PALLIATIVE PEARLS
BY ENCLARA PHARMACIA

Insomnia: Identifying Causes & Best Practices in Management
August 2021

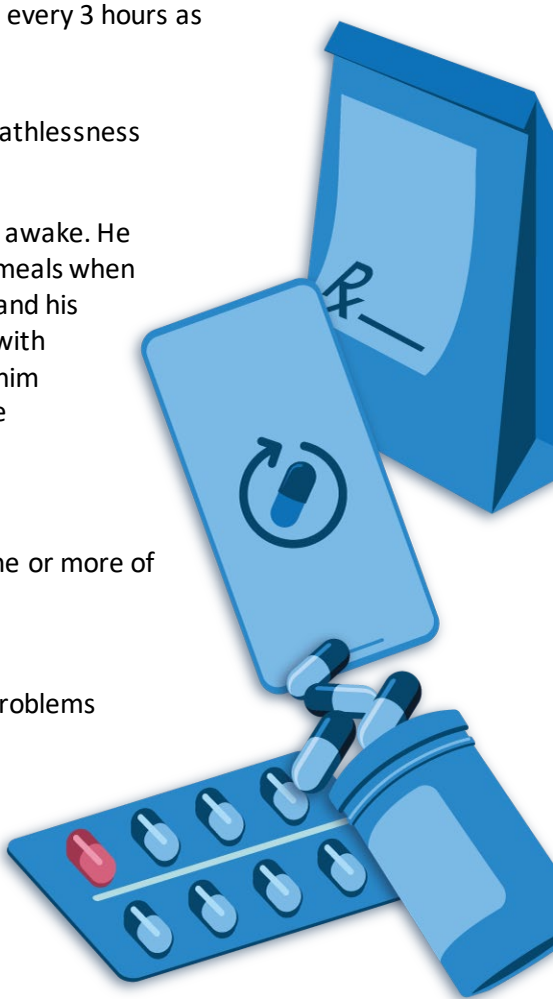
PATIENT CASE

DB is a 70-year-old male living with a primary diagnosis of dementia and comorbidity of COPD. He was admitted to home hospice 3 months ago and currently resides in a skilled nursing facility.

MEDICATIONS

- Advair Diskus 250/50mcg; inhale 1 puff twice daily
- Albuterol HFA inhaler; inhale 2 puffs every 4 hours as needed for breathlessness
- Morphine 20mg/ml oral concentrate; take 0.25ml (5mg) by mouth every 3 hours as needed for pain or breathlessness
- Dexamethasone 4mg; take 1 tablet by mouth twice daily
- Oxygen; inhale 2 liters per min via nasal cannula as needed for breathlessness
- Senna 8.6mg; take 2 tablets by mouth twice daily

The facility staff state that DB often presents as anxious and restless when awake. He frequently misses meals due to sleeping during the day and often refuses meals when awake due to nausea. DB is often found awake for long periods overnight and his hallucinations often disturb other residents. DB was trialed on lorazepam with titration up to a 2mg dose bedtime to manage insomnia however it made him even more restless. Zolpidem (Ambien®) was then trialed up to a 5mg dose however he awoke every morning feeling "hung over" and groggy.



INSOMNIA OVERVIEW [1-4]

Insomnia is defined as dissatisfaction with sleep quality or quantity with one or more of the following symptoms:

- Difficulty initiating sleep
- Difficulty maintaining sleep, described by frequent awakening or problems returning to sleep
- Early-morning awakenings with inability to return to sleep

Insomnia is one of the most common symptoms for which adults seek medical advice. Pharmacotherapy may often be sought and initiated first-line but is only recommended as a part of an integrated approach that includes behavioral strategies and management of underlying

comorbidities.[2] Most adults do not experience full remission of their insomnia symptoms. Remission is especially low in patients with medical and psychiatric comorbidities.

Childhood insomnia may present with various behavioral and medical problems, typically manifested as bedtime resistance, difficulty initiating sleep, night waking, or combinations of these symptoms. Most sleep disturbances in children and adolescents are managed with behavioral therapy alone, considered first-line therapy. Little evidence exists on the effectiveness of hypnotics in children with most trials demonstrating little or no efficacy. If pharmacotherapy is initiated, therapy must be individualized to the symptoms displayed, with consideration of potential comorbid conditions, effect of sleep disturbance on the child's health, and realistic treatment goals.

INSOMNIA IN PALLIATIVE CARE[4]

The prevalence of insomnia in the palliative care population is over 60 percent.[5-8] Certain populations have an increased incidence of insomnia, including patients with cancer, COPD, Parkinson's disease, dementia, and heart failure. There are known changes in older patients' sleep structure and quality that may contribute to daytime fatigue and more frequent napping. Potentially reversible contributors to insomnia in this patient population include pain, anxiety, depression, and cough. Identifying these underlying causes and managing accordingly is recommended.

Those with refractory symptoms may benefit from medications indicated for more than just insomnia. For example, mirtazapine is indicated for depression however has a side effect profile that makes it useful for insomnia and appetite stimulation when these symptoms coexist with depression. Another example is trazodone, indicated for depression but also useful for insomnia. It's important to remain wary of the side effect profile of these and hypnotic medications as they may not always be helpful. Patients approaching end of life are more susceptible to the side effects of medications due to drug-drug interactions and/or the presence of end-organ impairment.

Medications used commonly in palliative care may have arousal or stimulant properties that can exacerbate sleep disturbances. These include opioids, steroids, beta-receptor agonists (e.g., albuterol), many antidepressants, and psychostimulants (e.g., methylphenidate). If these types of drugs are necessary, choose ones with the fewest likely adverse effects, start at the lowest potential effective dose, and use time-limited trials; note that for most hypnotics, starting doses are lower for older adult patients.

INSOMNIA MANAGEMENT

Non-Pharmacological Therapies [4,9]

Sleep hygiene education is important for all with insomnia. These principles are incorporated in the guidance below. Some may be difficult for seriously ill patients, particularly maintaining a regular routine for hospitalized patients and avoiding naps for fatigued, seriously ill patients.

- Address the environment – assess temperature of the room, surrounding noise, and lighting; establish a connection between the bedroom and sleep; avoid watching TV and reading in bed or using the bedroom for any other activity (except sexual activity); avoid checking the clock at night to limit arousal and wakefulness
- Lifestyle modifications - avoid long daytime naps, alcohol, nicotine, and caffeine; avoid large meals or excessive fluids before bed
- Exercise - limited evidence shows a potential for significant improvements in insomnia symptoms in patients who participated in low impact aerobic exercise such as brisk walking
- Promote physical comfort – new mattress, new pillows, egg crate cushion on top of the mattress
- Encourage healthy sleep-wake cycles - advise patients and caregivers to keep a regular sleep schedule (bedtime and rise time)-this means going to bed and waking up at the same time every day
- Minimize disruptions – most important in institutional settings to create a calm environment (e.g., dimming lights) and avoid unnecessary interruptions during scheduled sleep times
- Relaxation Therapy - muscle relaxation, guided imagery, meditation, breathing exercises

Pharmacological Therapies [2,4,10]

Patients at an advanced stage of illness are more likely to suffer adverse effects from medications for sleep.[4] Medications prescribed for insomnia are suggested only after attempting nonpharmacologic modifications. Attention to associated symptoms may be especially important in this population because of the risk of unintended consequences such as worsening delirium (e.g., zolpidem, benzodiazepines, diphenhydramine) and worsening respiratory function (e.g., benzodiazepine use in end-stage COPD).[4]

- **Sedating antidepressants** – Consider for concomitant insomnia and depression; not recommended to treat insomnia in patients who are not depressed because the sedating effect tends to be short-lived and other side effects are common.
    - Doxepin (Sinequan®) – anticholinergic side effects (dizziness, dry mouth, blurred vision, constipation, and urinary retention) limit its utility although antihistamine properties may be useful for patients with concomitant, chronic pruritus
    - Trazodone (Desyrel®) - less anticholinergic than doxepin; an observational study in patients with Alzheimer disease and other dementias with insomnia reported that two-thirds of patients derived a benefit from trazodone dosed at 50mg[11]
    - Mirtazapine (Remeron®) - some evidence for insomnia in depression

- **Nonbenzodiazepine hypnotics** – Limited data suggest that they may be safer than benzodiazepines in patients with respiratory disease[12] and that they do not predispose patients to tolerance with longer-term use;[13] may cause somnolence, drowsiness, dizziness, and ataxia.
    - Eszopiclone (Lunesta®)
    - Zaleplon (Sonata®)
    - Zolpidem (Ambien®)

- **Selective melatonin receptor agonists** – In contrast to benzodiazepines these are non-habit forming and do not appear to have the adverse effects associated with other hypnotics. Agents

in this class are metabolized primarily through the CYP450 1A2 pathway and thus are associated with drug-drug interactions with inhibitors and inducers of this isoenzyme. Access the Flockhart Cytochrome P450 Drug Interaction Table for more information on inhibitors and inducers of isoenzyme 1A2.

  - Ramelteon (Rozerem®)

- **Benzodiazepine hypnotics** – Their most appropriate use is therapy in patients with insomnia caused by anxiety or depression. Outside of anxiety-induced insomnia, it is recommended to generally avoid this class based on the longer half-lives of several, higher risk of dependence and habituation, and the availability of safer options.
  - Agents indicated for insomnia: estazolam (ProSom®), flurazepam (Dalmane®), temazepam (Restoril®), triazolam (Halcion®), and quazepam (Doral®)
  - Agents used off-label for insomnia: lorazepam (Ativan®), alprazolam (Xanax®), oxazepam (Serax®), diazepam (Valium®), clonazepam (Klonopin®)

- **Dual orexin receptor antagonists (DORAs)** – These medications block neurotransmitters that promote wakefulness. Medications in the class are not proven more effective than other sleep aids, may cause sleep paralysis, interact with one of the major isoenzymes of the CYP450 system (3A4)[14] and are currently cost-prohibitive.
  - Lemborexant (Dayvigo®)
  - Suvorexant (Belsomra®)

- **Over-the-counter remedies**
  - Diphenhydramine (Benadryl®) – Anticholinergic adverse effects (e.g., dry mouth, decreased cognitive function, delirium), the rapid development of tolerance, and the lack of safety data in palliative care patients limit the use of this sleep aid option.
  - Melatonin – Available literature is inconsistent regarding dose-response relationships, benefits, and risks, although most experts believe that, at doses ranging from 0.3 to 20 mg, melatonin is well tolerated without major adverse effects.[4] Commonly reported adverse effects include vivid dreams and nightmares, dizziness, daytime sleepiness, depression, irritability, stomach cramps.

MONITORING [2]

- Central nervous system (CNS) depressant effects
  - Include impaired alertness, motor incoordination, and next-morning impairment
  - Highest risk with benzodiazepines and DORAs
  - Lowest risk with low-dose doxepin and ramelteon

- Abnormal thinking and behavioral changes
  - Includes hallucinations, agitation, and amnesia

- Complex sleep-related behaviors
    - Includes sleepwalking, driving, making telephone calls, eating, and having sex while not fully awake
    - More common with zolpidem, zaleplon, and eszopiclone

- Risk of worsening depression and suicidal ideation

PATIENT CASE ASSESSMENT AND RECOMMENDATIONS

DB's insomnia is causing him suffering and is disruptive to those around him. Assessing sleep hygiene is an important first step to identifying issues that may be contributing to insomnia. The frequent day-time napping may be contributing to his insomnia issues. In addition, dexamethasone, which may be stimulating for patients, is being administered at 8AM and 8PM.

Initial recommendations:

1. Incorporate nonpharmacological strategies to support a normal sleep-wake cycle
2. Adjust the administration time for the second dose of dexamethasone to 12PM

DB's dexamethasone regimen was changed to 8AM and 12PM administration times. The facility staff kept DB active during daytime hours including morning walks when possible and moved him to a room that gets plenty of natural light during the day. These interventions provided some benefit initially which was enhanced when DB's family became more engaged in his care and began visiting earlier in the day.

After two weeks DB was now sleeping close to 6 hours every night compared to his previous 3 hours (a goal for efficacy that was set with staff and family at initiation). They also note that he is less nauseous, appetite is improved and appears to be less anxious during interactions.

For more on mood and behavioral issues in hospice, consider review of these related topics:

- Depression at End of Life
- Discontinuing Dementia Medications
- Agitation in a Nursing Home
- Recognizing Delirium in Home Hospice
- Symptom Management of Brain Metastases

REFERENCES:

1. Chawla J. Insomnia. In: Medscape Drugs & Diseases: Neurology. Benbadis SR, ed. Updated January 5, 2020. Article link
2. Neubauer DN. Pharmacotherapy for Insomnia in Adults. In: UpToDate. Benca R, et al., eds. Waltham, MA: UpToDate, Inc. Updated April 4, 2021.
3. Owens JA. Pharmacotherapy for Insomnia in Children and Adolescents: A Rational Approach. In: UpToDate. Chervin RD, Eichler AF, eds. Waltham, MA: UpToDate, Inc.; Updated September 10, 2020.
4. Hirst JM. Overview of Insomnia in Palliative Care. In: UpToDate. Block SD, et al, eds. Waltham, MA: UpToDate, Inc.; Updated May 26, 2021.
5. Kvale EA, Shuster JL. Sleep disturbance in supportive care of cancer: a review. *J Palliat Med.* 2006 Apr;9(2):437-50.
6. Hugel H, et al. The prevalence, key causes, and management of insomnia in palliative care patients. *J Pain Symptom Manage*. 2004;27(4):316.
7. Mercadante S, et al. Sleep Disturbances in Patients with Advanced Cancer in Different Palliative Care Settings. *J Pain Symptom Manage.* 2015 Dec;50(6):786-92.
8. Yennurajalingam S, et al. Patient-reported sleep disturbance in advanced cancer: frequency, predictors, and screening performance of the Edmonton Symptom Assessment System sleep item. *BMJ Support Palliat Care*. 2017;7(3):274.
9. Arnold R, et al. Palliative Care Network of Wisconsin Fast Facts #104: Insomnia: Non-Pharmacologic Treatments. July 2013. Article link
10. Clinical Resource, "Comparison of Insomnia Treatments." Pharmacist's Letter/Prescriber's Letter. May 2020.
11. McCleery J, Cohen DA, Sharpley AL. Pharmacotherapies for sleep disturbances in Alzheimer's disease. *Cochrane Database Syst Rev.* 2014; :CD009178.
12. Sharafkhaneh A, Jayaraman G, Kaleekal T, et al. Sleep disorders and their management in patients with COPD. *Ther Adv Respir Dis.* 2009; 3:309.
13. Randall S, Roehrs TA, Roth T. Efficacy of eight months of nightly zolpidem: a prospective placebo-controlled study. *Sleep*. 2012; 35:1551.
14. Indiana University School of Medicine. Department of Medicine. Clinical Pharmacology. Flockhart Cytochrome P450 Drug Interaction Table. Site link