



Suvorexant

Updated: September 25, 2021.

OVERVIEW

Introduction

Suvorexant is an orexin receptor antagonist used for the treatment of insomnia and sleep disorders. Suvorexant therapy is associated with rare occurrence of transient serum enzyme elevations, but has not been implicated in cases of clinically apparent liver injury.

Background

Suvorexant (soo" voe rex' ant) is an orexin receptor antagonist which is used to treat insomnia. Central nervous system neurons with orexin receptors are involved in wakefulness and are inactive during sleep. Engagement of the orexin receptor results in wakefulness, and loss of the receptor can result in excessive daytime sleepiness and narcolepsy. Inhibition of orexin receptor signaling using suvorexant has been shown to shorten the time to falling asleep and to prolong sleep in patients with sleep-onset and sleep-maintenance insomnia. Suvorexant was approved for use in the United States in 2014, the first such orexin based drug approved for insomnia. Suvorexant is available in 5, 10, 15 and 20 mg tablets under the brand name Belsomra. The recommended dose is 10 mg taken orally within 30 minutes of bedtime. The dose can be increased to 20 mg. Side effects are few, but may include daytime somnolence, fatigue, dizziness, headache and vivid or abnormal dreams. Rare but potentially severe side effects include sleep paralysis, cataplexy, nightmares, excessive daytime sleepiness, worsening of depression and suicidal ideation and behaviors. Suvorexant is classified as a Schedule 4 controlled substance, meaning that it has a low potential for abuse or dependence and has an approved medical use.

Hepatotoxicity

In several clinical trials, suvorexant was found to be well tolerated, with serum ALT elevations in 0 to 5% of patients, usually with higher doses, and resolving spontaneously without dose modification. In the registration trials of suvorexant, there were no reports of clinically apparent liver injury. Suvorexant has been available for a limited period of time, but has yet to be implicated in causing clinically apparent liver injury even with an overdose.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which suvorexant might cause liver injury is unknown. Suvorexant is metabolized by the cytochrome P450 system (predominantly CYP3A4) and the dose may need to be altered in patients taking

strong inhibitors (decreasing dose) or inducers (increasing dose) of the enzymes. The relative lack of serious liver related adverse events is probably due to the low doses used and its uncommon, intermittent use.

Drug Class: [Sedatives and Hypnotics](#)

Other Related Drug for Insomnia: [Lemborexant](#)

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Suvorexant – Belsomra®

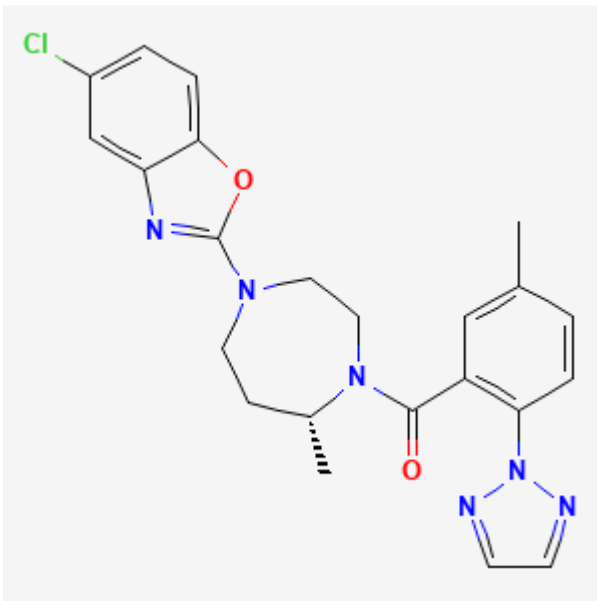
DRUG CLASS

Sedatives and Hypnotics

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Suvorexant	1030377-33-3	C ₂₃ -H ₂₃ -Cl-N ₆ -O ₂	 <p>The chemical structure of Suvorexant is shown. It features a central piperazine ring system. One nitrogen atom of the piperazine is substituted with a 5-chloro-1H-benzotriazol-2-yl group. The other nitrogen atom is substituted with a 4-methyl-1H-imidazol-2-yl group. A methyl group is attached to the piperazine ring at the 4-position, shown with a dashed bond. A carbonyl group is attached to the piperazine ring at the 2-position, which is further substituted with a 4-methyl-1H-imidazol-2-yl group.</p>

ANNOTATED BIBLIOGRAPHY

References updated: 25 September 2021

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 731-4.

(Expert review of hepatotoxicity published in 1999; suvorexant and the orexin receptor antagonists are not discussed).

Larrey D, Ripault MP. Anxiolytic agents. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 455-6.

(Review of hepatotoxicity of hypnotics and sedatives discusses benzodiazepines, buspirone and valerian, all of which have been linked to rare cases of liver injury; suvorexant and orexin receptor antagonists are not discussed).

Mihic SJ, Mayfield J, Harris RA. Hypnotics and sedatives. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 339-354.

(Textbook of pharmacology and therapeutics).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204569Orig1s000MedR.pdf

(FDA website with product labels and multiple disciplinary review that supported approval of suvorexant in the United States, mentions that there were no hepatic serious adverse events, no discontinuations for hepatic events, and no significant shift or change in serum ALT or AST levels during therapy, no instance of ALT elevation with jaundice, and in registration trials enrolling more than 2,500 subjects, ALT elevations of more than 3 times ULN arose in 0.5% of suvorexant and 0.3% of placebo recipients).

Herring WJ, Snyder E, Budd K, Hutzelmann J, Snively D, Liu K, Lines C, et al. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology*. 2012;79:2265–74. PubMed PMID: 23197752.

(Among 254 patients treated with one of 4 doses of suvorexant or placebo in a cross over design, adverse events were more common with higher doses and consisted mainly of somnolence [2-12%], headache [0-5%], dizziness [0-5%] and abnormal dreams [0-5%], with rare instances of ALT elevations [1.6-3.4% with higher doses vs 0.4% with placebo], all of which resolved spontaneously without dose modification).

Herring WJ, Connor KM, Ivgy-May N, Snyder E, Liu K, Snively DB, Krystal AD, et al. Suvorexant in patients with insomnia: results from two 3-month randomized controlled clinical trials. *Biol Psychiatry*. 2016;79(2):136–48. PubMed PMID: 25526970.

(In two 3-month controlled trials of suvorexant versus placebo for primary insomnia in 2040 patients, “No clinically relevant changes in laboratory ... measures were observed” and no serious hepatic adverse events were reported).

Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snively DB, Hutzelmann J, Walsh JK, 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. *Lancet Neurol*. 2014;13:461–71. PubMed PMID: 24680372.

(Among 522 patients with insomnia treated with suvorexant or placebo for one year, rates of adverse events with similar in the two groups and “there were no clinically meaningful differences between groups in vital signs or laboratory values”).

Yin J, Mobarec JC, Kolb P, Rosenbaum DM. Crystal structure of the human OX (2) orexin receptor bound to the insomnia drug suvorexant. *Nature*. 2015;519(7542):247–50. PubMed PMID: 25533960.

(Resolution of the crystal structure of the human orexin receptor bound to suvorexant).

Suvorexant (Belsomra) for insomnia. *Med Lett Drugs Ther*. 2015;57(1463):29–31. PubMed PMID: 25719996.

(Concise review of the efficacy, safety and costs of suvorexant as therapy of insomnia shortly after its approval in the US, mentions the most common side effect as being next day somnolence [in 7-13% of recipients]; no mention of hepatotoxicity or ALT elevations).

Patel KV, Aspesi AV, Evoy KE. Suvorexant: A dual orexin receptor antagonist for the treatment of sleep onset and sleep maintenance insomnia. *Ann Pharmacother*. 2015;49(4):477–83. PubMed PMID: 25667197.

(Review of 3 randomized, controlled trials of suvorexant as therapy of insomnia mentions that somnolence, fatigue and headache were more common with drug than placebo; no mention of ALT elevations or hepatotoxicity).

Chalasan N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. *Gastroenterology*. 2015;148:1340–52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 82 [9%] were attributed to agents active in the central nervous system, but none were sedatives or sleeping aids).

Drugs for insomnia. *Med Lett Drugs Ther*. 2015;57(1472):95–8. PubMed PMID: 26147892.

(Concise review of the mechanism of action, efficacy, safety and costs of drugs for insomnia including benzodiazepine receptor agonists, benzodiazepines, melatonin receptor agonists, orexin receptor antagonists such as suvorexant and other agents including nonprescription and herbal products; no mention of ALT elevations or hepatotoxicity).

Schroeck JL, Ford J, Conway EL, Kurtzhals KE, Gee ME, Vollmer KA, Mergenhagen KA. Review of safety and efficacy of sleep medicines in older adults. *Clin Ther*. 2016;38:2340–72. PubMed PMID: 27751669.

(Systematic review of the literature on the safety and efficacy of sleep aids in the elderly focuses upon common adverse events such as somnolence, fatigue, headache and dry mouth with special emphasis on dementia, forgetfulness, daytime somnolence, falls and fractures; no mention of ALT elevations or hepatotoxicity).

Kuriyama A, Tabata H. Suvorexant for the treatment of primary insomnia: A systematic review and meta-analysis. *Sleep Med Rev*. 2017;35:1–7. PubMed PMID: 28365447.

(Systematic review of the safety and efficacy of suvorexant does not mention effects on ALT levels or hepatotoxicity).

Drugs for chronic insomnia. *Med Lett Drugs Ther*. 2018;60(1562):201–205. PubMed PMID: 30625122.

(Concise review of the mechanisms of action, relative clinical efficacy, safety and costs of medications used to treat chronic insomnia mentions that suvorexant's most common adverse events are somnolence, fatigue and nightmares and that it may cause impairment of next day driving performance and rarely has been linked to complex-sleep related disorders such as cataplexy and leg weakness; no mention of ALT elevations or hepatotoxicity).

Borchert JS, Wang B, Ramzanali M, Stein AB, Malaiyandi LM, Dineley KE. Adverse events due to insomnia drugs reported in a regulatory database and online patient reviews: comparative study. *J Med Internet Res*. 2019;21:e13371. PubMed PMID: 31702558.

(Search of regulatory databases of adverse event reports attributed to drugs for insomnia discusses suvorexant, the main reported side effects being nightmares, headache, somnolence, sleep paralysis, abnormal dreams, feeling abnormal, insomnia, and hangover; no mention of liver test abnormalities or hepatotoxicity).

Muehlan C, Vaillant C, Zenklusen I, Kraehenbuehl S, Dingemans J. Clinical pharmacology, efficacy, and safety of orexin receptor antagonists for the treatment of insomnia disorders. *Expert Opin Drug Metab Toxicol*. 2020;16:1063–1078. PubMed PMID: 32901578.

(Review of the role of orexin in sleep and wakefulness, and the mechanism of action, pharmacology, clinical efficacy and safety of orexin receptor antagonists including suvo-, lembo-, darido- and selto-rexant, all of which have similar side effects but are generally “well tolerated”).

Ito H, Ogawa Y, Shimojo N, Kawano S. Suvorexant poisoning in a patient with cirrhosis and renal failure. *Cureus*. 2021;13:e14329. PubMed PMID: 33968537.

(83 year old man with nonalcoholic steatohepatitis and cirrhosis, hepatocellular carcinoma and renal failure took 270 mg of suvorexant [18 of his 15 mg tablets] in a suicide attempt and slept for 10 hours but then presented

with normal cognition, no sedation, no asterixis and normal ALT, AST, alkaline phosphatase, bilirubin and INR, with no worsening of his renal failure).