MANAGEMENT OF INSOMNIA AND OTHER NON-OSA SLEEP DISORDERS

Eric Heckman MD

Program directory BIDMC / BCH sleep medicine fellowship

September 9, 2023

SLEEP DISORDERS COVERED

- Insomnia
- Restless leg syndrome
- Circadian rhythm sleep-wake disorders
  - Advanced sleep-wake phase disorder
  - Delayed sleep-wake phase disorder
  - Shift work disorder

https://hitandruncandlesticks.com/drinking-from-a-fire-hose-of-data/

Assess the complaint: What do you mean you can't sleep?

The answer is in the sleep timing

- When do you get home from work?
- When do you get in bed? What are you doing before bed?
- How long before sleep onset?
  - If time is prolonged what are you doing?
- Arousals after onset?
  - What triggers?
  - What time?
- Can you easily return to sleep?
  - If not what do you do?
- What time to you wake up? What time do you get out of bed?
  - If there is a big difference what are you doing?
- Naps? When? How long?
- Does your schedule differ on other days of the week?

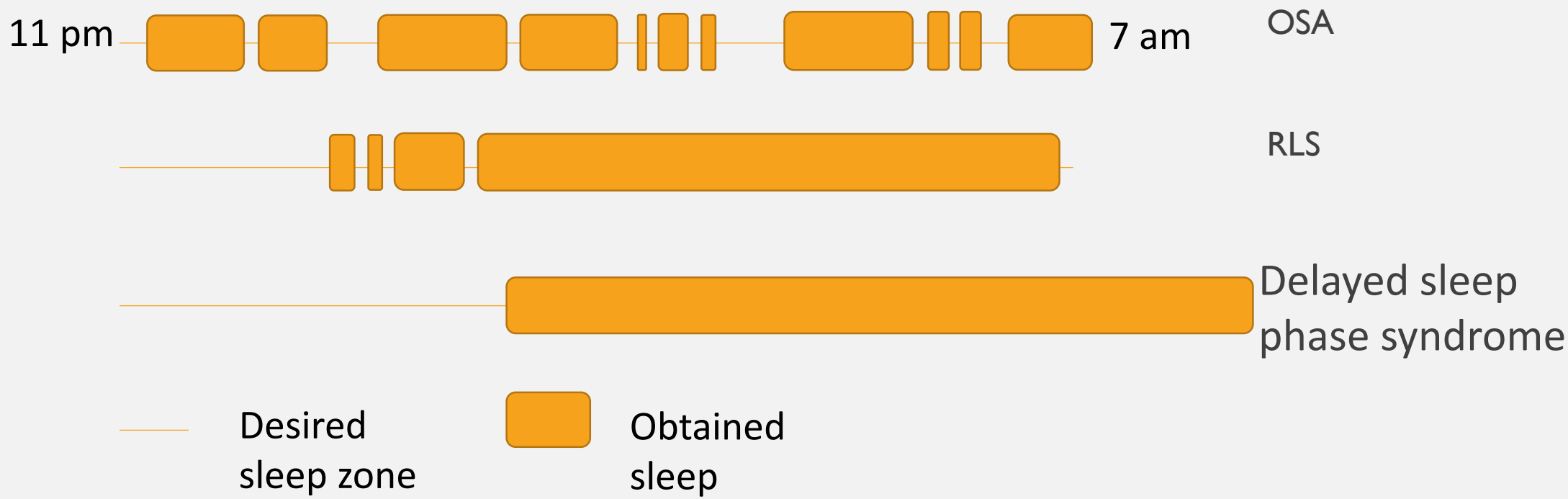
Sleep Review of symptoms

Fragmentation contributors

- Sleep apnea:
  - Snoring, witnessed apneas, gasping arousals, morning headaches, morning dry mouth
- Restless leg syndrome
  - Leg discomfort, urge to move.
  - Worsening around biologic nighttime
  - Temporary improvement with movement
  - Interferes with sleep
- Parasomnia
  - Sleep walking, talking, dream enactment
- Hypersomnia
  - Sleep paralysis, hypnogogic hallucinations, cataplexy

Are the symptoms really primary insomnia?

Is another sleep disorder to blame?



Sweetman, Sleep Med Rev. 2021 Dec;60:101519

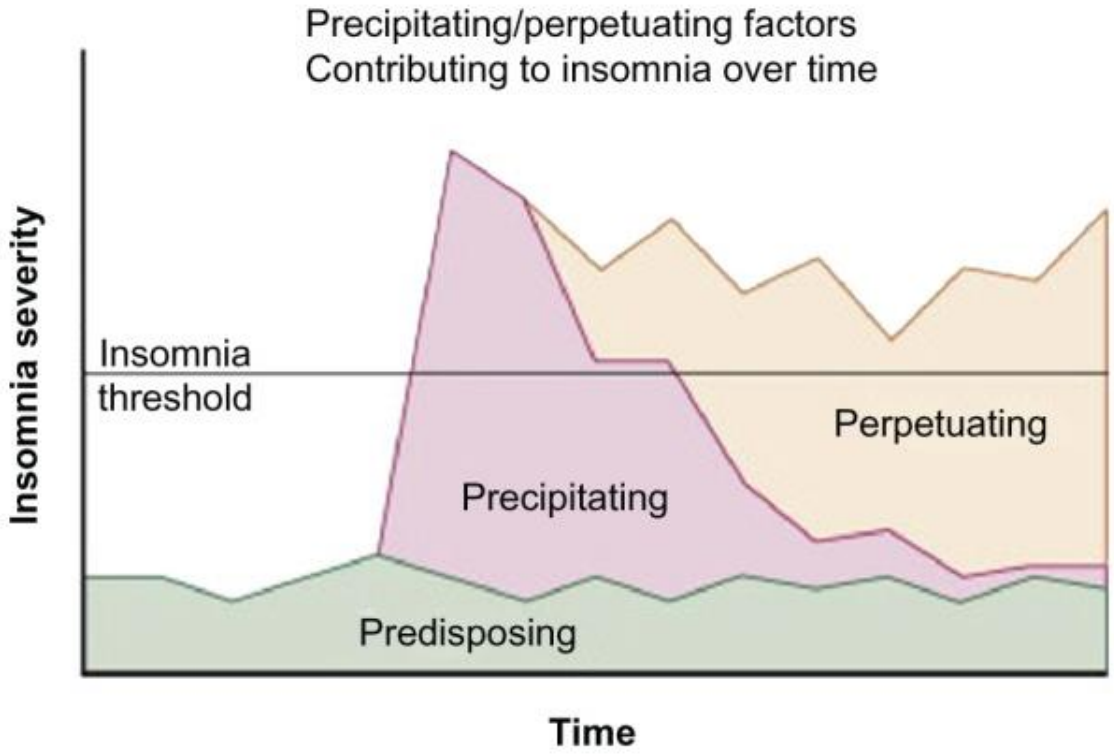
INSOMNIA

- characterized by dissatisfaction with sleep quantity or quality, associated with difficulty initiating sleep, maintaining sleep or early-morning awakenings.
- Distress or impairment that is caused by insomnia symptoms
- Must have adequate opportunity for sleep and insomnia not better explained by another sleep disorder,
- Chronic insomnia is defined as symptoms that occur at least three times per week and persist for at least three months
- Short term insomnia disorder (< 3 months)

American academy of sleep medicine. International classification of sleep disorders, 3rd ed. Darien, IL: American academy of sleep medicine, USA.

Goal: Address the Root Causes of Current Symptoms

Figure 1



Conceptual model of the development of chronic insomnia and the changing factors that play a role over the course of the disorder.

Palesh et al. Nat Sci Sleep. 2012 Dec 17;4:151-162

AASM Clinical Guidelines for chronic insomnia

Behavioral approaches

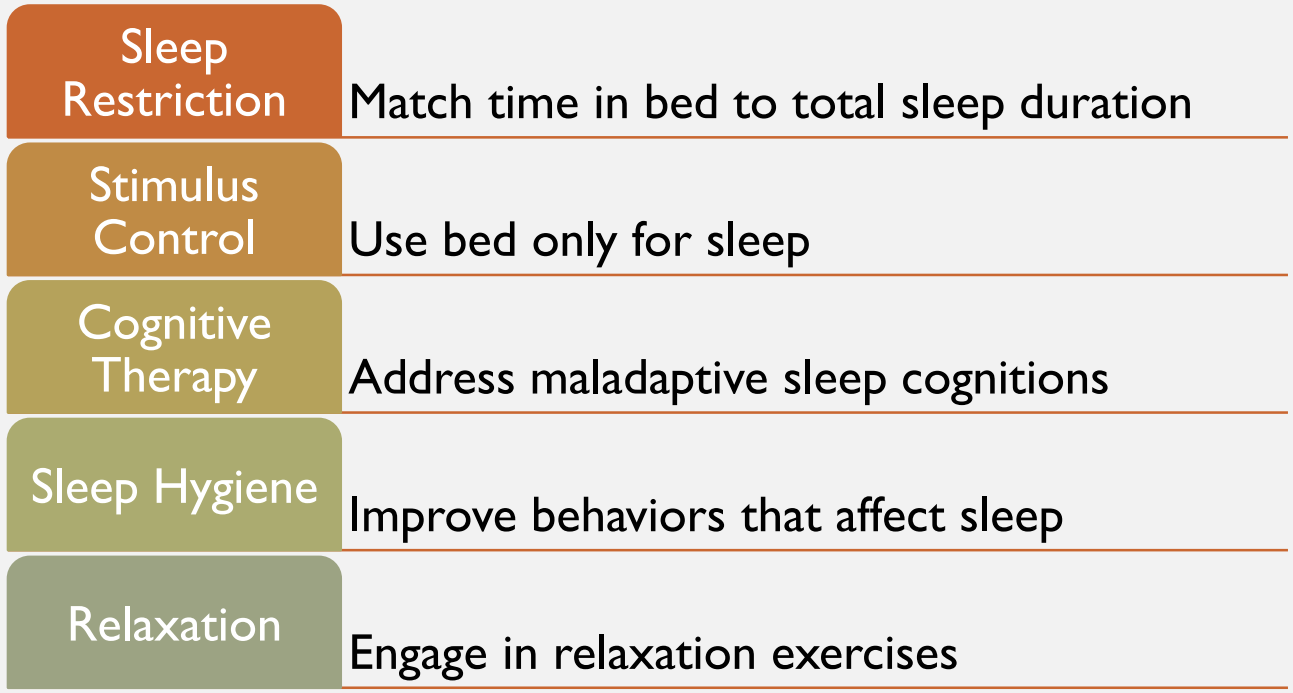


Figure from Dr Eric Zhou.

- Multicomponent cognitive behavioral therapy for insomnia strongly recommended
- Monotherapy with sleep hygiene recommendations not recommended.

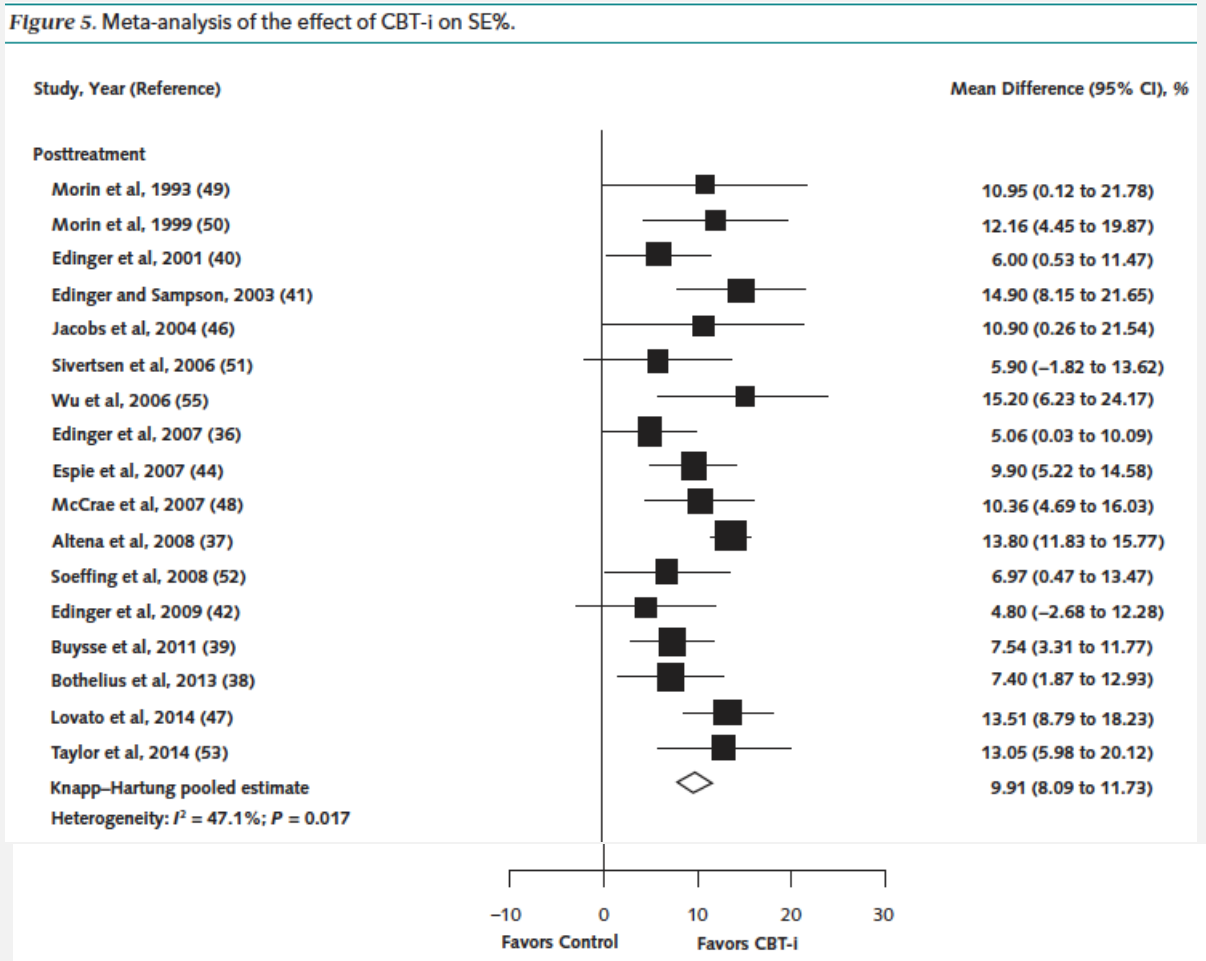
Edinger et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: An American academy of sleep medicine clinical practice guideline. J Clin Sleep Med. 2021 Feb 1;17(2): 55-262. doi: 10.5664/jcsm.8986

Cognitive Behavioral Therapy for Insomnia

It works well.

Improves:

- Sleep onset latency
- Total sleep time
- Wake after sleep onset
- Sleep efficiency

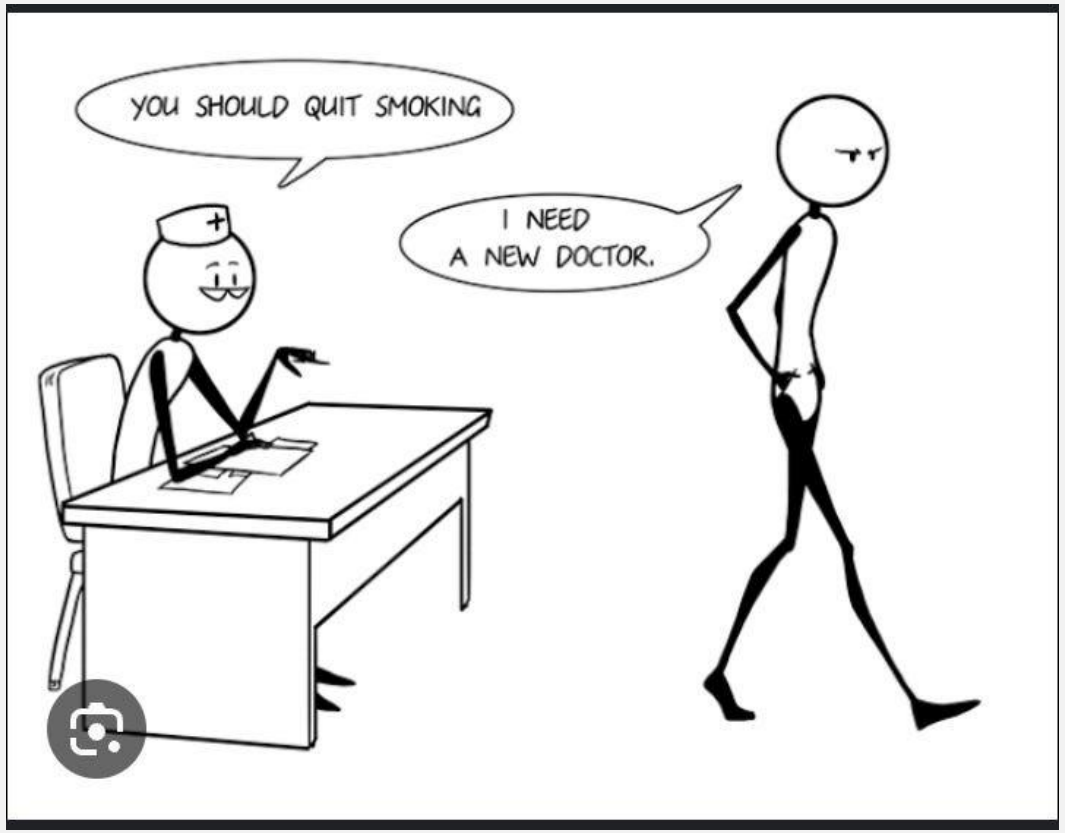


Modified from Ann Intern Med 2015;163:191-204.

Cognitive Behavioral Therapy for Insomnia

Is it a practical option?

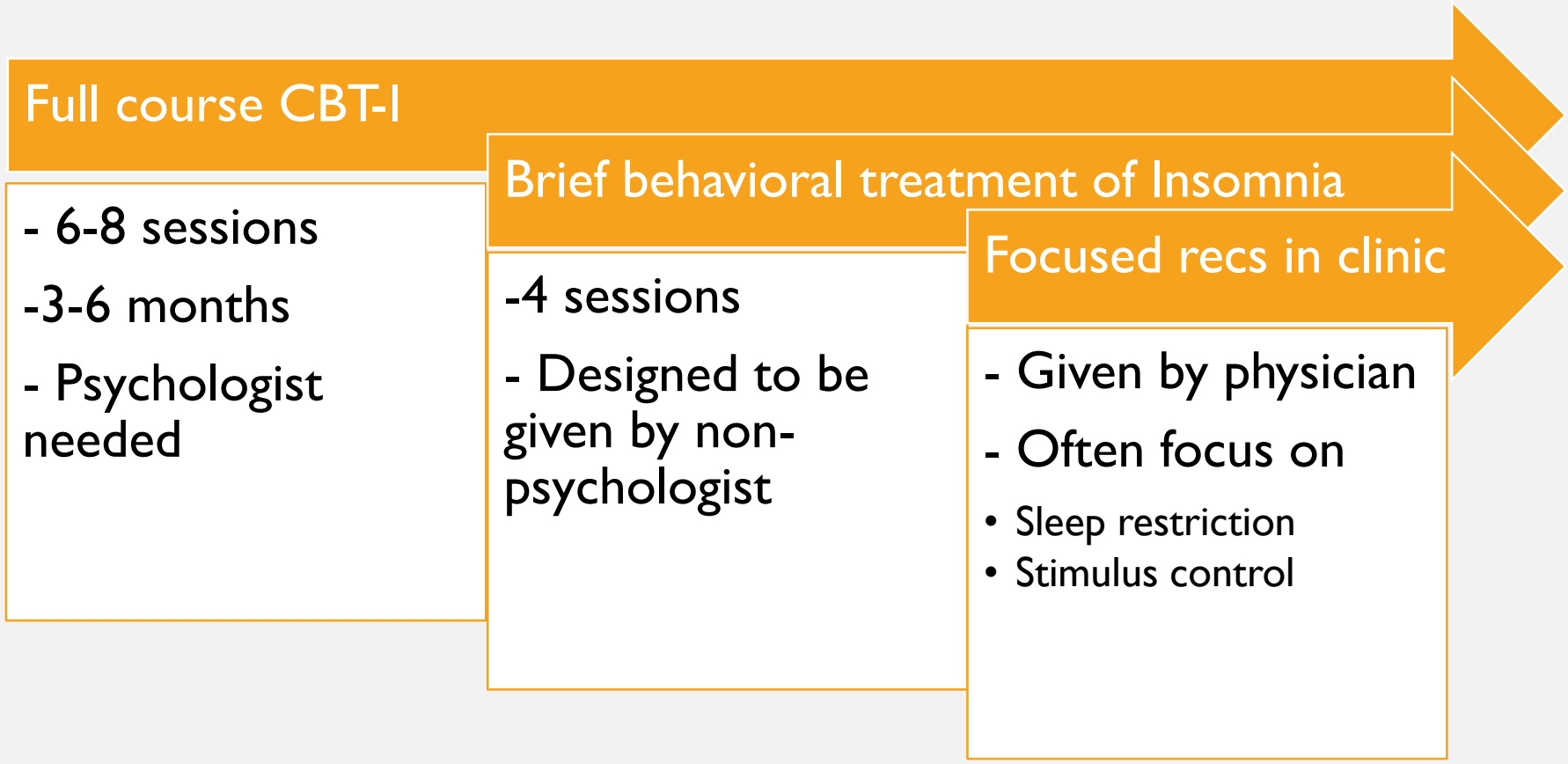
- CBT-I practitioners in high demand
- Insurance coverage?
- Options limited with language barrier
- Is the patient willing to take introspective look into habits around sleep?



https://medium.com/@nimra10801080/smoke-free-journey-five-effective-strategies-to-quit-smoking-and-achieve-lasting-freedom-4a4173e4d2f6

A Spectrum of Behavioral Interventions

How much time does the patient have?



Gunn, Sleep Med Clin. 2019 Jun;14(2):235-243
Fernando, J Prim Health Care. 2013 Mar 1;5(1):5-10.
Edinger, J Clin Sleep Med. 2021;17(2):255-262.
Edinger, Sleep 2003;2:177-182

Risks of Pharmacotherapy

- Tolerance, dependence, abuse, withdrawal
  - Best defined with benzodiazepines but not exclusively
- You make things worse
  - Hypnotic for very severe OSA
- Giving medication undercuts the patient motivation to focus on necessary behavioral interventions

Carter, Sleep Medicine Reviews 58 (2021) 101492
O'Brien, J Clin Psychiatry 2005;66[suppl 2]:28-33.
Schifano, International Journal of Neuropsychopharmacology (2019) 22(4):270-277

Risks of Pharmacotherapy

- Side effects
  - Oversedation
  - Parasomnias with non-benzodiazepine, benzodiazepine receptor agonists (“Z drugs”)
  - Long term risk for dementia
    - Is risk from medication or chronic poor sleep?
  - Polypharmacy

Sleep Medicine Reviews 2018;37:105-113.
Prog Brain Res 2011;190:89-103.
PLoS ONE 7:e49113.
Neurosci Bull January, 2020;36:77-84.

Benefits of Pharmacotherapy

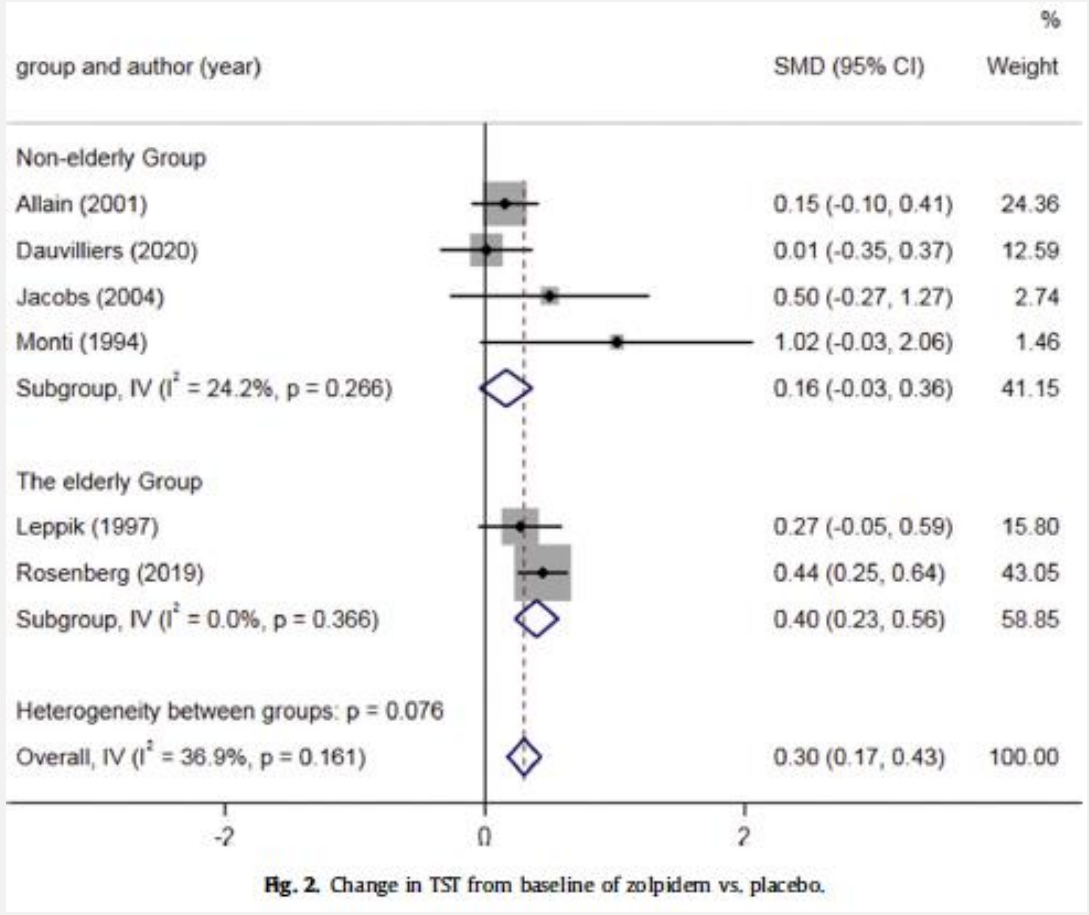


Fig. 2. Change in TST from baseline of zolpidem vs. placebo.

- Hypnotics (e.g., zolpidem) improve
  - Sleep onset
  - Total sleep time
  - Wake after sleep onset
- However, most studies are short-term

Sleep Medicine 2021;87:250-256.
Clin Ther 2014;36:1676-1701.

PCP: Try some level of behavioral intervention

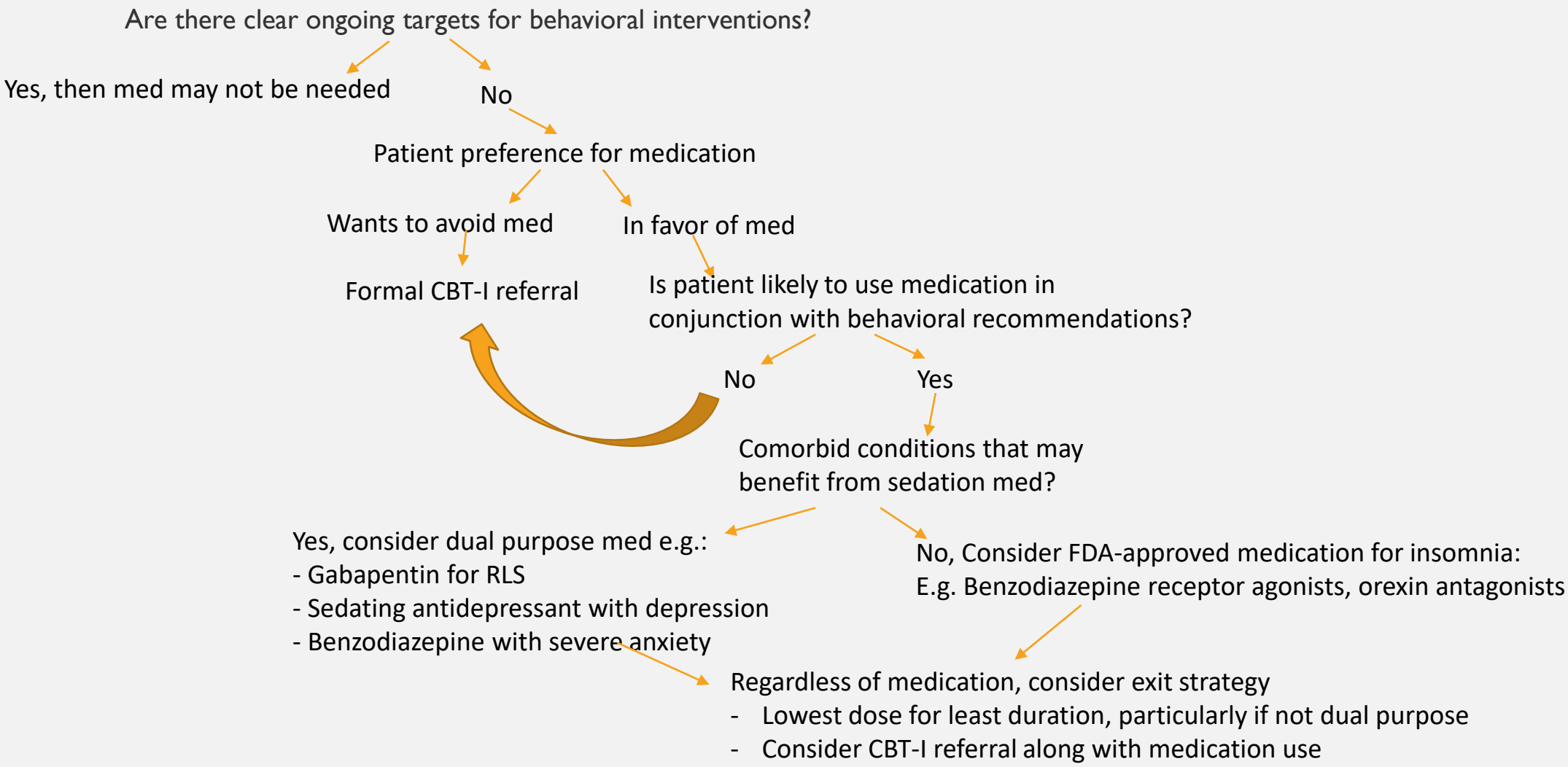
- Full CBTI course may not always be necessary
- Encourage physicians to gain comfort with stimulus control and sleep restriction

FOUR SLEEP RULES	RATIONALE
1. Reduce time in bed (usual TST + 30 min, never reduce TIB below 6 h)	1. ↑ Homeostatic sleep drive; ↓sleep latency
2. Establish consistent wake time	2. Strengthen circadian signaling, ↓ chance of phase delay; ↑ homeostatic sleep drive
3. Go to bed when sleepy	3. ↑ Homeostatic sleep drive, ↑ awareness of internal cues of sleepiness
4. Get out of bed when not sleeping in 30 min	4. Facilitates reconditioning to associate bed with sleep

Key: TST total sleep time, TIB Time in bed

Adapted from Table 1. Sleep Med Clin 2019;14:235-243.

Strategy for Addition of Medications



Libman H, Zhou ES, Heckman E, Smetana GW. How would you manage this patien twith chronic insomnia? : Grand rounds discussion from Beth Israel Deaconess Medical Center. Ann Intern Med. 2022 Dec;175(12):1746-1753

Pharmacologic Options for Chronic Insomnia

American Academy of Sleep Medicine Recommendations

Treatment (Drug Class)	Bedtime Dose Recommendation	AASM Recommended and Insomnia Type	Evidence Strength	Evidence Quality	Notable Adverse Events† (Reference)
Suvorexant (orexin receptor agonist)	10–20 mg	Yes, maintenance	Weak	Low	Sleep paralysis Cataplexy REM behavior disorder (38)
Eszopiclone (benzodiazepine receptor agonist)	2–3 mg	Yes, onset and maintenance	Weak	Very low	Unpleasant taste (39) Parasomnias
Zaleplon (benzodiazepine receptor agonist)	10 mg	Yes, onset	Weak	Low	Parasomnias (40)
Zolpidem (benzodiazepine receptor agonist)	10 mg	Yes, onset and maintenance	Weak	Very low	Parasomnias
Triazolam (benzodiazepine)	0.25 mg	Yes, onset	Weak	High	Higher misuse and withdrawal potential (23)
Temazepam (benzodiazepine)	15 mg	Yes, onset and maintenance	Weak	Moderate	Higher misuse and withdrawal potential
Ramelteon (melatonin agonist)	8 mg	Yes, onset	Weak	Very low	–
Melatonin (melatonin agonist)	2 mg	No	Weak	Very low	Vivid dreams (41)
Doxepin (heterocyclic)	3–6 mg	Yes, maintenance	Weak	Low	Suicidality (42) Orthostasis Anticholinergic effects (43)
Trazodone (heterocyclic)	50 mg	No	Weak	Moderate	Suicidality Orthostasis Priapism (44)

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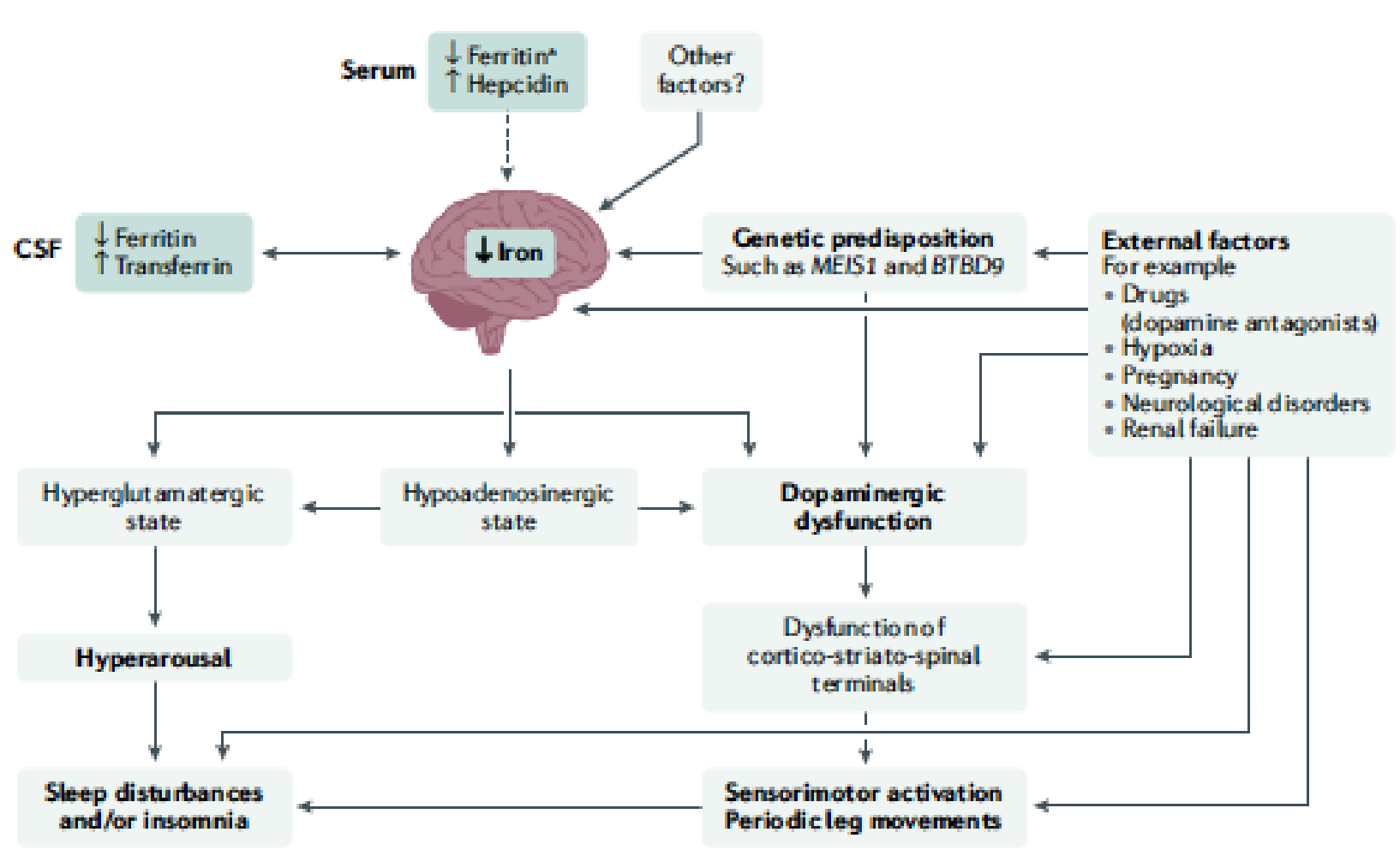
RESTLESS LEGS SYNDROME
WILLIS-EKBOM DISEASE

- A clinical diagnosis
- **Urge** to move the legs, usually with unpleasant, uncomfortable sensations in the legs,
- **Rest**, begins or worsens during periods of rest or inactivity
- **Getting up and going.** Movement like walking or stretching partially improves symptoms
- **Evening**. Occurs exclusively or predominantly in the biologic evening or night.
- Symptoms cause distress, sleep disturbance, or impairment.

American academy of sleep medicine. Internatinoal classification of sleep disorders, 3rd ed. Darien, IL: American academy of sleep medicine, USA.

PATHOGENESIS OF RLS



Manconi et al. Nature Rev Dis Primers. 2021 Nov 3;7(1):80. doi: 10.1038/s41572-021-00311-z

APPROACH TO RLS

- Avoidance of exacerbating factures
  - Etoh
  - Caffeine
  - Medications
    - SSRI
    - Antihistamine
      - Don't forget about OTC sleep aids
- Treatment of other causes of sleep fragmentation
- Medications for RLS generally are more effective if in the system PRIOR to typical symptoms onset, rather than attempting to abort active symptoms

FIRST LINE PHARMACOTHERAPY

Suggested initial dose and maximum recommended dose for dopamine agonists.

	Initial dose	Max. recommended dose
Pramipexole	0.125 mg/day	0.75 mg/day
Ropinirole	0.25 mg/day	4 mg/day
Rotigotine	1 mg/day	3 mg/day

- Increasingly dopamine agonists are being discouraged as first line
- As there are high rates of Augmentation:
  - RLS symptoms appear earlier than when drug first started
  - Higher doses are needed overtime
  - Intensity of symptoms worsen since starting the medication
  - Symptoms spread to other parts of body (eg arms)
- Rates as high as 76%, yearly incidence of 8%
- Higher dose and longer duration are risk factors
- Shorting acting agents, like Levodopa have higher risk
- When Augmentation occurs generally best to cross taper to alternative class

Garcia-Borreguero Et al. Guidelines for the first-line treatmetn of restless legs syndrome/ Willis-Ekbom disease, prevention and treatment of dopaminergic augmentatino: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundatino. Sleep Medicine 21 (2016) 1-11

ALPHA 2 DELTA LIGAND

α2δ ligand suggested doses*.

	Starting dose		Usual effective daily dose
	<65 years	>65 years	
α2δ ligands			
Approved (USA, Japan as of 2015)			
Gabapentin enacarbil	600 mg	300 mg	600–1200 mg
Not approved			
Pregabalin	75 mg	50 mg	150–450 mg
Gabapentin*	300 mg	100 mg	900–2400 mg

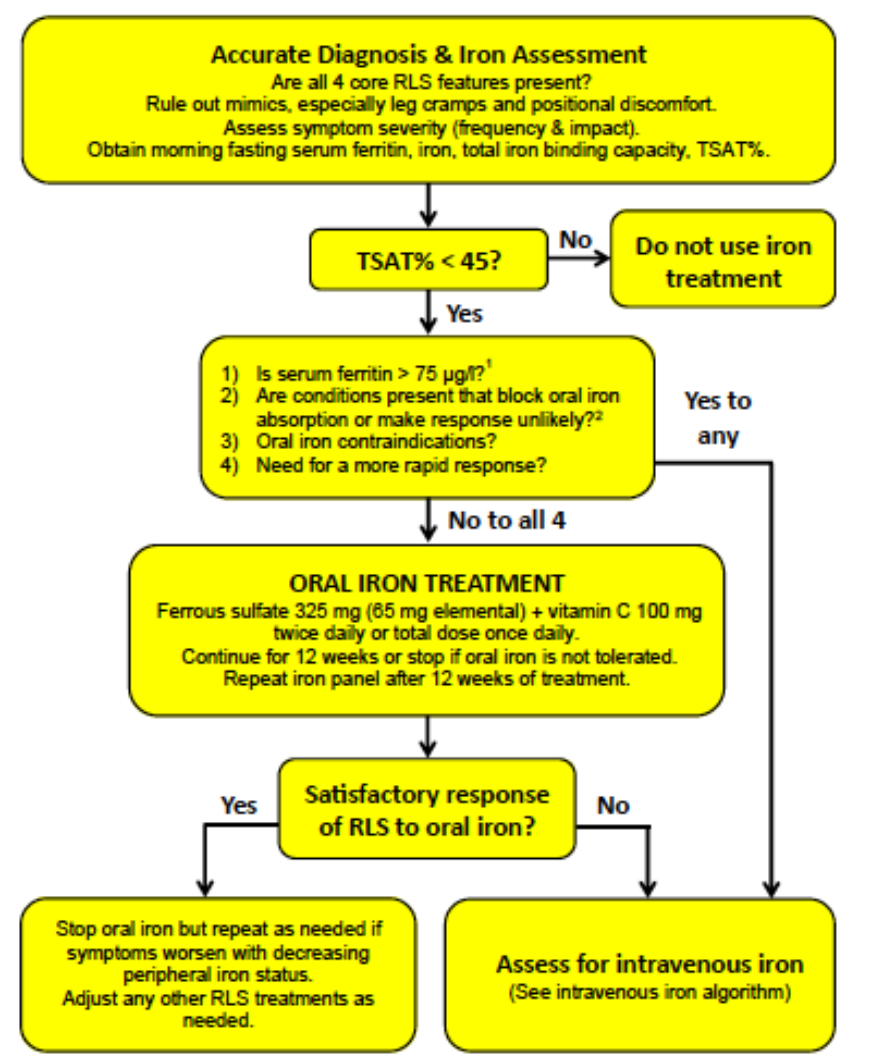
* Long-term studies have not been performed with gabapentin in RLS/WED and

- Recommended as first line by some societies (RLS foundation)
- No Augmentation
- May have effects for comorbid neuropathy
- Sedation effect could be advantageous
- If they have failed in the past assure dose was adequately escalated.
- Expense of gabapentin enacarbil often limits use despite FDA approval.

Garcia-Borreguero Et al. Guidelines for the first-line treatmetn of restless legs syndrome/ Willis-Ekbom disease, prevention and treatment of dopaminergic augmentatino: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundatino. Sleep Medicine 21 (2016) 1-11

Silber MH et al. The management of restless legs syndrome: An updated Algorithm. Mayo Clin Proc. 2021 Jul;96(7): 1921-1937

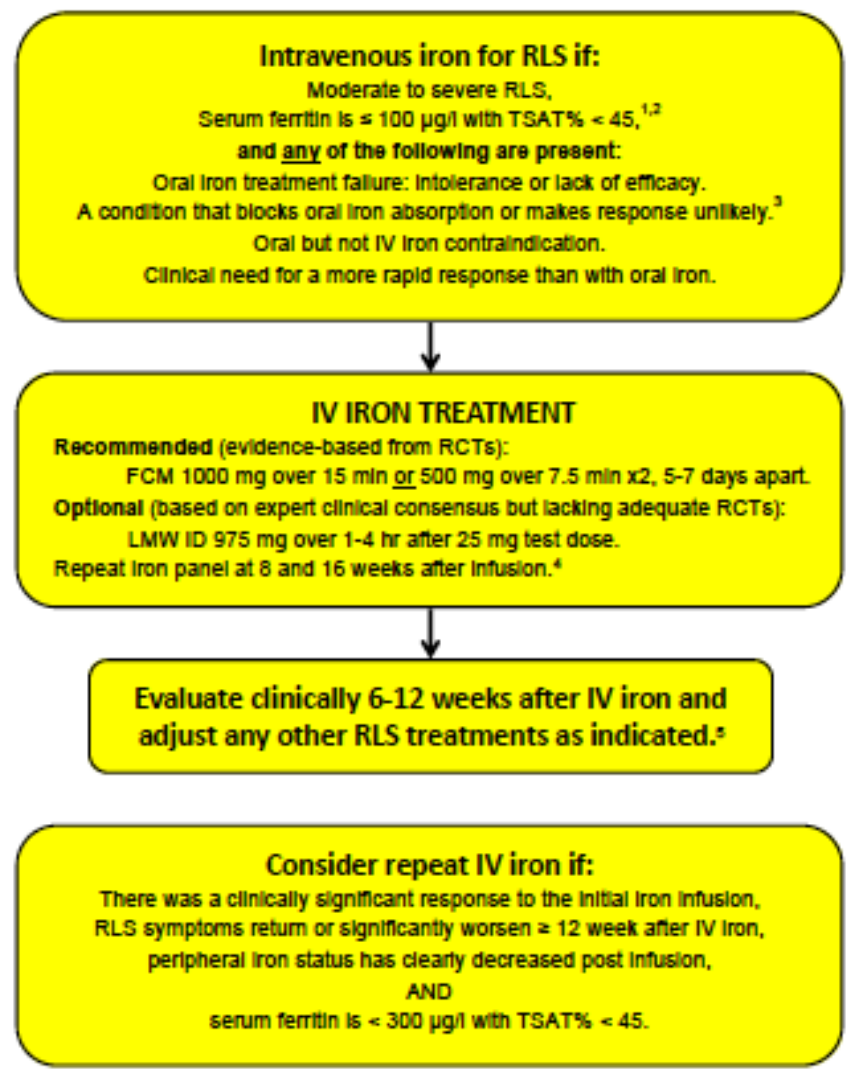
IRON, A LOW HANGING FRUIT



- Replenishing Iron can often improve symptoms or reduce need for other medications
- Checking iron status for a patient with RLS should be standard and iron therapy is an acceptable first line therapy
- No Augmentation Risk
- No risk for oversedation
- Absorbtion of oral preparations diminishes with higher Ferritin levels
- Iron panel, ideally fasting
- Recall Ferritin is an acute phase reactant

Allen RP et al. Evidence-based and consensus clinical practice guidelines for the iron traetmetn of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Medicine 41 (2018) 27-44.

INTRAVENOUS IRON



- Can be considered if ferritin < 300, TSAT % < 45 but data is more limited for higher ferritins
- Effect of therapy is not instantaneous, can take multiple months
- Typically our clinic uses LMW iron dextran given lower cost compared to alternative preparations
- Anaphylaxis risk low
  - Serious adverse reactions about 1:250,000

Allen RP et al. Evidence-based and consensus clinical practice guidelines for the iron traetmetn of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Medicine 41 (2018) 27-44.

OPIOIDS FOR RLS

- Can be quite effective
- Often helpful in patients with severe augmentation from dopamine agonists or refractory cases
- Has been studied long term.
- Tramadol does seem to have some risk for augmentation but less than dopamine agonists.

Table 1 Therapeutic doses of opioids for restless legs syndrome

Drug	Usual daily dose range
Tramadol	50–150 mg, divided q6 h
Oxycodone	2.5–40 mg, divided q4 h
Controlled-release oxycodone	5–80 mg, divided q12 h
Methadone	2.5–20 mg daily

q × *h* every *x* h

Mackie SE, Winkelman JW. Therapeutic Utility of Opiods in Restless Legs Syndrome. Drugs. 2017 Aug;77(12): 1337-1344

SLEEP DISORDERS COVERED

- Insomnia
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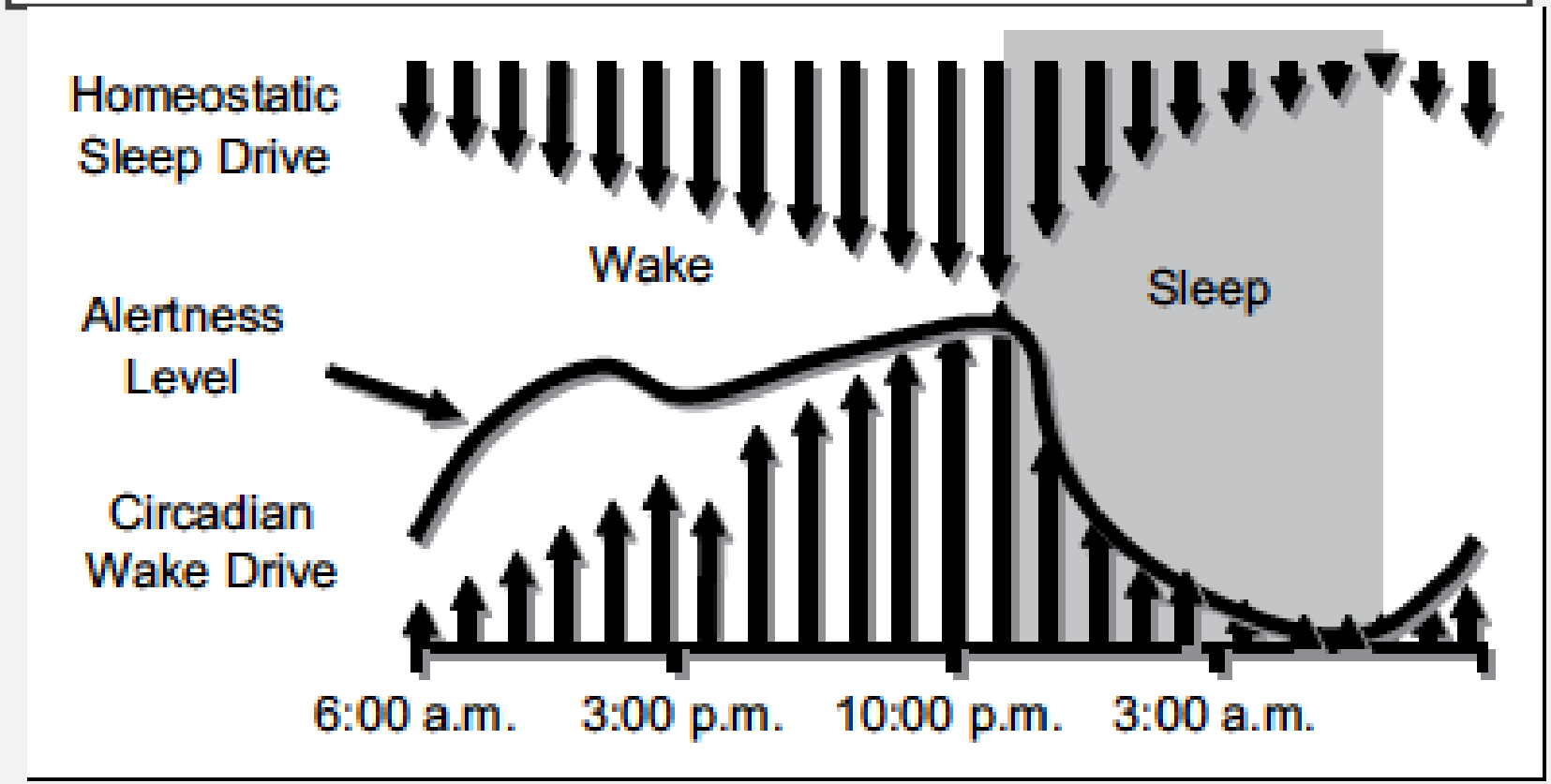
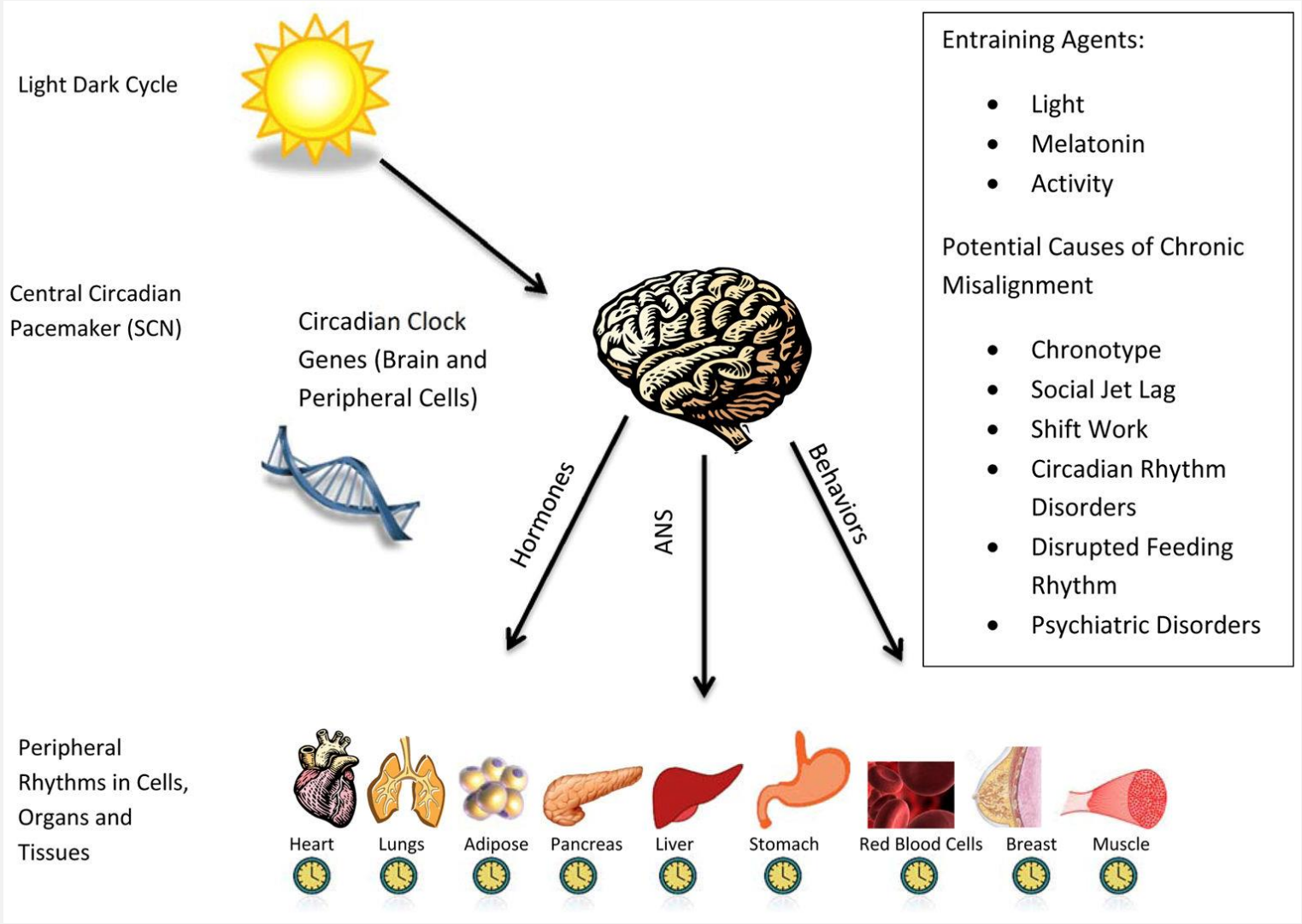
- Circadian rhythm sleep-wake disorders
  - Advanced sleep-wake phase disorder
  - Delayed sleep-wake phase disorder

THE TWO-PROCESS MODEL OF SLEEP REGULATION



Owens et al, J of Attention disorders, 2013

CENTRAL AND PERIPHERAL CIRCADIAN RHYTHM



Baron, In Rev Psychiatry 2014

CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS DEFINITIONS

- General Criteria:
- Chronic or recurrent pattern of sleep-wake rhythm disruption primarily due to alteration of endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the desired or required sleep wake cycle for the individual
- Disruption leads to insomnia and/or excessive sleepiness
- Disturbance causes clinically significant distress or impairment.
- Symptoms for at least 3 months (exception jet lag)
- Sleep log and Actigraphy typically used as supporting evidence

American academy of sleep medicine. Internatinoal classification of sleep disorders, 3rd ed. Darien, IL: American academy of sleep medicine, USA.

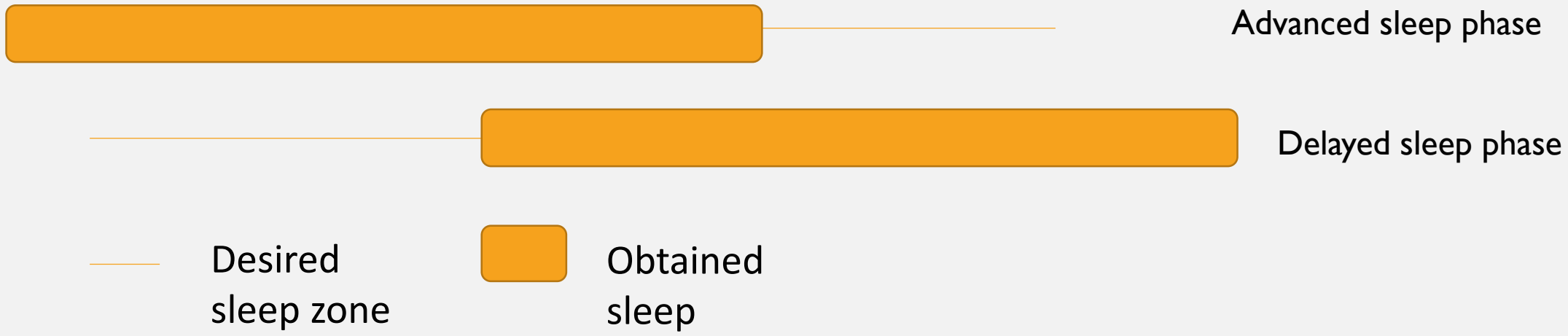
CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS DEFINITIONS

- Delayed Sleep-Wake Phase Disorder
  - Difficulty with onset to sleep and to get up early
- Advanced Sleep-Wake Phase Disorder
  - Difficulty staying awake until bedtime and morning arousal earlier than desired
- Irregular Sleep-Wake Phase Disorder
  - Erratic sleep schedule with no clear pattern
- Non-24-Hour Sleep-Wake Phase Disorder
  - Lack of entrainment with endogenous rhythm with (typically) gradual delay to sleep onset and rise time leading to cyclic insomnia and daytime sleepiness.
- Shift Work Disorder
  - Reduction in total sleep time related to recurrent work schedule that overlaps with usual sleep time
- Jet Lag Disorder
  - Insomnia or daytime sleepiness related to transmeridian plan travel across at least 2 time zone.

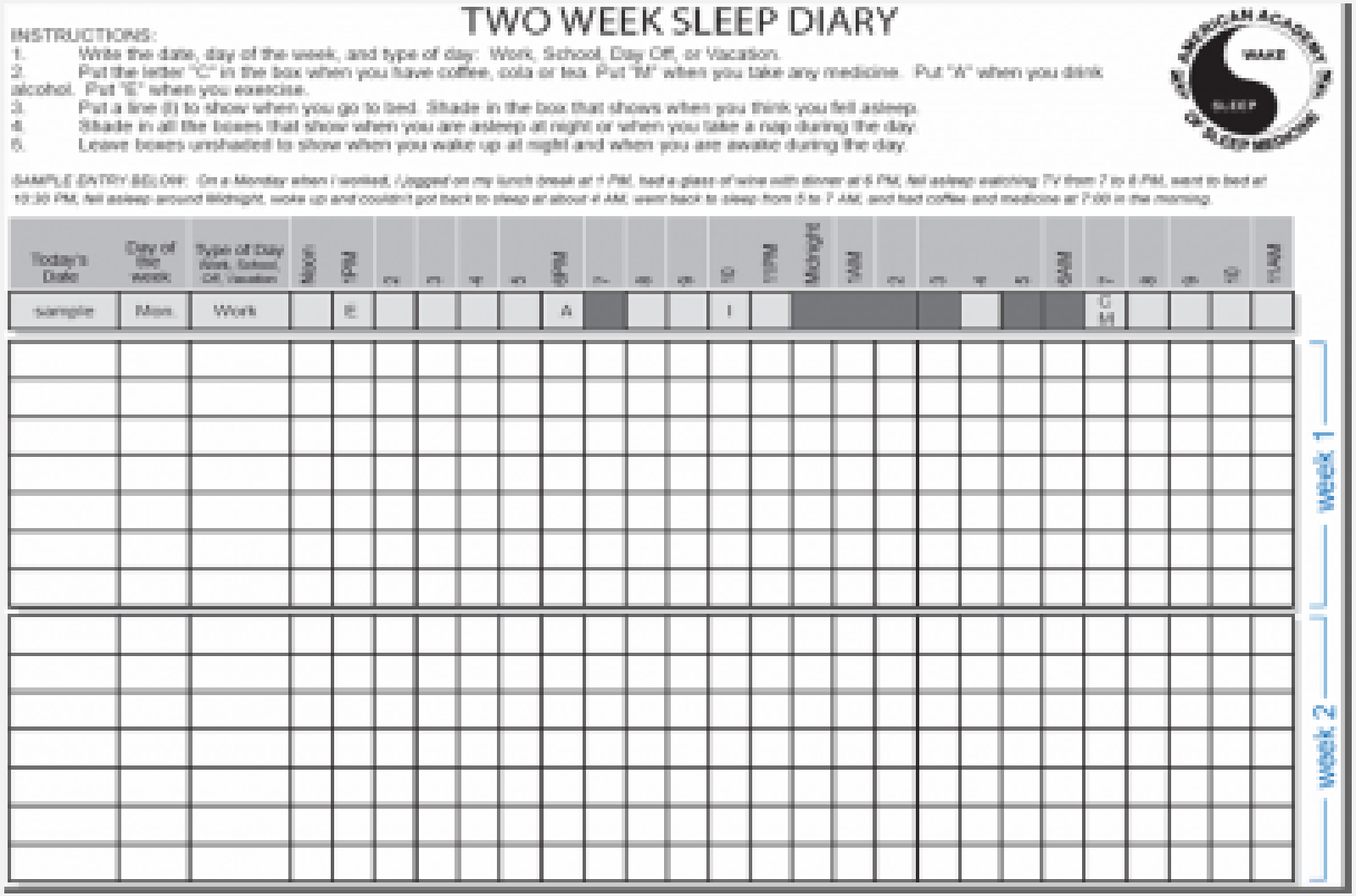
American academy of sleep medicine. Internatinoal classification of sleep disorders, 3rd ed. Darien, IL: American academy of sleep medicine, USA.

CIRCADIAN DISORDER

- Can misalignment explain your "insomnia"
- Work off hour shifts?
- What is their sleep schedule on vacation? On weekends?



SLEEP LOG TO SEE PATTERNS



TWO WEEK SLEEP DIARY

INSTRUCTIONS:

1. Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation.
2. Put the letter "C" in the box when you have coffee, cola or tea. Put "M" when you take any medicine. Put "A" when you drink alcohol. Put "E" when you exercise.
3. Put a line (|) to show when you go to bed. Shade in the box that shows when you think you fell asleep.
4. Shade in all the boxes that show when you are asleep at night or when you take a nap during the day.
5. Leave boxes unshaded to show when you wake up at night and when you are awake during the day.

SAMPLE ENTRY BELOW: On a Monday when I worked, I jogged on my lunch break at 1 PM, had a glass of wine with dinner at 6 PM, fell asleep watching TV from 7 to 8 PM, went to bed at 10:30 PM, fell asleep around Midnight, woke up and couldn't get back to sleep at about 4 AM, went back to sleep from 5 to 7 AM, and had coffee and medicine at 7:00 in the morning.

Today's Date	Day of the week	Type of Day (Work, School, Off, Vacation)	Noon	1PM	2	3	4	5	6PM	7	8	9	10	11PM	Midnight	1AM	2	3	4	5	6AM	7	8	9	10	11AM
sample	Mon.	Work		E					A				I									C M				

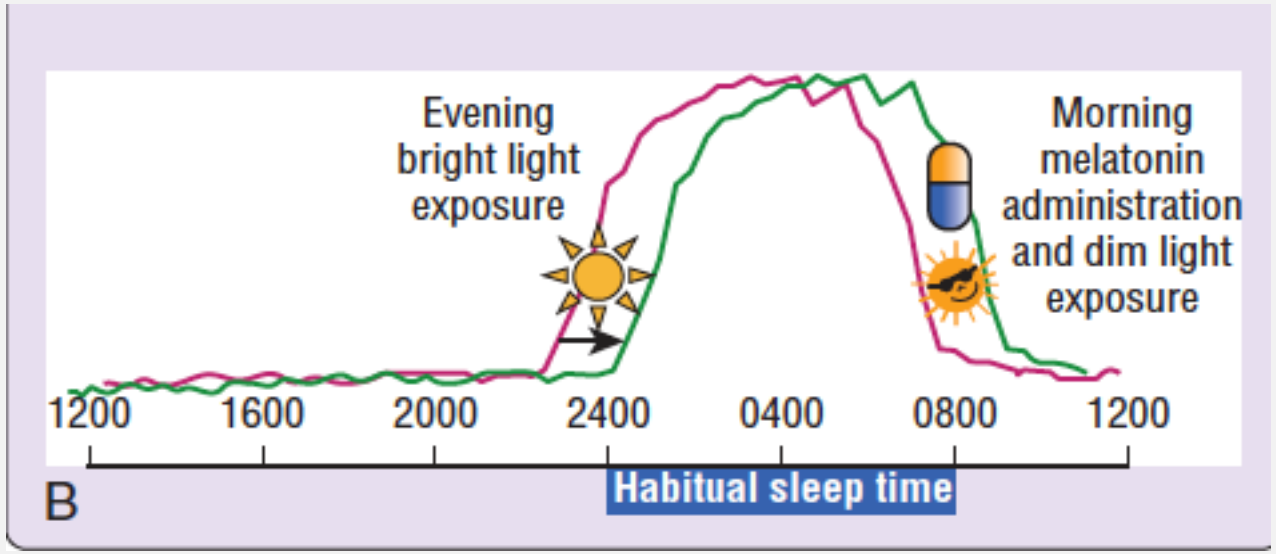
week 1

week 2

https://emedicine.medscape.com/article/1187829-workup#c11

STRATEGIES TO DELAY CIRCADIAN RHYTHM

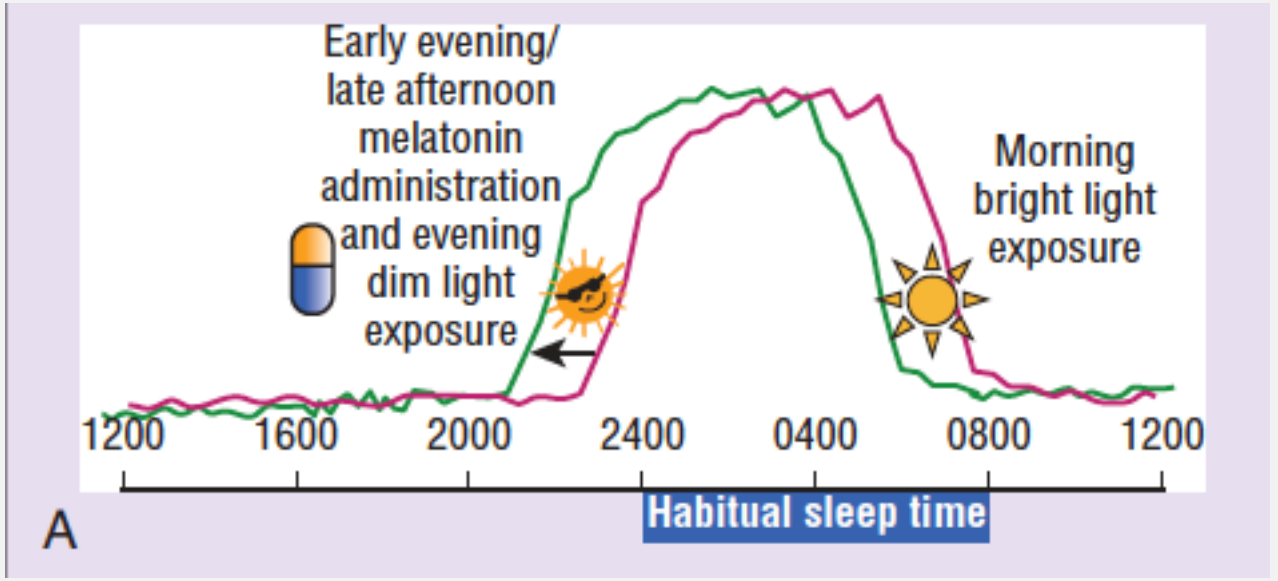
- Applications
  - Treatment for Advanced sleep phase
  - Preparation for a string of night shifts
- Light box 20-30 min 1 hour prior to normal bedtime
- Avoidance of light after wake up earlier than desired
- LOW dose melatonin (1mg max) on arousal.
- Slowly delay bedtime and wake time 15 min every 2-3 days.



Kryger Principles and Practice of Sleep Medicine (Sixth Ed) Chap 75

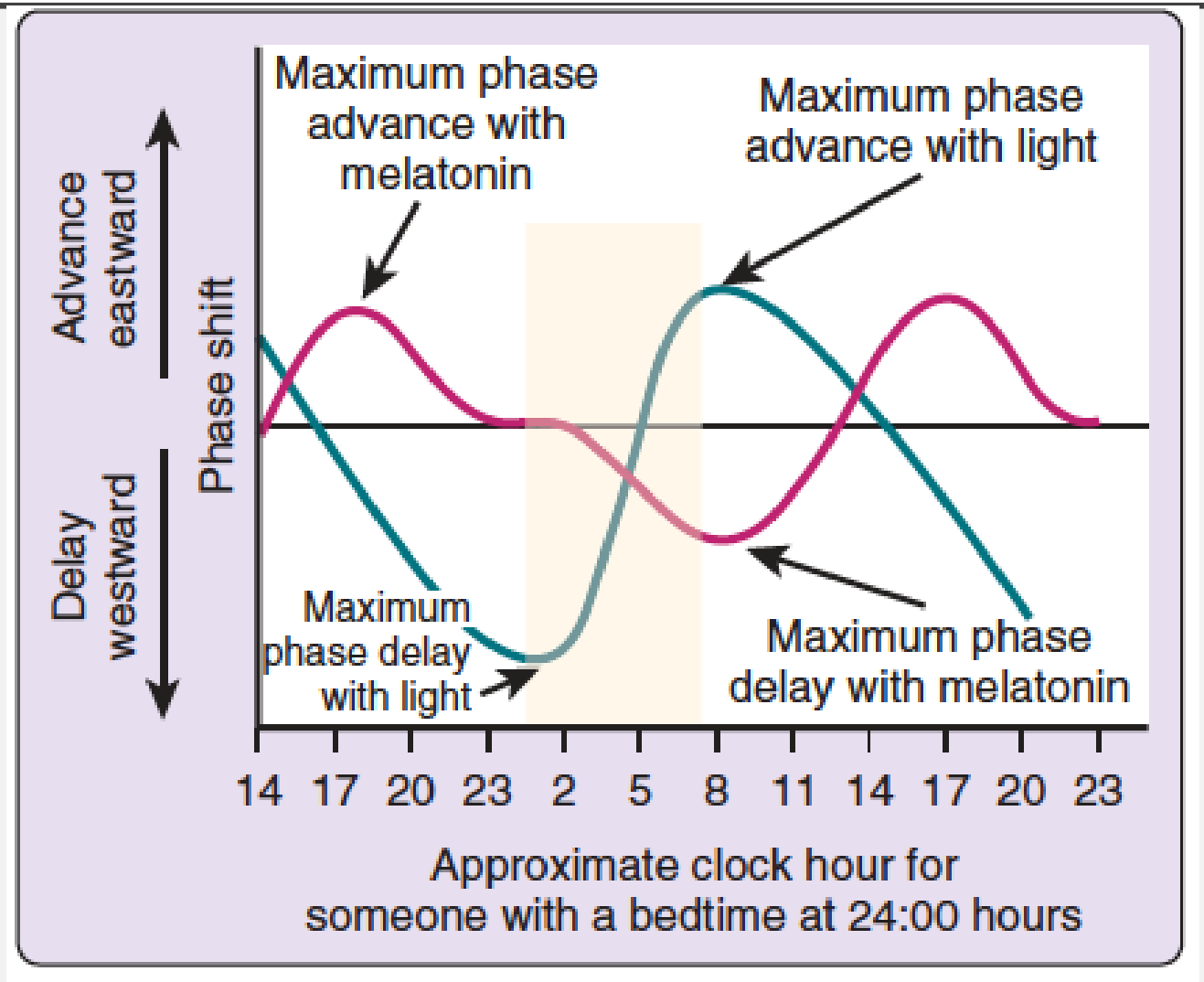
STRATEGIES TO ADVANCE CIRCADIAN RHYTHM

- Applications:
  - Delayed sleep phase
  - Recover from a string of night shifts
- LOW dose melatonin (max 1.5 mg) 3-4 HOURS prior to current bedtime
- Avoidance of strong light in the 2 hours prior to bed
- Lightbox 20-30 min after NATURAL wake time
- Slowly Advance bedtime and wake time by 15 min every 2-3 days.



Kryger Principles and Practice of Sleep Medicine (Sixth Ed) Chap 75

MELATONIN AND LIGHT, TIMING MATTERS



Kryger Principles and Practice of Sleep Medicine (Sixth Ed) Chap 75

COPING FOR A 1X NIGHT SHIFT

- Not feasible to adjust your rhythm
- Pre-shift nap
- Caffeine at start of shift
- Napping during shift if rotation allows
- Sunglasses on way home to increase chance will fall asleep after shift ends
- NO DROWSY DRIVING
- Recovery sleep less than normal sleep zone (4-5 hours)
- Better to have enough sleep debt to sleep on typical schedule following night than to sleep all day and be up all night.
- Realize you are not fully recovered the next day

AASM PRACTICE PARAMETERS FOR SHIFT WORK DISORDER

Indicated

- Planned napping before or during the night shift
- Timed light exposure in the work environment and light restriction in the morning
- Melatonin prior to daytime sleep
- Hypnotic medications may be used to promote daytime sleep
- Modafinil and Caffeine for enhanced alertness during night shift

- Try to maintain similar sleep schedules on work and off days.
  - Avoid complete flips from day to night sleep zones on days off.

Morgenthaler et al. Sleep 2007

CONCLUSIONS

- Prior to labeling a patient as having insomnia analyze sleep times and sleep review of system to identify other potential sleep disorders
- Although medications can be efficacious for chronic insomnia, CBT-I should be considered first link therapy
- Dopamine agonists should be used with caution in RLS given the risk of augmentation.
- Accessing iron status in RLS is recommended
- Circadian misalignment should be screened for in those with sleep disruption
- Appropriately timed light and melatonin can assist in aligning circadian rhythms.

BIBLIOGRAPHY

American academy of sleep medicine. International classification of sleep disorders, 3rd ed. Darien, IL: American academy of sleep medicine, USA.

Allen RP et al. Evidence-based and consensus clinical practice guidelines for the iron traetmetn of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Medicine 41 (2018) 27-44.

Baron KG, Reid KJ. Circadian misalignment and health. Int Rev Psychiatry 2014;26:139-54

Carter SG, Eckert DJ. Effects of hypnotics on obstructive sleep apnea endotypes and severity: Novel Insights onto pathophysiology and treatment. Sleep Med Rev. 2021 Aug;58:101492. doi: 10.1016/j.smrv.2021.101492. Epub 2021 Apr 22.

Chen PL, Lee WJ, Sun WZ, Oyang YJ, Fuh JL. Risk of dementia in patients with insomnia and long-term use of hypnotics: a population-based retrospective cohort study. PLoS One. 2012;7(11):e49113. doi: 10.1371/journal.pone.0049113. Epub 2012 Nov 7.

Edinger JD, Sampson WS. A primary care "friendly"cognitive behavioral insomnia therapy. Sleep. 2003 Mar 15;26(2):177-82. doi: 10.1093/sleep/26.2.177.

Edinger 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 Feb 1;17(2): 55-262. doi: 10.5664/jcsm.8986

Fernando A, Arroll B, Falloon K. A double-blind randomized controlled study of a brief intervention of bedtime restriction for adult patients with primary insomnia. J Prim Health Care. 2013 Mar 1;5(1):5-10.

Garcia-Borreguero Et al. Guidelines for the first-line treatmetn of restless legs syndrome/ Willis-Ekbom disease, prevention and treatment of dopaminergic augmentatino: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundatino. Sleep Medicine 21 (2016) 1-11

Gunn HE, Tutek J, Buysse DJ. Brief Behavioral Treatment of Insomnia. Sleep Med Clin. 2019 Jun;14(2):235-243. doi: 10.1016/j.jsmc.2019.02.003. Epub 2019 Apr 1. PMID: 31029189."

Libman H, Zhou ES, Heckman E, Smetana GW. How would you manage this patien twith chronic insomnia? : Grand rounds discussion from Beth Israel Deaconess Medical Center. Ann Intern Med. 2022 Dec;175(12):1746-1753

Mackie SE, Winkelman JW. Therapeutic Utility of Opiods in Restless Legs Syndrome. Drugs. 2017 Aug;77(12): 1337-1344

MacFarlane J, Morin CM, Montplaisir J. Clin Ther. 2014 Nov 1;36(11):1676-701. doi: 10.1016/j.clinthera.2014.09.017. Epub 2014 Nov 19.

Macnoni M, Borreguero DG, Schormair B, Videnovic A, Berger K, Ferri R, Dauvilliers Y. Restless legs syndrome. Nature Rev Dis Primers. 2021 Nov 3;7(1):80. doi: 10.1038/s41572-021-00311-z

BIBLIOGRAPHY

Morgenthaler TI, Lee-Chiong T, Alessi C, Friedman L, Aurora N, Boehlecke B, Brown T, Chesson Jr AL, Kapur V, Maganti R, Owens, J, Pancer J, Swick TJ, Zak R,. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disordersSleep 2007;30(11): 1445-1459

O'brien CP. Benzodiazepine use, abuse, and dependence. J Clin Psychiatry. 2005;66 Suppl 2:28-33.

Owens J, Gruber R, Brown T, et al. Future research directions in sleep and ADHD: report of a consensus working group. J Atten Disord 2013;17:550-64

Palesh O, Peppone L, Innominato PF, Janelsins M, Jeong M, Sprod L, Savard J, Rotatori M, Kesler S, Telli M, Mustian K. Prevalence, putative mechanisms, and current management of sleep problems during chemotherapy for cancer. Nat Sci Sleep. 2012 Dec 17;4:151-162. doi: 10.2147/NSS.S18895. PMID: 23486503; PMCID: PMC3593248.

Principles and practice of sleep medicine. Sixth ed. Philadelphia, PA, USA: Elsevier; 2017.

Schifano F, Chiappini S, Corkey JM, Guirguis A. An insight into Z-drup abuse and dependence: An examination of reports to the European medicines agency database of suspected adverse drug reactions. Int J Neuropsychopharmacol. 2019 Apr 1;22(4):270-277. doi: 10.1093/ijnp/pyz007

Silber MH et al. The management of restless legs syndrome: An updated Algorithm. Mayo Clin Proc. 2021 Jul;96(7): 1921-1937.

Stallman HM, Kohler M, White J. Medication induced sleepwalking: A systematic review. Sleep Med Rev. 2018 Feb;37:105-113. doi: 10.1016/j.smrv.2017.01.005. Epub 2017 Jan 29.

Sexton CE, Sykara K, Karageorgiou E, Zitser J, Rosa T, Yaffe K, Leng Y. Connections between insomnia and cognitive aging. Neurosci Bull. 2020 Jan;36(1):77-84. doi: 10.1007/s12264-019-00401-9. Epub 2019 Jun 20.

Sweetman A, Lack L, McEvoy RD, Smith S, Eckert DJ, Osman A, Carberry JC, Wallace D, Nguyen PD, Catcheside P. Bi-directional relationships between co-morbid insomnia and sleep apnea (COMISA). Sleep Med Rev. 2021 Dec;60:101519. doi: 10.1016/j.smrv.2021.101519.

Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-analysis. Ann Intern Med. 2015 Aug 4;163(3):191-204. doi: 10.7326/M14-2841. PMID: 26054060

Vermeeren A, Coenen AML. Effects of the use of hypnotics on cognition. Prog Brain Res . 2011;190:89-103. doi: 10.1016/B978-0-444-53817-8.00005-0.

Xiang T, Cai Y, Hong Z, Pan J. Efficacy and safety of Zolpidem in the treatment of insomnia disorder for one month: a meta-analysis of a randomized controlled trial. Sleep Med. 2021 Nov;87:250-256. doi: 10.1016/j.sleep.2021.09.005. Epub 2021 Sep 20. PMID: 34688027."