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Suvorexant, Novel Dual Orexin Receptor Antagonist for Management of Insomnia: A Systematic Review:

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ABSTRACT

Insomnia is a serious medical and social problem, its prevalence in the general population ranges from 9 to 35% depending on the country and assessment method. Often, patients are subject to inappropriate and therefore dangerous pharmacotherapies that include prolonged administration of hypnotic drugs, benzodiazepines and other GABAA receptor modulators. This usually does not lead to a satisfactory improvement in patients' clinical states and may cause lifelong drug dependence. Orexins/hypocretins are key neuropeptides responsible for regulating central arousal and reward circuits. Due to their interaction with the sleep–wake regulating neuronal population, they can activate vigilance-promoting regions and prevent unwanted sleep intrusions. Understanding the multiple orexin modulatory effects is crucial in the context of pathogenesis of insomnia and should lead to the development of novel treatments. An important step in this process was the synthesis of dual antagonists of orexin receptors. Two receptors respond to orexin signaling, orexin 1 receptor (OX_1R) and orexin 2 receptor (OX_2R) with partially overlapping nervous system distributions. Suvorexant (MK-4305) is a potent, selective, and orally bioavailable antagonist of OX_1R and OX_2R currently under clinical investigation as a novel therapy for insomnia. This new pharmacological approach might be the most appropriate to treat insomnia. Consistent cross-species sleep/wake architecture changes produced by Suvorexant highlight a unique opportunity to develop dual orexin antagonists as a novel therapy for insomnia. This article reviews the management procedure of insomnia by using this novel drug Suvorexant.

Keywords: orexins, sleep disorders, suvorexant, insomnia, benzodiazepines, sleep.

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INTRODUCTION

Sleep is a physiological state that has been shown to be necessary to maintain homeostasis, proper body functioning and mental health in humans. The control of sleep and wakefulness is a complex process involving the coordinated activity of numerous neuronal circuits. It is thought that a fundamental role in this phenomenon is played by a relatively small group of hypothalamic neurons that synthesize and release orexins (also known as hypocretins).

In humans, the orexinergic cell population is formed by near about 80 000 neurons that are exclusively localized in the perifornical nucleus and the lateral and posterior hypothalamic area.[1] They are therefore in an ideal position to influence both sleep and wakefulness. Similar to other neuropeptides, orexins have a broad spectrum of regulatory effects in the central nervous system. They influence the physiology of virtually all brain functions, from sleep and homeostasis to memory, emotions and reward.[2]

This review aims at reporting and discussing recent evidence highlighting a key role of orexinergic neurons in the context of pathogenesis of insomnia and the development of new treatments targeting this system.

Insomnia is characterized subjectively and may consist of a variety of complaints, including difficulty falling asleep, difficulty maintaining sleep, or experiencing non restorative sleep. Despite a number of available treatments, insomnia is the most common medical complaint in general practice.[3] It affects up to 30% of the adult population.[4] It is also a major risk factor for anxiety disorder, substance abuse, and major depression, and it may lead to a decreased quality of life.[4]

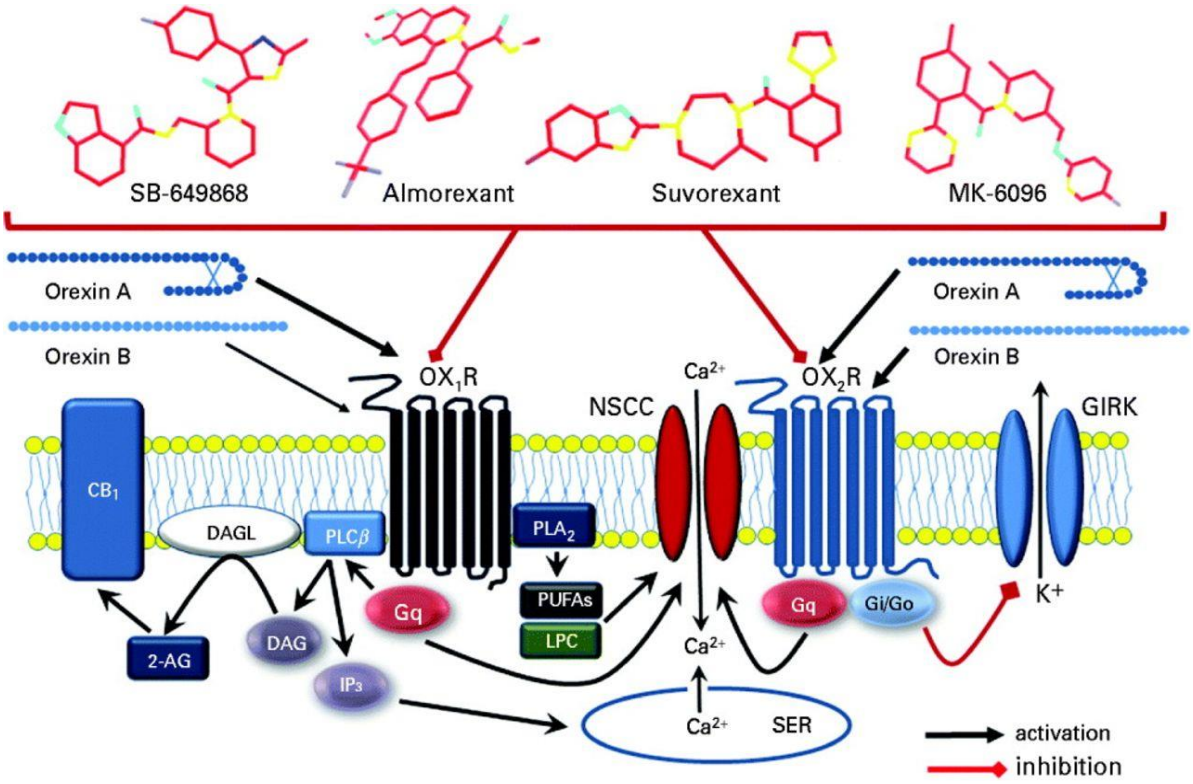
Reported prevalence rates vary, but it is estimated that insomnia occurs in 10–20% of the general population and is twice as common in women as it is in men.[3] Insomnia can impair daytime functioning and lead to serious health problems including depression, anxiety and metabolic and cardiac diseases. In response to difficulties initiating or maintaining sleep, many people seek treatment with prescription sleep aids. A recent CDC report on prescription sleep aid use in the U.S. found that approximately 4% of adults aged 20 and over reported using a prescription sleep aid in the past month.[4]

Involvement of orexinergic signalling in sleep–wake cycle regulation:

Orexins were independently isolated in 1998 by two groups searching either for neuropeptides specifically expressed in the hypothalamus[5] or for endogenous ligands of orphan receptor HFGAN72, defined today as orexin receptor 1.[6] They belong to and possess a structural

homology to other known neuropeptides of the incretin family. The group is composed of two peptides: orexin A and B. They are derivatives of one polypeptide precursor called prepro-orexin and are generated following post-translational activity of convertases. Orexin A and B are peptides with fundamentally different characteristics, well preserved among vertebrates. Orexin A is composed of 33 amino acids with two disulphide bridges (Cys6 –Cys12 and Cys7 –Cys17) in its molecule. It is characterized by a higher stability in the cerebrospinal fluid and in blood than orexin B. On the other hand, orexin B is a linear molecule composed of 28 amino acids and its concentration in the brain is 2–5 times higher in comparison to orexin A.[7] Orexins act via two receptors, known as OX1R and OX2R, belonging to the G-protein-coupled receptor family. They are composed of seven trans membrane domains encoded by separate exons and show significant homology among mammals. They show diverse affinity to orexins: OX1R has higher affinity to orexin A, whereas OX2R is equally sensitive for both peptides. Their activation always induces excitation of target neurons through cascades of secondary transmitters.[8]

An outline model of interaction of orexins and selected dual orexin receptor antagonists (DORAs) with the orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R) molecules:

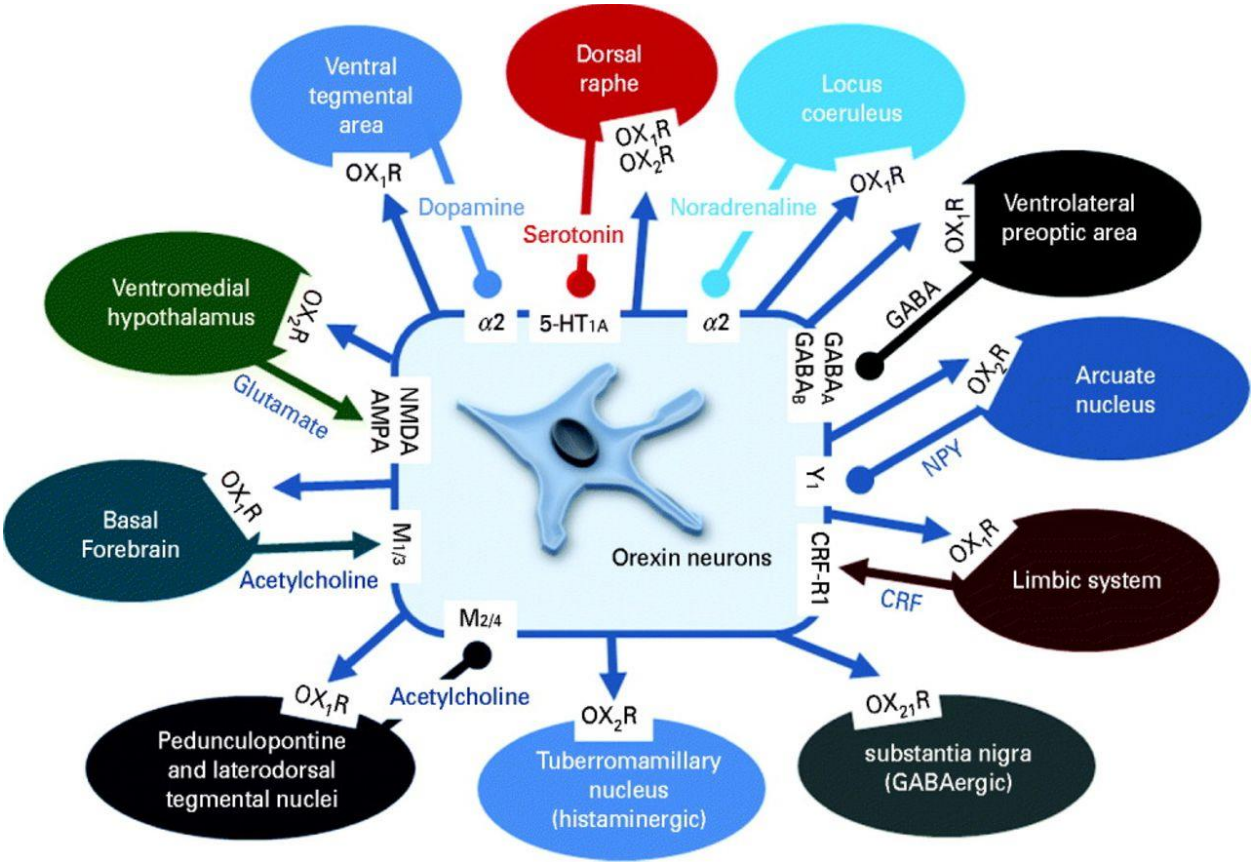


OX1R is a Gq-coupled receptor, its excitation causes phospholipase Cβ (PLCβ) pathway activation, which leads to calcium ions release from endoplasmic reticulum and subsequent neuron depolarization. Extracellular Ca2+ can also flow through an alternative way via non-

selective cationic channels (NSCC) in the cell membrane opened with the help of Gq. OX1R may also activate phospholipase A2 leading to the production of lysophosphatydylcholine (LPC) and polyunsaturated fatty acids (PUFAs), mainly arachidonic acid. These substances promote the opening of NSCC and activate Ca2+ influx. Diacylglycerol lipase (DAGL) converts diacylglycerol to endocannabinoid – 2-arachidonoyl glycerol (2-AG), which stimulate the cannabinoid 1 (CB1) receptors. As opposed to OX1R, OX2R is conjugated with Gq as well as Gi/o protein. In the case of Gi/o protein activation, the closing of G-protein gated inwardly rectifying potassium (GIRK) channels occurs, followed by an inhibition of K+ outflow leading to an increase of neuronal excitability.[8]

Orexinergic cells, which co-express glutamate and dynorphin, are projection neurons that target multiple brain regions involved in the execution of sleep/wake cycles.[7] Many of these targets are reciprocally connected to orexinergic cells providing feedback and feed-forward information.[8]

Schematic representation of the main inputs/outputs of the hypothalamic orexinergic neurons:



The diagram showing the stimulatory (arrow) and inhibitory (round ended line) signalling. OX1R, Orexin receptor 1, OX2R, orexin receptor 2; GABA, γ-aminobutyric acid; NPY, neuropeptide Y.

The main orexinergic projections target wakefulness-promoting regions such as the histaminergic tuberomammillary nucleus in the posterior hypothalamus, the cholinergic neurons of the basal forebrain and the brainstem, the monoaminergic neurons in the brainstem such as the locus coeruleus (LC) and the raphe nuclei. Moreover, they are innervated by neurons originating from serotoninergic raphe nuclei and noradrenergic LC cells. Both monoamines have inhibitory effects on orexinergic neurons. An additional source of inhibition is indirectly mediated by dopamine from the ventral tegmental area via α2-adrenoreceptors and glycinergic inhibitory fibres.[9] Importantly, orexinergic cells receive excitatory cholinergic inputs from the basal forebrain.[7] In agreement with the observed widespread orexin action in the central nervous system, their receptors have been identified in various brain regions.[10]

A variety of treatment options are available for insomnia. The most common pharmacological interventions are benzodiazepines (BZDs) and the non-BZD gamma-amino-butyric acid (GABA)–acting hypnotics such as zolpidem (Ambien, Sanofi), eszopiclone (Lunesta, Sunovion), and zaleplon (Sonata, Pfizer).[3] Other less frequently prescribed agents include sedating antidepressants, melatonin agonists, and antihistamines.[4] Diminished efficacy and negative side effects limit the use of these treatment options for many patients. GABAergic agents also carry with them the risk for physical and psychological dependence and the potential for a withdrawal syndrome with abrupt discontinuation. Future hypnotic agents should improve sleep induction, quality and maintenance of sleep and next day functioning. In addition, they should lack dependency, tolerance, rebound and withdrawal effects and lack adverse effects on respiration, cognition and gait.[11]

Extensive research has demonstrated that the orexin system plays a critical role in the regulation of the transition between sleep and arousal.[12-18] Orexinergic neurons are primarily localized to the lateral hypothalamus and have ascending projections to the cerebral cortex and descending projections to the wakefulness-promoting cell groups of the arousal system, including the monoaminergic and cholinergic cell groups.[19] The actions of orexin neuropeptides are mediated by two G protein-coupled ligand receptors, orexin R1 and R2 (OX_1R and OX_2R).[20,21] Orexin knockout/mutations have been linked to narcolepsy in human and animals.[22,23] Antagonism of orexin receptors is hypothesized to facilitate sleep by transiently blocking orexinergic activity from the lateral hypothalamus and interconnected lower brainstem nuclei that sustain arousal/vigilance. Recently developed investigational orexin receptor antagonists, such as almorexant (ACT-078573) and GW-649868 (SB-649868), have been shown to promote sleep in animals and humans.[24-28] The orexin 1 receptor shows higher affinity for orexin A than orexin B,

while the orexin 2 receptor binds both orexin A and orexin B with similar affinities.[15,16] Orexin neurons are distributed within the lateral hypothalamus and project throughout the brain and spinal cord. Orexin neurons promote wakefulness through excitement of brain regions involved in arousal and attention including the locus coeruleus and dorsal raphe.[17]

Suvorexant...orexin receptor antagonist:

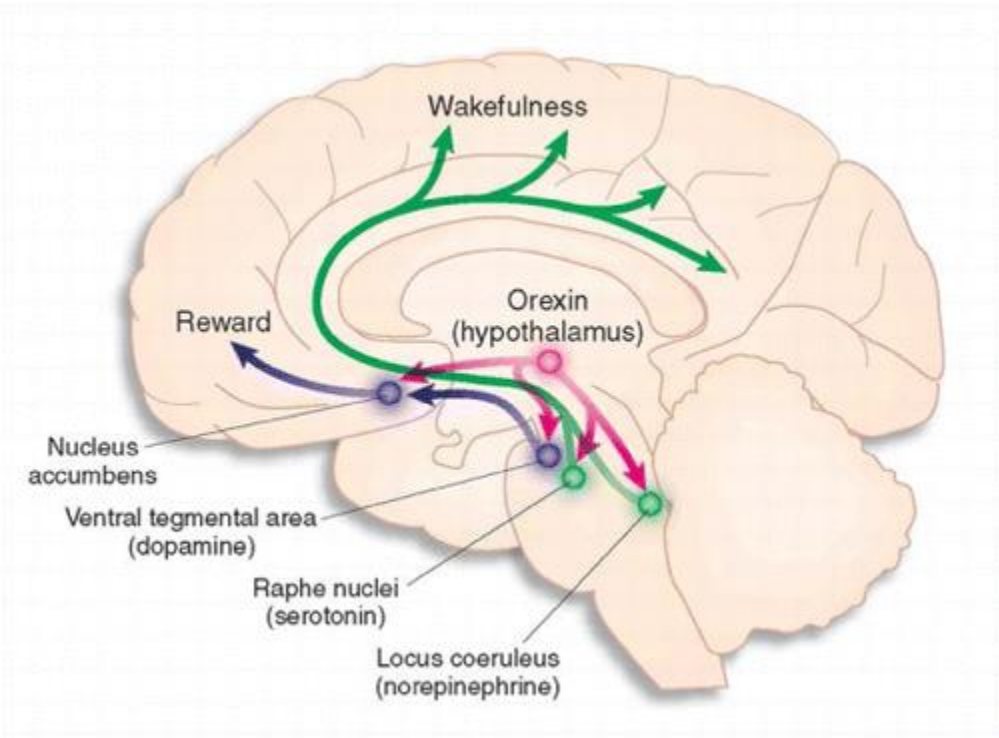


Figure:

Orexin neurons are most active during periods of wakefulness and lowest during non-REM and REM sleep. Permanent deficits in orexinergic function are found in humans and animals with narcolepsy leading to cataplexy (loss of muscle tone in response to emotional stimuli), excessive daytime sleepiness, impaired REM sleep and disrupted nocturnal sleep. Unlike GABA which has broad inhibitory effects on brain activity, orexins produce selective wake-promoting signals. Blocking orexin activity may be more effective at targeting the underlying issue of excess alertness in insomnia compared to promoting sleep by inhibiting brain activity as with GABAergic agents.[18]

Orexin receptor antagonists have a distinctly different mechanism from the benzodiazepine receptor agonists, which are the most common drugs prescribed for the treatment of insomnia. It is possible that orexin receptor antagonists, which have focused effects on a small group of

neurons mediating the transition between arousal and sleep, may have clinical advantages compared to currently available sedative-hypnotics.

Suvorexant (MK-4305, Merck), an orexin receptor antagonist (ORA), is the first in a new class of drugs in development for the treatment of insomnia. The tablets promote the natural transition from wakefulness to sleep by inhibiting the wakefulness-promoting orexin neurons of the arousal system.[29] Suvorexant improves sleep onset and sleep maintenance. This unique alternative has a favorable tolerability and limited side-effect profile.[30]

Suvorexant: Fast Facts

Brand Name: Belsomra

Class: Dual Orexin-receptor antagonist

Indication: Insomnia characterized by difficulty with sleep onset or sleep maintenance, or both.

FDA approval date: August 13, 2014

Availability date: Early 2015

Manufacturer: Merck

Dosage Forms: 5mg, 10mg, 15mg & 20mg tablets.

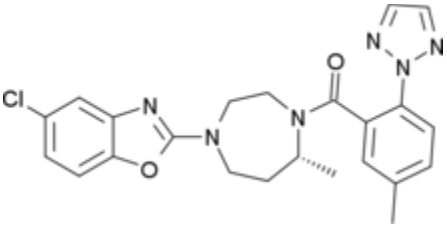
Recommended Dosage: 10mg taken only once within 30minutes of going to bed, with at least 7hours remaining before the planned time of awakening.

Clinical Pharmacology:

Composition:

The molecular formula for suvorexant is $C_{23}H_{23}ClN_6O_2$. The molecular weight is approximately 450.932 g/mol.[31]

Chemical Structure of Suvorexant[(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone):



Mechanism of Action:

Suvorexant is a potent dual orexin receptor antagonist that blocks both OX1R and OX2R. It promotes sleep through the binding inhibition of orexin A and B, neuropeptides that promote

wakefulness. Roughly 70,000 orexin neurons are in the human brain, located in the perifornical lateral hypothalamus, which send signals throughout the brain and spinal cord.[33]

Pharmacodynamics and Pharmacokinetics:[34]

Merck's application to the FDA for approval included 32 studies that enrolled more than 900 subjects (both those who were healthy and those with insomnia). Suvorexant was effective and generally well tolerated. An advantage of suvorexant over previous insomnia therapies is the low potential for addiction or dependence. Studies demonstrated that plasma concentrations were higher in obese women than in men with a normal body mass index (BMI).[30] However, there was no difference among patients with moderate hepatic or renal dysfunction, a desirable finding in the elderly population. Suvorexant, as with other hypnotic agents, should be avoided in individuals with severe hepatic impairment.[34]

Absorption.

The onset of sleep occurred between 56 and 68 minutes after oral administration. Onset was most rapid in those who received 40 mg.[35] Median peak plasma concentrations occur approximately two hours after administration and are not affected by food.

Distribution.

Suvorexant has a volume of distribution of 105.9 L and is highly protein bound (99.5%).

Metabolism.

The agent is primarily metabolized by the cytochrome P450 (CYP3A4) enzyme system, with some contribution from CYP2C19 into M9, an inactive metabolite.

Elimination.

Suvorexant is eliminated primarily via inactive metabolites in the feces; there is no renal elimination. The half-life is approximately 12.2 hours on average (range 8–19 hours). Steady-state plasma concentrations occur in about three days with daily administration.

Indication:

The proposed indication for suvorexant is the treatment of insomnia (difficulty with sleep onset or sleep maintenance) in adults 18 years of age and older.[34]

SAFETY PROFILE:

Contraindications:

Suvorexant is contraindicated in patients with narcolepsy.[37] The underlying pathology of narcolepsy involves a marked reduction in orexin functioning with corresponding excessive sleepiness and related symptoms, such as cataplexy, hypnagogic hallucinations, and sleep paralysis. Although suvorexant has not been evaluated in patients with narcolepsy, the drug

might, hypothetically, put patients at higher risk of the full spectrum of narcolepsy symptoms. There are no other contraindications for suvorexant.

Adverse Drug Reactions:

As with other insomnia medications, suvorexant has the potential to produce drowsiness the next day that might interfere with daily activities. This effect is observed with doses higher than 40mg and increases proportionally with dosage increases.[37]

Drug Interactions:

Patients should avoid taking other CYP3A medications while they are taking suvorexant. Potent CYP3A inhibitors such as fluconazole (Diflucan, Pfizer) increase plasma concentrations, placing patients well above the desired therapeutic threshold. Moderate inhibitors such as diltiazem (Cardizem, AbbVie) can be used safely, especially in the elderly when lower doses (e.g., 10 mg) of suvorexant are administered[34] CYP3A inducers, such as rifampin (Rifadin, Sanofi), result in significantly reduced suvorexant plasma concentrations. Suvorexant is a mild inhibitor of CYP3A, but when administered with CYP3A substrates, including oral contraceptives and warfarin, it had minimal effects. [34]

Dosage & Administration:

Although the original recommended dose was 40 mg, this dose was associated with safety concerns. As a result, the recommended initial daily dose is 10 mg. Doses may be titrated to a maximum of 40 mg daily, and escalation is advised only in those patients who can tolerate lower doses with no adverse effects.

Efficacy:

Low-dose (20-mg) and high-dose (40-mg) suvorexant in individuals younger than age 65 years both proved superior to placebo in the following categories: waking after sleep onset (WASO), latency to persistent sleep (LPS), mean subjective total sleep time (sTSTm), mean subjective waking after sleep onset (sWASOm), and mean subjective time to sleep onset (sTSOm). The data suggest that suvorexant effectively decreases time to onset of sleep and increases maintenance of sleep. In clinical trials, no evidence of rebound insomnia was observed after a minimum of three months and a maximum of 12 months.[34]

Unique clinical issues:

The U.S. Drug Enforcement Agency has categorized suvorexant as a Schedule IV controlled substance. Although there is no evidence of physiological dependence or withdrawal symptoms with suvorexant, studies with recreational substance abusers have shown that the likability rating is similar to that of zolpidem.[41]

Bottom Line:

Suvorexant is FDA-approved for treating sleep onset and sleep maintenance insomnia. The drug is a dual orexin-receptor antagonist, which targets persistent CNS hyper arousal. In clinical trials, suvorexant improved the ability to fall asleep and remain asleep in patients with insomnia. It is generally safe and well tolerated. However, these studies evaluated dosages higher than those approved by the FDA.

CONCLUSION:

Although benzodiazepines and nonbenzodiazepines are effective for insomnia, their adverse-effect profiles and recommended limitations on long-term use may prompt patients and clinicians to seek other options. Patients who experience both sleep onset and sleep maintenance insomnia may be particularly challenging to treat. The recent discovery of orexins and their receptors has led to the development of new therapy targets. Suvorexant is an effective orexin receptor antagonist with a unique clinical profile. Evidence suggests that this medication offers a sustained benefit for patients with symptoms of chronic insomnia.

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