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:

New Medication Review: Quviviq® (daridorexant) for Insomnia

Background:

Daridorexant is an orexin receptor antagonist
- Initial approval: 2022
- Indicated for: insomnia, sleep onset and/or sleep maintenance
- Available as: 25mg and 50mg tablets

Importance:

Around 60% of the palliative care population reports insomnia. It is important to for palliative care clinicians to be aware of new potential treatment options that come to market along with the evidence to support their use for symptomatic relief.

Pharmacology:

Mechanism of Action	Orexin receptor antagonist (OX1R and OX2R); orexin signaling system plays a role in wakefulness; blocking the binding of orexin is thought to suppress wake drive
Absorption	Tmax within 1-2 hours, bioavailability of 62% Time to sleep onset may be delayed if taken with or soon after a meal
Distribution	99.7% bound to plasma proteins
Metabolism	Hepatic via CYP3A4
Excretion	Half-life is 8 hours Primary route of excretion is feces followed by urine primary as metabolites

Other Clinical Pearls:

Contraindications	Use in patients with narcolepsy
Warnings and Precautions	• CNS depression, daytime impairment (including driving), worsening of suicidal ideation, sleep paralysis, hallucinations, complex sleep behaviors (eg. sleepwalking, sleep-driving) • Has not been studied in patients with compromised respiratory function (eg. OSA, severe COPD) • Reduced ability to drive safely morning after taking medication • Do not take unless able to stay in bed for a full night (at least 7 hours) before you must be active again
Adverse Reactions	Headache (>5%), somnolence/fatigue (>2%), dizziness (>2%), nausea (>2%)
Drug Interactions	• Avoid co-administration with CNS depressants or alcohol, strong CYP3A4 inducers (eg. anticonvulsants, barbituates, carbamazepine, phenytoin, glucocorticoids) or inhibitors (eg. azole antifungals, antiretrovirals) • Reduce dose to 25mg when used with moderate CYP3A4 inhibitors
Dose Adjustments	Reduce for moderate hepatic impairment Not recommended to use in severe hepatic impairment No adjustments necessary for renal impairment
Other	Has not shown withdrawal symptoms when abruptly discontinued

The Literature:

Lancet Neurol. 2022 Feb; 21(2):125-139.

Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

Objective: To assess safety and efficacy of daridorexant, a novel orexin receptor antagonist, on night-time and daytime symptoms of insomnia

Methods: Adults (aged ≥18 years) with moderate-severe insomnia disorder were randomly assigned (1:1:1) to receive daridorexant 50 mg, 25 mg, or placebo (study 1) or daridorexant 25 mg, 10 mg, or placebo (study 2) every evening for 3 months; intention to treat

Outcomes:

Primary: Change in baseline in wake time after sleep onset (WASO) and latency to persistent sleep (LPS), measured by polysomnography at months 1 and 3

Secondary: change in baseline in self-reported total sleep time and the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score at months 1 and 3 (daily eDiaries), change from baseline in other IDSIQ domain scores and total IDSIQ score at months 1 and 3, change from baseline in total sleep time at months 1 and 3 measured by polysomnography

Results: Intention to treat analysis: Between 20-25 patients did not complete study period in each group but were included in the analysis

Trial 1: n = 930; daridorexant 25 mg (n=310), daridorexant 50 mg (n=310), or placebo (n=310); 67% female, 39% older than 65

- Efficacy
  - WASO significantly reduced in 50mg vs. placebo: least squares mean difference (LSM) -22.8 min (month 1) and -18.3 min (month 3) and 25mg vs placebo: -12.2 min (month 1) and -11.9 (month 3)
  - LPS significantly reduced in 50mg vs. placebo: -11.4 mins (month 1) and -11.7 min (month 3); 25mg vs. placebo: -8.3 min (1 month) and -7.6 min (3 month)
  - Self-reported TST significantly increased from baseline in 50mg vs. placebo: 22.1 min (month 1) and 19.8 min (month 3); 25mg vs. placebo: 12.6 min (month 1) and 9.9 min (month 3)
  - IDSIQ sleepiness domain score was significantly reduced 50mg vs. placebo from baseline at months 1 and 3 (-1.8 and -1.9 respectively); 25mg vs. placebo: no significant difference at months 1 or 3

Trial 2: n = 924; daridorexant 10 mg (n=307), daridorexant 25 mg (n=309), or placebo (n=308); 69% female, 39% older than 65

- Efficacy
  - WASO significantly reduced among 25 mg vs. placebo group: LSM -11.6 min (month 1) and -10.3 min (month 3) ; no significant difference in 10mg vs. placebo
  - Self-reported TST significantly increased in 25mg vs. placebo group: 16.1 min (month 1) and 19.1 min (month 3) ; no significant difference in 10mg vs. placebo
  - LPS: no significant difference in either group
  - IDSIQ sleepiness domain score: no significant difference in either group

Safety (both trials): most common ADE: headache, accidental overdose, dizziness, somnolence, nausea

Conclusion: *"Daridorexant 25 mg and 50 mg improved sleep outcomes, and daridorexant 50 mg also improved daytime functioning, in people with insomnia disorder, with a favourable safety profile"*

Discussion:

- Two phase 3 trials showed improvement in insomnia: sleep onset and/or sleep maintenance. Clinical relevance of outcomes likely dose dependent with 50mg with more improvement than 25mg
- See here for a Clinical Review
  - We do not have head-to-head data to compare daridorexant with other sleep agents
- It is fairly well-tolerated with similar side effects to other sleep agents on the market such as somnolence, dizziness, nausea, and headache. Does not seem to pose a higher risk than other agents already in use. Long-term safety outcomes not studied.
- It's expensive… Average wholesale price: $575 for 30-day supply; manufacturer Coupon is available
- Simple dosing regimen (once daily oral tablet taken ~30 minutes before bedtime); although is a Schedule IV controlled substance
- Inpatient Use at UPMC is restricted to continuation of home therapy

CLINICAL PEARL: Daridorexant (Quviviq®) is an orexin receptor antagonist approved in 2022 for sleep onset and/or maintenance insomnia.