UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Dual Orexin Receptor Antagonists (DORAs) for chronic insomnia

Background:

Efficacy, safety, and difficulty accessing treatments create significant unmet needs for treating insomnia. Since 2014, the FDA approved 3 drugs of a novel mechanism (dual orexin receptor antagonists, or DORAs) for primary insomnia in adults for sleep onset insomnia and sleep maintenance insomnia: suvorexant (10-20mg), lemborexant (5-10mg), and daridorexant (25-50mg). Orexin (hypocretin) signaling pathway is an upstream controller of the sleep-wake cycle and binding of orexin A and B at the receptors induces wakefulness. This class of medication competitively inhibits the orexin receptor 1 and orexin receptor 2 – hence the name dual orexin receptor antagonists (DORAs) - and induces and maintains sleep. Due to its selectivity in receptor binding, DORAs are expected have fewer nonspecific side effects.

In 2017, a task force of insomnia experts published a guideline (2017 Insomnia Guidelines) on pharmacologic treatment of insomnia. Although this guideline makes weak recommendations for all treatments due to paucity of robust research, it did endorse a weak recommendation in favor of DORAs based on low quality evidence.

Importance:

Insomnia is of considerable importance to patients and is highly prevalent (~60%) in palliative care patients. This novel drug class may provide our patients with an effective and safe alternative to existing treatments. It is important for palliative care clinicians to be aware of the newer data for these agents in the treatment of insomnia.

The Literature:

JAMA Netw Open. 2019 Dec; 2(12): e1918254.

Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial (The SUNRISE 1 trial)

Objective: To measure the safety and efficacy of lemborexant compared to placebo and standard of care pharmacologic intervention in adults >55 with a confirmed insomnia disorder of moderate severity or higher.

Methods: randomized, double-blind, multinational phase 3 study

- Interventions: placebo, zolpidem tartrate ER 6.25mg, lemborexant 5 mg, 10 mg
- Patients were treated for 30 nights followed by a 14 day follow up period
- Patients completed a baseline polysomnography (PSG) test, PSG on night 1 and 2, and PSG on night 29 and 30
- patients completed daily entries in a sleep diary

Outcomes:

- Primary outcome: change in sleep onset (latency to persistent sleep) from baseline PSG after 1 month of treatment
- Secondary:
    - objective change from baseline in sleep maintenance (sleep efficiency, wake after sleep onset total, wake after sleep onset in second half of the night) as measured by PSG
    - subjective change from baseline in sleep onset, sleep maintenance (subjective sleep efficiency, subjective wake after sleep onset, overall Insomnia Severity, daily functioning, incidence of rebound Insomnia) as measured by a sleep diary
    - withdrawal side effects
    - Adverse events/safety outcomes

Results: (N = 1006, 86% female, median age 63, 95% completion rate)

- Both lemborexant 5 and 10mg significantly improved OBJECTIVE measurements of sleep onset (latency to persistent sleep) and sleep maintenance (sleep efficiency, wake after sleep onset total, and wake after sleep onset in second half of the night) compared to both placebo AND zolpidem both at treatment onset and persistently.
- Both lemborexant 5 and 10mg significantly improved SUBJECTIVE measurements of sleep onset (subjective sleep onset latency) and sleep maintenance (subjective sleep efficiency, subjective wake-after-sleep-onset) compared to placebo both at treatment onset and persistently.
- Lemborexant significantly improved patient-perceived insomnia severity and daily functioning compared with placebo.
- Although lemborexant improved OBJECTIVE measures of sleep onset and maintenance compared to zolpidem, its effect on SUBJECTIVE measurements was inconsistent. Compared to zolpidem, lemborexant improved subjective sleep onset latency but not subjective measures of sleep maintenance, patient-perceived insomnia severity, or daily functioning.
- The authors estimate that lemborexant treatment effectively increased sleep time by more than 60 minutes per night.
- No evidence of rebound insomnia or withdrawal side effects upon discontinuation.
- None of the 8 serious adverse events were treatment-related.

Conclusion:

- Lemborexant 5 and 10mg improves sleep onset and sleep maintenance and may be more effective than zolpidem 6.25mg.
- The effect of lemborexant is fast-onset, persistent, and not accompanied by discontinuation side effects.
- Lemborexant was safe and did not have adverse side effects at higher rates than placebo. The most common side effects were headache (~15%) and somnolence (~15%).

CLINICAL PEARL: DORAs seem to be safe and effective for chronic insomnia; unfortunately, cost likely limits their use overall.

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Sleep. 2020 Sep 14;43(9):zsaa123

Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2

Objective: a follow up study to SUNRISE 1 evaluating the long-term efficacy and safety of lemborexant

Methods: participants completed daily entries in a sleep diary

Results: (N= 949)

- Lemborexant 5 and 10mg significantly improved subjective measures of sleep onset, sleep maintenance, and sleep quality compared to placebo at 6 months of treatment
- Serious TEAEs were uncommon and similar across groups
- Most common AE was somnolence, with increasing incidence with higher dose (10mg vs. 5mg) of lemborexant
- Discontinuation of treatment due to any adverse event was 8.3% for lemborexant 10mg, 4.1% for lemborexant 5mg and 3.8% for placebo

Conclusion: The efficacy and safety of lemborexant observed in the SUNRISE 1 trial extended to 6 months of therapy

J Clin Sleep Med. 2016 Sep 15;12(9):1215-25

Suvorexant in Patients with Insomnia: Pooled Analyses of Three-Month Data from Phase-3 Randomized Controlled Clinical Trials

Objective: To measure the safety and efficacy of suvorexant 20mg compared to placebo in adults >18 with a confirmed insomnia disorder of moderate severity or higher.

Methods: Prespecified analysis of pooled data from two identical randomized, double-blind, placebo-controlled phase 3 studies with very similar protocols/measurements to the above lemborexant trial. There was no active comparator.

Results: (N =)

- Suvorexant 20 mg significantly improved sleep onset and sleep maintenance by both objective and subjective measurements compared to placebo. Efficacy was noted both initially and persistently (at 1 month and at 3 months) except for sleep onset as measured by PSG at 3 months.
- 3% of patients discontinued suvorexant due to adverse effects after 3 months
- After 3 months of treatment, no withdrawal or rebound insomnia occurred upon discontinuation

Conclusion:

- Suvorexant 20 mg improved sleep onset and maintenance over 3 months of nightly treatment and was generally safe and well tolerated.

Neuropsychopharmacol Rep. 2021 Dec; 41(4):450-458.

Evidence-based insomnia treatment strategy using novel orexin antagonists: A review

- This network meta-analysis used RCT comparisons of suvorexant and lemborexant to placebo in order to estimate a head-to-head comparison of suvorexant and lemborexant.
- The data suggests that lemborexant 10mg has a greater effect on improving sleep onset AND sleep maintenance than suvorexant 20mg or lemborexant 5mg.
- However, this improvement in efficacy comes with a greater risk of discontinuation due to adverse effects.

Bottom Line:

- DORAs consistently demonstrate efficacy for sleep onset and maintenance outcomes, have a good safety profile, lack rebound insomnia or withdrawal symptoms, but are limited by cost
- All DORAS are similarly expensive, ranging from $330 for lemborexant to $500 for daridorexant (with GoodRx coupon), and are often not covered by insurance **or require prior authorization after exhausting other pharmacologic options for sleep**
- DORAs may be an effective alternative to treating insomnia in the palliative care population but the risks and benefits have not been specifically studied in this population. Read more about insomnia in palliative care: Insomnia in Palliative Care
- DORAs are not on UPMC inpatient formulary, see UPMC guidelines for *acute* insomnia last updated 2016: UPMC Acute Insomnia Guidelines
- *If initiating a DORA, a reasonable approach is to start with Lemborexant 5mg PO at bedtime and increase to 10mg if not seeing therapeutic benefit. This approach aligns both cost and data suggesting superiority efficacy and similar safety to suvorexant.*

CLINICAL PEARL: DORAs seem to be safe and effective for chronic insomnia; unfortunately, cost likely limits their use overall.