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Varenicline

Updated: December 1, 2013.

OVERVIEW

Introduction

Varenicline is a partial agonist of the nicotinic acetylcholine receptor and is used to help in smoking cessation. Varenicline has been associated with a low rate of serum enzyme elevations during therapy, and since approval and its widescale use, with rare instances of clinically apparent mild liver injury.

Background

Varenicline (var en' i kleen) is a partial agonist of the α4 β2 nicotinic acetylcholine receptor and appears to act by blocking the binding of nicotine to this receptor while providing partial agonist effect thus relieving nicotine craving. Use of varenicline in a program to stop smoking has been shown to increase the rate of smoking cessation and to decrease relapse. Varenicline was approved for use in the United States in 2006 and is widely used in smoking cessation programs. Varenicline is available in tablets of 0.5 and 1 mg under the brand name Chantix. The usually recommended regimen is to start with 0.5 mg once daily and increase to a maintenance dose of 1 mg twice daily, continuing therapy for at least 12 weeks after smoking cessation. Common side effects include nausea, vivid dreams, insomnia, anxiety, depression, dizziness, drowsiness, headache, dry mouth, and change in appetite, some of the symptoms being those of nicotine withdrawal. Varenicline has been reported to cause hypersensitivity reactions including Stevens Johnson syndrome.

Hepatotoxicity

Varenicline has not been associated with rates of serum enzyme elevations during therapy greater than occurs with placebo therapy, but information on these abnormalities is limited and occasional instances of asymptomatic ALT elevations leading to drug discontinuation have been reported. In prelicensure pivotal registration trials in several thousand patients, varenicline was not associated with cases of jaundice or hepatitis. Since licensure, rare case reports of serum enzyme elevations without jaundice arising within 4 weeks of starting varenicline have been published, but largely in patients with other causes of liver injury (alcoholic liver disease, hepatitis C). Thus, clinically apparent liver injury with jaundice due to varenicline must be very rare, if it occurs at all.

Mechanism of Injury

The mechanism by which varenicline might cause liver injury is not known. Varenicline undergoes minimal hepatic metabolism and is excreted largely unchanged in the urine.

Outcome and Management

The rare reports of hepatotoxicity attributed to varenicline therapy have been mild and self-limiting. Varenicline has not been linked to cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome.

Agents in clinical use to aid in smoking cessation and to treat nicotine withdrawal symptoms include bupropion, nicotine, and varenicline.

Drug Class: Substance Abuse Treatment Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Varenicline – Chantix®

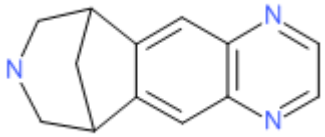
DRUG CLASS

Substance Abuse Treatment Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Varenicline	249296-44-4	C13-H13-N3	

ANNOTATED BIBLIOGRAPHY

References updated: 01 December 2013

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Expert review of hepatotoxicity published in 1999 before the availability of varenicline).

O'Brien CP. Nicotine. Drug addiction. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 657-8.

(Textbook of pharmacology and therapeutics mentions that varenicline partially stimulates nicotinic receptors, thereby reducing craving and preventing most withdrawal symptoms).

Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, et al; the Varenicline Phase 3 study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006; 296: 47-55. PubMed PMID: 16820546.

(Controlled trial of varenicline vs bupropion vs placebo for 12 weeks in 1025 smokers; no instances of hepatitis or clinically apparent liver injury were reported, but results of blood chemistry testing not discussed).

Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, et al; Varenicline Phase 3 study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006; 296: 56-63. PubMed PMID: 16820547.

(Controlled trial of varenicline vs bupropion vs placebo for 12 weeks in 1027 smokers; no instances of hepatitis or jaundice were reported; results of serial blood chemistry determinations not given).

Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR; Varenicline Phase 3 Study Group. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA 2006; 296: 64-71. PubMed PMID: 16820548.

(Controlled trial of varenicline vs placebo continuation for 12 weeks after achieving abstinence with initial 12 weeks of therapy; no hepatic serious adverse events occurred, no discussion of ALT elevations).

Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R, Reeves KR. Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist. Arch Intern Med 2006; 166: 1561-8. PubMed PMID: 16908788.

(Controlled trial of several doses of varenicline vs bupropion or placebo for 12 weeks in 626 smokers; "The frequency of clinically significant laboratory test abnormalities was low and similar across all treatment groups").

Oncken C, Gonzales D, Nides M, Rennard S, Watsky E, Billing CB, Anziano R, et al.; Varenicline Study Group. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. Arch Intern Med 2006; 166: 1571-7. PubMed PMID: 16908789.

(Controlled trial of 3 regimens of varenicline vs placebo for 12 weeks in 647 smokers; "results of clinical laboratory tests...demonstrated no clinically meaningful differences between varenicline and placebo").

Williams KE, Reeves KR, Billing CB Jr, Pennington AM, Gong J. A double-blind study evaluating the long-term safety of varenicline for smoking cessation. Curr Med Res Opin 2007; 23: 793-801. (Among 377 patients enrolled in a placebo controlled trial of varenicline for smoking cessation, the most common side effects were nausea, gastrointestinal symptoms, weight gain, insomnia and abnormal dreams; 2 patients stopped therapy because of ALT or AST elevations, but values and follow up not provided). PubMed PMID: 17407636.

Hays JT, Ebbert JO, Sood A. Efficacy and safety of varenicline for smoking cessation. Am J Med 2008; 121 (4 Suppl 1): S32-42. PubMed PMID: 18342165.

(Review of mechanism of action, clinical efficacy and safety of varenicline; in placebo controlled trials "the frequency of clinically significant laboratory test abnormalities was low and similar across the treatment groups").

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to varenicline).

Franck AJ, Sliter LR. Acute hepatic injury associated with varenicline in a patient with underlying liver disease. Ann Pharmacother 2009; 43: 1539-43. PubMed PMID: 19638471.

(53 year old man with end-stage alcoholic liver disease [initial ALT ~30 U/L, Alk P ~130 U/L] awaiting liver transplantation developed nausea and pruritus 1 week after starting a course of varenicline [bilirubin 1.0 mg/dL, ALT 657 U/L, Alk P 183 U/L], resolving within 1-2 months of stopping).

Silva RR. Two recent updates for psychiatric conditions. J Child Adolesc Psychopharmacol 2009; 19: 207. PubMed PMID: 19364299.

(Brief editorial review of the postmarketing product update on varenicline and bupropion warning of suicidal ideation and behaviors with their use).

Jiméz-Ruiz C, Berlin I, Hering T. Varenicline: a novel pharmacotherapy for smoking cessation. Drugs 2009; 69: 1319-38. PubMed PMID: 19583451.

(Review of the structure, pharmacology, metabolism, clinical efficacy and safety of varenicline; no discussion of hepatotoxicity).

Safety of smoking cessation drugs. Med Lett Drugs Ther 2009; 51 (1319): 65. PubMed PMID: 19696706.

(Concise review of safety of medications used for smoking cessation; varenicline is mentioned as the most effective drug available, common side effects are nausea, sleep disturbances, vivid dreams, headache, constipation, vomiting, flatulence and dry mouth; no mention of hepatic effects).

McNeil JJ, Piccenna L, Ioannides-Demos LL. Smoking Cessation-Recent Advances. Cardiovasc Drugs Ther 2010; 24: 359-67. PubMed PMID: 20602163.

(Review of mechanisms of action, efficacy and safety of smoking cessation therapies; hepatotoxicity is not discussed).

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: 20949552.

(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 to varenicline or other agents used to treated substance abuse).

Cui Q, Robinson L, Elston D, Smaill F, Cohen J, Quan C, McFarland N, et al. Safety and tolerability of varenicline tartrate (Champix(®)/Chantix(®)) for smoking cessation in HIV-infected subjects: A pilot open-label study. AIDS Patient Care STDS 2012; 26: 12-9. (Among 36 HIV-positive smokers treated with varenicline for 24 weeks, mild ALT elevations occurred in 19%, but none were above 2.5 times ULN or associated with symptoms or jaundice). PubMed PMID: 22007690.

Sprague D, Bambha K. Drug-induced liver injury due to varenicline: a case report. BMC Gastroenterol 2012; 12: 65. PubMed PMID: 22681894.

(69 year old man developed nausea followed by jaundice within 1 week of starting varenicline and stopped it promptly, presenting several weeks later [bilirubin 12 mg/dL, ALT 1592 U/L, Alk P 254 U/L], resolving within two months; patient was also positive for anti-HCV and HCV RNA and liver biopsy during follow up showed chronic hepatitis).