Insomnia and Parasomnias Brain Summit 2025

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* No disclosures to declare

Insomnia

Common condition

Comprehensive evaluation - “Insomnia”

Different models of insomnia

- 3 P’s
- Arousals
- Parallel process model

CBT – cognitive behavioral therapy

Medications

- DORAs

Wearables?

Parasomnia

Uncommon condition

- “Things that go bump in the night”
- “Bizarre events/stories”

Comprehensive evaluation

- Sleep evaluation
- Polysomnography

Treatment

- Safety
- Pharmacology options

Relevance

- Tie in with neurodegenerative conditions

REM behavior disorder

BOOK CHAPTER

Advances in Insomnia Pathophysiology and Treatment : An Introduction

Christopher L. Drake; Julio Fernandez-Mendoza

Principles and Practice of Sleep Medicine, Chapter 89, 821-824

"One thing about insomnia is the longer it lasts, the weirder it gets." William C. Dement

Everyone is familiar with sleeplessness in some way, and many curse its grip on our lives. Insomnia is an uninvited houseguest, both coda to the day's harshness and a prelude to tomorrow's worries. At times this houseguest visits just for the night, gone by the morning; other times, insomnia overstays so long we cannot remember what brought its arrival. Yet, we hope that if we lie in bed for just a little longer, it will take the hint and leave. Instead, insomnia makes itself comfortable, humming unsleepable nocturnes with its feet up on the bed.

Principles and Practice of Sleep Medicine

Seventh Edition

Insomnia – Reflections through the years

- A thorough evaluation of insomnia takes time.
  - Multiple factors and other influences
  - Medical history, childhood history, environmental history
    - "Sleep deserts" - Sleep Health, National Sleep Foundation – August 2025
    - Neighborhoods and environments that undermine sleep
  - Is there something else that is treatable? Or that explains the problem?

- Patient perceptions regarding insomnia is challenging.
  - "Burgeoning literature emphasizes that untreated insomnia deteriorates quality of life, social interactions and well-being and increases the risk of mental disorders."
  - Irritability, reduced motivation, concentration, attention, and memory functioning
  - Fatigue >>>> sleepiness
  - Frustrated

- There's a lot of pharmacologic options for insomnia. But it begs the question – what's worse – insomnia, or the treatment for insomnia?
  - Side effects of medications
  - DORA – exciting potential?

- There's a lot of behavioral interventions for insomnia that works, but it takes a lot of patience and discipline.
  - Behavioral and psychological care inadequate

- Emergence of wearable technology
  - To help or not to help, that is the question

- Did I mention that treating insomnia is tough?
  - Sleep medicine experts, all over the world…

Reason for referral –"Insomnia"
"not all that is insomnia, is….insomnia"

Sleep questionnaire

Sleep schedule

- Weekday
- Weekend
- Naps

Sleep environment

Daytime impact

Childhood sleep problems?

What medications do you take before bedtime?

How much alcohol do you drink?

Other sleep disorders

- Sleep apnea screening questions
- Restless legs syndrome
- Circadian rhythm disorders

Medical history

- Mood disorders
- Medical conditions
- Pain conditions

TABLE 5 Major medical comorbidities or contributory factors to chronic insomnia

Mental	Medical	Neurological	Substance use/dependence
Depressive disorders	Cardiovascular disorders	Neurodegenerative diseases	Alcohol
Bipolar disorders	Diabetes mellitus	Cerebrovascular diseases	Nicotine
Anxiety disorders	Chronic kidney diseases	Traumatic brain injury	Caffeine
Borderline personality disorder	Chronic obstructive pulmonary diseases	Multiple sclerosis	Tetrahydrocannabinol /marihuana
Posttraumatic stress disorder	Rheumatic disorders	RLS/PLMD	Opioids
Schizophrenia	Chronic pain	Fatal familial insomnia	"Designer" drugs
Substance use disorders	Any kind of malignant disorder		Cocaine
	SRBD/OSA		Amphetamines

Abbreviations: OSA, obstructive sleep apnea; PLMD, periodic limb movement disorder; RLS, restless legs syndrome; SRBD, sleep-related breathing disorder.

ICSD-3 (International Classification of Sleep Disorders)

CHRONIC INSOMNIA

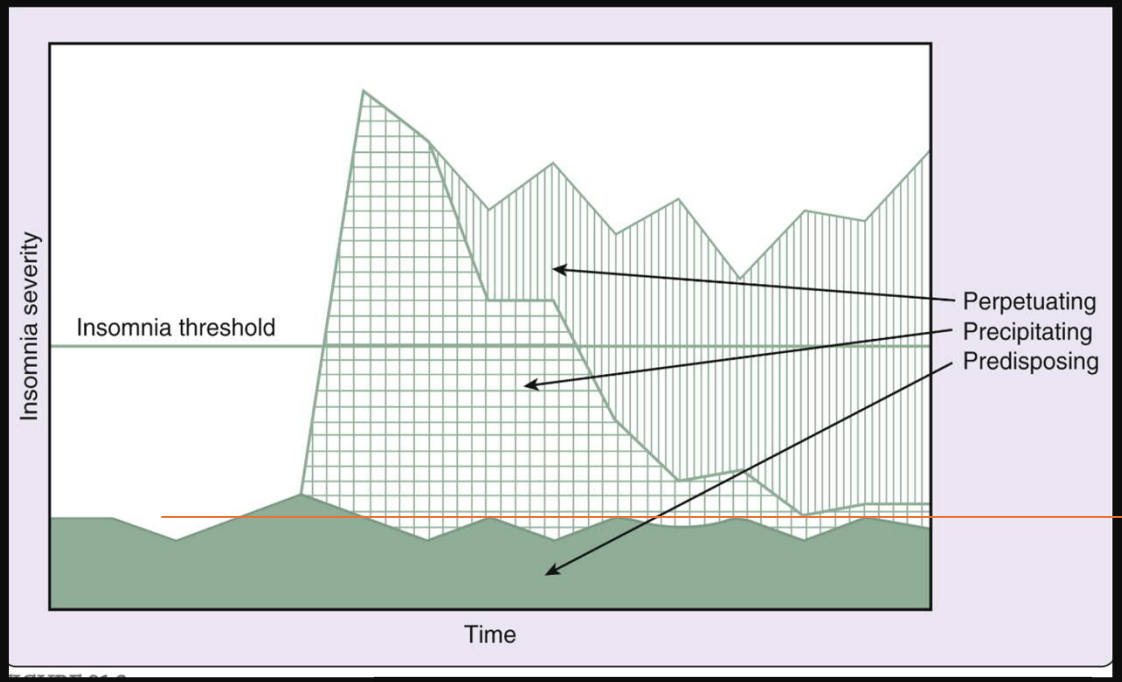
- Patient reports...
- Patient reports...impact on the patient..
- Not explained by another reason...or another sleep diagnosis...
- Duration
  - 3 x week
  - 3 months

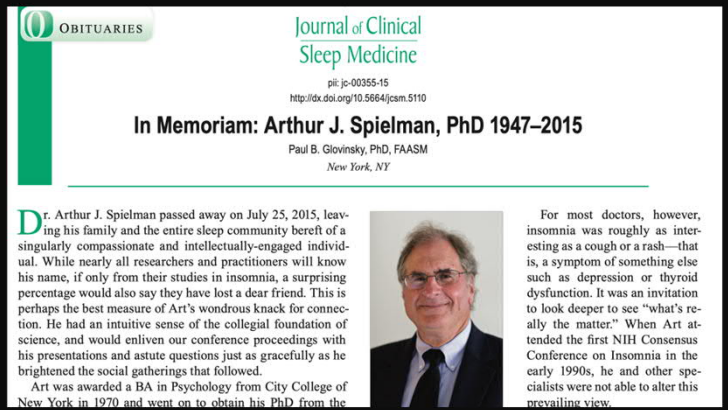
TABLE 2 Diagnostic criteria for chronic insomnia disorder according to ICSD-3 (AASM, 2014)

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:
1. Difficulty initiating sleep
2. Difficulty maintaining sleep
3. Waking up earlier than desired
4. Resistance to going to bed on appropriate schedule
5. Difficulty sleeping without parent or caregiver intervention
B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty:
1. Fatigue/malaise
2. Attention, concentration or memory impairment
3. Impaired social, family, occupational or academic performance
4. Mood disturbance/irritability
5. Daytime sleepiness
6. Behavioural problems (e.g. hyperactivity, impulsivity, aggression)
7. Reduced motivation/energy/initiative
8. Proneness for errors/accidents
9. Concerns about or dissatisfaction with sleep
C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e. enough time is allotted for sleep) or inadequate circumstances (i.e. the environment is safe, dark, quiet and comfortable) for sleep
D. The sleep disturbance and associated daytime symptoms occur at least three times per week
E. The sleep disturbance and associated daytime symptoms have been present for at least 3 months
F.The sleep/wake difficulty is not better explained by another sleep disorder

The 3 P Model of Insomnia

- Predisposing
  - Personality
  - Genetics
- Precipitating
  - Stress and life events
- Perpetuating
  - Anxiety
  - Maladaptive strategies
    - Too much time in bed
    - Ethanol





OBITUARIES

Journal of Clinical Sleep Medicine

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In Memoriam: Arthur J. Spielman, PhD 1947–2015

Paul B. Glovinsky, PhD, FAASM
New York, NY

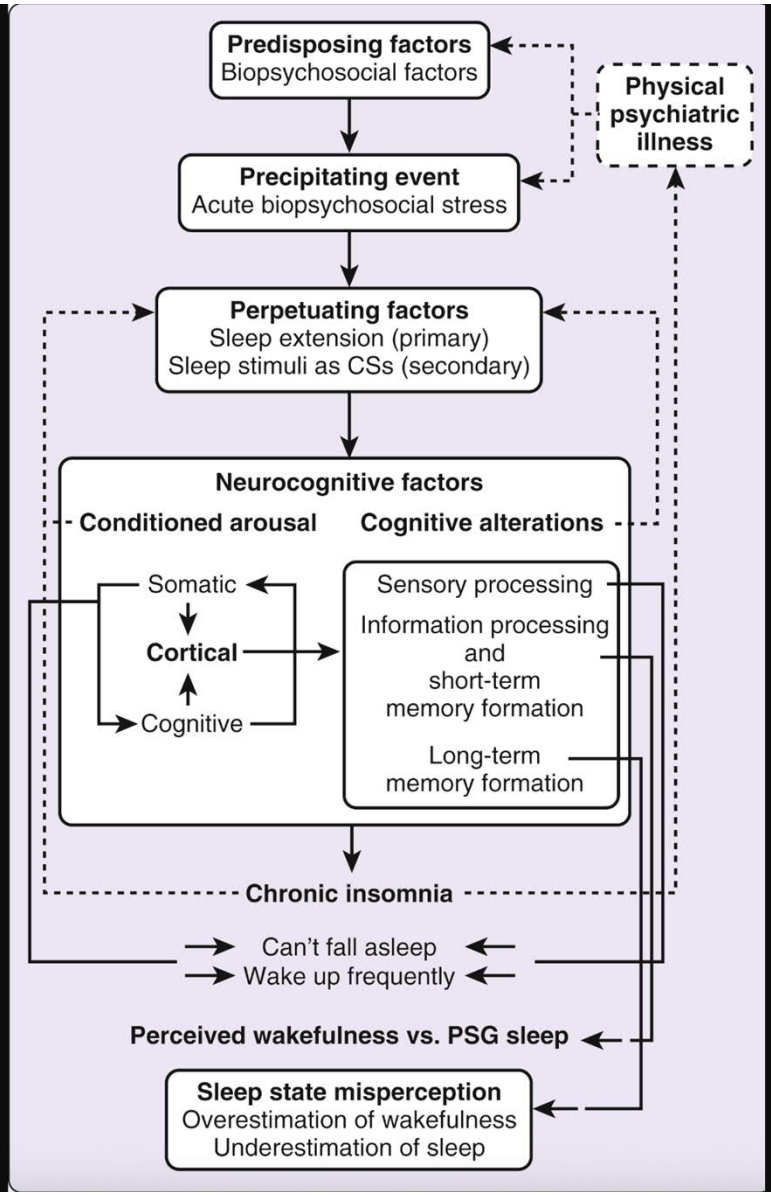
Dr. Arthur J. Spielman passed away on July 25, 2015, leaving his family and the entire sleep community bereft of a singularly compassionate and intellectually-engaged individual. While nearly all researchers and practitioners will know his name, if only from their studies in insomnia, a surprising percentage would also say they have lost a dear friend. This is perhaps the best measure of Art's wondrous knack for connection. He had an intuitive sense of the collegial foundation of science, and would enliven our conference proceedings with his presentations and astute questions just as gracefully as he brightened the social gatherings that followed.

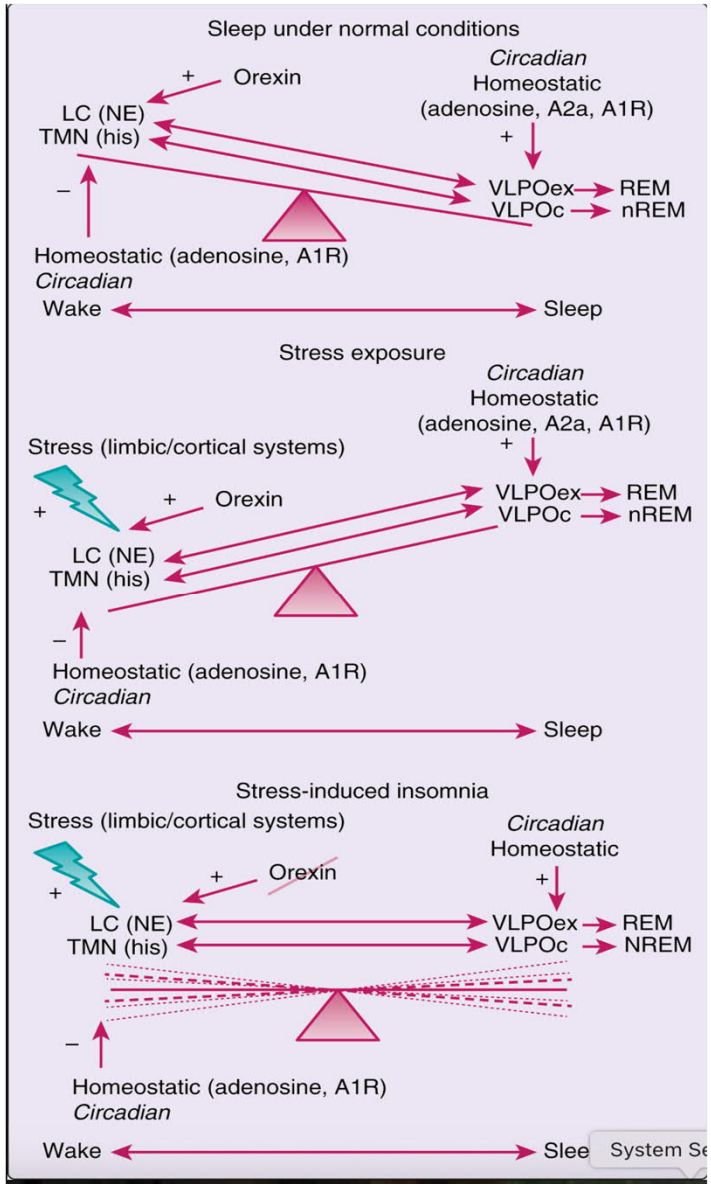
Art was awarded a BA in Psychology from City College of New York in 1970 and went on to obtain his PhD from the

For most doctors, however, insomnia was roughly as interesting as a cough or a rash—that is, a symptom of something else such as depression or thyroid dysfunction. It was an invitation to look deeper to see "what's really the matter." When Art attended the first NIH Consensus Conference on Insomnia in the early 1990s, he and other specialists were not able to alter this prevailing view.

Neurocognitive Model of Insomnia

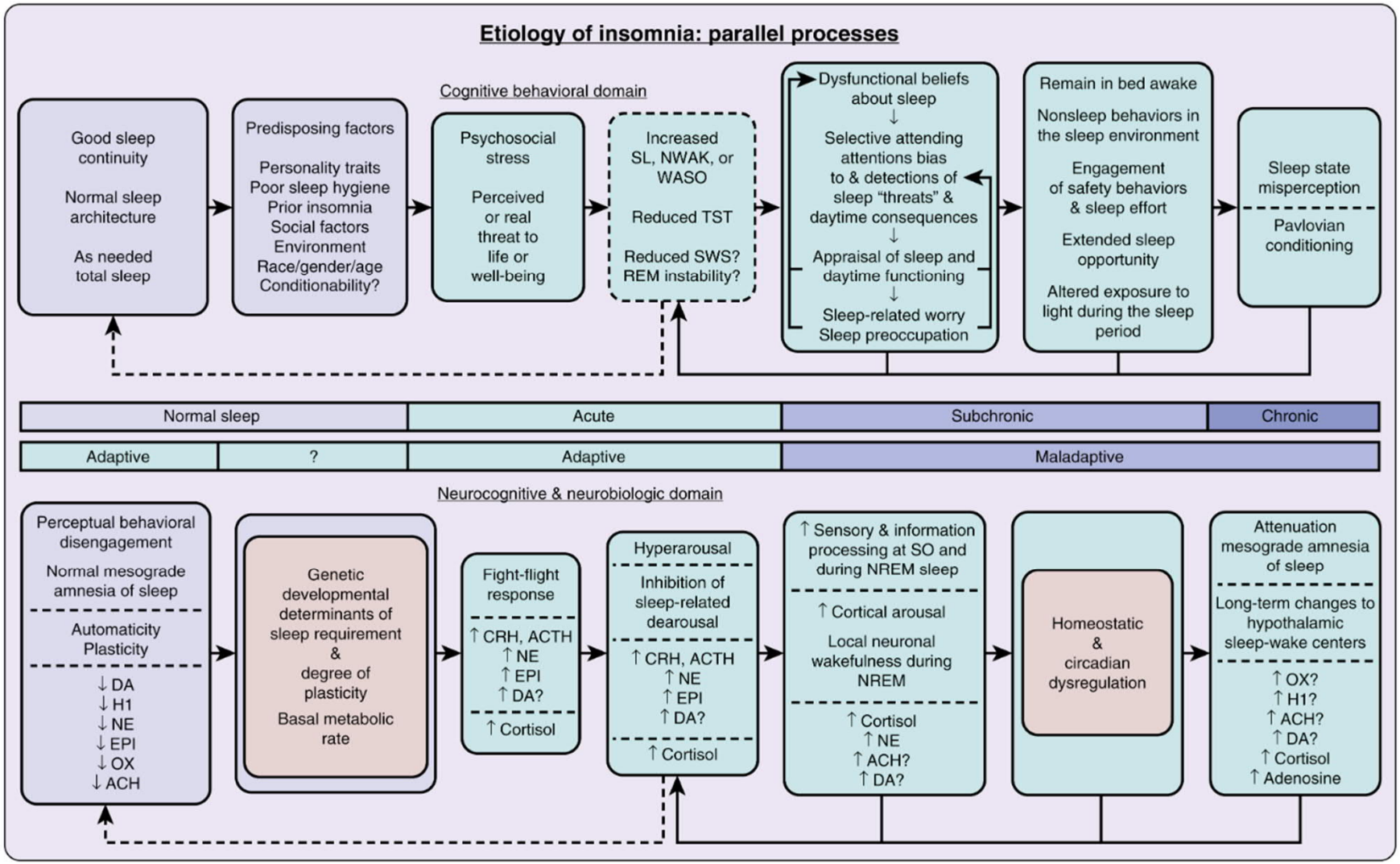
- Central to this model →
  - CORTICAL AROUSAL
- Increased sensory and information processing at sleep onset and during NREM sleep
  - "I can't turn my mind off…"
- SLEEP STATE MISPERCEPTION





Cano-Saper model

- Wake/Sleep
- Homeostatic factors
- Circadian factors
- Neurotransmitters
- Stress impact/disruption



Parallel Process Model

3 P's

Genetics

Neurotransmitters

Cortical arousals

Homeostatic and circadian dysregulation

Insomnia – Reflections through the years

- A thorough evaluation of insomnia takes time.
  - Multiple factors and other influences
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    - "Sleep deserts" - Sleep Health, National Sleep Foundation – August 2025
    - Neighborhoods and environments that undermine sleep
  - Is there something else that is treatable? Or that explains the problem?
- Patient perceptions regarding insomnia is challenging.
  - "Burgeoning literature emphasizes that untreated insomnia deteriorates quality of life, social interactions and well-being and increases the risk of mental disorders."
  - Irritability, reduced motivation, concentration, attention, and memory functioning
  - Fatigue >>>> sleepiness
  - "I can't shut my mind off…"
- There's a lot of pharmacologic options for insomnia. But it begs the question – what's worse – insomnia, or the treatment for insomnia?
  - Side effects of medications
  - DORA – exciting potential?
- There's a lot of behavioral interventions for insomnia that works, but it takes a lot of patience and discipline.
  - Behavioral and psychological care inadequate
- Emergence of wearable technology
  - To help or not to help, that is the question
- Did I mention that treating insomnia is tough?
  - Sleep medicine experts, all over the world…

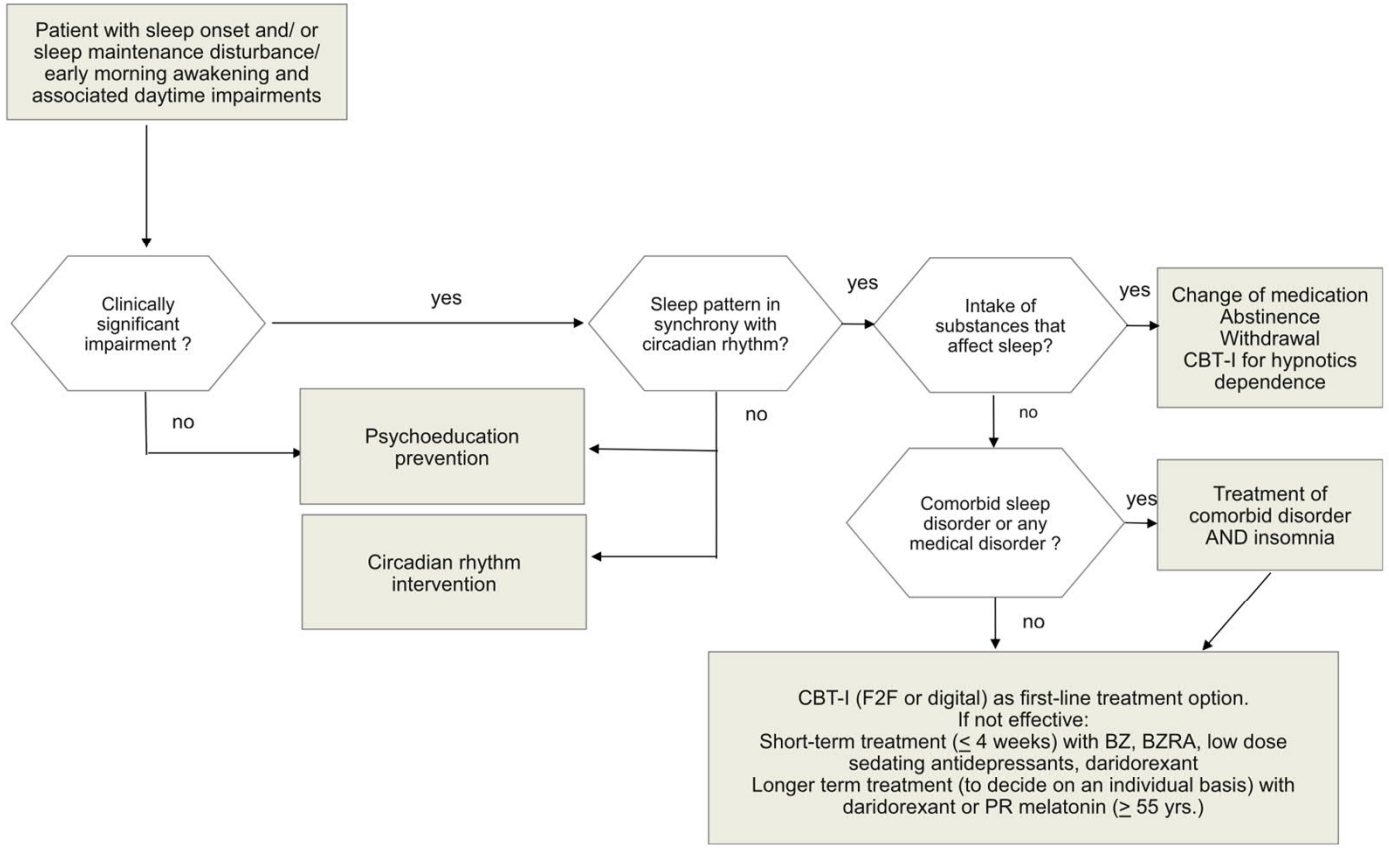

FIGURE 1 Clinical algorithm. [Color figure can be viewed at wileyonlinelibrary.com]

SECTIONS

RECOMMENDATIONS: The following recommendations are intended as a guide for clinicians in choosing a specific behavioral and psychological therapy for the treatment of chronic insomnia disorder in adult patients. Each recommendation statement is assigned a strength ("strong" or "conditional"). A "strong" recommendation (ie, "We recommend…") is one that clinicians should follow under most circumstances. A "conditional" recommendation is one that requires that the clinician use clinical knowledge and experience, and to strongly consider the patient's values and preferences to determine the best course of action.

1. We recommend that clinicians use multicomponent cognitive behavioral therapy for insomnia for the treatment of chronic insomnia disorder in adults. (STRONG)
2. We suggest that clinicians use multicomponent brief therapies for insomnia for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)
3. We suggest that clinicians use stimulus control as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)
4. We suggest that clinicians use sleep restriction therapy as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)
5. We suggest that clinicians use relaxation therapy as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)
6. We suggest that clinicians *not* use sleep hygiene as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)

CITATION: Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2021;17(2):255–262.

Stimulus Control

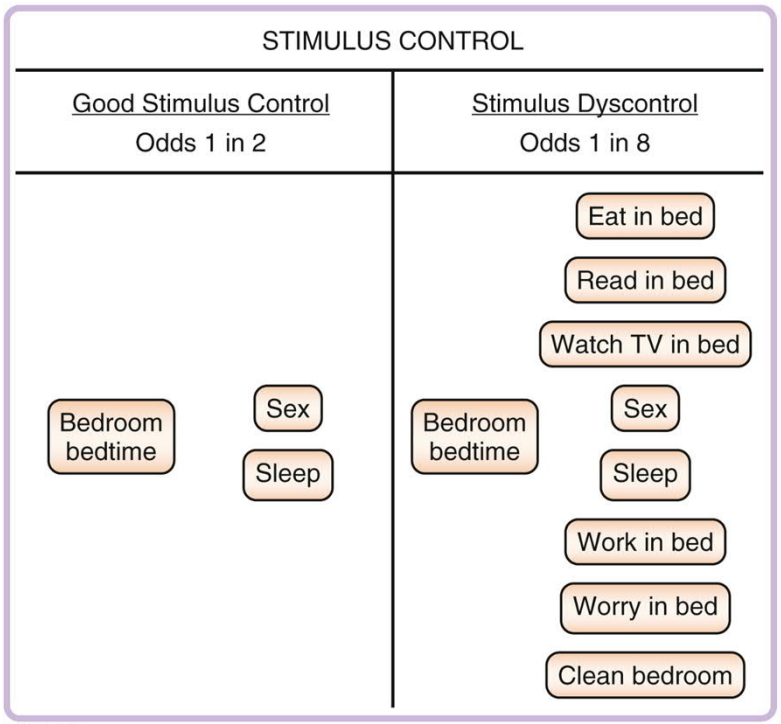

FIGURE 91.1

- For good sleepers..
  - Whereas for good sleepers, the bed and bedroom are cues for sleep, the sleep environment becomes a cue for wakefulness for many with chronic insomnia disorder.
- For chronic insomnia…
  - “I can’t turn my mind off.”
  - “Anxiety”
  - “It’s as if I just walk into the bedroom and I am suddenly wide awake…it’s like some switch got flipped from sleepy to wide-awake…”

Table 95.1 Behavioral Approaches

Psychological Treatments	Treatment Summary
Stimulus control	Follow five rules to reassociate the bed with sleep only: 1. Do not go to bed until you are sleepy (e.g., actively falling asleep). 2. If you are in a sleep-incompatible state while in bed, leave the bed/bedroom; do not return until you are sleepy. 3. Get out of bed at the same time every morning, irrespective of how you slept. 4. Reserve the bed for sleep only (do not engage in wakeful activities in bed). 5. No naps.
Sleep restriction therapy	Restrict time in bed to the average total sleep time of the last 2 weeks. After implementing the prescription for 2 weeks: 1. If the sleep problem has resolved, continue with the prescription. 2. If there is evidence of excessive sleepiness, extend the time in bed prescription by 15 to 30 minutes for the next 2 weeks, and continue extending at subsequent appointments until sleepiness has resolved. Any reemerging sleep problems are addressed by restricting time in bed back to the previously effective prescription
Relaxation therapy	Collection of relaxation practices that entail daily practice of one or more of the following: 1. Progressive muscle relaxation 2. Imagery/autogenic training 3. Deep/diaphragmatic breathing
Paradoxical intention	Instruction to go to bed at regular time and initiate effort to stay awake while in bed, all night long.
Cognitive therapy	Direct challenge of sleep believes using one or more of the following: 1. Thought records 2. Socratic questioning 3. Behavioral experiments
Counterarousal Strategies	Addressing active mind in the presleep period. Commonly used counterarousal strategies include 1. Buffer zone (wind-down time before bed) 2. Constructive worry or scheduled worry hour 3. Daily mindfulness practice
Sleep hygiene	Set of rules derived from basic sleep research to correct habits that could interfere with sleep: 1. Caffeine: cessation by early afternoon and limit use to no more than (dose and timing instructions tend to vary) 2. Nicotine reduction/elimination 3. Exercise regularly but not within a few hours of bedtime 4. Avoid middle-of-the-night eating 5. Reduce alcohol, marijuana, and other sleep-interfering substances 6. Optimize environment: limit light, noise, and extremes in temperature
Cognitive behavioral therapy for insomnia	Multicomponent, empirically based and empirically supported therapy to modify sleep-interfering behaviors. The most common elements are 1. Stimulus control 2. Sleep restriction 3. Cognitive therapy 4. Counterarousal strategies; some versions have relaxation therapy 5. Sleep hygiene
Mindfulness	Daily practice of directing one's attention to the present moment, nonjudgmentally

Table 95.2 Sample Session-by-Session Outline for a Four-Session Model

Week	Therapeutic Activities
Week 1 Week 2	Diagnostic and treatment planning assessment, assign diaries
Week 3	Completion of sleep diaries Begin psychoeducation, stimulus control, sleep restriction therapy, and sleep hygiene instructions
Week 4	At-home implementation of strategies
Week 5	Troubleshoot adherence to homework and determine if changes are necessary to schedule Begin cognitive therapy and time permitting, add counterarousal strategies/relaxation therapy
Week 6	At-home implementation of strategies
Week 7	Troubleshoot adherence and determine if changes are necessary to schedule Continue with cognitive therapy; add counterarousal strategies (if it was not added at session 2) Introduce termination issues
Week 8	At-home implementation of strategies
Week 9	Troubleshoot adherence Determine if changes are necessary to schedule Finish cognitive therapy Termination issues and relapse prevention

From Edinger JD, Carney CE. *Overcoming Insomnia: A Cognitive-Behavioral Therapy Approach, Therapist Guide*. 2nd ed. Oxford University Press; 2015:141.

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What is Cognitive Behavioral Therapy for Insomnia (CBT-I)

CBT-I is a pretty remarkable thing. With regard to treatment, it has been shown that pharmacotherapy and cognitive behavioral treatment of insomnia have comparable efficacy in the short term and that only CBT-I has durable effects upon treatment discontinuation. CBT-I is a short term intervention where up to 70% of subjects exhibit a treatment response and nearly 40% recover good sleep. In addition, there is emerging evidence that CBT-I also produces significant clinical gains with respect to comorbid conditions. For example, CBT-I in combination with escitalopram (vs. escitalopram alone) doubles response and remission rates in depression and produces substantial reductions in suicidal ideation. There is also emerging evidence that CBT-I affects pain tolerance and quality of life indicators in patients with chronic pain. With respect to medical disorders, treatment for insomnia holds the promise of having positive effects on hypertension, cardiovascular disease, diabetes, and dementia.

Given the exceptional attributes of CBT-I, it is not surprising (though still pretty remarkable) that the American College of Physicians recently recommend that CBT-I be the first line treatment for Chronic Insomnia.

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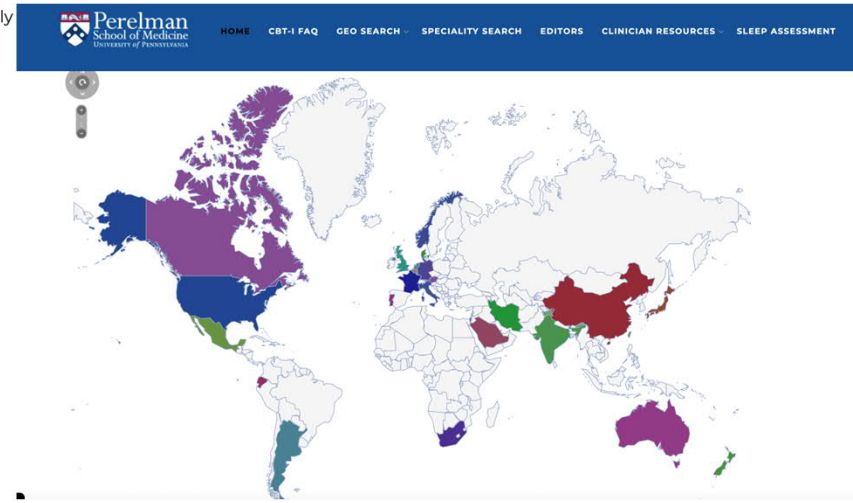

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REVIEW ARTICLE

The European Insomnia Guideline: An update on the diagnosis and treatment of insomnia 2023

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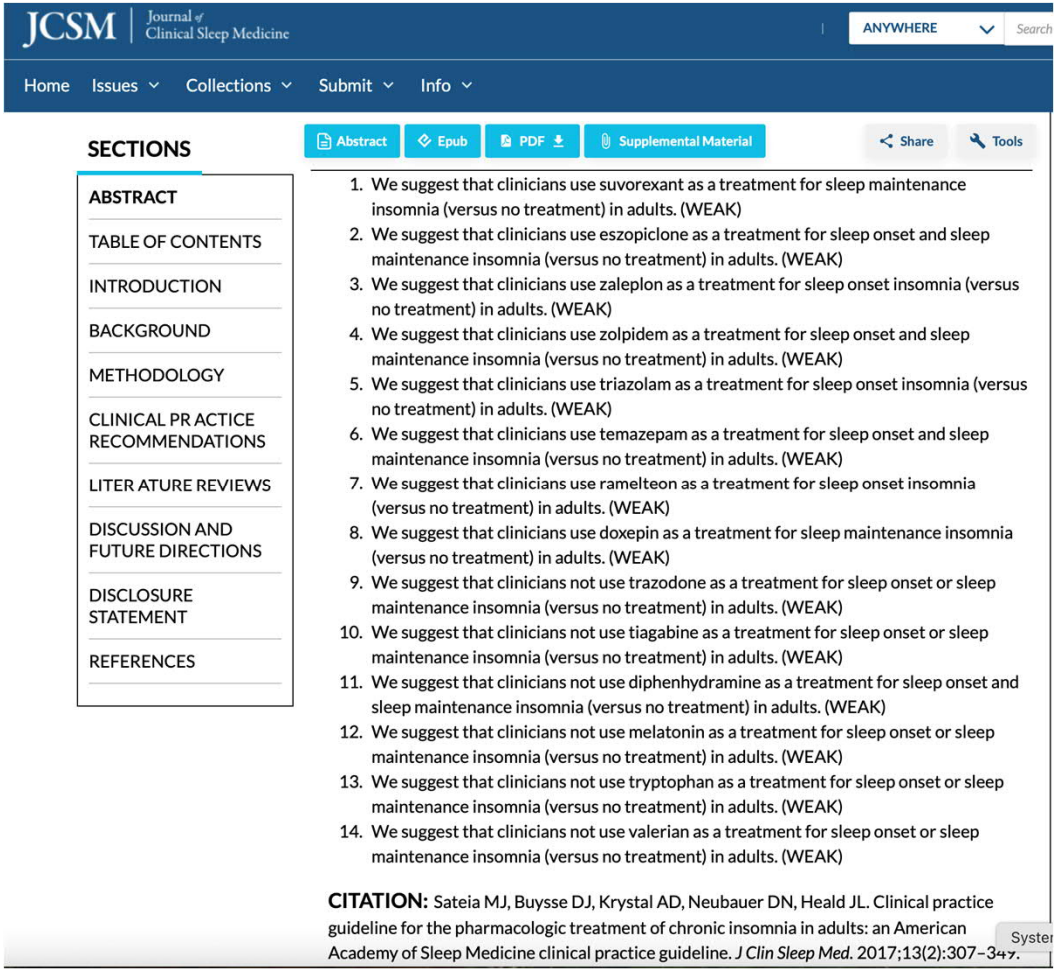
Summary

Progress in the field of insomnia since 2017 necessitated this update of the European Insomnia Guideline. Recommendations for the diagnostic procedure for insomnia and its comorbidities are: clinical interview (encompassing sleep and medical history); the use of sleep questionnaires and diaries (and physical examination and additional measures where indicated) (A). Actigraphy is not recommended for the routine evaluation of insomnia (C), but may be useful for differential-diagnostic purposes (A). Polysomnography should be used to evaluate other sleep disorders if suspected (i.e. periodic limb movement disorder, sleep-related breathing disorders, etc.), treatment-resistant insomnia (A) and for other indications (B). Cognitive-behavioural therapy for insomnia is recommended as the first-line treatment for chronic insomnia in adults of any age (including patients with comorbidities), either applied in-person or digitally (A). When cognitive-behavioural therapy for insomnia is not sufficiently

TABLE 16 Recommendations for the treatment of chronic insomnia in adults of all ages

Treatment considerations
• Insomnia disorder should be actively treated whenever it presents (A)
• In the presence of comorbidities, clinical judgement should decide whether insomnia or the comorbid condition are treated first or whether both are treated at the same time (A)
CBT-I
• CBT-I should be provided as the the first-line treatment for insomnia disorder in adults of any age, regardless of comorbidities (A)
• CBT-I may be delivered either in-person or digitally (A)
• Sleep restriction and stimulus control are the most active ingredients of CBT-I (B)
Pharmacological interventions
• A pharmacological intervention can be proposed if CBT-I is not effective (A)
• BZs and BZRAs can be used in the short-term treatment of insomnia (≤ 4 weeks) (A)
• Longer-term treatment (off-label use) with BZ or BZRA, either daily or preferably intermittently, may be initiated in some cases, and the advantages and disadvantages need to be discussed on an individual basis (B)
• Low doses of sedating antidepressants can be considered (off-label use) in the short-term treatment of insomnia; contraindications have to be carefully considered (B)
• Longer-term treatment of insomnia disorder (without comorbidities; off-label use) with low-dose sedating antidepressants may be initiated in some cases, and the advantages and disadvantages need to be discussed on an individual basis (B)
• Orexin rexceptor antagonists can be used for a period of up to 3 months in the treatment of insomnia (A)
• Longer-term treatment of insomnia disorder with orexin receptor antagonists may be initiated in some cases, and the advantages and disadvantages need to be discussed on an individual basis (A)
• Because of insufficient evidence and possible risks, antihistamines are not recommended for insomnia treatment (A)
• Because of insufficient evidence and in light of their side-effects, antipsychotics are not recommended for insomnia treatment (A)
• Melatonin (fast-release, OTC or as a prescription drug) in general is not effective in the treatment of insomnia (A), if no circadian factors are involved
• Longer-term treatment of insomnia disorder with PR melatonin (in patients > 55 years) up to 3 months may be effective in some cases (B)
Other therapies
• Herbal remedies/phytotherapeutics are not recommended for the treatment of insomnia because of insufficient evidence (A). Light therapy and exercise regimes may be useful as adjunct therapies to CBT-I (B)

Abbreviations: BZ, benzodiazepines; BZRA, benzodiazepine receptor agonists; CBT-I, cognitive-behavioural therapy for insomnia; OTC, over-the-counter; PR, prolonged-release.



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SECTIONS

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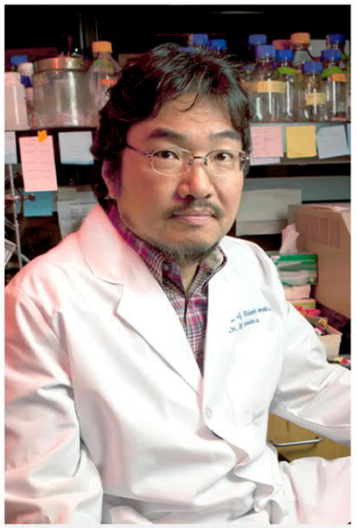
1. We suggest that clinicians use suvorexant as a treatment for sleep maintenance insomnia (versus no treatment) in adults. (WEAK)
2. We suggest that clinicians use eszopiclone as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. (WEAK)
3. We suggest that clinicians use zaleplon as a treatment for sleep onset insomnia (versus no treatment) in adults. (WEAK)
4. We suggest that clinicians use zolpidem as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. (WEAK)
5. We suggest that clinicians use triazolam as a treatment for sleep onset insomnia (versus no treatment) in adults. (WEAK)
6. We suggest that clinicians use temazepam as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. (WEAK)
7. We suggest that clinicians use ramelteon as a treatment for sleep onset insomnia (versus no treatment) in adults. (WEAK)
8. We suggest that clinicians use doxepin as a treatment for sleep maintenance insomnia (versus no treatment) in adults. (WEAK)
9. We suggest that clinicians not use trazodone as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults. (WEAK)
10. We suggest that clinicians not use tiagabine as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults. (WEAK)
11. We suggest that clinicians not use diphenhydramine as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. (WEAK)
12. We suggest that clinicians not use melatonin as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults. (WEAK)
13. We suggest that clinicians not use tryptophan as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults. (WEAK)
14. We suggest that clinicians not use valerian as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults. (WEAK)

CITATION: Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2017;13(2):307–347.

Dr. Yanagisawa discovered orexin in 1998 when he was a full-time UTSW faculty member. In 1999, he showed that orexin deficiency causes narcolepsy, leading to new vistas in sleep research and to a better understanding of the brain's sleep/wake switching mechanisms.

More than a decade ago, recognizing that the fundamental mechanism of sleep homeostasis still remained a mystery, Dr. Yanagisawa launched an ambitious two-continent, large-scale forward genetics program to screen for sleep/wake abnormalities in mice, encouraged by discussions with UTSW Neuroscience Chair Joseph Takahashi, Ph.D., a specialist in the study of the body's clocks and in forward genetics.

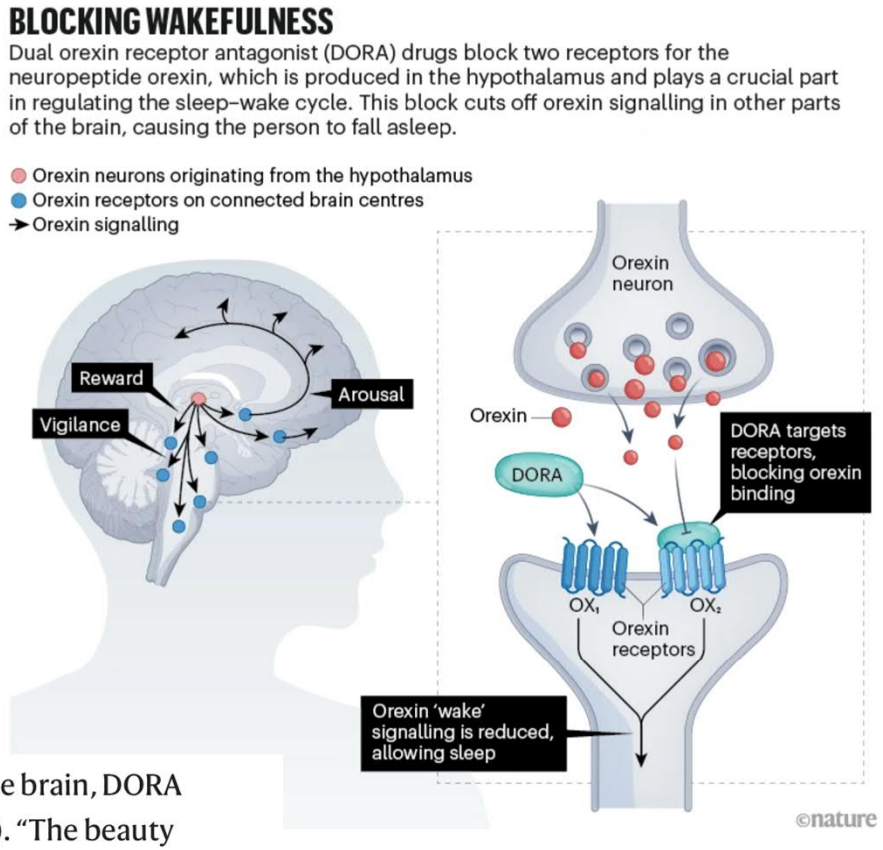
"My many discussions with Joe Takahashi were a major factor for me to launch the high-risk, high-



Dr. Yanagisawa, who was recruited to UTSW by Nobel Laureates Drs. Michael Brown and Joseph Goldstein, discovered orexin in 1998. His research showed that orexin deficiency causes narcolepsy.

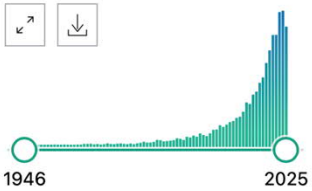
DORAs and efficacy

- Three dual orexin receptor antagonists
- Daridorexant (Quviviq)
- Lemborexant (Dayvigo)
- Suvorexant (Belsomra)
- are available in the United States for treatment of insomnia in adults;



Compared with benzodiazepines and Z-drugs, which inhibit activity all over the brain, DORA drugs affect only the neurons activated by orexins (see 'Blocking wakefulness'). "The beauty of it is it does nothing but block the stimulation of wakefulness," says neurologist Joe Herring, who heads neuroscience clinical research at Merck in Rahway, New Jersey. "It's a physiologically better way to promote sleep."

RESULTS BY YEAR



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- Meta-Analysis
- Randomized Controlled Trial
- Review
- Systematic Review

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1 Cite

Implications of **sleep** disturbance and inflammation for Alzheimer's disease **dementia**.

Irwin MR, Vitiello MV.

Lancet Neurol. 2019 Mar;18(3):296-306. doi: 10.1016/S1474-4422(18)30450-2. Epub 2019 Jan 17.

PMID: 30661858 Review.

Accumulating evidence shows that **sleep** disturbance contributes to cognitive decline and might also increase the risk of Alzheimer's disease **dementia** by increasing beta-amyloid burden. That **sleep** disturbance would be a candidate risk factor for Alzheimer's dis ...

2 Cite

Sleep disturbances increase the risk of **dementia**: A systematic review and meta-analysis.

Shi L, Chen SJ, Ma MY, Bao YP, Han Y, Wang YM, Shi J, Vitiello MV, Lu L.

Sleep Med Rev. 2018 Aug;40:4-16. doi: 10.1016/j.smrv.2017.06.010. Epub 2017 Jul 6.

PMID: 28890168

Sleep disturbances and **dementia** are two common and significant health problems in older adults. Investigations suggest that **sleep** disturbances might increase the risk of **dementia**. The aim of the present study was to systematically review and meta-analy ...

3 Cite

Sleep Duration and Executive Function in Adults.

Sen A, Tai XY.

Curr Neurol Neurosci Rep. 2023 Nov;23(11):801-813. doi: 10.1007/s11910-023-01309-8. Epub 2023 Nov 14.

PMID: 37957525 Free PMC article. Review.

We consider how other **sleep** metrics, such as **sleep** quality, may be a more meaningful measure of **sleep**. We then discuss the putative mechanisms between **sleep** and cognition followed by their contribution to developing **dementia**. ...Poor **sleep** ...

4 Cite

Association Between Slow-Wave **Sleep** Loss and Incident **Dementia**.

Himali JJ, Baril AA, Cavuoto MG, Yiallourou S, Wiedner CD, Himali D, DeCarli C, Redline S, Beiser AS, Seshadri S, Pase MP.

JAMA Neurol. 2023 Dec 1;80(12):1326-1333. doi: 10.1001/jamaneurol.2023.3889.

PMID: 37902739 Free PMC article.

Aging was associated with SWS loss across repeated overnight **sleep** studies (mean [SD] change, -0.6 [1.5%] per year; P < .001). Over the next 17 years of follow-up, there were 52 cases of incident **dementia**. ...CONCLUSIONS AND RELEVANCE: This cohort study found tha

DORAs and Alzheimer's

Suvorexant Acutely Decreases Tau Phosphorylation and Aβ in the Human CNS

Brendan P. Lucey, MD, MSCI,[1,2,3] Haiyan Liu, MD,[1] Cristina D. Toedebusch, BS,[1] David Freund,[1] Tiara Redrick, MS,[1] Samir L. Chahin, MS,[1,2] Kwasi G. Mawuenyega, PhD,[4] James G. Bollinger, PhD,[1,2] Vitaliy Ovod, MS,[1,2] Nicolas R. Barthélemy, PhD,[1,2] and Randall J. Bateman, MD[1,2]

Objective: In Alzheimer's disease, hyperphosphorylated tau is associated with formation of insoluble paired helical filaments that aggregate as neurofibrillary tau tangles and are associated with neuronal loss and cognitive symptoms. Dual orexin receptor antagonists decrease soluble amyloid-β levels and amyloid plaques in mouse models overexpressing amyloid-β, but have not been reported to affect tau phosphorylation. In this randomized controlled trial, we tested the acute effect of suvorexant, a dual orexin receptor antagonist, on amyloid-β, tau, and phospho-tau.
Methods: Thirty-eight cognitively unimpaired participants aged 45 to 65 years were randomized to placebo (N = 13), suvorexant 10 mg (N = 13), and suvorexant 20 mg (N = 12). Six milliliters of cerebrospinal fluid were collected via an indwelling lumbar catheter every 2 hours for 36 hours starting at 20:00. Participants received placebo or suvorexant at 21:00. All samples were processed and measured for multiple forms of amyloid-β, tau, and phospho-tau via immunoprecipitation and liquid chromatography-mass spectrometry.
Results: The ratio of phosphorylated-tau-threonine-181 to unphosphorylated-tau-threonine-181, a measure of phosphorylation at this tau phosphosite, decreased ~10% to 15% in participants treated with suvorexant 20 mg compared to placebo. However, phosphorylation at tau-serine-202 and tau-threonine-217 were not decreased by suvorexant. Suvorexant decreased amyloid-β ~10% to 20% compared to placebo starting 5 hours after drug administration.
Interpretation: In this study, suvorexant acutely decreased tau phosphorylation and amyloid-β concentrations in the central nervous system. Suvorexant is approved by the US Food and Drug Administration to treatment insomnia and may have potential as a repurposed drug for the prevention of Alzheimer's disease, however, future studies with chronic treatment are needed.

ANN NEUROL 2023;94:27–40

Article | Published: 27 May 2025

Lemborexant ameliorates tau-mediated sleep loss and neurodegeneration in males in a mouse model of tauopathy

Samira Parhizkar, Xin Bao, Wei Chen, Nicholas Rensing, Yun Chen, Michal Kipnis, Sihui Song, Grace Gent, Eric Tycksen, Melissa Manis, Choonghee Lee, Javier Remolina Serrano, Megan E. Bosch, Emily Franke, Carla M. Yuede, Eric C. Landsness, Michael Wong & David M. Holtzman

Nature Neuroscience **28**, 1460–1472 (2025) | Cite this article

Abstract

Sleep disturbances are associated with the pathogenesis of neurodegenerative diseases such as Alzheimer's disease and primary tauopathies. Here we demonstrate that administration of the dual orexin receptor antagonist lemborexant in the P301S/E4 mouse model of tauopathy improves tau-associated impairments in sleep–wake behavior. It also protects against chronic reactive microgliosis and brain atrophy in male P301S/E4 mice by preventing abnormal phosphorylation of tau. These neuroprotective effects in males were not observed after administration of the nonorexinergic drug zolpidem that similarly promoted nonrapid eye movement sleep. Furthermore, both genetic ablation of orexin receptor 2 and lemborexant treatment reduced wakefulness and decreased seeding and spreading of phosphorylated tau in the brain of wild-type mice. These findings raise the therapeutic potential of targeting sleep by orexin receptor antagonism to prevent abnormal tau phosphorylation and limit tau-induced damage.

CBD Cannabinoids Insomnia ?

Sleep Medicine Reviews 84 (2025) 102156

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

Effectiveness of cannabinoids on subjective sleep quality in people with and without insomnia or poor sleep: A systematic review and meta-analysis of randomised studies

Giovanna Hanike Santos da Silva [a,*], Eduardo Cerchi Barbosa [b], Fernanda Ribeiro de Lima [c], Douglas Carneiro Barroso [d], Loyná Euá Flores E. Paez [e], Felipe Bandeira de Melo Guimarães [f], Saulo Bernardo Lança [g], Stephanie Brito Ceolin de Faria [h], Arthur Bezerra Cavalcanti Petrucci [i], Alicja Garbacka [j], Jennifer H. Walsh [k,l]

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ARTICLE INFO

Handling Editor: Monica Andersen

Keywords:
Cannabinoids
CBD
Insomnia
Sleep

ABSTRACT

Study objectives: This systematic review and meta-analysis assessed the efficacy of cannabinoids compared to placebo for improving sleep quality.
Methods: Searches were conducted in MEDLINE, Embase, and Cochrane databases for randomised controlled trials comparing cannabinoids vs. placebo for improving sleep quality in adults with or without insomnia or poor sleep. The primary outcome was self-reported sleep quality (PROMIS, PSQI, LSEQ, Sleep Diary). Secondary outcomes included actigraphy parameters, anxiety (GAD-7, STAI-T), well-being (WHO-5 index), and insomnia severity (ISI). Additional analyses focused on sleep quality in (1) participants with insomnia or poor sleep, and (2) cannabidiol (CBD) vs. non-CBD interventions. Statistical analysis was performed using RevMan 5.4.1, with $p < 0.05$ considered significant.
Results: Six trials (1077 patients) were included. Cannabinoids significantly improved sleep quality compared to placebo [SMD 0.53; 95 % CI 0.03–1.02; $p = 0.04$; $I2 = 88$ %], particularly in those with insomnia or poor sleep [SMD 0.60; 95 % CI 0.09–1.11; $p = 0.02$; $I2 = 89$ %]. Non-CBD cannabinoids demonstrated greater efficacy [SMD 0.82; 95 % CI 0.24–1.40; $p = 0.005$], whereas CBD-only therapies showed no significant effect [SMD 0.13; 95 % CI -0.38-0.65; $p = 0.61$].
Conclusion: Cannabinoids, particularly non-CBD formulations, improve sleep quality, justifying further investigation as therapeutic options for insomnia or poor sleep.

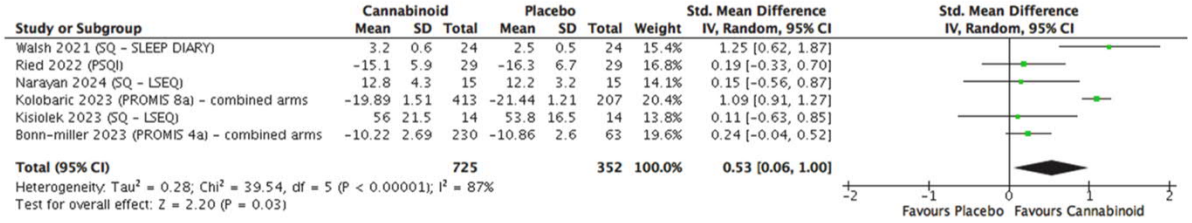


Fig. 1. Improved subjective sleep quality with cannabinoid therapy compared to placebo.

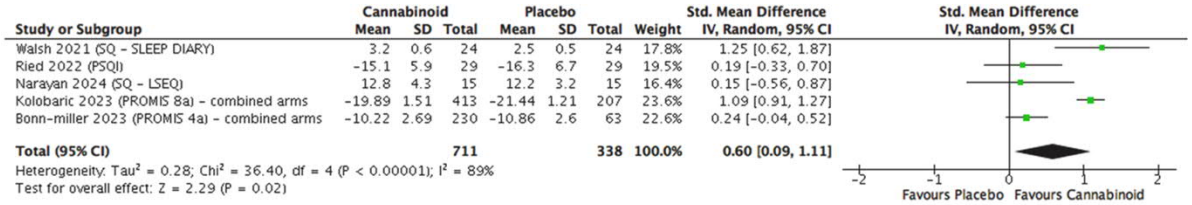


Fig. 2. Improved subjective sleep quality with cannabinoid therapy compared to placebo in populations with insomnia or poor sleep.

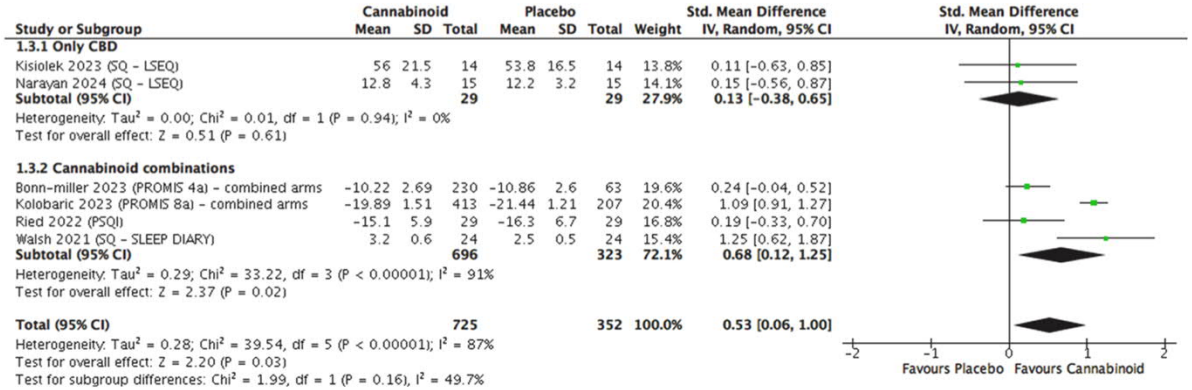
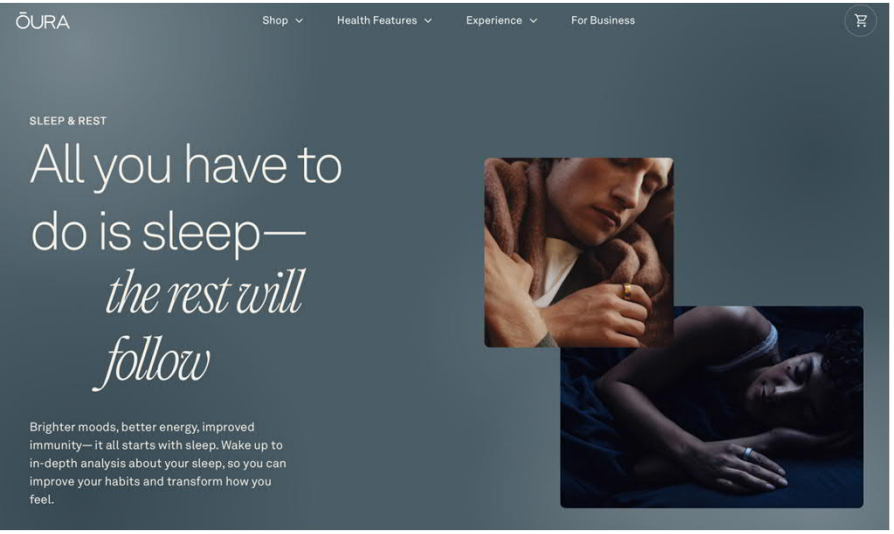


Fig. 3. Subgroup analysis of cannabinoid constituents: No improvement in subjective sleep quality with CBD-only therapy, but significant improvement with therapies inclunding THC and/or other cannabinoids compared to placebo.

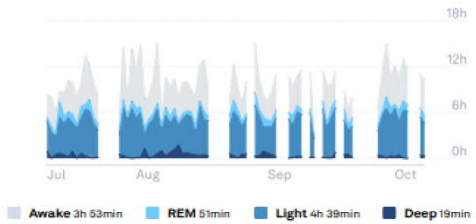
90 days data
Oura Ring



Previous 90 days	Bedtime	Latency	REM sleep	Total sleep time	Wake-up time
	8:03 PM	28 min	15 %	6 h 6 min	6:21 AM
Typical (all time)	7-10 PM	8-28 min	12-21 %	4-7 h	4-7 AM

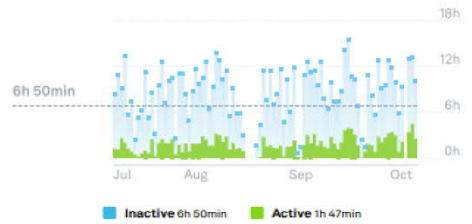
Previous 90 days

Sleep stages



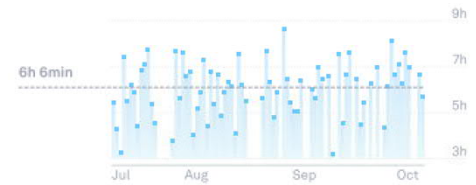
While deep sleep restores your body, REM sleep re-energizes your mind. A good balance is 15% deep sleep and 20% REM sleep a night.

Daily movement



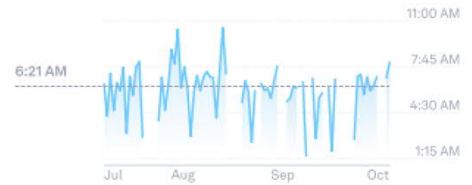
An active lifestyle that has less than 8 hours of inactive time a day has many health benefits.

Total sleep time



7-9 hours of sleep is usually enough for most adults to perform and stay healthy, but this can vary from person to person.

Wake-up time



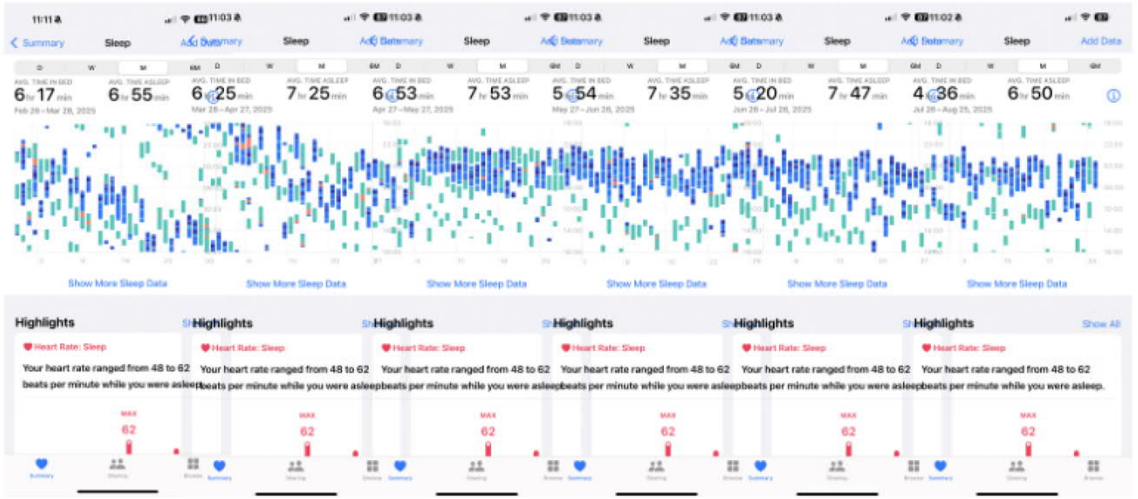
A consistent sleep routine with a regular bedtime and wake-up time keeps you well-rested and energized throughout the week.

Track your sleep with Apple Watch

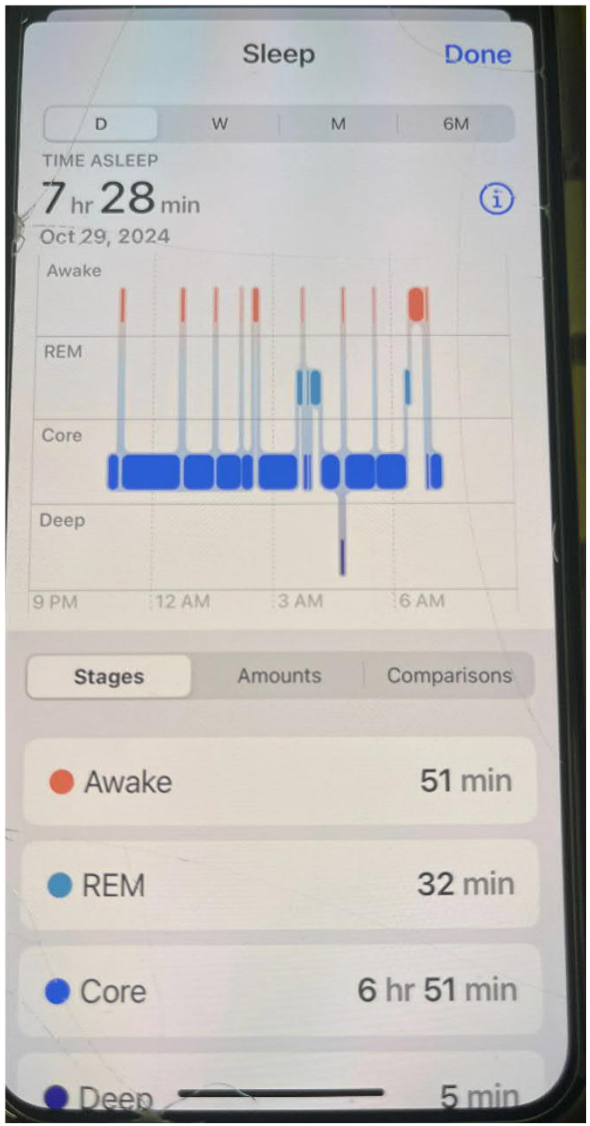
With the Sleep app on Apple Watch, you can create sleep schedules to help you meet your sleep goals. Wear your watch to bed, and Apple Watch can estimate the time you spent in each sleep stage—REM, Core, and Deep—as well as when you might have woken up. When you wake up, open the Sleep app to learn how much sleep you got and see your sleep trends over the past 14 days.

Siri: On supported models, ask Siri something like, "How much did I sleep last night?" (Not available in all languages or regions.) See Keep track of your health and fitness with Siri.

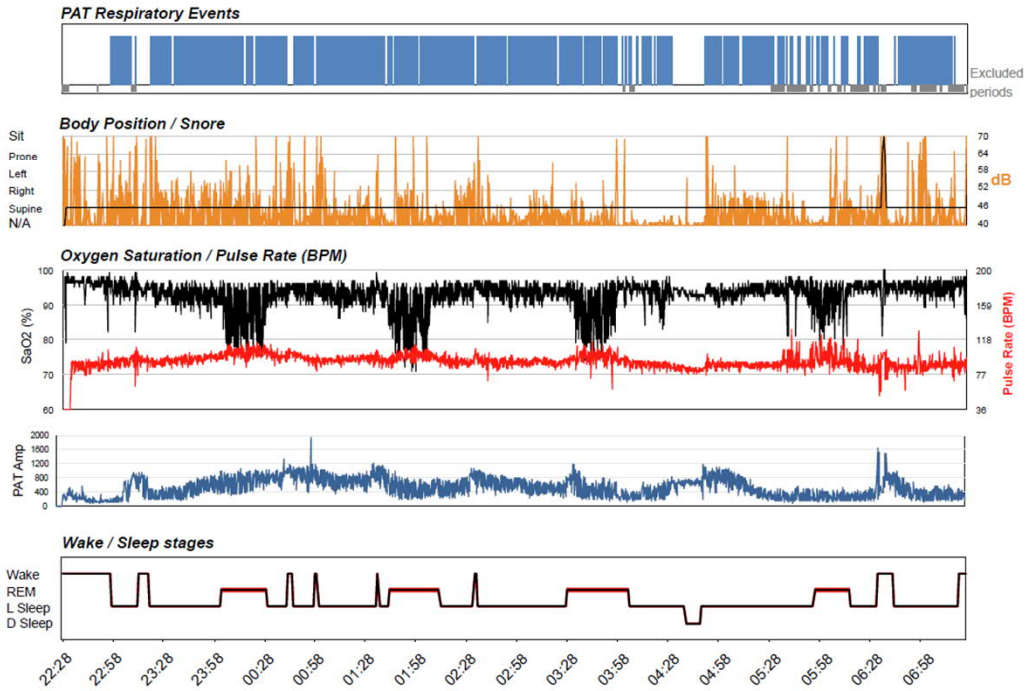
If your Apple Watch is charged less than 30 percent before you go to bed, you're prompted to charge it. In the morning, just glance at the greeting to see how much charge remains.

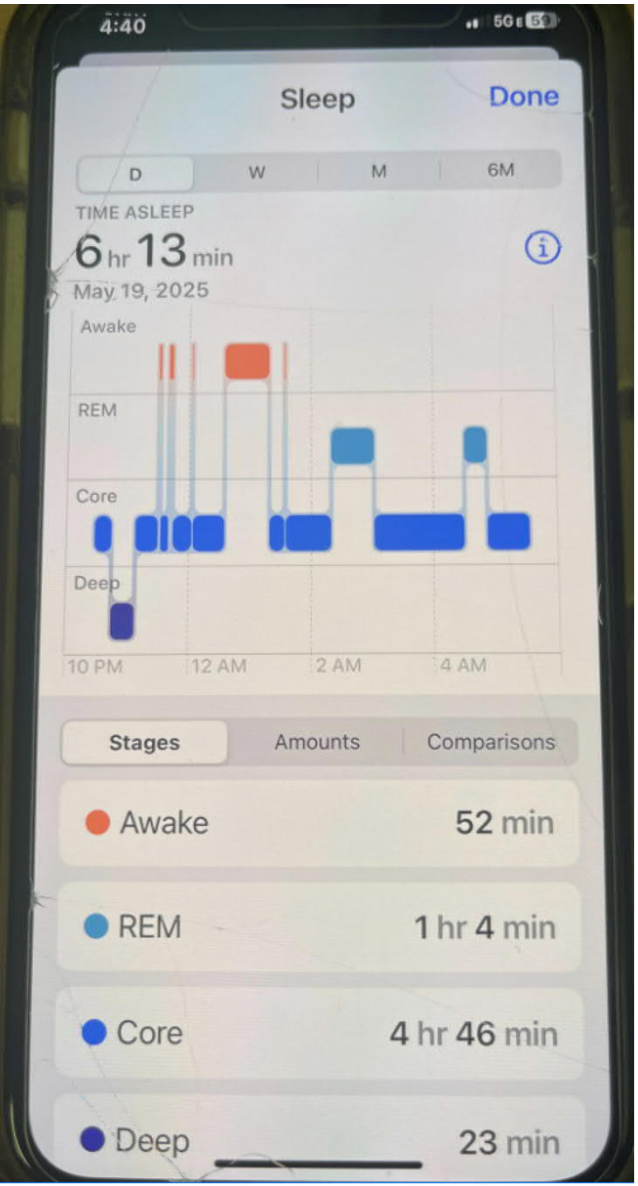


APPLE WATCH SLEEP LOG AFTER STARTING TASIMELTEON



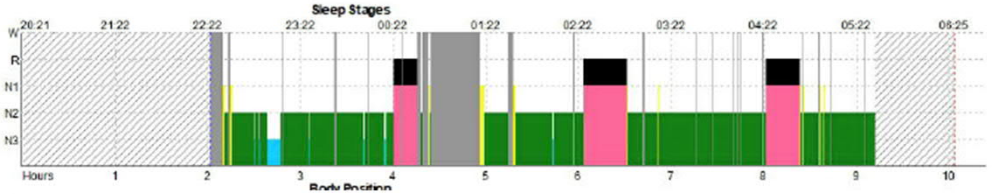
Sleep	Sleep Latency (min): 29	REM Latency (min): 65	Sleep Efficiency: 89%
	Estimated % REM: 23.5%	Est % Deep Sleep: 2.2%	Est % Light Sleep: 74.3%
Respiration	**pAHI (3%): 65.9/hr**	pAHI in REM: 54.6/hr	pAHI in Supine pos: 65.9/hr
	pAHI (4%): 55.8/hr	pAHI in Non-REM: 69.4	pAHI in Non-supine pos: N/A
	pRDI: 66.0/hr	pRDI in REM: 54.6/hr	pRDI in Supine pos: 66.0/hr
Snoring	Average level: 42 dB		
Body Position	Supine: 474.5 min. (100.0%)	Lateral: 0.0 min. (0.0%)	Prone: 0.0 min. (0.0%)
Heart Rate (bpm)	Average HR: 93	Maximum HR: 129	Minimum HR: 59
Oxygen Saturation	**Overall ODI (3%)**: 68.2/hr**	ODI in REM: 57.4/hr	ODI in supine pos: 68.2/hr
	Overall ODI (4%): 55.4/hr**	**Minimum SpO2: 71%**	Total # of OD Events: 409
	SpO2 <=88: 47.8 minutes	Average SpO2: 92%	





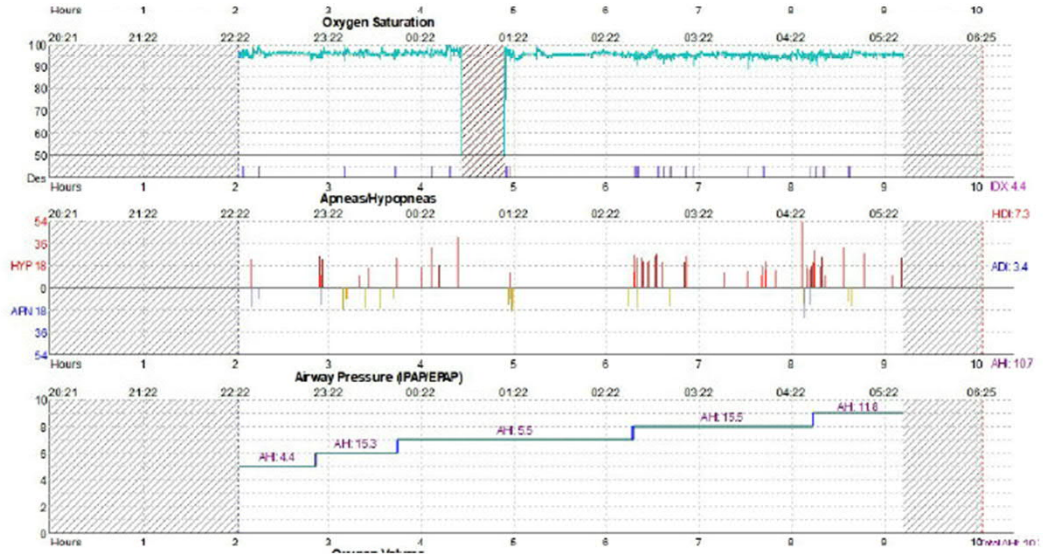
Sleep time 6 hours 15 minutes sleep
REM sleep – 17.6% = 1 hour and 8 minutes
Deep sleep – 3.5% = 21 minutes
Light sleep (core sleep) = 4 hours and 40 minutes

Graphical Summary of Polysomnogram



STUDY DETAILS: Lights off was at 22:24: and lights on 05:34: (7.2 hours in bed).

Sleep and EEG: Total sleep time was 369.0 minutes (100.0% supine; 0.0% lateral), with a normal sleep efficiency of 85.7%. Sleep latency was normal at 7.5 minutes. REM sleep latency was increased at 111.0 minutes. Arousals and awakening index was 21/hr. Of the total sleep time, the percentage of stage N1 sleep was 2.8%, stage N2 sleep was 76.0%, stage N3 sleep was 3.5%, and REM sleep was 17.6%. The following abnormalities were observed on limited EEG: none.



Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

World Sleep Society recommendations for the use of wearable consumer health trackers that monitor sleep

Michael WL. Chee [a,*], Mathias Baumert [b], Hannah Scott [c], Nicola Cellini [d,e], Cathy Goldstein [f], Kelly Baron [g], Syed A. Imtiaz [h], Thomas Penzel [i], Clete A. Kushida [j], on behalf of the World Sleep Society Sleep Tracker Task Force

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[b] Discipline of Biomedical Engineering, School of Electrical and Mechanical Engineering, The University of Adelaide, Adelaide, Australia
[c] Flinders Health and Medical Research Institute: Sleep Health, College of Medicine & Public Health, Flinders University, Adelaide, Australia
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ARTICLE INFO

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Wearable sleep monitoring

ABSTRACT

Wearable consumer health trackers (CHTs) are increasingly
debated within the sleep community. To na

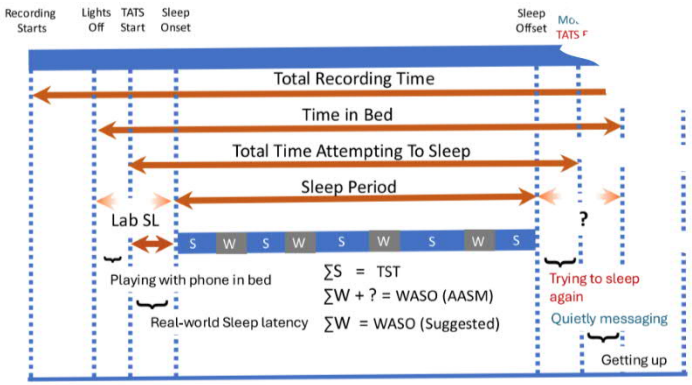
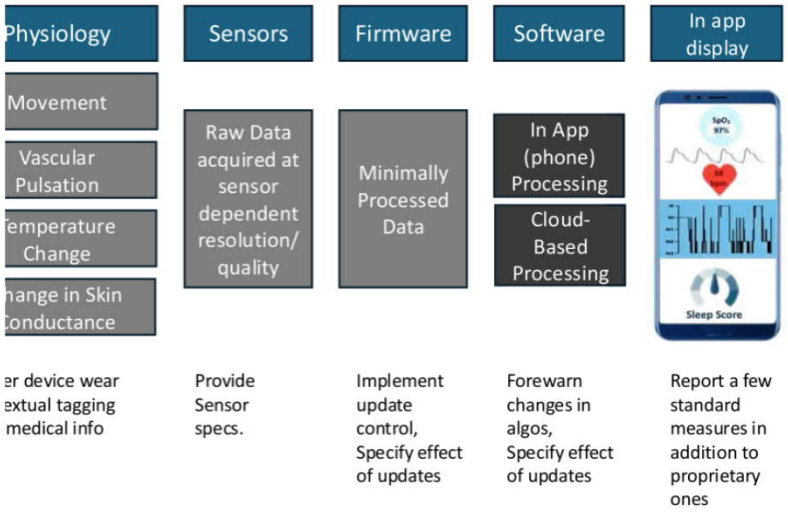


Fig. 2. Schematic showing measures used in wake-sleep classification as inherited from laboratory studies and the challenges in inferring "Lights off" (a proxy for



Wearables Technology?

What is a parasomnia?

- An undesirable physical event or sensory experience that occur with entry into, during, or arousing from sleep
  - Common and usual behaviors – sleep talking
  - Bizarre and unusual events – dream enactment
    - “entertaining stories from bed partners or roommates”

Table 115.1 Parasomnia Classification

NREM Sleep–Related Parasomnias

Disorders of arousal (from NREM sleep)
- Confusional arousals
- Sleepwalking
- Sleep terrors

Sleep-related eating disorder

REM Sleep–Related Parasomnias

REM sleep behavior disorder
Recurrent isolated sleep paralysis
Nightmare disorder

Other Parasomnias

Exploding head syndrome
Sleep-related hallucinations
Sleep enuresis
Parasomnia due to a medical disorder
Parasomnia due to a medication or substance
Parasomnia, unspecified

NREM, Non–rapid eye movement; REM, rapid eye movement.

Principles and Practice of Sleep Medicine. 7th ed. 2022.

Table 115.2 Distinguishing Features of Nocturnal Events

Feature	Disorders of Arousal	Sleep-Related Eating Disorder	REM Behavior Disorder	Recurrent Isolated Sleep Paralysis	Exploding Head Syndrome	Periodic Limb Movements of Sleep	Psychogenic Events	Nocturnal Seizures
Behavior	Confused; semipurposeful movement with eyes open	Eating typically high-calorie foods; eyes open	Sometimes combative with eyes closed	Episodes of inability to move	Painless sensation of explosion inside the head	Typically triple flexion of the leg	Variable	Dependent on the portion of brain involved
Age of onset	Childhood and adolescence	Variable	Older adult	Variable	Adult	Any but more common in adults	Adolescence to adulthood	Variable
Time of occurrence	First third of night	First half of night	During REM	Typically on awakening	Usually near sleep onset but can be variable	More common in the first half of night	Anytime	Anytime
Frequency of events	Less than one per night	Variable	Multiple per night	Variable less than weekly	Rare	Every 10–90 sec	Variable	Frontal seizures: multiple per night
Duration	Minutes	Minutes	Seconds to minute	Seconds to minutes	Seconds	Typically less than 5 sec	Variable minutes or longer	Usually <3 min
Memory of event	Usually none	Usually none or limited	Dream recall	Yes	Yes	Variable	None	Usually none
Stereotypic movements	No	No	No	No	Similar sensation	Yes	No	Yes
Polysomnogram findings	Arousals from slow wave sleep	Arousal from NREM sleep	Excessive electromyogram tone during REM sleep	Arousal from REM sleep	Usually occurs in light sleep	Periodic limb movements	Occur from awake state	Potentially epileptiform activity

NREM, Non–rapid eye movement; REM, rapid eye movement.

Table 115.3 Indications for Polysomnography in Patients with Nocturnal Events

Atypical presentation for a parasomnia (time of night, behavioral description)
Events injurious or with significant potential for injury
Significant disturbance to patient's home life
Unusual age of onset
Events stereotypic or repetitive
Unusual frequency of the events
Patient has excessive daytime sleepiness or complaints of insomnia
Complaints suggestive of sleep apnea, periodic limb movements, or other sleep disorders

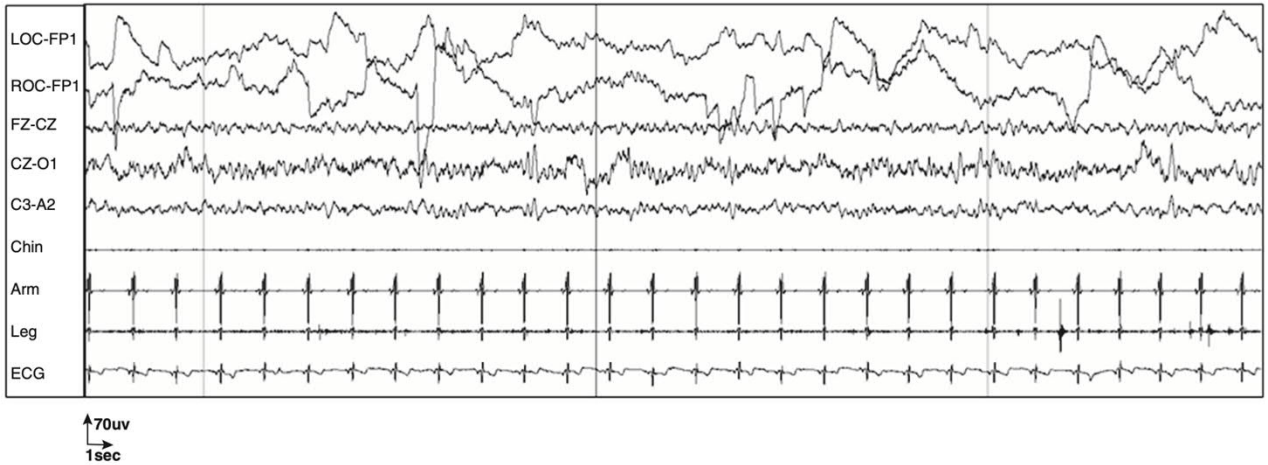


Figure 118.1 Normal REM sleep atonia. A 30-second polysomnogram epoch demonstrates normal REM sleep levels of atonia in submentalis, arm, and anterior tibialis leg leads on the electromyogram.

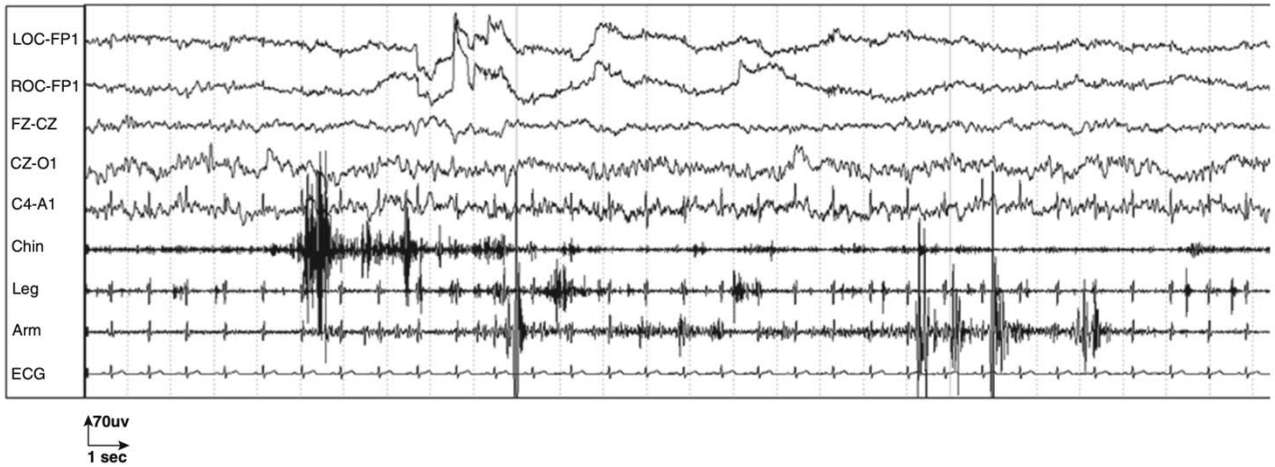


Figure 118.2 Abnormal REM sleep without atonia. Increased phasic/transient muscle activity is shown in the submentalis, anterior tibialis, and arm electromyographic leads in this 30-second polysomnogram epoch. A more sustained lower-grade elevation of muscle tone lasting for longer than one-half of the epoch represents abnormal tonic muscle activity, seen in the submentalis and arm channels of the electromyogram.

Table 116.2 Key Similarities and Differentiating Features among the Non–Rapid Eye Movement and Rapid Eye Movement Parasomnias, as well as Nocturnal Seizures

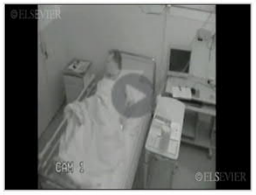
	Disorders of Arousal			REM Parasomnias		
	Confusional Arousals	Sleepwalking	Sleep Terrors	REM Sleep Behavior Disorder	Nightmares	Nocturnal Seizures
Timing at night and sleep-stage specificity	Usually occur in the first half of the night and typically out of stage N3 slow wave sleep.			Occur from REM sleep and typically occur in the last third of the night.		At any time of night, but usually out of NREM sleep. Favoring occurrence when EEG is synchronized.
Family history	Usually positive for similar events			No	May be positive	May be positive.
Behavior semiology	Sudden arousals followed by confusion, disorientation, and amnesia for the event	Abrupt arousal confused/agitated if interrupted. Amnesia at the end	Sudden arousal intense screaming, inconsolable crying, agitation, and heightened autonomic discharge	Purposeful dream enactment behaviors, including yelling, punching, kicking, to fighting a supposed intruder/animal	Paroxysmal awakenings with anxiety and dream recall.	Stereotyped, monomorphic, paroxysmal events often with dystonic limb posturing, vocalizations, and confusions. May encounter partial recall/ amnesia.
Event duration	Few seconds to minutes	Usually 1–10 minutes	Few seconds to minutes	Usually <10 minutes	Few seconds to minutes	Few seconds to few minutes.
Frequency	Few times per month-week, very rarely >1 episode in a single night					Frequent: may occur multiple times in a night.
Postspell behavior	Limited to no recall of the events with confusion			Recall is usually present at times with vivid details. Patients with RBD often describe needing to protect themselves from an attacker (animal/intruder)		Complete/ partial recall to amnesia and confusion.
Polysomnography	Abrupt arousal from slow wave sleep (stage N3) with expression confusion/ambulation/intense fright in CA/SW/ST, followed by return to sleep. Increase cyclic alternating pattern (CAP)			Abnormal increased chin or limb EMG tone (atonia is noted during normal REM sleep).	Dense eye (phasic) movements during REM	Epileptiform activity/muscle artifact/or normal EEG if limited montage
Treatments	Safety interventions, protect patients, remove sharp objects from bedroom, cover windows, barricade furniture, place door alarms. Avoidance of precipitating factors, protecting sleep environment, improving sleep hygiene, avoidance of sleep deprivation. Hypnosis, anticipatory awakenings are helpful. If episodes are frequent, severe, and disruptive to sleep continuity, or result in daytime sleepiness or injury, consider pharmacotherapy			REM sleep behavior disorder Level A: Promote safety Level B: Pharmacotherapy with Melatonin or Clonazepam Nightmares: Reassurance, avoid injury, treat precipitating factors.		Antiepileptic drugs, carbamazepine most frequently used for normal seizures.

Modified after Avidan AY, Kaplish N. The parasomnias: epidemiology, clinical features, and diagnostic approach. *Clin Chest Med*. 2010;31:353–70.

- Timing of night is helpful
- Semiology
- Event duration

Parasomnias

VIDEO



Violent Behavior during REM in a 68-Year-Old with Parkinson Syndrome

Published

Violent Behavior during REM in a 68-Year-Old with Parkinson Syndrome Kryger, Goldman, Roth, Dement Parkinson patient, 68 years old, with rapid eye movement (REM) sleep behavior disorder. The patient dreams that he is arguing and fighting with a st...

VIDEO

Violent Behavior during REM in a 52-Year-Old with Parkinson Syndrome

Published

Violent Behavior during REM in a 52-Year-Old with Parkinson Syndrome Kryger, Goldman, Roth, Dement Parkinson patient with bradykinesia before sleep onset (subtitled in French " EVEIL" for wakefulness) and disappearance of parkinsonism during rapid...

Parasomnias

- https://www-clinicalkey-com.foyer.swmed.edu/#!/browse/book/3-s2.0-C20201045178

Parasomnias

- https://www-clinicalkey-com.foyer.swmed.edu/#!/browse/book/3-s2.0-C20201045178

Chapter 118

Rapid Eye Movement Sleep Parasomnias

Michael H. Silber; Erik K. St Louis; Bradley F. Boeve

Chapter Highlights

- Rapid eye movement (REM) sleep behavior disorder (RBD) is a unique parasomnia characterized by loss of REM sleep atonia and dream-enactment behavior. This chapter explores the epidemiology, clinical features, pathophysiology, diagnosis, and management of the condition.
- RBD is commonly seen in patients with a group of neurodegenerative disorders known as the synucleinopathies, including Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. RBD is designated as idiopathic when the disorder takes place without a comorbid neurologic disorder or identifiable cause. Robust evidence confirms that a majority of patients with idiopathic RBD also harbor synucleinopathy pathology. RBD may be associated with antidepressant use, certain rare autoimmune disorders, and narcolepsy.
- RBD is diagnosed through clinical history and polysomnography. Quantitative assessments of muscle activity in REM sleep can result in greater diagnostic accuracy.
- Management includes prognostic counseling and injury prevention by addressing bedroom safety and the use of medications such as melatonin and clonazepam.
- Other REM sleep parasomnias include nightmare disorder, recurrent isolated sleep paralysis, and sleep-related painful erections. The epidemiology, clinical features, and management of the latter two conditions are discussed in this chapter.

CLINICAL PEARLS

- Rapid eye movement sleep behavior disorder (RBD) occurs predominantly in men (79% of patients), but this difference becomes less marked when the disorder commences before the age of 50 years.
- RBD can result in serious injuries to both patients and their bed partners, including fractures, subdural hematomas, ecchymoses, lacerations, and dental injuries.
- RBD is strongly associated with fully expressed synucleinopathies (Parkinson disease, dementia with Lewy bodies, and multiple system atrophy), and in 74% of patients with idiopathic RBD, a fully expressed synucleinopathy will develop within 12 years of RBD diagnosis.
- In patients with idiopathic RBD, decreased olfaction, changes in color vision, and autonomic findings may indicate a greater risk for an underlying synucleinopathy.
- Although both clonazepam and melatonin are effective in treating RBD, clonazepam has many side effects, especially in elderly and neurologically disabled persons, and melatonin should be the first drug tried in these patients.
- Recurrent isolated sleep paralysis may occur in 6% of the population but should be regarded as a disorder only if it results in significant distress, including bedtime anxiety or difficulty initiating sleep.

Table 118.1 Prodromal Features of Fully Expressed Synucleinopathies in Patients with Idiopathic Rapid Eye Movement Sleep Behavior Disorder

Physiologic Abnormalities

Reduced olfaction
Reduced color vision
Autonomic dysfunction (symptoms, cardiovascular tests,[123] I-MIBG myocardial scintigraphy)
Motor dysfunction
Cognitive dysfunction
EEG power abnormalities

Imaging Abnormalities

Midbrain: transcranial sonography
Striatal dopamine transporters: SPECT scans
Putaminal volume: MRI scans
Parkinson disease–related covariance pattern: PET and SPECT scans
Hyperperfusion and hypoperfusion of various brain regions: SPECT scans
Pons and midbrain abnormalities: MRI diffusion tensor imaging
Hippocampal gray matter: voxel-based morphometry
Cerebellum and pontine tegmentum: voxel-based morphometry
Increased cholinergic innervation of brainstem: PET scan

Pathologic Abnormalities

α-Synuclein deposits in:
Skin
Salivary glands
Colonic mucosa

EEG, Electroencephalogram; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

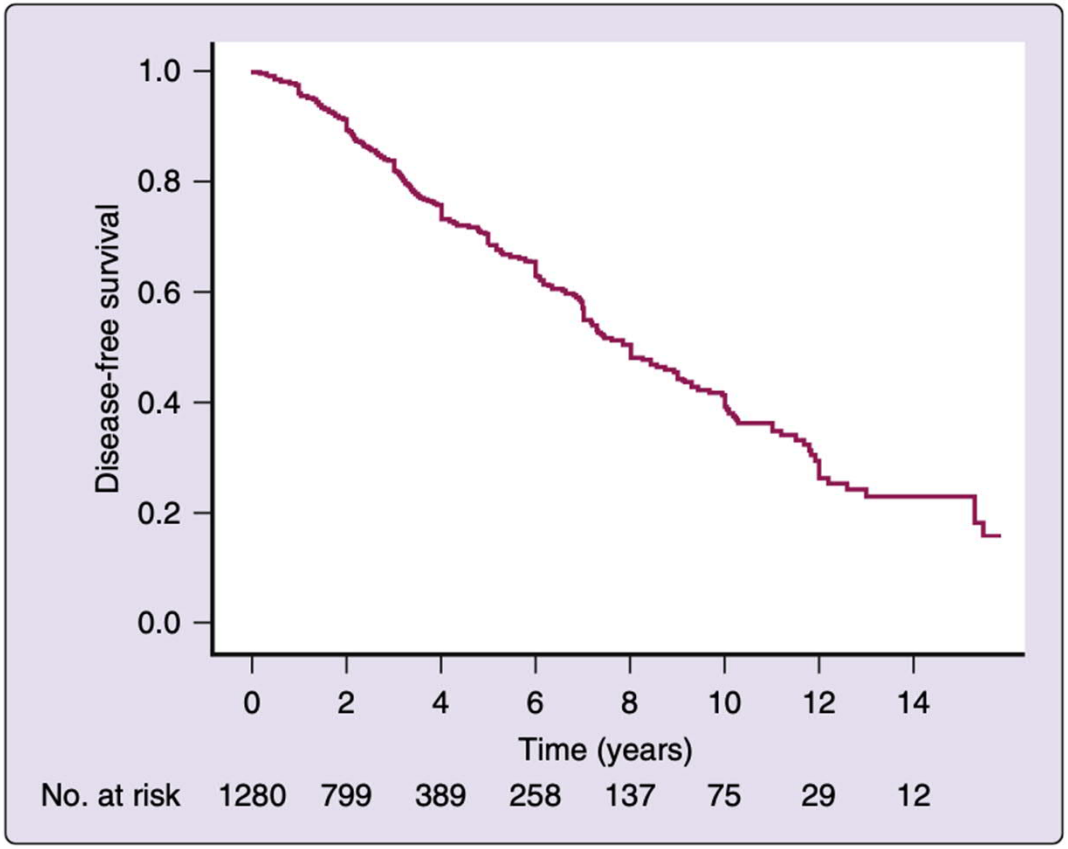
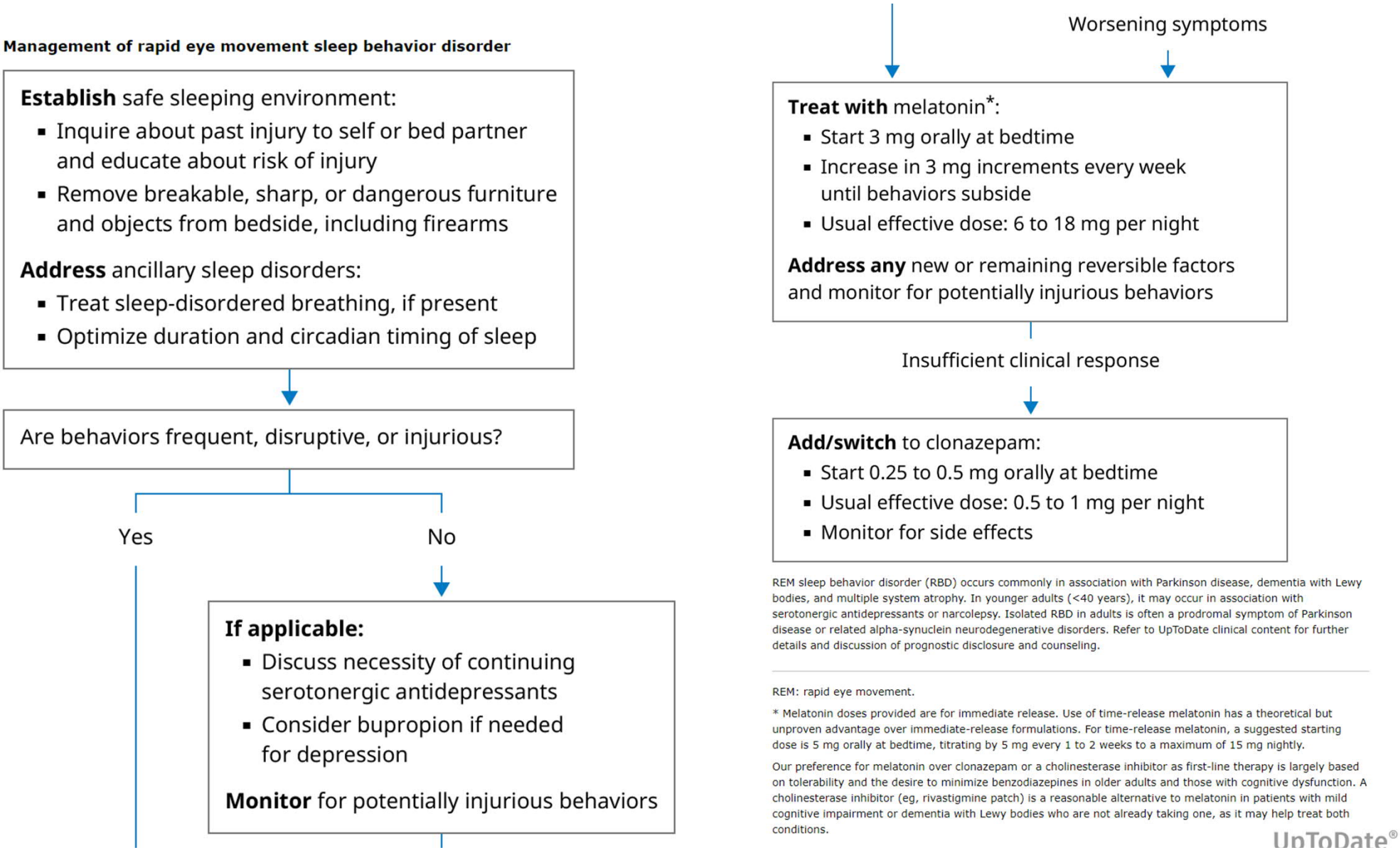


Figure 118.3 Progression from idiopathic REM sleep behavior disorder (iRBD) to fully developed synucleinopathies. Kaplan-Meier curve showing the rate of progression from iRBD to fully developed synucleinopathies. (Modified from Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behavior disorder: a multicenter study. *Brain*. 2019;142:744–59; with permission.[74])

Management of rapid eye movement sleep behavior disorder



REM sleep behavior disorder (RBD) occurs commonly in association with Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. In younger adults (<40 years), it may occur in association with serotonergic antidepressants or narcolepsy. Isolated RBD in adults is often a prodromal symptom of Parkinson disease or related alpha-synuclein neurodegenerative disorders. Refer to UpToDate clinical content for further details and discussion of prognostic disclosure and counseling.

REM: rapid eye movement.

* Melatonin doses provided are for immediate release. Use of time-release melatonin has a theoretical but unproven advantage over immediate-release formulations. For time-release melatonin, a suggested starting dose is 5 mg orally at bedtime, titrating by 5 mg every 1 to 2 weeks to a maximum of 15 mg nightly.

Our preference for melatonin over clonazepam or a cholinesterase inhibitor as first-line therapy is largely based on tolerability and the desire to minimize benzodiazepines in older adults and those with cognitive dysfunction. A cholinesterase inhibitor (eg, rivastigmine patch) is a reasonable alternative to melatonin in patients with mild cognitive impairment or dementia with Lewy bodies who are not already taking one, as it may help treat both conditions.

Sleep and sleep disorders in people with Parkinson's disease

Alex Iranzo, Valerie Cochen De Cock, María Livia Fantini, Laura Pérez-Carbonell, Lynn Marie Trotti

Sleep disorders are common in people with Parkinson's disease. These disorders, which increase in frequency throughout the course of the neurodegenerative disease and impair quality of life, include insomnia, excessive daytime sleepiness, circadian disorders, obstructive sleep apnoea, restless legs syndrome, and rapid eye movement (REM) sleep behaviour disorder. The causes of these sleep disorders are complex and multifactorial, including the degeneration of the neural structures that modulate sleep, the detrimental effect of some medications on sleep, the parkinsonian symptoms that interfere with mobility and comfort in bed, and comorbidities that disrupt sleep quality and quantity. The clinical evaluation of sleep disorders include both subjective (eg, questionnaires or diaries) and objective (eg, actigraphy or video polysomnography) assessments. The management of patients with Parkinson's disease and a sleep disorder is challenging and should be individualised. Treatment can include education aiming at changes in behaviour (ie, sleep hygiene), cognitive behavioural therapy, continuous dopaminergic stimulation at night, and specific medications. REM sleep behaviour disorder can occur several years before the onset of parkinsonism, suggesting that the implementation of trials of neuroprotective therapies should focus on people with this sleep disorder.

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Sleep disorders in patients with established Parkinson's Disease

Insomnia – multi-factorial – 44% of PD	• Bradykinesia, dyskinesias, dystonia, leg cramps, nocturia
Excessive daytime sleepiness - 33% of PD	• Related to the disease, or dopaminergic agents side/effects • Dysfunction of dopaminergic and non-dopaminergic networks • Hypocretin/orexin cell loss
Circadian rhythm disorder	• Degeneration of the dopaminergic cells → retina, SCN, pineal gland • Advanced sleep phase – dopaminergic agents • Irregular sleep-wake pattern
REM behavior disorder	• 25-50% of PDs, 20% of cases preceding the onset of PDs → "idiopathic RBD" • RE: damage to the lower brainstem that generate muscle atonia

Sleep disorders in patients with established Parkinson's disease

- Video polysomnography studies
  - Decreased total sleep time
  - Increased wake time after sleep onset
  - Periodic leg movements in sleep
  - REM behavior disorder

- Progression of PD → changes…
  - Reductions in sleep efficiency
  - Reductions in slow wave sleep
  - Disorganized sleep architecture
  - Irregular medium amplitude delta activity without K complexes and sleep spindles
  - Alterations in glymphatic system?
    - CSF clearance of alpha-synuclein, amyloid, and tau

Overall, there is agreement that sleep disorders in people with established Parkinson's disease are frequent, impact patients' daily functioning, and increase in frequency with age.[4–7,19]

Video polysomnography studies in patients with de novo untreated Parkinson's disease show either normal sleep architecture or abnormalities, such as reduced total sleep time, increased wake time after sleep onset, periodic leg movements in sleep, and RBD.[20] As the disease progresses, sleep architecture becomes abnormal, with reductions in sleep efficiency and slow-wave sleep.[20] In people with advanced Parkinson's disease, particularly in those with dementia, video polysomnography studies have shown disorganised sleep architecture when conventional sleep stages cannot be recognised using standard criteria established by the American Academy of Neurology due to: slow dominant occipital frequency during wakefulness; disappearance of conventional non-REM sleep substituted by irregular continuous medium-amplitude delta activity without K complexes and sleep spindles; and an absence of muscle atonia in REM sleep.[21]

There is some evidence that reduced slow-wave sleep might alter the glymphatic system, a CSF transport system in the brain that clears proteins such as α-synuclein, amyloid, and tau.[22] Consequently, the loss of slow-wave sleep seen in Parkinson's disease is associated with motor progression and cognitive decline.[23] Interestingly, some patients with Parkinson's disease experience an improvement of parkinsonism upon awakening before taking their morning dopaminergic dose. This sleep benefit has been speculated to occur in patients with continuous and stable nocturnal sleep, which allows the correct clearance of toxins and proteins from the brain during normal slow-wave sleep through the glymphatic system.[4] These observations highlight the concept that sleep and Parkinson's disease have a bidirectional relationship.

Clinical Investigation

Sleep and Parkinson's Disease

	Status	Intervention	Study aim	Primary outcome	Participants (N)
NCT03111485*	Completed	Pharmacological	To assess whether long-acting levodopa at night improves obstructive sleep apnoea in patients with Parkinson's disease, compared with placebo	Apnoea–hypopnoea index at 2 weeks	36
NCT04986995*	Active, not recruiting	Pharmacological	To assess the efficacy of 50 mg opicapone administered with levodopa plus a dopa decarboxylase inhibitor, in patients with Parkinson's disease with end-of-dose motor fluctuations and associated sleep disorders	Total score on the Parkinson's Disease Sleep Scale Version 2 at up to 6 weeks	22
NCT03968744	Recruiting	Pharmacological	To evaluate the effect of safinamide on sleep quality and polysomnography parameters in patients with Parkinson's disease	Changes in Parkinson's Disease Sleep Scale Version 2 score and changes in sleep maintenance and sleep efficiency scores measured by polysomnography at 12 weeks	23 (intended)
NCT02209363	Completed	Device	To assess the effect of positive airway pressure therapy on global cognitive function in patients with Parkinson's disease with obstructive sleep apnoea and cognitive impairment	Changes in cognitive function as per MoCA score at 6 months	91
NCT05070013	Recruiting	Device	To investigate the effects of adaptive subthalamic stimulation in sleep maintenance and quality in patients with Parkinson's disease	Sleep fragmentation frequency and duration, measured by actigraphy and change in subjective sleep quality between three stimulation conditions, measured by Pittsburgh Sleep Diary at 1–3 years	20 (intended)
NCT05599035	Completed	Device	To analyse sleep disturbances in patients with Parkinson's disease compared with healthy controls and to evaluate the impact of repetitive transcranial magnetic stimulation on sleep disorders	Parkinson's disease sleep scale and polysomnography parameters at 1 month	40 (intended)
NCT05348837	Recruiting	Device	To assess sleep of patients with Parkinson's disease with wearable devices, on and off medications, before and after deep brain stimulation implantation	Change in total sleep time measured by headband polysomnography and averaged over the 3-night study period at 6 months	15 (intended)
NCT05184270	Completed	Device	To investigate the effect of acoustic stimulation on the sleep of patients with Parkinson's disease and deep brain stimulation (measured by STN-LFP)	Identification of STN-LFP correlates of cortical slow waves; comparing the slope, amplitude, and incidence of slow waves across the night between surface EEG and STN-LFP; effect of acoustic stimulation on frequencies >4 Hz and on slow-wave activity, slope, and amplitude of slow waves in surface EEG and STN-LFP through study completion, an average of 2 years	15
NCT05771558	Recruiting	Device	To assess the effects of tailored lighting intervention on sleep, fatigue, and circadian entrainment via urinary melatonin levels in patients with Parkinson's disease	Change in sleep duration measured by actigraphy at 4 weeks and 8 weeks	50 (intended)
NCT05524961	Recruiting	Device	To evaluate the effect of bright light therapy on self-reported daytime sleepiness in patients with Parkinson's disease	Change in Epworth Sleepiness Scale score at 6 weeks	69 (intended)
NCT04116996	Recruiting	Device	To investigate the effect of globus pallidus external stimulation on insomnia in patients with Parkinson's disease	Change in self-reported insomnia severity index questionnaire score at 3 months and 6 months	10 (intended)
NCT04736017	Recruiting	Device	To assess the efficacy of auditory slow-wave sleep enhancement in patients with Parkinson's disease and patients with amnestic mild cognitive impairment	Differences in objective excessive daytime sleepiness, measured by the MSLT in patients with Parkinson's disease; differences in verbal episodic memory performance, measured with the Hopkins Verbal Learning Test in patients with mild cognitive impairment, at day 15 after each intervention	48 (intended)
NCT06002581	Recruiting	Device	To investigate the effect of repetitive transcranial magnetic stimulation in regulating slow-wave sleep to delay the progression of Parkinson's disease	Change in Unified Parkinson's Disease Rating Scale 3 score at day 14; secondary outcomes include change in slow-wave sleep proportion and Epworth Sleepiness Scale score at days 14, 28, and 56	56 (intended)
NCT05962489	Recruiting	Device	To describe how activation of distinct pathways in and around the subthalamic nucleus and internal segment of the globus pallidus correlate to changes in sleep outcomes in patients with Parkinson's disease	Percentage of pallidopeduncular and pedunculopallidal pathway activation and globus pallidus externa activation; sleep quality measured by actigraphy and Pittsburgh Sleep Quality Index; and Epworth Sleepiness Scale score at 6 months and 12 months	64 (intended)
NCT05644327	Recruiting	Behavioural	To assess the impact of cardiovascular, resistance, and multimodal (ie, a combination of cardiovascular and resistance) training on sleep quality and architecture in people with Parkinson's disease	Objective changes in sleep (sleep efficiency, slow-wave power, spindles density, and rapid eye movement sleep proportion, measured by polysomnography) and changes in Parkinson's Disease Sleep Scale version 2 score, at 12 weeks (post intervention) and 8 weeks (follow-up)	150 (intended)
NCT04796506	Recruiting	Behavioural	To evaluate the effects of exercise rehabilitation on cognition and in slow-wave sleep in patients with Parkinson's disease	Change in executive function on the Stroop inhibition test at 12 weeks	120 (intended)

(Table continues on next page)

Insomnia

Common condition

Comprehensive evaluation - “Insomnia”

Different models of insomnia

- 3 P’s
- Arousals
- Parallel process model

CBT – cognitive behavioral therapy

Medications

- DORAs

Wearables?

Parasomnia

Uncommon condition

- “Things that go bump in the night”
- “Bizarre events/stories”

Comprehensive evaluation

- Sleep evaluation
- Polysomnography

Treatment

- Safety
- Pharmacology options

Relevance

- Tie in with neurodegenerative conditions

REM behavior disorder

Insomnia and Parasomnias Brain Summit 2025

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* No disclosures to declare