

Orexin receptor antagonists: Novel hypnotic agents

Chandra K. Cooper, PharmD, BCPP

ABSTRACT

Dual acting orexin antagonists are a novel class of medications in development for the treatment of insomnia. This article reviews the available data on these agents.

KEYWORDS

orexin receptor antagonist, hypnotic, insomnia, hypocretin

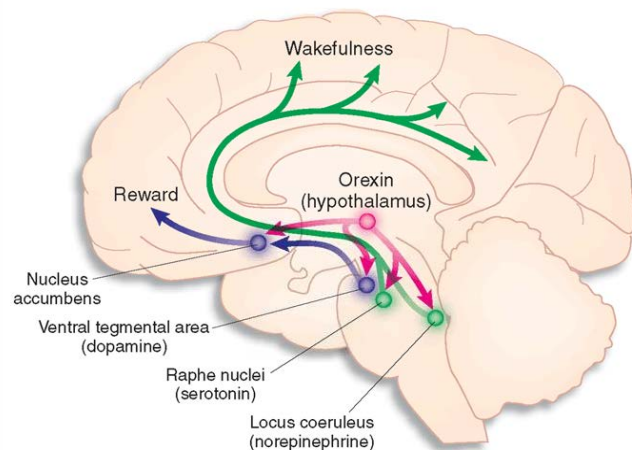
Reported prevalence rates vary, but it is estimated that insomnia occurs in 10-20% of the general population and is twice as common in women as it is in men.¹ Insomnia can impair daytime functioning and lead to serious health problems including depression, anxiety and metabolic and cardiac diseases. 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.²

Currently available pharmacological treatment options for insomnia include GABA_A receptor modulators, histamine receptor antagonists and melatonin receptor agonists. Some of the limitations of currently available treatments include residual daytime sleepiness, cognitive impairment, confusion, dizziness and impaired motor coordination. 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.³

The dual acting orexin antagonists are a novel drug class in development for the treatment of insomnia. The orexins (hypocretins) are recently discovered hypothalamic neuropeptides thought to have an important role in the regulation of sleep and arousal states. Orexin neural pathways have also been found to be involved in the regulation of reward, appetite, stress and emotional control. The actions of orexin A (hypocretin-1) and orexin B (hypocretin-2) are mediated through two receptors, orexin 1 receptor (OX1R or HCRTR1) and orexin 2 receptor (OXR2 or HCRTR2). 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.^{4,5} 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 (Figure 1).⁶

Figure 1 Reprinted with permission from Macmillan Publishers Ltd: *Nature Medicine*. 2007; 13(2): 126-128.



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.⁷ The dual orexin receptor antagonists in development can be found in Table 1. The sleep parameters utilized in trials of these agents are described in Table 2.

Table 1. Dual orexin receptor antagonists (DORA) in development⁸⁻¹¹

Compound	ACT-078573 (Almorexant)	MK-4305 (Suvorexant)	MK-6096	SB-649868
Company	Actelion & GlaxoSmithKline	Merck & Co.	Merck & Co.	GlaxoSmithKline
Clinical Trial	Phase III, discontinued	Phase III completed, NDA submitted Nov 2012, denied FDA approval July 2013	Phase II completed	Phase II completed
Indications	Insomnia	Insomnia	Insomnia, migraine prophylaxis, diabetic neuropathy, depression	Insomnia
T _{1/2} (hours)	21	12	NA	3-6
Metabolism	hepatic CYP3A4 (S/I)	hepatic CYP3A4 (S)	NA	hepatic CYP3A4 (S/I)

S=substrate; I=inhibitor; NA=not available

Table 2. Sleep parameters used in insomnia research⁹

Sleep Disturbance	Definition	Abbreviation	Assessment
			Subjective Tool vs. objective
Sleep onset	Latency to the onset of persistent sleep (time from lights out until first 10 minutes of consistent sleep)	LPS	Objective PSG
	Subjective time to sleep onset	sTSO	Subjective Sleep diary
Sleep maintenance	Wake after persistent sleep onset (time spent awake after initial sleep until final awakening)	WASO	Objective PSG
		sWASO	Subjective Sleep diary
	Total sleep time	TST sTST	Objective PSG Subjective Sleep diary
Global	Sleep efficiency = total sleep time divided by time spent in bed x 100 (reported as percentage)	SE	Objective PSG

ALMOREXANT

Almorexant is a reversible, selective dual OX₁ and OX₂ receptor antagonist (DORA). In studies, almorexant increased deep sleep and REM sleep (unlike GABA receptor modulators which decrease REM sleep). In a Phase II study of 161 patients with primary insomnia, almorexant 400mg significantly reduced LPS (mean treatment effect -18 min; p=0.02) and WASO (mean treatment effect - 54 min; p<0.001) compared to placebo. Dose-related increases in TST were found in all (400 mg, 200 mg and 100 mg) almorexant groups compared with placebo. The most commonly reported adverse effects in the almorexant treated patients were dizziness, nausea, fatigue, headache and dry mouth. Almorexant had no effect on subjective WASO at any dose, but objective WASO decreased in a dose-dependent fashion. The

higher almorexant doses (400 mg and 200 mg) were associated with some residual effects on next-day performance as evidenced by increased mean reaction times and lower scores on the digit span test. At doses up to 1000 mg, there were no reports of cataplexy or narcolepsy in almorexant treated patients.¹⁰

Actelion's first Phase III study of almorexant (RESTORA 1) was a 2-week randomized, double-blind trial in 707 patients with primary insomnia. Patients were randomized to almorexant 100 mg, almorexant 200 mg, placebo or zolpidem 10 mg (active comparator). The primary endpoint was change from baseline to Day 1&2 in WASO. Both almorexant groups showed statistically significant (p<0.001) improvements in wake after sleep onset with median reductions of 29 minutes and 40 minutes in the 100 mg and 200 mg groups respectively,

versus 11 minutes in the placebo group.¹² Although almorexant was generally well-tolerated in this study, safety signals led to further investigations of the clinical safety of almorexant. These expanded studies led to the discontinuation of almorexant development for undisclosed human tolerability issues.¹³ A study sponsored by Northern California Institute of Research and Education in collaboration with U.S. Army Medical Research and Materiel Command is in the recruitment stage to compare the effects of almorexant, placebo and zolpidem on neurocognitive performance in healthy volunteers.¹⁴

SUVOREXANT

Suvorexant is another reversible dual orexin receptor antagonist (DORA) in development for the treatment of insomnia. Suvorexant has been studied in 36 trials and 2869 subjects (1784 of those in phase III trials). Suvorexant's NDA was accepted for review by the FDA in November 2012. Merck's proposed indication is treatment of insomnia characterized by difficulty with sleep onset and/or sleep maintenance and the proposed dosage range is 20 – 40 mg in adults and 15 – 30 mg in elderly. The pharmacokinetics of suvorexant is characterized by $t_{1/2}$ of 12 hours, T_{max} of 2 hours and CYP3A4-mediated metabolism.⁹

A Phase II randomized, double-blind, placebo-controlled polysomnography study was performed in 254 patients with primary insomnia to assess 4 doses of suvorexant (10mg, 20mg, 40mg, 80mg). The crossover study used two 4-week treatment periods separated by 1-week placebo washout. The primary endpoint was SE on night 1 and at end of week 4. Secondary endpoints included WASO and LPS. All doses of suvorexant were more effective than placebo in improving SE (5.2%-12.9% [night 1]; 4.7%-10.4% [week 4]) and WASO (-21.2 to -36.8 min [night 1]; -21.4 to -33.2 min [week 4]). The study was not adequately powered to evaluate the LPS endpoint. Increases in TST for suvorexant ranged from 22 to 62 minutes depending on dose and evaluation night and were mainly attributable to greater time spent in REM and stage-2 sleep. Patient-reported outcomes included improvement in subjective sleep onset and maintenance in the 40 mg and 80 mg groups, but not in the 10 mg and 20 mg groups.

The most commonly reported adverse effects were dose related and included somnolence, headache, dizziness, abnormal dreams, upper respiratory infection, urinary tract infection and increased ALT. There were no reports of cataplexy-like events; however, there were two reports of sleep paralysis (one each in 40- and 80-mg groups), two

reports of visual hallucinations (one each in placebo washout following 40 mg dose and 80 mg group) and one report of excessive daytime sleepiness in the 80 mg group.¹⁵

Results of suvorexant Phase III trials have not been published; however, they were presented in the FDA Peripheral and Central Nervous System Advisory Committee Meeting in May 2013. Of the phase III trials, two of them were short-term confirmatory efficacy studies and one was a long-term (>12 month) safety study in 160 patients. Dosages of 20 mg (15 mg for elderly) and 40 mg (30 mg for elderly) were selected for evaluation in Phase III trials based on objective and subjective efficacy and tolerability profiles in prior trials. In both short-term efficacy studies, both low and high dose suvorexant improved sleep onset and maintenance parameters versus placebo, however only the high dose consistently reached statistical significance. High dose suvorexant showed greater subjective and objective improvements in LPS, TSO, TST, WASO compared to low dose suvorexant in both studies. In the long-term study, high dose suvorexant maintained subjective efficacy over the 12-month study period.

Rates of discontinuation due to adverse effects were comparable in placebo and suvorexant groups with the most common reason for discontinuation being somnolence. The safety profile at 3 months and 12 months was similar. Although suvorexant had no effect on depressive symptoms over the course of treatment (up to 12 months), suicidal ideation was reported in 0.7% of patients in the high dose suvorexant group, compared to 0.2% of patients in the low dose group and 0.1% of patients in the placebo group (reportedly all in the context of factors associated with increased risk, e.g., prior history, current depression, psychosocial stressors). There was no evidence of withdrawal symptoms or rebound insomnia with discontinuation of suvorexant therapy and it appeared to have a low potential for abuse.⁹

In July 2013, Merck received a complete response letter from the FDA for their orexin receptor antagonist suvorexant. Suvorexant was denied FDA approval due to safety concerns raised by the FDA Peripheral and Central Nervous System Drugs Advisory Committee. The committee expressed concerns about the upper limit of the dosage range secondary to a significant increase in next-day somnolence and excessive daytime sleepiness at those levels. The agency's major safety concerns included: daytime somnolence, impaired driving, unconscious nighttime behaviors, suicidal ideation and

narcolepsy-like syndrome.¹⁶ According to Merck, the FDA advised the company that the efficacy of suvorexant has been established at doses of 10 to 40 mg, but safety data do not support approval of doses at 30 and 40 mg. The FDA also advised that the starting dose be 5 mg for patients on concomitant CYP3A4 inhibitors. Merck reports that additional clinical studies will not be necessary, but manufacturing studies will be required to advance the 10 mg dosage form.¹⁷

OTHER AGENTS

Seven studies (6 Phase I and 1 Phase II) of GlaxoSmithKline's dual orexin receptor antagonist, SB-649868, have been completed. A study of the pharmacokinetics of SB-649868 in elderly and female study subjects was stopped before recruitment for a preclinical safety finding in rats.

One study in 51 healthy volunteers showed both 10 mg and 30 mg doses of SB-649868 increased TST and reduced LPS.¹⁸ Development of this agent was placed on hold in late 2007 for an undescribed toxicity, but is currently listed as being in Phase II development.⁵

In addition to suvorexant, Merck is developing another DORA, MK-6096, for which Phase II trials have been completed. This agent is actively being studied for treatment of depression, diabetic peripheral neuropathy and migraine in addition to insomnia.¹⁴ Merck's website still lists this agent as Phase II in development for insomnia as of July 2013.

CONCLUSIONS

The orexin antagonists improved both sleep initiation as well as maintenance in published clinical trials. It remains to be seen if they will have detrimental effects on daytime functioning.

Based on their novel mechanism of action and selective pharmacologic profile, orexin antagonists should lack some of the adverse effects of currently available hypnotic agents including amnesia, unsteady gait, respiratory depression, orthostasis and abuse potential. However, this class may have its own set of unique adverse effects resulting from dysregulation of REM sleep leading to the potential for hypnagogic hallucinations, sleep paralysis or cataplexy. More research will be necessary to determine if orexin antagonists will produce symptoms of narcolepsy. It is not known whether acute blockade of orexin signaling by orexin antagonists will have different effects than those that result from chronic loss of orexin function as seen in narcolepsy.

If and when an orexin antagonist is brought to market, what will be its role in insomnia management? Since orexin activity is highest during active wakefulness, not during sleep periods, these agents may be ineffective for certain types of insomnia. Perhaps the utility of these agents will be highest in those with jet lag or shift workers trying to sleep when orexin tone is high. These agents may also be chosen preferentially in elderly to avoid gait disturbances and confusion and in those with substance abuse histories to avoid dependence and abuse.

Since orexin enhances activity in mesolimbic pathways regulating reward and motivation, reduced activity in the orexin system could theoretically worsen mood or motivation. This would dictate cautious use in patients with underlying mood disorders especially since there were reports of suicidal ideation in high dose suvorexant studies. Orexin receptor antagonists may offer yet another viable option for the pharmacological management of insomnia. Longer term studies and head-to-head comparisons with existing hypnotics will be crucial to determine the benefit-risk ratio of these agents.

REFERENCES

1. Roth T, Coulouvrat C, Hajak G, Lakoma MD, Sampson NA, Shahly V, et al. Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. *Biol Psych*. 2011; 69(6): 592-600.
2. Prescription Sleep Aid Use Among Adults: United States, 2005-2010; Center for Disease Control Web Site. NCHS Data Brief. Number 127; August 2013. <http://www.cdc.gov/nchs/data/databriefs/db127.htm> Accessed August 29, 2013.
3. Zisapel N. Drugs for insomnia. *Expert Opin Emerg Drugs*. 2012;17(3):299-317. DOI: [10.1517/14728214.2012.690735](https://doi.org/10.1517/14728214.2012.690735). PubMed PMID: [22681198](https://pubmed.ncbi.nlm.nih.gov/22681198/).
4. Mieda M, Sakurai T. Orexin (hypocretin) receptor agonists and antagonists for treatment of sleep disorders. Rationale for development and current status. *CNS Drugs*. 2013;27(2):83-90. DOI: [10.1007/s40263-012-0036-8](https://doi.org/10.1007/s40263-012-0036-8). PubMed PMID: [23359095](https://pubmed.ncbi.nlm.nih.gov/23359095/).
5. Scammell TE, Winrow CJ. Orexin receptors: pharmacology and therapeutic opportunities. *Annu Rev Pharmacol Toxicol*. 2011;51:243-66. DOI: [10.1146/annurev-pharmtox-010510-100528](https://doi.org/10.1146/annurev-pharmtox-010510-100528). PubMed PMID: [21034217](https://pubmed.ncbi.nlm.nih.gov/21034217/).
6. Scammell TE, Saper CB. Orexins: looking forward to sleep, back at addiction. *Nat Med*. 2007;13(2):126-8. DOI: [10.1038/nm0207-126](https://doi.org/10.1038/nm0207-126). PubMed PMID: [17290266](https://pubmed.ncbi.nlm.nih.gov/17290266/).
7. Mignot E. Physiology. The perfect hypnotic? *Science*. 2013;340(6128):36-8. DOI: [10.1126/science.1237998](https://doi.org/10.1126/science.1237998). PubMed PMID: [23559238](https://pubmed.ncbi.nlm.nih.gov/23559238/).
8. Ockert W. A new dawn in the sleep disorders pipeline? *Nat Rev Drug Discov*. 2012;11(8):595-6. DOI: [10.1038/nrd3789](https://doi.org/10.1038/nrd3789). PubMed PMID: [22814416](https://pubmed.ncbi.nlm.nih.gov/22814416/).
9. Food and Drug Administration. FDA Peripheral and Central Nervous System Advisory Committee Meeting May 22, 2013. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM354216.pdf>
10. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM352970.pdf> Accessed July 23, 2013

11. Hoever P, Dorffner G, Beneš H, Penzel T, Danker-Hopfe H, Barbanoj MJ, et al. Orexin receptor antagonism, a new sleep-enabling paradigm: a proof-of-concept clinical trial. *Clin Pharmacol Ther.* 2012;91(6):975-85. DOI: [10.1038/clpt.2011.370](https://doi.org/10.1038/clpt.2011.370). PubMed PMID: [22549286](https://pubmed.ncbi.nlm.nih.gov/22549286/).
12. Renzulli C, Nash M, Wright M, Thomas S, Zamuner S, Pellegatti M, et al. Disposition and metabolism of [¹⁴C]SB-649868, an orexin 1 and 2 receptor antagonist, in humans. *Drug Metab Dispos.* 2011;39(2):215-27. DOI: [10.1124/dmd.110.035386](https://doi.org/10.1124/dmd.110.035386). PubMed PMID: [21045199](https://pubmed.ncbi.nlm.nih.gov/21045199/).
13. Almorexant (ACT 078573) in Adult Subjects With Chronic Primary Insomnia (RESTORA 1). ClinicalTrials.gov Web Site <http://www.clinicaltrials.gov/ct2/show/results/NCT00608985?term=almorexant+restora&rank=1>; Accessed August 14, 2013.
14. Actelion and GSK discontinue clinical development of almorexant. Actelion Web site. <http://www1.actelion.com/en/our-company/news-and-events/index.page?newsId=1483135>. Accessed July 23, 2013.
15. U.S. National Institute of Health. ClinicalTrials.gov Web Site. www.clinicaltrials.gov Accessed July 23, 2013.
16. Herring WJ, Snyder E, Budd K, Hutzelmann J, Snively D, Liu K, et al. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology.* 2012;79(23):2265-74. DOI: [10.1212/WNL.0b013e31827688ee](https://doi.org/10.1212/WNL.0b013e31827688ee). PubMed PMID: [23197752](https://pubmed.ncbi.nlm.nih.gov/23197752/).
17. Farkas R. Suvorexant safety and efficacy. Food and Drug Administration Web Site. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM354215.pdf> Accessed July 23, 2013.
18. Merck receives complete response letter for suvorexant, Merck's investigational medicine for insomnia. Merck Web Site. <http://www.mercknewsroom.com/press-release/research-and-development-news/merck-receives-complete-response-letter-suvorexant-merck> Accessed July 23, 2013.
19. Bettica P, Squassante L, Groeger JA, Gennery B, Winsky-Sommerer R, Dijk DJ. Differential effects of a dual orexin receptor antagonist (SB-649868) and zolpidem on sleep initiation and consolidation, SWS, REM sleep, and EEG power spectra in a model of situational insomnia. *Neuropsychopharmacology.* 2012;37(5):1224-33. DOI: [10.1038/npp.2011.310](https://doi.org/10.1038/npp.2011.310). PubMed PMID: [22237311](https://pubmed.ncbi.nlm.nih.gov/22237311/); PubMed Central PMCID: [PMC3306884](https://pubmed.ncbi.nlm.nih.gov/PMC3306884/).

How to cite this article

Cooper CK. Orexin Receptor Antagonists: Novel Hypnotic Agents. *Ment Health Clin* [Internet]. 2014;4(2):73-7. Available from: <http://dx.doi.org/10.9740/mhc.n190094>