under patent will be expensive and so access will be limited through prior authorization.
- CPAP failure will likely be a requirement for access to medications.
- Clear documentation of symptoms will likely be a requirement as well.
- The relatively high cost of pharmaceuticals may lead to improved coverage of oral appliances or positional therapy as additional treatments that need to be failed before pharmaceutical coverage.

Can I prescribe any drugs now?

<u>On-label indications:</u>

- In patients who have co-morbid obesity, diabetes, renal disease, heart disease:

- Incretins – semaglutide (Ozempic, Rybelsus, Wegovy), tirzepatide (Mounjaro)

- SGLT2 inhibitors – dapagliflozin (Farxiga), empaglifozin (Jardiance), ertugliflozin (Steglatro), bexagliflozin (Brenzavvy), canagliflozin (Invokana).

Can I prescribe any drugs now?

Off-label indications:

- Acetazolamide
- Atomoxetine plus oxybutynin
- Dronabinol

All of these drugs have substantial side effects and have not been studied long term in sleep apnea, so would be very cautious in prescribing before long term trials are completed.

Incretin therapy in sleep practices

- If tirzepatide (or other incretins) obtain FDA approval for OSA, who will prescribe?

SCENARIO 1

- Easy access to medications:

PCPs will prescribe as first line and stop referring patients to sleep medicine.

SCENARIO 2

- Limited access to medications:

Sleep medicine must prescribe in order to adequately document steps necessary for prior authorization.

Will get many patients not interested in OSA but just wanting the diagnosis to get drug for weight loss.

Requirements for prescribing tirzepatide

- Nursing staff to teach patients how to do subcutaneous injections.
- Ability to manage injection complications.
- Comfort with tracking GI side effects and adjusting dose over time.

Long term effects of OSA pharmacotherapy

If there are multiple drug options for OSA treatment:

- PCPs will not have the expertise to counsel patients on the best drug to use for a particular patient.
- Sleep clinicians will need to develop skills to help individualize the best treatment option (including combination therapy) for each patient based on:
  - Underlying physiology
  - Symptom complex
  - Side effect profile

Conclusions

- There is a huge unmet need to treat OSA and CSA with medications.
- Industry is investing lots of money in this area for the first time.
- Preliminary findings of AHI reduction need to be followed up with demonstration of improvements in symptoms and long-term safety.
- There will likely be FDA-approved medications in the next 2 years and sleep specialists will need to grow comfortable managing patients on these drugs.
- There are also going to be increasing number of patients on medications aimed at treating symptoms alone (e.g., orexin agonists).