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

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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

Lexicomp Online. Hudson, Ohio: Lexi-Comp; 2014; September 2014
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

SOL = sleep onset latency, time to fall asleep
LPS= latency to persistent sleep
WASO = wake time after sleep onset
TST = total sleep time
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. Study Design

- Evaluated sleep efficiency (defined as TST/time in bed) on night 1 and end of week 4
  - Significant dose-related improvement compared to placebo (P<0.01)
- Secondary endpoints were sleep maintenance (WASO) and sleep onset
  - Dose-related effects found for both
Suvorexant Effectiveness

- TST ranged from 22-62 minutes depending on dose
- No difference in sleep awakenings
- 40 and 80mg doses, patients self reported sTST 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

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)
Michelson D, et al. Suvorexant Efficacy

## Suvorexant Adverse Effects

<table>
<thead>
<tr>
<th>General categories of events</th>
<th>Suvorexant, N=521</th>
<th>Placebo, N=258</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 adverse event</td>
<td>362 (69.5%)</td>
<td>164 (53.6%)</td>
<td>5.9 (-1.1 to 13.1)</td>
</tr>
<tr>
<td>≥1 drug-related adverse event*</td>
<td>182 (34.9%)</td>
<td>53 (20.5%)</td>
<td>14.4 (7.8 to 20.6)</td>
</tr>
<tr>
<td>≥1 serious adverse event</td>
<td>27 (5.2%)</td>
<td>17 (6.6%)</td>
<td>-1.4 (-5.5 to 1.9)</td>
</tr>
<tr>
<td>≥1 serious drug-related adverse event*</td>
<td>1 (0.2%)</td>
<td>3 (1.2%)</td>
<td>-1.0 (-3.2 to 0.1)</td>
</tr>
<tr>
<td>Discontinued owing to adverse event</td>
<td>61 (11.7%)</td>
<td>22 (8.5%)</td>
<td>3.2 (-1.5 to 7.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Events showing an increase versus placebo</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>69 (13.2%)</td>
<td>7 (2.7%)</td>
<td>10.5 (6.8 to 14.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34 (6.5%)</td>
<td>5 (1.9%)</td>
<td>4.6 (1.6 to 7.4)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>26 (5.0%)</td>
<td>4 (1.6%)</td>
<td>3.4 (0.7 to 5.9)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10 (1.9%)</td>
<td>0</td>
<td>1.9 (0.4 to 3.5)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>9 (1.7%)</td>
<td>0</td>
<td>1.7 (0.3 to 3.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prespecified events of clinical interest</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal ideation</td>
<td>4 (0.8%)</td>
<td>0</td>
<td>0.8 (-0.7 to 2.0)</td>
</tr>
<tr>
<td>Events suggesting drug-abuse potential†</td>
<td>18 (3.5%)</td>
<td>10 (3.9%)</td>
<td>-0.4 (-3.8 to 2.2)</td>
</tr>
<tr>
<td>Complex sleep-related behaviours</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0.2 (-1.3 to 1.1)</td>
</tr>
<tr>
<td>Hypnagogic hallucination</td>
<td>3 (0.6%)</td>
<td>0</td>
<td>0.6 (-0.9 to 1.7)</td>
</tr>
<tr>
<td>Hypnopompic hallucination</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0.2 (-1.3 to 1.1)</td>
</tr>
<tr>
<td>Excessive daytime sleepiness‡</td>
<td>13 (2.5%)</td>
<td>2 (0.8%)</td>
<td>1.7 (-0.5 to 3.6)</td>
</tr>
<tr>
<td>Sleep paralysis</td>
<td>2 (0.4%)</td>
<td>0</td>
<td>0.4 (-1.1 to 1.4)</td>
</tr>
<tr>
<td>Sleep onset paralysis (adjudicated)</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0.2 (-1.3 to 1.1)</td>
</tr>
<tr>
<td>Cataplexy (adjudicated)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Falls‡</td>
<td>12 (2.3%)</td>
<td>8 (3.1%)</td>
<td>-0.8 (-3.9 to 1.5)</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

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References

• Mieda, M, et al. Orexin (hypocretin) receptor agonists and antagonists for treatment of sleep disorders.. CNS Drugs 2013 (27);2:83-90.
• Lexicomp Online.Hudson, Ohio: Lexi-Comp; 2014; September 2014.