



Sleep Disorders with New Perspectives:

Overcoming challenges in Treating Insomnia and OSA

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Disclosures

- My presentation is not representative of any position of the US government or Department of Veteran Affairs
- I don't have any conflict of interest pertaining to the material presented in this talk



LEARNING OBJECTIVES

- **Update on Insomnia**
 - Define and describe Insomnia disorder
 - Summarize recent changes in the nomenclature of insomnia
 - Identify neurotransmitter systems involved in sleep
 - Identify newer medications and their mechanism of action
 - Summarize American College of Medicine guidelines
- **Update on OSA Treatments**
 - Identify 2 newer treatment options for OSA



Sleep Disorders are very common and often go unrecognized and untreated





Sleep Apnea and Insomnia are the most common





**As physicians you see these patients
every day**





Treating sleep disorders help with other co-morbid medical and psychiatric disorders





Insomnia Disorder DSM-5

- Dissatisfaction with sleep quantity or quality, with one or more of the following symptoms: difficulty initiating sleep, difficulty maintaining sleep, early-morning awakening
- The sleep disturbance causes significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning
- The sleep difficulty occurs at least 3 nights/week, for at least 3 months, and despite adequate opportunity for sleep
- The insomnia does not co-occur with another sleep disorder
- The insomnia is not explained by coexisting mental disorders or medical conditions



INSOMNIA

- Marked Departure from the ICSD-2 and DSM IV
- No distinction of Acute vs Chronic
- No distinction of Primary Vs. Secondary



NIH State-of-the-Science Conference and Co-Morbid Insomnia

- As much as 85% of insomnia may be co-morbid with other conditions
- "Co-morbid insomnia" is an appropriate term
 - Mechanistic and causal pathways not known
- WHY CHANGE
 - The term secondary insomnia may promote under-treatment
 - Share many characteristics between primary and secondary
- NIH National Institute of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults. Sleep 2005



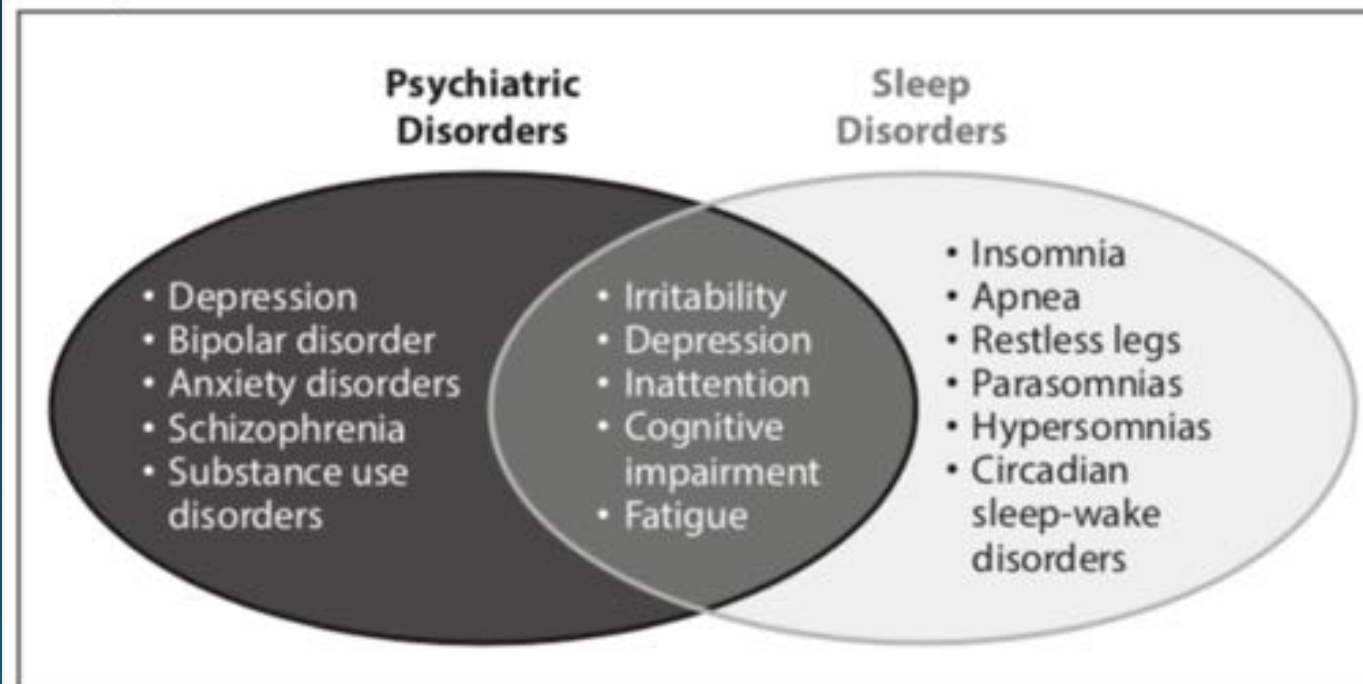
INSOMNIA (ICSD-3)

- Chronic Insomnia Disorder
- Short-Term Insomnia Disorder
- Other Insomnia Disorder



Insomnia as a disorder rather than a symptom

Figure 1. Overlap of Symptoms Between Psychiatric and Sleep Disorders^a



^aBased on American Psychiatric Association¹ and Palmer and Alfano²



Overview of Neurotransmitter System Relevant to Sleep



Sleep Promoting and Wake Promoting Neurotransmitters

Neurotransmitters That Increase the Activity of Sleep-Promoting Systems:

- Adenosine
- Gamma-aminobutyric acid (GABA)-A
- Galanin
- Melatonin

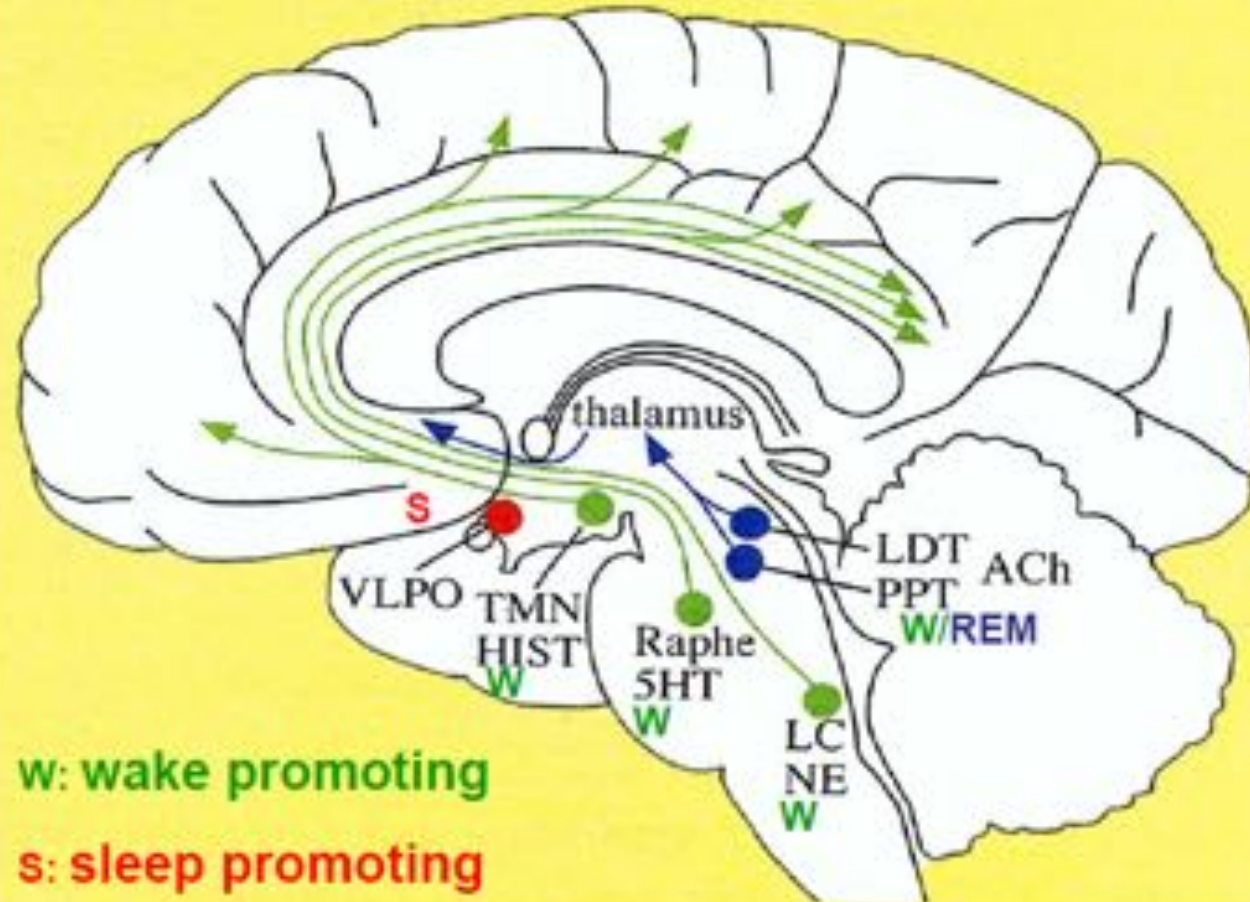
Neurotransmitters That Block the Activity of Wake-Promoting Systems:

- Norepinephrine
- Serotonin
- Acetylcholine
- Histamine
- Orexin/hypocretin

(Saper et al., 2005)

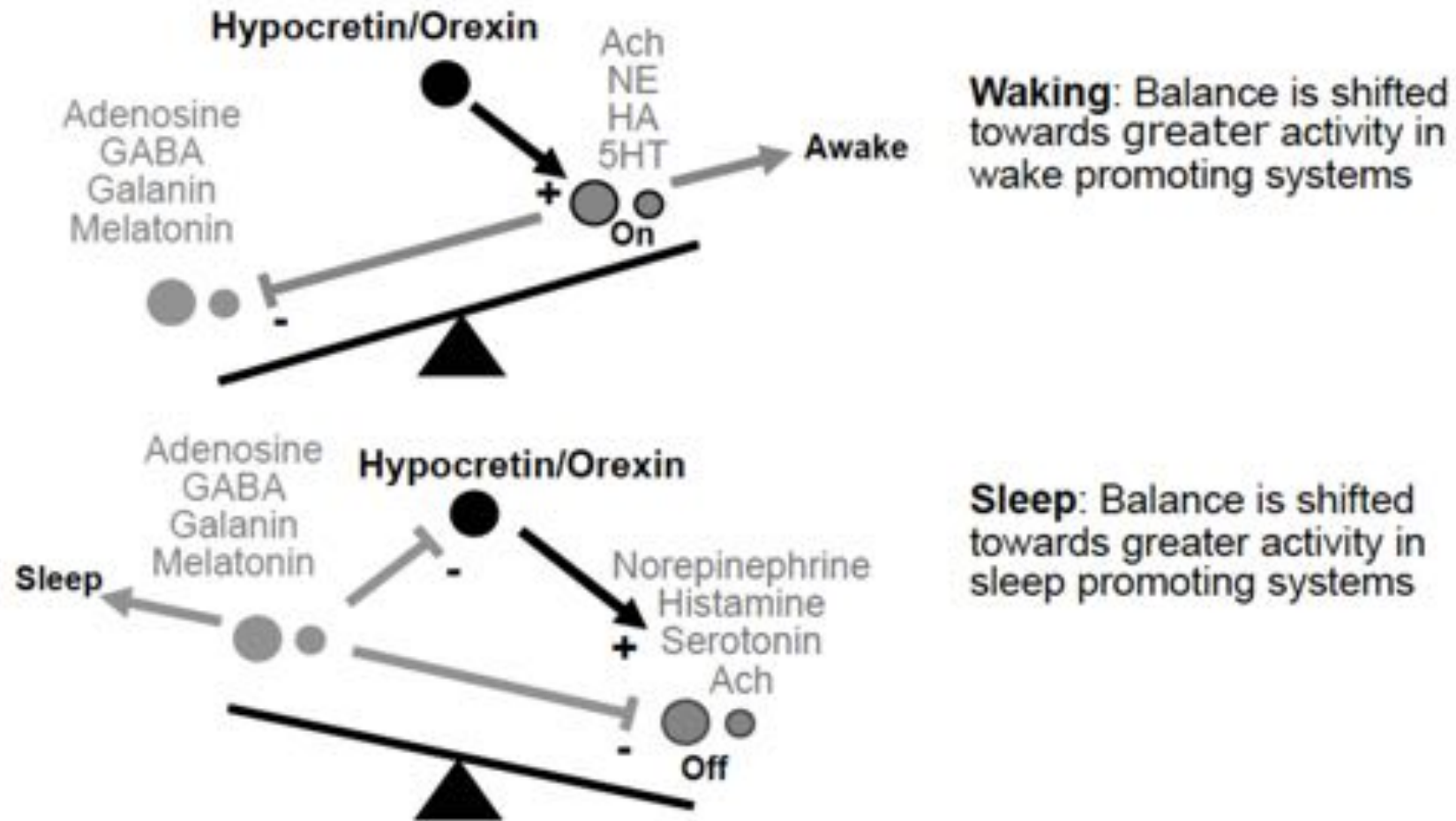


Sleep and Wake Neurotransmitters





Brains' Flip Flop Switch



Modified from Saper CB, et al. *Nature*. 2005;437(7063):1257-1263.

Prescription Drugs used for Insomnia: Main Characteristics

Drug	Mode of Action	T _{1/2} h	Recommended Use	Dose (mg)	FDA
NBBzRA					
Zopiclone	GABA(A) alpha 1,2,3	5	Sleep onset/ maintenance	3.75-7.5	+
Eszopiclone	GABA(A) alpha 1,2,3	6	Sleep onset/ maintenance	1-3	+
Zolpidem	GABA(A) alpha 1,2,3	2.6	Sleep onset/ maintenance	1.75-10 6.25-12.5 ER	+
Zaleplon	GABA(A) alpha 1,2,3	0.7-1.4	Sleep onset	5-20	+

Prescription Drugs used for Insomnia: Main Characteristics

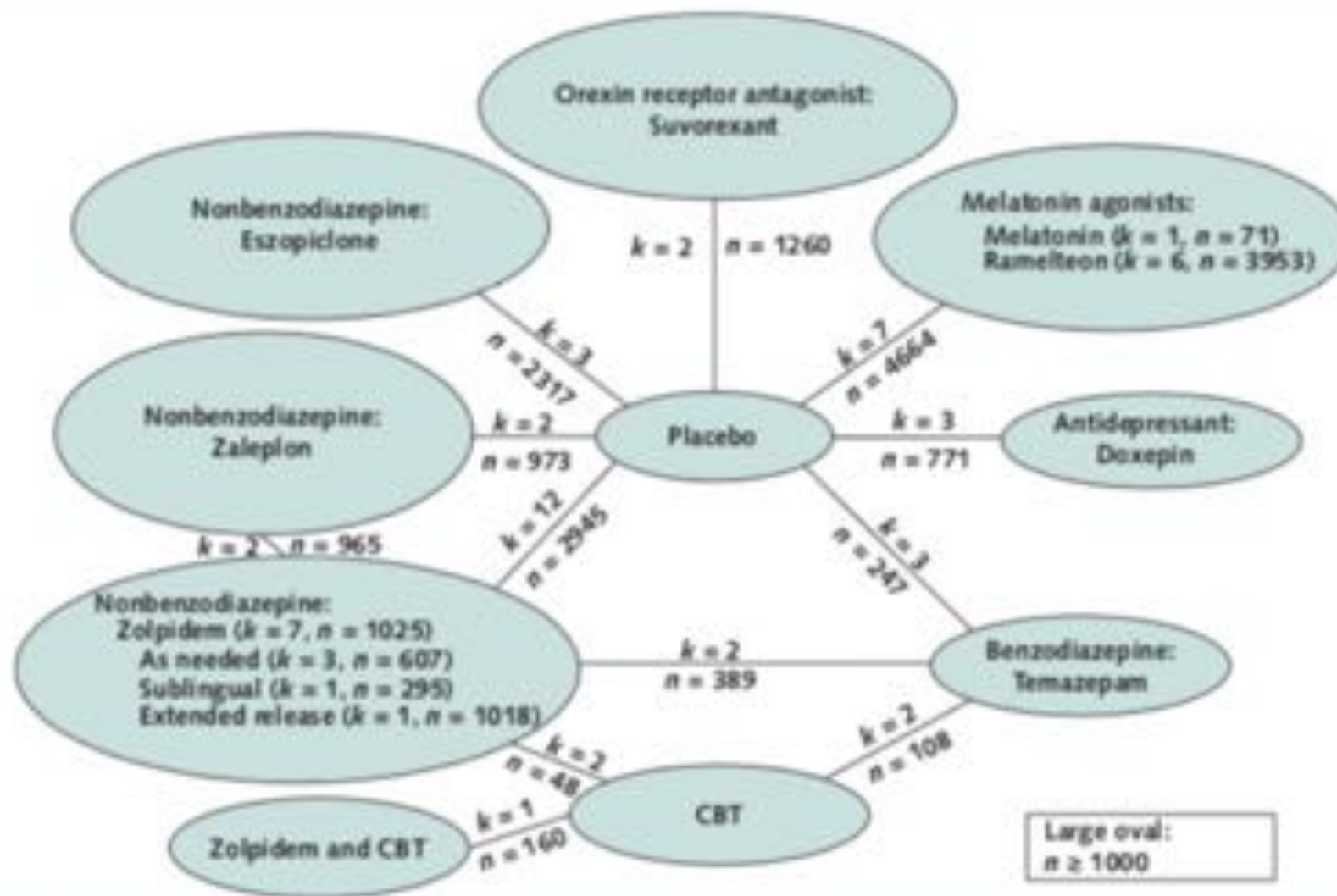
Drug (Class)	Mode of Action	T _{1/2} (h)	Recommended Use	Dose (mg)	FDA
Orexin receptor antagonists					
Suvorexant	OxR ₁ and OxR ₂	12	Sleep onset / Maintenance	5-20	+
Melatonin and Melatonin receptor agonists					
Ramelteon	Receptor agonism	1-2.5	Sleep onset	8	+
Melatonin	Receptor agonism	~0.75	Not recommended		N/A
Circadin	Receptor agonism	3.5-4	Sleep onset/ Maintenance age >55 y	2	-

Prescription Drugs used for Insomnia: Main Characteristics-Cont.

Drug (Class)	Mode of Action	T _{1/2} (h)	Recommended Use	Dose (mg)	FDA
Antidepressants					
Doxepin	H ₁ antagonism	20	Sleep maintenance	3-6	+
Amitriptyline	H ₁ , alpha ₁ , M ₁ antagonism	30	Not recommended		-
Trazodone	5HT _{2A} , alpha ₁ antagonism	9	Not recommended		-
Mirtazapine	H ₁ ,5HT _{2A/2C}	25	Not recommended		-
Antipsychotics					
Quetiapine	H ₁ ,alpha ₁ ,M ₁ ,5HT, D ₂ antagonism	6	Not recommended		-
Olanzapine	H ₁ ,alpha ₁ ,M ₁ ,5HT, D ₂ antagonism	20-54	Not recommended		-



Studies on Treatments of Insomnia Disorder



The k values refer to number of studies. CBT = cognitive behavioral therapy.

Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Devan Kansagara, MD, MCR; Mary Ann Forciea, MD; Molly Cooke, MD; and Thomas D. Denberg, MD, PhD; for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the management of chronic insomnia disorder in adults.

Methods: This guideline is based on a systematic review of randomized, controlled trials published in English from 2004 through September 2015. Evaluated outcomes included global outcomes assessed by questionnaires, patient-reported sleep outcomes, and harms. The target audience for this guideline includes all clinicians, and the target patient population includes adults with chronic insomnia disorder. This guideline grades the evidence and recommendations by using the ACP grading system, which is based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Recommendation 1: ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. (Grade: strong recommendation, moderate-quality evidence)

Recommendation 2: ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence)

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For author affiliations, see end of text.
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CBT-I

Shared
decision
making
approach



Update on Obstructive Sleep Apnea Treatments





Some Newer Treatments

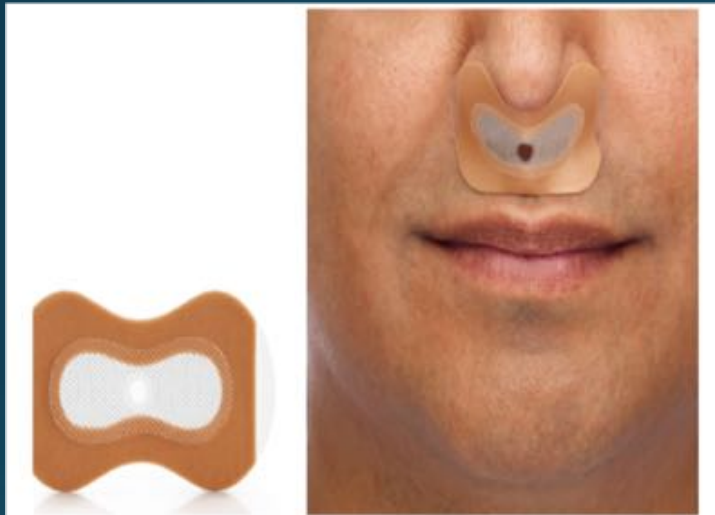


Fig. 1. Theravent nasal EPAP device

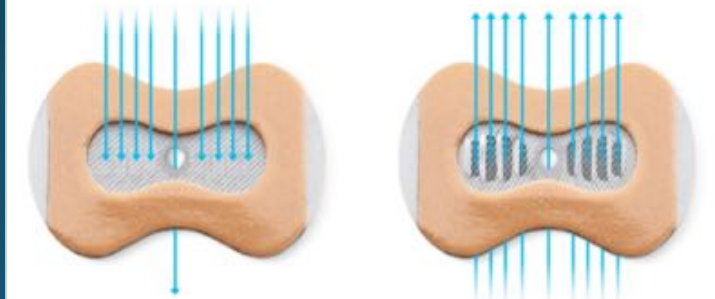
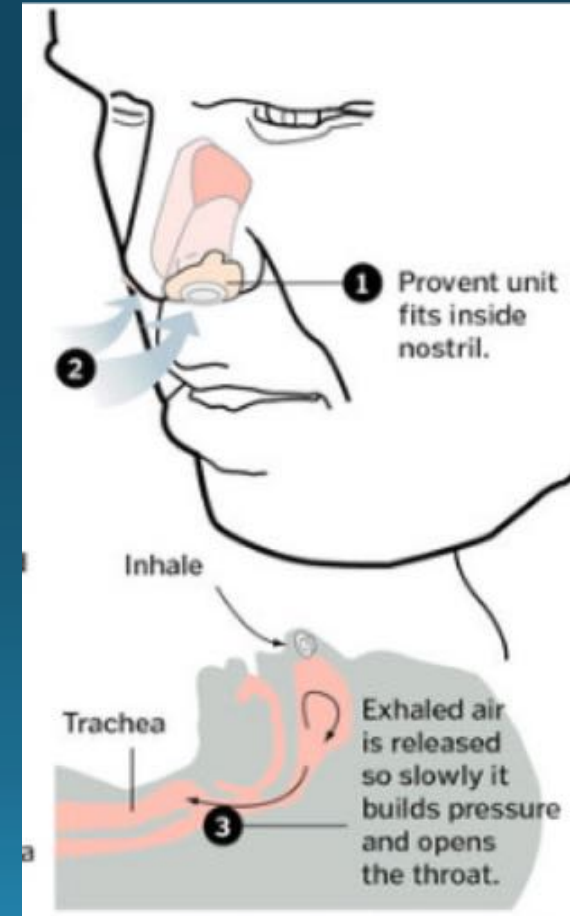
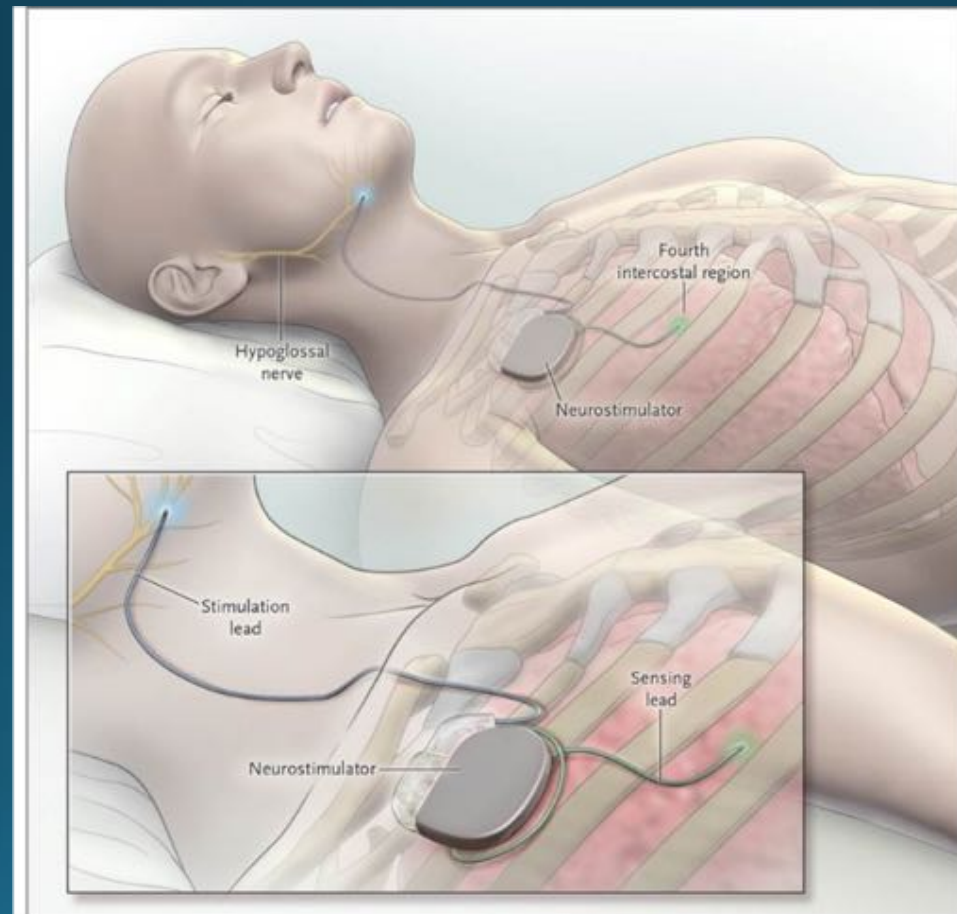


Fig. 2. Theravent microvalves during expiration and inspiration respectively



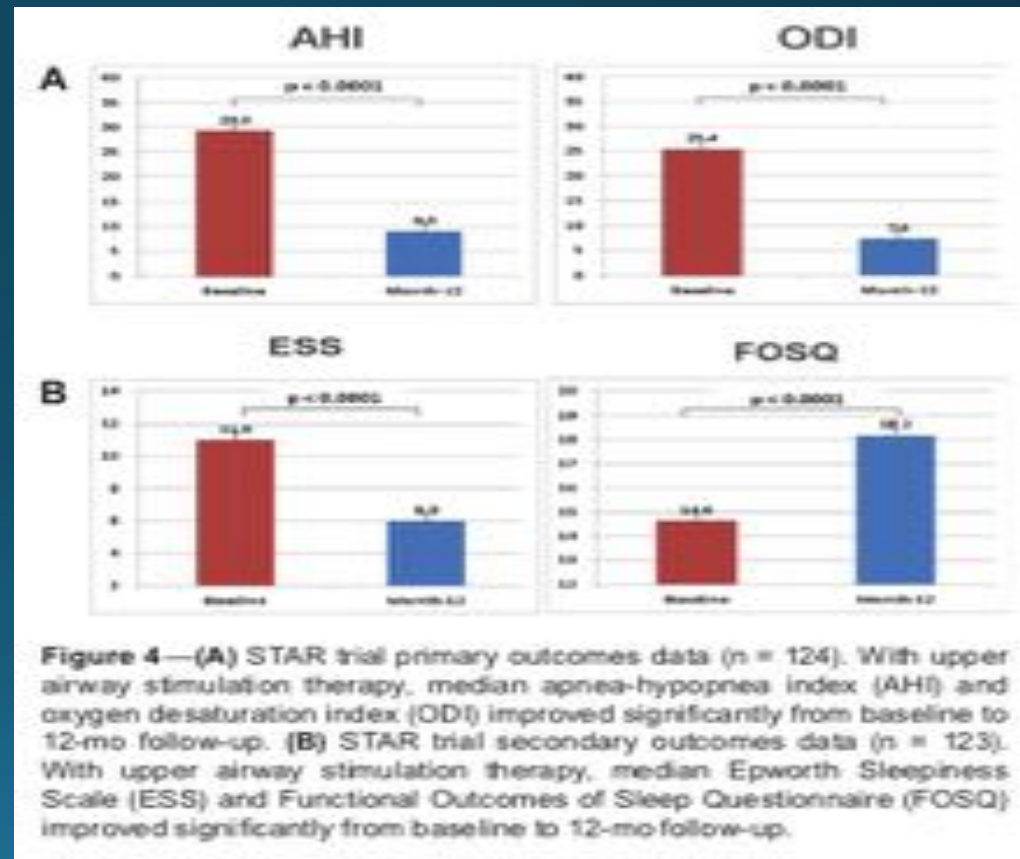
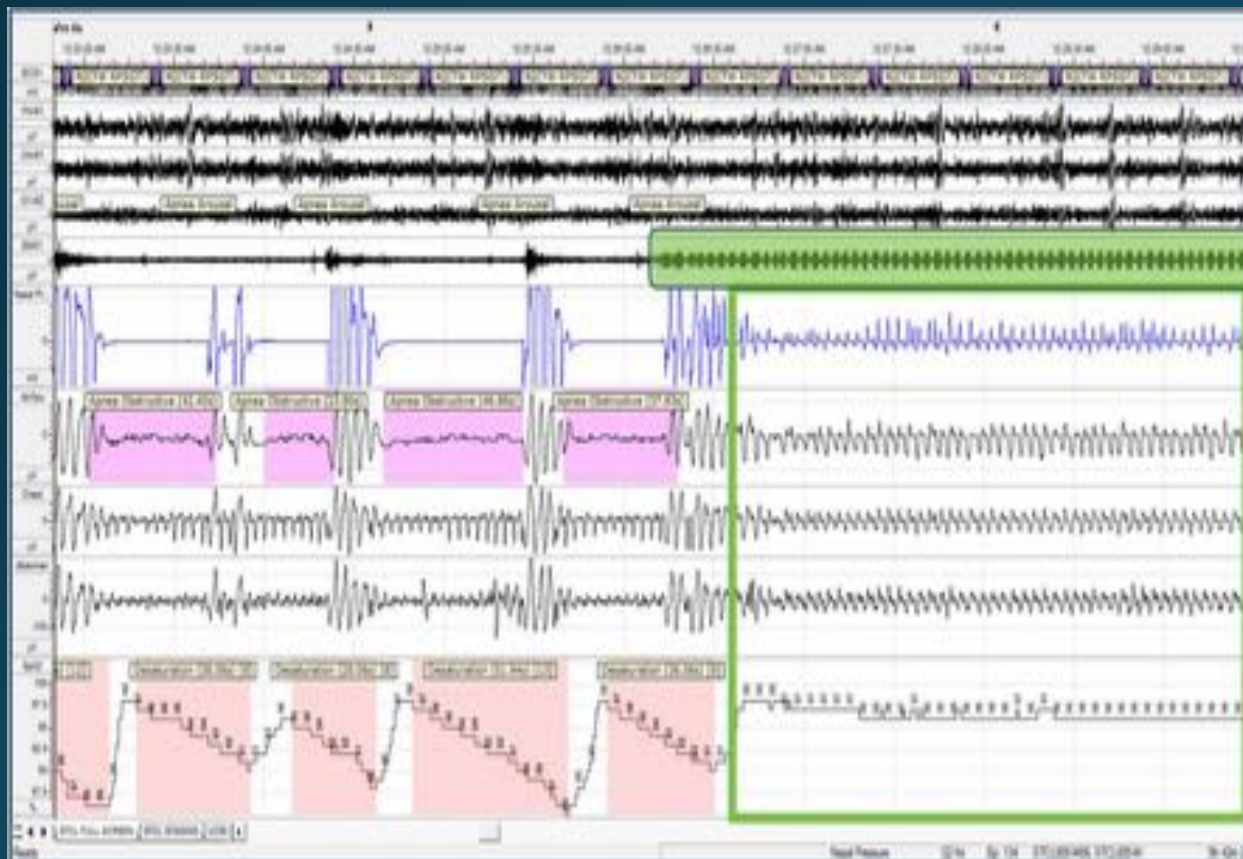


Hypoglossal Nerve Stimulation for OSA





Primary and Secondary Improvements with Hypoglossal Nerve Stimulation in the STAR Trial



Kezirian EJ et al; Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes. *J Sleep Res* 2014;23:77-83.



Conclusion

- Insomnia is a chronic condition which is co-morbid with many psychiatric and medical disorders
- Insomnia should be considered as a separate disorder and treated simultaneously with co-morbid conditions
- Some newer hypnotic medications are safer, but the first line of treatment is CBT-I
- CPAP and dental appliances are the main treatment options for OSA
- Upper airway stimulation is a novel treatment option for patients in which CPAP does not work