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Having the Snooze Blues?

State of the Science on Sleep in Depressive Disorder

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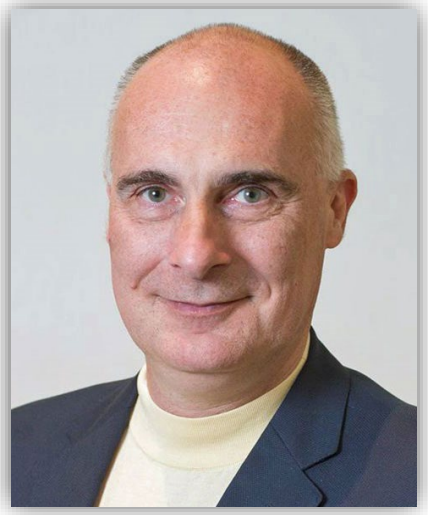
Our Featured Speakers

Marie Anne Gebara, MD

- Assistant Professor of Psychiatry
- University of Pittsburgh Department of Psychiatry
- Expertise in Treatment Resistant Depression, Sleep & Mood



Vladimir Maletic, MD, MS

- Clinical Professor of Neuropsychiatry and Behavioral Science at the University Of South Carolina School Of Medicine in Columbia, South Carolina
- Consulting Associate in the Division of Child & Adolescent Psychiatry at Duke University Medical Center in Durham, North Carolina

Moderator

Beth DiNapoli, PhD

- Senior Clinical & Scientific Liaison, Otsuka Neuroscience Medical Affairs

Objectives

- Provide a brief overview of sleep statistics and clinical assessment
- Discuss the relationship between sleep and **depressive** disorders
- Highlight strategies to manage insomnia, improve sleep quality, and digitally monitor sleep patterns

Sleep Is a Vital, Complex, and Organized Physiological State Involving Multiple Regulatory Processes

Sleep drive[1]

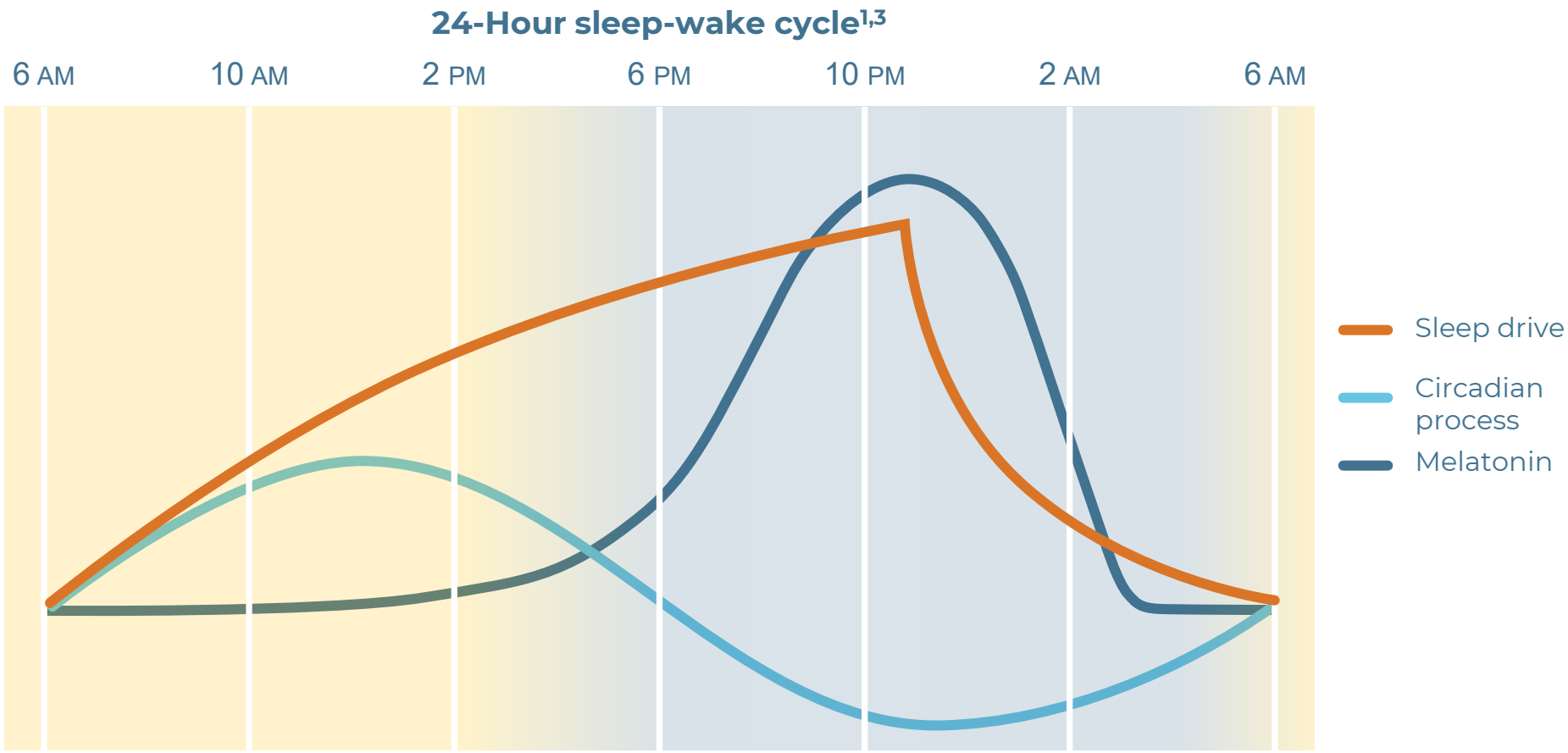
Increases while awake and decreases while asleep

Circadian process[1]

Determined by the circadian pacemaker, irrespective of behavioral state

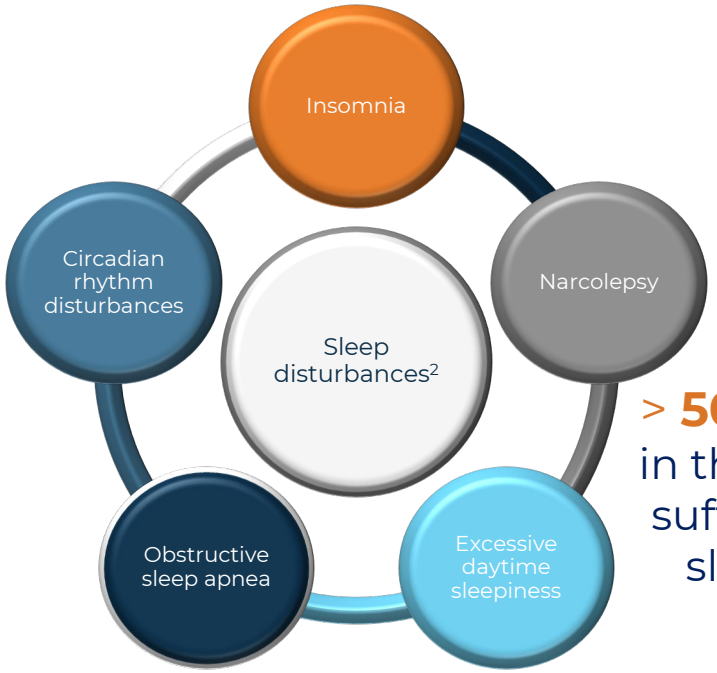
Melatonin[2,3]

Released in the evening to enhance sleep onset

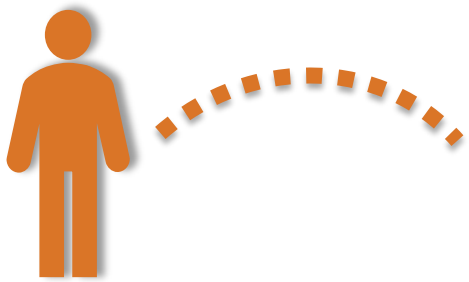


1. Beersma and Gordijn. *Physiol Behav.* 2007;90:190-195. 2. Borbély et al. *J Sleep Res.* 2016;25:131-143. 3. National Sleep Foundation. www.sleepfoundation.org/articles/melatonin-and-sleep. Accessed December 15, 2019.

Insomnia is Common



> **50 million** people in the United States suffer from various sleep disorders[1]



~10% of the general population suffers from insomnia[3]

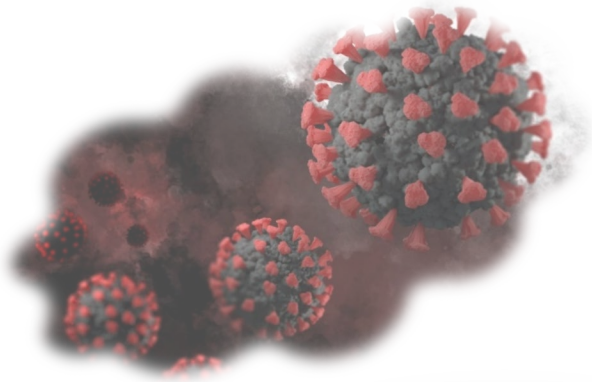
Insomnia is characterized by chronic difficulties falling asleep, staying asleep, or waking up too early[4]

Clinical features

- Causes clinically significant distress or impairment in important areas of functioning
- Occurs:
  - at least 3 nights per week
  - for at least 3 months
  - despite adequate opportunity for sleep
- Cannot be explained by and does not occur exclusively during another sleep-wake disorder
- Not attributable to the physiological effects of a drug of abuse or medication
- Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia

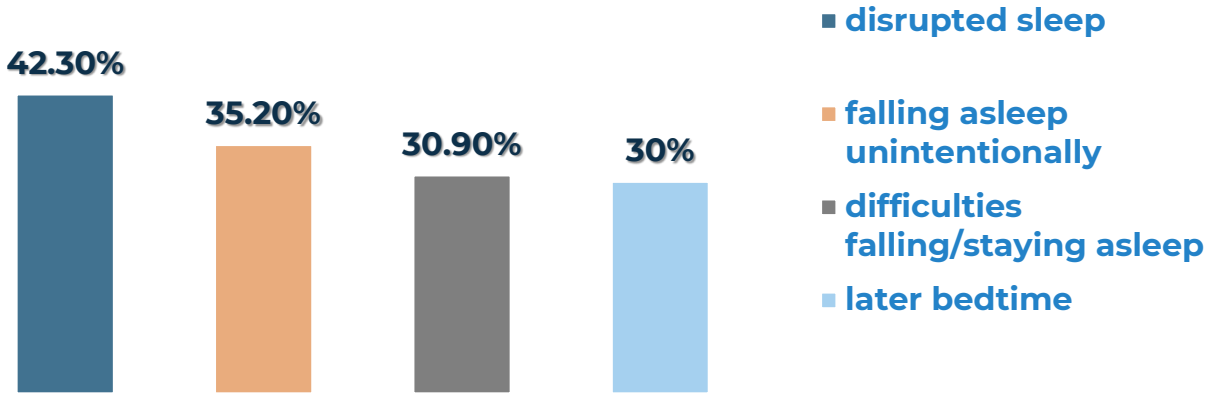
1. American Sleep Apnea Association. www.sleephealth.org/sleep-health/the-state-of-sleephealth-in-America. Accessed December 10, 2019.
2. Alvaro et al. *Sleep*. 2013;36:1059-1068.
3. Brietzke et al. *Expert Opin Pharmacother*. 2019;20:1341-134.
4. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.).

Sleep Disturbances Have Escalated During the Pandemic



- 2020 survey found:
  - ~70% of respondents reported a change in their sleep pattern (44.7% reported less refreshing sleep)
  - ~65% reported an impact on their mental health*
  - ~26% reported drinking more alcohol during lockdown
  - Respondents with COVID had more nightmares & abnormal sleep rhythms

Most frequently reported sleep-related observations



*Impact on mental health was strongly correlated with sleep-related alterations

1. Pérez-Carbonell *J Thorac Dis* 2020;12(Suppl 2):S163-S175.

Sleep Disturbances Have Escalated During the Pandemic, (continued)

- 2021 publication (N=3,533 from 50 countries surveyed) found:
  - 58% of respondents were unsatisfied with their sleep
  - 40% reported reduced sleep quality vs prior to pandemic
  - 20% increased consumption of sleeping pills
  - Variables associated with greater impact on sleep quality:
    - Female Sex
    - Quarantine status
    - Livelihood being adversely affected by crisis
    - Reduction in physical activity
    - Age, with those 31-45 years of age range most impacted

1. Mandelkorn *J Clin Sleep Med*. 2021;17(1):45–53.

Insomnia and Specific Sleep Disturbances Can be Assessed in Clinical Interviews

Insomnia is primarily diagnosed by clinical evaluation through sleep, medical, substance use, and psychiatric history[1]

- Self-administered questionnaires, at-home sleep logs, symptom checklists, psychological screening tests, and bed partner interviews are used for evaluation[1]
- Interviews can help explain the nature, history, and severity of sleep difficulties[2]

Self-report instruments[3]

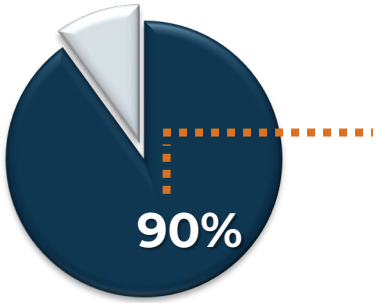
- Insomnia Severity Index (ISI)
- Athens Insomnia Scale (AIS)
- Pittsburgh Sleep Quality Index (PSQI)

Objective measures[4,5]

- **Polysomnography** – laboratory study used to diagnose sleep disorders usually occurring overnight
- **Actigraphy** – device that monitors rest and/or activity cycles usually worn for several days

1. Schutte-Rodin et al. *J Clin Sleep Med.* 2008;4:487-504.
2. Bastien et al. *Sleep Med.* 2001;2:297-307.
3. Chung et al. *Sleep Med.* 2011;12:463-470.
4. Armon PSG Medscape 2020. https://emedicine.medscape.com/article/1188764 Accessed February 13, 2021.
5. McCall C., McCall W. Comparison of actigraphy with polysomnography and sleep logs in depressed insomniacs. J Sleep Res. 2012 (DOI: 10.1111/j.1365-2869.2011.00917.x

There Is a Bidirectional Relationship Between Sleep Disturbances and Depression



Up to 90% of patients with MDD may experience insomnia at some point during their illness[4]

Depression

Patients with depression often experience shortened REM latency and diminished slow-wave sleep[1]

Patients with depression have reported significantly poorer perceived sleep quality[2]

Some medications commonly used to treat depression can worsen sleep disturbances[3]

Sleep disturbances

Residual insomnia may relate to depression relapse[3]

Insomnia can be a risk factor for or a prodromal symptom of subsequent depression development[3]

MDD, major depressive disorder; REM, rapid eye movement.

1. Krystal. *Neurol Clin.* 2012;30:1389-1413.
2. Nutt et al. *Dialogues Clin Neurosci.* 2008;10:329-336.
3. Fang et al. *J Cell Mol Med.* 2019;23:2324-2332.
4. Brietzke et al. *Expert Opin Pharmacother.* 2019;20:1341-1349

There Are Several Proposed Mechanistic Pathways Linking Depression and Sleep Disturbances[1]

Inflammation hypothesis

- Sleep loss may cause an elevation in cellular inflammation
- Markers of inflammation have been shown to be higher in depressed patients than in individuals without depression

Genetic correlation

- Heritable
- Additional genetic influences on insomnia overlap significantly with MDD
- Insomnia polygenic risk scores derived from population-based studies predicted insomnia in depressed cases[2]

Biochemical pathway

- Simultaneous effects of cholinergic and monoaminergic neurons regulate the onset of REM sleep
- The monoamine hypothesis assumes that changes in monoamine levels are the cause of depression

Circadian rhythm

- Genes that are integral to the regulation of circadian rhythm were found to be involved in depression
- The circadian rhythm plays an important role in sleep-wake cycle regulation

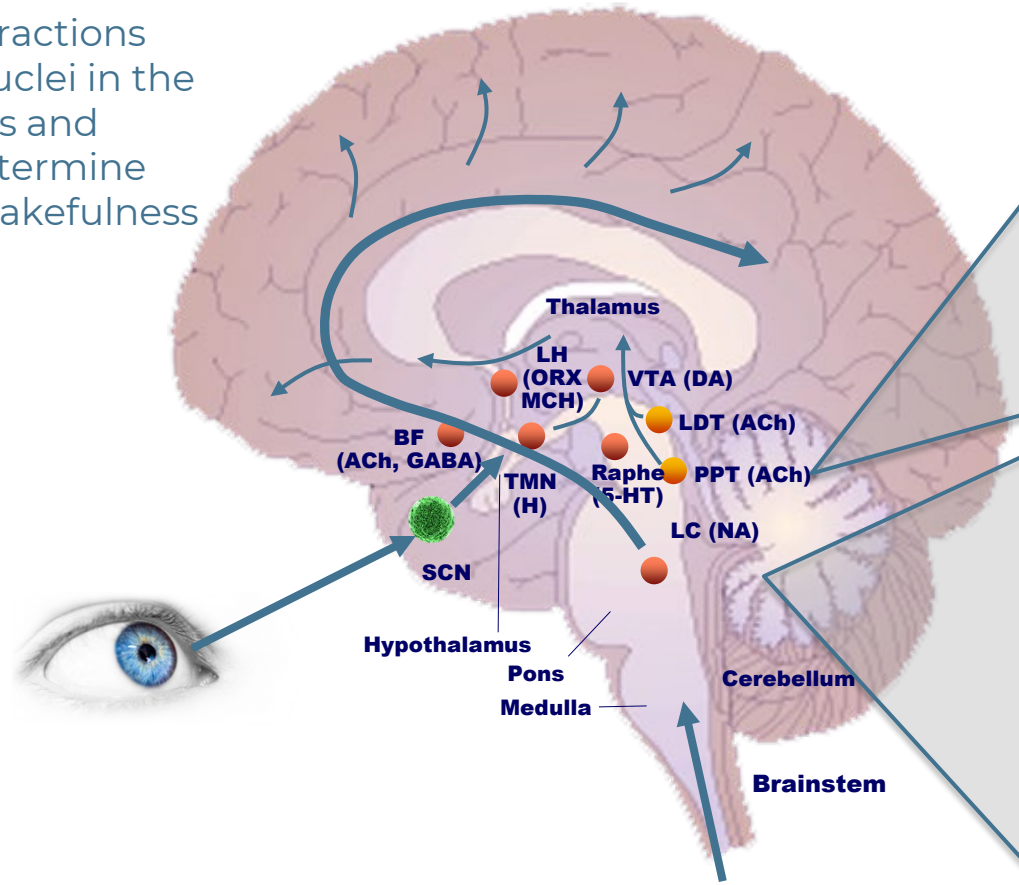
A better understanding of the molecular, neural, and behavioral mechanisms between sleep disturbances and depression may help improve the management of coincident depression and sleep disturbances

MDD, major depressive disorder; REM, rapid eye movement.

1. Fang et al. *J Cell Mol Med.* 2019;23:2324-2332. 2. Melhuish Beaupre, L. M. et al. *Frontiers in Psychiatry*. 2021; doi: 10.3389/fpsyt.2021.734077

Neural Wake-Promoting Pathways

Complex interactions among the nuclei in the hypothalamus and brainstem determine the state of wakefulness



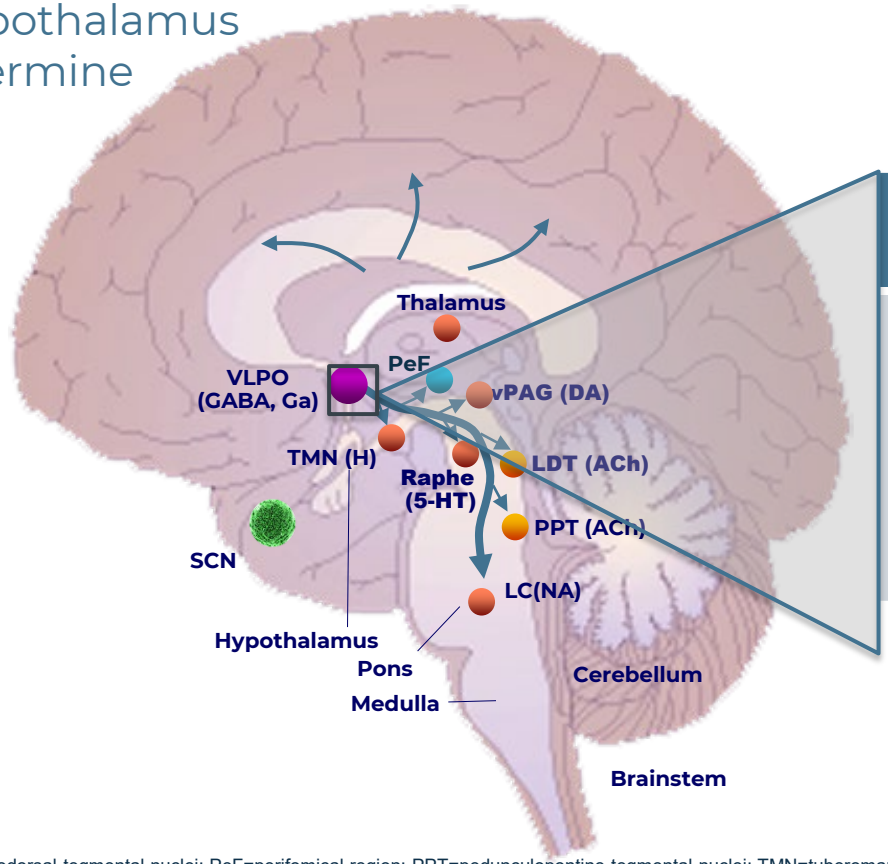
Role	Locus
Activates thalamic relay neurons (orange)	Pedunculopontine nuclei
	Laterodorsal tegmental nuclei
Activates the cerebral cortex (red)	Locus coeruleus
	Raphe nuclei
	Ventral periaqueductal gray
	Tuberomammillary nucleus
	Lateral hypothalamus
	Basal forebrain

ARAS = ascending reticular activating system; BF = basal forebrain; LC=locus coeruleus; LDT=laterodorsal tegmental nuclei; LH=lateral hypothalamus; PPT=pedunculopontine tegmental nuclei; TMN=tuberomammillary nucleus; VTA=ventral tegmental area.

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

Neural Sleep-Promoting Pathways

Complex interactions among the nuclei in the hypothalamus and brainstem determine the onset of sleep

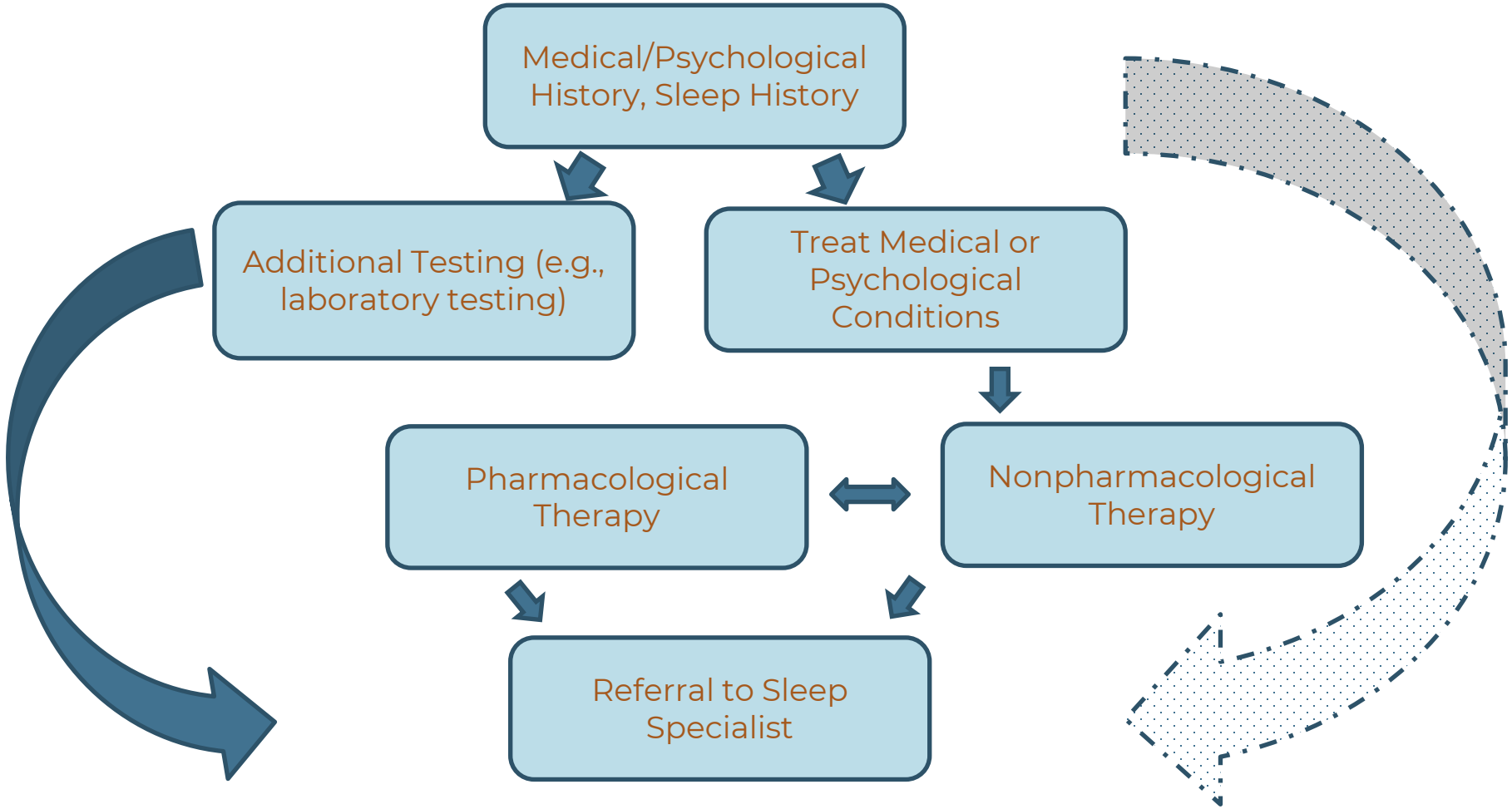


Role	Locus
Inhibits wake-promoting neurons	Ventrolateral Preoptic Nucleus (VLPO)

BF=basal forebrain; LC=locus coeruleus; LDT=laterodorsal tegmental nuclei; PeF=perifomical region; PPT=pedunculopontine tegmental nuclei; TMN=tuberomammillary nucleus; SCN=suprachiasmatic nucleus; VLPO=ventrolateral preoptic nucleus; vPAG=ventral periaqueductal gray matter.

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

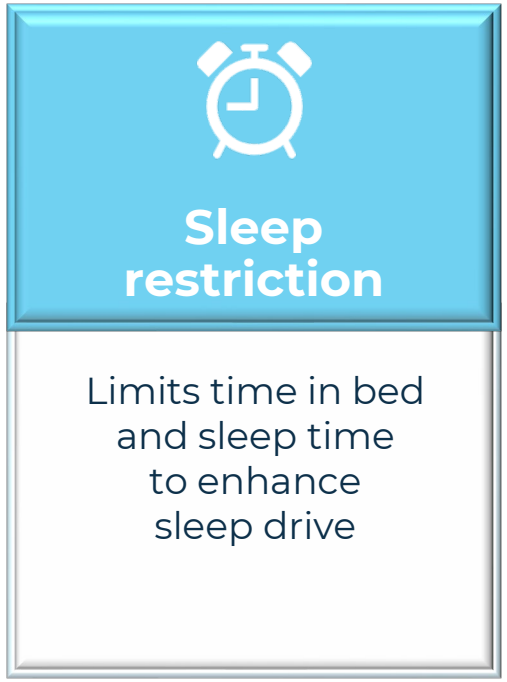
Management of Insomnia



1. Maness DL and Muneeza K. American Family Physician 2015;92(12):1058-1064

Behavioral Interventions for Insomnia Involve Multiple Active Treatment Components

Behavioral treatment components



1. Schutte-Rodin et al. *J Clin Sleep Med.* 2008;4:487-504.

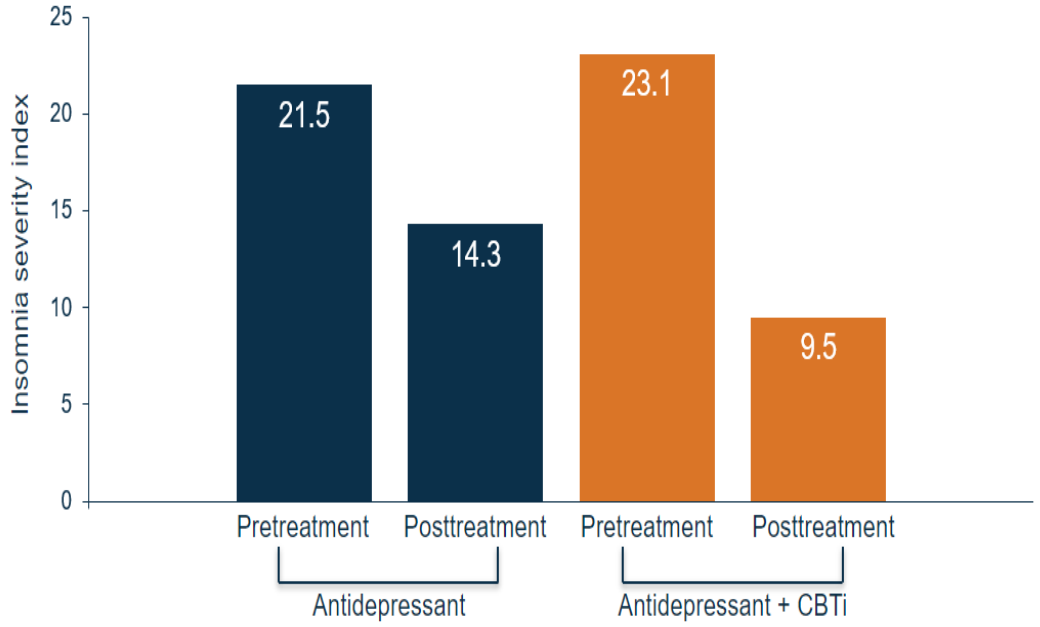
Sleep Hygiene

- Caffeine, Nicotine, & Alcohol – Avoid close to bedtime
- Manage Stress
- Exercise – vigorous physical activity, regularly
- Reduce bedroom noise
- Avoid naps during the day
- Regular sleep schedule, even on weekends
- Practice relaxing bedtime rituals

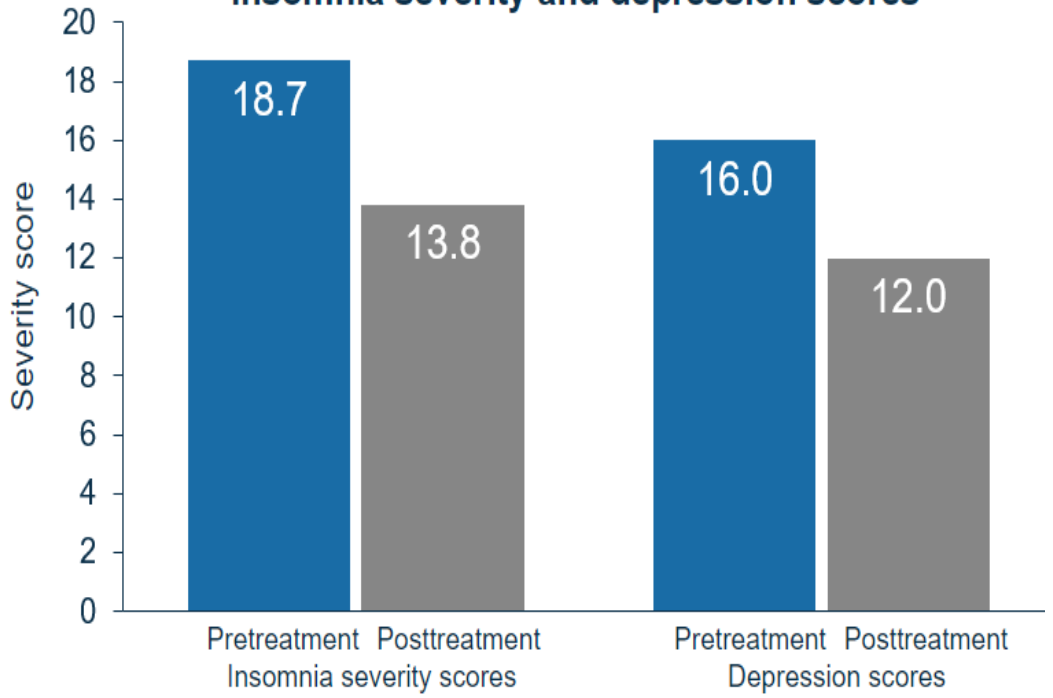
1. Irish, L.E. et al. *Sleep Med Rev.* 2015;22:23-36.

Behavioral Therapies Can Be Efficacious for Patients With Insomnia and Depression

Insomnia severity index pre- and posttreatment with antidepressant alone or in combination with cognitive behavioral therapy for insomnia (CBTi)[1]



In a small pilot trial (N=11), 4 weeks of BBTI reduced insomnia severity and depression scores[2]



Improvements in sleep may be longer lasting with behavioral therapies than with pharmacological treatments[3]

CBTi, cognitive behavioral therapy for insomnia – effect size (Cohen's d = 1.03); BBTI, brief behavioral treatment for insomnia – effect size for insomnia scores (d = 1.06) and effect size for depression scores (d = 0.54)

1. Manber et al. *Sleep*. 2008;31:489-495. 2. Gebara and Karp, et al. *Sleep Biol Rhythms*. 2019;17:287-295. 3. Morin et al. *JAMA*. 1999;281:991-999.

Classes of Sleep Medicines

- **Benzodiazepine Site $GABA_A$ Receptor Agonists (BzRAs)**[1,2]
  - All bind to GABAA receptor
    - **Benzodiazepines** are full and non-selective GABA receptor alpha subunit agonists
    - **Non-benzodiazepines** ('Z drugs') are selective alpha-1 subunit agonists
  - All products in this class are Schedule IV controlled substances

- **Histamine H1 receptor antagonists ('Antihistamines')**[3]
  - Strong and consistent evidence exist to suggest that histamine, acting via H1 and/or H3 receptor has a pivotal role in the regulation of sleep-wakefulness
  - Administration of histamine or H1 receptor agonists induced wakefulness, whereas administration of H1 receptor antagonists promoted sleep

- Sedating antidepressants
- Melatonin Receptor Agonists
- Dual Orexin Receptor Antagonists (DORA)

Data from systematic reviews and randomized studies reviewed in the American Academy of Sleep Medicine (AASM) 2017 Clinical Practice Guidelines [4]

1. Mendelson WB. Sleep Med Reviews 2004;8:7-17.
2. Lie E et al. Pharmacological Treatment of Insomnia. P&T. 2015;40(11):759-765.
3. Thakkar, M. *Sleep Med Rev*. 2011; 15(1): 65–74.
4. Sateia, M. J. et al. *J Clin Sleep Med*, 2017; 13(2): 307-349.

Therapies for Sleep Disturbances May Affect Depression

Therapy	Effect on depression
Sedating antidepressants	Positive[1]
Antipsychotics	Positive[2]
Behavioral therapy	Positive[1]
Melatonin	No effect[3,4]
Sedative hypnotics	Potentially negative[1]

1. Fang et al. *J Cell Mol Med.* 2019;23:2324-2332.
2. Wang and Si. *Shanghai Arch Psychiatry.* 2013;25:134-140.
3. Gebara et al. *Depress Anxiety*. 2018;35:717-731.
4. Dalton et al. *J Psychiatry Neurosci.* 2000;25:48-52.

Consumer Sleep Technologies

- A non-prescription device directly marketed to consumers that may perform sleep monitoring, tracking or sleep-related interventions[1]
- Include:[2]
  - **Mobile device apps**: May facilitate sleeping via use of the device capabilities
    - Meditation Apps and Sleep Trackers
  - **Wearable devices**: An attachment or sensor placed directly on the body, attached to clothing, or embedded in clothing
  - **Embedded devices**: A non-wearable that is embedded into the user's native sleep environment (e.g., sensor embedded into a sleep mattress or camera embedded into a bedroom wall)
  - **Desktop/website resources**: Computer programs or websites that are designed to run on a full desktop operating system
  - **Accessory appliances** (e.g., Smart speakers, Smart bulbs, white noise machines)

1. Khosla, S. et al. *Journal of Clinical Sleep Medicine*, 2018; 14. 2. Ping-Ru, T. Ko. et al. *J Clin Sleep Med*., 2015; 11(12): 1455-1461.

Summary

Thank You and Sleep Well

Get Your Resources On The Go

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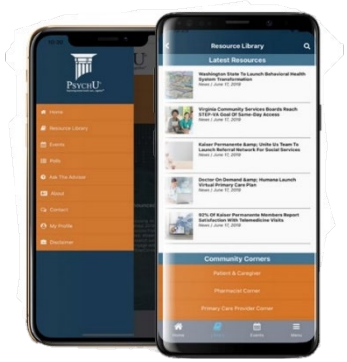

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