Sleep Disorders — Evidence Based Pharmacologic Interventions

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Learning Objectives

• Review evidence for the use, risks and limitations of pharmacologic therapies for insomnia

• Review resources available for reference and future learning

• Convince you to just re-watch Kyle Davis’s lecture from 2 weeks ago on CBT for insomnia and apply all of his tips prior to using any medications
Insomnia

• Accounts for 5.5 million visits in primary care
• Particularly common in adults over 65
  – Up to 65% report problems with sleep in some studies
• More women affected
• Also more common in individuals who are unemployed, divorced, widowed, separated or of lower socioeconomic status
• High risk during alcohol or opiate withdrawal
Resource Plug

• Choosing Wisely Campaign

• *Choosing Wisely* is an initiative of the ABIM Foundation that seeks to advance a national dialogue on avoiding unnecessary medical tests, treatments and procedures.

• 540 specialty society recommendations

• Additional recommendations for insomnia:
  
  • *Avoid use of hypnotics for chronic insomnia in adults. Instead offer cognitive behavior therapy and reserve medication as adjunctive treatment*—American Acad Sleep Medicine
  
  • *Do not routinely prescribe antipsychotic medications as a first-line intervention for insomnia*
Medication utilization

• Prescriptions increased from 5.3 million in 1999 to 20.8 million in 2010

• OTC use levels hard to determine
  – One study: 10% of adults 18-45 use OTC sleep aids
  – Older adults similar, but more likely to use chronically
Over-the-counter sleep aids-Antihistamines

- First generation antihistamines
  - Diphenhydramine (Benadryl, Tylenol PM, Excedrin PM, Advil PM, ZzzQuil)
    - Approximate ½ life: 8.5 hours
  - Doxylamine (Unisom SleepTabs, Equaline Sleep Aid, Good Sense Sleep Aid)
    - Approximate ½ life: 10 hours
- Marketed prior to 1972, No RCTs needed, “grandfathered”
- Subjective sleep improvement
- Residual psychomotor, cognitive impairment, particularly elderly
- Anticholinergic effects
- Consider for pregnant women (doxylamine/B6)
OTC sleep aids: Melatonin

- Regulates sleep/wake cycle
- Good for insomnia related to changing time zones/jet lag or during shift work
  - Also has been studied in children
- 2013 meta-analysis: 0.1-5 mg. Mild improvement in sleep latency (7.1 m) and total sleep time (8.3 m)
- Most studies controlled release formula
- Not FDA regulated, but may be as effective as Ramelteon, a melatonin agonist which is
- Cost per month melatonin: $1
- Cost per month Ramelteon: $350
- Few adverse events, not habit-forming
OTC sleep aids: Valerian

• Plant derivative widely used for sleep/anxiety
• Powder, extract
• Paucity of data supporting efficacy despite widespread use for insomnia
• Unregulated products
• Relatively benign side effect profile
Resource Plug

• Therapeutic Research Center (TRC): Prescriber’s Letter and additional role-based publications, CME, resources
• Natural Medicines database for product information available
Benzos

- Try to stop them—slow taper may be needed
- Don’t start them for insomnia alone, especially in the elderly
- Choosing Wisely/American Geriatrics Society: *Do not use benzodiazepines or other sedative-hypnotics in older adults as a first choice for insomnia, agitation, or delirium*
Z-Drugs

• Nonbenzodiazepine hypnotics: zaleplon (Sonata), zolpidem (Ambien, Edluar), and eszopiclone (Lunesta)
• GABA_\text{A} \text{ receptor like benzos, but more selective, less anxiolysis}
• Reasonable efficacy on sleep latency
• Memory loss, dizziness, disinhibition, GI upset
• Complex sleep behaviors: new recommendation to stop medicine if this has ever happened
Resource Plug

• RESOURCE PLUG: deprescribing.org—evidence based guidelines for deprescribing appropriately
Doxepin/antidepressant notes

• Antidepressants widely used for sedation, but only TCA doxepin (Silenor, SINEquian) 3 mg and 6 mg is FDA approved
• Improves sleep efficiency, total sleep time, maintenance
• 6 mg dose improves sleep latency
• Adverse effects in older adults similar to placebo, BUT does have anticholinergic effects—use with caution
• 10 mg doxepin not as well studied, but much cheaper
• Evidence for trazodone is weak, not considered first line
• Consider along with mirtazapine, amitriptyline and nortriptyline only if there is another indication
Resource plug

• Anticholinergic burden calculator:
  —acbcalc.com—Calculates anticholinergic burden in patients over 65. 3+ is high risk.
Treatment of insomnia: One approach

Patient diagnosed with insomnia

Behavioral interventions; address any medical condition that may be contributing

Symptom resolution? Yes

Reinforce intervention and continue

No

Determine insomnia type

Sleep-onset insomnia
- Melatonin, controlled release
- Eszopiclone (Lunesta)
- Zaleplon (Sonata)
- Zolpidem (Ambien)

Sleep-maintenance insomnia
- Eszopiclone
- Doxepin (Silenor)
- Zolpidem

Insomnia in older adults
- Doxepin
- Melatonin, controlled release
- Ramelteon (Rozerem)

Depression and insomnia
- Doxepin
- Mirtazapine (Remeron)

NOTE: Medications are listed in order of preference for each indication.
Resource plug

• THE PLACEBO EFFECT
  – 2014 study: Migraine sufferers given migraine medications. One group took the drug labeled with the drug’s name, one took a drug labeled placebo and one took nothing. Placebo 50% as effective as migraine medication
  – Harness it and help patients harness it.
    • Provider relationships
    • Patient self care
    • Ritualized healing
Key Points

• Behavioral strategies first, second, third
• Medicate gently and rarely
• Ensure safe prescribing practices by using evidence-based resources
• Ask about sleep and OTC product use regularly at office visits based on provider role
References


• Culpepper, L and Wingertzahn MA. Over-the-Counter Agents for the Treatment of Occasional Disturbed Sleep or Transient Insomnia: A Systematic Review of Efficacy and Safety. Prim Care Companion CNS Disord. 2015; 17(6)


• Additional resources available upon request