UW PACC

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

SLEEP DISORDERS AND MEDICATIONS

SEETA PATEL, MD

UW INTEGRATED CARE FELLOW

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

GENERAL DISCLOSURES

The University of Washington School of Medicine also gratefully acknowledges receipt of educational grant support for this activity from the Washington State Legislature through the Safety-Net Hospital Assessment, working to expand access to psychiatric services throughout Washington State.

SPEAKER DISCLOSURES

✓ NO CONFLICTS OF INTEREST

UW PACC

OBJECTIVES

1. Sleep disorders: definitions
2. Hypnotics and pharmacologic management
3. Cannabis and sleep

UW PACC

SLEEP DISORDERS:

- Primary
- Comorbid – due to a general medical condition, related to a psychiatric disorder, secondary to substance abuse

UW PACC

SLEEP-WAKE DISORDERS:

- Primary insomnia
- Breathing-related disorders (eg. obstructive sleep apnea)
- Narcolepsy
- Parasomnias
- Circadian rhythm sleep-wake disorders

UW PACC

EPWORTH SLEEPINESS SCALE

Chart 1. Epworth Sleepiness Scale.

Likelihood to fall asleep in the following situation
1. Sitting and Reading .....
2. Watching TV .....
3. Sitting, inactive in a public place ..... (e.g., waiting room, a theater or a meeting)
4. As a passenger in a car for an hour without a break .....
5. Lying down to rest in the afternoon when circumstances permit .....
6. Sitting and talking to someone .....
7. Sitting quietly after lunch without alcohol .....
8. In a car, while stopped for a few minutes in traffic .....
0- would never doze off
1- slight chance of dozing off
2- moderate chance of dozing off
3- high chance of dozing off

UW PACC

PRIMARY INSOMNIA DISORDER:

- Dissatisfaction with sleep quantity or quality, associated with one or more of the following:
  - 1) Difficulty initiating sleep
  - 2) Difficulty maintaining sleep
  - 3) Early morning awakening
- Significant distress or impairment

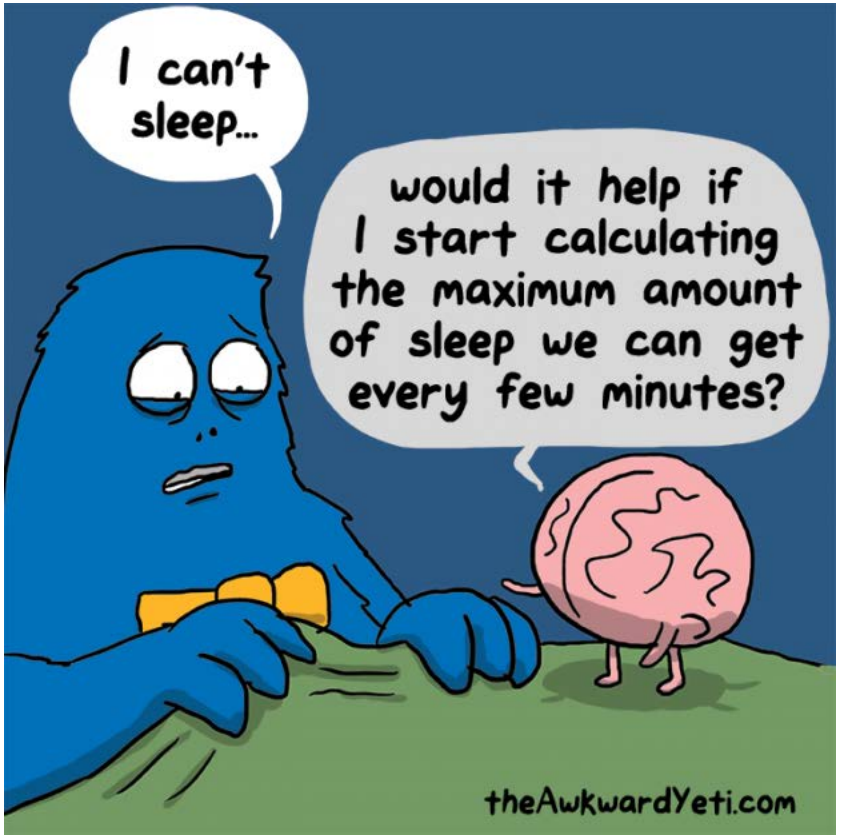
UW PACC

INSOMNIA DISORDER:

- Occurring at least 3 nights/week, for at least 3 months
- Occurs despite adequate opportunity for sleep
- Exclusions
  - 1) Does not occur during the course of another sleep-wake disorder
  - 2) Not due to a substance
  - 2) Coexisting psychiatric disorders and medical conditions do not explain the insomnia

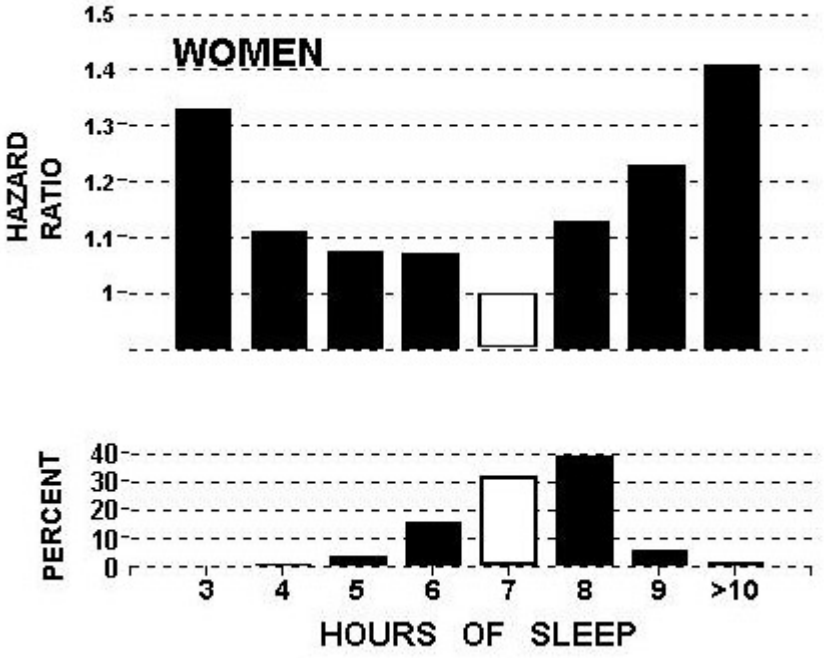
MISCONCEPTIONS: DURATION OF SLEEP

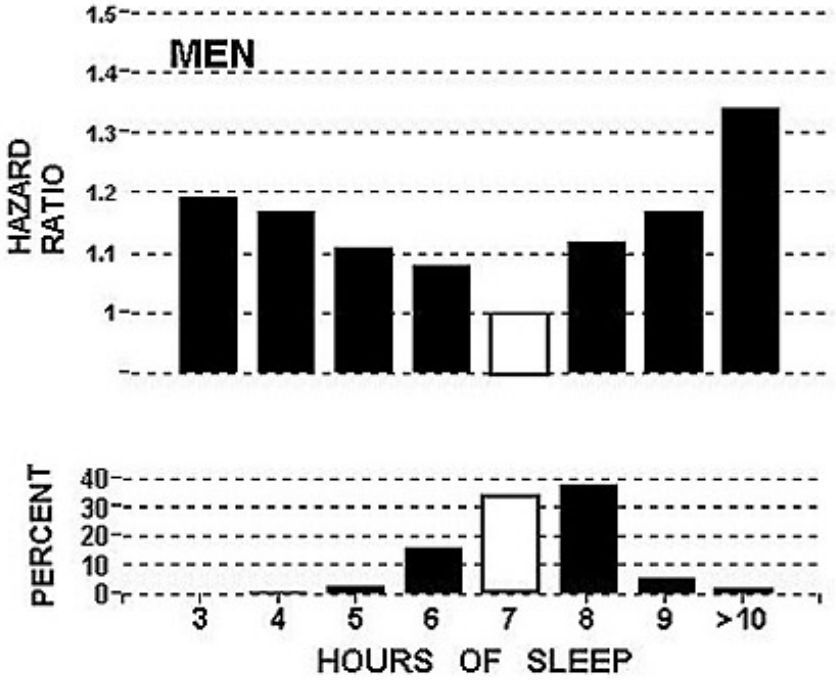
- Lowest mortality hazard was experienced by participants reporting usual sleep of 7 hours (6.5-7.4)
- Participants sleeping 8 hours or more, or 6 hours or less, experienced significantly increased mortality hazard



Kripke et al., *Arch. Gen. Psychiatry* 2002;59:131-136

MISCONCEPTIONS: DURATION OF SLEEP





Kripke et al., *Arch. Gen. Psychiatry* 2002;59:131-136

UW PACC

CURRENT GUIDELINES PER AMERICAN ACADEMY OF SLEEP MEDICINE: TREATMENT OF PRIMARY INSOMNIA:

- Start CBT (for both primary and secondary insomnia)
- If that is not effective, can consider trial of a short or intermediate acting hypnotic or ramelteon.
- Consider symptom pattern, past response, cost, patient preference, individual factors.
- Use lowest effective dose.
- Brief, intermittent use (initial treatment period of 2-4 weeks, then re-evaluate)
- If trial fails, try alternative drug from same class
- If still not response, consider sedating antidepressant (e.g. trazodone, doxepin) in low dose

VA | U.S. Department of Veterans Affairs

VA Clinician's Guide to Managing Insomnia, 2014

UW PACC

SPECIAL POPULATIONS:

- Comorbid depression and insomnia → consider sedating antidepressant at an earlier stage
- Bipolar disorder with insomnia → consider quetiapine or olanzapine
- PTSD with sleep disturbance → Prazosin for nightmares/or nighttime hyperarousal; trazodone for sleep initiation
- Patients with hx of substance abuse disorders → avoid benzodiazepines
- Chronic pain and insomnia → gabapentin or pregabalin may be appropriate

HYPNOTIC MEDICATIONS: INDICATIONS

- FDA indications:
  - 1) Sleep initiation only
  - 2) Sleep initiation and sleep maintenance
- For increased sleep latency
  - 1) Medications with fast onset and short duration of action (to avoid excessive daytime sedation)
- For increased nocturnal awakenings and early morning awakenings
  - 1) Medications with longer duration of action
  - 2) Medications with sleep initiation/maintenance indication

UW PACC

HYPNOTIC MEDICATIONS:

Benzodiazepines

Hypnotic agent	Recommended Dose Range (mg)	Half-life (hours)	Onset
quazepam	7.5 - 15	39 - 200	fast
flurazepam	15- 30	4 days + (metabolites)	fast
estazolam	0.5 - 2	10 - 24	fast-moderate
temazepam	7.5 - 30	8 - 20 hr	fast-moderate
triazolam	0.125 – 0.5	1.5 - 5.5	fast

UW PACC

HYPNOTIC MEDICATIONS:

Non-benzodiazepines

Hypnotic agent	Recommended Dose Range (mg)	Half-life (hours)	Onset
Eszopiclone	1 -3	6 – 9	fast
Zolpidem	5 - 10	2 - 5	fast
Zaleplon	5 - 20	1	fast

BENZODIAZEPINE VS. NON-BENZODIAZEPINE HYPNOTICS:

- Abuse potential for non-benzo hypnotics purportedly less than benzodiazepines, however they are still not free from the risk of dependence and other side effects

- Insufficient evidence that non-benzo hypnotics are more effective or safer than benzos

BENZODIAZEPINE HYPNOTICS:

- Commonly prescribed for treatment of anxiety and insomnia, despite many potential risks
- An estimated 1.8-8.2% of hip fractures in five Western European countries and the US may be attributable to benzo use (Khong, de Vries et al. 2012)
- Short-acting benzos appeared associated more with hip fractures than long-acting benzos
- Memory and cognitive impairment
- Increased risk of traffic accidents
- Risk of tolerance, dependence, abuse potential
- Avoid in: elderly, patients with TBI, OSA, dementia, substance use disorders, if receiving other CNS depressants

NON-BENZO HYPNOTICS:

- Adverse effects:
  - Automatic sleep behaviors: may occur with zolpidem at high doses
  - Rebound insomnia
  - Impaired motor function
  - Falls
  - Impaired cognitive function, including amnesia
  - Daytime impairment

FDA SAFETY ANNOUNCEMENTS:

- 2013:
  - Women: recommended dose of zolpidem lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR)
  - Men: consider prescribing the lower doses—5 mg for immediate-release products and 6.25 mg for extended-release products

FDA SAFETY ANNOUNCEMENTS:

- 2014:
  - Eszopiclone 3 mg dose causes impairment to driving skills, memory, and coordination lasting more than 11 hours after evening dose
  - Recommended starting dose of 1 mg for both men and women

HYPNOTIC MEDICATIONS:

- NIH-sponsored meta-analysis raised a question of whether hypnotics ("Z" drugs) produce any significant increase in objective (EEG) total sleep time for chronic insomnia.

- Found that the drug groups had a "significantly higher risk of harm" than placebo. Participants taking "Z" drugs experienced more adverse symptoms.

Buscemi N, Vandermeer B, Friesen C et al. The Efficacy and Safety of Drug Treatments for Chronic Insomnia in Adults: A Meta-analysis of RCTs. *J Gen Intern Med* 2007;22:1335-50.

IS USAGE OF HYPNOTICS ASSOCIATED WITH MORTALITY?

- Mallon et al. found that patients taking hypnotics died sooner than hypnotic-free patients, controlled for many variables.

- Men with regular hypnotic use had 4.54 times the all-cause mortality; was a risk factor for coronary artery disease death, cancer death, suicide and death from "all remaining causes."

Mallon, L., Broman, J. E., and Hetta, J. Is usage of hypnotics associated with mortality? *Sleep Med* 10(3), 279-286. 2009.

HYPNOTICS:

een studied with intermittent dosing at this time.

VA Clinician's Guide to Managing Insomnia, 2014

MELATONIN:

- Secreted by pineal gland; decreases with age
- Darkness stimulates release, light suppresses it
- Melatonin as sleep aid:
  - Significantly decreases sleep onset latency in delayed sleep phase syndrome
  - Marginally decreases sleep onset latency in primary insomnia (better effectiveness in children) and not at all in secondary insomnia
  - Need more controlled studies of long-term usage
  - Lack of systematic data on side effects

RAMELTEON:

- Melatonin agonist – binds to M1 and M2 receptors
- Half-life of 1.5 to 5 hours
- Metabolized by the liver; used with caution in hepatic insufficiency
- Weak evidence for reduction of sleep latency at recommended prescribed dosage (8 mg)
- No consistent evidence of improvement in other objective or subjective parameters
- Benign side effect profile

TRAZODONE FOR INSOMNIA:

- Start at 25-50 mg qhs; increase in 25-50 mg qhs increments, as tolerated; typical dose of 50-200 mg qhs.
- Onset of action: 20-60 minutes
- Effect on sleep stages:
  - Increases stage 4
  - Slight decrease in REM

TRAZODONE FOR INSOMNIA:

- Advantages
  - Rapid onset of action
  - Usually minimal or no tolerance
- Disadvantages
  - Hypotension, dizziness
  - GI disturbance
  - Daytime sedation
  - Priapism in men
  - Cardiac rhythm effects
  - Efficacy not well-established
  - Not many studies of hypnotic efficacy beyond 2 weeks

MIRTAZAPINE:

- H1 antagonism
- Lower doses (7.5-15 mg qhs) may be more sedating
- Low risk of medication interactions
- Less sexual side effects than SSRIs
- Side effects: drowsiness, orthostasis, increased appetite, weight gain

DOXEPIN:

- FDA approved at low doses (3 or 6 mg) for treatment of insomnia; licensed as Silenor
- Acts primarily as an H1 antagonist and has a side effect profile comparable to placebo at low doses
- May be useful for sleep maintenance, e.g., for early awakening.
- Risk of toxicity in overdose

QUETIAPINE:

- Antihistaminic effects
- Minimal evidence to support use in insomnia
- Increase in subjective total sleep time and decrease in subjective sleep latency were found, but differences were not statistically significant
- Metabolic side effects; even at low doses may still be associated with weight gain
- Should not be used for sleep unless there is an approved indication for use of an antipsychotic (eg. acute bipolar depression)

ANTIHISTAMINES:

- Hydroxyzine may have more acute effects on sleep compared to OTC antihistamines
- Limited evidence
- May cause insomnia or worsen existing insomnia
- Negative effects on next-day functioning
- Onset 45 min - 1 hour; variable duration- frequently longer than 8 hours

ANTIHISTAMINES – SIDE EFFECTS:

- Confusion - especially in elderly
- Anticholinergic - e.g., urinary retention
- Morning sedation
- Habituation
- REM rebound on withdrawal
  - Causes and/or worsens insomnia
  - Can result in chronic use when acute treatment was planned

SUVOREXANT (BELSOMRA):

- Selective, dual orexin (hypocretin) receptor antagonist made by Merck & Co.
- Promotes sleep by reducing arousal and wakefulness
- Narcolepsy like side effects - cataplexy, impaired driving, nighttime behaviors, suicidal ideation
- 12 hour half-life
- Schedule IV
- Insufficient evidence to support use at this time

VALERIAN ROOT

- Binds to GABA-A receptors
- Produces subjective improvement in sleep quality
- No improvement in quantitative measures of sleep
- Effective dosage unclear, possible side effects, drug interactions

CANNABIS AND SLEEP

- Low doses of THC (4 to 20 mg) - mild suppressive effects on REM; total sleep time or stage 3-4 sleep was increased but then decreased to baseline levels after a week of repeated nightly use
- High doses of THC (50 to 210 mg) – also suppress REM; no effects on total sleep time; stage 3-4 sleep reduced in one report

CANNABIS AND SLEEP (CONTINUED)

- Upon discontinuation: REM rebound, as well as reduction in total sleep time, and an increase in sleep latency

Roehrs, T. & Roth, T. (2011). Medication and Substance Abuse in Kryger, M. H., Roth, T. & Dement, W. C. *Principles and Practice of Sleep Medicine 5th Edition.* St. Louis, Missouri: Elsevier Saunders.

KEY POINTS:

- Cognitive-behavioral therapy is the best treatment for chronic insomnia, with long-term efficacy and least side effects
- The risks of hypnotics may outweigh their benefits in some patients. Consider alternative strategies to reduce risk. Long-term use is not recommended.
- Association between cannabis and impaired sleep quality

UW PACC

REFERENCES:

- Buscemi N, Vandermeer B, Friesen C et al. The Efficacy and Safety of Drug Treatments for Chronic Insomnia in Adults: A Meta-analysis of RCTs. *J Gen Intern Med* 2007;22:1335-50.
- Cappuccio et al., Sleep Duration and All-Cause Mortality: A Systematic Review and Meta-Analysis of Prospective Studies. *Sleep* 2010; 33:585-592
- Kripke et al. Mortality associated with sleep duration and insomnia. *Arch. Gen. Psychiatry* 2002;59:131-136
- Kryger, Meir H., T. Roth, and William C. Dement. *Principles and Practice of Sleep Medicine*. Philadelphia, PA: Elsevier/Saunders, 2005.
- Leshner AI, et al. National Institutes of Health state of the science conference statement: Manifestations and management of chronic insomnia in adults June 13-15, 2005. *Sleep* 2005;28(9):1049-57.
- Mallon, L., Broman, J. E., and Hetta, J. Is usage of hypnotics associated with mortality? *Sleep Med* 2009 10(3), 279-286.
- Morin CM. Contributions of cognitive-behavioral approaches to the clinical management of insomnia. *Primary Care Companion J Clin Psychiatry* 2002;4(suppl 1):21-6
- Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13(2):307–349.
- Stern T, Herman J. Massachusetts General Hospital Psychiatry Update & Board Preparation. Mc Graw-Hill Medical Publishing Division. (3rd Edition).
- Walsh JK, Krystal AD, Amato DA et al. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. *Sleep* 2007;30(8):959-68
- Walsh JK. Zolpidem "as needed" for the treatment of primary insomnia: A double-blind placebo-controlled study. *Sleep Medicine Reviews* 2002;6(Suppl. 1):S7-S11.
- Wells, D, et al., Va Clinician's Guide to Managing Chronic Insomnia, 2014. U.S. Department of Veterans Affairs

UW PACC