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Flibanserin

Updated: January 26, 2018.

OVERVIEW

Introduction

Flibanserin is a serotonergic antidepressant used to treat hypoactive sexual desire disorder. Flibanserin has been associated with a low rate of minor serum aminotransferase elevations during treatment, but has not been linked to instances of clinically apparent acute liver injury.

Background

Flibanserin (flib an' ser in) is a serotonergic mixed agonist and antagonist that was initially developed as an antidepressant when it was found to have possible effects on sexual desire and drive. In vitro, flibanserin acts predominantly as a serotonin (5-HT) 1A receptor agonist, but it also has antagonist activity against other serotonin receptors, such as 5-HT 2C and 2B, as well as less defined activity at dopamine D4 receptors. Flibanserin also has variable regional activities, increasing or decreasing serotonin, dopamine and norepinephrine in different brain areas. While its exact mechanism of action is unclear, flibanserin was found to improve subjective measures of sexual desire and satisfaction in multiple large clinical trials done mostly in premenopausal women who fulfilled the clinical criteria for hypoactive sexual desire disorder. Flibanserin was approved for use in the United States in 2015 for use in treatment of hypoactive sexual desire disorder in premenopausal women. There is limited clinical experience with its use. Concurrent alcohol use is considered contraindicated when taking flibanserin, and caution is recommended against its use with antidepressants or sedatives and in patients wtih hepatic impairment. Flibanserin is available in tablets of 100 mg under the commercial name Addyi. The recommended dose is 100 mg once daily at bedtime. Common side effects include dizziness, fatigue, somnolence, insomnia, nausea and drug mouth. Less common, but potentially serious side effects include hypotension, syncope and next day somnolence or sedation. Because of the severity of these adverse events, flibanserin is available only as a part of a rigorous Risk Evaluation and Mitigation Strategy (REMS) that requires registration, certification of the prescribers and pharmacies, and regular reporting.

Hepatotoxicity

In placebo controlled trials, liver test abnormalities were no more common with flibanserin than with placebo treatment, and what abnormalities occurred were mild and resolved spontaneously, usually without need for dose interruption. During these premarketing clinical trials and since its more widespread clinical availability, no instances of acute liver injury with jaundice have been reported attributable to flibanserin. However, the total clinical experience with flibanserin use has been limited. Many other serotonergic agents, such as the SSRIs, have been implicated in rare instances of clinically apparent liver injury. The latency to onset is typically 1 to 8 weeks and the pattern of enzyme elevations varies, ranging from cholestatic to hepatocellular. Mild signs and

symptoms of hypersensitivity (rash, fever, eosinophilia) are common, but usually not prominent. Autoantibody formation is rare. The course is generally self-limited and mild-to-moderate in severity, but fatalities have been reported with some SSRIs. However, flibanserin itself has not been implicated in similar cases.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which flibanserin might cause serum aminotransferase elevations or liver injury is not known. Flibanserin is metabolized by the liver via the cytochrome P450 system (predominantly CYP 3A4 and 2C19) and is susceptible to drug-drug interactions with agents that induce or inhibit these enzymes. Combination of flibanserin with other serotonergic agents may precipitate the serotonin syndrome marked by fever, tachycardia, hypertension and agitation and can be accompanied by mild serum aminotransferase elevations.

Outcome and Management

The serum aminotransferase elevations that occur on flibanserin therapy are usually self-limited and do not require dose modification or discontinuation of therapy. No instances of acute liver failure or vanishing bile duct syndrome due to flibanserin have been reported. There is no information on cross sensitivity to liver injury between flibanserin and other antidepressants.

Drug Class: Antidepressant Agents, Serotonergic Agents, Miscellaneous (Agents for Hypoactive Sexual Desire Syndrome)

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Flibanserin – Addyi®

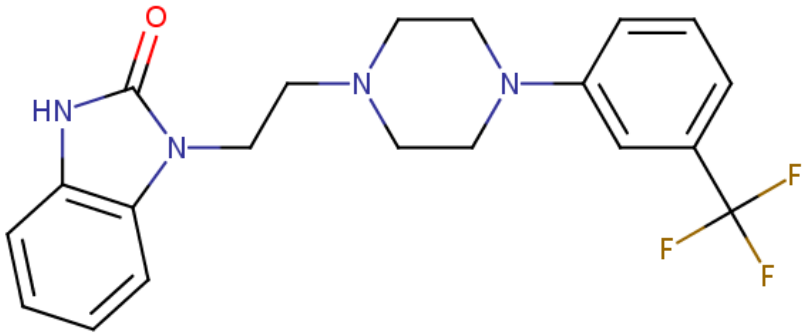
DRUG CLASS

Antidepressant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Flibanserin	167933-07-5	C20-H21-F3-N4-O	

ANNOTATED BIBLIOGRAPHY

References updated: 26 January 2018

Zimmerman HJ. Antidepressants. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 493-8.

(Expert review of hepatotoxicity of antidepressants published in 1999; flibanserin is not discussed).

Larrey D, Ripault MP. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 443-62.

(Review of antidepressant hepatotoxicity; flibanserin is not discussed).

O'Donnell JM, Shelton RC. Drug therapy of depression and anxiety disorders. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 397-416.

(Textbook of pharmacology and therapeutics: flibanserin is not discussed).

Drugs for female sexual dysfunction. Med Lett Drugs Ther 2010; 52 (1353-1354): 100-2. PubMed PMID: 21150835.

(Concise review of drugs for female sexual dysfunction including discussions of systemic estrogens, androgens, bupropion and topical agents and creams, mentions that flibanserin was reported to increase libido, but had worrisome side effects such as dizziness and fainting; no mention of ALT elevations or hepatotoxicity).

Moynihan R. Drug for low sexual desire carries significant harms, FDA advisers find. BMJ 2010; 341: c3339. PubMed PMID: 20610515.

(News report on the 2010 FDA advisory committee decision to not recommend approval of flibanserin mentions side effects of dizziness, somnolence and sedation, but does not mention ALT elevations or hepatotoxicity).

Stahl SM, Sommer B, Allers KA. Multifunctional pharmacology of flibanserin: possible mechanism of therapeutic action in hypoactive sexual desire disorder. J Sex Med 2011; 8: 15-27. PubMed PMID: 20840530.

(Review of the mechanism of action of flibanserin in enhancing female sexual desire through its mixed agonism and antagonism of different serotonin receptor subtypes).

Jayne C, Simon JA, Taylor LV, Kimura T, Lesko LM; SUNFLOWER study investigators. Open-label extension study of flibanserin in women with hypoactive sexual desire disorder. J Sex Med 2012; 9: 3180-8. PubMed PMID: 23057791.

(Among 1723 women treated with flibanserin for up to 12 months in an open label study in subjects who had completed a placebo-controlled trial of the agent, 11% discontinued the agent because of adverse events, mostly related to somnolence and dizziness, but "safety measures, including laboratory tests… did not show any clinically important findings").

Derogatis LR, Komer L, Katz M, Moreau M, Kimura T, Garcia M Jr, Wunderlich G, et al.; VIOLET Trial Investigators. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the VIOLET Study. J Sex Med 2012; 9: 1074-85. PubMed PMID: 22248038.

(Among 880 premenopausal women with hypoactive sexual desire disorder treated with flibanserin [50 or 100 mg at bedtime] or placebo for 24 weeks, "clinically significant changes" in laboratory values did not occur more frequently with flibanserin than with placebo therapy; no mention of ALT elevations or hepatotoxicity).

Thorp J, Simon J, Dattani D, Taylor L, Kimura T, Garcia M Jr, Lesko L, et al.; DAISY trial investigators. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. J Sex Med 2012; 9: 793-804. PubMed PMID: 22239862.

(Among 1185 premenopausal women with hypoactive sexual desire syndrome treated with flibanserin [25, 50 or 100 mg at bedtime] or placebo for 24 weeks, sexual desire scores were higher in those who received 100 mg of flibanserin compared to placebo as were rates of discontinuations for adverse events, but "clinically significant changes" in laboratory values did not occur more frequently with flibanserin than placebo).

Park SH, Ishino R. Liver injury associated with antidepressants. Curr Drug Saf 2013; 8: 207-23. PubMed PMID: 23914755.

(Among 1087 premenopausal women with hypoactive sexual desire disorder treated with flibanserin [100 mg at bedtime] or placebo for 24 weeks, sexual desire measures improved more with flibanserin treatment and "there were no significant safety concerns", the most frequent adverse events being somnolence [14%], dizziness [10%], nausea [8%] and fatigue [6%]; and "there were no clinically significant differences in laboratory" results between treatment groups).

Katz M, DeRogatis LR, Ackerman R, Hedges P, Lesko L, Garcia M Jr, Sand M; BEGONIA trial investigators. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. J Sex Med 2013; 10: 1807-15. 23672269. PubMed PMID: 23672269.

(Among 1087 premenopausal women with hypoactive sexual desire disorder treated with flibanserin or placebo for 24 weeks, adverse events were generally mild, and there were no treatment related serious adverse events and no "clinincally significant differences in laboratory parameters" between the 2 groups).

Simon JA, Kingsberg SA, Shumel B, Hanes V, Garcia M Jr, Sand M. Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the SNOWDROP trial. Menopause 2014; 21: 633-40. PubMed PMID: 24281236.

(Among 949 postmenopausal women with hypoactive sexual desire disorder treated with flibanserin [100 mg at bedtime] or placebo for 24 weeks, subjective measures of sexual desire improved more with flibanserin than placebo, but adverse events were also more common resulting in discontinuation in 8%; no mention of changes or elevations in ALT levels or instances of hepatotoxicity).

Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry 2014; 171: 404-15. PubMed PMID: 24362450.

(Commentary by 3 members of the FDA advisory committee who reviewed the safety and efficacy data in support of flibanserin for hypoactive sexual desire disorder mentions the statistically significant, but numerically small treatment differences compared to placebo and the frequency of worrisome side effects such as hypotension, dizziness and sedation; no mention of ALT elevations or hepatotoxicity).

Gellad WF, Flynn KE, Alexander GC. Evaluation of flibanserin: science and advocacy at the FDA. JAMA 2015; 314: 869-70. PubMed PMID: 26148201.

(Commentary on the FDA decision to approve flibanserin and the possible roles of vocal advocacy groups, shifting efficacy end points, use of patient-reported outcome measures, the unmet medical need and the tenous risk-benefit ratio of the agent).

Jaspers L, Feys F, Bramer WM, Franco OH, Leusink P, Laan ET. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: a systematic review and meta-analysis. JAMA Intern Med 2016; 176: 453-62. PubMed PMID: 26927498.

(Systematic review of the efficacy and safety of flibanserin mentions severe adverse events of hypotension and syncope, but no mention of ALT elevations or hepatotoxicity).

Portman DJ, Brown L, Yuan J, Kissling R, Kingsberg SA. Flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the PLUMERIA Study. J Sex Med 2017; 14: 834-42. PubMed PMID: 28583342.

(Among 748 postmenopausal women with hypoactive sexual disorder treated with flibanserin or placebo for up to 16 weeks, common adverse events included insomnia [8% vs 3%], somnolence [7% vs 2%], dizziness [6% vs 4%] and nausea [5% vs 4%], and there were "no clinically relevant differences" in laboratory test results between the two groups).

Clayton AH, Croft HA, Yuan J, Brown L, Kissling R. Safety of Flibanserin in women treated With antidepressants: a randomized, placebo-controlled Study. J Sex Med 2018; 15: 43-51. PubMed PMID: 29289374.

(Among 111 women on antidepressant therapy who had symptoms of hypoactive sexual desire disorder and were treated with one of 2 dose regimens of flibanserin or placebo for 12 weeks, adverse events rates were similar in the different groups and there were no liver related severe adverse events and no mention of changes in ALT levels).