



TBI-BH ECHO

Traumatic Brain Injury - Behavioral Health ECHO
UW Medicine | Psychiatry and Behavioral Sciences

Sleep & Traumatic Brain Injury (TBI)

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Sleep Medicine Fellow



Learning Objectives

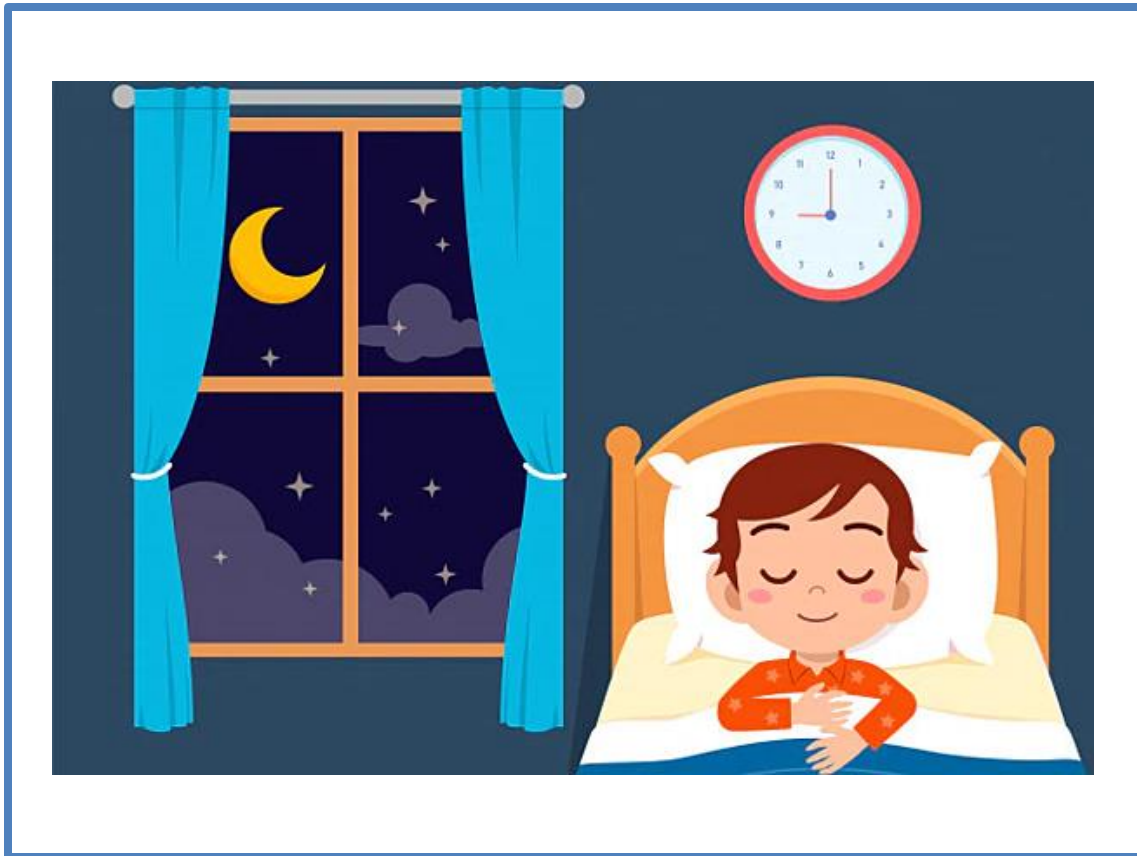
-
- 1) Review the physiology of sleep
 - 2) Sleep and Traumatic Brain Injury
 - ▶ Symptoms & Disorders
 - ▶ Diagnosis
 - ▶ Treatment & Referral

Disclosures

- ▶ No Disclosures to Report



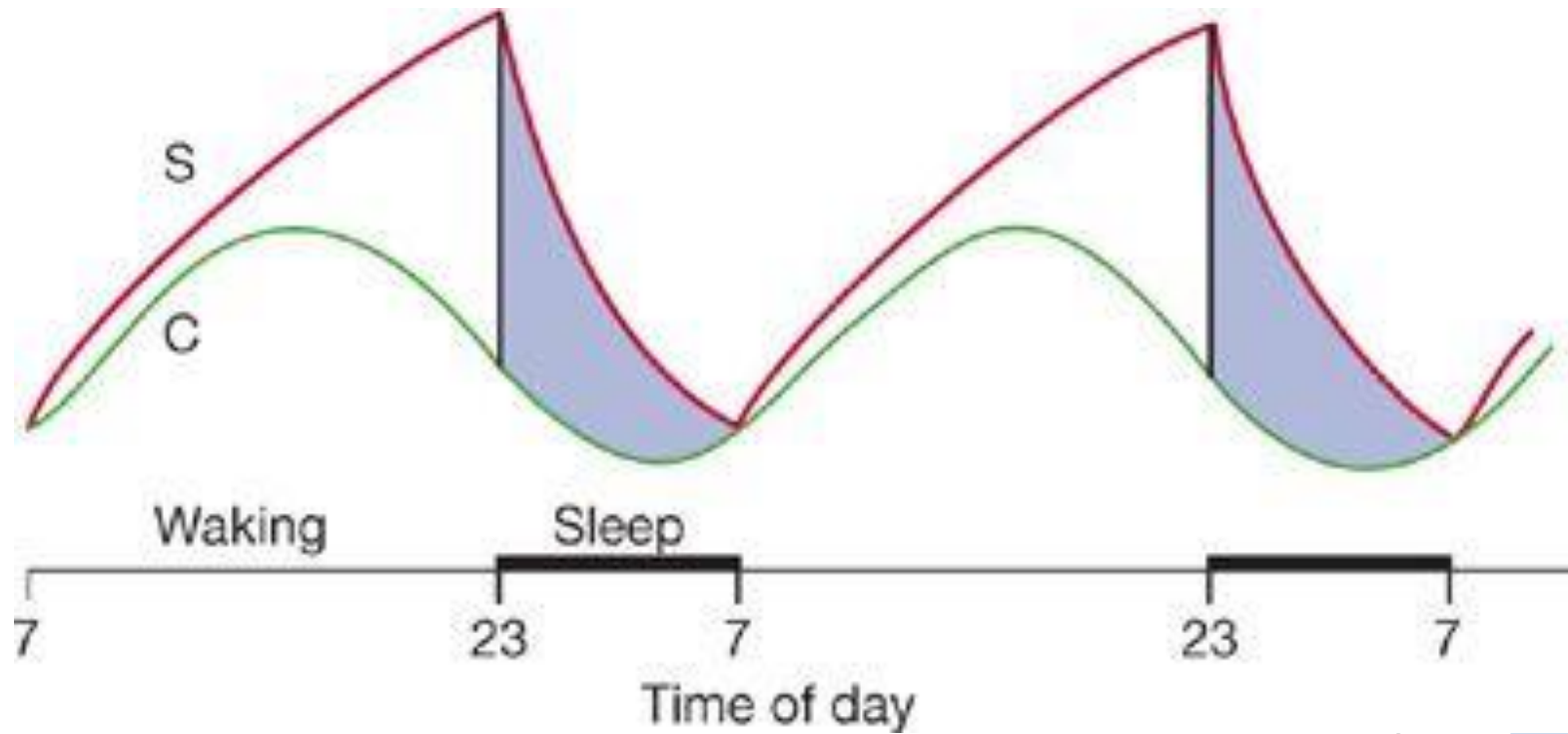
Why Do we Sleep?



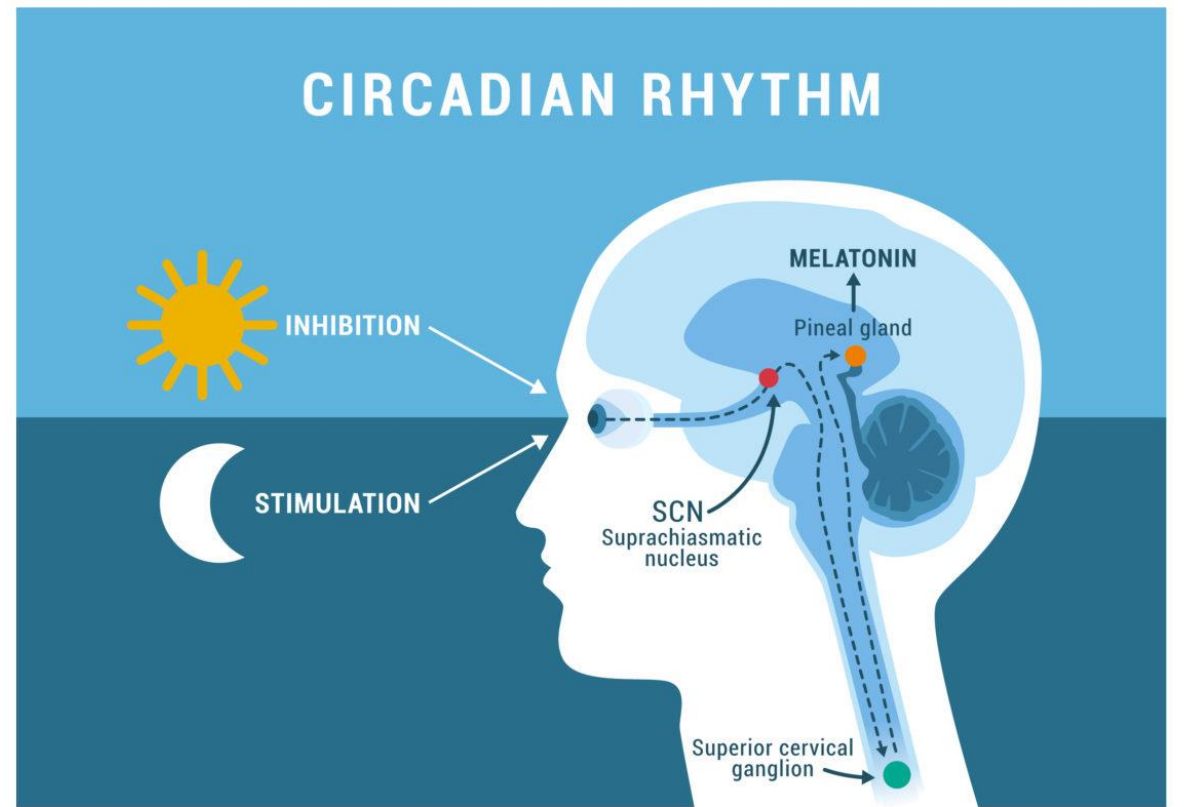
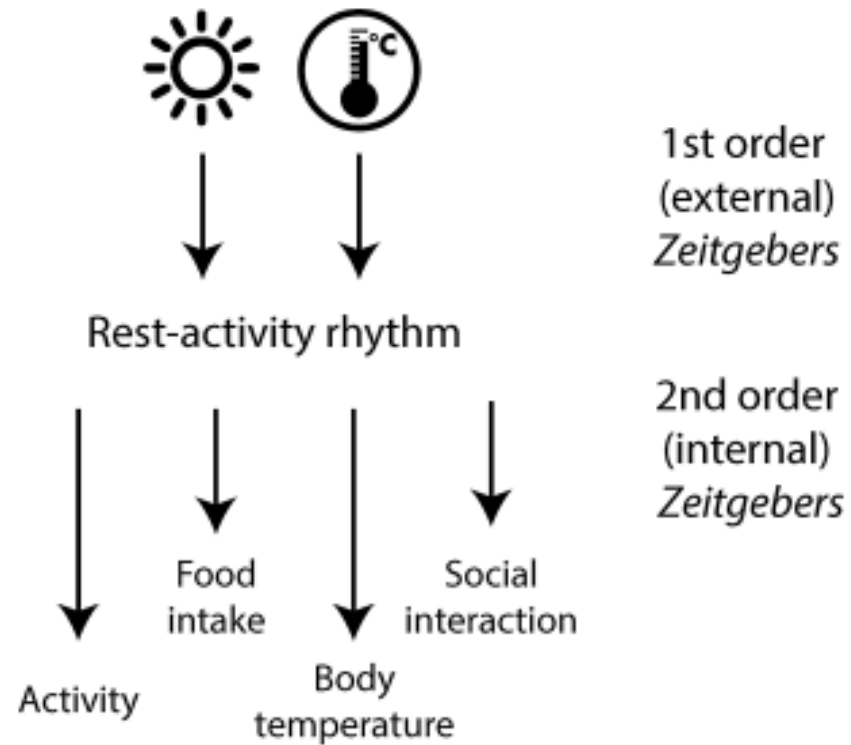
- ▶ Memory and Cognition
- ▶ Alertness and Performance
- ▶ Mood and Behavior
- ▶ Immunity and Healing
- ▶ Hormones and Metabolism



How do we Sleep?



What Affects Sleep?



Sleep and Traumatic Brain Injury

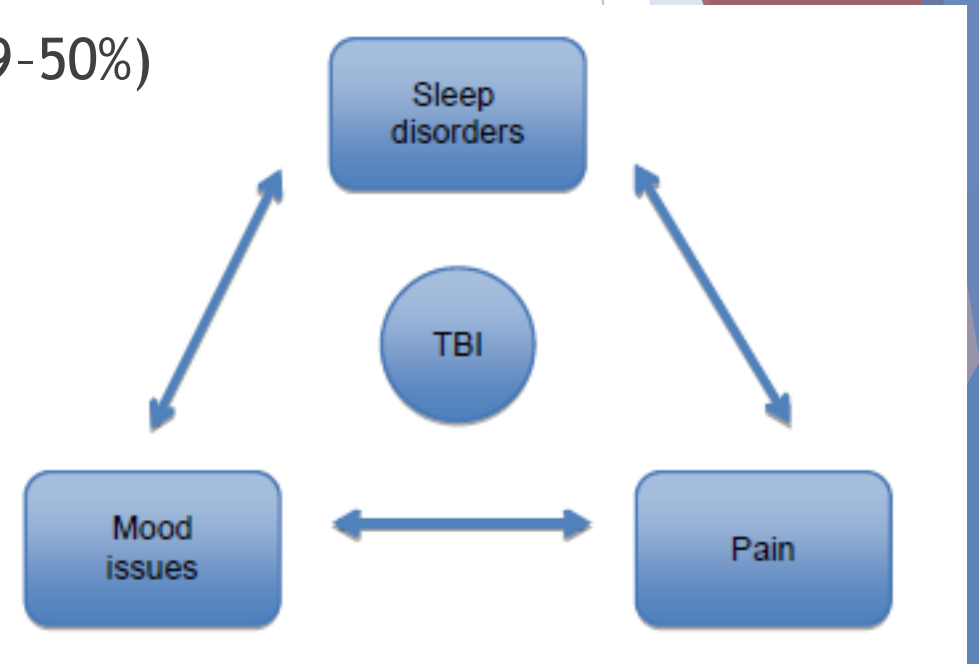


Diagnosis Overview

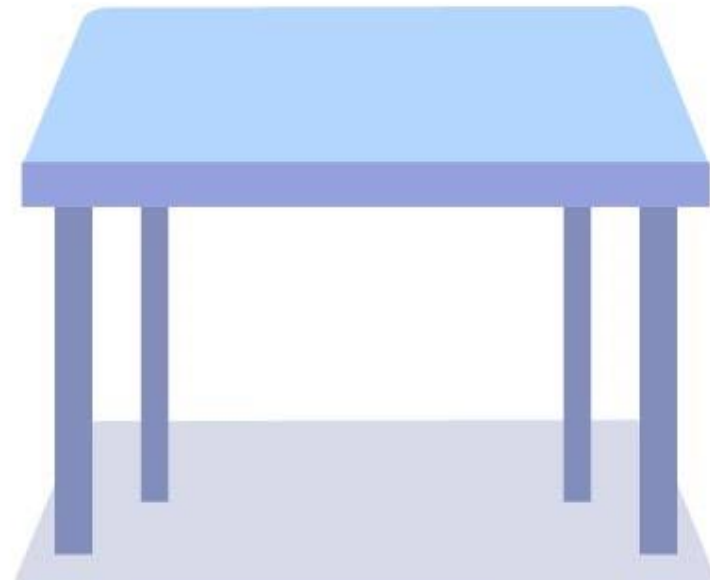
- ▶ **Insomnia**
 - ▶ Short-Term Insomnia Disorder (F51.02)
 - ▶ Chronic Insomnia Disorder (F51.01)
 - ▶ Psychophysiological insomnia
 - ▶ Insomnia due to (a) medical condition
 - ▶ Insomnia due to drug or substance
 - ▶ Other Insomnia Disorder (F51.09)
- ▶ **Circadian Rhythm Sleep-Wake Disorder**
 - ▶ Advanced Sleep-Wake Phase Disorder (G47.22)
 - ▶ Delayed Sleep-Wake Phase Disorder (G47.21)
 - ▶ Circadian Sleep-Wake Disorder NOS (G47.20)
- ▶ **Central Disorder of Hypersomnolence**
 - ▶ Hypersomnia due to Medical Disorder (G47.14)
- ▶ **Sleep Related Breathing Disorder**

Sleep Disturbance After TBI

- ▶ Insomnia (50%)
- ▶ Poor sleep maintenance and sleep efficiency (49-50%)
- ▶ Delayed sleep onset (36%)
- ▶ Early morning awakenings (38%)
- ▶ Hypersomnia
- ▶ Nightmares (27%)

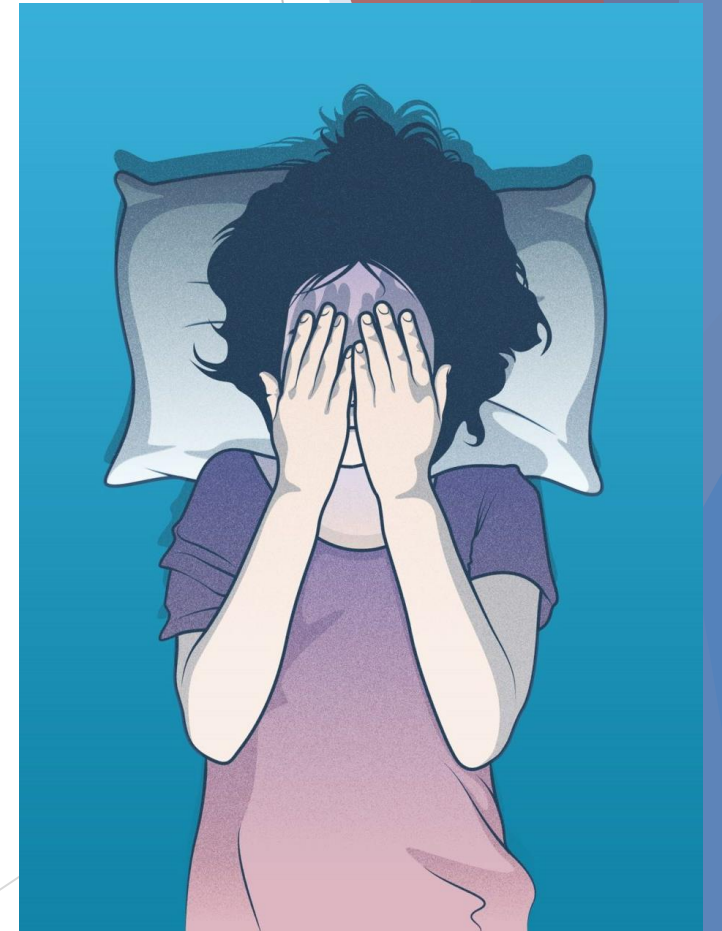


Treatment



Sleep Disorders

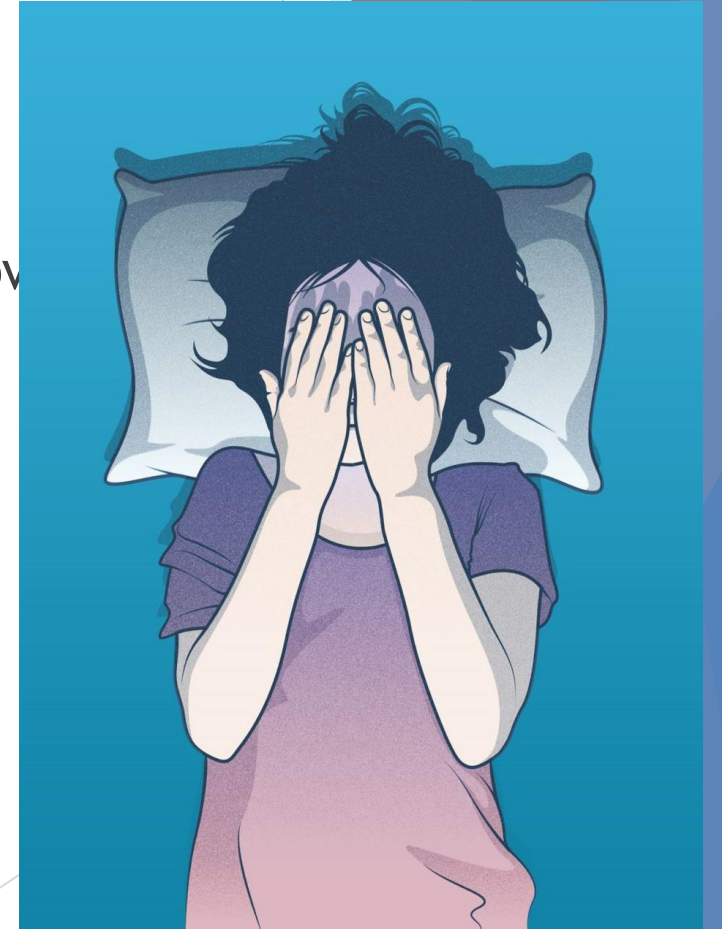
- ▶ **Insomnia**
- ▶ Circadian Rhythm Sleep-Wake Disorder
- ▶ Central Disorder of Hypersomnolence
- ▶ Sleep Related Breathing Disorder



Chronic Insomnia After TBI

► Insomnia

- Can be frequently reported with milder TBI
- May be due to psychological insult related to trauma or recovery
- Linked to TBI induced light sensitivity
- Risks associated with medication and cognitive impairment



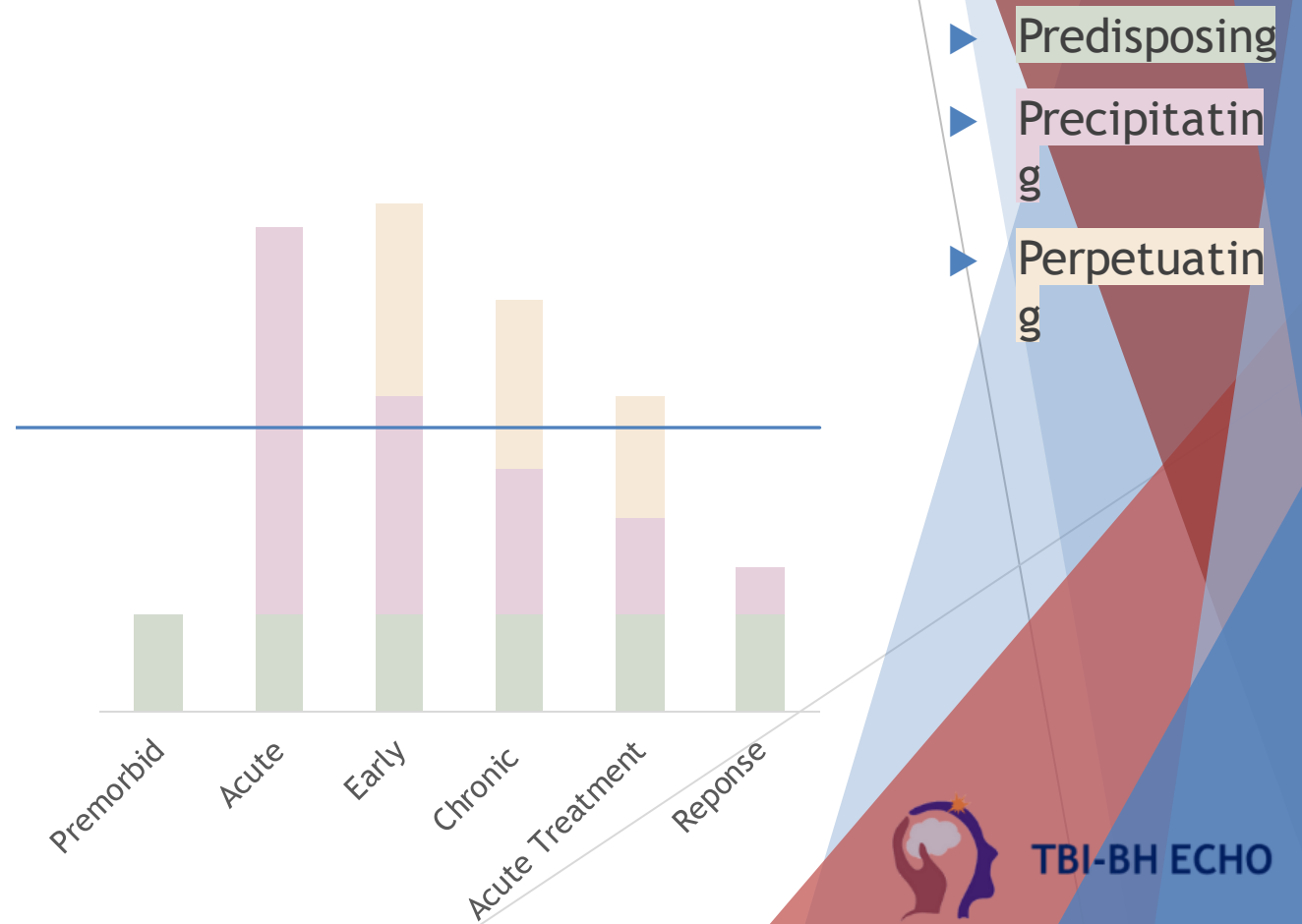
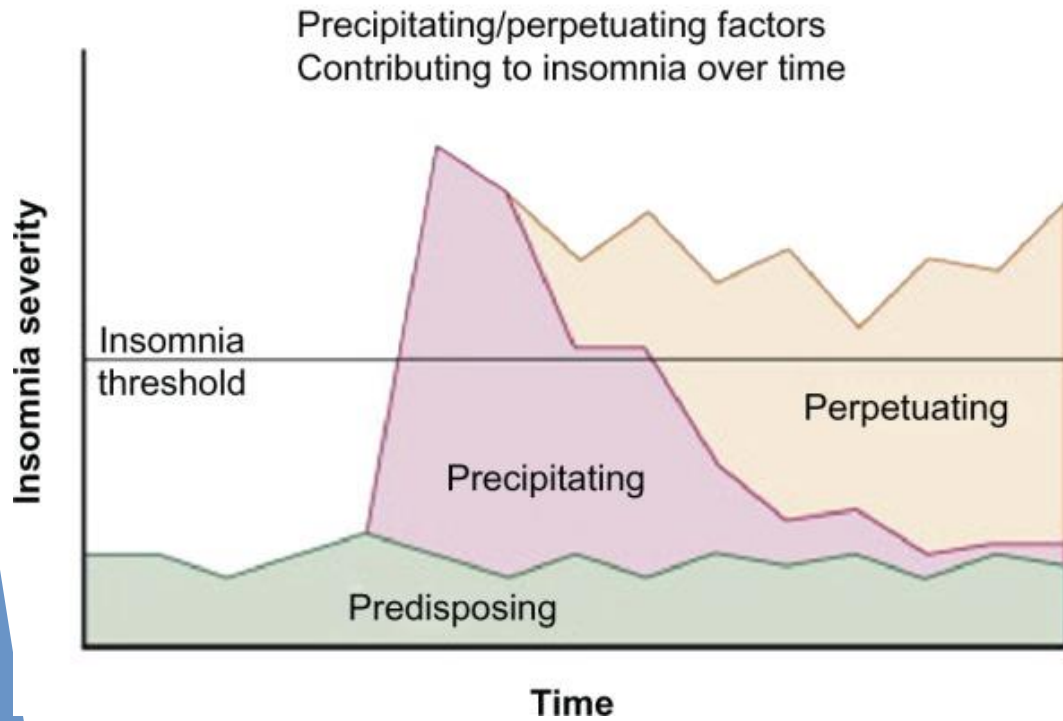
11. Duclos (2014) ISSN 0369-8114

12. Kaufman (2001) PMID: 11275462

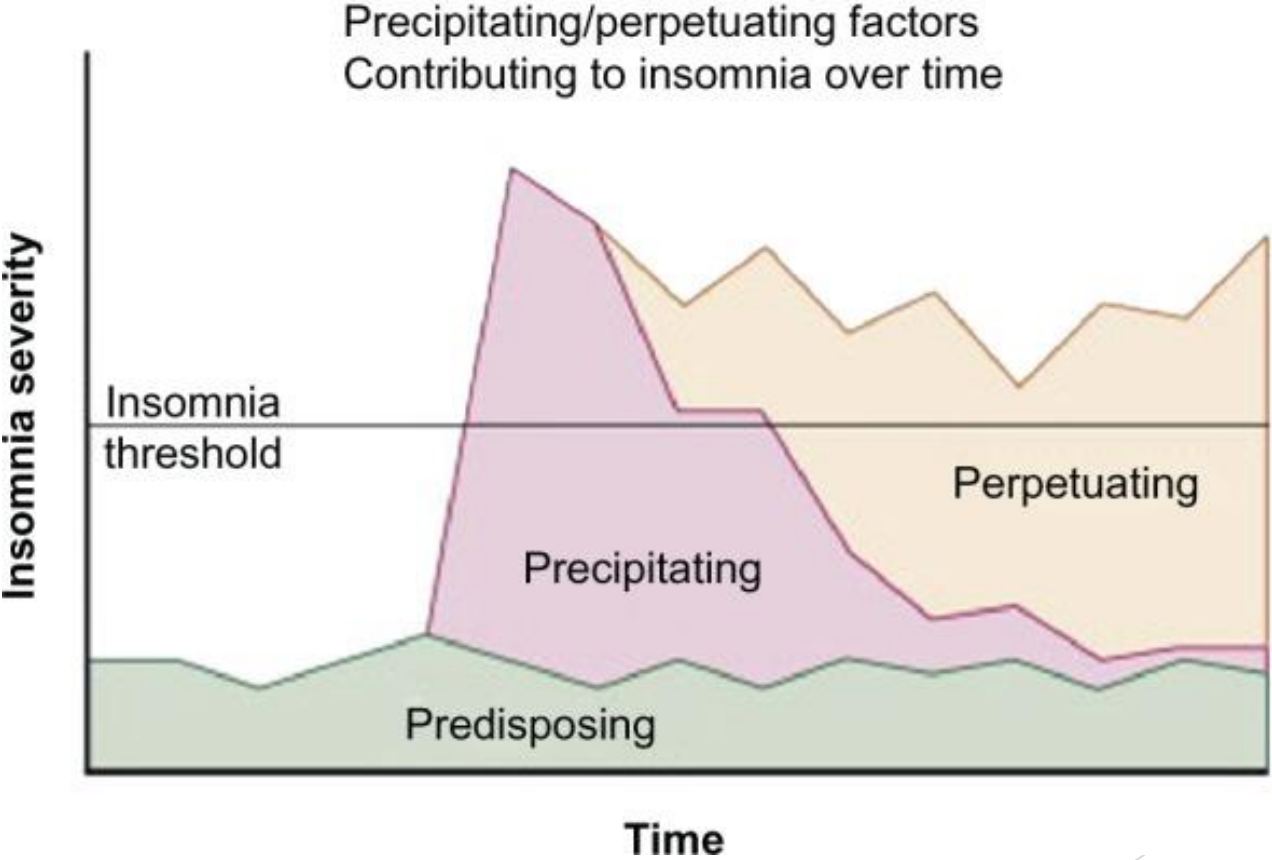
13. Ouellet (2006) PMID: 16934524

<https://www.sleepcycle.com/wp-content/uploads/2021/11/insomnia-1920x1270.jpg>

The 3 “P” model of Insomnia



Identify Underlying Factors



SLEEP HYGIENE

ADD SOME MODERATE EXERCISE

Studies show regular exercise leads to deeper sleep.

Tip: Intense exercise can cause sleep disruptions, so practice yoga instead.



CREATE A COMFORTABLE SPACE

Studies show optimal sleep temperature is 65 degrees.

Tip: Cool down your room before bed or sleep with a fan.



HAVE A BEDTIME ROUTINE OR RITUAL

Studies show consistent bedtime routines lead to quality sleep.

Tip: Take a warm bath or shower up to 90 minutes before bed.



LIMIT CAFFEINE

Caffeine consumption up to 6 hours before bedtime can impact sleep.

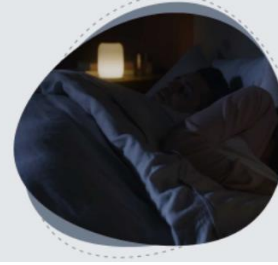
Tip: Stop drinking caffeine 2-5 hours before bedtime.



DIM THE LIGHTS

Dimmed lights signal the body to make melatonin.

Tip: Spend the last few hours before bed in a dim room.



MEDITATE

Adults with sleep disturbances show improvement after practicing meditation.

Tip: Download a meditation app and practice before bed.



LIMIT ALCOHOL

One drink can decrease sleep quality by 24%.

Tip: Stop drinking alcohol within 4 hours of bed.



TURN OFF ELECTRONICS

Blue light from our phones, tablets, and televisions limit the production of melatonin and keep us awake.

Tip: Turn the TV off 30 minutes before bed.



GET SOME SUNLIGHT

Studies show exposure to sunlight helps regulate melatonin.

Tip: Go for a midday walk or open the blinds during the day.



STIMULUS CONTROL

Go to Bed Only
When Sleepy



Use Bed Only for
Sleep and Sex



Don't Watch
the Clock!



TBI-BH ECHO

Cognitive Distortions addressed in Cognitive Behavioral Therapy



FILTERING

Focussing on the negative
Ignoring the positive



CATASTROPHIZING

Expecting the worst case scenario
Minimizing the positive



OVERGENERALIZATION

Assumes a rule from one
experience



JUMPING TO CONCLUSIONS

Makes assumptions based on
little evidence



POLARIZED THINKING

All-or-nothing thinking
Ignoring complexity



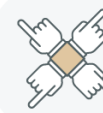
HEAVEN'S REWARD FALLACY

Expecting self-sacrifice
to be rewarded



EMOTIONAL REASONING

"If I feel it, it must be true."



BLAMING

Assumes everyone else at fault



CONTROL FALLACIES

Assumes only others to blame
Assumes only self to blame



ALWAYS BEING RIGHT

Being wrong is unacceptable
Being right supercedes everything



FALLACY OF CHANGE

Expects others to change



GLOBAL LABELLING

Extreme generalization



FALLACY OF FAIRNESS

Assumes life should be fair



PERSONALIZATION

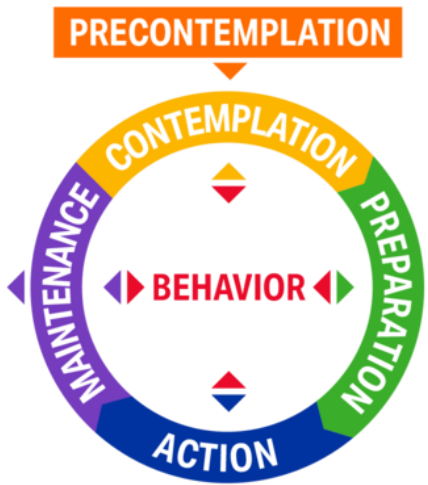
Always assuming self responsible



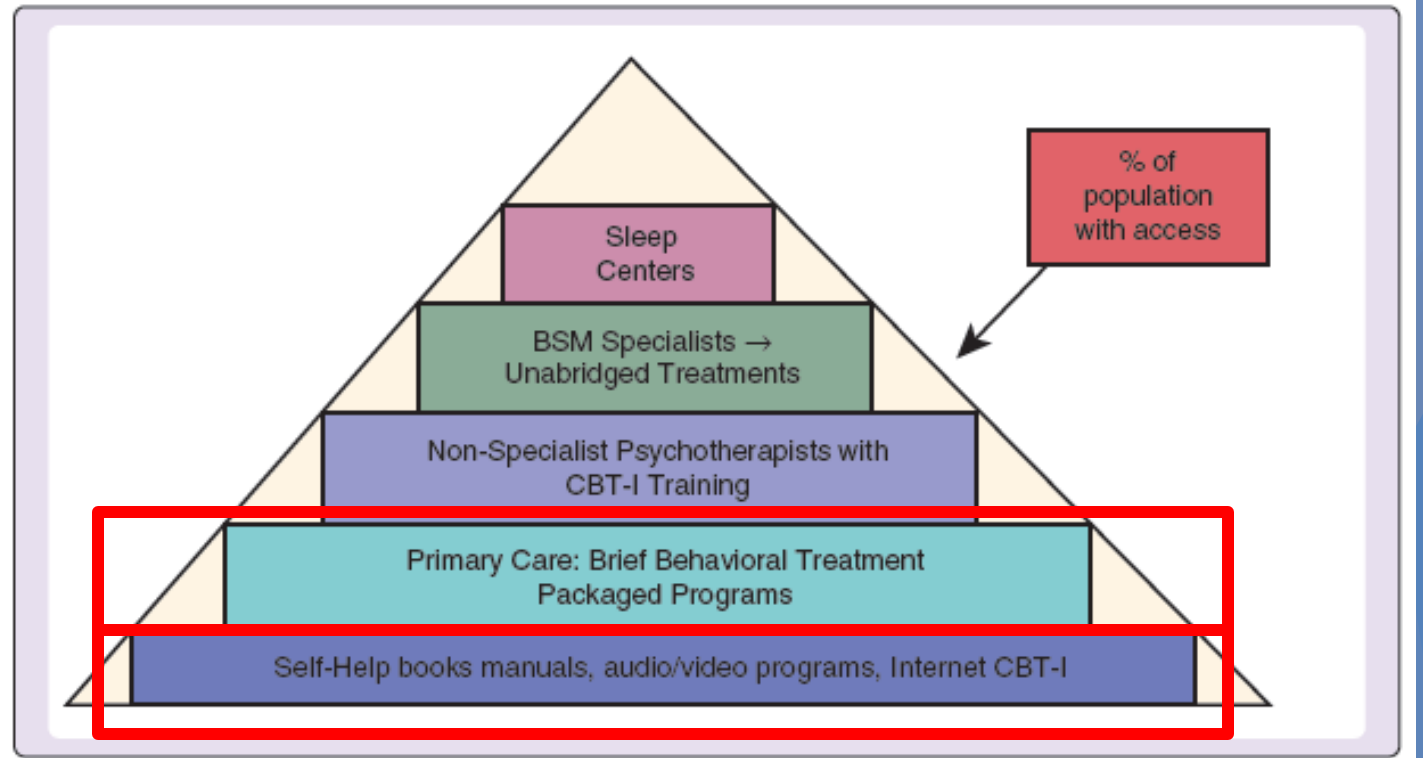
"SHOULD"

Holds tight to personal rules of behaviour
Judges self and others if rules broken

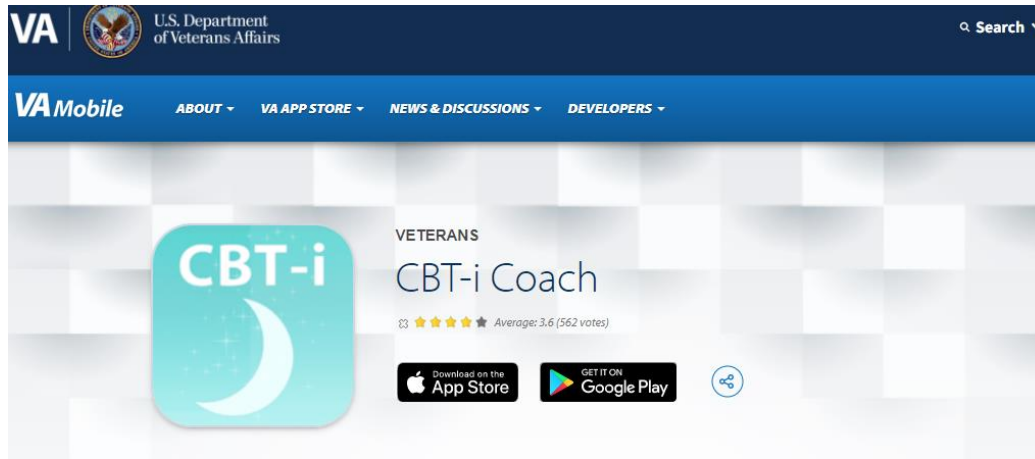
Referral to CBT-I



- PRECONTEMPLATION**
Build awareness for my need to change
- CONTEMPLATION**
Increase my pros for change and decrease my cons
- PREPARATION**
Commit and plan
- ACTION**
Implement and revise my plan
- MAINTENANCE**
Integrate change into my lifestyle



Digital CBT-I & Referral Network



University Of Pennsylvania CBTI Directory

https://www.med.upenn.edu/cbti/provder_directory.html

CBT-I PROVIDER DIRECTORY

We are in the process of opening a new provider directory. Registration should be completed on the new website. Please click the image below.

Cognitive Behavioral Therapy for Insomnia Provider Directory



To search for a clinician, please click below

[FIND A CLINICIAN](#)

To register, complete an entry, or to update your entry, please click below

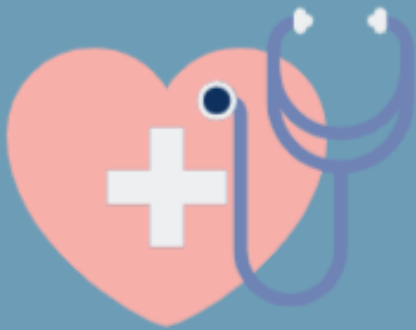
[REGISTER AS A CLINICIAN](#)



TBI-BH ECHO

Brief Behavioral Treatment Intervention (BBTI)

BBTI differs from standard CBT-I in a few important ways:



BBTI uses fewer in-person visits.



BBTI is quicker, using 2 in-person visits over 4 weeks versus 6-8 visits over 8 weeks.



BBTI focuses on targeting the behavioral (sleep habits) vs. cognitive features of insomnia.



TBI-BH ECHO

Considerations for Pharmacotherapy

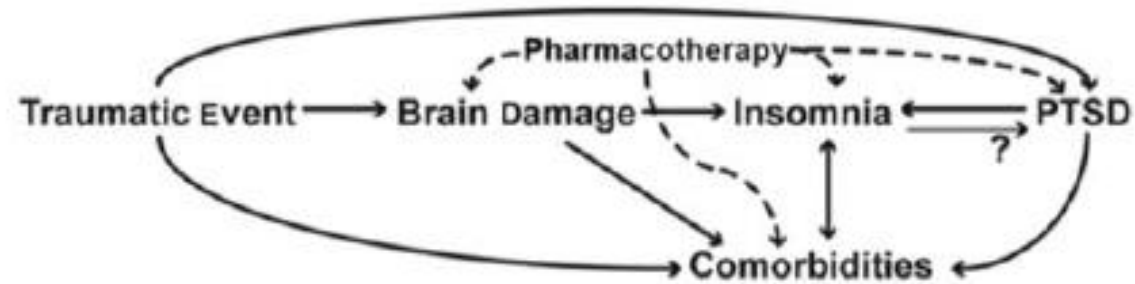


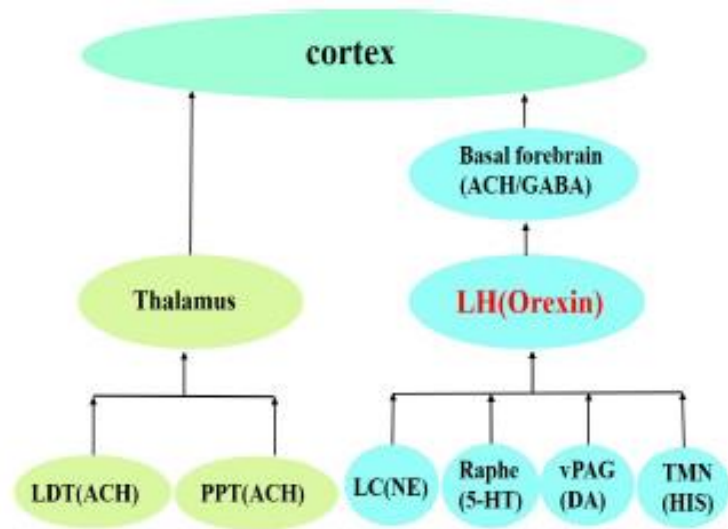
Figure.

Schema of complex relationship between traumatic brain injury, insomnia, and posttraumatic stress disorder (PTSD), as well as associated comorbidities and pharmacotherapy. Single-ended arrows show directional relationships; double-ended arrows show reciprocal relationships. Question mark (“?”) indicates possible, though not proven, causal relationship.

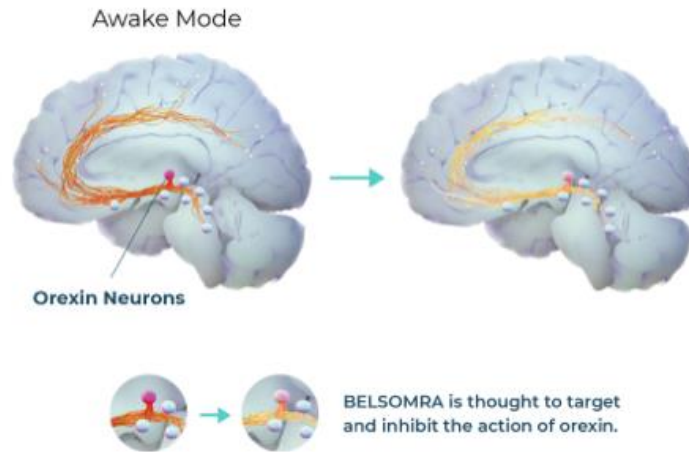


Pharmacologic Targets

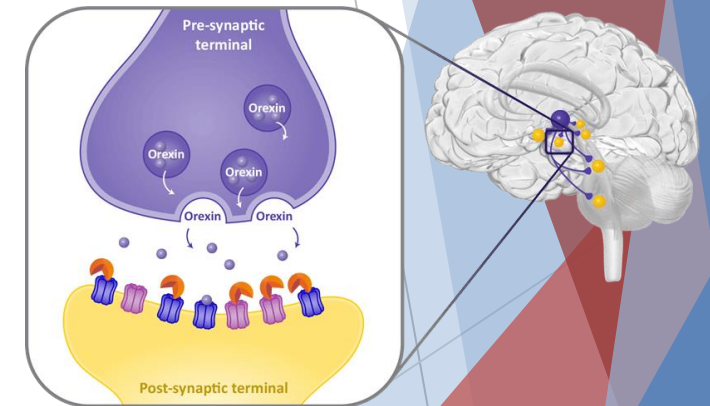
Orexin-B (Hypocretin 2)



Suvorexant (Belsomra) - August 2014



Lemborexant (Dayvigo) - December 2019



- Orexin-producing neurons
- Orexin
- Orexin neuron projections through the brain
- Major wake-controlling neurons expressing orexin receptors
- DAYVIGO
- OX1R
- OX2R

20. Tang (2019) PMID: 31663471
 21. Baumann (2005) PMID: 16009905
 23. Thomsay (2019) PMID: 30136622

<https://www.belsomra.com/what-is-belsomra/>, <https://www.pharmacytimes.com/view/daily-medication-pearl-suvorexant-belsomra->, <https://www.dayvigohcp.com/about-dayvigo>, <https://www.eisai.com/news/2019/news201993.html>

Pharmacotherapy for Insomnia

Sleep Onset Insomnia:

- ▶ **Eszopiclone (Lunesta)** - *Weak (14 min)*
 - ▶ (1 mg) 2 mg and 3 mg doses
- ▶ **Ramelteon (Rozerem)** - *Weak (9 min)*
 - ▶ 8 mg
- ▶ **Temazepam (Restoril)** - *Weak (37 min)*
 - ▶ (7.5 mg) 15 mg
- ▶ **Triazolam (Halcion)** - *Weak (9 min)*
 - ▶ 0.25 mg
- ▶ **Zaleplon (Sonata)** - *Weak (0-19 min)*
 - ▶ 5mg to 10mg
- ▶ **Zolpidem (Ambien)** - *Weak (5-12 min)*
 - ▶ (5 mg) 10mg (6.25-12.5 mg ER)

Sleep Maintenance Insomnia

- ▶ **Doxepin (Silenor)** - *Weak (TST +26-32 min)*
 - ▶ 3mg to 6mg
- ▶ **Eszopiclone (Lunesta)** - *Weak (TST +18-76 min)*
 - ▶ 2mg to 3mg
- ▶ **Temazepam (Restoril)** - *Weak (TST +99 min)*
 - ▶ 15 mg
- ▶ **Suvorexant (Belsomra)** - *Weak (TST +2-19 min)*
 - ▶ 10mg, 15/20mg, 20mg
- ▶ **Zolpidem (Ambien)** - *Weak (TST +29 min)*
 - ▶ 10mg

Lemborexant (Dayvigo): Not included in latest recommendations

We suggest that clinicians **not** use the following drugs for the treatment of sleep onset or sleep maintenance: - *Weak*
Diphenhydramine, Melatonin, Tiagabine, Trazodone, L-tryptophan, Valerian



2019: Black Box Warning of Z Drugs

- ▶ Eszopiclone (Lunesta)
- ▶ Zaleplon (Sonata)
- ▶ Zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, and Zolpimist).

- ▶ NREM parasomnia history is a contraindication
- ▶ Sleepwalking, or performing other tasks while sleeping or otherwise not fully awake which can result in injury or death.
- ▶ Involve the patient's Mental health professional when treating patients with Depression as Z drugs as they have been linked to worsening depression and suicidal ideation.



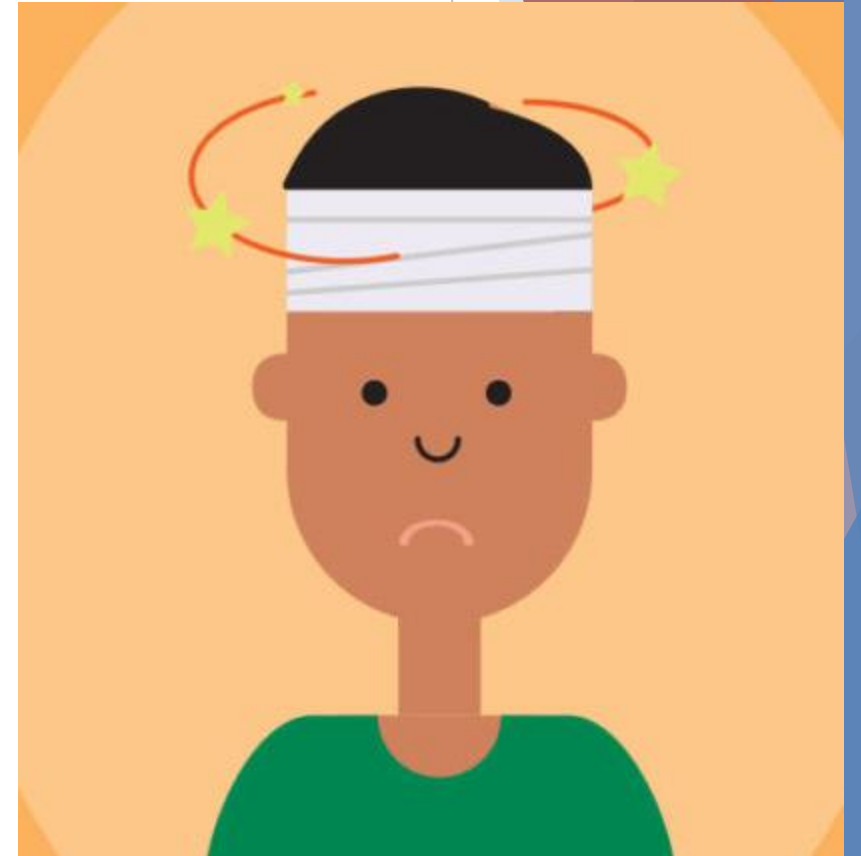
Side Effects

Medication	Side effect
Insomnia	
Temazepam	Rebound insomnia, altered sleep architecture, dependence, abuse potential, paradoxical aggression
Zolpidem	Amnesia, impaired motor skills, rebound insomnia, rare somnambulism, somnolence, dizziness
Zaleplon	Somnolence, less likely to cause next-day impaired psychomotor skills
Eszopiclone	Amnesia and impaired motor skills while drug is active, noting relatively long half-life. Bitter taste, dry mouth, dizziness, and somnolence
Trazodone	Dizziness, dry mouth, nausea, blurry vision, drowsiness, hypotension, rebound insomnia, psychomotor impairments, potential QT prolongation
Mirtazipine	Drowsiness, dry mouth, increased appetite, weight gain, dizziness. Impaired driving performance
Melatonin	Headache, confusion
Ramelteon	Drowsiness, fatigue, and dizziness
Hypersomnolence	
Methylphenidate	Arrhythmias, heart rate (HR) and blood pressure (BP) changes, seizures, weight loss
Amantadine	Arrhythmias, agranulocytosis, headaches
Modafinil	Headache, elevated BP and HR, elevated liver enzymes
Armodafinil	Headache, elevated BP and HR



Sleep Disorders

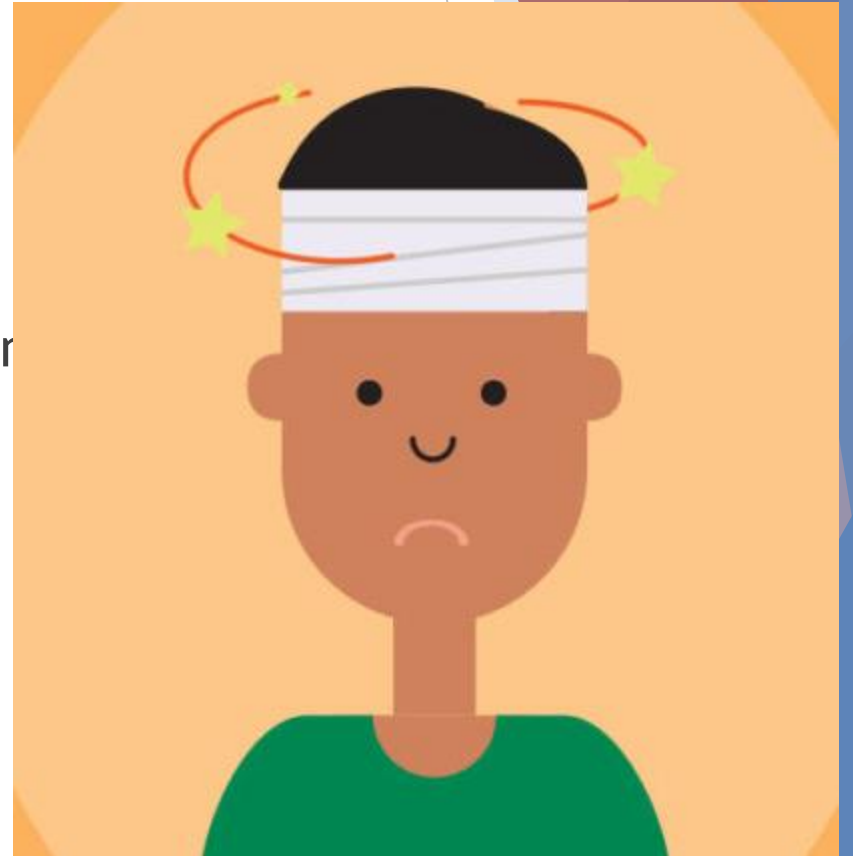
- ▶ Insomnia
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- ▶ Central Disorder of Hypersomnolence
- ▶ Sleep Related Breathing Disorder



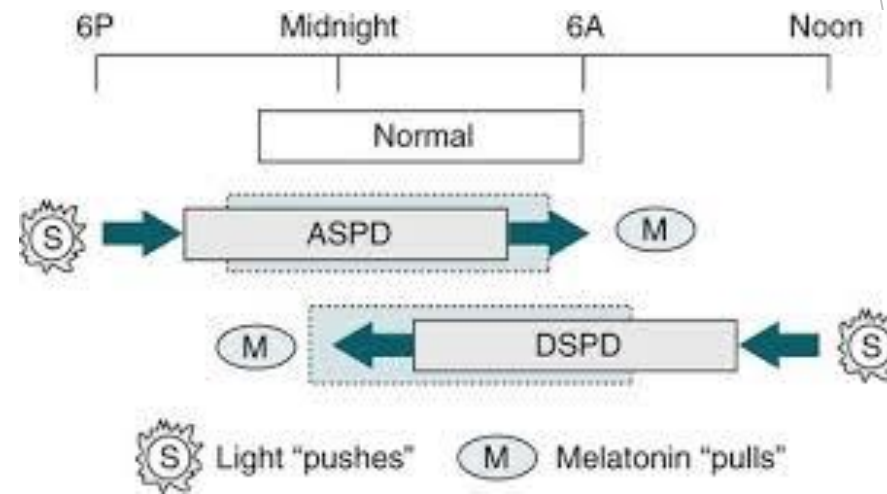
Circadian Rhythm Disturbance After TBI

► Circadian Rhythm

- Most severe effects in first 1-2 days
- Usually improve by day 8
- Recovery of sleep timing correlates with better outcomes



Therapy for Sleep-Wake Phase Disorder



19. Aulinas (2019)

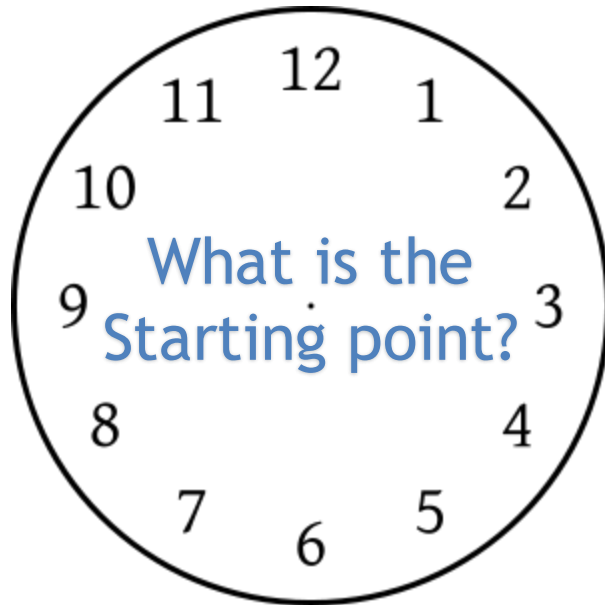
25. Bell (2021) PMID: 33459040

<https://jameshewittperformance.com/wp-content/uploads/2020/04/Do-you-have-social-jetlag.001-1024x576.jpeg>,

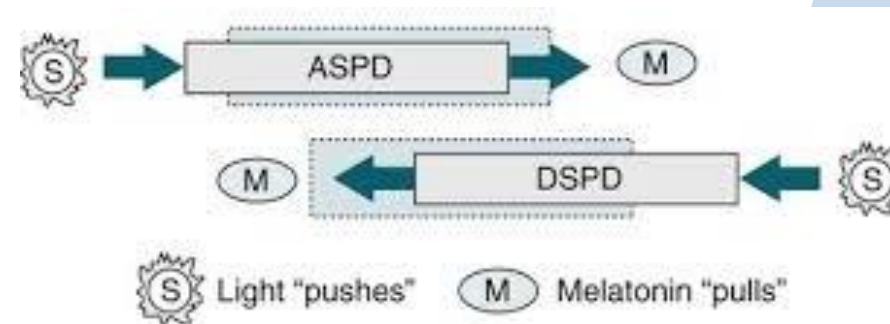
<https://images.english.elpais.com/resizer/fJrrFVz1bc-kM1efsLLtrjTs2so=/980x735/cloudfront-eu-central-1.images.arcpublishing.com/prisa/ECIN6AKIGMJQZ3DL2YSHDW55I.jpg>



Therapy for Sleep-Wake Phase Disorder

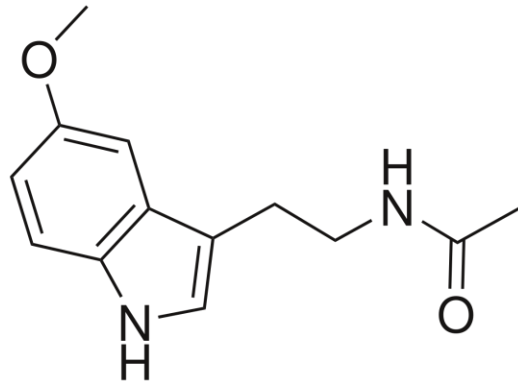


11:00 PM	Midnight	1:00 AM	2:00 AM	3:00 AM	4:00 AM	5:00 AM	6:00 AM	7:00 AM	8:00 AM	9:00 AM	10:00 AM	11:00 AM	12:00 PM	1:00 PM	2:00 PM	3:00 PM	4:00 PM	5:00 PM	6:00 PM	7:00 PM	8:00 PM	9:00 PM	10:00 PM
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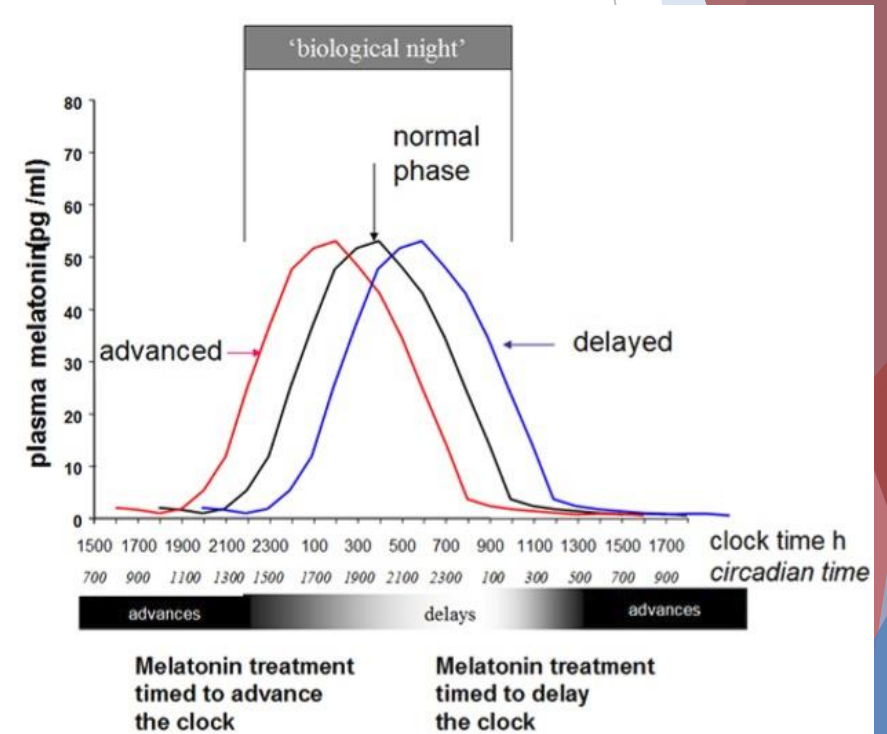
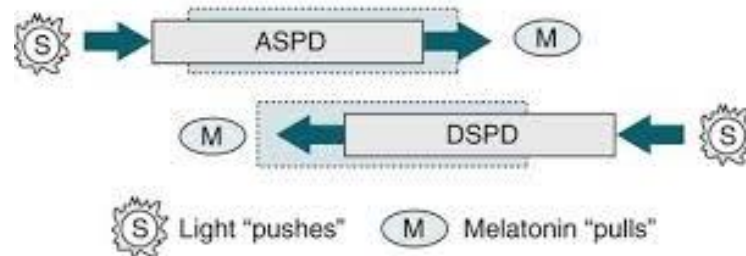


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<https://images.english.elpais.com/resizer/fJrrFVz1bc-kM1efsLLtrjTs2so=/980x735/cloudfront-eu-central-1.images.arcpublishing.com/prisa/ECIN6AKIGMJJQZ3DL2YSHDWS5I.jpg>

Therapy for Sleep-Wake Phase Disorder



Melatonin

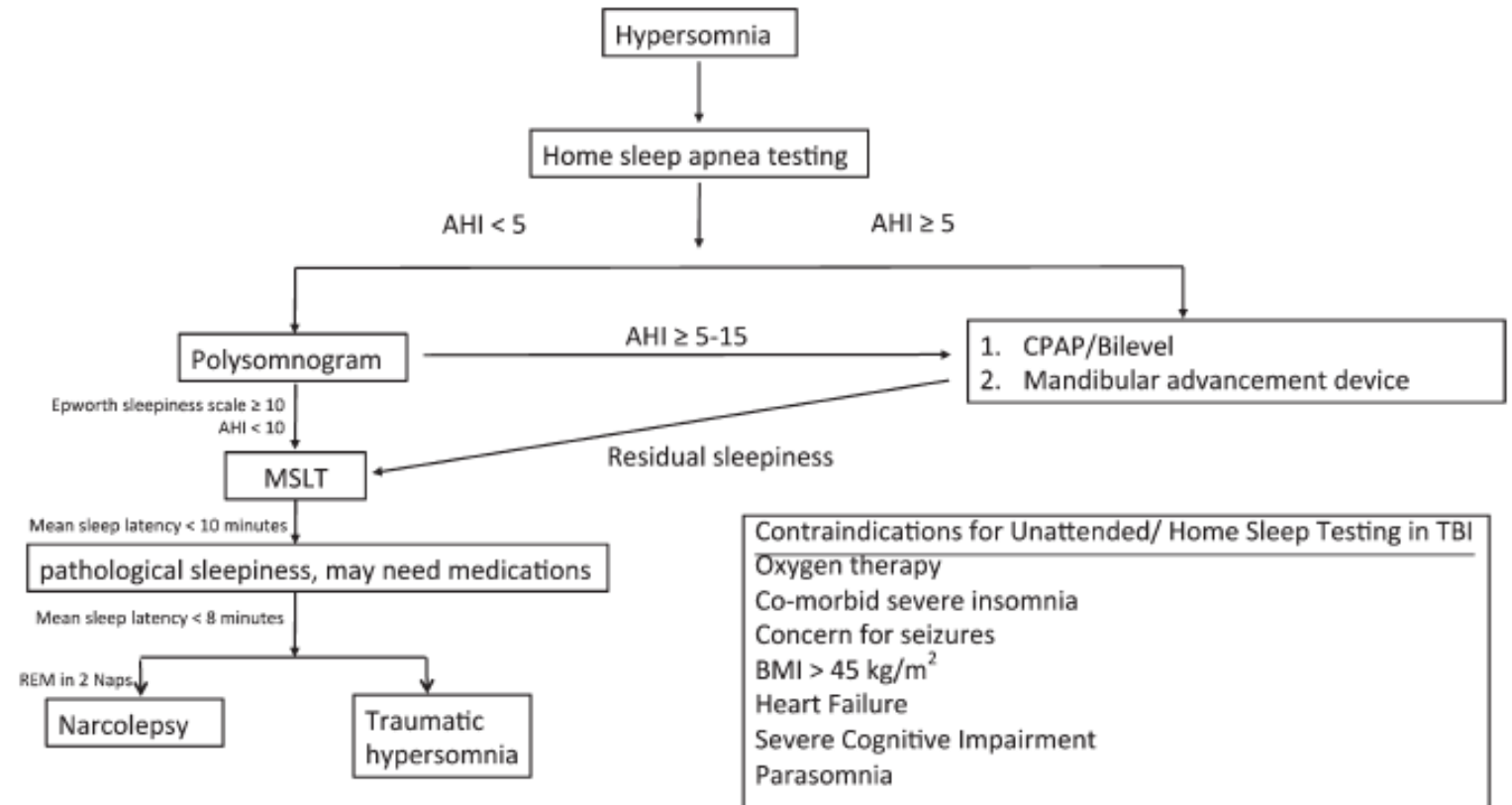


- ▶ Insomnia
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- ▶ **Central Disorder of Hypersomnolence**
- ▶ Sleep Related Breathing Disorder

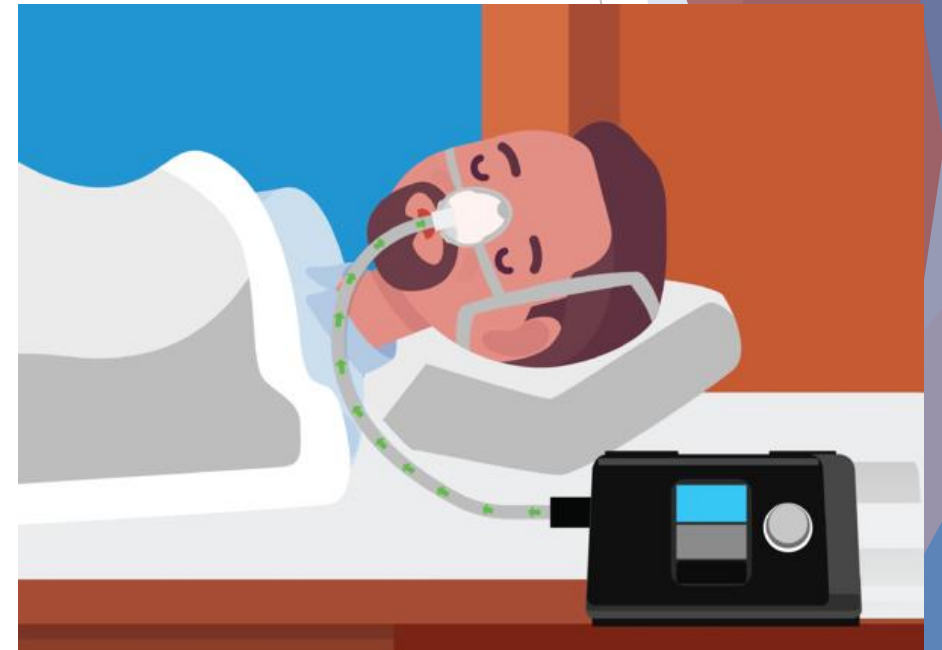


Post Traumatic Hypersomnia

- ▶ Hypersomnia
 - ▶ Rule out other primary sleep disorders
 - ▶ Usual Workup with considerations
- ▶ Posttraumatic Hypersomnia
 - ▶ Unrefreshing sleep and very long total sleep times



- ▶ Insomnia
- ▶ Circadian Rhythm Sleep-Wake Disorder
- ▶ Central Disorder of Hypersomnolence
- ▶ **Sleep Related Breathing Disorder**



Obstructive Sleep Apnea

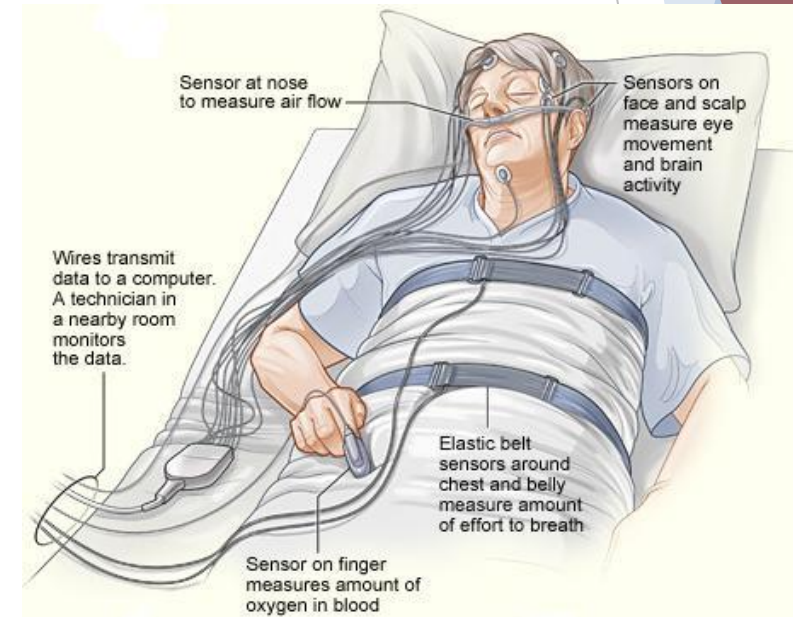
Home Sleep Apnea Test

Less sensitive Screening Test



Polysomnography

Most Sensitive Gold Standard



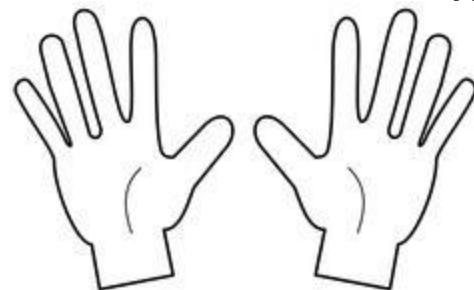
integration of the sleep disorders and TBI care

5 Finger Approach

- ▶ Attention to circadian misalignment
- ▶ Pharmacologic factors
- ▶ Medical factors
- ▶ Psychological factors
- ▶ Primary sleep disorders

10 Finger Approach

- ▶ Defining areas and mechanisms of injury
- ▶ Understanding new interventions
- ▶ Provide social supports to provide external structure to better prevent sleep issues
- ▶ Provide a physical environment that better supports sleep



emand improved access to sleep are for those with TBI



Conclusion

- ▶ Identify Area of Primary Concern related to Sleep & Traumatic Brain Injury
 - ▶ Insomnia
 - ▶ Circadian Rhythm
 - ▶ Hypersomnia
 - ▶ Underlying Sleep Disorder

- ▶ **Insomnia Treatment**

- ▶ Identify modifiable contributing factors
- ▶ Sleep Hygiene & Stimulus Control
- ▶ BBTI & CBTI
 - ▶ You can provide some of this help, but if it becomes too much, refer when the patient is stable to participate!
- ▶ Short Term Pharmacotherapy
 - ▶ Ramelteon, Doxepin or Suvorexant or others like Eszopiclone, Zaleplon or Zolpidem

- ▶ **Circadian Rhythm**

- ▶ Melatonin & Light Therapy

- ▶ **Hypersomnia**

- ▶ Evaluation by sleep specialist for diagnostics



AASM Resources

Fact-

AMERICAN ACADEMY OF SLEEP MEDICINE | PROVIDER FACT SHEET

Insomnia

Quick Facts:

Insomnia is characterized by frequent and persistent difficulty initiating or sustaining sleep despite adequate sleep opportunities and circumstances. Those with insomnia may present with sleep dissatisfaction and impaired daytime functioning. Insomnia can occur in isolation or comorbidly with mental disorders, medical conditions, or substance abuse. Symptoms must occur at least three times per week for at least three months to meet criteria for chronic insomnia.



It is thought that insomnia is affected by a combination of factors, and these have been summarized as the "3 P's of insomnia":

- Predisposing factors of insomnia are characterized by general "hyperarousal" states that lower one's threshold for waking and are often difficult to modify. Addressing predisposing factors of insomnia may considerably help improve the severity of a patient's insomnia. Examples of predisposing factors include genetic predisposition to insomnia and pre-existing conditions (eg, chronic pain, chronic mood/affective disorders, sleep-disordered breathing, bladder dysfunction).
- Precipitating factors of insomnia are triggers for the onset of insomnia or changes in the patient's life. Examples of precipitating factors include acute or intense emotional experiences (these can be positive or negative) and cognitive and behavioral interventions can mitigate the intensity of these experiences.
- Perpetuating factors of insomnia are repeating behaviors or responses to interventions. Examples of perpetuating factors include about insomnia and its effects, and environmental factors. Treatment options include therapy, modifications to sleep hygiene, and medications.

Why It Matters

- Anyone can suffer insomnia at any age; 33% of adults experience insomnia at least intermittently, as well as 20-40% of children and teenagers.
- Insomnia comes at a high price to society; the total annual direct costs of insomnia to the U.S. economy is projected to exceed \$90 billion.
- Insomnia can reduce life expectancy and increase the risk of cardiovascular events, compromised immunity, obesity, diabetes, seizures and asthma.

What You Can Do

- Start the conversation about your patient's sleep quality. Ask about sleep latency or waking during the middle or end of the night.
- Look for comorbidities and behaviors that may contribute to or mask insomnia. These include mental health conditions (eg, anxiety, depression), medical conditions (eg, pain, sleep disorder), the use of medications or substances, or issues with sleep hygiene (eg, excessive caffeine or alcohol intake).
- Consider an evidence-based psychological/behavioral treatment for adults. Treatment can include sleep hygiene education, stimulus control, sleep restriction, relaxation, and cognitive behavioral therapy for insomnia. Remember that sleep hygiene education alone is insufficient.
- Consider an evidence-based pharmacological treatment. These include benzodiazepine receptor agonist hypnotics (eg, zolpidem, eszopiclone, zaleplon, temazepam, flurazepam, estazolam), doxepin, ramelteon, and suvorexant. Other agents with some evidence for efficacy, but without a specific FDA indication for insomnia, can also be considered. These include benzodiazepine receptor agonists not specifically indicated for insomnia treatment (eg, clonazepam, lorazepam); sedating antidepressants, used alone or in combination with benzodiazepine receptor agonists or ramelteon; and, for patients with specific comorbidities, other agents such as gabapentin, tiagabine, quetiapine, or olanzapine. Avoid hypnotics as first-line therapy for chronic insomnia.
- Treat any identified underlying psychiatric conditions, such as anxiety, with cognitive behavioral therapy or selective serotonin reuptake inhibitors.
- Verify improvement of daytime functioning after insomnia treatment.

When to Refer?

- Consider referral to a psychology specialist for cognitive behavioral therapy for insomnia.
- Consider referral to sleep medicine physician to address contributing sleep disorders such as obstructive sleep apnea or restless legs syndrome, or when unsure of the cause of the insomnia.

Patient Information Websites:

- National Library of Medicine: <https://medlineplus.gov/insomnia.html>
- National Heart, Lung, and Blood Institute: <https://www.nhlbi.nih.gov/health-topics/insomnia>
- Online cognitive behavioral therapy program (commercial): <http://www.myshuti.com/>

AASM DEVELOPED BY THE AMERICAN ACADEMY OF SLEEP MEDICINE

AMERICAN ACADEMY OF SLEEP MEDICINE | PROVIDER FACT SHEET

Brief Behavioral Treatment for Insomnia (BBTI)

Quick Facts:

Insomnia is a condition characterized by difficulty falling asleep, difficulty in maintaining sleep, or waking up too early despite adequate opportunity to sleep. Insomnia often results in some type of daytime impairment such as symptoms of fatigue, mood disturbance, daytime sleepiness, reduced energy, difficulty with attention or concentration, as well as impairment in social, family or occupational performance.

Chronic insomnia is defined as the presence of symptoms for more than three months. It is a highly prevalent condition, seen in about 10 percent of the population.

Once insomnia starts, a negative and maladaptive response develops that associates the bed with wakefulness. Frustration and worry become connected with the bed and bedtime, and this conditioned cortical arousal perpetuates wakefulness. There are two modalities for treatment of chronic insomnia - psychological and pharmacological treatments.

Cognitive Behavioral Therapy for Insomnia (CBT-I) is a type of psychological treatment that ut is extended by making bedtime gradually earlier.

Unfortunately, access to CBT-I is limited due to a shortage of trained clinicians. In addition, CBT-I typically requires 10 sessions of about an hour each, over a six to 20-week period, which may be too frequent for many patients.



What is Brief Behavioral Treatment for Insomnia (BBTI):

BBTI is a psychological treatment modality, derived from CBT-I, which is delivered over four consecutive weeks (total of four sessions), and focuses on altering behaviors in order to improve sleep. In comparison to CBT-I, this treatment is shorter in duration, can be delivered by a range of clinicians who are familiar with health promotion and health coaching, and thus can potentially reach many more patients.

BBTI, like CBT-I, utilizes two critical behavioral principles: sleep restriction and stimulus control that enable the patient to produce sleep predictably and reliably.

One of the two key components of BBTI is sleep restriction. Patients with insomnia typically spend several more hours in bed than the time they spend sleeping. This perpetuates the insomnia as it strengthens the association of the bed with wakefulness rather than sleep and weakens the sleep drive. Patients are instructed to limit the time they spend in bed. Based on review of sleep diaries, a "sleep prescription"

is formulated to limit time about 30 minutes (account and nocturnal awakening).

The second key component is stimulus control. The rationale is clear and positive association. The patient is instructed to sleep and reserve the bed for sleep and reserve the bed for sleep and reserve the bed for sleep. If the patient is unable to fall asleep (perceived time, rather than actual time, should get out of bed, and return to bed when feeling sleepy for the morning).

BBTI is comprised of four sessions: one is in-person and the other three are telephone based.

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What You Can Do

- Identify and eliminate barriers to sleep (e.g. stimulating prescription drugs, caffeine, nicotine, long naps, excessive screen time right before bed, stimulating activities at night).
- Reduce time in bed to increase sleepiness. Patients should stay up later and reduce their total hours in bed. A typical starting point is limiting time in bed to just 6 hours per night. Once time to fall asleep is <30 minutes, time in bed can be extended by making bedtime gradually earlier.
- Set a fixed wake up time. Waking up at the same time (or earlier) is more important than having a fixed bedtime and helps reset the homeostatic sleep clock. Sleeping late or lingering in bed is deleterious to falling asleep well that night. Patients should not go to bed just because "it's bedtime", but rather when they are sleepy enough to fall asleep quickly even if that means a short period of sleep that night.
- Instruct patients to reduce time spent awake in bed. Limit time in bed to sleep and intimate activity. Getting into bed for other purposes rehearses being awake in bed and sabotages sleep.
- Limit patients from "trying" to sleep for more than approximately 20 minutes both at bedtime and if they awaken during the night. They should get out of bed if not asleep in 20 minutes and return to bed when they become sleepy.
- Weekly checkups for three weeks (in-person or by phone) are valuable for reinforcing behavioral changes.
 - If patient is falling asleep in less than 30 minutes AND spending less than 30 minutes awake during night, THEN increase time in bed by 15 minutes the next week
 - If patient is taking more than 30 minutes to fall asleep OR spending more than 30 minutes awake during the night, THEN reduce time in bed by 15 minutes the next week

When to Refer?

- Sleep restriction therapy is not recommended for patients with conditions such as bipolar disorder, psychotic disorders, or seizures, as restricting sleep hours can exacerbate these conditions. These patients should be seen for cognitive-behavioral therapy with a behavioral sleep medicine provider.
- If sleep has not improved after four weeks, consider referring for a full course of cognitive-behavioral therapy.
- Patients should be referred for a sleep medicine evaluation if there are co-morbid sleep disorders such as obstructive sleep apnea, restless leg syndrome, or parasomnias that are contributing to poor sleep.
- Circadian rhythm disorders can mimic insomnia. If patients can sleep well on their own schedules but not on the schedule required for work or school, a referral to sleep medicine or behavioral sleep medicine to evaluate for a circadian disorder is recommended.

One example of the BBT-I approach is found in materials licensed by the University of Pittsburgh and is available for non-commercial use from Dr. Daniel Buysse at buyssejd@upmc.edu.

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