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Vilazodone

Updated: June 8, 2015.

OVERVIEW

Introduction

Vilazodone is a selective serotonin reuptake inhibitor (SSRI) and partial serotonin receptor agonist which is used in the therapy of major depressive disorders. In premarketing clinical trials, vilazodone therapy was not associated with an increased rate of elevations in serum aminotransferase levels, and it has yet to be linked to instances of clinically apparent acute liver injury.

Background

Vilazodone (vil az' oh done) is an SSRI that acts by blocking the reuptake of serotonin in CNS synaptic clefts, thus increasing serotonin levels in the brain which is associated with its psychiatric effects. Vilazodone is also a partial serotonin (5-HT1A) receptor agonist, which may add to its antidepressant effects. Vilazodone was approved for use in the United States in 2011 for use in treatment of major depressive disorder. There is limited clinical experience with its use. Vilazodone is available as tablets of 10, 20 and 40 mg under the brand name Viibryd. The recommended initial dose of vilazodone in adults is 10 mg daily, which can then be increased to the typical maintenance dose of 40 mg once daily. Common, non-serious side effects include diarrhea, nausea, fatigue, drowsiness, headache, insomnia, weight gain and sexual dysfunction. Overdose is associated with acute serotonin syndrome. Rare, but potentially severe adverse effects include suicidal thinking and behavior, activation of symptoms of mania, sexual dysfunction, hyponatremia and hypersensitivity reactions.

Hepatotoxicity

In premarketing studies, liver test abnormalities were uncommon in patients taking vilazodone (<1%) and no more frequent than in placebo recipients. No instances of acute, clinically apparent liver injury attributed to vilazodone have been reported. However, vilazodone has been in use for a short period of time. Most other SSRIs in clinical use have been associated with rare instances of acute liver injury, usually arising within 2 to 8 weeks of starting therapy. The pattern of serum enzyme elevations varied from hepatocellular to cholestatic. Autoimmune markers are not common, but immunoallergic features (rash, fever, eosinophilia) are frequent but usually not prominent. Most cases of acute liver injury due to SSRIs are mild-to-moderate in severity and resolve within one to three months. Acute liver failure due to the SSRIs has been described, but is very rare. No such cases have been linked to vilazodone use.

Mechanism of Injury

The mechanism by which vilazodone might cause liver injury is not known. Vilazodone is metabolized in the liver at least in part through cytochrome P450 pathways, predominantly CYP 3A4. It is susceptible to significant

drug-drug interactions with increased serum levels when given with strong CYP 3A4 inhibitors (such as ketoconazole) and with reduced concentrations when given with strong inducers (such as carbamazepine).

Outcome and Management

The serum aminotransferase elevations that occur on amoxapine 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 amoxapine have been reported. There is no information on cross sensitivity to liver injury between amoxapine and other tricyclic antidepressants, but switching to another class of agents (such as the selective serotonin reuptake inhibitors) is probably prudent.

Drug Class: Antidepressant Agents

Other Drugs in the Subclass, SNRIs/SSRIs: Citalopram, Escitalopram, Duloxetine, Fluoxetine, Fluvoxamine, Levomilnacipran, Paroxetine, Sertraline, Venlafaxine, Vortioxetine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Vilazodone – Viibryd®

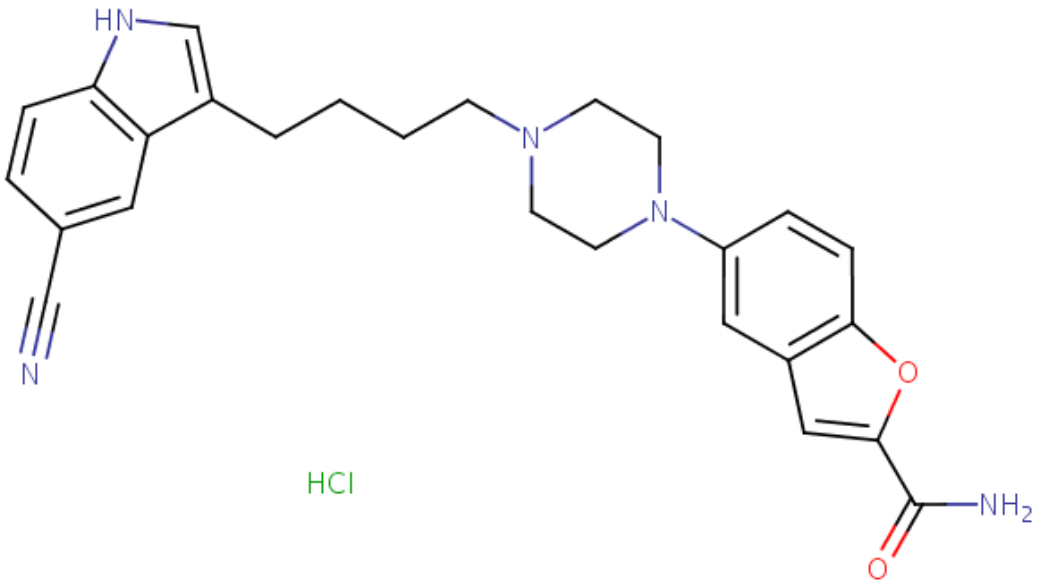
DRUG CLASS

Antidepressant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Vilazodone	163521-08-2	C26-H27-N5-O2.Cl-H	

ANNOTATED BIBLIOGRAPHY

References updated: 08 June 2015

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 published in 1999; before the availability of vilazodone).

Larrey D. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 2nd ed. New York: Informa Healthcare USA, 2007, pp. 507-26.

(Review of hepatotoxicity of antidepressants published in 2007; clinically apparent liver injury from the SSRIs is rare, but probably underreported. "The clinical picture is variable, acute hepatocellular hepatitis appearing to be the most frequent event." No mention of vilazodone).

Baldessarini RJ. Pharmacotherapy of depression and anxiety disorders. In, Brunton LL, Lazo JS, Parker KL, eds. Goodman & Gilman.s the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2006, pp. 429-59.

(Textbook of pharmacology and therapeutics).

Mourilhe P, Stokes PE. Risks and benefits of selective serotonin reuptake inhibitors in the treatment of depression. Drug Saf 1998; 18: 57-82. PubMed PMID: 9466088.

(Review of pharmacology, efficacy and safety of SSRIs; no mention of ALT elevations or hepatotoxicity or of vilazodone).

Lucena M, Carvajal A, Andrade R, Velasco A. Antidepressant-induced hepatotoxicity. Expert Opin Drug Saf 2003; 2: 249-62. PubMed PMID: 12904104.

(Review of hepatotoxicity of antidepressants; antidepressant use has increased markedly between 1992 and 2002, accounting for 5% of cases of hepatotoxicity; SSRIs are less likely to cause injury than tricyclics and MAO inhibitors; range of presentations, typically self-limited and rapid recovery; no hallmarks of hypersensitivity; no mention of vilazodone).

Spigset O, Hä S, Bate A. Hepatic injury and pancreatitis during treatment with serotonin reuptake inhibitors: data from the World Health Organization (WHO) database of adverse drug reactions. Int Clin Psychopharmacol 2003; 18:157-61. PubMed PMID: 12702895.

(Among 27,542 reports of hepatic injury in WHO database, 786 were related to SSRIs [3%], including citalopram 42, fluoxetine 222, fluvoxamine 54, paroxetine 191, sertraline 112, nefazodone 91 and venlafaxine 74; only nefazodone has an excess of hepatic reports in relationship to total reports; no mention of vilazodone).

Degner D, Grohmann R, Kropp S, RüE, Bender S, Engel RR, Schmidt LG. Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. Pharmacopsychiatry 2004; 37 Suppl 1: S39-45. PubMed PMID: 15052513.

(Analysis of adverse drug reactions reported from 1993-2000 in 35 psychiatric hospitals; 0.7% of SSRI recipients had a severe adverse event, hepatic in 0.05%).

Pinzani V, Peyriere H, Hillaire-Buys D, Pageaux GP, Blayac BP, Larrey D. Specific serotonin recapture inhibitor (SSRI) antidepressants: hepatotoxicity assessment in a large cohort in France. J Hepatol 2006; 44: S256. Not PubMed.

(Abstract: Analysis of French Pharmacovigilance data on SSRIs found 63 cases of hepatotoxicity from paroxetine, 45 fluoxetine, 30 citalopram, 18 sertraline, and 2 fluvoxamine; vilazodone not mentioned).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949331.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were linked to any of the SSRIs).

Laughren TP, Gobburu J, Temple RJ, Unger EF, Bhattaram A, Dinh PV, Fossom L, et al. Vilazodone: clinical basis for the US Food and Drug Administration's approval of a new antidepressant. J Clin Psychiatry 2011; 72: 1166-73. PubMed PMID: 21951984.

(FDA analysis of data on safety and efficacy of vilazodone that led to its approval; 2989 subjects were exposed to vilazodone in 32 trials; common side effects were diarrhea [28%], nausea [23%], vomiting [5%], insomnia [6%], palpitations, fatigue and sexual dysfunction; overdose was associated with acute serotonin syndrome; "vilazodone was not associated with any clear finding of drug related changes in laboratory parameters, vital signs or weight").

Vilazodone (Viibryd)--a new antidepressant. Med Lett Drugs Ther 2011; 53 (1368): 53-4. PubMed PMID: 21738107.

(Concise review of mechanism of action, efficacy, safety and cost of vilazodone shortly after its approval in the US mentions that common side effects are diarrhea and nausea and occasionally insomnia, dizziness, headache, weight gain and rarely sexual dysfunction; no mention of ALT elevations or hepatotoxicity).

Choi E, Zmarlicka M, Ehret MJ. Vilazodone: a novel antidepressant. Am J Health Syst Pharm 2012; 69: 1551-7. PubMed PMID: 22935937.

(Review of the structure, mechanism of action, pharmacology, efficacy and safety of vilazodone; in three clinical trials, ALT elevations were not mentioned or said to be no more frequent with vilazodone than placebo).

Citrome L. Vilazodone for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract 2012; 66: 356-68. PubMed PMID: 22284853.

(Systematic review of safety and efficacy of vilazodone in depression; "Vilazodone was not associated with any clinically important changes in laboratory test parameters in serum chemistry, including liver function tests").

Robinson DS, Kajdasz DK, Gallipoli S, Whalen H, Wamil A, Reed CR. A 1-year, open-label study assessing the safety and tolerability of vilazodone in patients with major depressive disorder. J Clin Psychopharmacol 2011; 31: 643-6. PubMed PMID: 21869687.

(Among 616 patients with depression enrolled in a 52 week open label study of vilazodone, common side effects were diarrhea and nausea, 21% of patients stopped therapy because of adverse events, and only 2 patients [0.4%] developed ALT elevations greater than 3 times ULN; no cases of clinically apparent liver injury were reported).

Iranikhah M, Wensel TM, Thomason AR. Vilazodone for the treatment of major depressive disorder. Pharmacotherapy 2012; 32: 958-65. PubMed PMID: 23033234.

(Review of the mechanism of action, pharmacokinetics, efficacy and safety of vilazodone, based largely on premarketing trials; ALT elevations and liver injury were not mentioned).

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

(Review of drug induced liver injury due to antidepressants including SSRIs, does not discuss vilazodone).

Bjöson ES, Bergmann OM, Bjöson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, one of which was attributed to venlafaxine, but none to other SSRIs or vilazodone).

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.

(Review of the frequency and clinical features of drug induced liver injury due to antidepressants; several SSRIs are discussed [sertraline, paroxetine, fluoxetine, citalopram, fluvoxamine], but not vilazodone).

Croft HA, Pomara N, Gommoll C, Chen D, Nunez R, Mathews M. Efficacy and safety of vilazodone in major depressive disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2014; 75: e1291-8. PubMed PMID: 25470094.

(Among 505 patients with major depression treated with vilazodone [40 mg/day] or placebo for 8 weeks, common side effects were nausea, diarrhea, dizziness and insomnia and changes in liver enzymes during therapy were mild and similar between groups, no patient developing both jaundice and hepatocellular enzyme elevations [>3 times ULN]).

Gommoll C, Durgam S, Mathews M, Forero G, Nunez R, Tang X, Thase ME. A double-blind, randomized, placebo-controlled, fixed-dose phase iii study of vilazodone in patients with generalized anxiety disorder. Depress Anxiety 2015; 32: 451-9. PubMed PMID: 25891440.

(Among 680 patients with generalized anxiety disorder treated with vilazodone [20 or 40 mg/day] or placebo for 8 weeks, common side effects were nausea, diarrhea, dizziness and fatigue and changes in liver enzymes during therapy were similar in all groups, no patient developing both jaundice and hepatocellular enzyme elevations [>3 times ULN]).

Chalasani 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, 20 cases were attributed to antidepressants including 5 to SSRIs [fluoxetine, escitalopram, sertraline], but none to vilazodone).