Restful Sleep or Getting Up to Eat? Suvorexant (Belsomra®)

Alyssa Penick, PharmD
PGY1 Pharmacy Resident
UC Health - University of Cincinnati Medical Center

Insomnia

- Most common sleep disorder
- Defined as "the subjective perception of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep that results in daytime impairment"
- FDA Indication for Suvorexant:
  - Insomnia characterized by difficulties with sleep onset and or sleep maintenance

Pharmacology

- New MOA: Dual orexin or receptor antagonist (DORA)
  - Acts on both orexin A and orexin B
- Agonism of orexin is associated with wakefulness/alertness
- Loss of orexin neurons can cause daytime sleepiness, narcolepsy and cataplexy

Clinical Guideline on for the Evaluation and Management of Chronic Insomnia in Adults

- Goals for Treatment:
  - Improve sleep quality and quantity
  - Enhance daytime function
  - Reduce SOL and WASO
  - Increase TST

Suvorexant

- Shown effectiveness with SOL and WASO
- Reduced risk of dependency
- Reduced risk of rebound insomnia
- Concerns for suicidal ideation (0.2-0.7%)
- Reports of daytime somnolence 7-11%, increases with increasing doses
  - driving concerns noted
- Reduced clearance in obese patients and in women

Clinical Trial Data
Sun, et al. Study Design

- Randomized, double-blind, placebo-controlled crossover trial
- Administered 10mg, 50mg, or 100mg suvorexant or placebo
- 22 healthy males 18-45 years old for 4 weeks
- Assessed affects on sleep based on polysomography and residual effects based on psychomotor performance tests and subjective assessments using a questionnaire

Sun, et al. Suvorexant Efficacy

- Statistically significant changes in sleep found in all doses
- 50 and 100mg - statistically significant decrease in latency to persistent sleep and WASO, also increases in sleep efficiency and TST
- 10mg - statistically significant decrease in WASO

Sun, et al. Suvorexant Safety

- Dose dependent residual side effects
- Statistically significant reaction time noted in 100mg group (not in 50mg or 10mg)
- Subjective questionnaire revealed patients taking 50mg and 100mg reported more difficulty awakening and maintaining alertness compared to placebo

Herring, et al. Study Design

- Randomized, double-blind, placebo, controlled polysomnography study
- 4-week treatment period with one week placebo wash out period
- 228 Men and women 18-64 years old with DSM IV diagnosis of primary insomnia
- Received doses of 10 mg, 20mg, 40mg or 80mg

Herring, et al. Suvorexant Effectiveness

- TST ranged from 22-62 minutes depending on dose
- No difference in sleep awakenings
- 40 and 80mg doses, patients self reported fTST better than placebo
- 20mg, 40mg, and 80mg showed improved insomnia according to Insomnia Severity Index, specifically improvements in "difficulty falling asleep" and "satisfaction with current sleep"
- Overall results suggest 40mg and 80mg have the best results for treating insomnia
**Herring, et al. - Adverse Effects**

- 80mg dose, 1 case of visual hallucination
- Dose related increase in adverse events
- Most commonly reported adverse effects: somnolence, headache, dizziness, abnormal dreams, upper respiratory tract infection, urinary tract infection, and increased alanine aminotransferase
- 2 cases of sleep paralysis (80mg lasting 2-3 min and 40mg lasting 10 min)
- 1 case of excessive daytime sleepiness- 80mg lasting 4 hours

**Herring, et al. Suvorexant Safety**

- No rebound insomnia detected when suvorexant was stopped, evaluated by sTST
- No differences between groups that would indicate withdrawal symptoms, evaluated by questionnaire

**Michelson D, et al. Study Design**

- RCT, parallel trial at 106 centers
- 522 Patients 18 years or older with primary insomnia (DSM-IV-TR criteria)
- 40mg for patients younger than 65 years, 30mg for patients 65 years and older
- 1 year and then randomized to abruptly discontinue and take placebo for 2 months

**Michelson D, et al. - Limitations**

- Trial did no include objective tests of daytime function or assessments of quality of life and work performance
  → limited information on next-day residual effects
- Did not include objective, polysomnographic measurements of sleep, relied on patient self-reporting
- Comparison to placebo, not active comparator

**Michelson D, et al. Suvorexant Efficacy**

- Most common adverse effect somnolence 13% in suvorexant group and 3% in placebo
- At month 1, suvorexant showed greater efficacy than placebo in improving subjective TST (38.7 minutes vs. 16.0 minutes; p=0.0001) and subjective time to sleep onset (18.0 minutes vs. 8.4 minutes; p=0.0002)
Suvorexant Adverse Effects

<table>
<thead>
<tr>
<th>Category</th>
<th>Suvorexant</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>3 (1.6%)</td>
<td>4 (2.6%)</td>
<td>-0.1 (1.0)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>4 (2.1%)</td>
<td>4 (2.6%)</td>
<td>-0.1 (2.0)</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>26 (11.6%)</td>
<td>15 (17.6%)</td>
<td>0.1 (2.0)</td>
</tr>
<tr>
<td>Sleep paralysis</td>
<td>5 (2.4%)</td>
<td>3 (3.9%)</td>
<td>-0.1 (3.0)</td>
</tr>
<tr>
<td>Sleep-related accidents</td>
<td>2 (1.0%)</td>
<td>3 (3.9%)</td>
<td>-0.1 (2.0)</td>
</tr>
<tr>
<td>Excessive daytime somnolence</td>
<td>5 (2.6%)</td>
<td>3 (3.9%)</td>
<td>-0.1 (1.0)</td>
</tr>
<tr>
<td>Total number of adverse events</td>
<td>22 (10.2%)</td>
<td>14 (16.4%)</td>
<td>0.1 (6.0)</td>
</tr>
</tbody>
</table>

Michelson D, et al.
Adverse Effects
- Non-statistically significant adverse effects:
  - 4 patients in suvorexant group experienced suicidal ideation
  - Motor vehicle accidents in suvorexant group 22 (6%) and 8 (4%) in placebo group
  - 2 cases of sleep paralysis
  - 1 fall caused by possible cataplexy in patient taking suvorexant

Warnings & Precautions
- CNS depressant effects
- Daytime impairment
- Abnormal thinking and behavioral changes
- Worsening of depression/suicidal ideation
- Patients with compromised respiratory function
- Sleep paralysis, hallucinations, cataplexy-like symptoms

Disease-Specific Warnings
- Depression
  - Suvorexant may worsen symptoms of depression or suicidal ideation
  - Increasing risk with increased doses
- COPD and Sleep Apnea
  - Suvorexant may compromise respiratory function

Common Adverse Effects
- Somnolence (7%)
- Diarrhea (2%)
- Upper respiratory tract infection (2%)
- Cough (2%)
- Headache (7%)
- Dizziness (3%)
- Abnormal dreams (2%)

Drug Interactions
- P-gp inhibition
  - Monitor for increased digoxin levels
- CYP3A Inhibitors
  - Risk of increased exposure suvorexant
  - Avoid taking with strong inhibitors such as: ketoconazole, itraconazole, clarithromycin, ritonavir
  - Recommended decreased dose to 5mg suvorexant with moderate inhibitors such as: atazanavir, ciprofloxacin, diltiazem, verapamil, erythromycin, fluconazole, grapefruit juice
- CYP3A Inducers
  - Risk of decreased efficacy with strong inducers such as: rifampin, carbamazepine, phenytoin
Dosing & Dosage Form

- **Dosing**
  - 1 tablet 30 minutes before bedtime with at least 7 hours for sleep
  - Recommended to start at 10mg for most patients, may increase if tolerated but not effective at lower doses
  - Patients, especially elderly, obese patients, and women should be started on lowest dose possible

- **Dosage Form**
  - Tablets: 5mg, 10mg, 15mg, and 20mg

Suvorexant Safety and Efficacy Considerations

- **Controversy surrounding drug approval**
  - In 2013 Merck applied for FDA approval of suvorexant 30mg and 40mg doses
  - better efficacy but greater safety concerns in higher doses than lower doses
  - FDA denied approval for safety concerns, suggested re-applying with lower doses, but Merck argued smaller doses including the 10mg dose would not be effective
  - In 2014 FDA approves suvorexant 5mg, 10mg, 15mg, and 20mg doses
  - Lacks evidence for use of 5mg in studies
  - 10mg has significantly less efficacy than higher doses

References

- Mieda, M, et al. Orexin (hypocretin) receptor agonists and antagonists for treatment of sleep disorders.. CNS Drugs 2013 (27);2:83-90

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