Pharmacologic Management of Insomnia

Pre-presentation Survey: Please complete the brief survey by using the QR code to the right or the URL below.

URL: https://www.pcmg-us.org/survey/pre/insomnia7

Pharmacologic Management of Insomnia
Stephen A. Brunton, MD, FAAFP, CDCES
Executive Director
Primary Care Metabolic Group

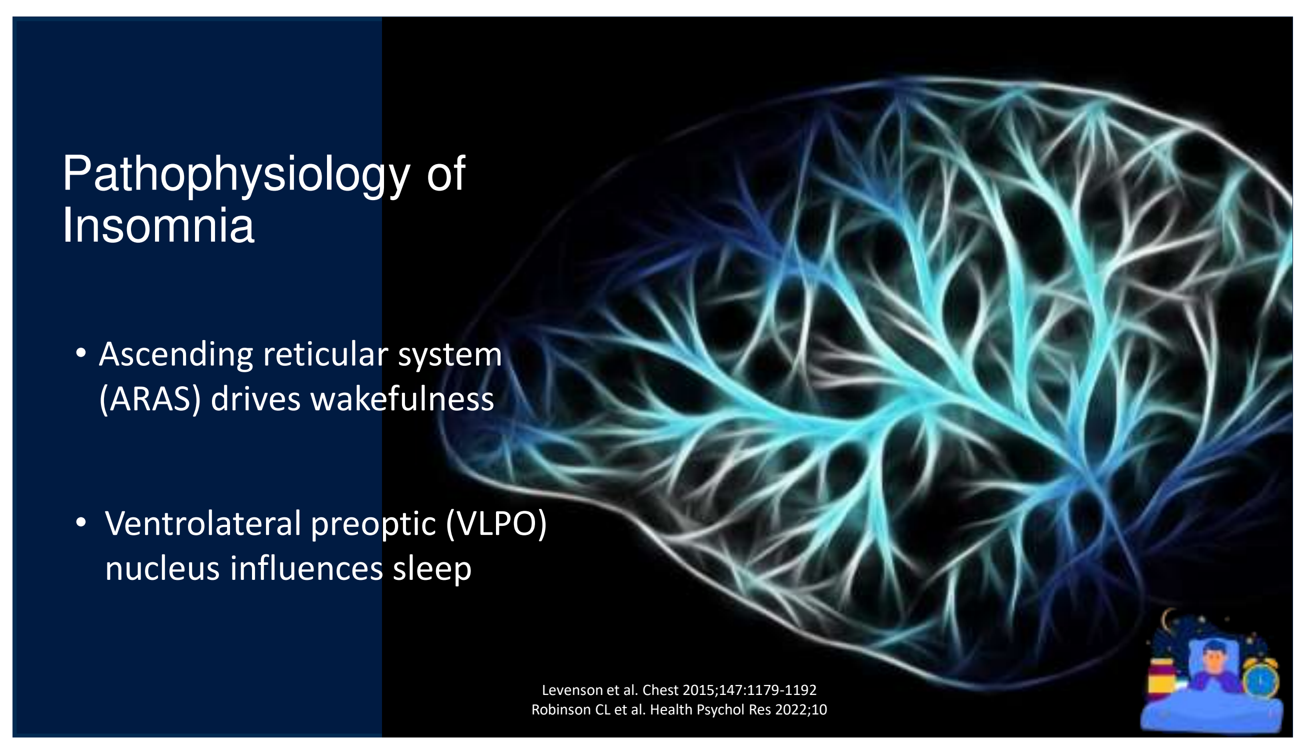
Disclosures

- **Stephen Brunton, MD, FAAFP, CDCES,** has disclosed that he is on the advisory board and/or speakers bureau for Abbott Diabetes, AstraZeneca, Bayer, Biolinq, Boehringer Ingelheim, Lifescan, Lilly, Novo Nordisk, Sanofi, and holds stock options for Paracrine.

- All relevant financial relationships have been mitigated.

Learning Objectives

Participants in this presentation should be able to…
Describe the physiology of sleep and wake as it relates to insomnia management.
Identify patients with insomnia by routinely asking about sleep and associated symptoms, as well as employing recommended diagnostic methods.
Select appropriate pharmacologic treatments for patients with insomnia, when indicated, based on patient characteristics and risk-benefit profiles.
Incorporate DORAs into the multimodal treatment approach for treating insomnia, as appropriate.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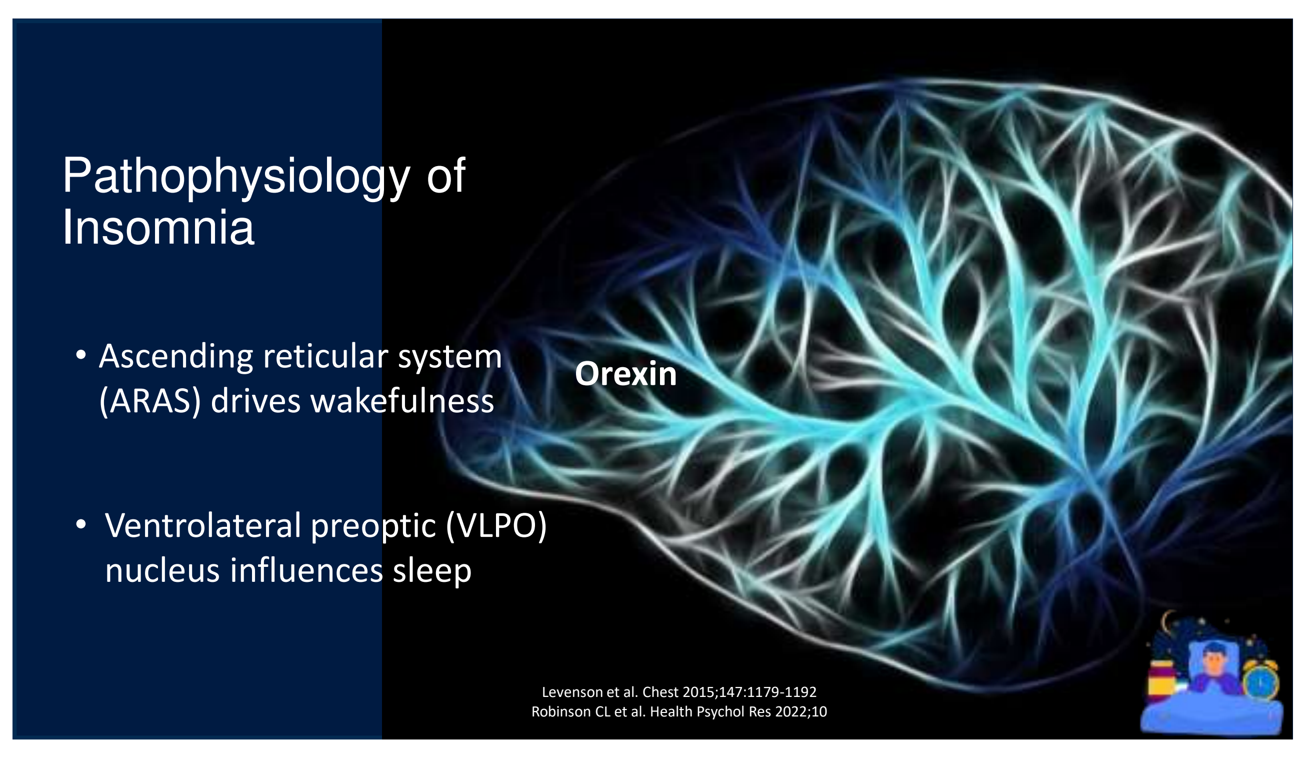
• Ascending reticular system (ARAS) drives wakefulness
• Ventrolateral preoptic (VLPO) nucleus influences sleep
Levenson et al. Chest 2015;147:1179-1192
Robinson CL et al. Health Psychol Res 2022;10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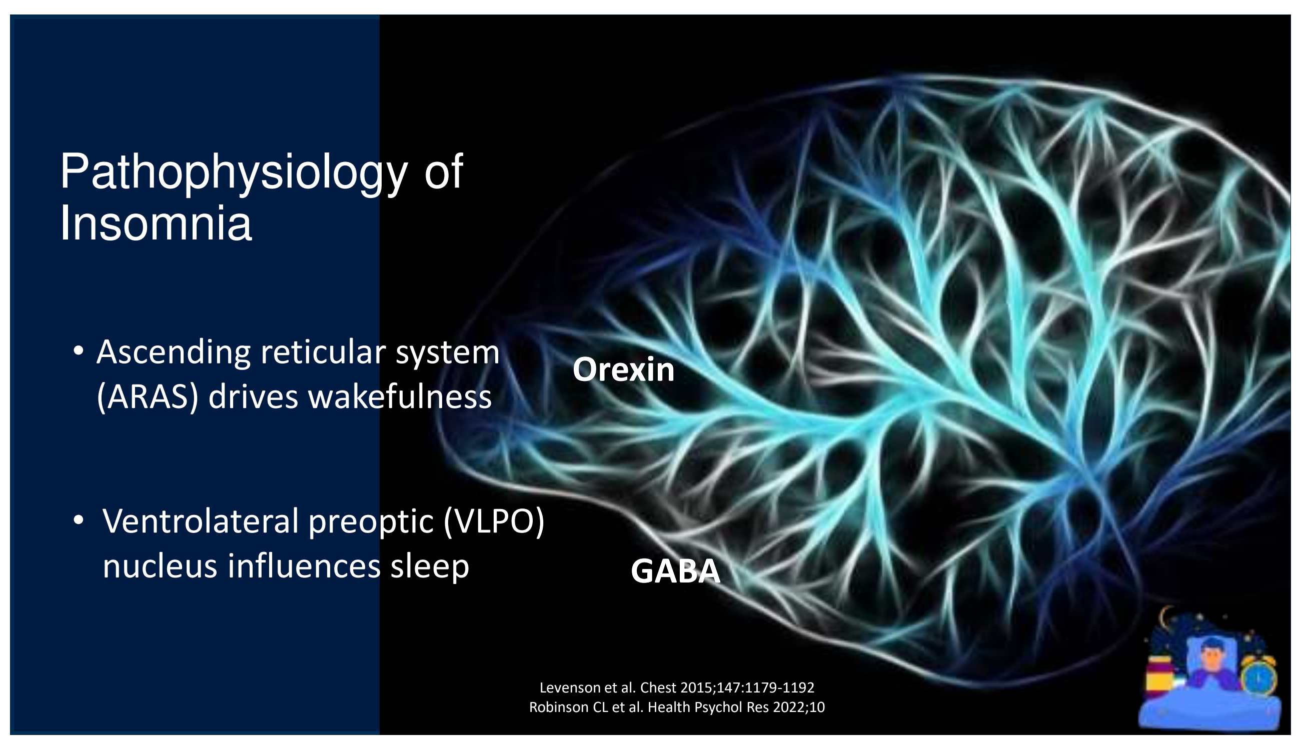
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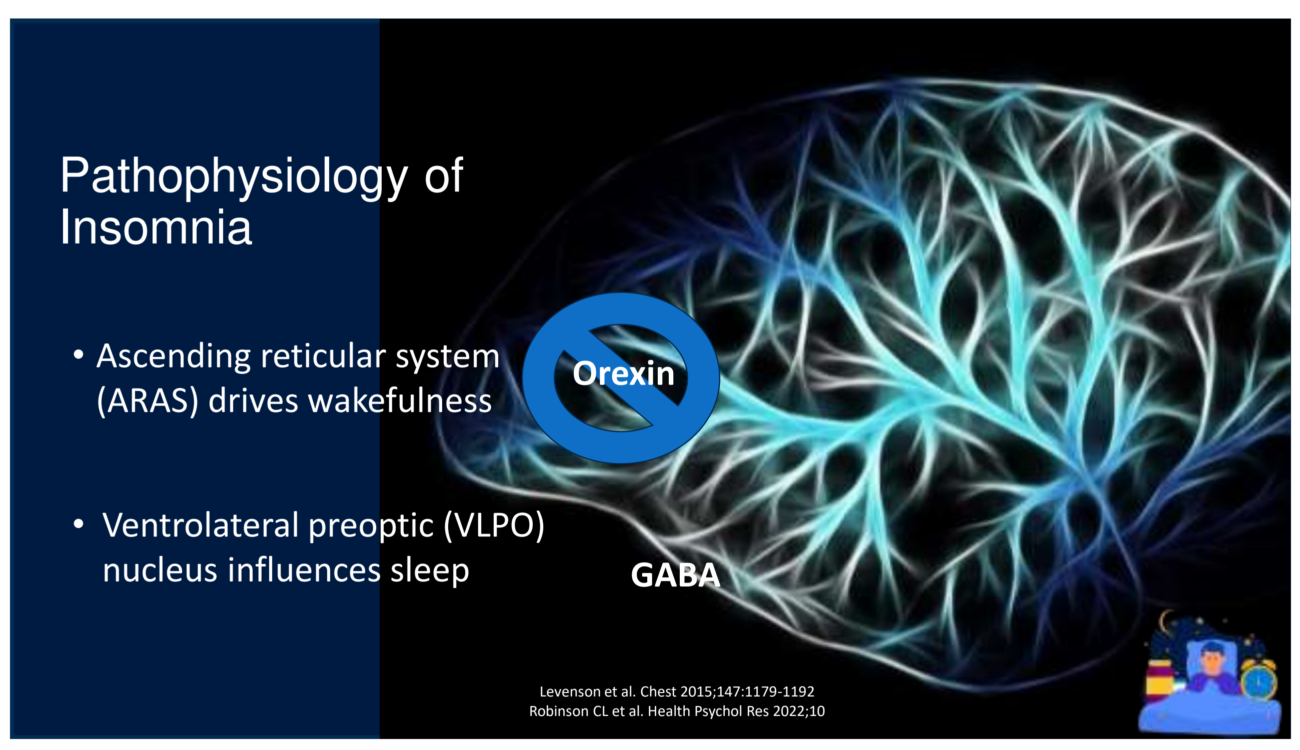
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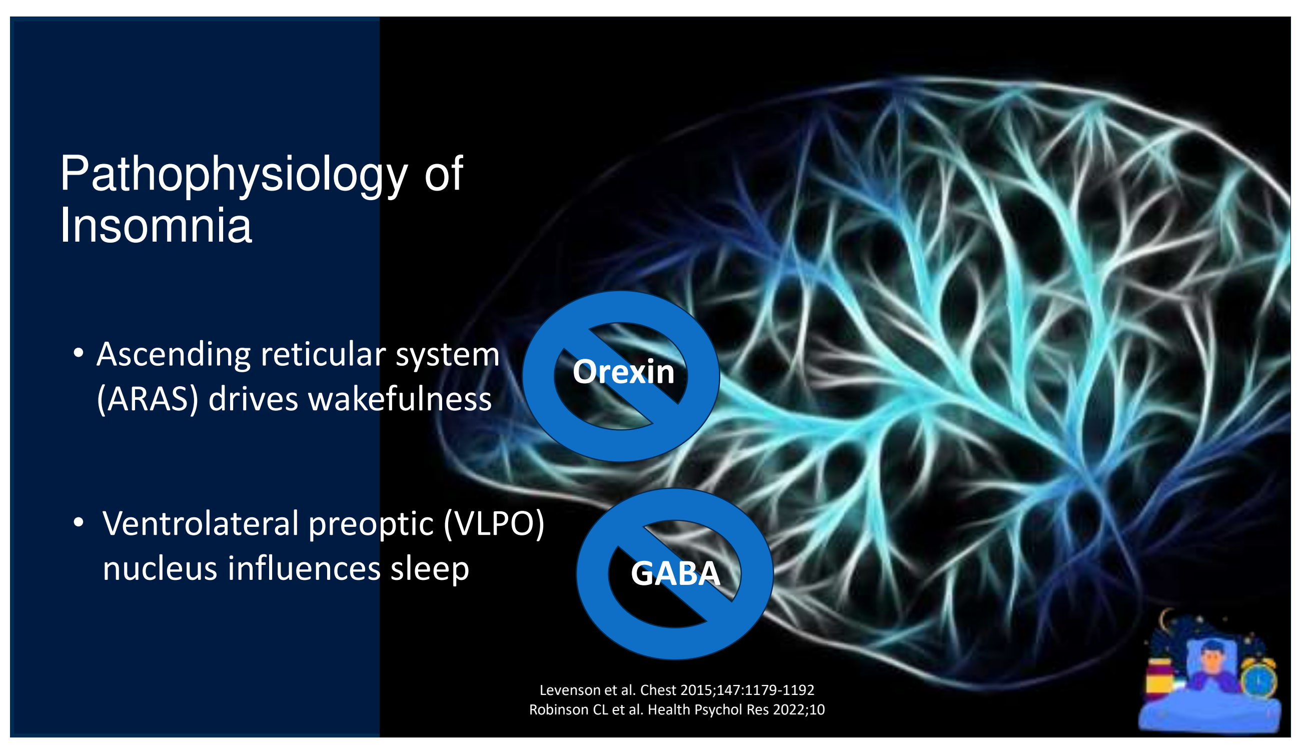

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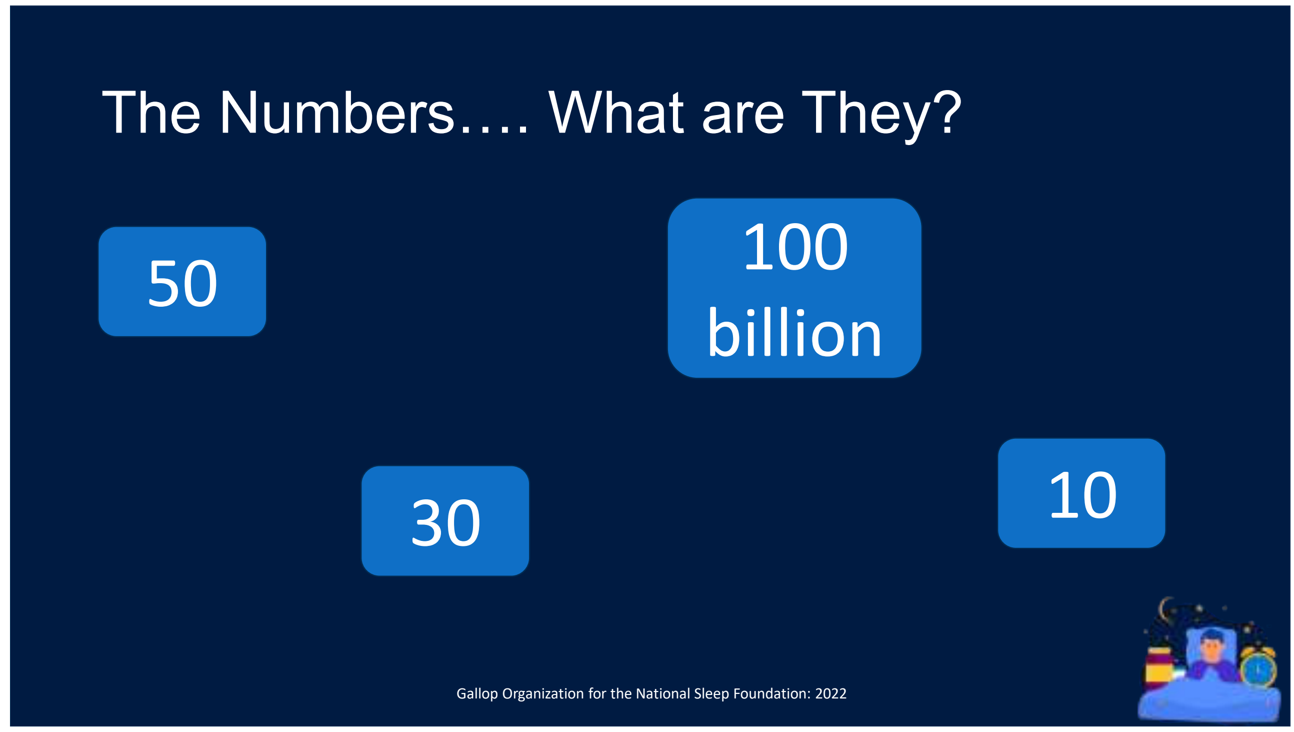
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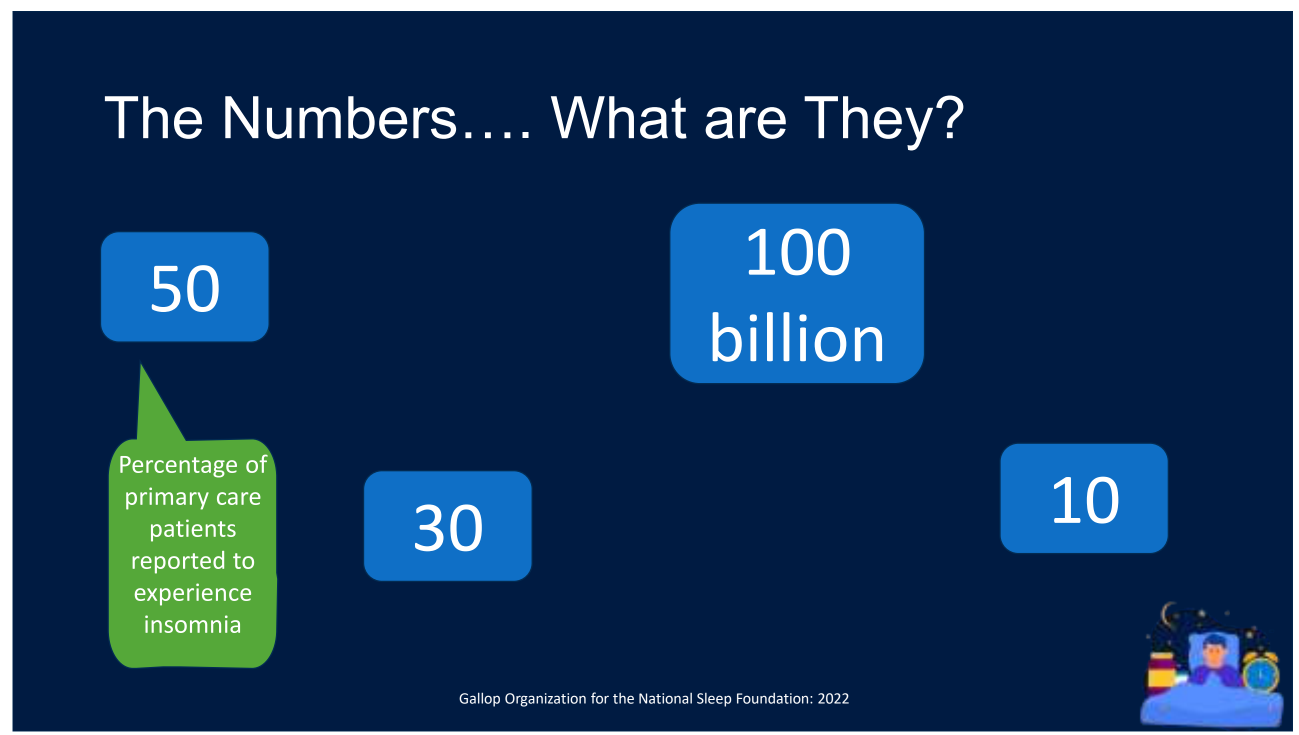
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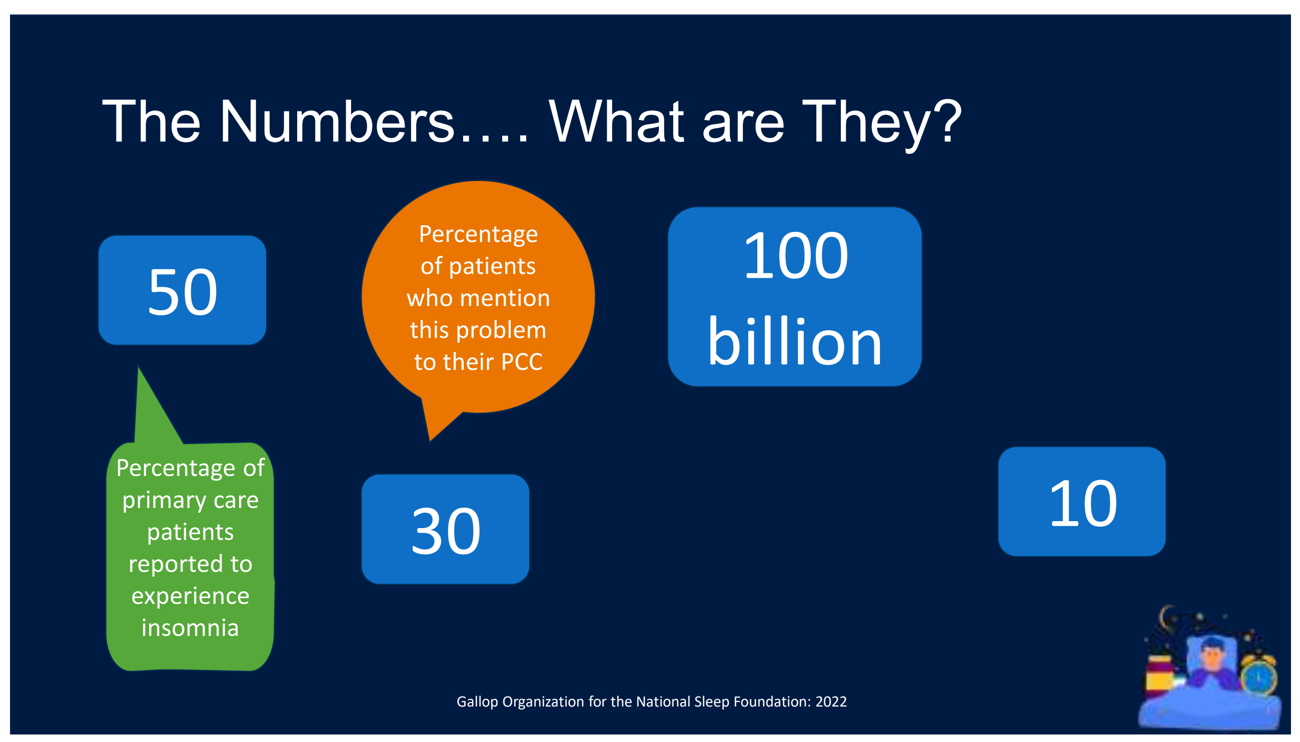
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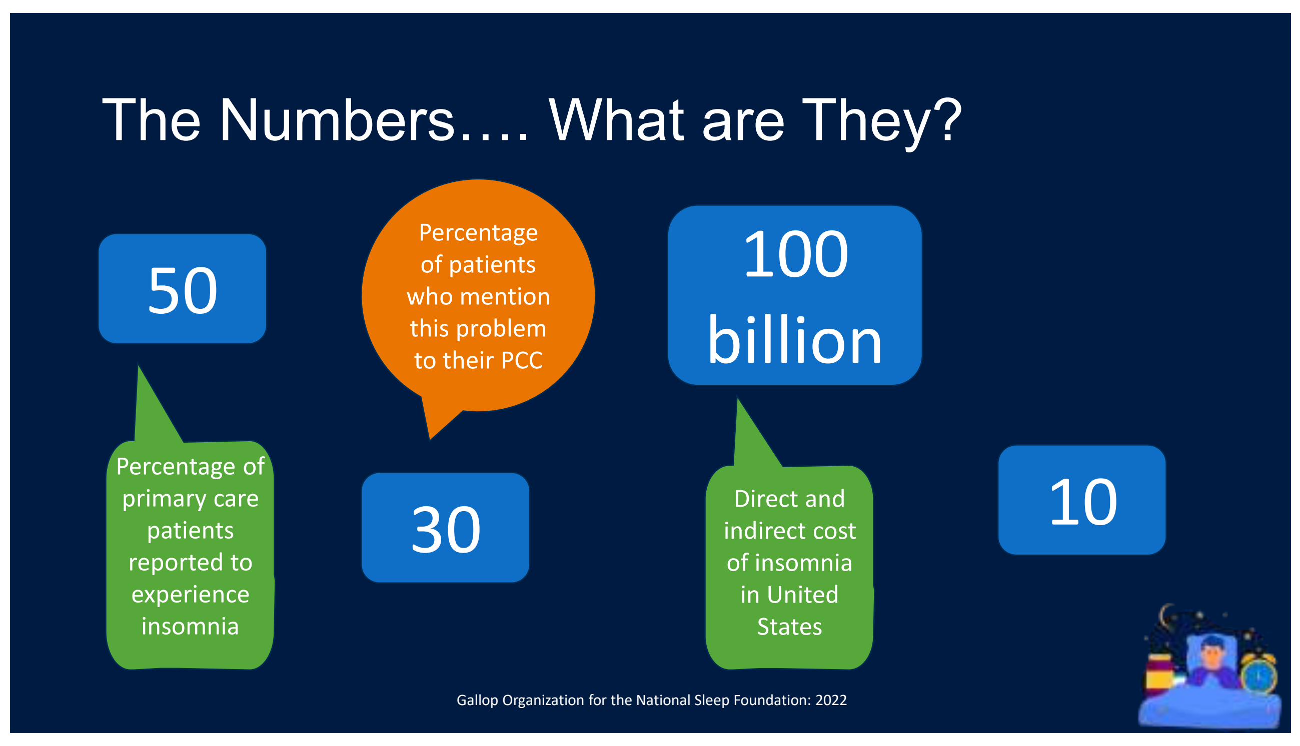
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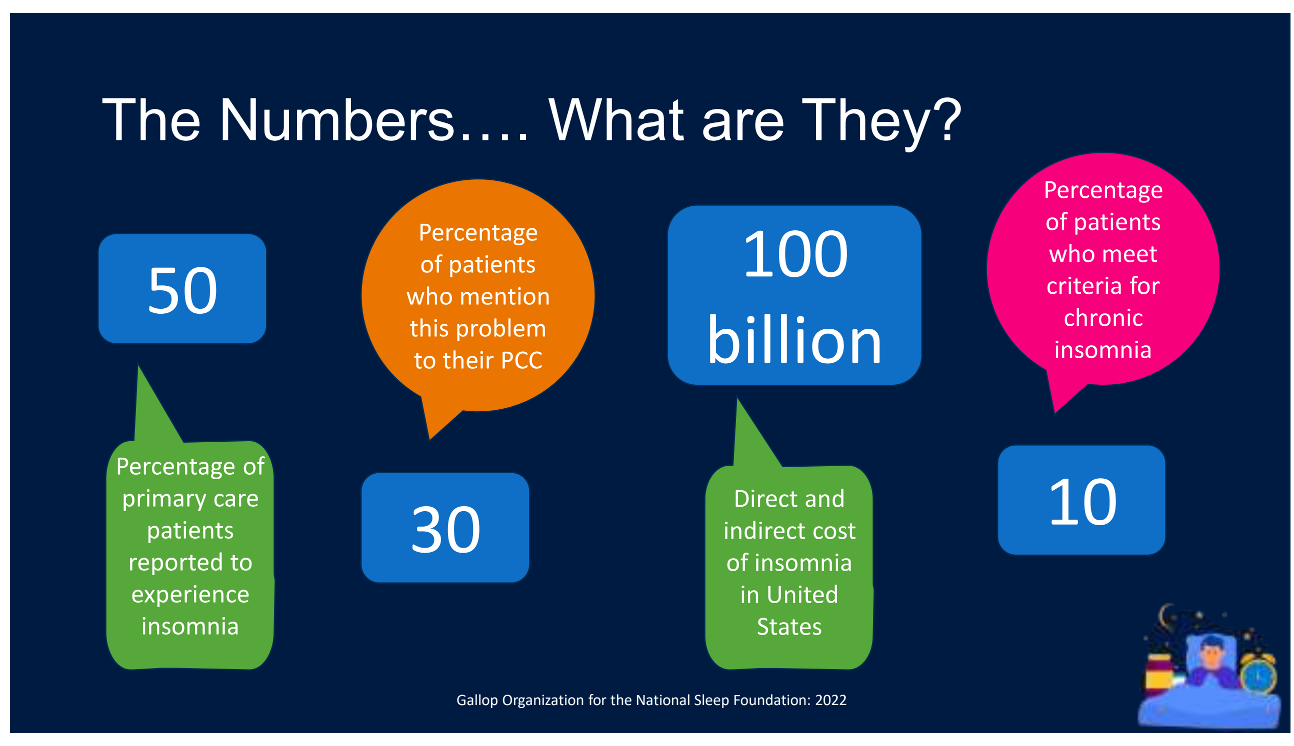
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Direct and indirect cost of insomnia in United States
Percentage of patients who meet criteria for chronic insomnia
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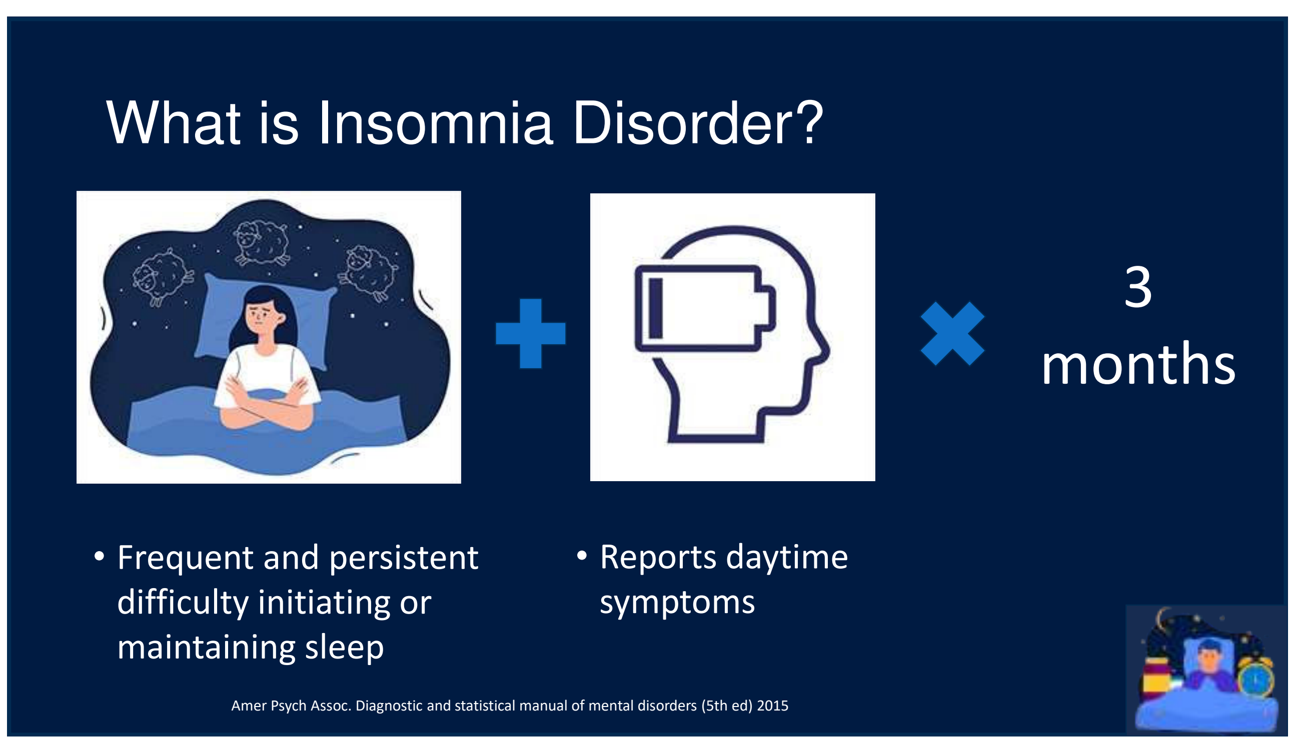
Gallop Organization for the National Sleep Foundation: 2022

Strategies to Combat Episodic Insomnia
COFFEE
www.thensf.org

Strategies to Combat Episodic Insomnia
• What is good sleep hygiene?
○ Consistent wake/bedtime in cool, dark environment
○ Allowing 7-9 hours nightly
○ Avoiding substances/food/activities before bed
○ Avoiding electronics an hour before bed and never in the bed
www.thensf.org
COFFEE


What is Insomnia Disorder?
3
months
• Frequent and persistent difficulty initiating or maintaining sleep
• Reports daytime symptoms
Amer Psych Assoc. Diagnostic and statistical manual of mental disorders (5th ed) 2015

Consequences of Insomnia

- Disability or medical leave
- Traffic accidents
- Depression, anxiety, alcohol use disorder, psychosis
- Alzheimer's disease
- Hypertension and cardiovascular disease, can be bidirectional
- Death

Deak et al. Neurolog Clin 2012;30(4):1045-66, JAMA 2013;309(7):706-16, Lancet 2012;379:1129-41

How to Assess for Insomnia

- Ask!

  Do you have trouble getting to sleep or staying asleep?
  Do you feel well rested during the day?

- Identify medical and psychiatric comorbidities
- Sleep diary
- Insomnia Severity Index, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale

Patient Evaluation of Sleep Disturbance

Comorbidities

Mental disorders
Cardiovascular diseases
Respiratory diseases
Rheumatologic diseases
Malignancies
Endocrine disorders
Neurogenerative disorders

Substance Use/ Dependence

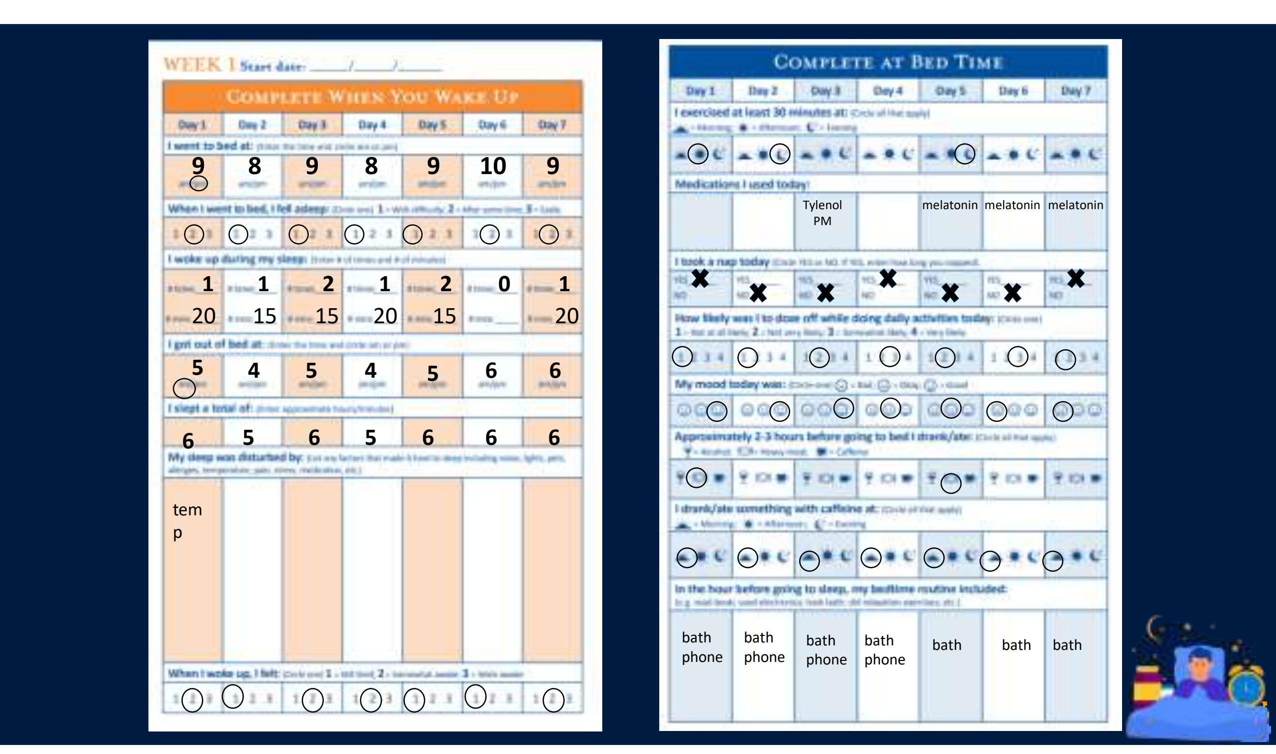
Alcohol
Nicotine
Caffeine
THC
Opioids
Cocaine
Amphetamines

Medications

ADHD stimulants
SSRIs/ SNRIs
Bupropion
Varenicline
Corticosteroids

Meet Mrs L

- Mrs L is a 64-year-old patient you have seen for 15 years. She has a past medical history of hypertension and depression, both currently well controlled on amlodipine 10mg-HCTZ 12.5mg daily and sertraline 100mg daily. She recently started a new job as a bus driver for the elementary school since the passing of her husband 6 months ago.
- During her visit today, she mentions to you how tired she is and that she is not sleeping well. After further discussion, you talk briefly about sleep hygiene, ask her to complete a sleep diary and return in 2-3 weeks...



WEEK 1 Start date: ____/____/____

Complete When You Wake Up

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
I went to bed at:	9	8	9	8	9	10	9
When I went to bed, I fell asleep:							
I woke up during my sleep: # times	1	1	2	1	2	0	1
# mins	20	15	15	20	15	___	20
I got out of bed at:	5	4	5	4	5	6	6
I slept a total of:	6	5	6	5	6	6	6
My sleep was disturbed by:	temp						
When I woke up, I felt:							

Complete at Bed Time

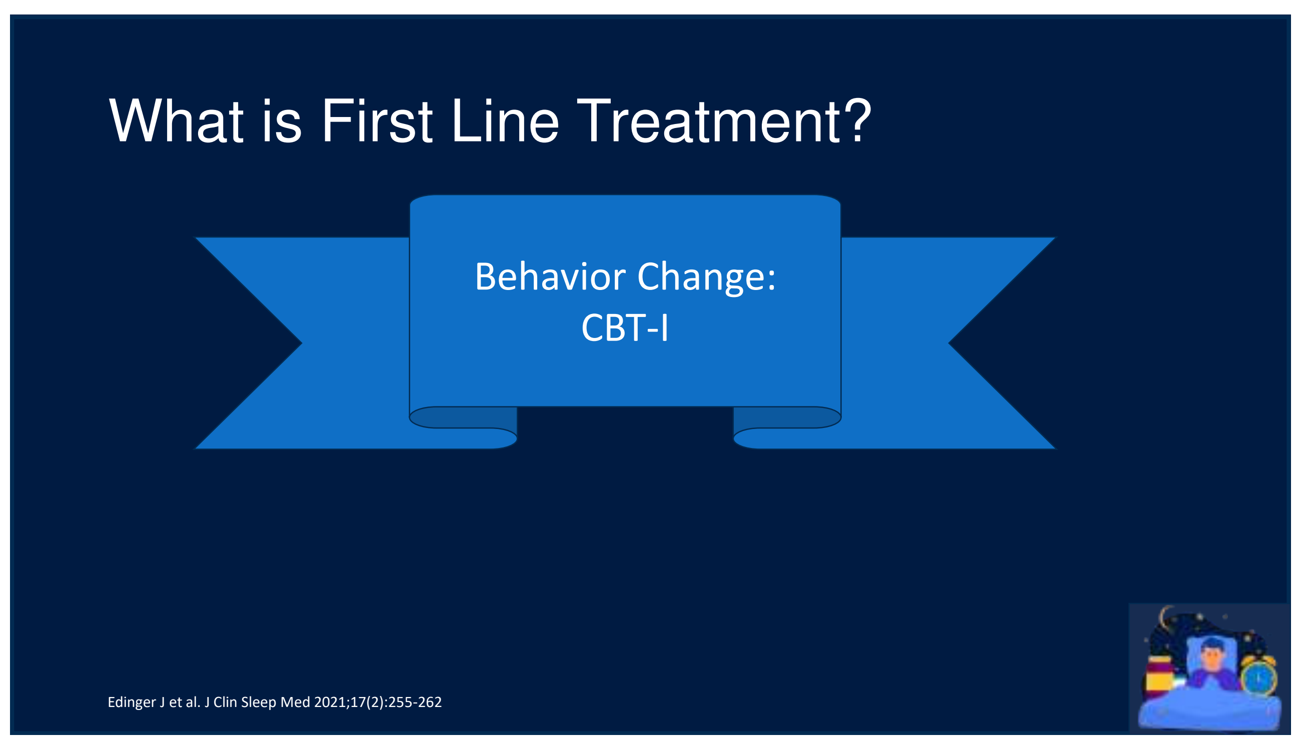
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
I exercised at least 30 minutes at:							
Medications I used today:			Tylenol PM		melatonin	melatonin	melatonin
I took a nap today							
How likely was I to doze off while doing daily activities today:							
My mood today was:							
Approximately 2-3 hours before going to bed I drank/ate:							
I drank/ate something with caffeine at:							
In the hour before going to sleep, my bedtime routine included:	bath phone	bath phone	bath phone	bath phone	bath	bath	bath

Return Visit...

- Mrs L completed her sleep diary and started taking melatonin supplements (5mg) during second week with no noticeable improvement.
- Upon questioning, she admits to scrolling through her social media in bed when she is frustrated about not sleeping, and sleeps with TV on with sound very low.
- Tylenol PM (taken once) caused excessive sleepiness the next day.
- Her PHQ-9 score is 8; she admits to being lonely but otherwise ok.

What is First Line Treatment?

Edinger J et al. J Clin Sleep Med 2021;17(2):255-262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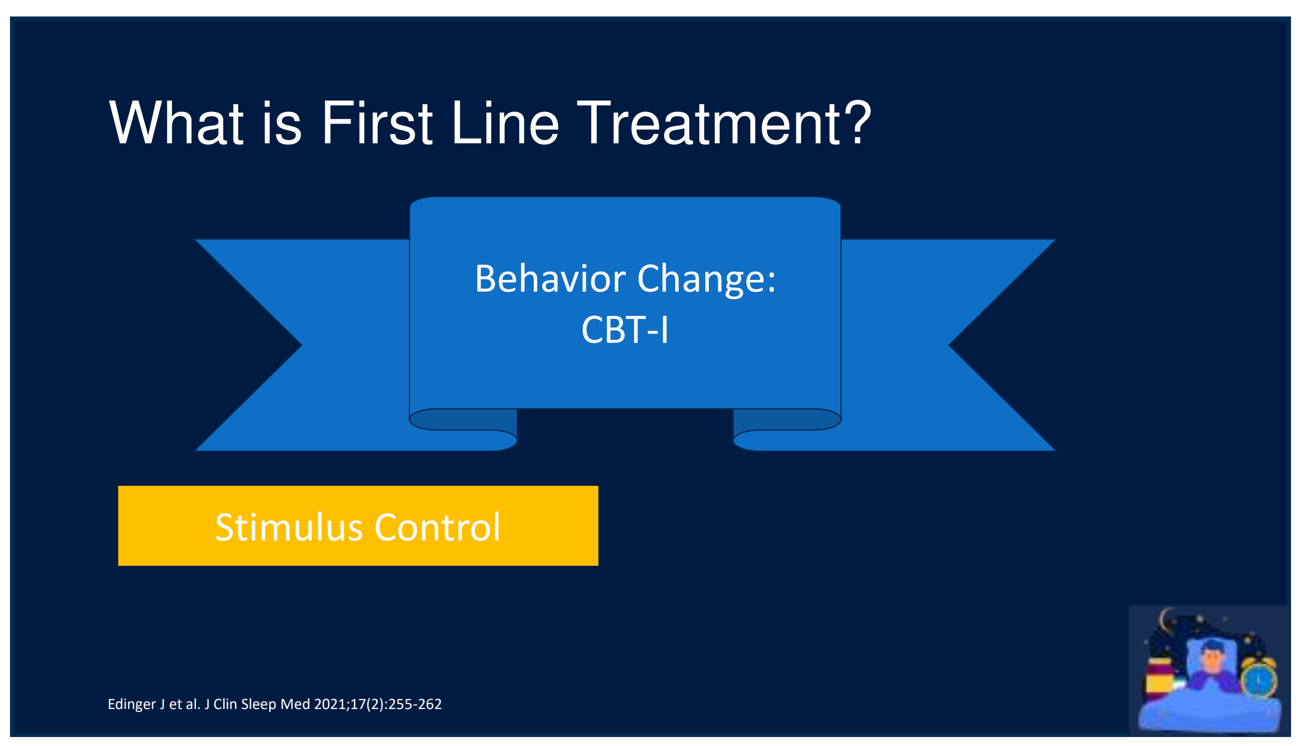
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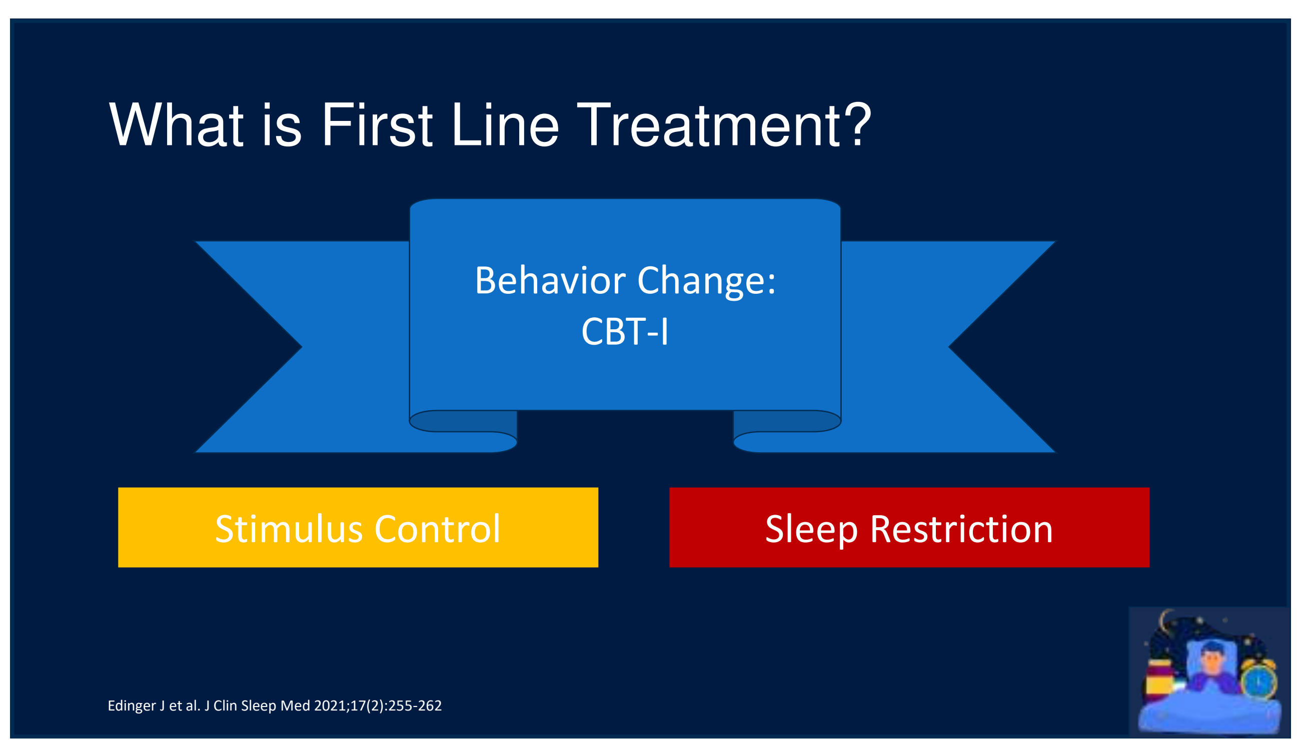
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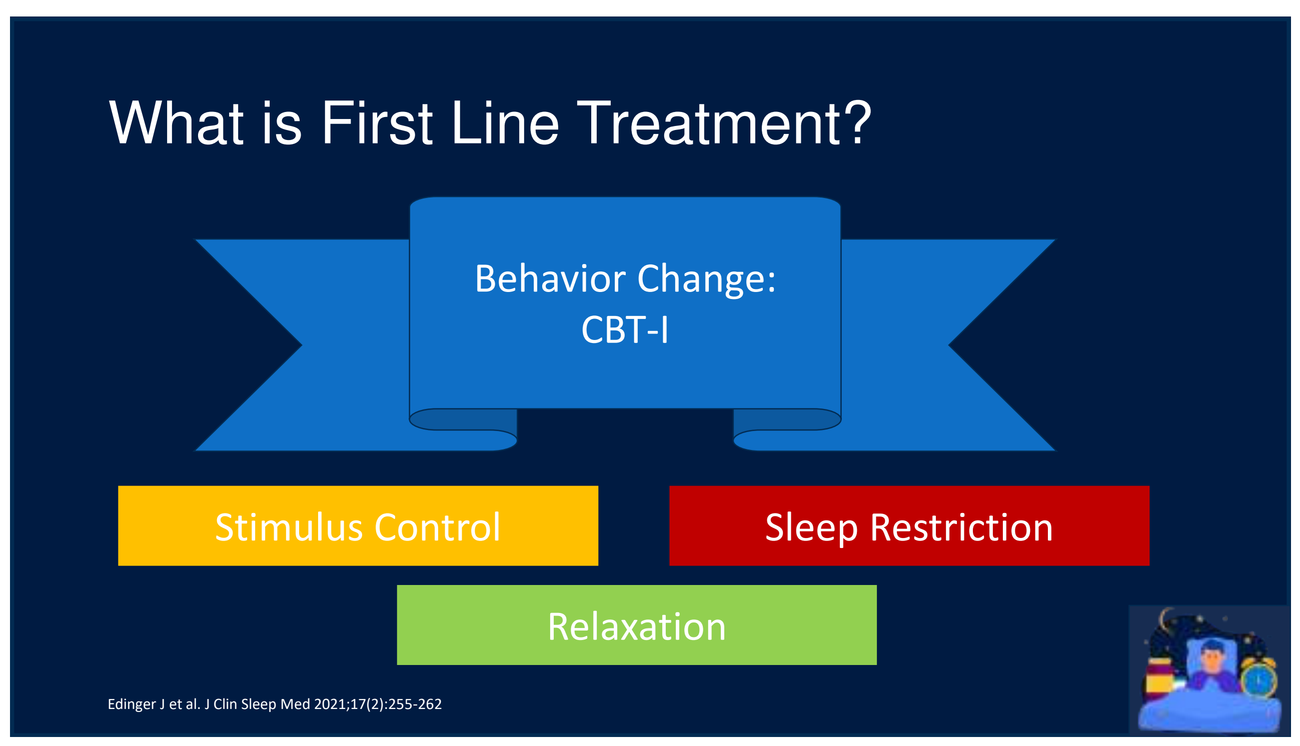
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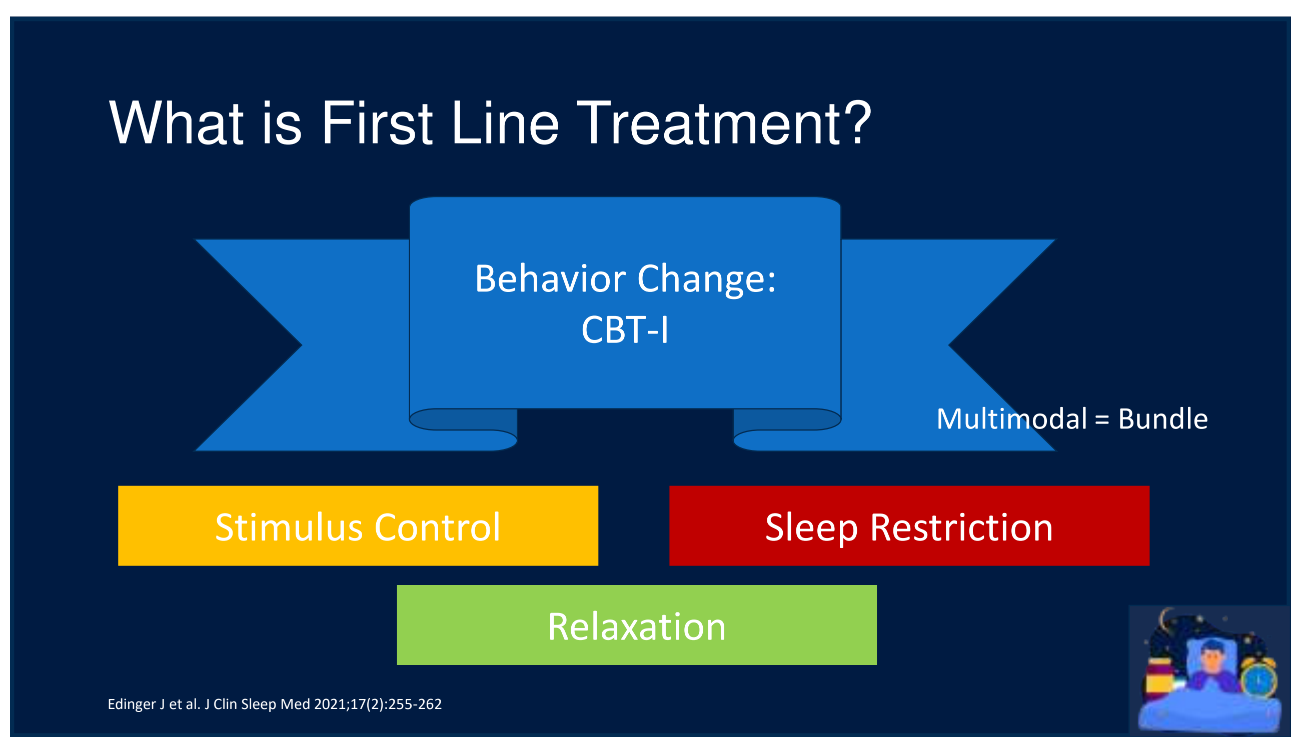
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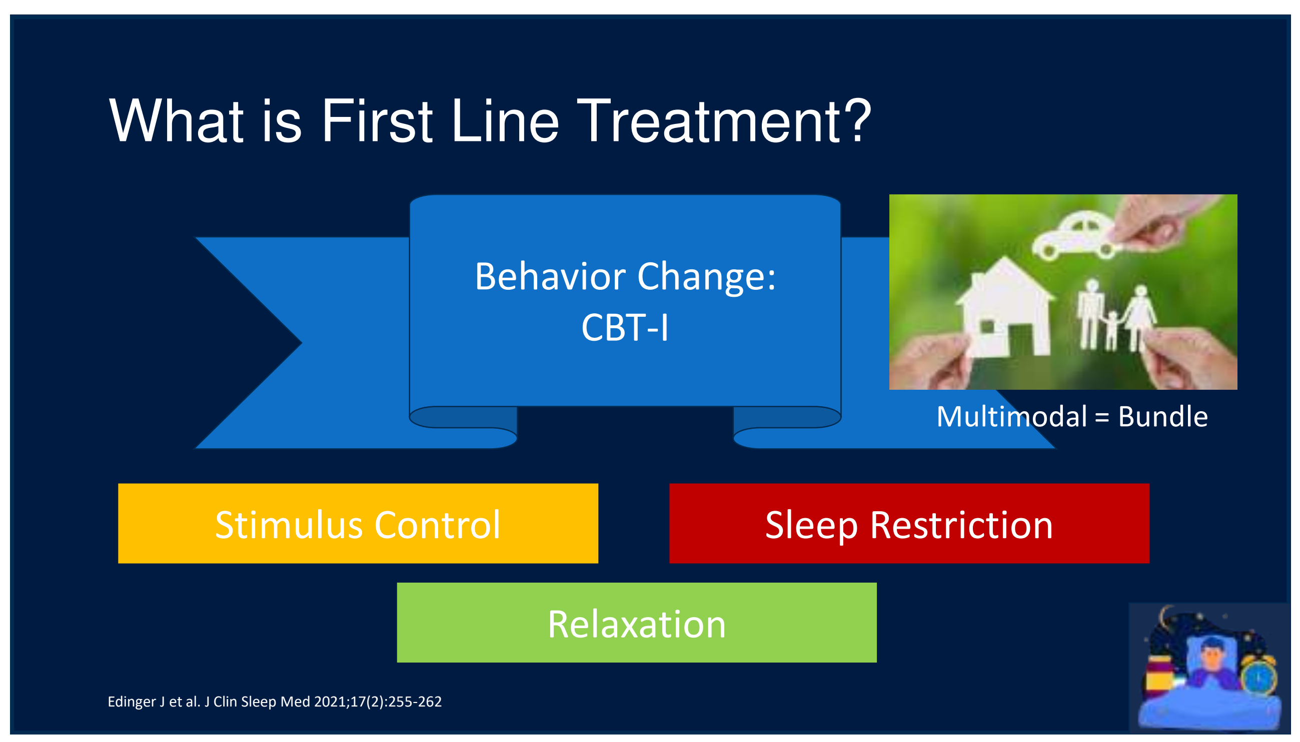
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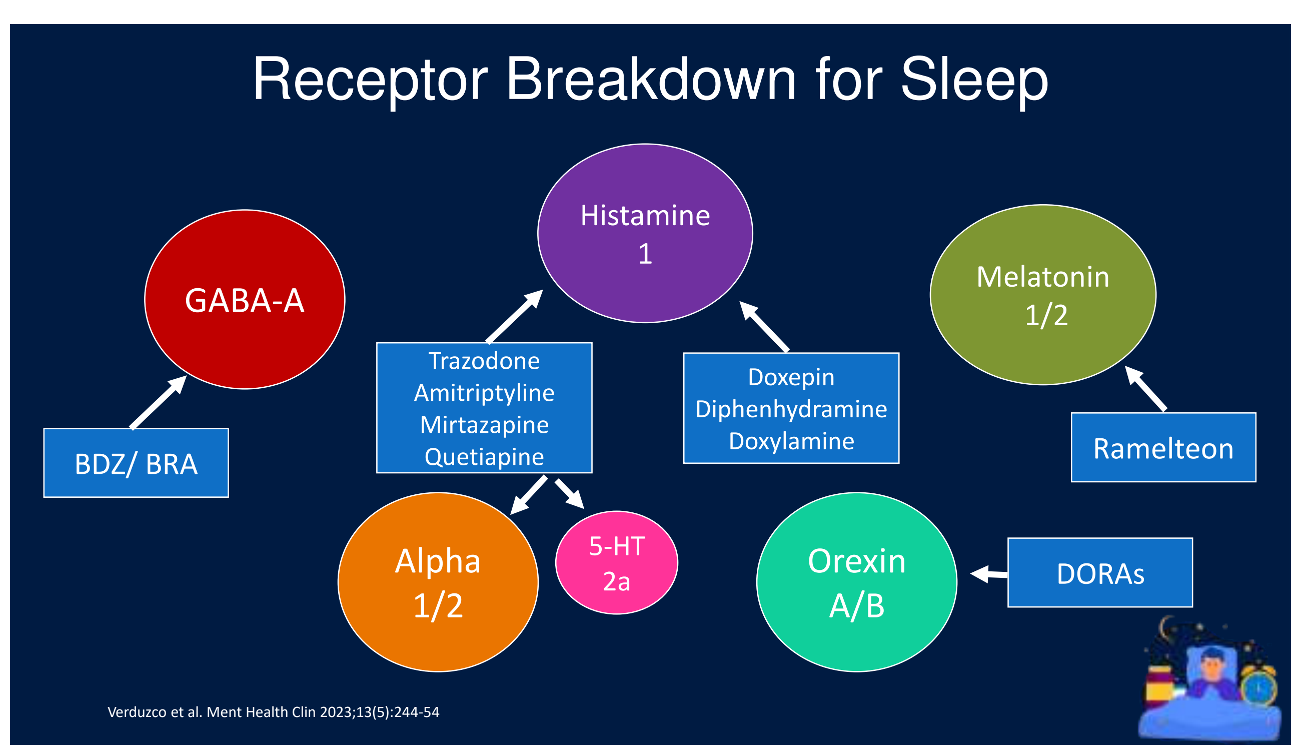
And if CBT-I Doesn't Work?

Commonly Used Medications for Sleep	
Sedating antidepressants	**Antipsychotics**
trazodone, doxepin, mirtazapine	quetiapine
Melatonin agonist	**Herbal supplements**
ramelteon	melatonin, L-tryptophan, valerian, chamomile
Benzodiazepine receptor agonists	**Antihistamines**
zolpidem, eszopiclone, zaleplon	diphenhydramine, doxylamine
Benzodiazepines	**Anticonvulsants**
temazepam, clonazepam, alprazolam	tiagabine
Dual orexin receptor antagonists	
suvorexant, lemborexant, daridorexant	



Receptor Breakdown for Sleep
Histamine 1
GABA-A
Melatonin 1/2
Trazodone
Amitriptyline
Mirtazapine
Quetiapine
Doxepin
Diphenhydramine
Doxylamine
BDZ/ BRA
Ramelteon
Alpha 1/2
5-HT 2a
Orexin A/B
DORAs
Verduzco et al. Ment Health Clin 2023;13(5):244-54

The Orexin Story

- Orexin (ORX-A and ORX-B) are neuropeptides discovered in 1998
- Involved in central physiological regulation of sleep and wakefulness, and maintenance of arousal
- Dual orexin receptor antagonists **(DORAs)** are FDA-approved for treatment of insomnia
  - Suborexant (2014)
  - Lemborexant (2019)
  - Daridorexant (2022)

What to Know about DORAs

- Pharmacokinetic half-life differences:
- Suvorexant 12 hours
- Lemborexant 18 hours
- Daridorexant 8 hours

- Work by reducing arousal but preserve person's ability to awaken in response to auditory stimuli
- FDA-approved for sleep onset and sleep maintenance insomnia
- Studies up to 3 months show continued efficacy, low risk of rebound insomnia upon discontinuation
- Next day cognition data is positive

DORA Counseling

Dosing	
Suvorexant	10mg, 30 min before bedtime
Lemborexant	5mg immediately before bedtime
Daridorexant	25-50mg within 30 min before bedtime

Adverse Effects

Headache
Dizziness
Daytime sleepiness
Sleep Paralysis
Hypnagogic hallucinations
Suicidal Ideations

Additional Info

- Contraindication: Narcolepsy
- Do not use in severe liver impairment & sleep apnea
- DORAs are CYP 3A4 substrates
- Time to sleep delayed with high-fat meal
- Schedule IV medicine
- Expensive

Verduzco A et al. Ment Health Clin 2023;13(5):244-54

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Suv 23/2027 (0.01%)
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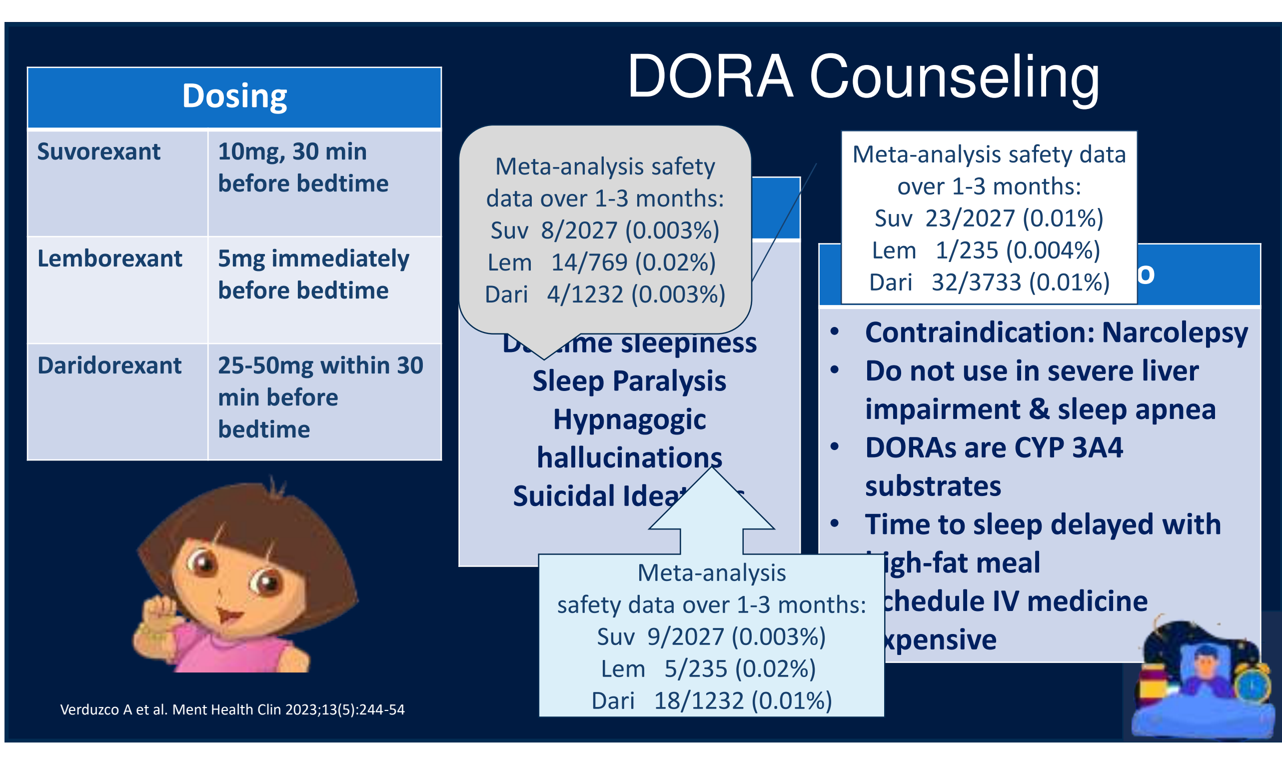

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Zzzzzzzz Drugs: Important Points

	Dosing	Unique Considerations
Zolpidem	IR or nasal spray: Men: 5-10mg Women: 5mg ER formulation: Men: 6.25-12.5mg Women: 6.25mg Elderly: 5mg	Visual disturbances Slower clearance in women and elderly ER: Do not perform next day activities requiring complete awareness
Eszopiclone	1 to 2mg	Unpleasant taste
Zaleplon	5 to 10mg	Shortest half-life:1 hour Sleep onset approval only

- Minimal anxiolytic effects compared to BDZ
- Lower risk of tolerance, abuse, dependence when compared to BDZ
- Short-term use (< 4 weeks) recommended

Z Drug Warnings and ADRs

Black Box Warning (2019): complex sleep disorders such as sleepwalking and sleep driving can result in serious injury or death

Adverse Effects

Headache, dizziness, confusion, next-day drowsiness, falls, amnesia, rebound insomnia, withdrawal

Remember This Survey Question?

?

Zolpidem 10mg at night is most appropriate for

A. 45-year-old man with heart disease.

B. 67-year-old female currently taking melatonin for sleep.

C. 40-year-old who drinks alcohol (1-2 drinks) most evenings.

D. 29-year-old truck driver.

A 10mg dose of zolpidem is not recommended in women or elderly (at least initially), should not mix with alcohol at all (increased risk of complex sleep behaviors), and should not be used for patients who require next day alertness for their job (like a commercial driver).

BDZs: Temazepam, Triazolam

Indicated for short-term treatment of insomnia (2 weeks)

Not generally recommended due to adverse effect potential:

- Next day fatigue
- Anterograde amnesia
- Depression (longer term use)
- Falls and fracture risk (on Beer's list of unsafe medications in elderly)
- CNS additive effects with alcohol
- Abuse potential

Verduzco A et al. Ment Health Clin 2023;13(5):244-54

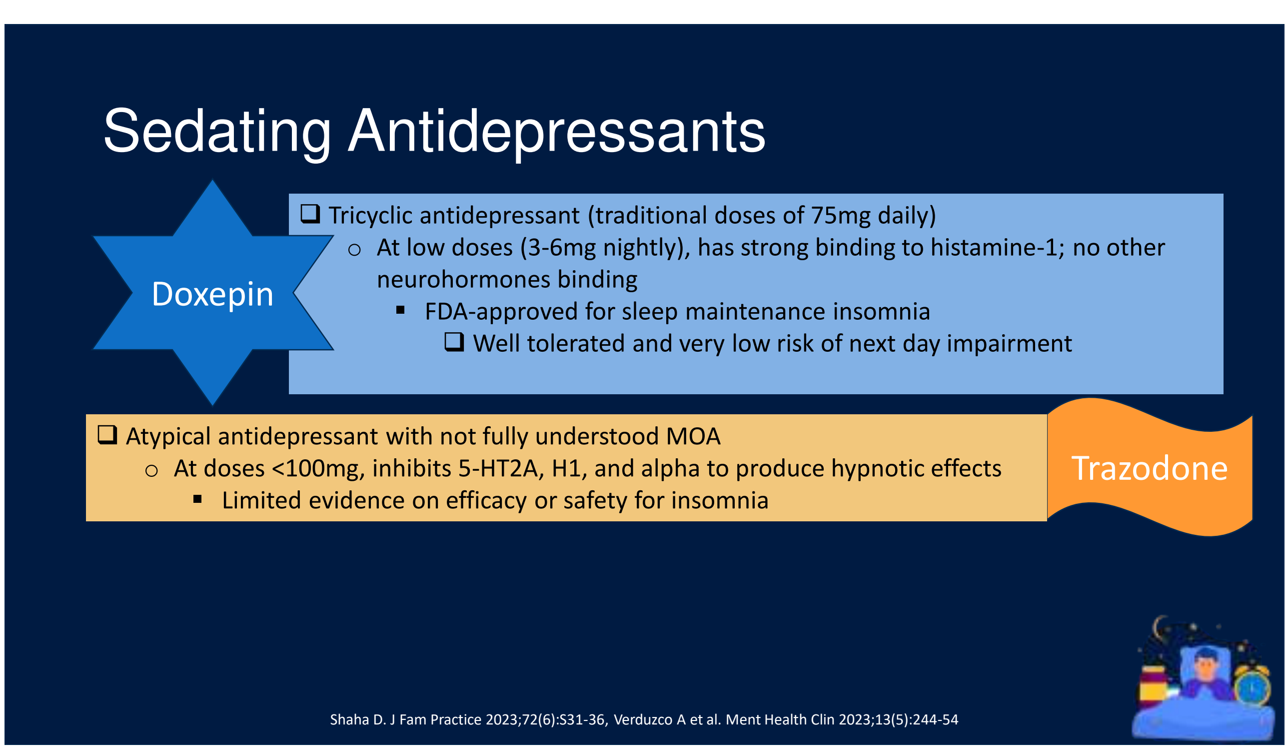
My Circadian Rhythm Needs Help!

- Ramelteon has 3 to 5 times the selective affinity for melatonin receptors
- FDA-approved for sleep onset insomnia

- Well tolerated
  - Safe with substance use disorders
  - Can cause next day drowsiness
- Generic now available
- Dose: 8mg at bedtime

Sedating Antidepressants

Sedating Antidepressants
Doxepin
Tricyclic antidepressant (traditional doses of 75mg daily)
At low doses (3-6mg nightly), has strong binding to histamine-1; no other neurohormones binding
FDA-approved for sleep maintenance insomnia
Well tolerated and very low risk of next day impairment
Shaha D. J Fam Practice 2023;72(6):S31-36, Verduzco A et al. Ment Health Clin 2023;13(5):244-54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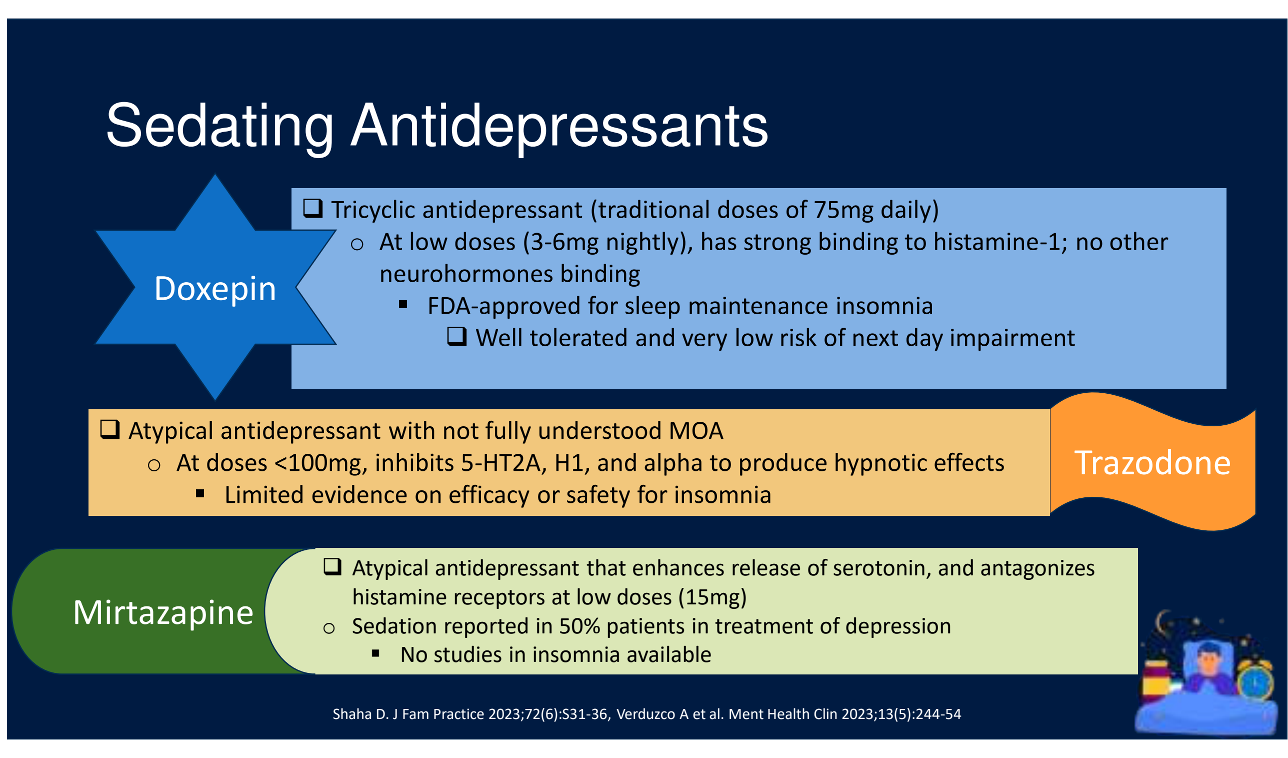
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▪ Limited evidence on efficacy or safety for insomnia
Trazodone
Mirtazapine
❑ Atypical antidepressant that enhances release of serotonin, and antagonizes histamine receptors at low doses (15mg)
○ Sedation reported in 50% patients in treatment of depression
▪ No studies in insomnia available
Shaha D. J Fam Practice 2023;72(6):S31-36, Verduzco A et al. Ment Health Clin 2023;13(5):244-54

How is Mrs L doing?

- During her follow-up visit, Mrs L agreed to stop scrolling through her phone in bed and try to sleep with TV off.
- Upon return 1 month later, she reports no phone/TV for an hour before bed, and instead started listening to white noise.
- She joined a local gym and started a senior adult class 4 days per week at 5pm, which has helped with her loneliness.
- Her sleep diary still shows only 5 to 6 hours of sleep nightly and she reports increased fatigue during the daytime.

Do We Have Good Guidance?

<table>
<tr><th colspan="2">2017 AASM</th><th colspan="2">2019 VA/DoD</th></tr>
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<tr><td>Weak for:
Temazepam
Eszopiclone
Zolpidem</td><td>
Zaleplon
Ramelteon
Triazolam
Doxepin
Suvorexant</td><td>Weak for:
Doxepin
Z-drugs</td><td>Weak Against:
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Melatonin
Antipsychotics
BZDs
Trazodone</td></tr>
<tr><td colspan="2">Not Recommended:
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Suvorexant
Strong Against: Kava</td></tr>
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Do We Have Good Guidance?

2017 AASM		2019 VA/DoD	
Strong for: **CBT-I (mod-qual)**		**Strong for:** **CBT-I**	
Weak for: Temazepam Eszopiclone Zolpidem Sleep onset & maintenance	Zaleplon Ramelteon Triazolam Doxepin Suvorexant	***Weak for:*** Doxepin Z-drugs	***Weak Against:*** Diphenhydramine Melatonin Antipsychotics BZDs Trazodone
Not Recommended: Diphenhydramine Melatonin Trazodone		***Neither for or Against:*** Ramelteon Suvorexant ***Strong Against:*** Kava	

Do We Have Good Guidance?

2017 AASM		2019 VA/DoD	
Strong for: CBT-I (mod-qual)		**Strong for:** CBT-I	
Weak for: Temazepam Eszopiclone Zolpidem (Sleep onset & maintenance)	Zaleplon Ramelteon Triazolam (Sleep onset) Doxepin Suvorexant	***Weak for:*** Doxepin Z-drugs	***Weak Against:*** Diphenhydramine Melatonin Antipsychotics BZDs Trazodone
Not Recommended: Diphenhydramine Melatonin Trazodone		***Neither for or Against:*** Ramelteon Suvorexant ***Strong Against:*** Kava	

Do We Have Good Guidance?

2017 AASM		2019 VA/DoD	
Strong for: CBT-I (mod-qual)		**Strong for: CBT-I**	
Weak for: Temazepam Eszopiclone Zolpidem (Sleep onset & maintenance)	Zaleplon Ramelteon Triazolam (Sleep onset) Doxepin Suvorexant (Sleep maintenance)	***Weak for:*** Doxepin Z-drugs	***Weak Against:*** Diphenhydramine Melatonin Antipsychotics BZDs Trazodone
Not Recommended: Diphenhydramine Melatonin Trazodone		***Neither for or Against:*** Ramelteon Suvorexant ***Strong Against:*** Kava	

Guideline Update 2023: Europeans

Strong for: CBT-I (A)	
< 4 weeks: BDZ/BRA (A) Daridorexant (A) Low-dose antidepressants (B)	***3 months:*** DORAs (A) Ramelteon (B)
Not Recommended: Antihistamines Antipsychotics Melatonin	

J Sleep Res 2023;32:e14035

Specific Patient Considerations

	Sleep-onset insomnia	Sleep maintenance insomnia	Vulnerability to substance disorder	Need for normal next-day function
DORAs	X	X	X	X
BDZ		X		
BRA*	X	X		
Doxepin		X	X	X
Ramelteon	X		X	

Shaha D. J Fam Practice 2023;72(6):S31-36, Rosenberg R et al. Prim Care Companion CNS Disord 2023;25

Remember This Knowledge Question?

What is a medication shown to improve sleep onset, sleep maintenance, and have a low risk of next day impairment and rebound insomnia or withdrawal?

A. trazodone
B. ramelteon
C. daridorexant
D. No such medicine exists

Trazodone is not well studied in insomnia, not FDA-approved, efficacy is doubted, and safety is unknown. Ramelteon is not FDA-approved for sleep maintenance and guidelines differ on efficacy recommendations (still better than OTC melatonin). Early clinical trials with daridorexant have indicated improved sleep onset, improved sleep maintenance and a low risk for the negative impacts described above.

Back to Mrs L

- At last visit, Mrs L was encouraged for making hard lifestyle changes and encouraged to continue. She also agreed to a sleep restriction trial during school Spring break (stayed up until midnight and got up at 6am, then increased bedtime by 30 minutes every night).
- She has returned 1 month later and reports improvement, but still struggling several nights per week and has fatigue during daytime, making it difficult to attend gym classes.
- You discuss medication to assist with insomnia...

You Choose

Based on the guidelines, what medication has the highest evidence for efficacy and safety for Mrs L?

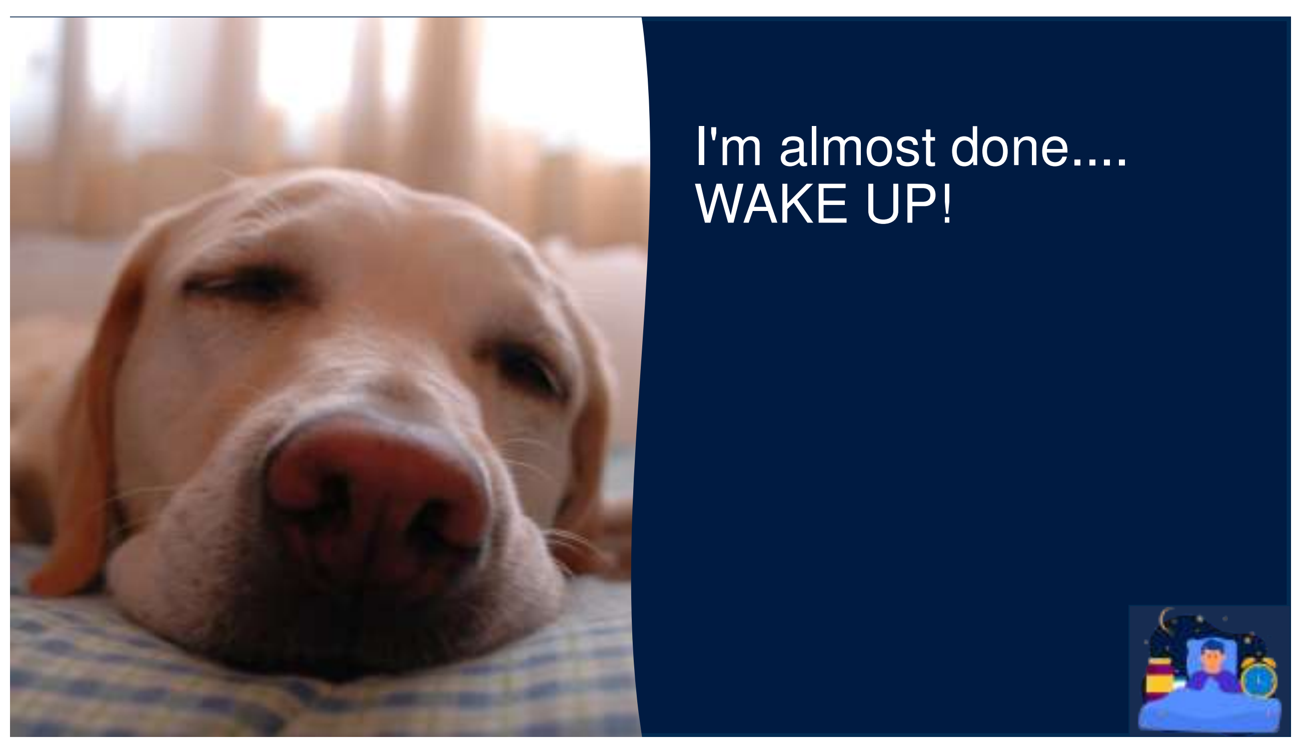
a. Trazodone
b. Daridorexent
c. Doxepin
d. Ramelteon

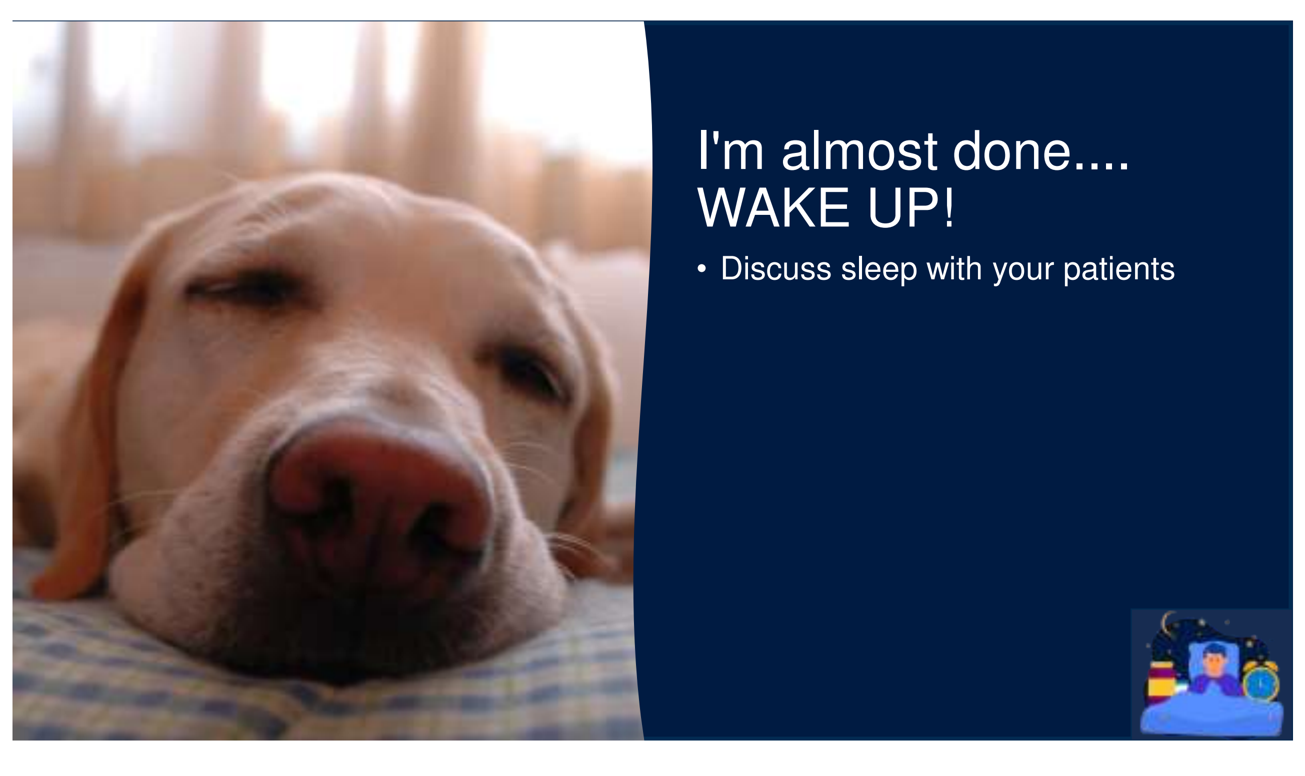
Correct Answer

Daridorexent

Based on sleep onset and sleep maintenance issues, and a need for early morning alertness for her job, B is the correct answer.

Another acceptable option would be doxepin 3mg with close follow up, but it is not great for sleep onset. The shortest acting BRA zaleplon could be a short-term option as well.


I'm almost done....
WAKE UP!


I'm almost done....
WAKE UP!
• Discuss sleep with your patients

I'm almost done.... WAKE UP!

- Discuss sleep with your patients
- Counsel on good sleep behaviors and strategies

I'm almost done.... WAKE UP!

- Discuss sleep with your patients
- Counsel on good sleep behaviors and strategies
- Carefully select appropriate patients for pharmacologic treatment IN ADDITION to behavior change

I'm almost done.... WAKE UP!

- Discuss sleep with your patients
- Counsel on good sleep behaviors and strategies
- Carefully select appropriate patients for pharmacologic treatment IN ADDITION to behavior change
- Follow-up with all patients!

Resource Toolkit

- More resources for you on insomnia can be found at our resource toolkit, which you can visit via the URL or QR Code below.
- You'll also find a video of this presentation if there is anything you wish to review.

Learning Objectives

Let's go over the learning objectives we covered in this presentation:
Describe the physiology of sleep and wake as it relates to insomnia management.
Identify patients with insomnia by routinely asking about sleep and associated symptoms, as well as employing recommended diagnostic methods.
Select appropriate pharmacologic treatments for patients with insomnia, when indicated, based on patient characteristics and risk-benefit profiles.
Incorporate DORAs into the multimodal treatment approach for treating insomnia, as appropriate.

Pharmacologic Management of Insomnia

Post-presentation Survey: Please complete the brief survey by using the QR code to the right or the URL below.

URL: https://www.pcmg-us.org/survey/post/insomnia7