# Insomnia
# Origins and Treatment

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"You can't walk in your sleep if you can't sleep" – The Go-Gos

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## Disclaimer

- I have a small amount of Pfizer stock, but none of the brand name medications I will mention are produced by Pfizer (They are from Merck, Eisai and Idorsia Pharmaceuticals).
- I will also be mentioning some off label uses of some medications to treat insomnia and will mention when they do not have FDA indication for insomnia.
- I have not done a fellowship in sleep medicine (but did consult with one who has).

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# Objectives

Understand normal sleep stages and regulators

Identify common psychiatric and medical causes of insomnia

Based on identifying a specific cause of insomnia, elect the most appropriate insomnia treatment strategy

Review the evidence and recommendations for medications for insomnia

Identify some OMT techniques that can be useful for insomnia

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# DSM definition of Insomnia

- A predominant c/o dissatisfaction w sleep quantity or quality associated with difficulty initiating or maintaining sleep.
- Causes clinically significant distress or impairment in social, occupational, or educational functioning.
- It occurs at least 3 nights per week and present for at least 3 months.
- It occurs despite adequate opportunity for sleep.
- It's not better explained by and doesn't occur exclusively during the course of another sleep-wake d/o
- It's not attributable to a substance
- Coexisting mental or medical conditions do not adequately explain the insomnia.

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# Why we treat insomnia

- Besides reducing overall quality of life, chronic insomnia is associated with a number of adverse effects, including increased rates of work absenteeism, MVAs, increased risk of developing psychiatric disorders, hypertension, CHF, DM and obesity (ACOFP).
- In the United States, chronic insomnia has a substantial economic burden as it is estimated to have direct costs of $2-$16 billion and indirect costs (absenteeism, reduced productivity, work related accidents, etc) of $75-$100 billion annually.

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# First, a little about normal sleep


## Consists of REM and NREM

## REM

- "Paradoxical sleep", physiological and brain activity similar to that when awake, sometimes even higher despite low levels of body activity.
- REM Latency: 90 mins after sleep onset 1st REM episode.
  - REM latency shortening occurs in depression and narcolepsy
- Thermoregulation is altered, body doesn't respond to changes in ambient temperature by sweating or shivering (poikilothermia).
- Near total paralysis of skeletal muscles
- Partial or full penile erection in males every REM period (useful in studying causes of ED)
- Occur ~ every 90 mins, 1st lasts <10 mins, later ones 15-40 mins
- Most occur in the last 3rd of the night.

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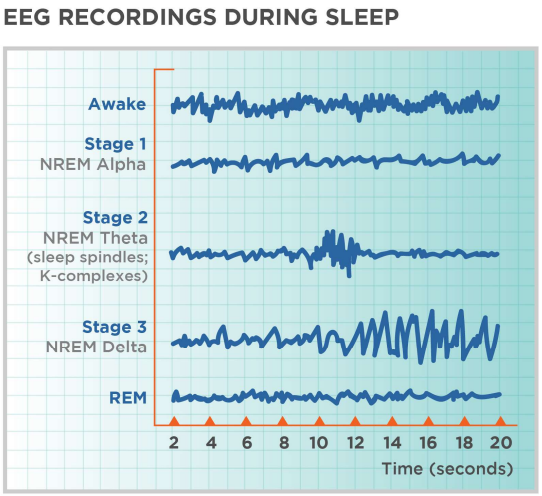
# NREM

- 75% of sleep time spent in NREM.
- Pulse rate, respiration and BP slightly lower than when in restful waking.
- Increases after exercise and starvation.
- Three stages:
  - Stage I – 1-7 mins
  - Stage II – 10-25 mins
  - Stage III – 20-40 mins
  - (REM – 10-60 min)

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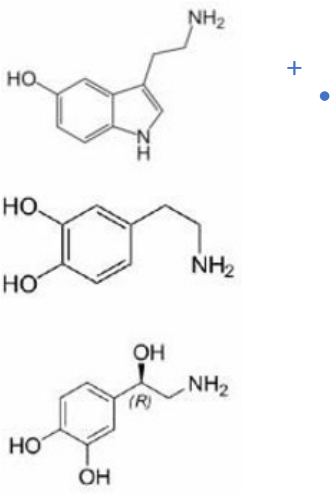
# Sleep Regulation

- Mostly located in the brainstem, but…
- Serotonin: Prevention of serotonin synthesis or destruction of the dorsal raphe nucleus significantly reduces sleep.
- Norepinephrine: Drugs that increase firing of the NE neurons in the locus coeruleus reduce REM and increase wakefulness
- Dopamine: Drugs that increase DA produce wakefulness, drugs that block DA increase sleep.

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# Sleep deprivation

- Long periods of sleep deprivation can lead to disorganization of thought, delusions, and hallucinations.
- REM rebound – REM periods increase in number and length when people are deprived of REM.
- REM deprivation leads to irritability, lethargy and poor concentration, increased sugar intake.
- Memory consolidation occurs during REM, so likely to do more poorly on tests after “all nighters”.


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# Sleep requirements

Most people require 6-9 hrs, but there are short sleepers <6 and long sleepers >9, long sleepers have more REM periods and more eye movement within each period (REM density).

Sleep needs changes based on age, physical work/exercise, illness, pregnancy, general mental stress and increased mental activity.

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## Sleep needs over the lifespan

- Babies 12-17 hrs
- Toddlers 10-14 hrs
- School kids 9-11 hrs
- Teens 8-10 hrs (circadian rhythm shifts later)
- Adults 7-9 hrs
- Seniors 6-8 hrs (circadian rhythm shifts earlier)

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## Sleep changes in seniors

- Sleep needs decrease for seniors, some will complain that they have insomnia because they can't sleep 8 hrs like they used to and now wake up earlier than they want. It is important to educate that 6 hrs can be their "new normal" and unless they are having daytime somnolence (not otherwise explained), no treatment is warranted.
- Different types of insomnia, when present, have different implications in development of dementia. A 2023 article in Journal of Preventative Medicine researchers looked at 10 yrs of data and were able to correlate sleep-initiation insomnia and sleep medication use with an increased risk of dementia. Interestingly, sleep-maintenance insomnia actually *significantly decreased* dementia risk.

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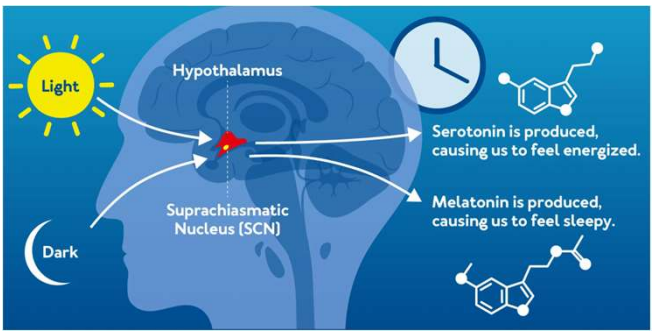
# Sleep-Wake Rhythm

- Circadian rhythm is set by suprachiasmatic nucleus of the hypothalamus.
- Without external cues like light/dark and meals, the natural body clock follows a 25 hr cycle.
- Naps vary in their amount of REM based on the time of day taken. AM naps have more REM, PM naps have much less.

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Sleep Disorders

Dyssomnias and Parasomnias

Dyssomnias are disorders of the amount or timing of sleep, they include insomnia and hypersomnia

Parasomnias involve abnormal behaviors during sleep or transitions between sleep and wakefulness.

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# Insomnia

- Almost always a symptom of something else rather than itself the illness.
- 1-yr prevalence rate of 30-45% in adults
- Common physical causes worsening sleep include OSA, BPH, RLS, GERD, pain, pregnancy, hyperthyroidism, hot flashes w menopause
- Medications: Diuretics, certain asthma medications, fluoxetine, bupropion are some offenders.

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# Short term vs chronic insomnia

- Occasional short-term insomnia affects 30%-50% of the adult population.
- Chronic insomnia affects 5%-10%, but notably higher in those with medical or psychiatric illness(es). Insomnia itself can trigger mood disorders.
- Those most at risk are older populations, female gender, comorbid medical/psych/sleep/SU disorders, shift work & possibly lower socioeconomic status.

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## Common psychiatric causes

- **Substance use** – Caffeine, alcohol, nicotine, THC, methamphetamines
- **Anxiety** – Typically have more trouble falling asleep vs staying asleep
- **Depression** – Disrupts architecture of sleep and the amount. More often have difficulty staying asleep, often have early waking and can't get back to sleep. Sleep disturbance up to 90% prevalence
- **Panic disorder** – abrupt awakenings secondary to sympathetic nervous system dysfunction.
- **ADHD** – Difficulty adhering to bedtime routine, get distracted and engage in activities that keep them from getting to bed on time.
- **OCD** – Engagement in rituals can keep them from getting to bed.
- **PTSD** – Nightmares
- **Bipolar** – Decreased need for sleep in hypomania/mania
- **Schizophrenia** – Increase in dopamine (causing delusions/hallucinations) decreases sleep.
- **Medication induced** – Fluoxetine, Bupropion, ADHD meds



## Medical meds implicated in insomnia

- Asthma and COPD meds – albuterol, ipratropium, montelukast
- Corticosteroids/prednisone
- B-blockers can cause insomnia in some per American Heart Association
- ACE inhibitors – can disrupt sleep with side effects of cough, restless legs or leg cramps
- Dopamine agonists in Parkinson's disease (carbidopa-levodopa, pramipexol for RLS)

# First steps in treating insomnia

- Goal is to ID the cause(s) whenever possible then address the cause such as treating depression, removal of offending agents, getting sleep study/CPAP, etc.


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# First line tx for all – Sleep Hygiene review

Bed is ONLY for sleep (and sex), no reading, no watching TV, no talking/texting/game playing on phone.

If using screens at night, turn on "night shift" mode as blue light suppresses melatonin release.

Get up if not asleep in 15 mins and do something calming (hot bath, reading).

Do exercise, but don't do it late at night.

No stimulants, alcohol, nicotine at night

Get up and go to bed at the same time every day, even weekends.

Avoid naps!

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## Cognitive Behavioral Therapy for Insomnia "CBT-I"

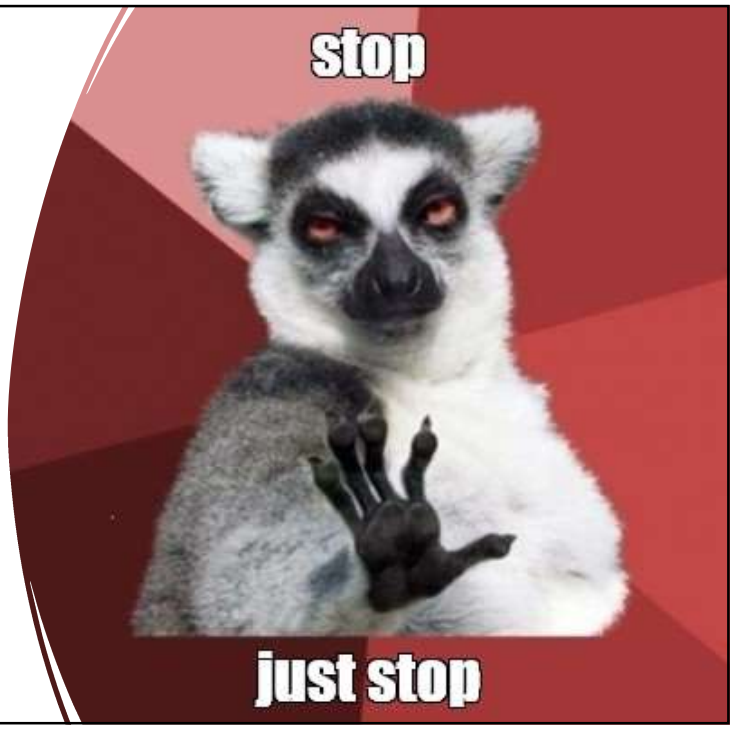
- Evidence based form of psychotherapy that can positively impact quality of sleep.
- In person, virtual, or CBT-I apps




## Substance Induced


- **Caffeine** ½ life is ~6 hrs, encourage none after lunchtime. Many folks will have a mid afternoon caffeinated drink to push through the rest of the work day. If one is consumed at 3 pm, ½ of it can still be present at 9 pm when most are starting to get ready for bed.
- **Alcohol** - Increases sleep onset, but it suppresses REM and increases NREM stage III leading to non-restorative sleep/daytime somnolence, which can lead to naps, worsening nighttime sleep. It also worsens OSA.
- **THC** – Varies based on use: Short term exposure can decrease sleep onset latency and wakings after sleep onset, but long term use increases these.
- **Amphetamines** – meth, especially, greatly reduces the need for sleep by increasing release of dopamine as well as blocking its reuptake.

# Tx for substance induced

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## Substance induced insomnia tx

- **Caffeine** – taper to avoid headaches, none after lunchtime
- **Alcohol** – if heavy, refer for detox (CBI, any private psych hospital), mild to moderate can use naltrexone, FDA approved to decrease frequency and volume of EtOH consumption. Acamprosate can be helpful, but TID dosing can be challenging. Very few agree to take disulfiram/Antabuse
- **THC** – Heavy users can experience withdrawal with abrupt cessation (irritability, mood swings, sleep difficulties, headaches, flu like symptoms for 1-2 wks), developing a tapering strategy may be more effective. Moderate exercise can curb THC use and cravings.
- **Methamphetamines** -Likely need extended inpatient rehab like Crossroads, etc. A small study showed some benefit from bupropion and naltrexone combo at reducing cravings in motivated individuals.

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# Anxiety induced insomnia & non-pharmacological tx

- Anxious ruminations delay sleep onset, easy time to worry as no activities of distraction like during the day.
- Often become anxious about the insomnia, making it even more difficult to sleep.
- Distract from ruminations with Calm app, free videos (to listen to, not watch) on YouTube, recommend guided meditation ones vs just relaxing noises like rain.
- CBT-I can be done in person, virtually, or even from an app
- SSRIs/SNRIs/buspirone all good options for reducing/preventing excessive anxiety. Buspirone has no sexual side effects, can be a good selling point.
- Panic attacks – if rare/occasional, a PRN BZD is fine, stick to shorter acting/faster onset, I prefer lorazepam. If frequent, should be on preventative med like a SSRI.
- OCD – also SSRIs/TCAs and CBT are tx of choice

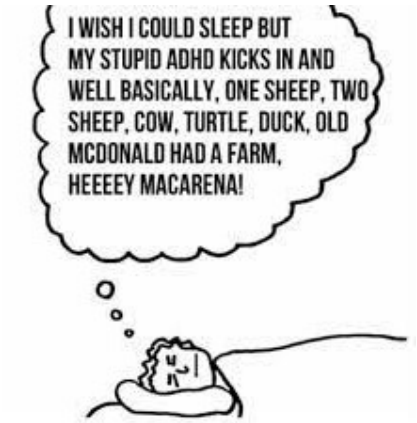


# Depression induced

- Anytime a pt comes to c/o insomnia, screen for the other symptoms of depression, the pt often doesn't realize he/she has depression.
- Appetite changes? Decreased concentration? Lack of enjoyment of activities they used to like? Decreased motivation? Feelings of hopelessness?
- CBT
- SSRIs/SNRIs/bupropion/TCAs
- Lack of response to 2 agents, refer to psychiatry (other options we have besides medications include TMS, ketamine, ECT for tx resistant depression, may be bipolar II which doesn't typically respond to SSRIs well).

# ADHD induced

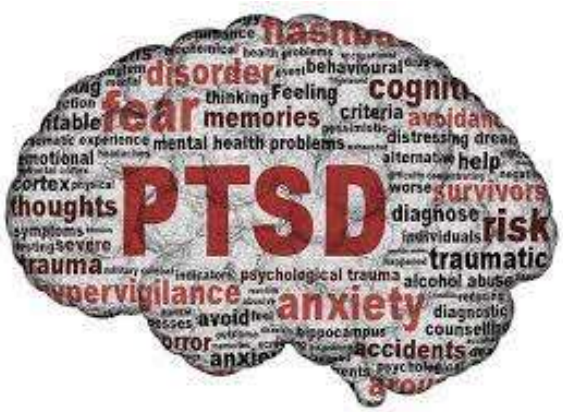
- How do you treat at night when you clearly want to avoid most ADHD medications?
- Behavioral interventions, setting several alarms/reminders to start getting ready for bed can be useful for some.
- Guanfacine is an alpha agonist that has indication for ADHD (although indication has only been obtained for children), side effects can include somnolence, so may be helpful in several ways. Caution in hypotensives.






# PTSD induced

- Therapies of choice are CBT and EMDR
- SSRIs/SNRIs beneficial
- Prazosin 1-15 mg qhs very helpful for PTSD related nightmares



You've eliminated all the usual suspects, then what?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# American Academy of Sleep Medicine

- "No formal, evidence-based standards of practice for pharmacological treatment of insomnia have been published"- Journal of Clinical Sleep Medicine

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## However…

The American Academy of Sleep Medicine commissioned a task force of four experts in sleep medicine who reviewed publications of RCTs and developed recommendations based on the quality of evidence (2017).

The found no better than “weak” evidence for all the medications evaluated (only for adults and vs no tx), but did rank them:

1. We suggest that clinicians use suvorexant as a treatment for sleep maintenance insomnia (WEAK)

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## Orexin Antagonists

- Orexin is a hypothalamic neuropeptide that promotes wakefulness (narcoleptics have 85-95% fewer orexin producing neurons). It stimulates the release of other neurotransmitters that promote wakefulness like dopamine, norepinephrine and serotonin. It is also implicated in appetite.
- Orexin antagonists are Schedule IV, can have same SEs as the z-drugs, but overall appear safer, they do not appear to cause respiratory depression, addiction or dependency/tolerance. They appear to improve REM, pts are more easily aroused from sleep than w BZDs/hypnotics. Not only less likely to negatively affect cognitive function, but in a small study published in the Annals of Neurology, amyloid-beta levels fell 10-20% vs placebo 5 hrs after suvorexant administration. Tau phosphorylation also fell.
- Improve sleep latency, wakings after sleep onset, sleep efficiency, total sleep time and sleep quality.

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# Orexin Antagonists

- Suvorexant (Belsomra) - Nonselective orexin receptor antagonist. Onset of action 30 mins, half-life of 12 hrs, peak plasma concentration in 2 hrs. Appears to be beneficial in preventing delirium.
- Lemborexant (Dayvigo) - More selective of orexin-2 receptor, peak plasma in 1-3 hrs, half-life 17-19 hrs.
- Daridorexant (Quiviviq) - Dual orexin 1 & 2 receptors antagonist, half-life 8 hrs.



# Recommendations, con't

- 2. We suggest that clinicians use eszopiclone as a tx for sleep onset and maintenance insomnia (WEAK)
- 3. We suggest that clinicians use zaleplon as a tx for sleep onset and maintenance insomnia (WEAK)
- 4. We suggest that clinicians use zolpidem as a tx for sleep onset and maintenance (WEAK).

# Z-drugs - bind to the benzodiazepine receptor & may enhance GABA inhibitory actions

- Upper end of list recommendations are eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien) in that order.
- But, zaleplon indication is "short term treatment"
- Zolpidem "Reevaluate if insomnia persists after 7-10 days". No more than 5 mg for females and both males and females over 65.
- Eszopiclone "Chronic studies suggest lack of notable tolerance or dependence developing over time", but also recommended to "reevaluate after 7-10 days", but it is not restricted to short term use.
- Schedule IV, all can produce CNS depression, amnesia and complex sleep-related bx's.
- Appear less likely to cause cognitive impairment than BZDs, structurally they are not BZDs, but they do bind to the BZD receptors agonizing effect on GABA.

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# AASM recommendations, con't

5. We suggest that clinicians use triazolam as a tx for sleep onset insomnia (WEAK).

6. We suggest that clinicians use temazepam as a tx for sleep onset and sleep maintenance insomnia (WEAK)

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# Benzodiazepines


- Many drawbacks, most are schedule III (except alprazolam - ?)
- Substantial issues, dependency and tolerance develop quickly and they can be extremely difficult to discontinue, often requiring long, slow tapering (and typically in highly motivated individuals). Can't start pain mgmt on them. American Geriatrics Society does not recommend use of BZDs.
- Risk of respiratory depression and death with additive effects of EtOH or opioids.
- In the elderly, use increases risk of falls, delirium, dementia.



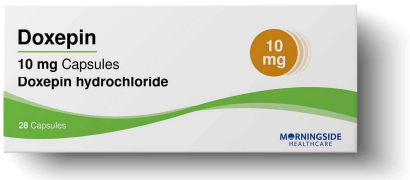
# Recommendations, con't

- 7. We suggest that clinicians use ramelteon as a tx for sleep onset insomnia (WEAK) **although benefit is small, it is approved for long term use (selective agonist of melatonin 1 and 2 receptors, but half-life is notably longer than melatonin).

# Melatonin receptor agonists

- Ramelteon (Rozerem) - Highly selective melatonin receptor 1 & 2 agonist (OTC melatonin non selective for 1,2 &3). It is NOT controlled. No additive effect w EtOH, unlikely to produce daytime grogginess or "hangover" effect. No evident for rebound insomnia or withdrawal on discontinuation. Benefits are not exactly robust, however.
- Tasimelteon (Hetlioz) – Non 24 hr sleep-wake disorder (esp in blind) and sleep disturbance in Smith-Magenis Syndrome.






# Recommendations, con't

- 8. We suggest that clinicians use doxepin as a tx for sleep onset or sleep maintenance insomnia (WEAK)

# Doxepin

- Pros: Has FDA indication for sleep maintenance, but at only 6 mg and even lower for elderly at 3 mg. By contrast, use for depression and/or anxiety, recommended dosing is 150-300 mg.
- At lower doses, it can have a hypnotic effect without major anticholinergic effects. Not to be taken within 3 hrs of a meal.
- Cons: Anticholinergic burden may cause cognitive issues in elderly (along w the usual dry mouth, constipation, etc). Antihistaminic, so wt gain also possible.

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# What about trazodone?

- 9. We suggest that clinicians ***not*** use trazodone as a tx for sleep onset or sleep maintenance (WEAK)
- What??? This recommendation was based on a single study of 50 mg "Pt reported data demonstrated a modest reduction in sleep latency which fell below the threshold for clinical significance... The moderate increase in total sleep time and the small reduction in waking after sleep onset did not reach the clinical threshold criteria. Quality of sleep was insignificantly improved and reduction in number of awakenings fell just below clinical significance".

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## Trazodone, con't


- Innovations in Clinical Neuroscience (a peer reviewed journal) published a review of 45 RCTs, meta analyses, observational studies and placebo-controlled trials involving the use of trazodone for primary and secondary insomnia
- They concluded: "Evidence for the efficacy of trazodone has been repeatedly demonstrated for primary insomnia, as well as secondary insomnia… A review of the literature suggests that there are adequate data supporting the efficacy and general safety of the low-dose use of trazodone for the treatment of insomnia".
- It has little to no anticholinergic burden. Wt gain very uncommon.



## AASM recommendations, con't

- 10. We suggest that clinicians *not* use tiagabine (Gabatril) as a tx for sleep onset or sleep maintenance insomnia (WEAK)
- 11. We suggest that clinicians *not* use diphenhydramine for S.O. or S.M.I. (WEAK). Trials based on 50 mg, mean reduction in pt reported sleep latency fell below clinically significant threshold. It judged the benefits vs harms as equal. Total sleep time measured by polysomnography reported an average increase of 12.37 mins, which was below the significant cut off of 20 min.

AASM recommendations, con't

12. We suggest that clinicians *not* use melatonin as a tx for S.O. or S.M.I. (based on 3 studies of trials of [only] 2 mg), and they add "overall quality of evidence was very low".

13. We suggest that clinicians *not* use L-tryptophan as a tx for S.O. or S.M.I. (250 mg, wakings were decreased slightly and sleep quality was mildly increased, but not to threshold of clinical significance. No papers reported any adverse effects).

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# More off label options

- Gabapentin – Pros: tolerated well, non habit forming, relatively short half life means unlikely to cause "hangover", increases slow wave sleep and improves sleep efficiency and lowers wakings. Usually dosed 100-400 mg. Cons: may not be strong enough
- Mirtazepine – Pros: Generally works well for sleep, doesn't cause dependence, helpful for depression without sexual side effects. Cons: Anticholinergic, antihistaminic.
- Hydroxyzine - 25-100 mg -mixed results, can have daytime somnolence, ½ life is 20-25 hrs


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# OMT approach to insomnia

- The Barcelona School of Osteopathy published two publications in 2017 with studies using OMT for insomnia. They found that applying CV4 compression, temporal bone rotation, synchronization of the reciprocal tension membrane and primary respiratory mechanism decreased the number of nighttime awakenings, decreased scores on the Pittsburgh Insomnia Rating Scale. There was also a decrease in hypnotic med use, improved sleep quality and daytime motivation.
- This occurred with just 3 treatment sessions over 5 months.

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# OMT, con't

- Their second study of just 2 tx sessions in 2 months utilized deep and soft tissue massage, venous sinus drainage and cranial OMT.
- On the Pittsburgh Insomnia Rating Scale (65 item questionnaire), pts with moderate insomnia improved from 3.4% to 0% and pts w subclinical insomnia improved from 79% to 17.2 then to 6.9%.




# ACOFP recommends the following techniques

Cranial techniques:

- 1. Compression of the 4th ventricle (CV4)
- 2. Temporal bone treatment
- 3. Synchronization of the reciprocal tension membrane and primary respiratory mechanism.
- 4. Pussy foot technique
- 5. Cranial lifts.
- 6. Occipitoatlantal decompression
- 7. Venous sinus drainage.

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ANS balancing techniques to reduce sympathetic tone and/or improve neuro-lymphatic function:

- 1. Seated rib raising
- 2. Paraspinal inhibition
- 3. Collateral ganglion inhibition
- 4. Thoracolumbar OMT
- 5. Soft tissue OMT
- 6. Myofascial release to include heart rate variability
- 7. Thoracic inlet release
- 8. Abdominal diaphragm doming.


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# One final, simple tip for better sleep.

- Our bodies were meant to be physically worn out by the end of the day. Becoming physically tired helps the brain become tired.
- Some good cardio exercise (not too late!) can make a huge difference in insomnia. I encourage at least 20 mins getting HR over 110 if older, 120 or more if younger.


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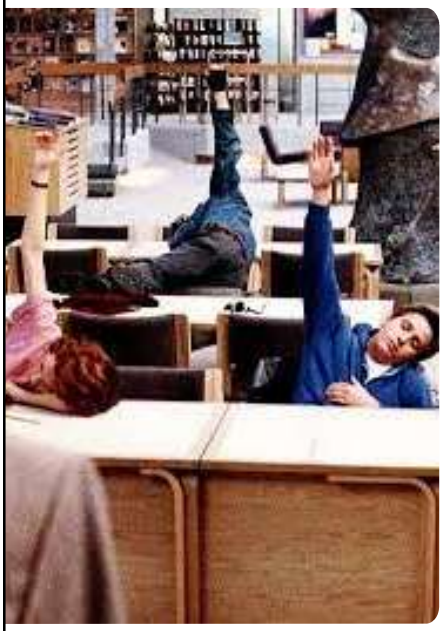

# Still awake?

Any questions?

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## References


- Kaplan & Saddock Synopsis of Psychiatry 10th edition
- Sateia, M.J., Buysse, D.J., et al. "Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline". Journal of Clinical Sleep Medicine Vol 12, issue 02
- Trivedi, M.H., Walter, R., Ling, W., et.al *Bupropion and Naltrexone in Methamphetamine Use Disorder* The New England Journal of Medicine 2021; 384: 140-53
- Mazzeo, S., Silverberg, C., Oommen, T., et.al. *Effects of Osteopathic Manipulative Medicine on Sleep Quality in Student Athletes After Concussion: A Pilot Study* Journal of the American Osteopathic Association, 2020, Aug 11


54

# References, con't


- Jaffer, K., Chang, T, Vanle B, et.al. "Trazodone for Insomnia: A Systematic Review" – Innovations in Clinical Neuroscience Jul-Aug 2017
- Lanspa, M, Nova SE University COM, 2022 Namey/Burnett Preventative Medicine Writing Award Winner, 1st Place www.(acofp.net/2022/03/22/lets-talk-about-sleep/
- Wong, R, Lovier, M, "Sleep Disturbances and Dementia Risk in Older Adults: Findings from 10 Years of National U.S. Prospective Data", American Journal of Preventative Medicine Vol 64, Issue 6, June 2023
- Sateia, M, Buysse, D, Krystal, A, et.al. "Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Practice Guideline" Journal of Clinical Sleep Medicine Vol 12, Issue 2 Feb 15, 2017
- Desk Reference to the Diagnostic Criteria from the DSM 5, American Psychiatric Association 2013.




# References, con't


- Guo, F., Yi, L., et al, "Association Between Z Drugs Use and Rsik of Cognitive Ipariment in Middle-Aged and Older Patients with Chronic Insomnia" Frontiers in Human Neuroscience, 2021; 25:775144
- Lucey, B, Haiyan, L, et al, "Suvorexant Acutely Decreases Tau Phosporhylation and Abeta in the Human CNS" Annals of Neurology, March 10, 2023
- Marshall, N. and Grunstein, R. "Orexin Antagonists – Two Steps Forward, One Step Back" New England Journal of Medicine, July 27, 2023 389: 373-375
- Monkemeyer, N., Thomas, S, et al "Insomnia Treatment Update with a Focus on Orexin Receptor Antagonists" US Pharmacist 2022; 47(5): 43-48
- Wikipedia – Orexin antagonists