U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Bupropion. [Updated 2017 Sep 11].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Bupropion

Updated: September 11, 2017.

OVERVIEW

Introduction

Bupropion is an aminoketone antidepressant that is widely used in therapy of depression and smoking cessation. Bupropion therapy can be associated with transient, usually asymptomatic elevations in serum aminotransferase levels and has been linked to rare instances of clinically apparent acute liver injury.

Background

Bupropion (bue proe' pee on) is an aminoketone derivative and antidepressant whose mechanism of action is not well understood. Bupropion has no activity against monamine oxidase and only weak inhibition of serotonin and norepinephrine reuptake. It appears to act via noradrenergic or dopaminergic mechanisms. Bupropion was approved for use in moderate and severe depression in the United States in 1985 and was later approved for use in seasonal affective disorder and in aiding smoking cessation. Bupropion is currently in wide use, approximately 4 million prescriptions being filled yearly. Bupropion is available as immediate and sustained release tablets of 75, 100, 150, 200 and 300 mg in several generic forms and under the brand name of Welbutrin. The recommended dosage for depression in adults is 75 to 300 mg daily either twice daily in immediate release forms or once daily in extended or sustained release forms. Separate formulations of sustained release forms are available for smoking cessation in tablets of 150 mg generically and under the brand name Zyban, recommended dosage being 150 to 300 mg daily. Common side effects of bupropion are drowsiness, dizziness, agitation, headahce, nausea, abdominal pain and dry mouth.

Hepatotoxicity

Liver test abnormalities have been reported to occur in less than 1% of patients on bupropion, and elevations are usually modest and usually do not require dose modification or discontinuation. Rare instances of acute, clinically apparent episodes of liver injury with marked liver enzyme elevations with or without jaundice have been reported in patients on bupropion (Case 1). The onset of injury is usually within 1 to 3 months and the pattern of serum enzyme elevations has been variable, from hepatocellular to cholestatic. Autoimmune (autoantibodies) are found in a proportion of cases, but in low titer. Immunoallergic features (rash, fever, eosinophilia) are uncommon. The injury is generally self-limited, but fatal cases have been reported.

Likelihood score: C (probable rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which bupropion causes liver injury is not known. Bupropion is extensively metabolized by the liver, mainly via the cytochrome P450 system (CPY2B6), and hepatotoxicity may be mediated by toxic intermediates of their metabolism.

Outcome and Management

The serum aminotransferase elevations that occur on bupropion therapy are usually self-limited and do not require dose modification or discontinuation of therapy. Rare instances of acute liver failure and chronic hepatitis have been attributed to bupropion therapy. Persons with intolerance to bupropion may have similar reactions to other antidepressants, and careful monitoring is warranted if other such agents are used.

Drug Class: Antidepressant Agents

CASE REPORT

Case 1. Acute liver injury due to bupropion.

[Modified from: Carlos Titos-Arcos J, Hallal H, Collados V, Plaza-Aniorte J. [Acute hepatitis secondary to bupropion]. Gastronterol Hepatol 2008; 31: 549. PubMed Citation]

A 48 year old man with chronic alcoholism being treated with disulfiram and naltrexone for alcohol addiction developed jaundice and fatigue 4 weeks after having bupropion added to his treatment regimen. He was jaundiced but had no fever or rash. Laboratory tests showed prominent elevations in both serum aminotransferases and alkaline phosphatase and a total bilirubin of 12.1 mg/dL. Bupropion was discontinued and he began to improve (Table). Tests for hepatitis A, B and C were negative. He had low levels of antinuclear antibody (ANA 1:80) and antimitochondrial antibody (AMA 1:80), but no smooth muscle antibody. An abdominal ultrasound showed no evidence of biliary obstruction. Within 3 months of stopping bupropion, serum enzymes and bilirubin levels had returned to baseline; the continued low level abnormal values during long term follow up were attributed to alcohol use. Serum ANA and AMA were negative.

Key Points

Medication:	Bupropion
Pattern:	Mixed (R=3.9)
Severity:	3+ (jaundice, hospitalization)
Latency:	1 month
Recovery:	2-3 months
Other medications:	Naltrexone, disulfiram

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre	Pre	86	182	0.9	Alcohol withdrawl
4 weeks	0	1405			Bupropion stopped
	3 days	1075	803	12.1	
	5 days	889	708	6.4	

Table continued from previous page.

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
5 weeks	7 days	561	324	3.6	
	9 days	271	317	1.3	
3 months	2 months	43	184	0.4	
7 months	6 months	62	185	1.0	
1 year	1 year	40	190	0.7	
2 years	2 years	67	178	0.8	
Normal Values		**<40**	**<115**	**<1.2**	

Comment

Bupropion is a commonly used antidepressant which is also used in therapy of smoking cessation. Liver enzyme elevations during bupropion therapy occur in less than 1% of patients and only rare instances of clinically apparent liver injury have been attributed to bupropion. In this instance, as with many case reports on bupropion, the patient had an underlying liver disease (suspected to be alcoholic liver disease), but the clinical presentation was unlikely due to alcoholism. The role of disulfiram was not discussed in the case report, but it is a well known cause of acute liver injury and its role in this case of an acute "mixed" hepatitis cannot be excluded.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Bupropion – Wellbutrin®

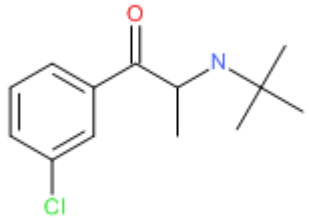
DRUG CLASS

Antidepressant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Bupropion	34911-55-2	C13-H18-Cl-N-O	

ANNOTATED BIBLIOGRAPHY

References updated: 11 September 2017

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; bupropion listed in a table as a rare cause of hepatocellular injury).

Larrey D, Ripault M-P. Bupropion. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 451.

(Review of hepatotoxicity of antidepressants mentions that bupropion is considered very safe but that cases of liver injury have been reported during the post-marketing period including two cases of liver failure).

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; bupropion appears to act via multiple mechanisms involving norepinephrine and dopamine).

Tucker WE Jr. Preclinical toxicology of bupropion: an overview. J Clin Psychiatry 1983; 44: 60-62. PubMed Citation

(In chronic dosing of animals there were slight to moderate increases in ALT and Alk P levels and 13% of animals developed focal nodular hyperplasia; no liver cancer).

Fleet JVW, Manberg PJ, Miller LL, Harto-Truax N, Sato T, Fleck RJ, Stern WC, et al. Overview of clinically significant adverse reactions to bupropion. J Clin Psychiatry 1983; 44 (Sec 2): 191-6. [Not in PubMed]

(Pooled data on 1153 patients treated with bupropion; "Elevated liver enzymes occasionally found during chronic administration of high doses of bupropion in animals were not seen during short- or long term treatment with therapeutic doses in humans").

Oslin DW, Duffy K. The rise of serum aminotransferases in a patient treated with bupropion. J Clin Psychopharmacol. 1993; 13: 364-5. PubMed PMID: 8227497.

(73 year old woman developed ALT elevations [5.4 times ULN] 54 days after starting bupropion, falling to normal within 10 days of stopping and recurring within 4 days with rechallenge [ALT 3.6 times ULN]).

Grohmann R, Rüther E, Engel RR, Hippius H. Assessment of adverse drug reactions in psychiatric inpatients with the AMSP drug safety program: methods and first results for tricyclic antidepressants and SSRI. Pharmacopsychiatry 1999; 32: 21-8. PubMed PMID: 10071179.

(Analysis of reporting of adverse events among pscyhiatric inpatients in 29 German hospitals between 1993 to 1997; 896 severe adverse events among 48,564 patients [1.8%], both total and hepatic events were more common with tricyclics than SSRIs).

Hu KQ, Tiyyagura L, Kanel G, Redeker AG. Acute hepatitis induced by bupropion. Dig Dis Sci 2000; 45: 1872-3. PubMed PMID: 11052334.

(41 year old man with chronic hepatitis C developed fever and malaise 41 days after starting bupropion [bilirubin 3.8 mg/dL, ALT 6660 U/L, Alk P 232 U/L, INR 1.7], resolving rapidly on stopping).

Alvaro D, Onetti-Muda A, Moscatelli R, Atili AF. Acute cholestatic hepatitis induced by bupropion prescribed as pharmacological support to stop smoking. A case report. Dig Liver Dis 2001; 33: 703-6. PubMed PMID: 11785718.

(49 year old woman developed jaundice one month after starting bupropion for smoking cessation [bilirubin 7.4 rising to 27.4 mg/dL, ALT 29 times ULN, Alk P 3 times ULN, ANA 1:80], improving with corticosteroid therapy and resolving within 50 days of stopping drug).

Carvajal Garcia-Pando A, Garrcia del Pozo J, Sanchez A, Velasco M, Rueda de Castro A, Lucena MI. Hepatotoxicity associated with the new antidepressants. J Clin Psychiatry 2002; 63: 135-7. PubMed PMID: 11874214.

(Analysis of cases of hepatotoxicity from antidepressants in Spanish Pharmacovigilance System from 1989-1999, identified 99 cases; among SSRIs, 26 due to fluoxetine, 14 paroxetine, 6 fluvoxamine, 5 sertraline, 3 venlafaxine and 2 citalopram; among tricyclics, 16 clomipramine, 7 amitriptyline, 6 imipramine; among miscellaneous, 3 nefazodone and 1 trazodone; but all similar in rate ~1-3 per 100,000 patient-years of exposure, except for nefazodone=29/100,000; bupropion not mentioned).

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; bupropion not mentioned).

Bagshaw SM, Cload B, Gilmour J, Leung ST, Bowen TJ. Drug-induced rash with eosinophilia and systemic symptoms syndrome with bupropion administration. Ann Allergy Asthma Immunol 2003; 90: 572-5. PubMed PMID: 12775141.

(24 year old man developed fever, rash and eosinophilia [10%] 21 days after starting bupropion, with subsequent relapsing course, developing jaundice on day 40 [bilirubin 3.1 mg/dL, ALT 4040 U/L, Alk P 388 U/L, ANA 1:40], possible renal and pulmonary involvement, but ultimate improvement on corticosteroids).

Khoo A-L, Tham L-S, Lee K-H, Lim G-K. Acute liver failure with concurrent bupropion and carbimazole therapy. Ann Pharmacother 2003; 37: 220-3. PubMed PMID: 12549952.

(41 year old man developed jaundice and acute liver failure 10 weeks after stopping 10 day course of bupropion while also on long term carbimazole [bilirubin 29 rising to 84 mg/dL, ALT 674 U/L, Alk P 138 U/L, protime rising to 42.4 sec], dying of hepatic failure 11 days after admission).

Boshier A, Wilton LV, Shakir SA. Evaluation of the safety of bupropion (Zyban) for smoking cessation from experience gained in general practice use in England in 2000. Eur J Clin Pharmacol 2003; 59: 767-73. PubMed Citation (Among 11,735 patients started on bupropion for smoking cessation on whom follow up was obtained by questionnaire from the prescribing physician, adverse events were reported in 350 [3%], but were mostly mild, nonspecific symptoms of insomnia, nausea, and dizziness; no mention of jaundice, hepatitis or death from liver injury).

Degner D, Grohmann R, Kropp S, Rüther E, 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 Citation

(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%).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants done in the US between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, only four being due to antidepressants: nefazodone [2], bupropion [1], and paroxetine [1]).

Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, et al.; Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005; 129: 512-21. PubMed PMID: 16083708.

(Reports to a Spanish network found 461 cases of drug induced liver disease; antidepressants accounted for 23 cases [5%]).

Björnsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. Dig Liver Dis 2006; 38: 33-8. (Survey of drug induced liver fatalities reported to WHO database between 1968-2003 revealed 4690 reports; no antidepressant ranked among the top 21 agents that were linked to at least 50 cases each) PubMed PMID: 16054882.

.

Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, Mas A, et al. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. Aliment Pharmacol Ther 2007; 25: 1401-9. PubMed PMID: 17539979.

(Among 126 cases of drug induced liver injury seen in Spain between 1993-2000, 3 were attributed to paroxetine and 3 to fluoxetine with a relative risk of injury to rate of use in the population of 3.0 and 1.8 respectively).

DeSanty KP, Amabile CM. Antidepressant-induced liver injury. Ann Pharmacother 2007; 41: 1201-11. PubMed Citation

(Review of antidepressant induced liver injury mentions that no cases of liver failure occurred during clinical trials of bupropion and elevated liver enzymes occurred in 0.1-1.0% of recipients, but that 5 cases of acute liver injury attributed to bupropion have been published, several of which were quite convincing).

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 from 2004 to 2008, 6 were attributed to duloxetine, 3 to atomoxetine, 2 to fluoxetine, 2 to bupropion, and 1 to sertraline as single agents).

Carlos Titos-Arcos J, Hallal H, Collados V, Plaza-Aniorte J. [Acute hepatitis secondary to bupropion]. Gastronterol Hepatol 2008; 31: 549. PubMed PMID: 18928762.

(48 year old man developed jaundice 1 month after starting bupropion [bilirubin 12.1 mg/dL, ALT 1405 U/L, Alk P 803 U/L, ANA 1:80], resolving within 3 months of stopping: Case 1).

Humayun F, Shehab TM, Tworek JA, Fontana RJ. A fatal case of bupropion (Zyban) hepatotoxicity with autoimmune features: Case report. J Med Case Reports 2007; 1: 88. PubMed PMID: 17877816.

(55 year old man developed jaundice 6 months after starting bupropion for smoking cessation [bilirubin 5.3 rising to 22.7 mg/dL, ALT 1459 U/L, Alk P 219 U/L, ANA 1:160], responding to prednisone therapy but relapsing when it was stopped, with progressive liver failure and death 105 days after onset).

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, 3 of which were linked to antidepressants: one each for nefazodone, fluoxetine and venlafaxine).

Alonso Rodríguez L, Barcina Pajares R, Fuentes Vigil J, Gutiérrez González A, Rodríguez Pérez L. [Acute toxic hepatitis secondary to a single dose of bupropion]. Gastroenterol Hepatol 2010; 33: 547-9. Spanish. PubMed PMID: 20435378.

(59 year old man developed abdominal pain 24 hours after a single 150 mg dose of bupropion [bilirubin 1.6 rising to 8.7 mg/dL, ALT 1116 U/L, Alk P 146 U/L], resolving rapidly within 3 weeks).

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; no discussion of bupropion).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver iInjury 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, none of which were attributed to bupropion).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases; one was attributed to amitryptilline, but none were attributed to buproprion or other antidepressants).

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 hepatotoxicity of antidepressants, mentions that 7 cases of hepatocellular and cholestatic hepatitis have been reported with bupropion, despite infrequency of ALT elevations and absence of clinical cases during clinical trials).

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.e7. 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 antidepressant medications including 4 to bupropion).

Tang DM, Koh C, Twaddell WS, von Rosenvinge EC, Han H. Acute hepatocellular drug-induced liver injury from bupropion and doxycycline. ACG Case Rep J 2015; 3: 66-8. PubMed PMID: 26504884.

(29 year old man developed jaundice 14 days after starting doxycycline and bupropion [bilirubin 19.9 mg/dL, ALT 896 U/L, Alk P 234 U/L, INR 3.0], with resolution within 2 months of stopping both drugs and with prednisone therapy).