General

Suvorexant, a Novel Dual Orexin Receptor Antagonist, for the Management of Insomnia

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Purpose of Review

The present investigation is a comprehensive review regarding the use of Suvorexant for insomnia treatment. It covers the background, pathophysiology, and significance of addressing insomnia, the pharmaceutical details of Suvorexant, and its safety, efficacy, and implications in treating insomnia. We further discuss Suvorexant's role in targeting insomnia with other comorbidities.

Recent Findings

Insomnia refers to poor quality and/or quantity of sleep. While there are many existing treatments such as benzodiazepines, melatonin agonists, TCAs, and atypical antipsychotics used to target various receptors involved in normal induction and maintenance of sleep, Suvorexant is an antagonist that specifically targets orexin receptors. Recent clinical studies suggest that Suvorexant is both clinically safe and effective. Quantity and quality of sleep are measured in various ways, yet the consensus points towards Suvorexant's effectiveness in improving sleep time, onset, latency, and quality compared to placebo. In addition to helping improve isolated insomnia, Suvorexant helps improve sleep in patients that have other comorbidities such as obstructive sleep apnea, Alzheimer's disease, dementia, acute stroke, and delirium. While Suvorexant is safe, there are still adverse effects associated with the drug that needs to be considered. The most common adverse effects include dizziness, somnolence, headaches, and cognitive impairment.

Summary

Insomnia is a major public health concern that affects many people worldwide and has been linked to many adverse health outcomes. While there are existing treatments that target different receptors and pathways of normal sleep induction and maintenance, Suvorexant is a novel drug that targets dual orexin receptors. Its safety and efficacy, mechanism of action, pharmacokinetic parameters, and relative lack of rebound and withdrawal effects render suvorexant a reliable choice for the treatment of insomnia.

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INTRODUCTION

Insomnia is a commonly used term to describe difficulty sleeping. Patients suffering from this disorder report dissatisfaction with the quality or quantity of sleep obtained despite attempts to obtain sleep.[1] With the advancement of society and living in a fast-paced technological world, more and more people are suffering from insomnia. It is estimated that roughly 30% of the general population suffers from insomnia, reporting to have experienced one or more symptoms of insomnia including difficulty initiating or maintaining sleep, waking too early, or poor quality of sleep.[2] However, a wide variation among estimates of insomnia prevalence exists, ranging from 10% - 40%, related to inconsistencies in the classification and criteria that studies use to diagnose the disorder.[3,4] This is in part due to the fact the underlying causes of insomnia have not been well defined, and the epidemiology of the disorder remains in its infancy.[5] Many experience insomnia as a persistent condition, with 74% reporting symptoms for at least one year.[6] In both men and women, the prevalence of insomnia increases with age. However, women more commonly report symptoms of insomnia and are more likely to be diagnosed than men, with a male-to-female ratio of 1:1.4 and 1:2, respectively.[7,8] Studies have also shown insomnia to be associated with socioeconomic factors such as lower income, lower education, and employment status.[8–11]

Insomnia is a major public health concern as it affects a large portion of the general population and has been linked to numerous adverse health outcomes such as diabetes, obesity, and heart disease.[12,13] Insomnia not only affects the patient's physical health but also leads to numerous psychological problems and is strongly correlated with two comorbid psychiatric disorders, depression and anxiety, although research into other mental disorders is scarce.[14–18] Some epidemiological studies have even investigated a possible link between insomnia and cancer, although current findings have not yet reached a consistent conclusion that a relationship does indeed exist between the two.[13] The strong correlation between insomnia and mental health disorders opens up the possibility of the use of insomnia treatment for the prevention of such mental disorders.

Insomnia is a frequent complaint encountered by clinicians, and a multitude of behavioral and pharmacological treatment options are available. Treatment for insomnia is important for not only treating sleep disturbance but also to prevent and/or minimize one's susceptibility to physical and mental health impairments. The development of novel hypnotics to treat insomnia with comparable efficacy and improved long-term safety hold a competitive advantage over current traditional medications. It is essential for patients suffering from insomnia to have treatment opinions that effectively promote sleep and lack physical dependence as well as other adverse side effects commonly associated with traditional insomnia medications.

METHODS

We conducted literature searches using PubMED and Google Scholar between October 2020 through March 2021. Articles were chosen based on relevance to suvorexant as a treatment option for insomnia. We selected primary literature as well as clinical trial studies to reflect validity of the review. Older articles were included as well to reference to previous background information.

The PubMED and Google Scholar keywords searched were as follows: suvorexant, insomnia, orexin, orexin A, orexin B, and antagonist.

PHYSIOLOGY OF SLEEP/WAKEFULNESS + PATHOPHYSIOLOGY OF INSOMNIA

While the current pathophysiology of insomnia is not entirely understood, greater comprehension is being developed through the analysis of several key genetic and cellular mechanisms. The disorder is characterized as one associated with difficulty falling asleep as well as maintaining proper sleep. Following the lack of sleep, functional impairment the next day commonly follows in many patients with the potential for experiencing daytime sleepiness, fatigue, and cognitive performance impairment.[19] Sleep onset and maintenance are both important factors that play a major role in contributing to the overactive state of wakefulness/arousal seen in insomnia.

The sleep onset process is associated with behavioral, physiological, and genetic markers. While the complete mechanisms behind the genetic markers involved in insomnia are not fully proven, commonalities among different genetic studies are being detected which is strengthening the potential significance for genetic factor components of many newer pathophysiology models. Potential candidate genes identified for roles in the pathophysiology of insomnia include ApoE4, PER3, HLA DB1 *0602, and the 5-HTTLPR.[19] Significant single-nucleotide polymorphisms associated with insomnia symptoms for stress reactivity and neuroplasticity included: STK39, USP25, MARP10, ROR1, PLCB1, EPHA4, and CACNA1A.[19]

Sleep onset and maintenance are associated with the sleep-wake cycle which is controlled by a variety of neurotransmitters and biological responses. For these activities to occur, the subcortical pathways are known as the "ascending arousal system" must be suppressed. Inhibitory neurons from the ventrolateral pre-optic area (VPLO) serve to carry out the suppression. Although not fully understood, molecules of adenosine are suspected to be the trigger for VPLO to begin inhibition through a mechanism of accumulation during the aroused/wake state and reduced levels throughout the maintenance of sleep.[20]

As a generalization, these regulatory molecules can be categorized into wake promotion/sleep suppression or sleep promotion/wake suppression. Molecular factors involved in the regulation of the sleep-wake cycle include a variety of chemicals such as catecholamine, histamine, orexin, serotonin, GABA, adenosine, and melatonin.[21] Of the factors, the wake-promotion/ arousal factors include

orexin, catecholamines, and histamine. Orexin in particular is thought to play a significant role in the state of wakefulness, and thus, antagonism of this molecule and the receptors have become an area of interest for pharmacologic research.

The hyperarousal state observed in insomnia is expected to be related to the principle of orexin neuropeptides produced by the lateral hypothalamus interacting with their dispersed receptors throughout the body. The specific orexin receptors are considered to be G-protein coupled receptors (OX1R and OX2R), and the interaction of the molecules is thought to contain a role in a variety of neurologic functions.[22] Among these roles, orexin stimulation is proven to be involved in wakefulness and arousal which is the core problem involved in insomnia. Contrary to a hyperactive state of wakefulness, narcolepsy is a problem of excessive daytime sleepiness with episodes of recurrent overwhelming sleepiness with the loss of orexin-producing neurons in the lateral hypothalamus.[22] With considerable involvement in both disorders, orexin is proving to be largely implicated in the pathophysiology of insomnia.

CURRENT PHARMACOLOGICAL TREATMENTS FOR INSOMNIA

With many potential treatment options available for insomnia, the goal of all the distinct pharmacological therapies regardless of the type used is to improve sleep quality for the proper sleep onset and maintenance. One of the mainstay treatments and most widely accepted treatments for insomnia is cognitive behavioral therapy for insomnia (CBT-I) which includes a variety of behavioral strategies such as stimulus control, sleep restriction, and relaxation techniques, but this analysis assesses a multitude of pharmacological treatment options that often follow this therapy.[23] Alternate options for treatment include a variety of pharmacotherapy alternatives that include but are not limited to benzodiazepine receptor agonists, melatonin agonists, sedating antidepressants, or atypical antipsychotics.[24]

The benzodiazepine receptor agonists contain different affinities for the $GABA_A$ receptor complex which alters the selectivity for the receptor subunits. This variance in subunit selectivity is suspected to result in fewer side effects to provide more tailored options for patients with differing conditions. The benzodiazepine options approved for insomnia treatment include a variety such as triazolam, estazolam, quazepam, and flurazepam. These drugs share a similar mechanism of action which includes interaction with the $GABA_A$ receptors on the neuronal membrane resulting in modification of the receptor to modulate its affinity for the inhibitory neurotransmitters. As a result, the increase in the frequency of chloride channel openings and chloride conductance leads to decreased neuronal excitability which makes them particularly useful for insomnia.[25] The difference among the several options listed is the duration of action for each drug which plays a role in the rapid tolerance development. These pharmacological therapies do contain the significant potential for dependence and abuse, and long-term utilization is not recommended.

Another treatment option available is the melatonin agonist, Ramelteon. This drug is one of the very limited approved options available for insomnia treatment through selective agonism of the melatonin receptors (MT_1 and MT_2). Contrary to the previously discussed pharmacotherapy, this drug does not interact with GABA receptors which makes it a candidate for further study in patients with chronic insomnia. The lack of affinity for the GABA receptors also diminishes the ability for substance abuse.[24] The drawback with ramelteon lies within the fact that the drug is rapidly absorbed through the first-pass metabolism which results in a limited bioavailability. Because of this, it is recommended that this pharmacotherapy not be used to treat patients with difficulty maintaining sleep, but instead the use is recommended for insomnia where the problem is with impaired onset of sleep.[26] This particular melatonin agonist is hepatically metabolized by cytochrome P_{450} (CYP 1A2), and therefore, ramelteon is recommended to be used with caution in patients with hepatic impairments. The efficacy of this treatment may be reduced with CYP 3A4 inducers such as rifampin.

Contrary to the melatonin agonist therapeutic option discussed, sedating tricyclic antidepressants such as doxepin are used for the treatment of insomnia where the problem is sleep maintenance. Doxepin in low doses (3-6 mg) has been proven to serve as a unique hypnotic for insomnia treatment. The drug functions through a variety of different mechanisms to increase the concentration of serotonin (5-HT) and norepinephrine (NE) within the synaptic cleft, all while antagonizing the histamine H1 receptors.[27] Due to this diverse mechanism of action, the effects on the serotonin concentrations make this drug a useful antidepressant. Doxepin does contain a list of side effects that are seen in high doses when used in depression such as dry mouth, constipation, prolonged QT interval, tachycardia, and the potential for orthostatic hypotension.[27] In the use of this drug for insomnia in low doses, minimal to no adverse effects were reported compared to the dosage used for depression.[28]

Quetiapine is commonly used off-label for treatment of insomnia related to the antagonism of Histamine H1 receptors. It is an ideal treatment option for patients with numerous psychiatric conditions including anxiety states, schizophrenia, bipolar I, and acute manic-depressive disorders.[28] Clinicians must consider the side effects of Quetiapine, including metabolic syndrome and extrapyramidal side effects, which may result in the consideration of another drug. In this regard, recent reviews have also linked Quetiapine and other “atypical” antipsychotics to an increased risk of sleep apnea.

Therefore, the variety of therapeutic options presented provide a multitude of choices for the treatment of insomnia. The different chemical receptor antagonists and agonists mentioned previously emphasized various aspects of the clinical disorder to treat both the sleep onset and maintenance dysregulation seen in insomnia. With emerging research of orexin and its receptors, the goal of treating in-

somnia through the proper regulation of the sleep-wake cycle is appearing to be promising.

SUVOREXANT DRUG INFORMATION

Suvorexant, is an orexin receptor antagonist used for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. It belongs to a novel class of therapeutic medications called dual orexin receptor antagonists (DORAs) and was the first agent of its class to gain U.S. Food and Drug Administration (FDA) approval in 2014.[29,30] Unlike other hypnotics, suvorexant blocks the binding of neuropeptides (orexin A and B) that promote wakefulness. It is a schedule IV controlled substance.[31,32] The current recommended dose is 10 mg, taken no more than once per night, and at least 30 minutes prior to going to bed with no less than 7 hours of sleep remaining. The dosage may be titrated to 20 mg if needed, although higher doses are known to increase the likelihood of daytime driving impairment.

Serious adverse side effects include abnormal thinking, behavioral changes, hypnagogic hallucinations, and sleep paralysis.[33] Less serious side effects include daytime somnolence, headache, dizziness, and abnormal dreams.[34–36] Suvorexant should be avoided in patients with depression because it may worsen symptoms. Patients suffering from narcolepsy, obstructive sleep apnea, or severe chronic obstructive pulmonary disease should also avoid taking this medication. Patients who have a previous history of drug abuse or addiction may be at increased risk for abuse and addiction to suvorexant and should be monitored carefully if prescribed the medication.[33] Currently, there are no well-controlled studies on the effect of suvorexant in pregnant women and should only be used during pregnancy if the potential benefits outweigh the potential risks to the fetus. It is also unknown whether suvorexant is excreted in human breast milk and caution is advised if suvorexant is prescribed to a woman currently breastfeeding.[33,36,37]

MECHANISM OF ACTION

Suvorexant, the first dual orexin receptor antagonist (DORA) to be approved for the treatment of insomnia, is a promising agent that offers a new option for patients seeking treatment for insomnia which acts in a unique manner different from the current standard medications available. Suvorexant is highly selective for blocking the neuropeptides orexin A and orexin B through reversibly binding to type 1 (OX1R) and type 2 (OX1R) orexin receptors, respectively, resulting in the suppression of wakefulness.[30] Both OX1R and OX2R are located in the brain regions responsible for promoting arousal and alertness. Orexin signaling follows a circadian rhythm, increasing during periods of wakefulness and decreasing during times of sleep.[38–40] Studies have demonstrated that blocking orexin receptors increases the time spent in all stages of sleep and most importantly, does not shift the sleep profile. Therefore, dual orexin receptor antagonists (DORAs), like suvorexant, may promote better sleep in cases of chronic insomnia.[41] In addition, preclinical studies show orexin receptors require approximately 65% - 80% occupancy by a receptor antagonist to promote sleep. The coupling of this requirement with the circadian pattern of orexin signaling led researchers to propose that suvorexant more easily blocks orexin-mediated arousal during periods of sleep, and its pharmacological effects lessen as the body returns to a wakeful state and orexin signaling in the brain increases.[42]

The balance between orexin receptor activity and drug action makes suvorexant an ideal medication for treating insomnia. It allows for the drug to have an optimal effect when needed to promote sleep and to wear off when its effects are no longer warranted when waking. However, it is important to note that suvorexant appears to bind to and release from its orexin receptors in a very slow manner, which fosters the potential for residual pharmacologic effects beyond those predicted by the pharmacokinetics of the agent.[43] Clinical trials determined suvorexant did not appear to produce physical dependence or withdrawal syndrome with discontinuation of the medication after chronic therapy of one year.[44] This finding makes suvorexant a more appealing option over other traditional drugs for insomnia, which act through benzodiazepine receptors and carry the risk of physical dependence with chronic use.[45]

PHARMACOKINETICS / PHARMACODYNAMICS OF SUVOREXANT

ABSORPTION AND DISTRIBUTION

Following oral administration of suvorexant, the median time-to-peak concentration (T_{max}) is approximately 2 hours (range 30 minutes – 6 hours) under fasted conditions.[33,46] The pharmacokinetics of suvorexant is similar among healthy subjects and patients with insomnia. The recommended 10 mg dose has a mean absolute bioavailability of 82%. Suvorexant exposure increases in a less than dose-proportional type manner over the range of 10 to 80 mg because of reduced absorption at higher doses.[33] Suvorexant exposure is higher in females than males, with a 17% increase in area under the curve (AUC) and a 9% increase in peak concentration (C_{max}).[33,47] Food ingestion does not significantly affect the AUC or C_{max} but can delay the T_{max} by 90 minutes, especially with the consumption of high-fat meals. Therefore, suvorexant should not be administered with or soon after a meal if faster sleep onset is preferred.[33,48] The mean volume of distribution of suvorexant is approximately 49 liters. Suvorexant is primarily bound (>99%) to human plasma proteins and does not preferentially distribute into red blood cells. Suvorexant binds to both human serin albumin and α1-acid glycoprotein.[33,49]

METABOLISM AND ELIMINATION

Suvorexant is primarily metabolized by CYP3A, with a minor contribution from CYP2C19.[33,35] The two major circulating entities are suvorexant and the non-active metabolite, hydroxy-suvorexant. Suvorexant is primarily eliminated through feces. When radiolabeled suvorexant was administered, 66% was excreted in the feces and 23%

was excreted in the urine.[33] Suvorexant displays linear systemic pharmacokinetics with an accumulation of approximately 1 to 2-fold for a once-daily dose and the steady-state is achieved by 3 days. The mean terminal elimination half-life ($t_{1/2}$) is approximately 12 hours (95% Confidence Interval: 12 to 13).[33,50,51] Suvorexant clearance is inversely related to body mass index (BMI).

DRUG INTERACTIONS

The use of strong CYP3A4 inhibitors is not recommended while taking suvorexant.[33] However, moderate CYP3A4 inhibitors can be used in combination with suvorexant. When using a moderate CYP3A4 inhibitor, it is recommended that the suvorexant dose be decreased to 5 mg. If the suvorexant dose is tolerated but not effective, a dose increase is acceptable but should not exceed 10 mg/dose.[30,35,47]

Suvorexant has been co-administered with midazolam, combined oral contraceptives (norgestimate-ethinyl estradiol), warfarin, and digoxin. No significant interactions with suvorexant were found.[30,33] However, studies did discover that coadministration of suvorexant with digoxin caused a slight increase in digoxin levels due to inhibition of intestinal P-glycoprotein and a narrow therapeutic index was observed. Therefore, clinicians should monitor digoxin concentrations when co-administered with suvorexant.[33,35] In addition, recent publications have confirmed that suvorexant is a reversible inhibitor of CYP3A4 and 2C19 and a weak inducer of CYP3A4, 1A2, and 2B6. However, it was concluded that the low plasma concentrations of suvorexant at the normal, recommended dose make it unlikely that it would cause any significant drug interactions related to its inhibition or induction of CYP enzymes.[52]

SAFETY AND EFFICACY OF SUVOREXANT IN TREATING INSOMNIA

Suvorexant has been shown to be both efficacious and safe in studies observing the treatment of insomniac patients with the orexin receptor antagonist.

A survey of insomnia patients in Japan treated for the first time with suvorexant showed that suvorexant can be utilized for the treatment of insomnia. Patients in this study had increased total sleep time and decreased sleep latency, with 73.2% of patients (n=3428) self-reporting improved sleep, and 74% of patients were reported as improved by licensed sleep physicians. Mean total sleep time was increased (from 300 to 360 minutes) and sleep latency decreased (from 60 to 50 minutes) Suvorexant was more efficacious in patients diagnosed with insomnia less than 1 year ago as compared to patients diagnosed 1 to 10 years ago and those diagnosed greater than 10 years ago. Improvement with suvorexant treatment was lower in patients with psychiatric disorders, particularly.[53]

A placebo trial in China studied 120 patients with insomnia who were given either placebo (n=60) or suvorexant (n=60). The suvorexant group significantly improved in terms of total sleep time (increased), time to sleep onset (decreased), and sleep quality (increased), as compared to placebo.[54]

Polysomnograms were analyzed from clinical trials involving 1518 insomniac patients receiving either suvorexant or placebo to evaluate the number of and time spent in wakeful bouts, as well as the associated sleep quality (self-reported by patients) with patients' wakeful bouts. Compared to placebo, suvorexant decreased the number and time spent in bouts longer than 2 minutes (long bout) and increased the number of bouts shorter than 2 minutes (short bout). Long bout total time was decreased by 32-54 minutes, and short bout time was increased by 2-6 minutes by treatment with suvorexant and was significant when compared to placebo. Reduced long bout time was associated with good or excellent sleep quality, and sleep quality was significantly different between the two groups. When comparing the placebo to the suvorexant group, the suvorexant group returned to sleep from their longest awakening twice as fast as the placebo patient.[55]

30 men underwent cognitive and physical function tests as well as polysomnography following treatment with suvorexant 20 mg, brotizolam (a GABAa agonist) 0.25 mg, or placebo 15 minutes prior to sleep. Subjects were forced awake at the 90-minute mark following the onset of sleep. Subjects performed cognitive and physical tests before sleep, after forced awakening, and the following morning. Regarding physical and cognitive performance, brotizolam impaired subjects significantly more than suvorexant and placebo. There was no significant difference in performance on physical and cognitive testing between the suvorexant and placebo groups. Suvorexant had effects on sleep efficacy, total sleep time, and sleep latency after awakening comparable to the GABAa receptor agonist brotizolam when compared with placebo.[56]

Pooled elderly (greater than or equal to 65 years of age) and non-elderly (18 to 65 years of age) subjects (n=1824) from previous phase 3 studies were evaluated. The insomnia severity index, a seven-question, self-rated scale, was utilized in assessing sleep quality of subjects at baseline and three months following the study. The impact of insomnia on the daily life portion of the subject-reported insomnia severity index was significantly improved in the group of subjects taking suvorexant compared to placebo; suvorexant improves sleep in insomniac patients and reduces the impact of insomnia on patients' daytime function.[57,58]

ELDERLY AND ADOLESCENTS

Sub-group analysis of a phase 3 trial demonstrates that suvorexant is safe and efficacious in elderly patients with insomnia. Three groups of elderly patients were observed, those under 65 years of age, those 65to 75, and those above 75 years of age. Self-assessments of quality of sleep, as well as physical assessments of insomnia patients' severity of symptoms, were performed, and all three groups were observed to have a 70-75% improvement in sleep quality.[59]

Treatment with suvorexant could be a treatment of insomnia in adolescents. The Athens Insomnia Scale was worse in patients who discontinued suvorexant compared

with those who continued treatment. Clinical global impression scale scores significantly decreased in patients who completed the treatment with suvorexant.[58]

SEX

An efficacy analysis of pooled data from two trials; both trials were randomized, double-blind studies of elderly (greater than 65 years of age) and non-elderly (18 to 64 years of age) patients on age-adjusted doses of suvorexant. Results of the two studies were assessed via patient-reported outcomes, as well as polysomnography. These two trials' data were then analyzed based on sex, n= 1264 women and n= 707 men. The data show that sleep time and sleep efficacy were improved in both men and women receiving suvorexant compared to the placebo groups.[60]

DOSING AND DRUG INTERACTION

A randomized, double-blind study phase 1 trial was performed to determine dosing indications for suvorexant. Subjects received either a placebo or an oral dose of suvorexant (10, 20, 40, 80, or 100 mg) nightly for 14 days. Subjects receiving 40, 80, or 100mg suvorexant had a 100% incidence of adverse effects. Subjects receiving 20mg suvorexant had an 83% incidence of adverse effects, while those subjects receiving 10mg had an incidence of 67%. Median time to maximum observed concentration was 1.5-4.0 hours, and the drug's half-life ranged from 7.7 to 14.5 hours. The data show that suvorexant is well-tolerated after single and multiple doses, and indicate nightly dosing.[61] Dose adjustment was not found to be necessary when administering suvorexant to men versus women.[60]

CYP3A4 inducers/inhibitors have an effect on suvorexant pharmacokinetics, however, single doses can be tolerated in patients on those medications. Exposure to suvorexant was increased with a CYP3A4 inhibitor. Suvorexant exposure was increased to a greater magnitude with a strong inhibitor (ketoconazole) as compared to a moderate inhibitor (diltiazem). In addition, when suvorexant was co-administered with a CYP3A4 inducer (rifampin), suvorexant exposure was decreased.[62]

ADVERSE EFFECTS

Adverse reactions were more common in subjects taking suvorexant compared with those receiving placebo.[54,60,61] Adverse reactions were most commonly somnolence,[53,59,61] dizziness,[53,59] headache,[61] insomnia[53,59] and nightmare.[53,58] Women are more likely to experience adverse effects when taking suvorexant as compared to men on similar dosages, however, the side effect profile was similar between the male and female groups.[60]

The incidence of adverse drug reactions in patients with psychiatric disorders was higher than the incidence in patients without psychiatric disorders when treated with suvorexant.[53] Patients who switch from another insomnia medication to suvorexant have a higher incidence of adverse effects compared to those who are hypnotic medication naive and to those using suvorexant as adjuvant therapy.[63]

Suvorexant has less impairment on cognitive and physical function when compared with GABAa receptor agonist brotizolam.[56] The incidence of adverse events was not significantly different between the suvorexant treatment and placebo groups in a subgroup analysis of five studies involving patients greater than 65 years of age who were diagnosed with insomnia.[64]

EFFICACY OF SUVOREXANT IN TREATING INSOMNIA WITH OTHER COMORBIDITIES

INSOMNIA WITH DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA

Suvorexant is a mild hypnotic that may be utilized for suspected OSA patients when they experience in-laboratory insomnia during PSG. An observational study of 149 suspected OSA patients, who did not have insomnia at home, were studied whilst undergoing overnight polysomnography in-lab. Patients who experienced difficulty falling asleep (n=84) were given an optional one-time dose of suvorexant, followed by an add-on dose of zolpidem if still wakeful 1 hour after suvorexant's administration. Of the 149 patients, 65 were placed in the "no insomnia group. Of the remaining 84 patients who had difficulty falling asleep, 52.4% of the patients achieved sleep sufficient for PSG analysis with a single dose of suvorexant, while the remaining 47.6% required the addition of zolpidem 1 hour later. There was no significant change between insomnia and no insomnia groups in regards to sleep time or quality, according to a subjective survey, and no adverse events occurred.[65]

ALZHEIMER'S DISEASE AND DEMENTIA

Suvorexant improved mean total sleep time in patients with probable Alzheimer's dementia and insomnia. A randomized, double-blind, 4-week trial of 1:1 placebo: suvorexant treatment was studied in patients (n=285) between the ages of 50-90 who met the DSM-5 criteria for Alzheimer's disease dementia (determined via investigator interview of the patient) and insomnia (determined via interview and PSG as a mean total sleep time of<6 hours per night). Patients were required to have a trial partner who resided with the patient overnight. Treatment /placebo was administered 30 minutes prior to the patient's bedtime and mean total sleep time and wake after sleep onset time were assessed by PSG. Subjective assessment of patient and partner sleep was given by the trial partner. Baseline mean sleep time for patients was 77 minutes in the suvorexant group (n=142) and 84 minutes in the placebo group (n=143) at the beginning of this trial. At week 4 of the trial, greater than or equal to 50-minute improvement in mean sleep time was seen in 62% of the suvorexant group and 45% of the placebo group; greater than or equal to 60-minute improvement in mean sleep time was seen in 55% of the suvorexant group and 40% of the placebo group. Baseline mean wake after sleep onset was 60 minutes for suvorexant patients and 61

Table 1. Safety and Efficacy of Suvexorant in treating insomnia

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Yee (2018)	Randomized, double-blinded, placebo-controlled, sequential panel, phase 1 trial performed on men (n= 40) to assess safety, tolerability, and pharmacokinetics of suvorexant. Subjects received either a placebo or an oral dose of suvorexant (10, 20, 40, 80, or 100 mg) nightly for 14 days.	39/40 subjects completed the trial. Those who received 40, 80, or 100mg nightly had a 100% incidence of adverse events, while subjects receiving 20 mg had an 83% incidence and those receiving 10 mg had a 67% incidence of adverse events. Adverse events included: somnolence (n=19), fatigue (n= 17), and headache (n= 15). Median time to maximum observed concentration was 1.5 – 4.0 hours. The half-life of the drug ranged from 7.7-14.5 hours.	Suvorexant is well tolerated after single and multiple doses, and nightly dosing is indicated.
Tackeuchi (2020)	Phase 3 trial sub-group analysis of drug-use survey used to evaluate safety and efficacy of suvorexant in elderly patients with insomnia. This survey compared 3 groups: those under 65 (group 1, n= 1490), those 65-74 (group 2, n= 730), and those above 75 (group 3, n= 1028).	These groups were compared in terms of adverse reactions, the patient's self-assessment, and their doctor's assessment. Adverse drug reactions were most commonly dizziness, somnolence, and insomnia. The incidence of these reactions in each group was: 11.28% (n= 168) in group 1, 8.63% (n= 63) in group 2, and 8.17% (n= 84) in group 3. 70-75% of each group was found on physician and self-assessment to be improved.	Suvorexant is safe and efficacious in the elderly.
Sano (2019)	Sub-group analysis of post-marketing survey, analyzing groups: hypnotic naïve (n= 1946), switching from a prior sleep medication (n= 703), add-on therapy (n= 536), and others (n= 63).	Adverse drug reactions occurred in 5.3% of those patients switching from another medication, as compared to 0.46% in patients who were hypnotic naïve, and 1.5% of the patients who were adding suvorexant onto their hypnotic regimen. Additionally, discontinuation of suvorexant due to inefficacy of therapy after 6 months of use occurred more often in patients switching from another medication (14.9%) than in patients who were hypnotic naïve (9.6%) and patients who were adding suvorexant onto their hypnotic regimen (10.4%).	Patients who are switching from one insomnia medication to suvorexant must be monitored more closely for drug efficacy and adverse drug reactions compared to a patient who is adding on suvorexant or starting a hypnotic for the first time for insomnia.
Asai (2019)	A survey of insomnia patients treated with suvorexant for the first time (n=3428). There was no control group for this study.	48.6% of patients received continuous treatment with suvorexant for 6 months. 51.4% of patients discontinued treatment before the time point of 6 months; 30% of patients discontinued treatment due to improvement of insomnia, with the mean time of treatment cessation being 62 days following treatment initiation. 9.7% of patients experienced adverse drug reactions: somnolence (3.6%) insomnia (1.2%), dizziness (1.1%), and nightmare (0.8%). Overall, 73.2% of patients improved in regards to self-assessment, 74% of patients improved according to sleep physicians. Mean total sleep time was increased (from 300 to 360 minutes) and sleep latency decreased (from 60 to 50 minutes). The improvement rate in the elderly (ages greater than 65 years of age) was not significant from the rest of the population. Improvement was lower in patients with psychiatric disorders. Suvorexant was more efficacious in patients diagnosed with insomnia less than 1 year ago as compared to patients diagnosed 1 to 10 years ago and those diagnosed greater than 10 years ago.	Suvorexant can be utilized for the treatment of insomnia, with patients benefitting from increased total sleep time and decreased sleep latency.

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Herring (2017)	An efficacy analysis of pooled data from two trials; both trials were randomized, double-blind studies of elderly (greater than 65 years of age) and non-elderly (18 to 64 years of age) patients on age-adjusted doses of suvorexant. Results of the two studies were assessed via patient-reported outcomes, as well as polysomnography. These two trials' data were then analyzed based on sex, n= 1264 women and n= 707 men.	Age-adjusted dosing was shown to be effective on night one of treatment via polysomnography, and this was usually maintained at the three-month mark of treatment. Effects were similar between men and women. Patients who were taking a higher dose of suvorexant had a higher incidence of adverse effects as compared to a lower dose of suvorexant and placebo. Across all treatment groups, women had a higher percentage of total adverse effects as compared with men. Both men and women on high or low-dose suvorexant experienced an increased incidence of somnolence as compared with placebo. The side effect profile was similar between men and women in all groups	Suvorexant is effective and well-tolerated in both men and women as a treatment for insomnia, and dose adjustment is not necessary based upon a patient's sex.
Seol (2019)	A double-blind, randomized, placebo-controlled study of male subjects (n = 30). Subjects took suvorexant 20 mg, brotizolam (a GABAa agonist) 0.25 mg, or placebo 15 minutes prior to sleep, and were forced awake at the 90-minute mark of sleep. Subjects performed cognitive and physical tests before sleep, after forced awakening, and the following morning. Polysomnography was used to evaluate sleep	Sleep time and efficacy were improved as compared with placebo in both groups receiving hypnotic agents. After forced awakening, sleep latency was 2 minutes in groups receiving hypnogogic agents, while latency was 24 minutes in those subjects receiving placebo. REM latency was significantly decreased in the suvorexant group (48.8 minutes) compared to the brotizolam (81.7 minutes) and placebo (98.8 minutes) groups In regards to physical and cognitive performance, brotizolam impaired subjects significantly more than suvorexant and placebo. There was no significant difference in performance on physical and cognitive testing between the suvorexant and placebo groups.	Suvorexant has less impairment of cognitive and physical functions after forced awakening compared to brotizolam and is comparable to brotizolam in regard to sleep latency, sleep time, and sleep efficacy.
Fan (2017)	120 patients with insomnia were randomly assigned to two groups; suvorexant 40mg or placebo were given to two groups of patients. Outcomes were measured in total sleep time, time to sleep onset, and sleep quality.	The suvorexant group improved in regard to total sleep time, time to sleep onset and sleep quality as compared with the placebo group. Adverse effects were more common in the group receiving suvorexant.	Suvorexant was well-tolerated and efficacious as a treatment for insomnia
Herring (2017)	Subgroup analysis of 3 efficacy and 2 safety studies involving patients greater than 65 years of age who were diagnosed with insomnia, where patients were randomized into groups receiving 15mg suvorexant (n=202), 30mg suvorexant (n = 319), or placebo(n=318). Outcomes were evaluated via patient report and polysomnography analysis was performed on: night 1, week 1, month 1, and month 3	6.4% of 30mg suvorexant group, 3.5% of 15mg suvorexant group, and 5.5% of the placebo group discontinued the study due to adverse effects, with somnolence being the most common adverse effect. The incidence of adverse events was not significantly different between the treatment and placebo groups. Baseline characteristics and symptom severity were similar across all groups at the beginning of the study. Baseline mean total sleep time was 5 hours, and total sleep onset time was 1 hour. Sleep onset time and total sleep time were significantly decreased with both the 15mg and 30mg doses of suvorexant at all time points.	Suvorexant improves sleep onset and sleep maintenance in elderly patients with insomnia, and was well-tolerated
Herring (2019)	Pooled elderly (greater than or equal to 65 years of age) and non-elderly (18 to 65 years of age) subjects (n=1824) from previous phase 3 studies were evaluated. The insomnia severity index, a seven-question, self-rated scale, was utilized in assessing sleep quality of subjects at baseline and three months following the study.	Treatment with an age-adjusted dose of suvorexant improved insomnia severity scores greater than a placebo at the 3-month time point. The impact of insomnia on daily life portion of the insomnia severity index was significantly improved in the group of subjects taking suvorexant compared to placebo.	Suvorexant improves sleep in insomniac patients and reduces impact of insomnia on patients' daytime function

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Svetnik (2018)	Polysomnograms were analyzed from clinical trials involving 1518 insomniac patients receiving either suvorexant or placebo to evaluate the number of and time spent in wakeful bouts, as well as the associated sleep quality (self-reported by patients) with patients' wakeful bouts	Compared to placebo, suvorexant decreased the number and time spent in bouts longer than 2 minutes (long bout) and increased the number of bouts shorter than 2 minutes (short bout). Long bout total time was decreased by 32-54 minutes, and short bout time was increased by 2-6 minutes by treatment with suvorexant. This was significant when compared to placebo. Reduced long bout time was associated with good or excellent sleep quality, and sleep quality was significantly different between the two groups. When comparing placebo to suvorexant groups, the suvorexant group returned to sleep from their longest awakening twice as fast as the placebo patient.	Suvorexant reduces wakefulness-after-sleep-onset, thus improving sleep quality.
Kawabe (2017)	Thirty patients (mean age 15.7 +/- 2.4) with diagnosed insomnia were administered suvorexant. Results were evaluated with the Athens Insomnia Scale and the Clinical Global Impression, in both of which higher scores are considered "worse."	56.7% of patients successfully continued taking suvorexant. 5 of the 13 who did not complete the trial were lost to follow-up, 4 discontinued by choice, 2 discontinues due to lack of efficacy. The remaining children who discontinued (n=2) had adverse effects, mainly abnormal dreams. The Athens Insomnia Scale was worse in patients who discontinued suvorexant compared with those who continued treatment. Clinical global impression scale scores significantly decreased in patients who completed the treatment with suvorexant.	Suvorexant could be a treatment of adolescents' insomnia
Wrishko (2019)	Patients were placed in open-label phase I trials were given a one-time dose of 4mg suvorexant. On the subsequent 10 days, suvorexant was administered with either: a strong CYP3A4 inhibitor (ketoconazole, n=10), a moderate CYP3A4 inhibitor (diltiazem, n=20), or a CYP3A4 inducer (rifampin=10). Plasma concentrations were collected and analyzed for maximum plasma concentration, half-life, and time to maximum concentration.	When suvorexant was administered with ketoconazole and diltiazem, exposure to suvorexant was increased. Exposure increase was greater with the strong inhibitor versus the moderate inhibitor. When suvorexant was co-administered with rifampin, exposure to suvorexant decreased. The most common adverse event was somnolence.	CYP3A4 inducers/inhibitors have an effect on suvorexant pharmacokinetics, however, single doses can be tolerated in patients on those medications.

minutes for the placebo group. At 4 weeks, mean change from baseline was -45 for the suvorexant group and -29 minutes for the placebo group, and this was pronounced during the last third of the night. Partners of the patient noted a significant improvement in sleep quality for the suvorexant group as compared to the placebo group and there were no differences between the groups in partner-rated assessment of the patient's sleep or clinician impression of the degree of patient insomnia.[66]

A clinical trial of 6 patients with dementia due to AD and insomnia (defined as sleeping for <4 hours continuously) showed suvorexant is adequate in treating insomnia in Alzheimer's dementia patients. Patients were evaluated at baseline with mini mental status exam (MMSE), physical self-maintenance scale (PSMS), and neuropsychiatric inventory (NPI). Patients were then given a daily dose of suvorexant and evaluated at weeks 1, 2, 3, and 4. Baseline scores for the MMSE and PSMS were 5.7 ± 5.89 and 10.8 ± 5.53 respectively. There were no significant changes in NPI scores. All patients reported being able to sleep continuously for >6 hours per night at trial's completion.[67]

ACUTE STROKE AND DELIRIUM RISK

A retrospective cohort study of sleep quality and delirium in patients with acute stroke when given ramelteon plus a GABAR agonist (n= 104) or ramelteon plus suvorexant (n= 128). Sleep quality was improved with the addition of suvorexant to ramelteon therapy as opposed to the addition of a GABAR agonist. Delirium was less frequent in the suvorexant group as compared with the GABAR agonist group, as was a reduced recurrence of delirium.

The addition of suvorexant to ramelteon therapy was associated with shorter hospital stays ([15-29], 21 days) in comparison to the addition of GABAR to ramelteon therapy ([18-33], 25 days). The data show that the addition of suvorexant to ramelteon therapy in patients with acute stroke improves their quality of sleep without inducing delirium.[68]

TYPE II DIABETES MELLITUS

A single-arm, open-label interventional trial with 18 patients who had type 2 diabetes mellitus (T2DM) and insomnia was performed; patients were monitored without treatment for days 1-3 and with treatment with suvorexant for days 4-6. Outcomes were monitored via continuous glucose monitoring (daily glucose levels), single-channel electroencephalography (sleep architecture), and accelerometry (autonomic nervous system function). Suvorexant treatment for 3 days improved patient sleep time from 340.3 minutes to 360.0 min. REM time was increased from 72.8min to 96.5 min. non-REM increased from 260.3 min to 272.0 min. The 24-mean glucose level of patients decreased significantly from 157.7 ± 22.9 during days 1-3 to 152.3 ± 17.8 mg/dL on days 4-6. This data demonstrate that treatment of insomnia with suvorexant in patients with T2DM improved their glycemic control in addition to their quality of sleep.[69]

CONCLUSION

Suvorexant offers an additional option for treating insomnia with a unique mechanism of action. Suvorexant is the first in a new class of insomnia agents designed to target orexin receptors involved in the regulation of arousal and wakefulness.[37] Suvorexant does not appear to have the adverse effects associated with traditional insomnia medications acting on benzodiazepine receptors such as amnesia, confusion, and gait disturbance.[45] Another advantage of suvorexant is its capacity to cause minimal physical dependence, making it a good alternative treatment option for patients who have a history of substance abuse.[44]

Despite advancements in medications to treat insomnia, substantial opportunity remains to address the unmet needs of the disorder. Significant progress has been made in understanding the role of the orexin system in physiological and pathological behaviors. Scientific advancements have allowed for more precise manipulation of orexin neurons and associated brain regions, uncovering the dysregulation of the orexin system in psychiatric disorders.[70] Therefore, targeting the orexin system may prove to be a promising strategy to treat such disorders. Further research into novel hypnotics can establish sleep disorders as an integral part of cognitive disorders rather than a secondary component.

Suvorexant has been proven to promote sleep and was the first orexin receptor antagonist approved by the FDA in 2014 for the treatment of insomnia.[45,71] The emergence of suvorexant for the treatment of insomnia has helped pave the way for the development of additional orexin receptor antagonists to treat other disorders including anxiety and addiction. However, further research is needed to optimize orexin receptor antagonists to achieve better physicochemical properties and pharmacodynamics. Suvorexant is currently the only DORA available to the public for the treatment of insomnia and received a favorable risk-benefit profile in clinical trials.[72] Its mechanism of action, pharmacokinetic parameters, and relative lack of rebound and withdrawal effects render suvorexant a reliable choice for the treatment of insomnia.

ETHICAL CONSIDERATIONS

HCA Centralized Algorithms for Research Rules on IRB Exemptions (CARRIE)/ IRB manager issued study exemption # 2022-854.

CONFLICTS OF INTEREST

None of the authors report any conflicts of interest.

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None of the authors have any funding to report for this work.

Table 2. Efficacy of Suvorexant in Treating Insomnia with other Comorbidities

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Matsumura (2019)	An observational study of 149 suspected OSA patients, who did not have insomnia at home, were studied whilst undergoing overnight polysomnography in-lab. Patients who experienced difficulty falling asleep (n=84) were given an optional one-time dose of suvorexant, followed by an add-on dose of zolpidem if still wakeful 1 hour after suvorexant's administration.	Of the 149 patients student, 65 were placed in the "no insomnia group. Of the remaining 84 patients who had difficulty falling asleep, 52.4% of the patients achieved sleep sufficient for PSG analysis with a single dose of suvorexant, while the remaining 47.6% required the addition of zolpidem 1 hour later. There was no significant change between the insomnia and no insomnia groups in regard to sleep time or quality, according to a subjective survey, and no adverse events occurred.	Suvorexant is a mild hypnotic that may be utilized for suspected OSA patients when they experience in-laboratory insomnia during PSG.
Herring (2020)	A randomized, double-blind, 4 week trial of 1:1 placebo: suvorexant treatment was studied in patients (n=285) between the ages of 50-90 who met the DSM-5 criteria for Alzheimer's disease dementia (determined via investigator interview of the patient) and insomnia (determined via interview and PSG as a mean total sleep time of<6 hours per night). Patients were required to have a trial partner who resided with the patient overnight. Treatment /placebo was administered 30 minutes prior to the patient's bedtime, and mean total sleep time and wake after sleep onset time were assessed by PSG. Subjective assessment of patient and partner sleep was given by the trial partner.	Baseline mean sleep time for patients was 77 minutes in the suvorexant group (n=142) and 84 minutes in the placebo group (n=143) at the beginning of this trial. At week 4 of the trial, greater than or equal to 50-minute improvement in mean sleep time was seen in 62% of the suvorexant group and 45% of the placebo group; greater than or equal to 60-minute improvement in mean sleep time was seen in 55% of the suvorexant group and 40% of the placebo group. Baseline mean wake after sleep onset was 60 minutes for suvorexant patients and 61 minutes for the placebo group. At 4 weeks, mean change from baseline was -45 for the suvorexant group and -29 minutes for the placebo group, and this was pronounced during the last third of the night. Partners of the patient noted a significant improvement in sleep quality for the suvorexant group as compared to the placebo group. There were no differences between the groups in partner-rated assessment of the patient's sleep or clinician impression of the degree of patient insomnia.	Suvorexant improved mean total sleep time in patients with probable Alzheimer's dementia and insomnia.
Hamuro (2018)	Clinical trial of 6 patients with dementia due to AD and insomnia (defined as sleeping for <4 hours continuously). Patients were evaluated at baseline with mini mental status exam (MMSE), physical self-maintenance scale (PSMS), and neuropsychiatric inventory (NPI). Patients were then given a daily dose of suvorexant and evaluated at weeks 1,2,3, and 4.	Baseline scores for the MMSE and PSMS were 5.7 ± 5.89 and 10.8 ± 5.53 respectively. There were no significant changes in NPI scores. All patients reported being able to sleep continuously for >6 hours per night at trial's completion.	Suvorexant is adequate in treating insomnia in Alzheimer's dementia patients
Kawada (2019)	Retrospective cohort study of sleep quality and delirium in patients with acute stroke where patients were given ramelteon plus a GABAR agonist (n= 104) or ramelteon plus suvorexant (n= 128).	Sleep quality was improved with the addition of suvorexant to ramelteon therapy as opposed to the addition of a GABAR agonist. Delirium was less frequent in the suvorexant group as compared with the GABAR agonist group, as was a reduced recurrence of delirium. The addition of suvorexant to ramelteon therapy was associated with shorter hospital stays ([15-29], 21 days) in comparison to the addition of GABAR to ramelteon therapy ([18-33], 25 days).	Addition of suvorexant to ramelteon therapy in patients with acute stroke improves their quality of sleep without inducing delirium.

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Toi 2019	Single-arm, open-label interventional trial with 18 patients who had type 2 diabetes mellitus (T2DM) and insomnia; pt were monitored without treatment for days 1-3 and with treatment with suvorexant for days 4-6. Outcomes were monitored via continuous glucose monitoring (daily glucose levels), single-channel electroencephalography (sleep architecture), and accelerometry (autonomic nervous system function).	Treatment of the patients with suvorexant for 3 days improved sleep time from 340.3 minutes to 360.0 min. REM time was increased from 72.8min to 96.5 min. non-REM increased from 260.3 min to 272.0 min. The 24-mean glucose level of patients decreased significantly from 157.7 ± 22.9 during days 1-3 to 152.3 ± 17.8 mg/dL on days 4-6.	Suvorexant treatment of insomnia in patients with T2DM improved their glycemic control in addition to their quality of sleep.

DISCLAIMER

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

REFERENCES

1. Sutton EL. Insomnia. *Medical Clinics of North America*. 2014;98(3):565-581. doi:10.1016/j.mcna.2014.01.008

2. Roth T. Insomnia: Definition, prevalence, etiology, and consequences. *Journal of Clinical Sleep Medicine*. 2007;3(5 suppl). doi:10.5664/jcsm.26929

3. Mai E, Buysse DJ. Insomnia: Prevalence, Impact, Pathogenesis, Differential Diagnosis, and Evaluation. *Sleep Medicine Clinics*. 2008;3(2):167-174. doi:10.1016/j.jsmc.2008.02.001

4. Ancoli-Israel S. The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *American Journal of Managed Care*. Published online 2006.

5. Ohayon MM. Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Medicine Reviews*. 2002;6(2):97-111. doi:10.1053/smrv.2002.0186

6. Morin CM, Bélanger L, LeBlanc M, et al. The natural history of insomnia: a population-based 3-year longitudinal study. *Arch Intern Med*. 2009;169(5):447. doi:10.1001/archinternmed.2008.610

7. Krystal AD, Prather AA, Ashbrook LH. The assessment and management of insomnia: an update. *World Psychiatry*. 2019;18(3):337-352. doi:10.1002/wps.20674

8. Ohayon MM. Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Medicine Reviews*. 2002;6(2):97-111. doi:10.1053/smrv.2002.0186

9. Leger D, Guilleminault C, Dreyfus JP, Delahaye C, Paillard M. Prevalence of insomnia in a survey of 12 778 adults in France. *J Sleep Res*. 2000;9(1):35-42. doi:10.1046/j.1365-2869.2000.00178.x

10. Bixler EO, Kales A, Soldatos CR, Kales JD, Healey S. Prevalence of sleep disorders in the Los Angeles metropolitan area. *American Journal of Psychiatry*. 1979;136(10):1257-1262. doi:10.1176/ajp.136.10.1257

11. Grandner MA. Sleep, Health, and Society. *Sleep Medicine Clinics*. 2017;12(1):1-22. doi:10.1016/j.jsmc.2016.10.012

12. Suls J, Green PA, Davidson KW. A biobehavioral framework to address the emerging challenge of multimorbidity. *Psychosomatic Medicine*. 2016;78(3):281-289. doi:10.1097/psy.0000000000000294

13. Shi T, Min M, Sun C, Zhang Y, Liang M, Sun Y. Does insomnia predict a high risk of cancer? A systematic review and meta-analysis of cohort studies. *J Sleep Res*. 2020;29(1). doi:10.1111/jsr.12876

14. Maggi S, Langlois JA, Minicuci N, et al. Sleep complaints in community-dwelling older persons: Prevalence, associated factors, and reported causes. *Journal of the American Geriatrics Society*. 1998;46(2):161-168. doi:10.1111/j.1532-5415.1998.tb02533.x

15. Ford DE, Kamerow DB. Epidemiologic Study of Sleep Disturbances and Psychiatric Disorders: An Opportunity for Prevention? *JAMA*. 1989;262(11):1479. doi:10.1001/jama.1989.03430110069030

16. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: An epidemiologic study of three communities. *Sleep*. 1995;18(6):425-432. doi:10.1093/sleep/18.6.425

17. Henderson S, Jorm AF, Scott LR, MacKinnon AJ, Christensen H, Korten AE. Insomnia in the elderly: Its prevalence and correlates in the general population. *Medical Journal of Australia*. 1995;162(1):22-24. doi:10.5694/j.1326-5377.1995.tb138406.x

18. Tamura H, Nishida T, Tsuji A, Sakakibara H. Association between excessive use of mobile phone and insomnia and depression among Japanese adolescents. *International Journal of Environmental Research and Public Health*. 2017;14(7):701. doi:10.3390/ijerph14070701

19. Levenson JC, Kay DB, Buysse DJ. The pathophysiology of insomnia. *Chest*. 2015;147(4):1179-1192. doi:10.1378/chest.14-1617

20. Carley DW, Farabi SS. Physiology of sleep. *Diabetes Spectrum*. 2016;29(1):5-9. doi:10.2337/diaspect.29.1.5

21. Kaur H, Bollu PC. *Insomnia, Chronic*. StatPearls Publishing; 2018.

22. Scammell TE, Winrow CJ. Orexin receptors: Pharmacology and therapeutic opportunities. *Annu Rev Pharmacol Toxicol*. 2011;51(1):243-266. doi:10.1146/annurev-pharmtox-010510-100528

23. Asnis GM, Thomas M, Henderson MA. Pharmacotherapy treatment options for insomnia: A primer for clinicians. *International Journal of Molecular Sciences*. 2015;17(1):50. doi:10.3390/ijms17010050

24. Lie JD, Tu KN, Shen DD, Wong BM. Pharmacological Treatment of Insomnia.

25. Triazolam | C17H12Cl2N4 - PubChem. Accessed June 13, 2021. https://pubchem.ncbi.nlm.nih.gov/compound/Triazolam

26. McGechan A, Wellington K. Ramelteon. *CNS Drugs*. 2005;19(12):1057-1065. doi:10.2165/00023210-200519120-00007

27. Almasi A, Meza CE. Doxepin - StatPearls - NCBI Bookshelf. Accessed June 13, 2021. https://www.ncbi.nlm.nih.gov/books/NBK542306/?report=reader

28. HIGHLIGHTS OF PRESCRIBING INFORMATION.

29. U.S. Food and Drug Administration, Merck & Co. Inc. BELSOMRA® (Suvorexant); 2014.

30. Norman JL, Anderson SL. Novel class of medications, orexin receptor antagonists, in the treatment of insomnia-critical appraisal of suvorexant. *Nature and Science of Sleep*. 2016;8:239-247. doi:10.2147/nss.s76910

31. Gauld AR. Suvorexant (Belsomra) for insomnia. *American Family Physician*. Published online 2016.

32. Citrome L. Suvorexant for insomnia: A systematic review of the efficacy and safety profile for this newly approved hypnotic - What is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract*. 2014;68(12):1429-1441. doi:10.1111/ijcp.12568

33. U.S. Food and Drug Administration, Merck & Co. Inc. BELSOMRA® (Suvorexant); 2014.

34. Janto K, Prichard JR, Pusalavidyasagar S. An update on dual orexin receptor antagonists and their potential role in insomnia therapeutics. *Journal of Clinical Sleep Medicine*. 2018;14(8):1399-1408. doi:10.5664/jcsm.7282

35. Citrome L. Suvorexant for insomnia: A systematic review of the efficacy and safety profile for this newly approved hypnotic - What is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract*. 2014;68(12):1429-1441. doi:10.1111/ijcp.12568

36. Gauld AR. Suvorexant (Belsomra) for insomnia. *American Family Physician*. Published online 2016.

37. Cada D, Levien T, Baker D. Suvorexant. *Hospital Pharmacy*. 2015;50(1):059-071. doi:10.1310/hpj5001-059

38. Uslaner JM, Renger JJ, Coleman PJ, Winrow CJ. A new class of hypnotic compounds for the treatment of insomnia: The dual orexin receptor antagonists. *Orexin and Sleep*. Published online 2015:323-338. doi:10.1007/978-3-319-23078-8_17

39. Jacobson LH, Callander GE, Hoyer D. Suvorexant for the treatment of insomnia. *Expert Review of Clinical Pharmacology*. 2014;7(6):711-730. doi:10.1586/17512433.2014.966813

40. Jacobson LH, Chen S, Mir S, Hoyer D. Orexin OX2 receptor antagonists as sleep aids. *Current Topics in Behavioral Neurosciences*. Published online 2017:105-136. doi:10.1007/7854_2016_47

41. Snyder E, Ma J, Svetnik V, et al. Effects of suvorexant on sleep architecture and power spectral profile in patients with insomnia: Analysis of pooled phase 3 data. *Sleep Medicine*. 2016;19:93-100. doi:10.1016/j.sleep.2015.10.007

42. Gotter AL, Winrow CJ, Brunner J, et al. The duration of sleep promoting efficacy by dual orexin receptor antagonists is dependent upon receptor occupancy threshold. *BMC Neurosci*. 2013;14(1). doi:10.1186/1471-2202-14-90

43. Jacobson LH, Callander GE, Hoyer D. Suvorexant for the treatment of insomnia. *Expert Review of Clinical Pharmacology*. 2014;7(6):711-730. doi:10.1586/17512433.2014.966813

44. Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: A phase 3 randomised, double-blind, placebo-controlled trial. *The Lancet Neurology*. 2014;13(5):461-471. doi:10.1016/s1474-4422(14)70053-5

45. Dubey AK, Handu SS, Mediratta PK. Suvorexant: The first orexin receptor antagonist to treat insomnia. *Journal of Pharmacology and Pharmacotherapeutics*. 2015;6(2):118-121. doi:10.4103/0976-500x.155496

46. Sun H, Kennedy WP, Wilbraham D, et al. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. *Sleep*. Published online February 1, 2013. doi:10.5665/sleep.2386

47. Cada D, Levien T, Baker D. Suvorexant. *Hospital Pharmacy*. 2015;50(1):059-071. doi:10.1310/hpj5001-059

48. Rhyne DN, Anderson SL. Suvorexant in insomnia: efficacy, safety and place in therapy. *Therapeutic Advances in Drug Safety*. 2015;6(5):189-195. doi:10.1177/2042098615595359

49. Dubey AK, Handu SS, Mediratta PK. Suvorexant: The first orexin receptor antagonist to treat insomnia. *Journal of Pharmacology and Pharmacotherapeutics*. 2015;6(2):118-121. doi:10.4103/0976-500x.155496

50. Sun H, Kennedy D, Lewis N, et al. THE SINGLE DOSE PHARMACOKINETIC (PK) AND PHARMACODYNAMIC (PD) PROFILES OF SUVOREXANT (MK-4305), A DUAL OREXIN RECEPTOR ANTAGONIST, IN HEALTHY MALE SUBJECTS. *Clinical Pharmacology & Therapeutics*. Published online 2012.

51. Sun H, Kennedy WP, Wilbraham D, et al. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. *Sleep*. Published online February 1, 2013. doi:10.5665/sleep.2386

52. Cui D, Cabalu T, Yee KL, et al. *In vitro* and *in vivo* characterisation of the metabolism and disposition of suvorexant in humans. *Xenobiotica*. 2016;46(10):882-895. doi:10.3109/00498254.2015.1129565

53. Asai Y, Sano H, Miyazaki M, Iwakura M, Maeda Y, Hara M. Suvorexant (Belsomra® Tablets 10, 15, and 20 mg): Japanese Drug-Use Results Survey. *Drugs R D*. 2018;19(1):27-46. doi:10.1007/s40268-018-0256-6

54. Fan B, Kang J, He Y, Hao M, Du W, Ma S. Efficacy and Safety of Suvorexant for the Treatment of Primary Insomnia among Chinese: A 6-Month Randomized Double-Blind Controlled Study.

55. Svetnik V, Snyder ES, Tao P, et al. Insight into reduction of wakefulness by suvorexant in patients with insomnia: Analysis of wake bouts. *Sleep*. 2018;41(1). doi:10.1093/sleep/zsx178

56. Seol J, Fujii Y, Park I, et al. Distinct effects of orexin receptor antagonist and $GABA_A$ agonist on sleep and physical/cognitive functions after forced awakening. *Proc Natl Acad Sci USA*. 2019;116(48):24353-24358. doi:10.1073/pnas.1907354116

57. Herring WJ, Connor KM, Snyder E, et al. Effects of suvorexant on the Insomnia Severity Index in patients with insomnia: analysis of pooled phase 3 data. *Sleep Medicine*. 2019;56:219-223. doi:10.1016/j.sleep.2018.09.010

58. Kawabe K, Horiuchi F, Ochi M, Nishimoto K, Ueno SI, Oka Y. Suvorexant for the Treatment of Insomnia in Adolescents. *Journal of Child and Adolescent Psychopharmacology*. 2017;27(9):792-795. doi:10.1089/cap.2016.0206

59. Takeuchi Y, Sano H, Asai Y, Miyazaki M, Iwakura M, Maeda Y. Real-world evidence of the safety and efficacy profile of suvorexant in elderly patients with insomnia: a sub-analysis of the post-marketing drug-use results survey in Japan. *Current Medical Research and Opinion*. 2020;36(3):465-471. doi:10.1080/03007995.2019.1700361

60. Herring WJ, Connor KM, Snyder E, et al. Clinical profile of suvorexant for the treatment of insomnia over 3 months in women and men: subgroup analysis of pooled phase-3 data. *Psychopharmacology*. 2017;234(11):1703-1711. doi:10.1007/s00213-017-4573-1

61. Yee KL, McCrea J, Panebianco D, et al. Safety, Tolerability, and Pharmacokinetics of Suvorexant: A Randomized Rising-Dose Trial in Healthy Men. *Clin Drug Investig*. 2018;38(7):631-638. doi:10.1007/s40261-018-0650-4

62. Wrishko RE, McCrea JB, Yee KL, et al. Effect of CYP3A Inhibition and Induction on the Pharmacokinetics of Suvorexant: Two Phase I, Open-Label, Fixed-Sequence Trials in Healthy Subjects. *Clin Drug Investig*. 2019;39(5):441-451. doi:10.1007/s40261-019-00764-x

63. Sano H, Asai Y, Miyazaki M, Iwakura M, Maeda Y, Hara M. Safety profile and clinical course of patients with insomnia administered suvorexant by initial treatment status in a post-marketing survey. *Expert Opinion on Drug Safety*. 2019;18(11):1109-1118. doi:10.1080/14740338.2019.1657091

64. Herring WJ, Connor KM, Snyder E, et al. Suvorexant in Elderly Patients with Insomnia: Pooled Analyses of Data from Phase III Randomized Controlled Clinical Trials. *American Journal of Geriatric Psychiatry*. 2017;25(7):791-802. doi:10.1016/j.jagp.2017.03.004

65. Matsumura T, Terada J, Yoshimura C, et al. Single-use suvorexant for treating insomnia during overnight polysomnography in patients with suspected obstructive sleep apnea: a single-center experience. *Drug Design, Development and Therapy*. 2019;13:809-816. doi:10.2147/dddt.s197237

66. Herring WJ, Ceesay P, Snyder E, et al. Polysomnographic assessment of suvorexant in patients with probable Alzheimer's disease dementia and insomnia: a randomized trial. *Alzheimer's & Dementia*. 2020;16(3):541-551. doi:10.1002/alz.12035

67. Hamuro A, Honda M, Wakaura Y. Suvorexant for the treatment of insomnia in patients with Alzheimer's disease. *Aust N Z J Psychiatry*. 2018;52(2):207-208. doi:10.1177/0004867417747402

68. Kawada K, Ohta T, Tanaka K, Miyamura M, Tanaka S. Addition of Suvorexant to Ramelteon Therapy for Improved Sleep Quality with Reduced Delirium Risk in Acute Stroke Patients. *Journal of Stroke and Cerebrovascular Diseases*. 2019;28(1):142-148. doi:10.1016/j.jstrokecerebrovasdis.2018.09.024

69. Toi N, Inaba M, Kurajoh M, et al. Improvement of glycemic control by treatment for insomnia with suvorexant in type 2 diabetes mellitus. *Journal of Clinical & Translational Endocrinology*. 2019;15:37-44. doi:10.1016/j.jcte.2018.12.006

70. Han Y, Yuan K, Zheng Y, Lu L. Orexin Receptor Antagonists as Emerging Treatments for Psychiatric Disorders. *Neurosci Bull*. 2019;36(4):432-448. doi:10.1007/s12264-019-00447-9

71. Sheridan C. Insomniacs get new mechanism sleep drug Belsomra. *Nat Biotechnol*. 2014;32(10):968-968. doi:10.1038/nbt1014-968

72. Norman JL, Anderson SL. Novel class of medications, orexin receptor antagonists, in the treatment of insomnia-critical appraisal of suvorexant. *Nature and Science of Sleep*. 2016;8:239-247. doi:10.2147/nss.s76910