

INSOMNIA AND POOR SLEEP QUALITY

REVIEW OF TREATMENTS

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LEARNING OBJECTIVES

- By the end of this presentation, participants should be able to
- 1. Summarize the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) criteria for insomnia
- 2. Describe the etiology of insomnia
- 3. Name what populations are affected by insomnia and why
- 4. Identify dangers associated with insomnia
- 5. Identify non-pharmacological treatment options
- 6. List pharmacological treatment options
- 7. Describe ways that we can have an impact on our patients with regards to insomnia and sleep

BACKGROUND

TERMS

- Sleep Latency – the ability to fall asleep
 - Ideally, we want this to be a small number¹
 - This can be measured through the multiple sleep latency test (MSLT)
- Sleep Maintenance – staying asleep for the desired amount of time²
 - Quantity of sleep differs amongst age groups
- Sleep Efficiency – the amount of time spent asleep
 - Ideally, we want this to be $\geq 85\%$ ¹
 - = Total Sleep Time (min) / Time in Bed (min)
- Sleep Quality – An individual's satisfaction with their sleep²
 - Integrates other aspects of sleep

1. Brandon Peters MD. How sleep latency has an impact on your sleep. Verywell Health. <https://www.verywellhealth.com/sleep-latency-3014920>. Published December 7, 2020. Accessed August 12, 2021.
2. Sleep dictionary: Definitions of common sleep terms. Sleep Foundation. <https://www.sleepfoundation.org/how-sleep-works/sleep-dictionary>. Published January 8, 2021. Accessed August 20, 2021.

Table 32-2.

DSM-5 diagnostic criteria for insomnia.

INSOMNIA
DEFINITION

- A. A predominant complaint of dissatisfaction with sleep quality, associated with one (or more) of the following symptoms:
 - 1. Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention.)
 - 2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention.)
 - 3. Early-morning awakening with inability to return to sleep.
- B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, education, academic, behavioral, or other important areas of functioning.
- C. The sleep difficulty occurs at least three nights per week.
- D. The sleep difficulty is present for at least 3 months.
- E. The sleep difficulty occurs despite adequate opportunity for sleep.
- F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, and a parasomnia).
- G. The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse or a medication).
- H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

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WHY DOES INSOMNIA OCCUR?

WHAT CAUSES INSOMNIA?



CROSSING TIME ZONES



BLUE LIGHT



STRESS



ALCOHOL, SMOKING OR CAFFEINE



HEAVY FOOD



MEDICINES



ENVIRONMENTAL FACTORS



UNCOMFORTABLE BED OR PILLOW

ETIOLOGY

- Insomnia is thought to have several different etiologies
 - Cognitive
 - Physiological
- Thought to be due to hyperarousal during the day
 - This translates to difficulty initiating and maintaining sleep at night.

4. Picture Retrieved From: <https://www.news-medical.net/health/Insomnia-Causes.aspx>

5. Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med. 2007;3(5 Suppl):S7-S10.

ETIOLOGY CONTINUED

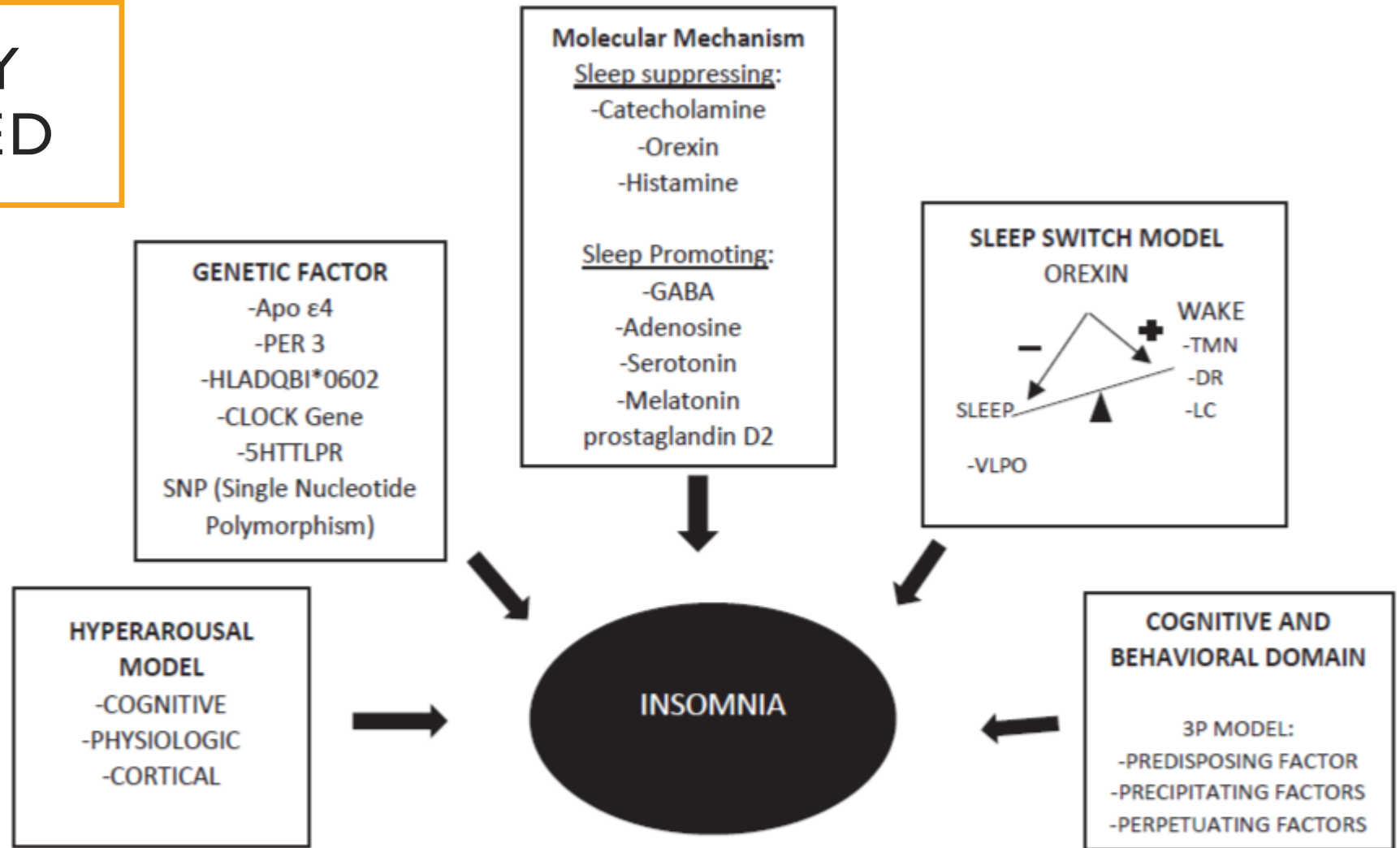


Figure 1. Pathophysiology of insomnia (VLPO: ventrolateral preoptic nucleus; TMN: Tuberomammillary nucleus; DR: dorsal raphe; LC: Locus coeruleus; GABA: gamma-aminobutyric acid)

INSOMNIA AS A MEDICATION SIDE EFFECT

- Data from the National Health and Nutrition Examination Survey (NHANES) from 1999 – 2016 and by using 118 out of 239 medications screened for insomnia as a side effect.
- Compared to non-users, participants who took two or more of these medications:
 - Were more likely to report insomnia symptoms (odds ratio (OR) = 1.78; 95% confidence interval (CI), 1.22 to 2.60)
 - Daytime sleepiness symptoms (OR = 1.73; 95% CI, 1.16 to 2.60)
 - Difficulty with at least two daytime activities due to sleepiness or tiredness (OR = 1.96; 95% CI, 1.28 to 3.00)
 - Common medications in the study: aripiprazole, bupropion, SSRIs, SNRIs, levothyroxine, pramipexole, tramadol, varenicline

WHO DOES IT EFFECT?



ADULT POPULATION

- Researches estimate that around 50% of adults have difficulty initiating or maintaining sleep⁹
- People aged 55+ have more complaints of:
 - Insomnia
 - Fragmented sleep
 - Poor-quality sleep

8. Picture Retrieved From: <https://www.nhlbi.nih.gov/health-topics/insomnia>

9. Crowley K. Sleep and sleep disorders in older adults. *Neuropsychol Rev.* 2011;21(1):41-53.
doi:10.1007/s11065-010-9154-6

ELDERLY

- Factors that affect sleep in the elderly
 - Chronic diseases
 - Renal disease
 - Cerebrovascular disease
 - Gastrointestinal disease
 - Chronic pain and arthritis
 - Cardiovascular disease
 - Medications that are used to treat chronic diseases

DANGERS OF INSOMNIA

MORTALITY RISK

- Inadequate sleep is associated with significant mortality in older adults
 - Sleep latency > 30 minutes can increase the risk of mortality (HR 2.14 (1.25-3.66, $p=0.05$)¹⁰
 - Sleep efficiency < 80% can increase the risk of mortality (HR 1.93 (1.14-3.25, $p=0.014$)¹⁰
 - In propensity score adjusted models, there was a 14% higher rate of death in the short sleep duration group compared with reference group (HR 1.14, 95% CI, 1.01-1.30)¹¹
 - Short sleep duration defined as < 6 hours on polysomnography (PSG)

10. Dew MA, Hoch CC, Buysse DJ, et al. Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up [published correction appears in *Psychosom Med*. 2003 Mar-Apr;65(2):210]. *Psychosom Med*. 2003;65(1):63-73. doi:10.1097/01.psy.0000039756.23250.7c

11. Bertisch SM, Pollock BD, Mittleman MA, et al. Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality: Sleep Heart Health Study. *Sleep*. 2018;41(6):zsy047. doi:10.1093/sleep/zsy047

Table 1. Characteristics of Participants Who Did and Did Not Fall, 1990–1991

Characteristic	Did Not Fall in Past (%)	Fell in Past Year (%)	OR	95% CI
Sociodemographic				
Age >71 years	48	54	1.25	0.97–1.63
Female	62	72	1.62	1.22–2.15
Unmarried	43	56	1.63	1.25–2.11
Live alone	32	39	1.34	1.03–1.75
Income <\$15,000 per year	21	29	1.52	1.11–2.09
Medication and substance use				
Prescription medication (yes/no)	74	79	1.32	0.97–1.81
Psychotropic medication (yes/no)	3	5	1.65	0.88–3.09
Alcohol (>1 drink per week)	33	25	0.69	0.52–0.93
Currently smoking	12	9	0.74	0.48–1.47
Mobility and fitness deficits				
Underactive	14	11	0.77	0.51–1.16
Difficulty Walking	11	22	2.39	1.71–3.34
Need to limit activity	42	60	2.09	1.61–2.72
Health and medical problems				
Chronic conditions (>1)	54	64	1.48	1.13–1.93
Hospitalized in past year	5	7	1.52	0.90–2.61
BMI >24.8	51	48	0.87	0.67–1.13
History of CVD	22	30	1.50	1.12–1.99
Hypertension	44	54	1.48	1.14–1.91
Osteoporosis	12	13	1.06	0.72–1.56
Diabetes	9	10	1.16	0.75–1.80
Arthritis	51	62	1.53	1.17–2.00
Presence of sensory impairment				
Vision	28	41	1.79	1.37–2.33
Hearing	42	43	1.02	0.79–1.33
Presence of psychological difficulties				
Depression	20	31	1.79	1.34–2.39
Stress	32	44	1.71	1.32–2.23
Lack of control	19	31	1.88	1.40–2.51
Sleep Difficulties				
Falling asleep at night	10	19	2.06	1.45–2.94
Waking up during the night	27	43	2.05	1.57–2.67
Waking up in the morning	4	10	2.55	1.58–4.12
Waking up too early in the morning and not being able to fall asleep again	9	18	2.14	1.49–3.07
Daytime sleepiness	3	6	2.40	1.31–4.39
Nap during the day	8	13	1.83	1.22–2.75
Less than 8 hours of sleep	63	64	1.04	0.79–1.36

OR = odds ratio; CI = confidence interval; BMI = body mass index; CVD = cardiovascular disease.

ASSOCIATED INCREASE IN MORBIDITY

- Older adults with sleep problems report high incidences of balance, ambulatory and visual difficulties, even after adjustment for medication use

Table 2. Healthcare Costs and Utilization of the Sample, After Matching, for Members With and Without an Insomnia Diagnosis

Parameter	Insomnia cohort N = 7647		Control cohort N = 7647		P ^a
	Mean	SD	Mean	SD	
Baseline					
ED visits	0.52	1.78	0.36	1.37	<.0001
IP visits	0.15	0.64	0.12	0.55	.0003
OP visits	10.72	13.30	9.49	12.28	<.0001
UC visits	0.28	0.99	0.18	0.69	<.0001
ED costs	172.92	736.00	115.06	533.06	<.0001
IP costs (\$)	2202.30	16,099.35	1205.38	8902.80	<.0001
OP costs (\$)	2161.58	5057.17	1824.60	4884.44	<.0001
UC costs (\$)	21.64	75.92	13.72	55.66	<.0001
RX costs (\$)	925.31	1845.82	777.99	1483.51	<.0001
Total costs (\$)	5484.01	18,651.46	3937.03	11,450.52	<.0001
Follow-up					
ED visits	1.00	3.52	0.57	1.93	<.0001
IP visits	0.27	0.89	0.17	0.70	<.0001
OP visits	26.00	27.01	17.51	21.80	<.0001
UC visits	0.55	1.70	0.34	1.01	<.0001
ED costs	332.91	1176.29	182.48	737.07	<.0001
IP costs (\$)	3249.78	17,551.59	1742.48	10,942.22	<.0001
OP costs (\$)	5317.14	10,567.13	3355.71	8282.75	<.0001
UC costs (\$)	42.41	130.29	27.09	88.57	<.0001
RX costs (\$)	2262.75	3635.37	1630.56	3086.06	<.0001
Total costs (\$)	11,206.13	25,027.14	6939.78	17,067.15	<.0001

Baseline, 6 months before insomnia diagnosis or index date; follow-up, 12 months after insomnia diagnosis or index date.

ED indicates emergency department; IP, inpatient; OP, outpatient; UC, urgent care; RX, pharmacy.

^at test.

COST

- Evaluation of healthcare costs in patients within a large midwestern health plan (> 600,000 patients)
- Insomnia diagnosis associated with higher costs

COST

■ **Table 3.** Two-Part Regression of Baseline Costs

Two-part model Dependent variable	Part I N = 15,294			Part 2: Cost Model N = 14,406		
	Any Cost in Baseline Period			Log of Total Baseline Cost		
	Parameter Estimate	Standard Error	P	Parameter Estimate	Standard Error	P
Intercept	0.14	0.14	.3364	5.52	0.11	<.0001
Insomnia diagnosis ^a	0.84	0.07	<.0001	0.23	0.02	<.0001
Age	0.04	0.00	<.0001	0.03	0.00	<.0001
Age squared				0.00	0.00	.0042
Female	1.00	0.07	<.0001	0.23	0.02	<.0001
Medicaid	0.50	0.16	<.0001	0.09	0.04	.0147
CCI score				1.01	0.02	<.0001
CCI score squared				-0.08	0.00	<.0001
Mental health diagnosis				0.63	0.02	<.0001
Antidepressant prescription				0.48	0.02	<.0001
Mood stabilizer prescription				0.68	0.04	<.0001

CCI indicates Charlson Comorbidity Index.

Predicted cost estimated using mean values of covariates for each cohort.

Baseline, 6 months before index date; follow-up, 12 months after index date.

^aPart 2: Insomnia diagnosis was associated with 26% higher costs. The percentage translated for dollars is equal to the exponent of the parameter for log dollars, minus 1.

- Insomnia diagnosis was associated with 26% higher costs at baseline
- These patients were not yet treated for insomnia

COST

- Insomnia diagnosis was associated with a 46% higher cost at follow up
- 12 months after diagnosis

Table 4. Two-Part Regression of Follow-up Costs

Two-part model	Part I N = 15,294			Part 2: Cost Model N = 14,975		
	Any Cost in Follow-up Period			Log of Total Follow-up Cost		
Dependent variable	Parameter Estimate	Standard Error	P	Parameter Estimate	Standard Error	P
Intercept	0.76	0.23	.0010	6.01	0.10	<.0001
Insomnia diagnosis ^a	5.89	1.00	<.0001	0.38	0.02	<.0001
Age	0.04	0.00	<.0001	0.04	0.00	<.0001
Age squared				0.00	0.00	<.0001
Female	1.04	0.12	<.0001	0.27	0.02	<.0001
Medicaid	0.25	0.24	<.0001	0.01	0.03	.7799
CCI score				0.76	0.02	<.0001
CCI score squared				-0.06	0.00	<.0001
Mental health diagnosis				0.47	0.02	<.0001
Antidepressant prescription				0.39	0.02	<.0001
Mood stabilizer prescription				0.74	0.03	<.0001
	Probability of Expenditures [95% CI]			Predicted 12-Month Expenditures [95% CI]		
Patients with insomnia diagnosis	100.0% [99.9-100.0]			\$9884 [\$9609-\$10,167]		
Matched comparison group	96.6% [96.2-97.0]			\$5489 [\$5335-\$5648]		
Difference	3%; P <.05			\$4395; P <.05		

CCI indicates Charlson Comorbidity Index; CI, confidence interval.
 Predicted cost estimated using mean values of covariates for each cohort.
 Follow-up, 12 months after index date.
^aPart 2: Insomnia diagnosis was associated with 46% higher costs. The percentage translated for dollars is equal to the exponent of the parameter for log dollars, minus 1.

HOW DO WE TREAT IT?

NON-PHARMACOLOGICAL THERAPY

CLEAN UP YOUR SLEEP HYGIENE

13 simple tricks, will help you get a good nights sleep.



1. Go to bed and get up at the same time every day, including on the weekends and during vacations.



2. If you can't fall asleep or wake up and can't get back to sleep, get out of bed, read, sketch, or do another calming activity in low light.



3. Make sure your bedroom is quiet, dark, relaxing, and at a comfortable temperature.



4. Remove electronic devices, such as TVs, computers, and smart phones, from the bedroom.



5. Use your bed only for sleep and sex.



6. Exercise, being physically active during the day can help you fall asleep more easily and sleep more deeply at night.



7. Keep a sleep diary, experiment and figure out what works best for you.



8. Limit exposure to bright light in the evenings, turn off electronic devices at least 30-60 minutes before bedtime.



9. Establish a relaxing bedtime routine.



10. Don't eat a large meal before bedtime. If you are hungry at night, eat a light, healthy snack.



11. Avoid consuming caffeine in the late afternoon or evening.

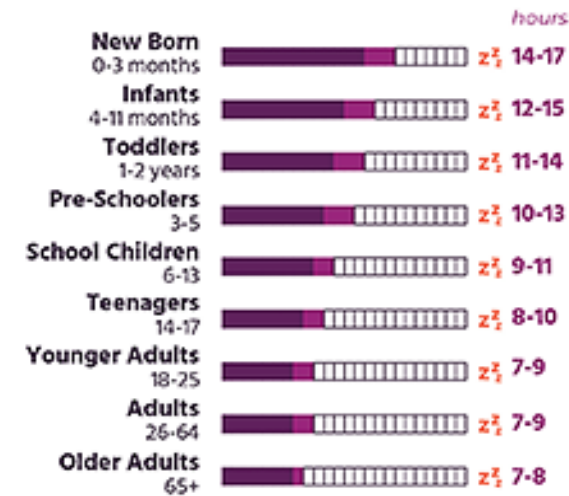


12. Avoid consuming alcohol, nicotine and THC before bedtime.



13. Reduce your fluid intake before bedtime.

WHAT'S THE RIGHT AMOUNT OF SLEEP FOR YOU?



Above are the current evidence-based recommendations for each age group, use this as a guide for how many hours of sleep you need to feel your best.

SLEEP HYGIENE

14. Picture Retrieved From: <https://neuropathycommons.org/neuropathy/neuropathy-sleep/sleep-hygiene>



MEDITATION

- Superiority trial for alternative insomnia treatments where patients were randomized into 1 of 3 groups
 - A standard meditation program (MSBR)
 - A tailored meditation program with behavior strategies for insomnia (MBTI)
 - A self-monitoring control group (SM)
- Findings provide important new evidence for the efficacy, credibility, and safety of meditation-based therapies.

MEDITATION STUDY

- Patients receiving MBSR or MBTI showed greater reduction in total wake time (TWT) than standard group
 - Average of 43.75 minutes from baseline to posttreatment
 - Average of 49.63 minutes from baseline to 6-month follow up

Table 2—Patient-reported outcomes

	Baseline Mean (SD)	Post Mean (SD)	Post Effect Size	3-month Mean (SD)	6-month Mean (SD)	Long-Term Effect Size
Sleep Diaries						
TWT (in minutes)						
MBSR	113.87 (56.75)	68.55 (43.70)	0.80	70.92 (58.08)	62.13 (27.80)	1.38
MBTI	115.65 (57.04)	73.47 (34.69)	0.92	60.64 (32.21)	68.13 (30.08)	1.05
SM	86.80 (67.08)	85.71 (72.08)	0.06			
TST (in minutes)						
MBSR	366.38 (74.84)	394.06 (65.49)	0.17	405.18 (69.69)	408.92 (42.48)	0.86
MBTI	376.81 (76.87)	379.31 (64.32)	0.12	399.03 (53.34)	401.73 (52.07)	0.17
SM	358.29 (66.87)	364.82 (83.13)	0.11			
SE (%)						
MBSR	76.19 (12.01)	84.34 (10.55)	0.60	85.26 (11.11)	86.86 (5.39)	1.34
MBTI	76.17 (13.35)	83.79 (8.22)	0.66	86.74 (7.24)	85.52 (6.55)	0.83
SM	81.72 (12.26)	80.76 (13.60)	0.03			
PSAS (total score)						
MBSR	35.05 (7.40)	27.21 (8.00)	1.02	27.31 (7.74)	29.83 (6.58)	0.88
MBTI	31.95 (7.80)	25.53 (6.37)	0.89	24.57 (6.77)	25.07 (5.15)	1.02
SM	29.69 (5.51)	29.53 (8.98)	0.01			
ISI (total score)						
MBSR	17.11 (4.57)	10.88 (5.82)	1.33	10.92 (5.79)	9.83 (4.84)	1.57
MBTI	18.11 (3.70)	10.27 (4.70)	2.07	7.07 (4.21)	8.00 (4.61)	2.56
SM	15.44 (4.30)	15.50 (5.50)	0.01			

TWT, total wake time; TST, total sleep time; SE, sleep efficiency; PSAS, pre-sleep arousal scale; ISI, Insomnia Severity Index; MBSR, mindfulness-based stress reduction; MBTI, mindfulness-based therapy for insomnia; SM, self-monitoring; SD, standard deviation. Participants in the SM group received behavior therapy (BT) following the post SM assessment. Therefore, SM did not have follow-up and the post SM served as the baseline for BT. Data for sleep diaries are averaged across one week at each assessment point. Long-term effect size is from baseline to 6-month follow-up. No significant differences were found at baseline on any of the patient-reported outcome measures.

UNDERSTANDING THE BENEFITS OF NON-PHARM THERAPIES IN THE ELDERLY

- There is insufficient evidence to consider psychological treatments as standalone therapy
 - Cognitive therapy
 - Relaxation
 - Sleep hygiene education
- What this means for us:
 - SLEEP HYGIENE IS STILL CONSIDERED 1ST LINE THERAPY
 - We can consider the use of relaxation/meditation, but we should also look to provide beneficial pharmacological therapy as well.

PHARMACOLOGICAL THERAPY

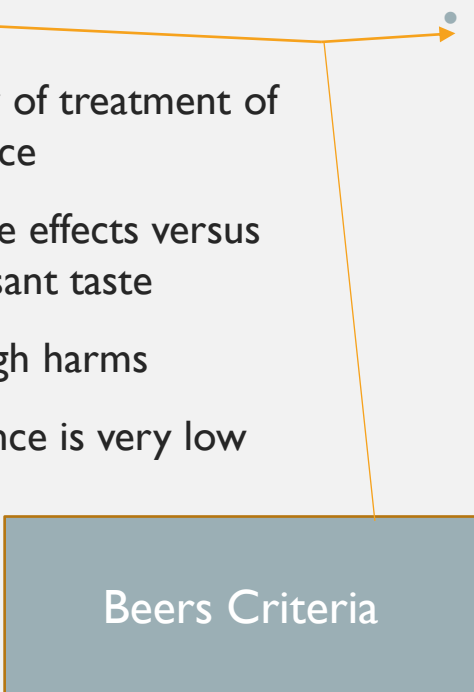
BACKGROUND ABOUT THE GUIDELINE

- Published in the Journal of Clinical Sleep Medicine in 2017
- The Academy of Sleep Medicine (AASM) commissioned four experts to perform systematic reviews of the literature and determine a recommendation
 - Board of directors approved of final recommendations
- Looking to provide evidence-based recommendations based on available literature for pharmacological treatment in the adult population
 - Diagnosed with primary chronic insomnia
 - Placebo controlled trials

GUIDELINE-DRIVEN THERAPY

- Common Medication Classes
 - Orexin receptor antagonists
 - Benzodiazepines receptor agonists
 - Benzodiazepines
 - Melatonin agonists
 - Heterocyclics
 - Anticonvulsants
 - Over-the-Counter Products (OTCs)

BENZODIAZEPINE RECEPTOR AGONISTS

- eszopiclone (Lunesta)
 - Weak evidence for efficacy of treatment of sleep onset and maintenance
 - Limited evidence in adverse effects versus placebo except for unpleasant taste
 - Benefits marginally outweigh harms
 - Overall quality of evidence is very low
 - zolpidem (Ambien)
 - Weak evidence for efficacy of treatment of sleep onset and maintenance
 - Limited evidence of mild adverse events except for excessive sleepiness
 - 10 mg dose less than 8 hours before awakening
 - Benefits marginally outweigh harms
 - Overall quality of evidence is very low
- 

Beers Criteria

BENZODIAZEPINES

- Temazepam
 - Weak evidence for efficacy of effect on:
 - Sleep onset
 - Total sleep time (TST)
 - Awakenings
 - Sleep efficiency
 - Wake-time after sleep onset (WASO)
 - Limited and inconsistent evidence in adverse events
 - Some evidence of daytime impairment with 30 mg dose
 - Benefits marginally outweigh harms
 - Overall quality of evidence is very low



HETEROCYCLICS



Beers
Criteria

- Doxepin
 - Weak evidence for efficacy in the treatment of sleep maintenance
 - Minimal evidence of adverse events versus placebo
 - Overall quality of evidence was moderate to low
 - Benefits were deemed to be greater than the harms
- Trazodone
 - Absence of significant efficacy for trazodone (50 mg)
 - Limited evidence of adverse events
 - Headache and somnolence most reported
 - Often prescribed by clinicians
 - Perception that trazodone is a “safer option”

OVER-THE-COUNTER PRODUCTS

Beers Criteria

Diphenhydramine

- Weak evidence for efficacy in treatment of sleep onset
- Minimal evidence of adverse events versus placebo
 - Dizziness, drowsiness, and grogginess
- Overall, low evidence
 - Benefits are approximately equal to harm

Melatonin

- Weak evidence for efficacy in treatment of sleep onset
 - Mixed evidence in improvement in sleep latency in elderly
- Minimal evidence about adverse events
 - No rebound or withdrawal effects
- Overall, very low evidence
 - Benefits are approximately equal to harm

GUIDELINE APPLICATION

- The evidence to support the use of majority of pharmacological options is weak
- Consider patient specific factors:
 - Age
 - Adverse effects
 - Drug interactions
 - Other disease states
 - Prior medications

WHAT CAN WE DO FOR OUR
PATIENTS?

MEDICATION RECONCILIATION

- Look for medications that have insomnia as a side effect
- Ask about prescription, over-the-counter, herbal products that patients use for sleep
 - Diphenhydramine in elderly patients
- Ask about non-pharmacological treatments such as sleep hygiene or meditation

IN SUMMARY WE LEARNED ...

- The DSM-V criteria for insomnia
- Insomnia is a disease state that has a variety of causes
- Insomnia mostly affects adults and older patients (55+)
- Insomnia has several other associated effects such as increased risk of mortality, morbidity, and higher healthcare costs
- There are a variety of non-pharmacological treatment options
 - Sleep hygiene or meditation
- There are several classes of medications used for insomnia, but the evidence for their support is generally weak
- How to differentiate treatments for patients
 - Risk vs. benefits, adverse effect profile, age of patient, other disease states, etc...

ASSESSMENT QUESTIONS

WHAT ARE SOME OF THE DANGERS ASSOCIATED WITH INSOMNIA?

- I. Increased risk of morbidity
- II. Increased risk of mortality
- III. Higher healthcare costs
- IV. I and III
- V. All of the above

WHAT POPULATION OF PATIENTS HAS THE
HIGHEST PREVALENCE OF INSOMNIA OR
PROBLEMS WITH SLEEP?

I. 0-18

II. 19-29

III. 30-54

IV. 55+

ZOLPIDEM (AMBIEN) HAS VERY STRONG EVIDENCE TO SUPPORT ITS USE IN INSOMNIA AND SHOULD BE USED IN ALL PATIENTS

I. False

II. True

WHICH OF THESE IS NOT CONSIDERED GOOD SLEEP HYGIENE

- I. Using the bed for sleep only
- II. Avoid using electronic devices 30-60 minutes prior to sleep
- III. Eat a large meal prior to bed
- IV. Avoid caffeine after the late afternoon

WHICH OF THE FOLLOWING MEDICATIONS
IS NOT LISTED IN BEERS CRITERIA?

- I. Trazodone
- II. Doxepin
- III. Temazepam
- III. Eszopiclone