

**A YEAR IN REVIEW**  
**ADULT PHARMACOLOGIC THERAPY FOR  
OBSTRUCTIVE SLEEP APNEA**

Serene Ozeir, DO  
Sleep Medicine Fellow  
Henry Ford Health

## CONFLICT OF INTEREST DISCLOSURES FOR SPEAKERS

Serene Ozeir, DO has no relevant financial relationships with ineligible companies to disclose.

# LEARNING OBJECTIVES

- Review the pathological causes of obstructive sleep apnea
- Discuss the impact of medication management on obstructive sleep apnea
- Explore new therapies under investigation for treating obstructive sleep apnea

# OBSTRUCTIVE SLEEP APNEA TREATMENTS

Behavioral measures

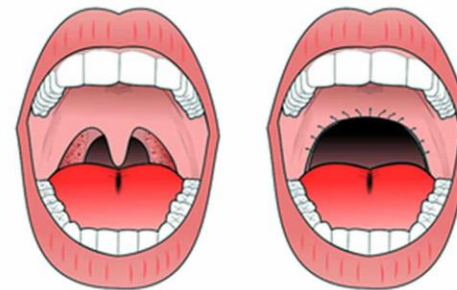
Myofascial exercises

Oral appliances

Surgeries

Positive Airway Pressure

Hypoglossal nerve stimulators



# PHARMACOLOGIC THERAPY



**Target Upper Anatomy**



**Muscle Responsiveness**



**Arousal Threshold**



**Reduce Loop Gain**

# CLINICS

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UNIVERSIDADE DE SÃO PAULO - SÃO PAULO, BRAZIL

# CLINICS

journal homepage: <https://www.journals.elsevier.com/clinics>



## Review articles

### Pharmacological treatment for obstructive sleep apnea: A systematic review and meta-analysis



Maria Luísa Nobre<sup>1</sup>, Ayane Cristine Alves Sarmiento<sup>1,2</sup>, Priscila Farias de Oliveira<sup>3</sup>,  
Felipe Ferreira Wanderley<sup>4</sup>, José Diniz Júnior<sup>5</sup>, Ana Katherine Gonçalves<sup>1,5,\*</sup>

<sup>1</sup> Programa de Pós-Graduação em Ciências da Saúde, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil

<sup>2</sup> Department of Clinical Analysis and Toxicology, Universidade Federal do Rio Grande do Norte, RN, Brazil

<sup>3</sup> Department of Surgery, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil

<sup>4</sup> Faculdade de Medicina, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil

<sup>5</sup> Department of Gynecology and Obstetrics, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil

## HIGHLIGHTS

- Obstructive sleep apnea affects one billion people worldwide and is associated with cardiometabolic risk and cognitive impairment.
- Drug therapy for the management of sleep apnea has been investigated, but no robust evidence that supports its benefits has been found to date.
- The combination of noradrenergic and antimuscarinic drugs shows promising results.

# PHARMACOLOGICAL TREATMENT FOR OBSTRUCTIVE SLEEP APNEA

Objective of this systemic review and meta-analysis was to summarize the evidence on drug therapies for adult obstructive sleep apnea

4930 articles obtained

68 met inclusion criteria

29 studies were combined

# DRUGS EVALUATED



## Target Upper Anatomy

Nasal Steroids  
Nasal Decongestants  
Weight loss medications



## Muscle Responsiveness

Atomoxetine + Oxybutynin  
Reboxetine + Oxybutynin  
Mirtazapine



## Arousal Threshold

Eszopiclone  
Sodium oxybate  
Trazadone  
Zolipem  
Zopiclone



## Reduce Loop Gain

Donepezil



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

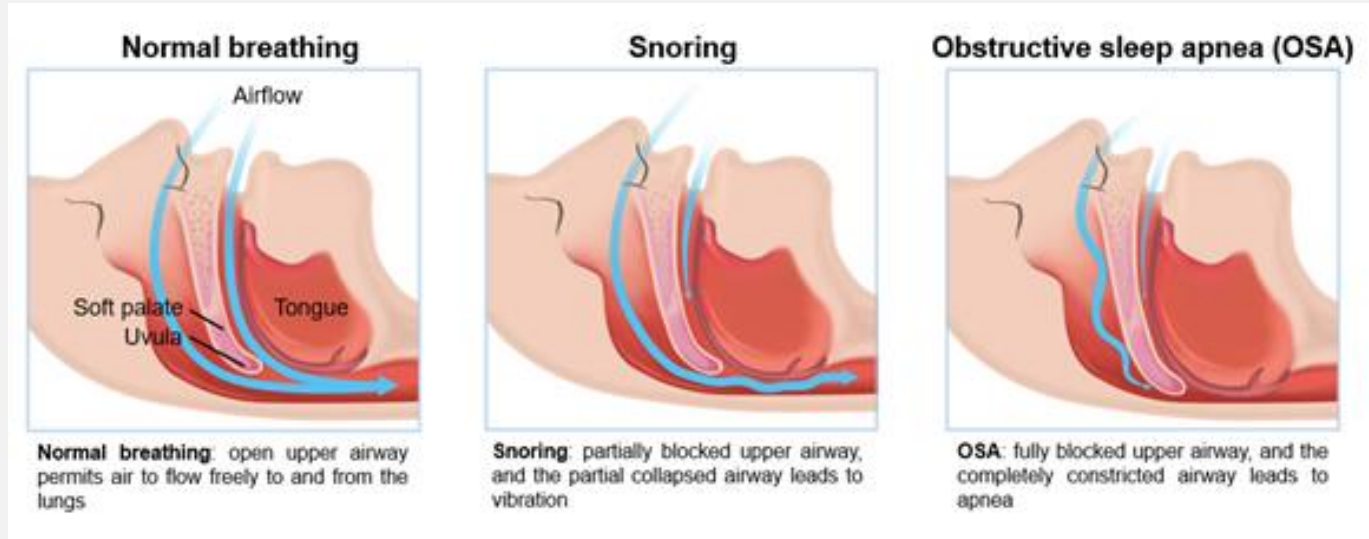
Atul Malhotra, M.D., Ronald R. Grunstein, M.D., Ph.D., Ingo Fietze, M.D., Terri E. Weaver, Ph.D., Susan Redline, M.D., M.P.H., Ali Azarbarzin, Ph.D., Scott A. Sands, Ph.D., Richard J. Schwab, M.D., Julia P. Dunn, M.D., Sujatro Chakladar, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Josef Bednarik, M.D., for the SURMOUNT-OSA Investigators\*

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ABSTRACT

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# UPPER AIRWAY ANATOMY



## UPPER AIRWAY ANATOMY

- Potential mechanisms to target collapsibility of the upper airways
  - Nasal obstruction
  - Weight loss medication
  - Diuretics

# UPPER AIRWAY ANATOMY

## NASAL STEROIDS

- Fluticasone (Flonase)
- Fluticasone/Monteleukast (Singulair)
- Mometasone (Nasonex, Clarinaze)

## NASAL DECONGESTANTS

- Xylometazoline (Otrivin)
- Oxymetazoline (Afrin)

Thorax. 2004 Jan; 59(1): 50–55.

PMCID: PMC1758841

PMID: [14694248](#)

Intranasal corticosteroid therapy for obstructive sleep apnoea in patients with co-existing rhinitis

[J Kiely](#), [P Nolan](#), and [W McNicholas](#)

Fluticasone (Flonase)

Intranasal fluticasone is of benefit to some patients with OSA and rhinitis

SCIENTIFIC INVESTIGATIONS

Effects of Medical Therapy on Mild Obstructive Sleep Apnea in Adult Patients

David F. Smith, MD, PhD<sup>1,2,3\*</sup>; Kathleen M. Sarber, MD<sup>1,2\*</sup>; Charlene P. Spiceland, PhD<sup>4</sup>; Stacey L. Ishman, MD, MPH<sup>1,2,3</sup>; Dianne M. Augelli, MD<sup>5</sup>; Ann M. Romaker, MD<sup>6</sup>

<sup>1</sup>Division of Pediatric Otolaryngology, Department of Otolaryngology–Head and Neck Surgery, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio; <sup>2</sup>Division of Pulmonary and Sleep Medicine, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio; <sup>3</sup>Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio; <sup>4</sup>College School of Business, Simmons University, Boston, Massachusetts; <sup>5</sup>Weill Medical College, Cornell University, New York, New York; <sup>6</sup>Department of Pulmonary, Critical Care and Sleep Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio; \*Contributed equally

Fluticasone/Montelukast (Singular)

No significant difference in AHI was found between treatment and placebo

The effects of mometasone furoate and desloratadine in obstructive sleep apnea syndrome patients with allergic rhinitis

Mustafa Acar <sup>1</sup>, Cemal Cingi, Oner Sakallioğlu, Turhan San, Mehmet Fatih Yimenicioglu, Cengiz Bal

Affiliations + expand

PMID: 23883803 DOI: [10.2500/ajra.2013.27.3921](#)

Mometasone (Nasonex, Clarinaze)

Treating allergic rhinitis has a positive effect on OSA severity

## Xylometazoline (Otrivin)

Nasal decongestion slightly reduced AHI

Journal of  
Sleep  
Research



### Does nasal decongestion improve obstructive sleep apnea?

CHRISTIAN F. CLARENBACH, MALCOLM KOHLER, OLIVER SENN, ROBERT THURNHEER, KONRAD E. BLOCH

First published: 28 November 2008 | <https://doi.org/10.1111/j.1365-2869.2008.00667.x> | Citations: 48

✉ Konrad E. Bloch, MD, Pulmonary Division, Department of Internal Medicine, University Hospital Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland. Tel.: +41-1-255 38 28; fax: +41-1-255 44 51; e-mail: [konrad.bloch@usz.ch](mailto:konrad.bloch@usz.ch)

# Nasal Decongestants

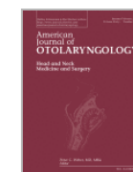
## Oxymetazoline (Afrin)

Improving nasal patency by decongestant could improve AHI



American Journal of Otolaryngology

Volume 40, Issue 1, January–February 2019, Pages 52-56



## The effects of nasal decongestion on obstructive sleep apnoea

Yunsong An<sup>a b</sup>, Yanru Li<sup>a b</sup>, Dan Kang<sup>a</sup>, S.K. Sharama-adhikari<sup>a b</sup>, Wen Xu<sup>a b</sup>, Yunchuan Li<sup>a</sup>,  
Demin Han<sup>a b</sup>  

## FINDINGS

- Both the use of intranasal steroids (3 studies) and nasal decongestants (2 studies) vs. placebo showed a tendency for improvement in AHI without statistical significance

# UPPER AIRWAY ANATOMY

## WEIGHT LOSS

- Tirzepatide (Monjaro, Zebound)
- SURMOUNT-OSA Trials



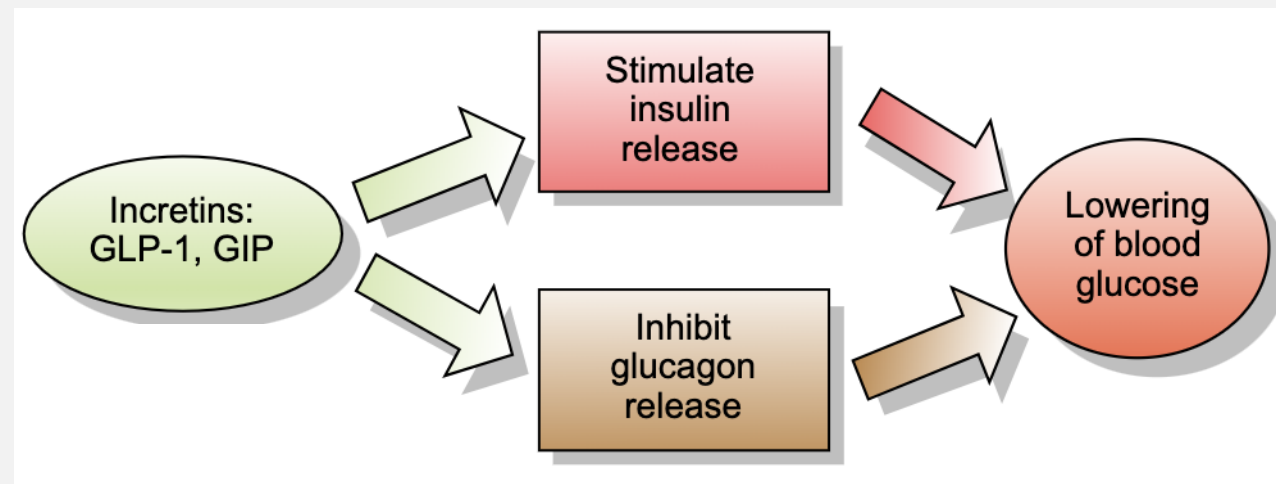


# TIRZEPATIDE

- Branded as
  - **Mounjaro** for diabetes treatment
  - **Zebound** for weight loss
- Dual glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP) receptor agonist
- Incretins
  - GLP-1
  - GIP

# INCRETINS

- Gut hormones that help regulate blood glucose
- Enhance the secretion of insulin from the pancreas
  - Glucose dependent manner



# INCRETINS

## GLP-1 RECEPTOR AGONIST

- Increased insulin release in response to meals (glucose-dependent)
- Inhibit glucagon
- Slow gastric emptying to reduce elevated postprandial glucose

## GIP RECEPTOR AGONIST

- Increased insulin release in response to meals (glucose-dependent)
- Inhibit glucagon
- May affect the basal metabolic rate
- Promote lipolysis
- Increase the oxidation of fatty acids

## SURMOUNT-OSA TRIALS

- Evaluated the efficacy and safety of the maximum tolerated dose of weekly Tirzepatide (10 mg or 15 mg) in adults with moderate to severe OSA (AHI  $\geq$  15 events/hour)

## SURMOUNT OSA TRIALS

- **Trial 1 Participants:** participants who were unable or unwilling to use PAP therapy
- **Trial 2 Participants:** participants who had been using PAP therapy for at least 2 consecutive months at the time of screening & who planned to continue PAP therapy during the trial
- Adults who received a diagnosis of moderate-to-severe OSA and obesity with **BMI  $\geq$  30** were eligible

## BOTTOM LINE

- In both trials participants who received Tirzepatide reduced
  - AHI
  - Body-weight
  - Hypoxic burden
  - hsCRP concentrations
  - Systolic blood pressure
- Improved sleep-related patient-reported outcomes in patients with moderate-to-severe OSA

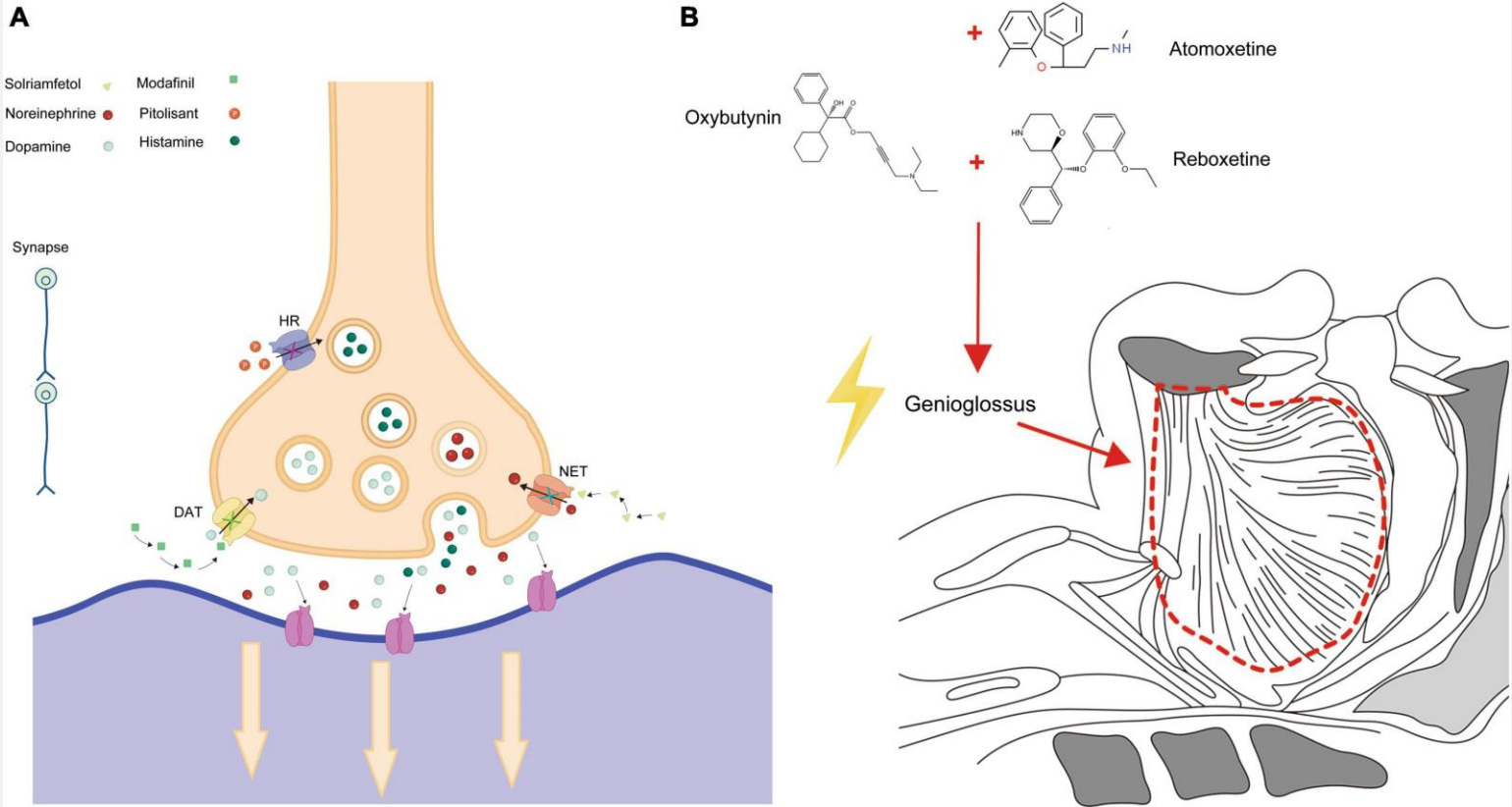
# MUSCLE RESPONSIVENESS

## MUSCLE RESPONSIVENESS

- Both noradrenergic and antimuscarinic muscles processes are involved in pharyngeal muscle activation during sleep
- Sleep-related hypotonia of pharyngeal muscles
- NREM vs REM sleep



# HOW DOES IT WORK?



ATO-OXY



Atomoxetine

Selective  
Norepinephrine  
Reuptake Inhibitor  
(SNRI)

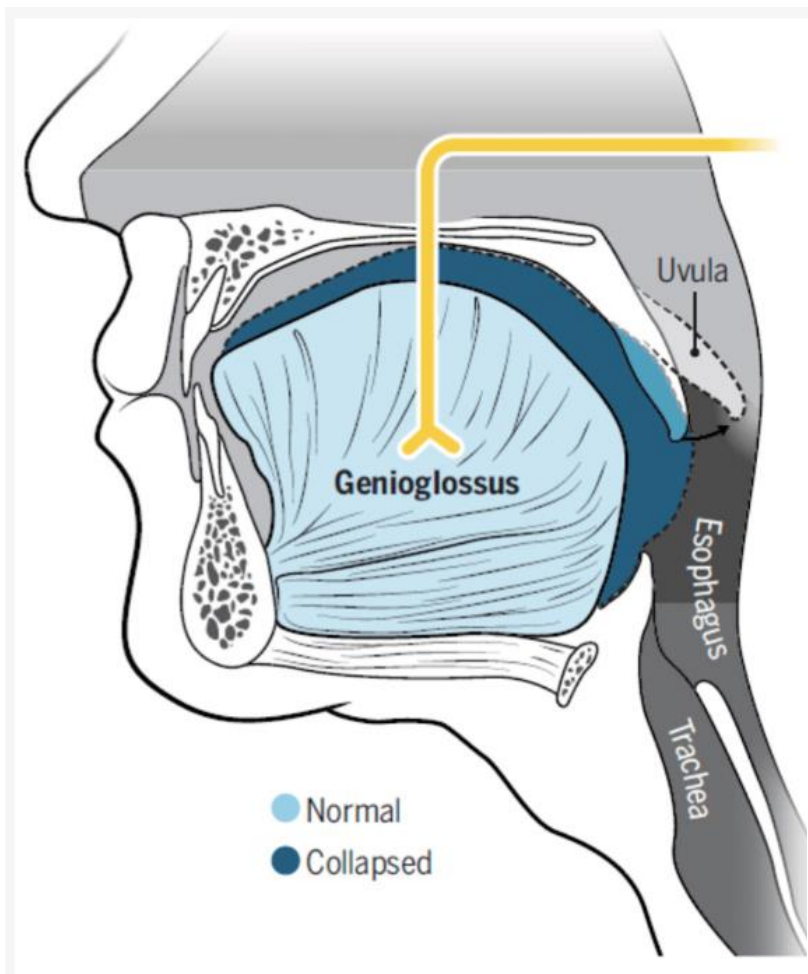
Typically used for  
ADHD



Oxybutynin

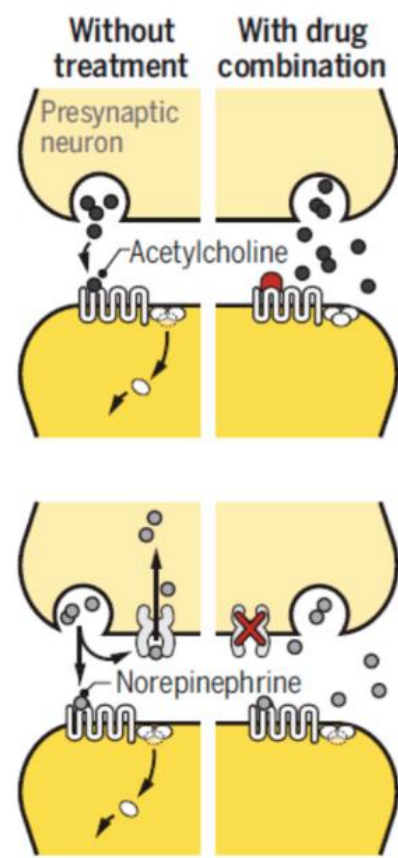
Anticholinergic  
medication

Primarily used to  
treat overactive  
bladder by reducing  
bladder muscle  
spasms



● Hypoglossal nerve

● Brainstem neurons



# REBOX-OXY



## Reboxetine

A norepinephrine reuptake inhibitor approved outside of the United States for the treatment of major depression



## Oxybutynin

Anticholinergic medication



Primarily used to treat overactive bladder by reducing bladder muscle spasms

Original Article

## Effects of the combination of atomoxetine and oxybutynin in Japanese patients with obstructive sleep apnoea: A randomized controlled crossover trial

**AtoOxy** therapy does not reduce AHI in Japanese OSA patients

## Effects of the Combination of Atomoxetine and Oxybutynin on OSA Endotypic Traits

[Luigi Taranto-Montemurro, MD](#) <sup>a</sup>   · [Ludovico Messineo, MD](#) <sup>a,b,c</sup> · [Ali Azarbarzin, PhD](#) <sup>a</sup> · ... · [David P. White, MD](#) <sup>a</sup> · [Andrew Wellman, MD, PhD](#) <sup>a</sup> · [Scott A. Sands, PhD](#) <sup>a</sup>... [Show more](#)

**AtoOxy** markedly improved the measures of upper airway collapsibility

### ORIGINAL ARTICLE

## The Combination of Atomoxetine and Oxybutynin Greatly Reduces Obstructive Sleep Apnea Severity

A Randomized, Placebo-controlled, Double-Blind Crossover Trial

Luigi Taranto-Montemurro<sup>1</sup>, Ludovico Messineo<sup>1,2</sup>, Scott A. Sands<sup>1</sup>, Ali Azarbarzin<sup>1</sup>, Melania Marques<sup>1,3</sup>, Bradley A. Edwards<sup>4,5</sup>, Danny J. Eckert<sup>6</sup>, David P. White<sup>1</sup>, and Andrew Wellman<sup>1</sup>

<sup>1</sup>Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham & Women's Hospital & Harvard Medical School, Boston, Massachusetts; <sup>2</sup>Respiratory Medicine and Sleep Laboratory, Department of Internal Medicine, Spedali Civili di Brescia, University of Brescia, Brescia, Italy; <sup>3</sup>Sleep Laboratory, Pulmonary Division, Heart Institute (InCor), Hospital das Clinicas, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil; <sup>4</sup>Sleep and Circadian Medicine Laboratory, Department of Physiology, and <sup>5</sup>School of Psychological Sciences and Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Melbourne, Victoria, Australia; and <sup>6</sup>Neuroscience Research Australia and the University of New South Wales, Randwick, New South Wales, Australia

**AtoOxy** greatly reduced OSA severity

SCIENTIFIC INVESTIGATIONS

## Combination of atomoxetine with the novel antimuscarinic aroxybutynin improves mild to moderate OSA

Russell Rosenberg, PhD<sup>1</sup>; Brian Abaluck, MD<sup>2</sup>; Stephen Thein, PhD<sup>3</sup>

<sup>1</sup>Neurotrials Research Inc, Atlanta, Georgia; <sup>2</sup>Brian Abaluck MD Sleep Medicine, Malvern, Pennsylvania; <sup>3</sup>Pacific Research Network, San Diego, California

**AtoOxy** has a statistically significant meaningful difference from placebo



[Sleep Breath.](#) 2023; 27(2): 495–503.

Published online 2022 May 13. doi: [10.1007/s11325-022-02634-x](https://doi.org/10.1007/s11325-022-02634-x)

PMCID: PMC9098382

PMID: [35551600](https://pubmed.ncbi.nlm.nih.gov/35551600/)

Efficacy of atomoxetine plus oxybutynin in the treatment of obstructive sleep apnea with moderate pharyngeal collapsibility

[Paula K. Schweitzer](#),<sup>✉1</sup> [James P. Maynard](#),<sup>2</sup> [Paul E. Wylie](#),<sup>3</sup> [Helene A. Emsellem](#),<sup>4</sup> and [Scott A. Sands](#)<sup>5</sup>

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**AtoOxy** improved AHI in patients with moderate pharyngeal collapsibility

[Chest](#). 2022 Jan; 161(1): 237–247.

PMCID: PMC10835052

Published online 2021 Sep 20. doi: [10.1016/j.chest.2021.08.080](https://doi.org/10.1016/j.chest.2021.08.080)

PMID: [34543665](https://pubmed.ncbi.nlm.nih.gov/34543665/)

## Reboxetine Plus Oxybutynin for OSA Treatment

A 1-Week, Randomized, Placebo-Controlled, Double-Blind Crossover Trial

[Elisa Perger](#), MD,<sup>a,b,\*</sup> [Luigi Taranto Montemurro](#), MD,<sup>c</sup> [Debora Rosa](#), PhD,<sup>a</sup> [Stefano Vicini](#), MD,<sup>a,b</sup> [Mariapaola Marconi](#),<sup>a</sup> [Lucia Zanotti](#), PhD,<sup>a</sup> [Paolo Meriggi](#), PhD,<sup>d</sup> [Ali Azarbarzin](#), PhD,<sup>c</sup> [Scott A. Sands](#), PhD,<sup>c</sup> [Andrew Wellman](#), MD, PhD,<sup>c</sup> [Carolina Lombardi](#), MD, PhD,<sup>a,b</sup> and [Gianfranco Parati](#), MD, PhD<sup>a,b</sup>

**ReboxOxy** did not improve OSA severity assessed by AHI, but lowered hypoxic burden

### SCIENTIFIC INVESTIGATIONS

## The norepinephrine reuptake inhibitor reboxetine alone reduces obstructive sleep apnea severity: a double-blind, placebo-controlled, randomized crossover trial

Thomas J. Altree, FRACP<sup>1</sup>; Atiqiya Aishah, BSc (Hons)<sup>1,2</sup>; Kelly A. Loffler, PhD<sup>1</sup>; Ronald R. Grunstein, FRACP, PhD<sup>3,4</sup>; Danny J. Eckert, PhD<sup>1</sup>

<sup>1</sup>Flinders Health and Medical Research Institute/Adelaide Institute for Sleep Health, Flinders University, Bedford Park, South Australia, Australia; <sup>2</sup>Neuroscience Research Australia (NeuRA), University of New South Wales (UNSW), Randwick, Sydney, New South Wales, Australia; <sup>3</sup>Centre for Sleep and Chronobiology, The Woolcock Institute of Medical Research, The University of Sydney and Royal Prince Alfred Hospital, Sydney, New South Wales, Australia; <sup>4</sup>Faculty of Medicine and Health, Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia

**Reboxetine** as a single agent or combined with oxybutynin improves AHI

## Effect of oxybutynin and reboxetine on obstructive sleep apnea: a randomized, placebo-controlled, double-blind, crossover trial

[Mathieu Berger](#)<sup>1,2</sup>, [Geoffroy Solelhac](#)<sup>1</sup>, [Nicola A Marchi](#)<sup>1</sup>, [Romane Dussez](#)<sup>1</sup>, [Brian Bradley](#)<sup>1</sup>, [Gianpaolo Lecciso](#)<sup>1</sup>, [Gregory Heiniger](#)<sup>1</sup>, [Virginie Bayon](#)<sup>1</sup>, [Sandra Van Den Broecke](#)<sup>1</sup>, [Jose Haba-Rubio](#)<sup>1</sup>, [Francesca Siclari](#)<sup>1</sup>, [Raphaël Heinzer](#)<sup>1</sup>

Affiliations + expand

PMID: 36861433 DOI: [10.1093/sleep/zsad051](https://doi.org/10.1093/sleep/zsad051)

**ReboxOxy** greatly decreased OSA severity and increased vigilance

ACTIONS

“ Cite

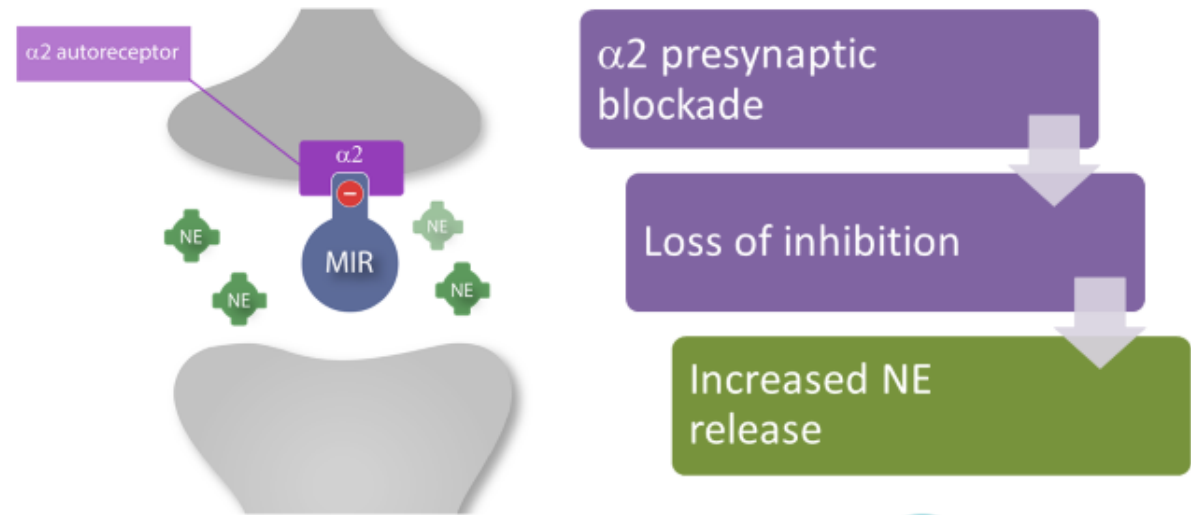
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# MIRTAZEPINE

- Tetracyclic antidepressant
- $\alpha_{2A}$  antagonist and mixed 5-HT<sub>2</sub>/5-HT<sub>3</sub> antagonist that also promotes serotonin release in the brain


Mirtazapine blocks  $\alpha_2$  presynaptic autoreceptors





# Efficacy of Mirtazapine in Obstructive Sleep Apnea Syndrome

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David W. Carley, PhD , Christopher Olopade, MD, Ge S. Ruigt, PhD,  
Miodrag Radulovacki, MD, PhD

*Sleep*, Volume 30, Issue 1, January 2007, Pages 35–41,

<https://doi.org/10.1093/sleep/30.1.35>

**Published:** 01 January 2007    **Article history** ▼

**Mirtazapine** lowered AHI but increased sedation and weight gain

# Mirtazapine

## OBSTRUCTIVE SLEEP APNEA

### Two Randomized Placebo-Controlled Trials to Evaluate the Efficacy and Tolerability of Mirtazapine for the Treatment of Obstructive Sleep Apnea

Nathaniel S. Marshall, PhD<sup>1</sup>; Brendon J. Yee, MB, ChB, PhD<sup>1</sup>; Anup V. Desai, MBBS, PhD<sup>1</sup>; Peter R Buchanan, MBBS, MD<sup>1</sup>; Keith KH Wong, MBBS (Hons)<sup>1</sup>; Renee Crompton, BSc (Hons)<sup>1</sup>; Kerri L Melehan, MResPSc, RPSGT<sup>1</sup>; Nadene Zack, MS<sup>2</sup>; Srinivas G Rao, MD PhD<sup>2</sup>; R. Michael Gendreau, MD, PhD<sup>2</sup>; Jay Kranzler, MD, PhD<sup>2</sup>; Ronald R. Grunstein, MD, PhD<sup>1</sup>

<sup>1</sup>NHMRC Centre for Sleep Medicine, Woolcock Institute of Medical Research, University of Sydney, NSW, Australia; <sup>2</sup>Cypress Bioscience, Inc, San Diego, CA

**Mirtazapine** did not improve OSA severity and induced weight gain

# MUSCLE RESPONSIVENESS FINDINGS

The combination of noradrenergic and antimuscarinic drugs was tested in different trials

Atomoxetine plus Oxybutynin (AtoOxy) showed a significant improvement in AHI

- Mean difference of  $-7.71$

Reboxetine plus Oxybutynin (ReboxOxy)

- No significance was found

Mirtazapine

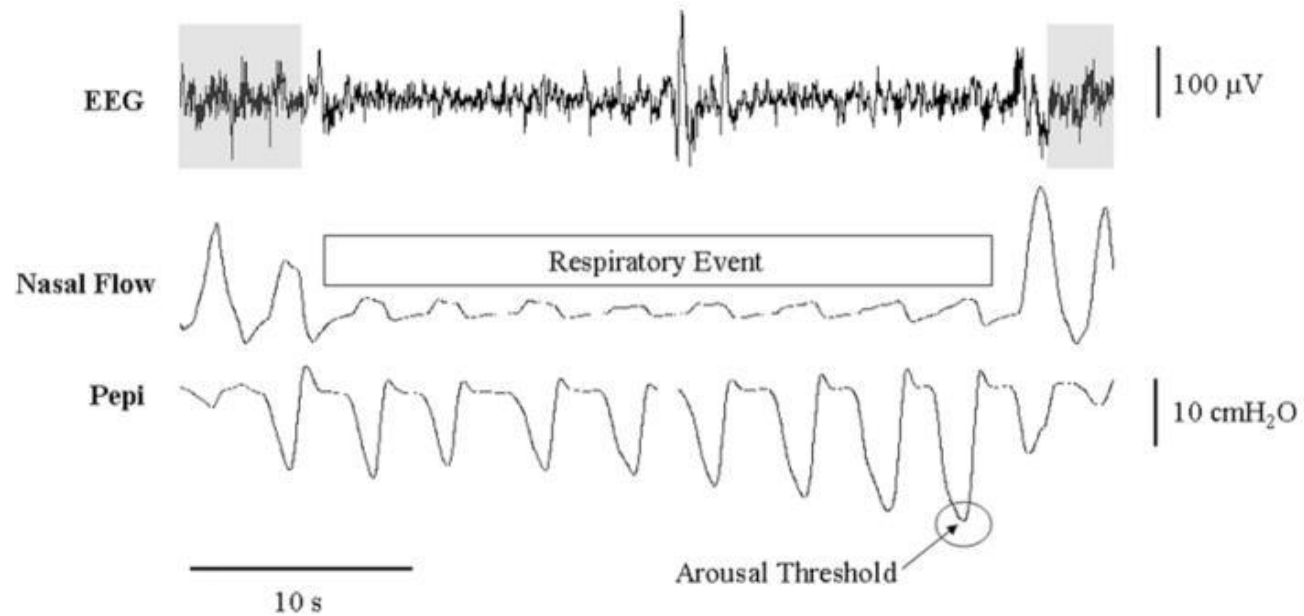
- No evidence of benefit

AROUSAL THRESHOLD

## AROUSAL THRESHOLD

- The level of ventilatory drive triggering arousal from sleep
- Elevated arousal thresholds may be protective of OSA via preservation of sleep and facilitation of upper airway muscle activity
- OSA patients are anatomically predisposed to airway collapse
- Pharyngeal dilator muscle reflexes can help to protect pharyngeal patency
- Agents which raise the arousal threshold could allow the accumulation of respiratory stimuli during sleep which could activate pharyngeal dilator muscles

# AROUSAL THRESHOLD



Arousal threshold is quantified as the average nadir pressure immediately preceding arousal

# AROUSAL THRESHOLD

- Eszopiclone (Lunesta)
- Zopiclone (Imovane, Zimovane)
- Sodium Oxybate (Xyrem)
- Trazadone
- Zolpidem (Ambien)

# AROUSAL THRESHOLD

## ESZOPICLONE (LUNESTA)

- Non-benzodiazepine sedative and hypnotic
- "Z" drug




## ZOPICLONE (IMOVALE, ZIMOVALE)

- Non-benzodiazepine sedative



## Eszopiclone Improves Overnight Polysomnography and Continuous Positive Airway Pressure Titration: A Prospective, Randomized, Placebo-Controlled Trial

[Get access >](#)

Christopher J. Lettieri, MD , Timothy N. Quast, MD, Arn H. Eliasson, MD, Teotimo Andrada, MS

*Sleep*, Volume 31, Issue 9, September 2008, Pages 1310–1316,

<https://doi.org/10.5665/sleep/31.9.1310>

Published: 01 September 2008 [Article history](#) ▾

## A pilot study evaluating acute use of eszopiclone in patients with mild to moderate obstructive sleep apnea syndrome

Russell Rosenberg <sup>1</sup>, James M Roach, Martin Scharf, David A Amato

Mean total AHI was not significantly different in **eszopiclone** from placebo

The severity of OSA did not differ between **eszopiclone and placebo**

## Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold

Danny J Eckert <sup>1</sup>, Robert L Owens, Geoffrey B Kehlmann, Andrew Wellman, Shilpa Rahangdale, Susie Yim-Yeh, David P White, Atul Malhotra

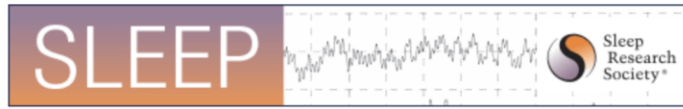
Affiliations [+ expand](#)

PMID: 21269278 PMCID: [PMC3415379](#) DOI: [10.1042/CS20100588](#)

**Eszopiclone** increased arousal threshold and lowered AHI in patients with OSA

# Eszopiclone





▶ Sleep. 2016 Apr 1;39(4):757-766. doi: [10.5665/sleep.5622](https://doi.org/10.5665/sleep.5622)

## Zopiclone Increases the Arousal Threshold without Impairing Genioglossus Activity in Obstructive Sleep Apnea

[Sophie G Carter](#)<sup>1,\*</sup>, [Michael S Berger](#)<sup>1,\*</sup>, [Jayne C Carberry](#)<sup>1</sup>, [Lynne E Bilston](#)<sup>1</sup>, [Jane E Butler](#)<sup>1</sup>, [Benjamin KY Tong](#)<sup>1</sup>, [Rodrigo T Martins](#)<sup>1</sup>, [Lauren P Fisher](#)<sup>1</sup>, [David K McKenzie](#)<sup>2</sup>, [Ronald R Grunstein](#)<sup>3</sup>, [Danny J Eckert](#)<sup>1,✉</sup>

**Zopiclone** increased arousal threshold with no impact on AHI



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## Effect of 1 month of zopiclone on obstructive sleep apnoea severity and symptoms: a randomised controlled trial

Sophie G. Carter, Jayne C. Carberry, Garry Cho, Lauren P. Fisher, Charlotte M. Rollo, David J. Stevens, Angela L. D'Rozario, David K. McKenzie, Ronald R. Grunstein, Danny J. Eckert  
European Respiratory Journal 2018 52: 1800149; DOI: 10.1183/13993003.00149-2018

There was a tendency of reduction of AHI with **Zopiclone**


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SLEEP: ORIGINAL RESEARCH · Volume 158, Issue 1, P374-385, July 2020

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## Randomized Trial on the Effects of High-Dose Zopiclone on OSA Severity, Upper Airway Physiology, and Alertness

[Sophie G. Carter, PhD](#)<sup>a</sup>  · [Jayne C. Carberry, PhD](#)<sup>a,b</sup> · [Ronald R. Grunstein, MD, PhD](#)<sup>c</sup> · [Danny J. Eckert, PhD](#)<sup>a,b</sup>

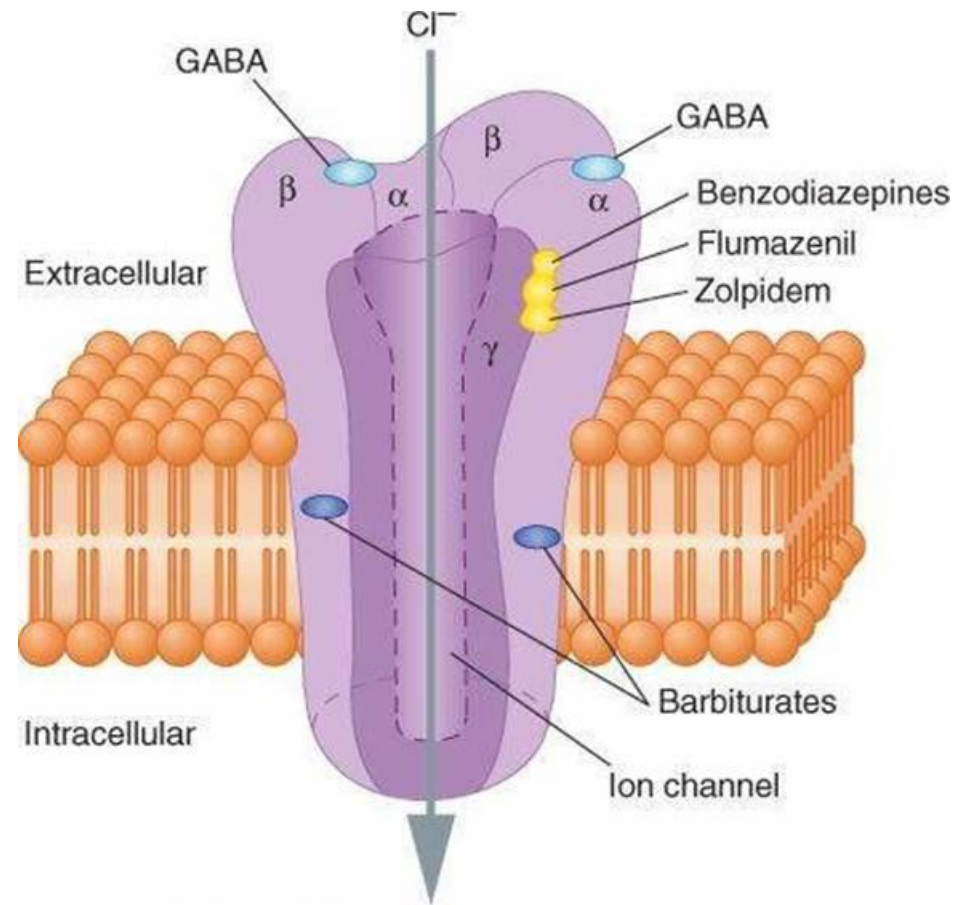
[Affiliations & Notes](#)  [Article Info](#) 

**Zopiclone** did not systemically reduce AHI or increase arousal threshold

**Zopiclone**

# ZOLPIDEM (AMBIEN)

- Insomnia
- Non-benzodiazepine receptor modulator
- Increases sleep stability
- Increase in deeper sleep stages (N1-N3) and decrease in REM sleep
- Hypnotic agent acting at the GABA<sub>A</sub> receptor benzodiazepine site
- Causes CNS depression



## Zolpidem increases sleep efficiency and the respiratory arousal threshold without changing sleep apnoea severity and pharyngeal muscle activity

Ludovico Messineo<sup>1,2</sup> , Danny J. Eckert<sup>1,2</sup> , Richard Lim<sup>1,2</sup> , Alan Chiang<sup>1</sup> , Ali Azarbarzin<sup>3</sup>, Sophie G. Carter<sup>1</sup> and Jayne C. Carberry<sup>2</sup> 

<sup>1</sup>Neuroscience Research Australia (NeuRA) and the University of New South Wales, Randwick, Sydney, New South Wales, Australia

<sup>2</sup>Adelaide Institute for Sleep Health (AISH), Flinders Health and Medical Research Institute (FHMRI), Flinders University, Bedford Park, Adelaide, South Australia, Australia

<sup>3</sup>Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham & Women's Hospital & Harvard Medical School, Boston, MA, USA

**Zolpidem** did not change AHI

# SODIUM OXYBATE (XYREM)

- Central nervous system depressant that treats narcolepsy and cataplexy by reducing brain activity
- Sodium salt of gamma-hydroxybutyrate
- May increase time spent in N2 and N3 sleep stages, while decreasing the shift to N1/Wake/REM stages



## **A 2-week, polysomnographic, safety study of sodium oxybate in obstructive sleep apnea syndrome**



Charles F. P. George · Neil Feldman · Yanping Zheng ·  
Teresa L. Steininger · Susanna M. Grzeschik ·  
Chinglin Lai · Neil Inhaber

It is not clear how **Sodium Oxybate** might reduce AHI in OSA patients

**Sodium  
Oxybate**

Original Article

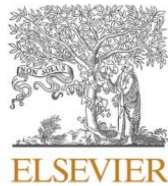
## A safety trial of sodium oxybate in patients with obstructive sleep apnea: Acute effects on sleep-disordered breathing

Charles F.P. George<sup>a</sup>  , Neil Feldman<sup>b</sup>, Neil Inhaber<sup>c</sup>, Teresa L. Steininger<sup>c</sup>,  
Susanna M. Grzeschik<sup>c</sup>, Chinglin Lai<sup>d</sup>, Yanping Zheng<sup>c</sup>

**Sodium oxybate** does not negatively impact sleep disordered breathing but might increase central apneas

**Sodium  
Oxybate/Zolipem**

# ON-SXB



Contents lists available at [ScienceDirect](#)

## Sleep Medicine: X

journal homepage: [www.sciencedirect.com/journal/sleep-medicine-x](http://www.sciencedirect.com/journal/sleep-medicine-x)



### Improvement in sleep latency with extended-release once-nightly sodium oxybate for the treatment of adults with narcolepsy: Analysis from the phase 3 REST-ON clinical trial



Michael J. Thorpy<sup>a</sup>, Clete A. Kushida<sup>b</sup>, Richard Bogan<sup>c</sup>, John Winkelman<sup>d</sup>,  
Maurice M. Ohayon<sup>e</sup>, Colin M. Shapiro<sup>f</sup>, Jennifer Gudeman<sup>g,\*</sup>

<sup>a</sup> Albert Einstein College of Medicine, New York, NY, USA

<sup>b</sup> Stanford University School of Medicine, Stanford, CA, USA

<sup>c</sup> Medical University of South Carolina, Charleston, SC, USA

<sup>d</sup> Massachusetts General Hospital, Boston, MA, USA

<sup>e</sup> Stanford University School of Medicine, Palo Alto, CA, USA

<sup>f</sup> University of Toronto, Toronto, ON, Canada

<sup>g</sup> Avadel Pharmaceuticals, Chesterfield, MO, USA

# TRAZADONE

- Antidepressant
- Serotonin reuptake inhibitor
- Blocks histamine and adrenergic blocker
- Sedative & hypnotic





[Ann Am Thorac Soc.](#) 2015 May; 12(5): 758–764.

doi: [10.1513/AnnalsATS.201408-399OC](https://doi.org/10.1513/AnnalsATS.201408-399OC)

PMCID: PMC4418332

PMID: [25719754](https://pubmed.ncbi.nlm.nih.gov/25719754/)

## Trazodone Effects on Obstructive Sleep Apnea and Non-REM Arousal Threshold

[Erik T. Smales](#),<sup>1,2</sup> [Bradley A. Edwards](#),<sup>2</sup> [Pam N. Deyoung](#),<sup>1,2</sup> [David G. McSharry](#),<sup>2</sup> [Andrew Wellman](#),<sup>2</sup>  
[Adrian Velasquez](#),<sup>2,3</sup> [Robert Owens](#),<sup>1,2</sup> [Jeremy E. Orr](#),<sup>1</sup> and [Atul Malhotra](#)<sup>1,2</sup>

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**Trazadone** resulted in a  
significant reduction in AHI

**Trazadone** significantly increased the  
percentage of slow wave sleep and  
improved AHI

[Randomized Controlled Trial](#) > [J Neurol.](#) 2021 Aug;268(8):2951-2960.

doi: [10.1007/s00415-021-10480-2](https://doi.org/10.1007/s00415-021-10480-2). Epub 2021 Feb 24.

## Trazodone improves obstructive sleep apnea after ischemic stroke: a randomized, double-blind, placebo-controlled, crossover pilot study

[Chung-Yao Chen](#)<sup>1 2</sup>, [Chia-Ling Chen](#)<sup>3 4</sup>, [Chung-Chieh Yu](#)<sup>5 6</sup>

Affiliations + expand

PMID: 33625584 DOI: [10.1007/s00415-021-10480-2](https://doi.org/10.1007/s00415-021-10480-2)

# Trazadone

# AROUSAL THRESHOLD

## NO CHANGE IN AHI

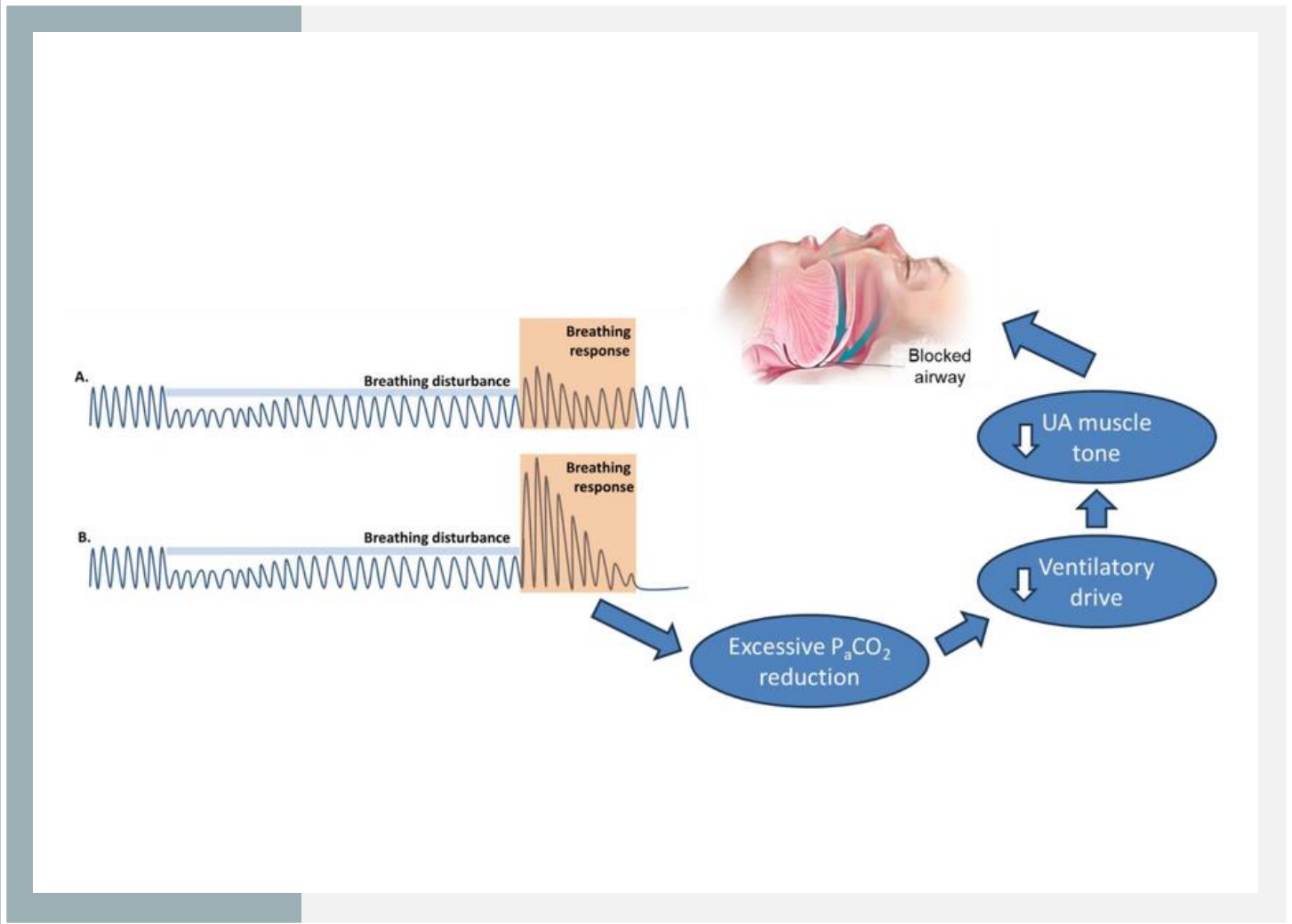
- Eszopiclone, Zolpidem, and Zopiclone were studied
- Sodium Oxybate vs placebo showed significant improvement in AHI
  - Mean difference of  $-5.50$
- Trazadone vs placebo

## IMPROVEMENT IN AHI

- Sodium Oxybate vs placebo
  - Mean difference of  $-5.50$
- Trazadone vs placebo
  - Mean difference of  $-12.75$

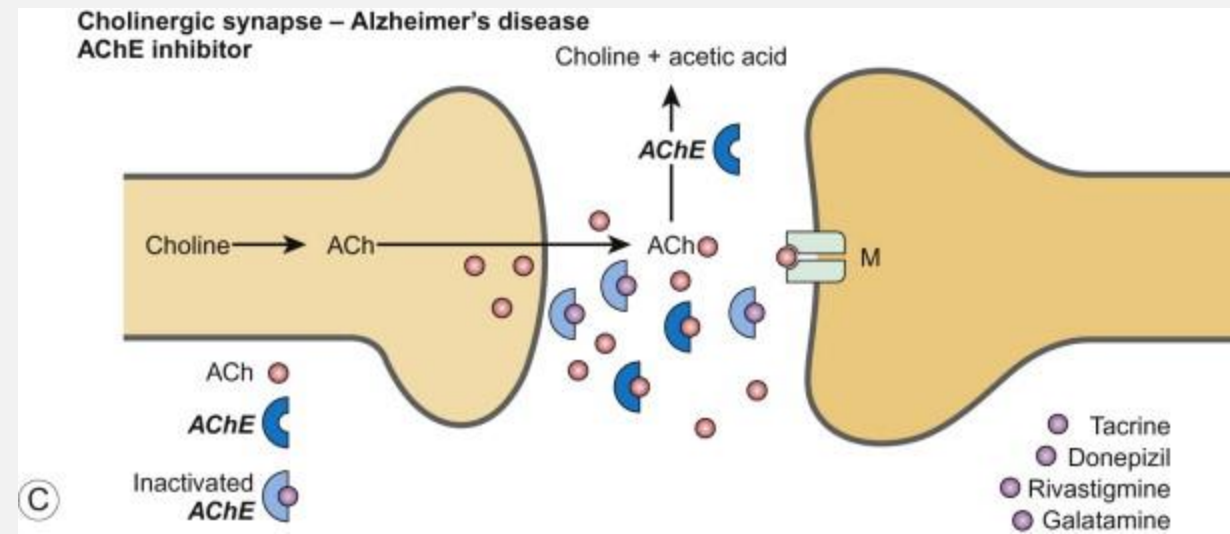
LOOP GAIN

# LOOP GAIN



# DONEPEZIL (ARICEPT)

- Acetylcholinesterase inhibitor
- Alzheimer's drug
  - Used to treat cognitive symptoms



## Beneficial effect of donepezil on obstructive sleep apnea: a double-blind, placebo-controlled clinical trial

Lucia Sukys-Claudino <sup>1</sup>, Walter Moraes, Christian Guilleminault, Sergio Tufik, Dalva Poyares

Affiliations + expand

PMID: 22281004 DOI: [10.1016/j.sleep.2011.09.014](https://doi.org/10.1016/j.sleep.2011.09.014)

**Donepezil** treatment improved OSA index and oxygen saturation

**ANNALS OF THE  
AMERICAN THORACIC SOCIETY™**  
formerly Proceedings of the American Thoracic Society®

[Ann Am Thorac Soc.](#) 2016 Nov; 13(11): 2012–2018.

doi: [10.1513/AnnalsATS.201605-384OC](https://doi.org/10.1513/AnnalsATS.201605-384OC)

PMCID: PMC5122481

PMID: [27442715](https://pubmed.ncbi.nlm.nih.gov/27442715/)

The Effect of Donepezil on Arousal Threshold and Apnea–Hypopnea Index. A Randomized, Double-Blind, Cross-Over Study

[Yanru Li](#),<sup>1,2</sup> [Robert L. Owens](#),<sup>2</sup> [Scott Sands](#),<sup>3,4</sup> [Jeremy Orr](#),<sup>2</sup> [Walter Moraes](#),<sup>5</sup> [Pamela DeYoung](#),<sup>2</sup> [Erik Smales](#),<sup>2</sup> [Rachel Jen](#),<sup>2,6</sup> and [Atul Malhotra](#)<sup>1,2</sup>

A single dose of **donepezil** did not appear affect the severity of OSA

Original Research

SLEEP MEDICINE

## Donepezil Improves Obstructive Sleep Apnea in Alzheimer Disease\* A Double-Blind, Placebo-Controlled Study

*Walter Moraes, MD, PhD; Dalva Poyares, MD, PhD;  
Lucia Sukys-Claudino, MD; Christian Guilleminault, MD, PhD;  
and Sergio Tufik, MD, PhD*

**Donepezil** improved AHI in patients with Alzheimer's Disease

## LOOP GAIN

- Donezepil vs placebo
  - Demonstrated improvement in OSA severity with a mean difference of  $-8.56$

## DISCUSSION

- The combination of Atomoxetine and Oxybutynin was found to provide the most significant enhancement in OSA severity
- Of the drugs that we previously thought would increase the arousal threshold actually worsened apnea by decreasing muscle dilatory response and promote collapsibility
- Include SURMOUNT POINT





## WHAT'S NEXT?

- Long-term efficacy and safety of new drugs
- Impact of combination therapies with CPAP
- Which patients would be most suitable for OSA pharmacologic therapy?

**THANK YOU!**