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Belsomra®: A Novel Dual Orexin Receptor Antagonist for the Treatment of Insomnia

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Key Terms
Belsomra®, Benzodiazepine; Dual Orexin Receptor Antagonist; DORA, Insomnia, Insomnia Treatment, Orexin, Suvorexant

Introduction
Insomnia refers to a disease state that involves persistent difficulty falling asleep and/or frequent awakenings during sleep. Over 35 percent of the adult population exhibits one or more symptoms associated with insomnia, with 12 percent to 20 percent actually demonstrating a symptom profile sufficient for diagnosis of the disorder.1 The lack of restful sleep may lead to symptoms such as daytime fatigue, daytime sleepiness, memory or concentration deficits, anxiety, depression, irritability, reduced energy and lack of motivation. Furthermore, insomnia is associated with changes in mood, poor job performance, disturbed personal relationships and difficulty in carrying out daily activities. Ozminkowski and colleagues have estimated that insomnia results in an enormous economic loss to society of approximately $30 billion per year, mostly through reduced productivity and absenteeism.2 Thus, effective insomnia treatments could not only improve quality of life via symptom relief but also have tremendous economic benefits to society.

Several treatment options are available for the treatment of insomnia; however, adverse effects associated with these treatment options make the management of insomnia challenging. Recently, suvorexant (trade name Belsomra®) was approved by the U.S. Food and Drug Administration (FDA) on Aug. 13, 2014, as a Schedule IV drug for insomnia.3 Suvorexant is a dual orexin receptor antagonist, and is the first medication in this class, offering a novel mechanism for the treatment of insomnia. This article will discuss the role of orexin neurons in sleep, the mechanism of action of suvorexant, various clinical studies that demonstrate efficacy of suvorexant, and finally the role of the pharmacist in dispensing and managing patients taking suvorexant. Additionally, potential challenges and unanswered questions associated with suvorexant treatment will be discussed.

Insomnia: Diagnosis, Current Treatment Options and Challenges With Current Treatment
Insomnia can be broadly divided into primary and secondary insomnia.1 The diagnosis of primary insomnia is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a sleep disturbance that affects sleep quantity or quality, causes impairment in activities of daily living, occurs at least three nights per week for at least three months, and is not due to substance use, other medical conditions and other sleep-wake disorders.4 Additionally, insomnia can be secondary to other medical diseases, may exacerbate other

Objective
After completion of this program, the reader should be able to:
1. List medications currently approved for treatment of insomnia.
2. Enumerate the limitations of benzodiazepines and non-benzodiazepines for insomnia treatment.
3. Describe the mechanism of action of suvorexant.
4. List the major adverse effects of suvorexant.
5. Describe the role of the pharmacist in counseling and managing patients on suvorexant therapy.

Abstract
Insomnia is a disease state characterized by a persistent difficulty in falling asleep, and results in enormous health-related and economic costs to both the individual and society. Several medications are currently available for the treatment of insomnia; however, these medications are associated with several limitations including anterograde amnesia, dependence, withdrawal symptoms upon stopping the medication and rebound insomnia. The U.S. Food and Drug Administration recently approved suvorexant (Belsomra®) as a treatment for insomnia. Suvorexant is a first-in-class dual orexin receptor antagonist for the treatment of insomnia. This review will first describe the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria used for diagnosing insomnia and current treatment options for insomnia and then will characterize the role of orexin neurons in the pathophysiology of sleep. Subsequently, pivotal clinical trials that evaluated the safety, efficacy and adverse effects associated with suvorexant will be discussed. Finally, the review will delineate the role of the pharmacist in managing patients on suvorexant. Current available data suggests that suvorexant possesses superior efficacy compared to placebo and a better safety profile compared to alternative insomnia treatments. Further study of suvorexant in larger and diverse populations is necessary to confirm existing findings. In particular, trials with longer durations, direct comparisons with currently available sleep medications and more participants would increase the confidence among prescribers and healthcare providers and promote the use of suvorexant for treatment of insomnia.
There are a wide range of treatment options available for insomnia patients. The two primary treatment strategy groups are cognitive-behavioral therapy (CBT) and pharmacological therapy. These treatment options are often used effectively in combination. Cognitive-behavioral therapy most commonly includes behavioral adjustments, such as having patients maintain a sleep diary, changing specific habits associated with pre-sleep behavior, and other priority changes for the patient. Currently, most commonly used medications for insomnia target the inhibitory neurotransmitter gamma aminobutyric acid (GABA). Broadly, pharmacological agents acting on the GABA receptors can be divided into benzodiazepines (BZD) such as flurazepam, triazolam, estazolam, and lorazepam, and non-benzodiazepines (non-BZD) such as zolpidem, eszopiclone, zaleplon, and zopiclone. In addition to GABA, histamine neurotransmission has been an important target for insomnia medications. Tricyclic antidepressants such as trazodone, doxepin and pivagabine, which have significant antihistaminic properties, and antihistamines such as diphenhydramine are sometimes used in the treatment of insomnia due to their sedative effects. Finally, a third group of drugs that are useful in insomnia treatment are anticonvulsants which can act by enhancing GABA neurotransmission or depressing neuronal activity in general.

Benzodiazepines and non-BZDs are the most common drug classes used as a product of their efficacy, however, they still present many challenges in clinical use. In terms of efficacy, both BZD and non-BZD drugs have been shown to significantly improve acute insomnia as measured by subjective total sleep time (sTST) (total length of time asleep, as measured by the patient) and time to sleep onset (sTSO) (total length of time from lying in bed to sleep initiation, as measured by the patient). Additionally, the adverse event profiles of BZD and non-BZD drugs are similar, with symptoms such as headache, fatigue and dizziness. BZDs are also associated with a number of serious adverse effects such as anxiety, anterograde amnesia, poor balance associated with an increase in falls and morning somnolence. Patients taking BZDs for insomnia also have reported abnormal sleep behaviors, such as sleep-related walking, eating, driving and sexual activity. Additionally, BZDs and non-BZDs are susceptible to abuse and dependency as they can produce either withdrawal or rebound insomnia upon treatment discontinuation, thus limiting their use for chronic insomnia. Currently, only eszopiclone (non-BZD) has been approved for chronic use in insomnia patients. Therefore, these concerns with adverse effects, abuse and dependency fostered a desire to develop a novel insomnia treatment that would offer patients a superior treatment option.

Suvorexant: A Novel Medication for Treatment of Insomnia

Suvorexant (Belsomra®) is a dual orexin receptor antagonist marketed by Merck Sharp & Dohme Corp. The action of suvorexant is achieved through interaction with a collection of neurons known as the orexin system, which coordinates the body's transition from a sleep-state to an alert-state. There are approximately 100,000 orexinergic neurons spread across the brain, but these neurons are located principally in the lateral hypothalamus and lower brainstem nuclei. The role of orexin in the sleep-wake cycle was elucidated by studying narcolepsy patients. Narcolepsy is a state characterized by excessive daytime sleepiness and intermittent uncontrollable episodes of daytime sleepiness. Narcolepsy patients were found to lack orexigenic neurons or have low levels of orexin, a neuropeptide. This discovery eventually led to the conclusion that the death of these neurons or absence of these neuropeptides is a leading cause in the narcolepsy-cataplexy disease state. Consistent with these findings, the knockout of orexin genes in animals resulted in the development of narcolepsy in animals. The effects of orexin released by orexigenic neurons is mediated by two receptors: orexin R1 (OX1R) and R2 (OX2R). Both orexin receptors are G-protein-coupled receptors. Animal studies support the important role of OX2R over OX1R in the regulation of the sleep-wake cycle. Binding of orexin to orexin receptors activates the brain's "wake-promoting system." Suvorexant reversibly inhibits both orexin receptors and, thus, promotes sleep by preventing activation of the wake-promoting system.

Clinical Studies Demonstrating Efficacy of Suvorexant

Several clinical studies have evaluated the efficacy and adverse effect profile of suvorexant. A summary of the trials discussed in this article can be found in Table 1.

Michelson and colleagues assessed the safety and efficacy of suvorexant over a one year period, followed by a two month discontinuation phase. They reported that suvorexant significantly improved sTST, sTSO and other common measures of sleep quality as compared to placebo over the course of therapy (P<0.0001). Specifically, a 9.5 minute average reduction in sTST and a 22.7 minute average increase in sTSO relative to placebo were demonstrated with suvorexant treatment. Importantly, no effect on mood was demonstrated, and the most common adverse effects were somnolence (13.2%), fatigue (6.5%), dry mouth (5.0%), dyspepsia (1.9%) and peripheral edema (1.7%). Abrupt discontinuation of suvorexant was well-tolerated, with rebound insomnia more predominant in those who were switched from suvorexant to placebo during the two-month discontinuation study. Additionally, no significant difference was observed between the suvorexant-suvorexant or suvorexant-placebo group in patients with withdrawal symptoms. Overall, the trial illustrated that suvorexant was effective in treating insomnia over the long-term with minimal adverse effects.
### Table 1. Summary of Major Trials.*10, 13-15

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<tr>
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<tbody>
<tr>
<td>Phase III, randomized, double-blinded, placebo-controlled</td>
<td>Two Phase III, randomized, double-blinded, placebo-controlled, parallel-group trials</td>
<td>Randomized, double-blinded, placebo-controlled, 2-period cross-over study</td>
<td>Randomized, double-blinded, placebo-controlled, 4-period cross-over study</td>
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<tr>
<td>Number of Patients</td>
<td>781 (522 suvorexant, 259 placebo)</td>
<td>Trial 1: 1021 total (254 suvorexant 20/15 mg; 383 suvorexant 40/30 mg; 384 placebo) Trial 2: 1009 total (239 suvorexant 20/15 mg; 387 suvorexant 40/30 mg; 383 placebo)</td>
<td>25 total</td>
<td>51 total</td>
</tr>
<tr>
<td>Study Duration</td>
<td>1 year, followed by 2-month discontinuation phase (primary endpoint: relapse prevention)</td>
<td>3 month trials, each with 1 week run-out period (discontinuation phase) to assess withdrawal and rebound insomnia</td>
<td>4 days per period with 7 day washout period. 2 periods total</td>
<td>2 nights per treatment session with 7 day washout period. 4 periods total</td>
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<tr>
<td>Inclusion Criteria</td>
<td>Patients aged 18 years and older who met primary insomnia criteria in DSM-IV</td>
<td>Patients aged 18 years and older who met primary insomnia criteria in DSM-IV</td>
<td>Patients aged 18-85 years with diagnosis of Chronic Obstructive Pulmonary Disease (COPD)</td>
<td>Male patients aged 18-55 years, body weight &gt;50kg, body mass index within 18.5-29.9kg/m², average bedtime 10pm-12am 5-7 days per week, average sleep duration of 6.5-8.5 hours over previous 3 months</td>
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<tr>
<td>Exclusion Criteria</td>
<td>Those who had confounding neurological disorders, unstable medical disorders, substance abuse, major affective or psychotic illness</td>
<td>Those who had other sleep disorders, confounding neurologic disorders, unstable medical disorders, substance abuse, major affective or psychotic psychiatric illness</td>
<td>Those who used continuous oxygen therapy, had other respiratory disorders, or had sleep disorders other than insomnia</td>
<td>Those who consumed medications or beverages that could interfere with study treatments, those with sleep apnea or other sleep disorders, those not prepared to meet study protocol requirements</td>
</tr>
<tr>
<td>Dose(s) Used</td>
<td>40 mg: patients aged 18-64.9 years 30 mg: patients aged 65 years and above</td>
<td>Both trials assessed: 20 mg, 40 mg: patients aged 18-64 years 15 mg, 30 mg: patients aged 65 years and above</td>
<td>40 mg: patients aged 18-64.9 years 30 mg: patients aged 65 years and above</td>
<td>Suvorexant 10 mg or 30 mg Zolpidem 10 mg</td>
</tr>
<tr>
<td>Primary Endpoint(s)</td>
<td>Assess tolerability and safety of suvorexant</td>
<td>Change from baseline in sTST and sTSO at months 1 and 3</td>
<td>Mean oxygen saturation (spO₂) for total sleep time (TST) on day 4</td>
<td>Change from baseline in sTST, wake after sleep onset and latency to persistent sleep</td>
</tr>
<tr>
<td>Secondary Endpoint(s)</td>
<td>Changes in sTST and sTSO</td>
<td>Changes from baseline in sTST and sTSO at week 1</td>
<td>Mean spO₂ on day 1 and in each sleep stage</td>
<td>Effect on REM and non-REM sleep</td>
</tr>
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*Studies listed here utilized the 4th edition of the Diagnostic and Statistical Manual. There is minimal change in definition of primary insomnia between the 4th and 5th editions (the 5th edition is currently in use).*
2,000 patients. The researchers reported improvement in sTST, sTST and other sleep measurement endpoints over the duration of suvorexant treatment, with less than 5 percent of patients discontinuing use of the drug due to adverse events. The trial also included a one week, randomized, double-blinded run-out period to assess withdrawal and rebound potential of suvorexant. No marked withdrawal or rebound symptoms were observed in patients after abrupt suvorexant discontinuation.

Bettica and colleagues compared the efficacy of suvorexant and zolpidem (a non-BZD) in a randomized, double-blinded, placebo-controlled trial in adult male volunteers in a simulated noisy environment. Suvorexant 10 mg and 30 mg were both shown to increase sTST by 17 and 31 minutes respectively as compared to 11 minutes by zolpidem. Additionally, rapid eye movement (REM) sleep was increased with suvorexant treatment and decreased with zolpidem. However, the trial did demonstrate more frequent side effects after suvorexant than after zolpidem due to differences in their pharmacological activity. More studies are needed to compare the efficacy of suvorexant to existing pharmacologic insomnia treatments.

Although suvorexant has demonstrated efficacy in promoting sleep maintenance in both healthy subjects and insomnia patients, its effects are more clear in the latter. A 2013 trial assessed the effects of suvorexant in healthy individuals without sleep problems. This study reported no electroencephalogram (EEG) improvements consistent with increases in deep sleep in these individuals, but the study did report improvements in other sleep measures including "latency to persistent sleep" (time before overnight sleep was sustained) and "wake after sleep onset" incidents. In both of these measures, suvorexant improved sleep quality in patients without sleep disorders.

In summary, clinical data available to date suggests that suvorexant is an effective sleep-promoting medication with an adverse effect profile better than currently available medications. Importantly, suvorexant has been shown to produce minimal withdrawal effects upon terminating use. Based on these data it is expected that suvorexant will have minimal to no abuse/dependence potential. However, future clinical studies directly comparing suvorexant to other currently used sleep medications and assessing the long-term effects/abuse potential of suvorexant are required.

**Pharmacist’s Role in Managing Patients on Suvorexant**

Pharmacists have an important role in educating patients on suvorexant use, side effects and cautions. Suvorexant is a white powder that is insoluble in water. Available in 5, 10, 15 and 20 mg strengths, the tablets should be stored at room temperature and protected from moisture and light. The onset of action of suvorexant is approximately 30 minutes, and reaches a maximal plasma concentration (T_max) in approximately two hours. Therefore, pharmacists should counsel patients to take suvorexant no more than 30 minutes before bed. Consumption of a high-fat meal delays the time taken to reach maximum levels (T_max) by about 1.5 hours. However, this does not otherwise affect the overall maximum concentration reached. Therefore, for rapid onset of action, patients may be advised to avoid taking suvorexant with or directly after a meal.

The adverse effect profile for suvorexant is fairly limited as the drug is generally very well-tolerated. Unsurprisingly, trials have documented somnolence and daytime sleepiness/fatigue. Incidence of dry mouth was increased in suvorexant treatment groups relative to placebo as well. Across the board, adverse effects occurred in a dose-dependent distribution. Furthermore, the long-term effects of suvorexant are not well understood, as most existing trials have had short durations. Central nervous system (CNS) adverse effects occur at very low frequencies and can include headache, abnormal dreams, sleep paralysis, mood changes, confusion, memory loss, hallucinations, somnambulism and suicidal ideation. Pharmacists should inform the patient to contact their doctor or pharmacist if any of these symptoms occur.

Suvorexant does not require laboratory monitoring, however, prescribers and pharmacists alike should monitor patients for signs of CNS depressant effects that could potentially harm the patient (e.g., operating a motor vehicle while experiencing daytime somnolence). Pharmacists should also consult the prescriber if the patient is currently taking any other CNS depressants. Due to their potential for additive effects, doses of CNS depressants and/or suvorexant should be adjusted.

Pharmacists will want to inform patients that a scheduled dose should not be taken if alcohol has been consumed that evening. Additionally, suvorexant should only be taken when the patient expects to receive at least seven hours of sleep. Suvorexant is contraindicated in patients with narcolepsy as suvorexant will exacerbate this condition. Lastly, patients taking high doses of suvorexant (20 mg a day) should be cautioned about operating motorized vehicles the day after due to a higher risk of daytime somnolence.

Certain populations, such as the elderly, may benefit from suvorexant use in comparison to first-line therapy. Benzodiazepines commonly cause loss of balance and vertigo, contributing to falls. However, suvorexant’s mechanism of action does not cause vertigo; therefore, some detrimental falls in elderly patients could be avoided. Additionally, obese patients often suffer from insomnia. Interestingly, suvorexant is cleared more slowly, and achieves higher peak levels in obese women (BMI > 30 kg/m^2) compared to non-obese women. This may result in increased adverse effects in obese women compared to non-obese women. Therefore, suvorexant therapy should be used with caution in obese patients, especially obese women.

Additionally, due to suvorexant’s metabolism by cytochrome P450 (CYP) 3A4 enzymes, it should not be taken concurrently with CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) which will decrease clearance, or with strong CYP3A4 inducers (e.g. rifampin, carbamazepine, phenytoin) which will reduce efficacy. If a patient is unable to
discontinue treatment with a CYP3A4 inhibitor, suvorexant should first be introduced at a reduced (5 mg) dose. Suvorexant is also not recommended for use in pregnancy; while no teratogenicity has been documented, suvorexant use was associated with decreased fetal body weight in animal models. Because of the risk of accumulation, suvorexant is also not recommended for patients with severe hepatic impairment.7

Challenges and Unanswered Questions
Unfortunately, suvorexant is not covered by all insurance companies. In fact, one pharmacy benefit management company (Catamaran®) has suggested zolpidem as an alternative to suvorexant. Without insurance, patients can expect to pay approximately $10.52 per tablet (regardless of dose). This can result in significant financial burden on patients and can serve as a disincentive for suvorexant as a treatment option.

Due to limited post-marketing research, there are very few documented and substantiated contraindications to suvorexant use. Future research could provide a more thorough understanding and awareness of potential risk factors and contraindications associated with suvorexant, as well as safety and efficacy with long-term use. Furthermore, a greater understanding of when suvorexant is most and least effective would cement suvorexant’s role in insomnia treatment going forward.

Conclusion
Suvorexant (Belsomra®) is a dual orexin receptor antagonist and is the first drug for insomnia acting via this mechanism. Findings from clinical studies suggest that suvorexant improves both sleep onset and total sleep time. In comparison with zolpidem, suvorexant has been found to significantly increase the quality and duration of sleep. In addition to improved efficacy, suvorexant does not result in withdrawal symptoms upon its discontinuation, which is commonly observed with many of the current insomnia treatments. However, one caveat is that long-term studies with suvorexant are currently unavailable. Cost of the medication may also be a problem for patients, as insurance companies and pharmacy benefit management companies may not include it on their formularies. In conclusion, suvorexant holds great promise due to its efficacy in insomnia patients and its potential to overcome some limitations associated with current first-line medications available for insomnia treatment.

References

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Assessment Questions

1. Which of the following is NOT a major adverse effect of suvorexant?
   A. Somnolence
   B. Nocturia
   C. Fatigue
   D. Dry mouth

2. Which of the following drug classes is NOT a current treatment option for insomnia?
   A. Benzodiazepine
   B. Anticonvulsant
   C. Tricyclic antidepressant
   D. Selective serotonin reuptake inhibitor

3. Which of the following is an advantage of suvorexant over benzodiazepines?
   A. Marked increase in rebound insomnia following suvorexant treatment as compared to benzodiazepines.
   B. No risk of withdrawal symptoms displayed upon abrupt discontinuation of suvorexant therapy.
   C. Marked increase in orexin neuron firing following suvorexant treatment.
   D. There is no significant advantage of suvorexant over benzodiazepines.

4. Which of the following patients would be the best candidate for suvorexant therapy?
   A. A well-managed insomnia patient who is struggling to afford his diazepam.
   B. An insomnia patient who has not experienced an increase in sleep time from treatment with a BZD.
   C. A patient without insomnia seeking relief from somnambulism.
   D. A narcoleptic patient who struggles to stay awake at work.

5. Which of the following medications would be safe to take in conjunction with suvorexant?
   A. Clarithromycin
   B. Carbamazepine
   C. Diazepam
   D. Methenamine

6. Which of the following counseling points would be appropriate when educating patients about suvorexant?
   A. Patients should only take suvorexant if they expect to receive at least seven hours of sleep.
   B. Patients taking high doses of suvorexant should not operate heavy machinery the following day until they know how the drug affects them.
   C. Patients who have consumed alcohol in an evening should still take their scheduled dose.
   D. Both A and B.
   E. All of the above.

7. At which receptor does suvorexant act? Does it act as an agonist or an antagonist at this receptor?
   A. Orexin; antagonist
   B. Gamma-amino butyric acid (GABA); agonist
   C. Orexin; agonist
   D. Gamma-amino butyric acid (GABA); antagonist

8. Suvorexant displays an onset of action in:
   A. 15 minutes
   B. 30 minutes
   C. One hour
   D. Two hours

9. Challenges to the use of suvorexant for treatment of insomnia include:
   A. The potential for rebound insomnia following suvorexant therapy.
   B. Few documented contraindications exist to suvorexant use.
   C. Limited coverage by insurance companies
   D. Both B and C.
   E. All of the above.

10. What specific sleep parameter(s) have demonstrated marked increase(s) following suvorexant treatment?
    A. sTST
    B. sTSP
    C. sTSA
    D. sTSS