Treatment of Insomnia - A Clinical Pharmacological Approach

Joanne Haeffele PhD APRN FNP BC
Associate Professor of Nursing
Director, Clinical DNP Program
Objectives

- This presentation should provide participants with the knowledge and skills to:
  - (RX) Comprehend the pharmacokinetics and pharmacodynamics of sleep medications
  - RX) Analyze the relationship between pharmacologic sleep medications and physiologic/pathologic processes
  - RX) Safely and appropriately select pharmacologic medications for the management of insomnia based on patient variations, current health problems, drug interactions and cost effectiveness
George’s Story
Consider Prescribing after...

HELPS YOU SLEEP

- Go to bed and get up at the same time every day
- Comfortable mattress and bedding
- Drink water
- Relaxation exercises
- Spend time outside
- Read a book in bed

SLEEP HYGIENE

- Avoid caffeine and alcohol at night
- Have an early light dinner

KEEPS YOU AWAKE

- Coffe and chocolates after dinner
- Poor quality bedding
- Stay indoors all day and do no exercise
- Stress and anxiety
- Use a tablet or phone in bed

- Hot bedroom with no air circulation
- Go to bed when you're not tired
- Lie in bed for hours getting stressed
- Lie in bed for hours getting stressed

www.nosleeplessnights.com
What is an ideal Sleep Agent?

- Induces sleep
- Rapidly, maintains sleep
- Is devoid of next-morning hangover effects
- No drug interactions
- Doesn’t worsen comorbid conditions
Patients are taking...
OTC Antihistamines

• Block histamine 1 receptors – decrease arousal
• Low efficacy
• Improve insomnia short period of time
• SE: due to systemic anticholinergic properties
• Avoid in pregnancy, breastfeeding and the elderly

• Unison, Sleepinal, and Sominex (HL 4-8 h) has FDA indication for insomnia

• Cost - $4.00-25.00 per 1-2 months
acetaminophen and diphenhydramine

- H1 receptor antagonist, block the action of histamine at the H₁ receptor
- Peaks 1-3 h & lasts up to 7 h
- No FDA indication for insomnia
- Not recommended - no improvement in quality of sleep over placebo
- Pregnancy category B
- SE: daytime drowsiness/grogginess, daytime impairment, dizziness, dyskinesia, xerostomia and urinary retention
- Cost $3.97 (24 tabs)

(Sateia, Buysse, Krystal, Neubauer & Heald, 2017)
Melatonin

- Sleep promoting hormone – pineal gland
- **Regulates circadian rhythm via melatonin receptors**

- For mild insomnia in adults and elderly

- Dose is 1-3 mg taken 1-2 hours before sleep
- Should note effect 7-14 days
- Continue for 2 months

- **SE:** arrhythmia's, HTN, GI motility, hyperglycemia and worsening depression
Hypnotics - Prescription Drugs for insomnia

- Controlled Substance (C-IV)
- Potential for abuse and dependence
- Must be written, oral order or faxed
- Cannot e-prescribe
- 6 months to fill rx from original date
- Refills only x 5
Hypnotics

• Pathways – GABAergic or central melatonergic to induce sleep
• a drug that causes drowsiness and facilitates the onset and maintenance of “natural sleep.”
• FDA approved – chronic insomnia
• Most published placebo controlled studies – efficacy and tolerability based on 2-6 week trials

(Ancoli-Israel, 2010)
Hypnotics - Reduce the brain’s response

- Sensory stimuli
- Impair learning and memory
- Depress alertness and cognitive function
- Reduce psychomotor activity and driving ability
- Impaired sleep dependent memory consolidation
- Impaired cortical plasticity
- Increased amnesia
Elderly-avoid Use of Hypnotics

- Confusion
- Falls
- Memory Loss
- Iatrogenic sleep disturbance
- Rebound insomnia
- Lack of efficacy

- BEERS Criteria – do not prescribe for greater than 90 days
Ambien

• a gamma-aminobutyric acid (GABA) A agonist

• Non-benzodiazepine

• Rapid onset – **sleep latency 5-12 min**

• **Moderate improvement in quality of sleep**

• Maintenance – 29 min longer
Ambien’s effect on the brain

![Adverse Effects of Ambien on the Brain]

Ambien affects chemicals in your brain by slowing down the activity in the brain. But Ambien can also cause many side effects, such as memory problems. More Here.

- Depersonalization
- Impaired memory
- Lethargy
- Abnormal dreams
- Memory loss
- Delirium
- Slow reflexes
- Depression
- Emotional liability
- Addiction
- Confusion
- Concentration difficulties
- Suicidal tendencies
- Amnesia
- Insomnia
The Food and Drug Administration is requiring makers of Ambien and similar sleeping pills to lower the dosage of their drugs, based on studies suggesting patients face a higher risk of injury due to morning drowsiness.

FDA Cites a Number of Car Accidents Tied to Sleep Meds

Recommend 5mg & CR 6.25 mg

(Associated Press, 2013)
Eszopiclone (Lunesta)

- Non-benzodiazepine
- Rapid onset – sleep latency 14 min
- Sleep maintenance- improved
- 1, 2 & 3 mg.
- Moderate to high improvement in sleep
- minimal rebound insomnia, withdrawal, and tolerance
- SE: taste, headaches and dry mouth
- Average cost $3.89 per pill
- FDA NOT restricted for short-term use

(Sateia, Buysse, Krystal, Neubauer & Heald, 2017)
Benzodiazepines

- anticonvulsant,
- anxiolytic, amnestic, and hypnotic features.
- bind with high affinity to neuronal GABAA receptors

- Risk for dementia in the elderly

- To discontinue – must wean

- All benzodiazepines can result in respiratory depression in patients with pulmonary disease and may lose sleep-inducing efficacy with prolonged use.\textsuperscript{10,12}

(Azparren & García, 2014)
**Benzodiazepines**

- Alprazolam (Xanax), Chlordiazepoxide (Librium), Clonazepam (Klonopin)
- Diazepam (Valium), Lorazepam (Ativan), Temazepam (Restoril), Triazolam (Halcion)

**Problems:**
- Long half lives
- Dependence and withdrawal symptoms
- Drowsiness and dizziness
- Amnesia
- Influence melatonin production and release
Temazepam (Restoril)

- Onset – sleep latency 37 min
- Maintenance – 99 min longer
- Half life – 10 hours

- capsules, 7.5 mg, 15 mg, 22.5 mg, and 30 mg

- Small improvement in quality of sleep

- SE - “hangover” feeling the day after taking RESTORIL
Tricyclic antidepressants

- **serotonin-norepinephrine reuptake inhibitors (SNRIs)** by blocking the serotonin transporter (SERT) and the norepinephrine transporter
  - amitriptyline (Elavil)
  - clomipramine (Anafranil)
  - desipramine (Norpramin)
  - doxepin (Sinequan)
  - imipramine (Tofranil)
  - nortriptyline (Pamelor)

- **SE** - dry mouth, constipation, sweating, weight gain
Doxepin 3-6 mg.

- **Tricyclic antidepressant and anxiolytic**
- potent in blocking the serotonin transporter than the norepinephrine transporter, in addition to exerting prominent blockade of histamine H₁ receptors.³

- **26-32 min longer**

- The studies demonstrate the efficacy of low-dosage doxepin therapy (3 and 6 mg qhs)
  - **Small to moderate** improvement in sleep

- Best for depression and insomnia

- SE: daytime fatigue and mental fog
Margaret – advanced sleep phase disorder

• 68 y/o female with sleeping difficulties – wakes too early
• Tired after dinner – falls asleep while watching TV
• Gets in bed at 10 – falls asleep in 5 min
• Wakes after 3 hours, awake for 30 min
• Wakes again at 4:30 am, stays in bed until 6:30 am

• Cause - early timed circadian rhythm
Ramelton (Rozerem) 8mg.

- Melatonin receptor agonist - **bind to and activate the melatonin receptor.**
- 8 mg or 16 mg
- RCT N=405
- Using a polysomnography – evaluated latency to persistent sleep (LPS),
- total sleep time, sleep efficiency, wake time after sleep & number of awakenings
- **Results: Ramelton reduced LPS over 5 weeks in participants with chronic insomnia**
- No change in sleep architecture, next-morning effects, rebound or withdrawal

(Zammit, Erman, Wang-Weigand et al., 2007)
Melatonin

- Sleep promoting hormone – pineal gland
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- For mild insomnia in adults and elderly

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Jet Lag

• This is the type of insomnia that we all want!
Insomnia Related to jet lag

- Zolpidem (Ambien) 10 mg, Non-benzodiazepine

- Eastward travel - Reported better sleep (especially first 2 nights) when compared to placebo

- Trans-Atlantic travel (crossing 5-9 time zones) – improved sleep quality and total sleep time
Case Study

- 45 year old NP Sara works in internal medicine and just completed a long day of challenging patients. She is exhausted physically and mentally at 9 pm and goes to bed. In bed, she thinks about some of her patients, one in particular who fell at home while on Coumadin and had extensive facial bruising, memory loss and headaches and did not go to the ER.
In bed, Sara tosses and turns finding it difficult to get comfortable. Her body and brain want to sleep but she is unable to fall and stay asleep. She gets up twice to urinate and is fully awake at 1 am – gets up and logs on to her EMR to complete her charting. Sara finally goes back to bed at 2 am and wakes at 6:30 for another workday.
Insomnia: Excessive Nighttime Arousal?

- **asleep**
- **deficient arousal**
- **overactivation**
- **normal baseline**
- **hypoactivation**

- **GABA_A**
- **PAMs (Z drugs)**
- **benzos**
- **H1 antagonists**
- **5HT2A/2C antagonists**

- **excessive arousal**

- **HA**
- **DA**
- **ACh**
- **5HT**
- **NE**
Treatment

- Benzodiazepines – with caution, short term
- H1 antagonist – Remeron
- Serotonin 2a 2c antagonists - Seroquel
Shift Work Sleep Disorder

• KD is a 29-year-old woman who works as an overnight stock clerk at a local grocery store. She reports that she is unable to fall asleep after returning home from work in the morning. As a result, she feels drowsy and sluggish as she begins her shift each night, and midway through her shift, she sometimes wishes she could take a nap. KD would like you to recommend for a treatment for her insomnia.

• KD needs a pharmacologic agents to promote restfulness and regulation of the circadian rhythm or alertness.
Melatonin

- Sleep promoting hormone – pineal gland
- Regulates circadian rhythm via melatonin receptors
- Melatonin produces a rapid, mild sleep-inducing effect
- SE: arrhythmia’s, HTN, GI motility, hyperglycemia and worsening depression

- Rozerem RX
- Melatonin 3 mg.
- Consider recommending a pharmaceutical grade

(Morgenthaler, Lee-Chiong, & Alessi, et al, 2007)
Case Study

- Jose is a 59 year old with insomnia. His wife reports that he snores loudly, has gasping and choking episodes and occasionally stops breathing at night. He wakes several times at night and finds his sleep restless. He has daytime sleepiness and his mallampati score is 4.

- What is the diagnosis?
A high Mallampati score represents a predisposing factor for obstructive sleep apnea syndrome, especially if it is associated with nasal obstruction.
Which of the following sleep agents can be safely prescribed for this patient?

1. Ramelton (Rozerem)
2. Esziplicone (Lunesta)
3. Zolpidem (Ambien)
4. Benzodiazepines
Melatonin and OSA

- Ramelton (Rozerem) – no effect on OSA
- Melatonin 3 mg. pharmaceutical grade

(Kryger, Wang-Weigand, & Roth, 2007)
Hypnotics and OSA

Zolpidem (Ambien)
- No worsening of OSA
- Lowered O2 levels

Esziplicone (Lunesta)
- No worsening of OSA
- Reduced the severity of OSA

Benzodiazepines
- Increased numbers and durations of pauses in sleep
- Lower oxygen levels

(Mason, Cates & Smith, 2015)
Jose’s second appointment

• Jose is a 59 year old
• He was diagnosed with OSA and was prescribed Zolpidem (Ambien) 5 and later 10 mg. and CPAP which he has been using for the past several months.

• Further history reveals for the past month he is having an urge to move, usually due to uncomfortable sensations (described as creeping, crawling, aching), primarily in the legs and that the Ambien is no longer working.
questions?

• What is the diagnosis now?

• Why isn’t the Ambien working for initiating sleep?

http://www.hopkinsmedicine.org/news/media/releases/restless_legs_syndrome_insomnia_and_brain_chemistry_a_tangled_mystery_solved
Case Study

- This 47-year-old female suffered from a sleep disorder since her daughter's birth 12 years prior. She had been unable to get a good night's sleep since and as a result is extremely fatigued. She also described trouble with **depression and mood swings** because of her extreme lack of sleep. She described most nights with frequent awakening without any consistent sleep hours in a row.

- **Insomnia as a cause for depression?**
# Non-FDA Approved Antidepressants for insomnia

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic/Trade</th>
<th>Dose/Half-life</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCA’s</strong></td>
<td>Trazadone, Amitriptyline, Nortriptyline</td>
<td></td>
<td>Nervous, fatigue, diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100-150 mg/7h 75 mg/15 h 25 mg/15-39 h</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiotoxicity, dysrhythmia</td>
</tr>
<tr>
<td><strong>H1 receptor antagonist</strong></td>
<td>Remeron</td>
<td>15 mg/26-37 h</td>
<td>Weight gain, increased appetite, liver toxicity</td>
</tr>
<tr>
<td><strong>SNRI, 5-HT2 antagonist</strong></td>
<td>Serzone</td>
<td>100 mg/2-4h</td>
<td>Headache, dizziness and confusion</td>
</tr>
<tr>
<td><strong>D2 and 5 HT2 receptor antagonist</strong></td>
<td>Seroquel</td>
<td>100-300 mg/6h</td>
<td>Agitation, dizziness extrapyramidal effects, weight gain</td>
</tr>
</tbody>
</table>
Insomnia & Depression Treatment combinations

- Nefaxadone & Amitriptyline
- Mirtazapine & Trazadone
- Eszopiclone & Fluoxetine
- Add Trazadone to SSRI
- SSRI’s alone
Case Study

• 66-year-old woman with a primary complaint of **sleeplessness and sleepiness** for approximately **8 months**. Initially, she only had difficulty staying asleep 2-3 nights per week. However, over the past 5 months, poor sleep and daytime fatigue have increased in severity and frequency.

• Wakes up 3 or more times per night at least 5 nights per week

• Trouble falling asleep

• She notes **increased irritability and lack of motivation**.

• What sleep agent will you prescribe?
Treatment options

Antidepressants
Lexapro, Celexa or Paxil

Non-benzodiazepines
Ambien
Lunesta

Melatonin agonist
Rozerem 8 mg
Melatonin 3 mg
35 year old female with Fibromyalgia reports fatigue and aches with poor sleep. She is tired and looks forward to getting a good night’s sleep but is unable to fall and stay asleep. She tosses and turns in bed trying to get comfortable. Maybe she gets a few hours of sleep – wakes tired most days.

What is the connection between sleep and chronic pain?

TCA - Amitriptyline
Mr. Pauli

• Mr. Pauli, a 45-year-old man presents with difficulty falling asleep and staying asleep. The problem started after the death of his sister 2 months previously. He is unable to fall sleep until at least an hour after going to bed. He has no previous sleep problems.

• Given a TCA – didn’t tolerate side effects

• He consumes 4 cups of coffee during the day and lately takes alcohol at night to aid sleep. The patient’s wife has noted that his legs jerk occasionally during the sleep though Mr. Tan is not aware of these movements.

• What is the cause of his sleep disorder – what med will you prescribe?

  (Ariff & Hassan, 2006)
Treatment – Mr. Pauli

• intermediate-acting benzodiazepine (e.g. lorazepam) for 2 weeks

• A non-benzodiazepine hypnotic - zolpidem is an alternative.

• The presence of depressive symptoms may warrant the use of a selective serotonin inhibitor (SSRI).

• Consider ordering a polysomnography for his sleep-related limb movements
“I can’t sleep”

- First Trimester – reproductive hormones
- Second Trimester – increase stage 3 NREM sleep
- Third Trimester - a rise in Stage 1 NREM reduction in Stage 3 and REM parts of sleep.
- Postpartum – it’s the baby!!
Hypnotic's in Pregnancy

- Data regarding their reproductive safety is limited and generally we try to avoid their use during pregnancy, **especially first trimester**

- **BUT, if absolutely necessary**…….
## Non-Benzodiazepines Hypnotic's in pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy Risk</th>
<th>Lactation Risk</th>
<th>Comments</th>
<th>Evidence for Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloral Hydrate</td>
<td>C</td>
<td>L3, moderately safe</td>
<td>Limited Risk</td>
<td>+++</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>C</td>
<td>NA</td>
<td>Limited Risk</td>
<td>+++</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>C</td>
<td>L2, safer</td>
<td>Limited Risk</td>
<td>+++</td>
</tr>
<tr>
<td>Zolpidem (Ambien)</td>
<td>B</td>
<td>L3, moderately safe</td>
<td>Limited Risk</td>
<td>+++</td>
</tr>
<tr>
<td>Diphenhydramine (Benadryl)</td>
<td>B</td>
<td>NA</td>
<td>Limited Risk</td>
<td>+++</td>
</tr>
</tbody>
</table>

*Hashmi, Bhatia, Bhatia, & Khawaja (2016)*
# Sedating TCA’s in Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lactation Risk</th>
<th>Comments</th>
<th>Evidence/Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>C</td>
<td>L2 safer</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use if primary disorder is depression</td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>C</td>
<td>L2 safer</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use if primary disorder is depression</td>
<td></td>
</tr>
<tr>
<td>Doxepin</td>
<td>C</td>
<td>L5 Avoid prescribing</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use if primary disorder is depression</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>C</td>
<td>L2 safer</td>
<td>+/-</td>
</tr>
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<td></td>
<td></td>
<td>Use if primary disorder is depression</td>
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</tbody>
</table>

*Hashmi, Bhatia, Bhatia, & Khawaja (2016)*
There are no approved sleep meds for pediatrics

Melatonin - (0.1–0.3 mg)
promotes sleep onset & maintenance
decreases sleep latency, increases sleep efficiency & improves total sleep time

(Dubocovich, 2007)
Mrs. Lee presents at the practice requesting for a prescription for diazepam (Valium -15 mg at hs to help her sleep and allay anxiety.

Started after the death of her husband 5 years ago

Her previous attempts to discontinue her medication had failed as it resulted in insomnia, anxiety, tremor, irritability, nightmares and tinnitus.

Complains of poor memory. Her NP recently advised discontinuation after a fall

Normal Physical Exam and Mini Mental Status Exam

Who wants to refill her Diazepam?

(Ariff & Hassan, 2006)
Diazepam (Valium)

- long-acting benzodiazepine hypnotic
- Half-life 20-80 h
- Se: CNS depression, disorientation, psychomotor impairment, aggression, excitement, confusion, and amnesia.
- Tolerance usually develops

- Wean off by 25% per week
- Rx Valproic acid during weaning – helps with agitation (Lindenmayer & Kotsaftis, 2000)
- Zolpidem (Ambien)

(Ariff & Hassan, 2006)
Not recommended

• No Improvement in Quality of Sleep
• Harmful Effects

• Zaleplon
• Tiagabine
• Trazadone 50 mg
• L-tryptophan
• Valerian
• Benadryl

(Sateia, Buysse, Krystal, Neubauer & Heald, 2017)
Monitoring for sleep effectiveness

• Patient’s self report – most important!

• Is there any improvement?
Merck’s Insomnia Medicine Belsomra C-IV Now Available in US

- Insomnia in adults - difficulty falling asleep and/or staying asleep.

- Only **orexin receptor antagonist** approved for the treatment of insomnia in the United States.

- **Belsomra** selectively blocks orexin receptors thought to suppress wake drive in the brain.

- Dose of Belsomra is 10 mg, within 30 minutes of going to bed, allowing for 7 hours of sleep

- Cost - $327.00 per month
Effect of insomnia

Effects of Sleep deprivation

- Irritability
- Cognitive impairment
- Memory lapses or loss
- Impaired moral judgement
- Severe yawning
- Hallucinations
- Symptoms similar to ADHD
- Impaired immune system
- Risk of diabetes Type 2

- Increased heart rate variability
- Risk of heart disease
- Decreased reaction time and accuracy
- Tremors
- Aches

Other:
- Growth suppression
- Risk of obesity
- Decreased temperature
Summary

• Insomnia is a huge medical and public health problem

• Studies report that sleep hygiene works

• Appropriate prescribing – based on the cause of insomnia, comorbid conditions and medications taken

• Need regular follow up appointments with documentation supporting appropriate use, tolerance and effectiveness.
Bibliography

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