Psychopharmacologic Treatment of Sleep Disorders

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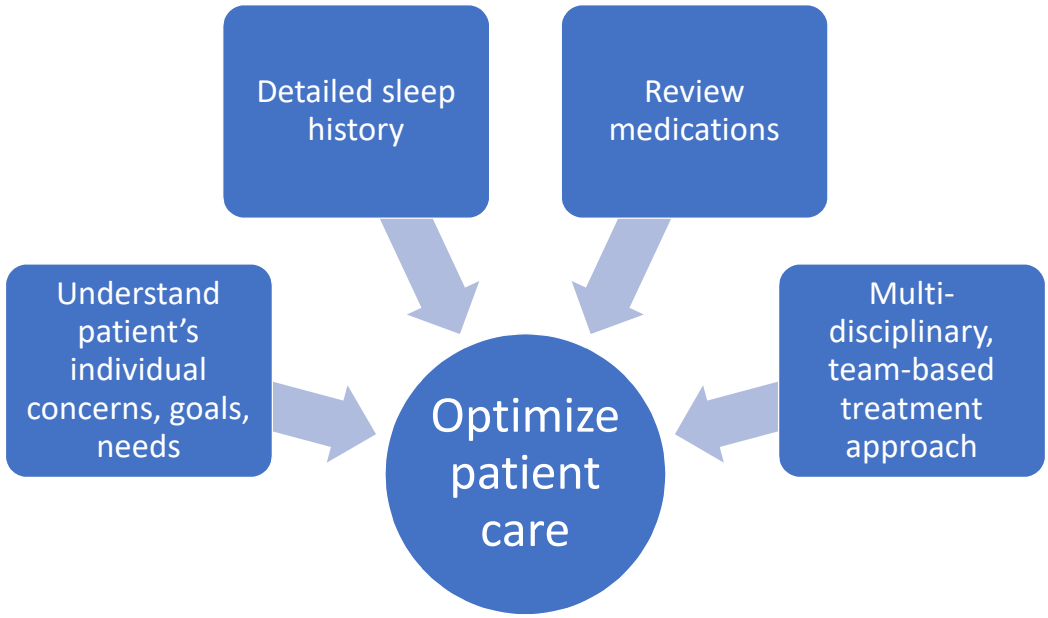
Other	

Learning Objectives:

- Understand how to screen and diagnose sleep disorders commonly comorbid with psychiatric illness
- Review differential diagnosis of sleep disorders
- Differentiate when to use pharmacotherapy versus cognitive behavioral therapy for insomnia management
- Review use of sleep medications in the elderly

Sleep Disorders

Insomnias	Hypersomnias	Parasomnias	Circadian Rhythm Disorders
• Primary insomnia • RLS • Medications • Poor sleep hygiene	• OSA • Narcolepsy • Medications	• Sleep walking/talking • night terrors • sleep eating • REM behavioral disorder	• Delayed Sleep Phase • Advanced Sleep Phase • Shift work sleep disorder



DSM-5 Insomnia disorder

Dissatisfaction with sleep quality or quantity associated with (at least one of):

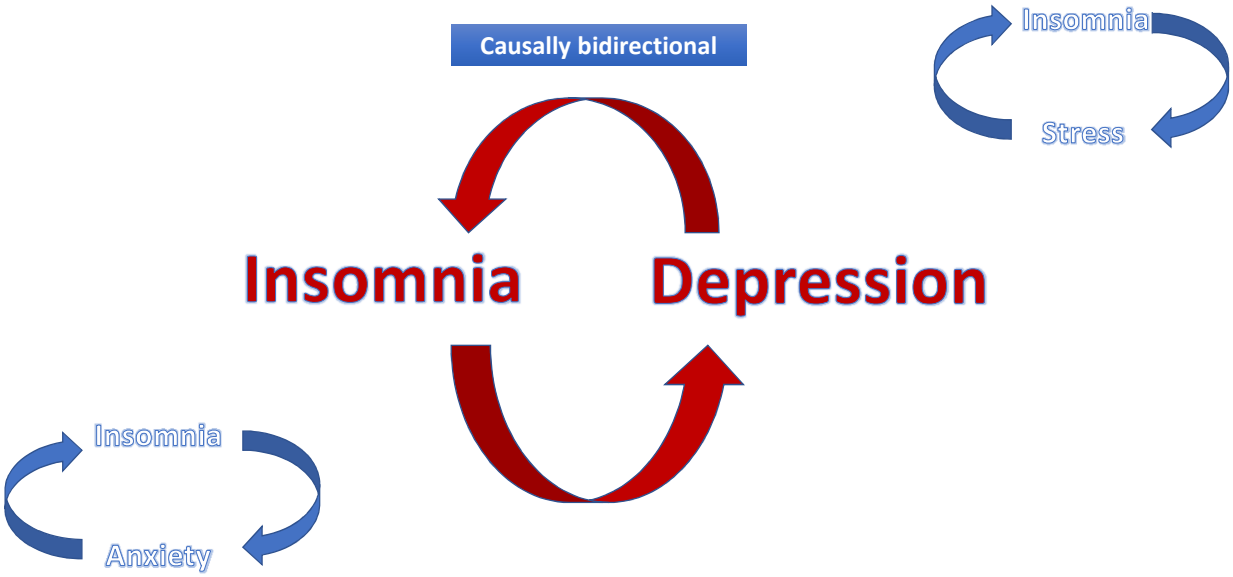
- difficulty initiating sleep
- difficulty maintaining sleep
- early morning awakening

Distress or dysfunction related to sleep disturbance

Minimum of 3x/wk for 3 months

The insomnia does not co-occur with another sleep disorder

The insomnia is not *explained* by coexisting mental disorders or medical conditions



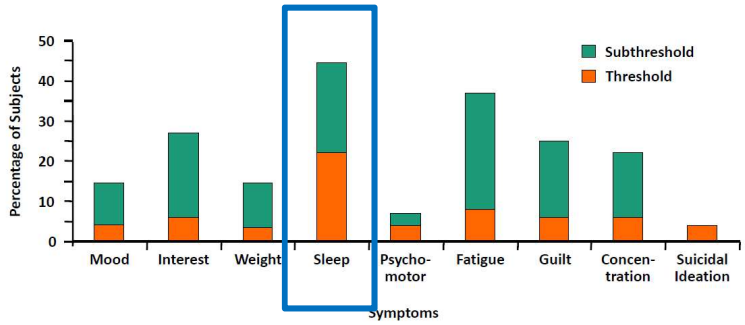
Gebara et al. Depress Anxiety 2018.
Carney et al. Sleep 2017.

Insomnia

- (1) predates the onset of MDD,[1]
- (2) increase the risk of suicide,[2]
- (3) show a suboptimal response to traditional depression treatment,[3]
- (4) remain after successful depression treatment,[4] and
- (5) increase risk for MDD relapse[5]

[1]Baglioni, et al. *EPMA J*. 2011 [2]Woznica AA, et al. *Sleep Med Rev*. 2015 [3]Buysse DJ, et al. *Neurospsychopharmacology*. 1999 [4]Carney CE, et al. Depress Anxiety. 2011 [5]Nierenberg et al. *Psychol Med*. 2010

Sleep disturbance is the most common persistent symptom in treated MDD



25% had treatment-emergent onset of nocturnal awakenings (Nierenberg et al, 2012)

MDD = Major depressive disorder.
Nierenberg AA et al. *J Clin Psychiatry*. 1999.

Courtesy of Dr. John Winkelman

Insomnia is stressful – or is it the stress that leads to insomnia?

Insomnia is not:

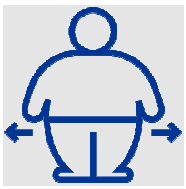
- Sleep deprivation
- Short sleep duration
- Sleep schedule disorder

Diagnosis can be a challenge!

Insomnia ≠ Sleep deprivation

	Insomnia	Sleep Deprivation
Sleep Opportunity	Adequate	↓
Sleep Ability	↓	Adequate

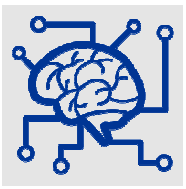
Insomnia is associated with increased risk of…



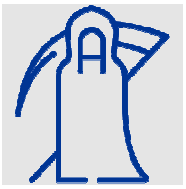
Obesity[1-2]

Hypertention[3-5]

Falls[6-11]



Cognitive decline[12-15]



Mortality?[16,17]

[1]Patel SR, et al. *Int J Obesity*. 2008 [2]Fogelholm M, et al. *Int J Obesity*. 2007 [3]Fung MM, et al. *Hypertension*. 2011 [4]Lofaso F, et al. Chest. 1996 [5]Redline S, et al. *Sleep*. 2005 [6]Avidan AY, et al. *J Am Geriatr Soc*. 2005 [7]Brassington GS, et al. J Am Geriatr Soc. 2000 [8]Latimer Hill E, et al. *J Gerontol A Biol Sci Med Sci*. 2007. [9]Stone KL, et al. Arch Internal Med. 2008 [10]Stone KL, et al. J Am Geriatr Soc. 2014 [11]Stone KL, et al. *J Am Geriatr Soc*. 2006 [12]Blackwell T, et al. Sleep. 2011 [13]Blackwell T, et al. *J Gerontol A Biol Sci Med Sci*. 2006 [14]Blackwell T, et al. *Sleep*. 2014 [15]Diem SJ, et al. *Am J Geriatric Psychiatry*. 2016 [16]Vgontzas A, MD, et al. *Sleep*. 2010. [17] Parthasarathy S, et al. *Am J Med*. 2015

Adapted from Daniel Buysse

Diagnosing Insomnia: Sleep History

Sleep routine

- time to bed, lights out, sleep latency, number and duration of awakenings, wake time, time out of bed, total sleep time, perceived quality of sleep

Potential daytime causes of sleep disturbance

- Naps, exercise, stressors, use of caffeine or alcohol

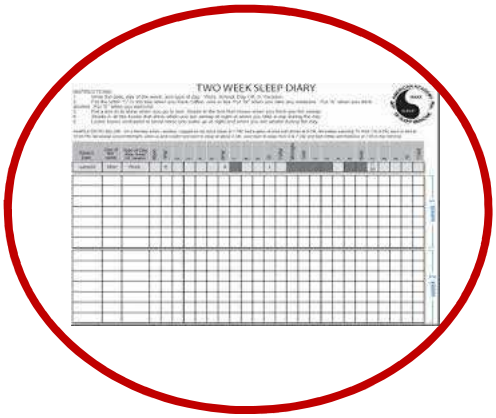
Non-sleep activities in bed

Sleep environment

- pets, bed partners, noise, light, temperature

Symptoms of *other* sleep disorders

- OSA (snoring, waking up gasping)
- RLS (urge to move legs)
- Circadian Rhythm Disorders (unusual sleep timing)



Diagnosing insomnia

Indications for Polysomnography:

Suspicion of sleep apnea (loud snoring *PLUS one of the following):*

- daytime sleepiness
- witnessed apneas
- refractory hypertension

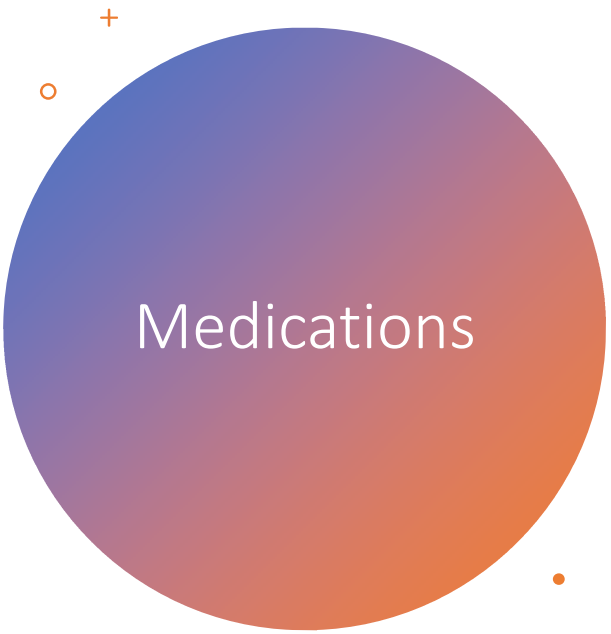
Abnormal behaviors or movements during sleep

Unexplained excessive daytime sleepiness

Refractory sleep complaints, particularly repetitive brief awakenings

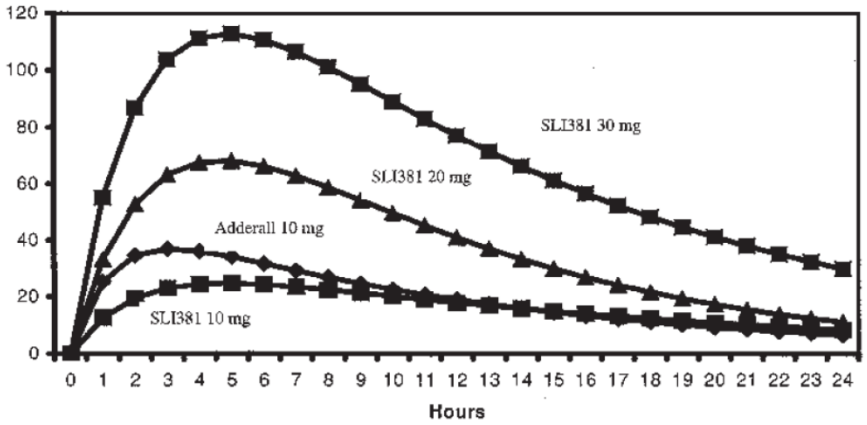
Differential Diagnosis

- Medications
- OSA
  - Up to 50% of patients with OSA c/o insomnia (COMISA)
- Restless leg syndrome
- Poor sleep hygiene
  - Alcohol use in evening
  - Afternoon naps
- Circadian Rhythm Disorders
  - **Delayed sleep phase** – difficulty falling asleep
  - Advanced sleep phase – waking too early
  - Shift work disorder



- Stimulants
  - Amphetamines – timing, dose
- Antidepressants
  - Wellbutrin
- Steroids, bronchodilators
- Decongestants (pseudoephedrine)
- Beta-blockers
  - More lipophilic – cross blood brain barrier
  - May impair melatonin synthesis

Stimulant Pharmacokinetics are not kind to sleep!



Courtesy of John Winkelman

Differential Diagnosis

- **Medications**
- **OSA**
  - Up to 50% of patients with OSA c/o insomnia (COMISA)
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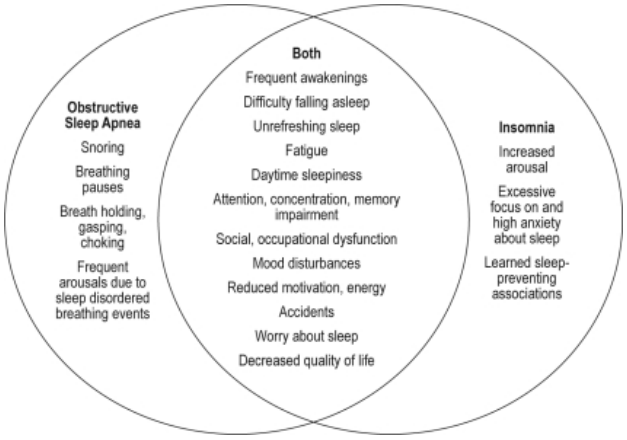
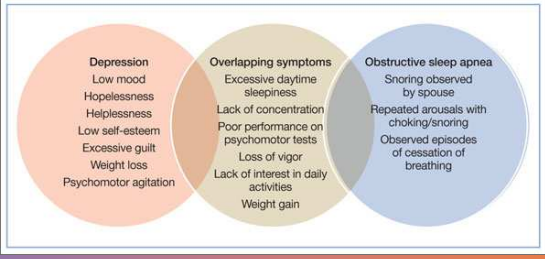
Comorbid Insomnia and OSA (COMISA)



Luyster et al. *JCSM* 2010

Figure

OSA and depression: Where is the common ground?

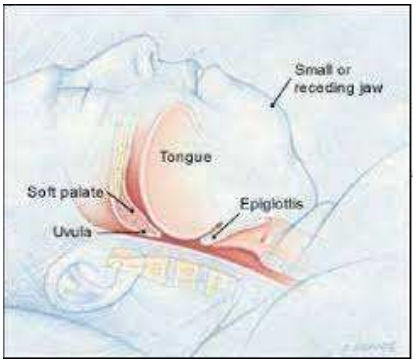


- Common but underdiagnosed[1]
- Presentation often atypical[1]
- Significant overlap with depression and anxiety[2]
- Increased cognitive decline with comorbid OSA[2]
- CPAP use independently improves depressive symptoms[3]
- CPAP use improves quality of life

[1]Vanek et al. *Sleep Med*. 2020 [2]Lin and Winkelman *Cur Psych Rep*. 2012 [3]El-Sherbini et al. *Neuropsychiatr Dis Treat*. 2011.

Risk factors:

- Male sex
- Menopause
- ↑ age
- Obesity
- Craniofacial abnormalities
- Neck circumference (≥17 men, ≥16 women)
- Enlarged upper airway tissues



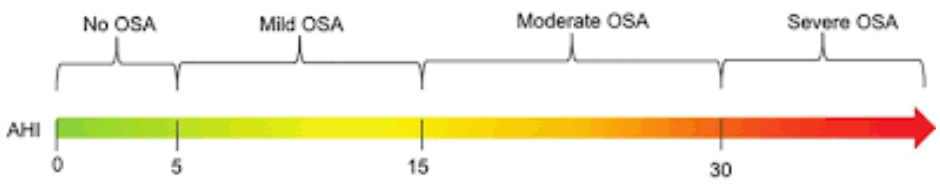
Symptoms

Snoring
Excessive daytime sleepiness
Waking up choking/gasping
Witnessed Apneas
Nocturia
Morning headache

Diagnosis

- Home sleep test – more cost-effective — 80% sensitivity
- Polysomnogram – gold standard

AHI: # of apneas/hypopneas per hour



AHI: apnea/hypopnea index
OSA: obstructive sleep apnea

Treatment

Other causes of excessive sleepiness:

- Medications!!!
  - Sedating anti-depressants
  - Gabapentin
  - Chronic pain management

- Central hypersomnia disorders
  - Narcolepsy
  - Idiopathic hypersomnia
  - Post-concussive

Narcolepsy with or without cataplexy

Fragmented nocturnal sleep – frequent and often brief awakenings

Sleep paralysis

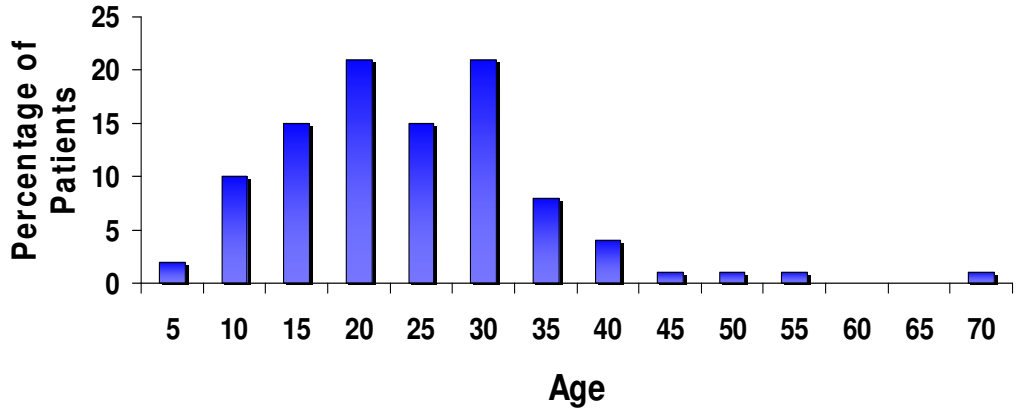
Hallucinations

- Hypnogogic – at sleep onset
- Hypnopompic – at wake onset

+/- Cataplexy – muscle weakness triggered by emotions

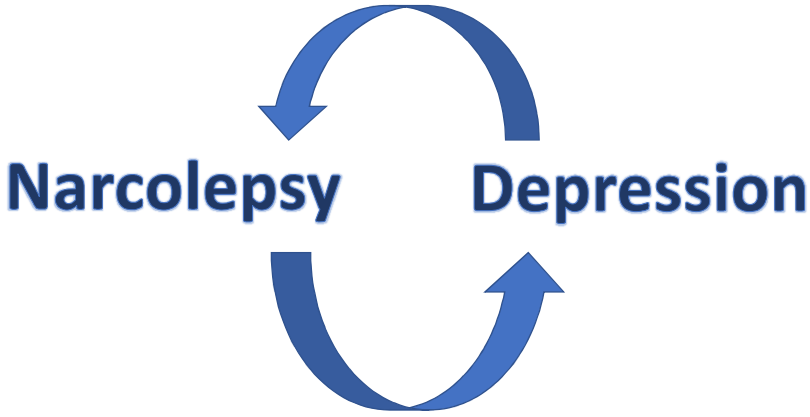
- May affect any voluntary muscle
- Consciousness maintained at the start

Symptom onset



Ohayon MM et al. *J Psychosomatic Res*. 2005

Bidirectional with mood disorders



Antidepressants mask some symptoms and can delay diagnosis!

Differential Diagnosis

- Medications
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- Restless leg syndrome
- Poor sleep hygiene
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- Circadian Rhythm Disorders
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Single question to diagnose RLS:

"When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?"

- 100% sensitivity
- 96.8% specificity

Secondary RLS

- **iron deficiency anemia**
- **pregnancy**
- **end-stage renal disease**
- vitamin B12/folate deficiency
- peripheral neuropathy (associated with diabetes mellitus)
- Parkinson's disease

RLS Management

- Treat iron-deficiency (goal ferritin>50 or 75)
- Avoid alcohol, caffeine, or nicotine
- Avoid SSRIs, dopamine antagonists, antihistamines, many anti-depressants
- Hot or cold baths
- Stretching/massaging affected area

Medication	Dosage range	Time to full effect of the therapeutic dose	Half-life	Adverse effects
First-line treatment: dopaminergic agents				
Ropinirole	0.25–4.0 mg	4–10 days	6 hours	Augmentation, impulse control disorder, nausea, low blood pressure, dizziness, headache, nasal congestion, sleepiness in susceptible patients
Pramipexole	0.125–0.75 mg	at first dose	8–12 hours	Augmentation, impulse control disorder, nausea, low blood pressure, dizziness, headache, nasal congestion, sleepiness in susceptible patients
Rotigotine	1–3 mg/24 hours	1 week	5–7 hours	Skin irritation, low risk of augmentation, nausea, low blood pressure, dizziness, headache, nasal congestion, sleepiness in susceptible patients
Pregabalin	2–300 mg	3–6 days	10 hours	Sleepiness, dizziness, headache, fluid retention
Gabapentin	300–2400 mg	3–6 days	5–7 hours	Sleepiness, dizziness, fluid retention

Augmentation

Paradoxical response to treatment

Symptoms worsen with increasing dose of medication

All dopaminergic drugs

Rates are lower using drugs with a longer half-life and the lowest effective dose

RLS summary:

Clinical diagnosis

Treat low iron with goal ferritin>50

Avoid triggers (meds, EtOH)

Treat with minimum effective dose of medication, ideally longer half life or gabapentin

Monitor for augmentation!

Differential Diagnosis

Medications

OSA

- Up to 50% of patients with OSA c/o insomnia (COMISA)

Restless leg syndrome

Poor sleep hygiene

- Alcohol use in evening
- Afternoon naps

Circadian Rhythm Disorders

- **Delayed sleep phase** – difficulty falling asleep
- Advanced sleep phase – waking too early
- Shift work disorder

Delayed Sleep Phase Syndrome

- "Night owl" circadian preference
- Delayed bed and wake times

  compared to conventional times → chronic sleep insufficiency and/or daytime impairment
- More common in adolescents
- Treat with melatonin, light therapy, and behavioral modification

Insomnia Treatment:

- Under-recognized and undertreated:
  - ~2/3 insomniacs unaware of treatment options
  - 40% self-medicate with alcohol and over the counter meds

Ancoli-Israel S et al. *Sleep.* 1999

1. Primary Goals:
   - Improvement in sleep quality and/or time.
   - Improvement of insomnia-related daytime impairments such as improvement of energy, attention or memory difficulties, cognitive dysfunction, fatigue, or somatic symptoms.
2. Other Goals:
   - Improvement in an insomnia symptom (SOL, WASO, # awakenings) such as:
     - SOL <30 minutes and/or
     - WASO <30 minutes and/or
     - Decreased frequency of awakenings or other sleep complaints
     - TST >6 hours and/or sleep efficiency >80% to 85%.
   - Formation of a positive and clear association between the bed and sleeping
   - Improvement in sleep related psychological distress

Schute-Rodin et al. *JCSM* 2008

Benzodiazepine Receptor Agonists commonly used as hypnotics:

Agent (brand name)	Dose range	Half-life
Clonazepam (Klonopin)	0.25 -1.0 mg	40 hr
Temazepam (Restoril)*	7.5-30 mg	4-18 hr
Lorazepam (Ativan)	0.5-2.0 mg	10-20 hr
Oxazepam (Serax)	10-30 mg	5-10 hr
Eszopiclone (Lunesta)*	1-3 mg	5.5-8 hr
Triazolam (Halcion)*	0.125-0.25 mg	2-3 hr
Zolpidem (Ambien)*	3.75-12.5 mg	2-3 hr (CR extends duration of action)
Zaleplon (Sonata)*	5-10 mg	1-2 hr

*FDA approved for insomnia.

Are Hypnotic Medications Dangerous?

- Commonly prescribed for insomnia but generally not approved for long term use (eszopiclone)
- Associated with excess mortality[1-3] and dementia[4]?
- As
- De
- Pc

"Substance use disorders occur when their recurrent use causes clinically and functionally significant impairment, such as health problems, disability, and failure to meet major responsibilities at work, school, or home."- DSM 5

2

[1]Weich S et al. *BMJ* 2014 [2]Kripke DF et al. *Biol Psychiatry*. 1998;43:687–693
[3]Kripke DF et al. *BMJ Open*. 2012;2(1) [4]Billiotti de Gage et al. *BMJ* 2014

Epidemiology of Misuse

3rd most commonly misused substance (illicit or prescription)

Factors associated with misuse:

- 3.5 to 24 times higher risk among those with h/o substance use disorders
- History of psychiatric symptoms or disorder
- Exposure to a prescription

Common reasons for misuse:

- Coping mechanism
- Self-treatment
- Recreational motivation

Misuse associated with:

- Mortality
- Emergency room visits

Votaw VR et al. *Drug Alcohol Depend*. 2019

Non-Z drug hypnotics approved for insomnia treatment:

Drug	Tradename	Onset of Action	½ life (h)	Dose
Zaleplon	Sonata	10-20 min	1.0	5-20mg
Eszopiclone	Lunesta	45-60 min	5-9	2-3 mg (1mg)
Zolpidem	Ambien	10-20 min	1.5-2.4	5-10mg
Zolpidem ER	Ambien CR	Biphasic (10-20 min, 3 hr)	3	6.25-12.5 mg

Drug	Tradename	½ life (h)	Dose (mg)	Approval
Orexin-antagonists				
Daridorexant	Quviviq	8	25-50 mg	Approved
Suvorexant	Belsomra	12	5-20 mg	Approved
Lemborexant	Dayvigo	17	5-10 mg	Approved
Sedating anti-depressants				
Doxepin	Silenor	15	3-6	Approved
Trazodone	Desyrel	5-9	50-100	Off-label
Amitriptyline	Elavil	13-36		Off-label
Mirtazapine	Remeron	20-40 (30)	7.5-30	
Quetiapine	Seroquel	6	20-50	Off-label
Anticonvulsants				
Gabapentin	Neurontin	5-9	100-900	Off-label
Pregabalin	Lyrica	6	50-300	Off-label
Melatonin agonists				
Melatonin		0.6-1	0.5-3 (up to 10)	No FDA approval
Ramelteon	Rozerem	1-2.6	8	Approved

Cognitive Behavorial Therapy for Insomnia (CBT-I)

Initial recommended treatment approach (along with sleep hygiene counseling)

Incorporates various techniques:

- Stimulus control therapy – remove factors that condition the mind to resist sleep
- Paradoxical intention
- Sleep restriction
- Sleep Hygiene
- Relaxation training

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

CBT-I vs Medications

CBT-I:

+ Addresses underlying causes of insomnia
+ More efficacious than meds long term[1, 2]
+ No side effects or dependence
- More time and effort

Medications:

- Treats symptoms, not underlying problem
+ More immediate relief during a period of high stress or grief
- Side effects/dependence
- Tolerance

[1]Ritterband LM et al. *Arch Gen Psychiatry*. 2009;66:692-698
[2]Mitchell, M et al. BMC Fam Pract. 2012; 13: 40

CBT vs Medications

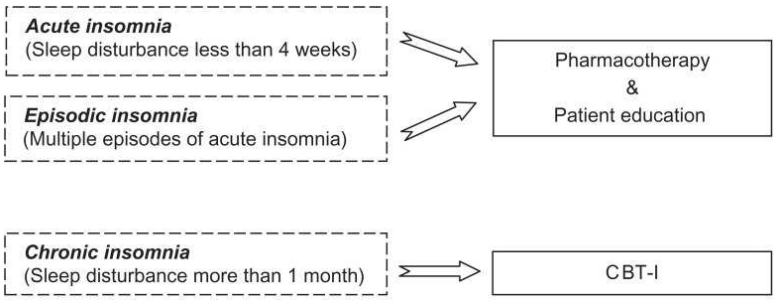
- 5 RCTs comparing CBT-I or pharmacotherapy directly comparing short and long-term benefits
- All show equal or better effects for CBT-I at post-treatment but consistently show significantly greater effects for CBT-I at long-term follow-up

Study:	CBT vs	N, mean age	Follow-up
McClusky et al. *Am J Psychiatry* 1991	TZ	30, 32	9 weeks
Morin et al. *JAMA* 1999	TM vs PL	78, 65	2 years
Jacobs et al. *Arch Intern Med* 2004	ZP vs PL	63, 47	1 year
Sivertsen et al. *JAMA* 2006	ZP vs PL	46, 62	6 months
Wu et al. *Psychother Psychosom*. 2006	TM vs PL	71, 38	8 months

TZ = triazolam
ZP= zoplicone
PL = placebo

Management:

A proposed model for insomnia clinical pathway in primary care:



**For chronic insomnia (at least 1-3 months duration) never wrong to refer to sleep clinic!!

Mack LJ et al. *Nat Sci Sleep*. 2011;3:87-99

2017 AASM Guidelines

Short-term pharmacotherapy with short to intermediate acting agents to supplement CBT

No over the counter sleep aids INCLUDING herbal and nutrition substances (ie MELATONIN, valerian, anti-histamines)

Review side effects, tolerance, rebound insomnia, and employ minimum effective dose and taper/discontinuation facilitated by CBTi

Schutte-Rodin et al. *JCSM*. 2017;13 (2):307-349

Medication use in Elderly

- Start low and go slow
- Evaluate falls risk
- Counsel on side effects, dependence, and addictive potential

Systemic reviews of efficacy and safety of non-hypnotics in patients > 65 years

Suvorexant (Belsomra)	Doxepin (Silenor)	Ramelteon
• improved sleep maintenance[1-2] • very mild SE profile[1-2] but some residual sedation reported[2]	• sustained improvement in sleep[1] • SE profile comparable to placebo[1] • 3-6 mg ideal, 10 mg capsule substitute for insurance	• Improved sleep latency[1-2] • Increased total sleep time[2] • Minimal SE[1-2]

[1]Sys J et al. *Eur J Clin Pharmacol*. 2020
[2]Schroek et al. *Clin Ther.* 2016

BzRA Risks in Elderly:

- Motor vehicle collisions –long $T_{1/2}$
- Hip Fractures - $T_{1/2}$ dependent
- Anterograde Amnesia
- Rebound Insomnia
  - Recommend very slow taper

Hemmelgarn B et al. *JAMA*. 1997;278:27-31. Cumming RG, Le Couteur DG. *CNS Drugs*. 2003;17:825-837. Woods JH, Winger G. *Psychopharmacology*. 1995;118:107-115. Krystal AD et al. *Sleep*. 2003;26:793-799.

Other options:

Mirtazapine (Remeron)	Gabapentin	No clear benefit in the literature from:
• Comorbid depression • Appetite induction	• Comorbid RLS • Comorbid neuropathic pain	• Melatonin - unregulated • Valerian – unregulated • Diphenhydramine – should be avoided

Summary of sleep disorders:

OSA

- HST usually sufficient
- Contributes to insomnia and depression
- CPAP first line but consider other options, esp for mild OSA

Delayed Sleep Phase

- Often misdiagnosed as insomnia
- Sleep diary to diagnose
- Behavioral modification key

RLS summary:

Clinical diagnosis

Treat low iron with goal ferritin>50

Avoid triggers

(meds, EtOH)

Treat with minimum effective dose of medication, ideally longer half life or gabapentin

Monitor for augmentation!

Summary of Insomnia:

Evaluation

- Detailed sleep history with possible triggers
- Rule out other sleep disorders
  - COMISA
  - RLS
  - Delayed Sleep Phase
- Comorbid mood disorders
- Medications!!!

Treatment

- Acute
  - Sleep hygiene counseling
  - Pharmacotherapy (< 30 days, short half-life preferred)
- Chronic (> 1 to 3 months)
  - CBTi +/- medications particularly to break the cycle