



PALLIATIVE CARE CASE OF THE MONTH

“DORA the Explorer Exploring the Novel Dual Orexin Receptor Antagonists (DORAs) for Insomnia”

by
Kendall Downer, MD

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Case: A 60 year-old female who was diagnosed six years ago with metastatic non-small cell lung cancer (adenocarcinoma) with metastases to adrenal glands, lungs, and liver, and who had been on a clinical trial drug, was admitted for acute cholecystitis and liver abscess. She stabilized after antibiotics and percutaneous cholecystostomy tube placement. She had recently been seen by our outpatient palliative care colleagues for insomnia; as an inpatient, she continued to report distress over insomnia to her inpatient providers, for which the inpatient palliative care team was consulted. She was a highly functional woman who had recently retired from running a biotech company with her husband. She reported waxing and waning insomnia that predated her cancer diagnosis and was associated with social stressors. Her most recent period of insomnia started about 2-3 months ago. Her nighttime symptoms were sleep maintenance disturbances, early morning awakenings, and non-restorative sleep, but not sleep latency issues (i.e. difficulty falling asleep). Her daytime symptoms were low energy level, impaired concentration, and low self-esteem. She did not have OSA, snoring or abnormal movements during her sleep including restless leg symptoms. She did not stay in bed if she could not fall back asleep. She did not consume caffeinated drinks past noon, nor alcohol. She denied depression and anxiety severe enough to impair function, but she had ongoing fears about her mortality, its impact on her family, and her loss of identity. She denied ruminations and negative thoughts keeping her awake. She had excellent prognostic awareness, was actively making meaningful memories with her family, and was creating legacy projects.

To help manage her insomnia, she had tried many pharmacologic interventions in the past including melatonin, Benadryl, zolpidem, eszopiclone, trazodone, sertraline, amitriptyline, buspirone, and marijuana in the past – all either without effect or with adverse effect. At the time of the inpatient consult, she was on clonazepam 1mg TID; a recent trial of substituting temazepam 15mg for her bedtime dose of clonazepam had been ineffective. She declined cognitive behavioral therapy because she did not want to use her limited time on therapy when she could be doing other things. Review of medications did not reveal any offending agents such as steroids. Given her financial resources, distress over sleep and fatigue, and inability to pursue behavioral interventions, a shared decision making conversation for a trial of a dual orexin receptor antagonist (DORA) occurred.

Diagnosis: Insomnia is a quantitative or qualitative dissatisfaction with sleep. The DSM-5, International Classification of Sleep Disorders Text Revision 3rd edition, and ICD-10 each defines insomnia slightly differently, but they generally include the following:

1. Nighttime characteristics: difficulty initiating or maintaining sleep, or waking up earlier than desired with an inability to return to sleep.
2. These sleep difficulties occur despite adequate opportunity for sleep.
3. These sleep difficulties are not solely explained by another condition or substance
4. Daytime characteristics: sleepiness, fatigue without sleepiness, poor attention/concentration, mood disturbance, reduced motivation, functional (occupational, social, interpersonal) impairment, ongoing worry about sleep, hyperactivity, impulsivity, or aggression.

Diagnosis is strictly based on the patient perception of sleep complaints rather than objective measures such as polysomnography (PSG), because there is substantial discrepancy between PSG data and patient reporting. Because recall error is a challenge both to making a diagnosis and elucidating exacerbating factors, the use of sleep diaries (such as this one) can be exceptionally helpful. Not only can sleep diaries provide accurate history and response to treatment, but these diaries may also help patients identify exacerbating factors themselves and correct their behaviors or environment on their own.

Differential Diagnosis: Important to rule out

1. Other sleep disorders such as OSA, restless leg syndrome, parasomnias, circadian rhythm disorders
2. Hypothyroidism
3. Depression
4. Pain
5. Medications
6. Sequelae of cancer treatments

Models of insomnia:

The traditional model of insomnia – the 3P model - is largely a psychological one based on three factors - predisposing, precipitating, and perpetuating factors. Predisposing factors are personal characteristics that make a person more or less susceptible to insomnia. An acute or chronic stressor precipitates the onset of insomnia. In many cases when the stressor resolves, so does the insomnia. However, sometimes maladaptive behavioral and cognitive responses develop to this sleep disturbance (frequent naps, going to bed earlier to compensate for sleep loss, worrying about daytime functioning) and perpetuate the insomnia even long after stressor is gone¹.

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More recently, this model has expanded to include neurobiological changes of a physiologic hyperarousal state. People suffering from insomnia often have decreased heart rate variability indicating reduced parasympathetic tone, elevated whole-body metabolic rate, and elevated cortisol during the early sleep period in patients ².

The 3P model is also adapting to new understandings of homeostatic sleep regulation on a neuronal level. Orexins (also known as hypocretins) are neuropeptides produced in the hypothalamus that bind to wake-promoting neurons in the locus coeruleus (which releases norepinephrine), the tuberomammillary nucleus (which releases histamine), and the raphe nuclei (which release serotonin) and sleep-promoting neurons in the ventrolateral preoptic nucleus (VLPO). The action of orexin receptors on both the wake-promoting nuclei and sleep promoting nuclei ultimately produce wakefulness.

Treatment:

Nonpharmacologic

First line treatment is generally Cognitive Behavioral Therapy – Insomnia (CBT-I), which includes 6 to 8 one-hour sessions with a trained therapist that focuses on both the counterproductive behaviors and cognitive distortions that perpetuate insomnia. The four core components of CBT-I are sleep restriction therapy, stimulus control therapy (strengthening association with sleep and the bedroom and weakening association with arousal and the bedroom by removing tvs and smartphones from the bedroom), sleep hygiene, and cognitive therapy. CBT-I is equally effective as sedative-hypnotics in the short term (4-8 weeks) and is much more effective in the long term (12+ weeks)¹. As with other types of therapy, the effectiveness of CBT-I is highly dependent upon the therapist's ability to garner patient “buy-in.” For patients who do not want such a large commitment, brief behavioral therapy for insomnia is an abbreviated version of CBT-I focusing solely on the two behavioral components: sleep restriction therapy and stimulus control therapy. Of note, providing only sleep hygiene education is not effective outside of CBT-I. Patients in Pittsburgh can be referred to multiple clinics for CBT-I, including:

1. UPMC’s Sleep Medicine
<https://www.upmc.com/services/pulmonology/our-services/sleep-medicine/conditions/insomnia#treatment>
2. Western Wellness
<https://www.upmc.com/services/behavioral-health/programs/adult/western-wellness-program>
3. The Hillman Cancer Sleep Clinic
<https://hillman.upmc.com/patients/support-services/sleep-clinic>

Although less rigorously studied, relaxation techniques such as progressive muscle tensing and relaxing, guided imagery, paced diaphragmatic breathing, and meditation can also reduce time to sleep.

Pharmacologic

The latest clinical practice guideline on chronic insomnia⁴ from the American Academy of Sleep Medicine does not provide recommendations on first line treatments for insomnia. However, it does specifically recommend against using melatonin, trazodone, and diphenhydramine. Choice of initial agent is dependent on risk of adverse events and comorbid symptoms. Starting doses of several commonly used pharmacologic agents can be found here.

Orexin receptor antagonists

Mechanism

A new class of medications, the dual orexin receptor antagonists (DORAs), inhibit the orexin receptors, leading to reduced wakefulness signals and overall increased onset and maintenance of sleep.

Efficacy

In large, well-performed RCTs, all DORAs performed better than placebo in both objective measures (polysomnography) and subjective measures (self-report in sleep diaries) of sleep^{5–8}. In all the trials, the effect of DORAs was quick. Participants noted subjective improvement in sleep complaints in 1-2 days. The effect was persistent for 3-6 months. Only one RCT compared a DORA to another pharmacologic treatment, zolpidem 6.25mg. Though this study found that Lemborexant improved objective measures of sleep onset and maintenance compared to zolpidem, it did not show any difference in patient-perceived insomnia severity or daily functioning compared to zolpidem⁶. Since the goal of our interventions is to improve patients’ experience of insomnia rather than objective clinical measures, one could draw the conclusion that DORAs and zolpidem are equally effective, and the deciding factor should come down to cost and potential for adverse effects, especially in elderly patients.

Safety

Due to its selectivity compared to traditional pharmacologic agents for insomnia, DORAs may have a better safety profile. This class of medications are not accompanied by discontinuation side effects such as rebound insomnia. They have similar adverse effect rates as placebo and do not appear to cause respiratory depression in patients with mild and moderate COPD^{9,10}. The most common side effects are headache (~15%) and somnolence (~15%). In addition, the pharmacokinetics of lemborexant were not sufficiently altered in renal impairment, though caution must be taken in liver impairment.

Costs

For a 30-day supply, cost ranges from \$350 for lemborexant to \$500 for daridorexant (with GoodRx coupon).

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Considerations

While the DORAs show promise for their novel mechanism of action, this class may be less effective for insomnia related to chronic stress from living with serious illness. Since the pathophysiology of insomnia is so complex, it is unlikely that a single drug will be effective, and we should set expectations on efficacy.

Case Conclusion:

Because DORAs have a short time to effect, we decided to pursue a five-day trial of Lemborexant to limit financial toxicity in the event the drug was not efficacious. The patient was prescribed five doses of Lemborexant 10mg QHS after her acute medical issues had stabilized. If she found the medication effective, she would call the Hillman palliative care clinic to request a refill and pay the high cost of the drug. She was given a GoodRx coupon for lemborexant which made the cost about \$12 per pill.

A few months later, she presented to Shadyside confused and dying from cancer, and insomnia was not the critical focus of her encounter. Unfortunately, we do not know the outcome for this patient, but this five-day trial strategy may be considered in patients who have the financial resources to pay for these medicines and are refractory to other interventions.

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