Suvorexant: The first orexin receptor antagonist to treat insomnia

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ABSTRACT

Primary insomnia is mainly treated with drugs acting on benzodiazepine receptors and a few other classes of drugs used for different co-morbidities. A novel approach to treat insomnia has been introduced recently, with the approval of suvorexant, the first in a new class of orexin receptor antagonists. Orexin receptors in the brain have been found to play an important role in the regulation of various aspects of arousal and motivation. The drugs commonly used for insomnia therapy to date, have often been associated with adverse effects, such as, day-time somnolence, amnesia, confusion, and gait disturbance, apart from the risk of dependence on chronic use. Suvorexant has not shown these adverse effects because of its unique mechanism of action. It also appears to be suitable as a chronic therapy for insomnia, because of minimal physical dependence. The availability of this new drug as an effective and safe alternative is an important and welcome development in insomnia management.

Key words: Insomnia, orexin receptor antagonist, suvorexant

INTRODUCTION

Insomnia is the most common sleep disorder, characterized by difficulty in falling asleep and/or maintaining sleep. Insomnia causes impaired cognitive and physical functioning during daytime. It can also lead to emotional consequences, which further lead to affective disorders, such as, depression and anxiety.[1] The prevalence of insomnia in the general population, by strictly applying the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria, is six percent, but the symptoms of insomnia are much more common, which trouble nearly one-third of the global adult population.[2] The pharmacological treatments used for treating insomnia are mainly benzodiazepines and non-benzodiazepine drugs, such as, zolpidem and zaleplon, both acting on benzodiazepine receptors. Antihistamines, antidepressants, antipsychotics, anticonvulsants, and melatonin receptor agonists have also been used to treat insomniac patients with different comorbidities.[3]

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Newer targets for treating insomnia have been persistently explored because none of the currently used drugs can be called 'ideal' in their therapeutic role of promoting sleep throughout the night, maintaining a normal sleep architecture, and being free of any residual morning adverse after effects. One such target of interest, for developing a potential insomnia therapy has been the orexin receptor. Suvorexant, the first in a new class of drugs to treat insomnia by targeting the orexin receptors, has been approved recently, on 13 August, 2014, by the US Food and Drug Administration (FDA). It has been developed

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by the pharmaceutical company Merck, under the brand name Belsomra®.[4]

PHARMACOLOGICAL BASIS FOR USE OF SUVOREXANT IN INSOMNIA

Orexins, also referred to as hypocretins, are neuropeptides secreted from the lateral hypothalamus neurons. Two orexin neuropeptides, orexin-A (OXA) and orexin-B (OXB), have been identified, which act with different affinities through two G-protein coupled receptors, OX1R and OX2R.[5] The orexin secreting neurons in the lateral hypothalamus are less than 100,000 in number, but their receptors are expressed in many areas of the brain with a suggested role in arousal, appetite, metabolism, reward, stress, and autonomic function. The projections of the orexin system are particularly extensive in the regions of the brain, which regulate various aspects of arousal and motivation such as the noradrenergic neurons of the locus coeruleus, the histaminergic neurons of the tuberomammillary nucleus, the serotonergic neurons of the raphe nuclei, and the dopaminergic neurons of the ventral tegmental area.[6]

During the initial studies on the orexin system, it was seen that loss of orexinergic neurons resulted in severe sleepiness in animals, with an inability to maintain wakefulness. Orexinergic neurons were found to be reduced significantly in the brain in humans suffering from narcolepsy, a disorder with excessive sleepiness. Once the role of orexins in maintaining normal wakefulness was established, it was followed with an exciting quest for an antagonist, which would be a novel manner in which to promote sleep and treat insomnia.[7] Suvorexant was the first selective dual orexin receptor antagonist (DORA) to be approved in recent times. It would bind reversibly with both the orexin receptors, OX1R and OX2R, and inhibit the activation of the arousal system, thus, facilitating sleep induction and maintenance.

Chemical structure

Suvorexant is described chemically as a [(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. The initial compound had a fluoroquinazoline ring, but it produced reactive metabolites in the microsomal incubations, so it was modified by replacing fluoroquinazoline with a chlorobenzoxazole moiety, and the modified compound, which was named MK- 4305, underwent the subsequent trials.[8]

Pharmacokinetics and dosage

It is well-absorbed orally, producing peak plasma concentrations in about two hours. Its plasma half-life is about twelve hours. Food does not interfere with the absorption of a suvorexant. It has a high plasma protein binding capacity and is mainly metabolized by the CYP3A4 system. Most of the metabolites are excreted through the feces. It is available in 5, 10, 15 or 20 mg tablets. The recommended dose is 10 mg once at night, which can be increased to a maximum of 20 mg.[4,9]

Clinical trials

Suvorexant was evaluated for safety and efficacy in a randomized, double-blind, placebo-controlled polysomnography study. It was a two-period (four weeks per period) crossover study. In one period comprising of total 243 patients, four different groups received suvorexant 10, 20, 40, and 80 mg. The other period comprising of 249 patients was on placebo. Polysomnography was done on the first night and at the end of the period, that is, after four weeks. Suvorexant showed significant dose-related sleep efficiency on the first night and at the end of four weeks, as compared to the placebo.[10] In another randomized, double-blind, placebo-controlled, crossover polysomnography study, which was conducted on healthy adults, the overnight sleep parameters were recorded and the morning after the residual effects were assessed for 10, 50 or 100 mg doses of suvorexant, as compared to the placebo. All the three doses were found to produce significant sleep-promoting effects.[11]

Adverse effects

Suvorexant has been found to be generally safe and well-tolerated in patients. At the recommended therapeutic dose of less than 20 mg, the most common adverse effect reported has been somnolence. Study on healthy volunteers has shown that there is no residual effect with suvorexant 10 mg on the following day, but the higher doses significantly reduce subjective alertness and prolong the reaction time.[11] In a phase 2, a randomized, double-blind trial on 229 patients of insomnia, change in the patient's neurophysiology on account of drugs or placebo, was assessed by electroencephalographic power spectral density. Suvorexant, at 10 mg, produced minimal neurophysiological disturbance as compared to placebo in healthy subjects and other treatments such as zolpidem.[12]

In a phase 3, randomized, double-blind, placebo-controlled trial of suvorexant for a one-year treatment of insomnia, 362 (69%) of a total of 521 patients experienced some adverse effects. Somnolence was the most common adverse event, reported for 69 (13%) patients. However, all the patients in this study had received a dose of 30 to 40 mg suvorexant, which was higher than the current approved dose of 10 mg.[13] Doses higher than 20 mg have also been reported to be associated with rapid onset of daytime somnolence, motor impairment, driving impairment, and unconscious night time activity, such as, sleep walking, suicidal ideation, hypnagogic hallucinations, abnormal dream pattern, and effects resembling mild cataplexy.[14] It may have a potential additive effect when used with antidepressants and other drugs with a sedative action. On

account of low-abuse liability, similar to zolpidem, it has been placed in Schedule IV of the Controlled Substances Act.[15] The drug is contraindicated in narcolepsy.[14]

In the clinical trials suvorexant did not appear to produce physical dependence and withdrawal syndrome on discontinuation after chronic therapy of one year.[13] This may be a point in favor of suvorexant over the other traditional drugs for insomnia, which act through benzodiazepine receptors and carry the risk of physical dependence on chronic use.

Promises and challenges ahead

Suvorexant has not yet been compared to other drugs approved for insomnia, so its relative advantages in terms of efficacy or adverse effect profile, will emerge more clearly in future, after head to head comparative trials with the already available drugs. This is not the first attempt at developing and marketing an orexin receptor antagonist for insomnia in recent years. Almorexant, a dual orexin receptor antagonist was being tried as a potential blockbuster drug by the pharmaceutical companies GlaxoSmithKline (GSK) and Actelion, but after the Phase III clinical trial in November 2009, the project was aborted citing tolerability issues, which were not disclosed.[16]

Suvorexant has been well-tolerated, without major safety issues, in all the studies so far, at the 10 mg dose. Suicidal ideation seen at higher doses in the clinical trials could be an adverse consequence of antagonism at the orexin receptors that are present in mesolimbic pathways regulating affect, reward, and motivation. Mood-related adverse effects will need monitoring at the reduced recommended dose also. Some of the other adverse effects at higher than 20 mg doses, such as, sleep walking, hypnagogic hallucinations, abnormal dreams, and cataplexy seem related to the rapid eye movement (REM) sleep interference caused by suvorexant. These adverse effects may not appear with a 10 mg dose; but larger studies are needed to confirm this.

It has been suggested that there is differential contribution of the two orexin receptors in regulating sleep/wakefulness, with a more important role of OX2R antagonism in inducing sleep as compared to OX1R.[17] Pharmacology of a more selective antagonism of either OX1R or OX2R alone has not been properly elucidated in the clinical studies because of the lack of suitable subtype-selective, orally bioavailable ligands.[18] In preclinical studies, comparing the effects of single orexin receptor antagonist (SORA) for the subtype OX2R, with the dual antagonist suvorexant, both decreased the wakefulness time with a similar efficacy in a dose-dependent manner. However, there was a slight difference in the type of effect on the sleep architecture, as the OX2R antagonist primarily increased the total non-rapid eye movement (NREM) sleep time with minimal effects on REM sleep, whereas, suvorexant increased both the total NREM and REM sleep time, with predominant effects on REM sleep.[19] It is to be seen in further trials whether OX2R subtype-selective antagonists are better in maintaining the normal sleep architecture.

CONCLUSION

With the approval of suvorexant as a treatment for insomnia, a novel method to regulate the arousal pathway in the brain by orexin antagonism has been introduced. The traditional use of drugs acting on benzodiazepine receptors for treating insomnia has its own limitations, especially in the elderly, because of the associated adverse effects, such as, amnesia, confusion, and gait disturbance. Suvorexant has not shown these adverse effects because of its unique mechanism of action. It also appears to be suitable for the chronic therapy of insomnia because of minimal physical dependence and can be a good alternative in patients who have a history of substance abuse. The availability of this first drug in the class of orexin receptor antagonists, with a potential to provide more peaceful sleep and less troublesome mornings, is an important and welcome development in insomnia management.

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