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# Alprazolam

Updated: January 24, 2017.

## OVERVIEW

### Introduction

Alprazolam is an orally available benzodiazepine used predominantly for therapy of anxiety. As with most benzodiazepines, alprazolam therapy has not been associated with serum aminotransferase or alkaline phosphatase elevations, and clinically apparent liver injury from alprazolam has been reported, but is very rare.

### Background

Alprazolam (al pra' zoe lam) is a benzodiazepine that is widely used in the therapy of anxiety and panic disorder. The antianxiety (anxiolytic) activity of the benzodiazepines is mediated by their ability to enhance gamma-aminobutyric acid (GABA) mediated inhibition of synaptic transmission through binding to the GABA A receptor. Alprazolam was approved in the United States in 1981, and currently more than 40 million prescriptions are filled yearly. Current indications are for anxiety and panic disorders. Alprazolam is available in multiple generic forms and under several brand names such as Xanax or Niravam in tablets of 0.25, 0.5, 1 and 2 mg, as well as in orally disintegrating tablets in similar concentrations and as an oral solution [1 mg/mL] for pediatric use. Extended release forms are available in tablets of 0.5, 1, 2 and 3 mg. The recommended initial dose for adults is 0.5 mg three times daily, increasing as needed to a maximum dose of 4 mg daily in divided doses. Higher doses are used for panic disorder. The most common side effects of alprazolam are dose related and include drowsiness, lethargy, ataxia, dysarthria and dizziness. Tolerance develops to these side effects, but tolerance may also develop to the anxiolytic effects.

### Hepatotoxicity

Alprazolam, like other benzodiazepines, is rarely associated with serum ALT elevations, and clinically apparent liver injury from alprazolam is extremely rare. There have been a few case reports of acute liver injury from alprazolam and recurrence on reexposure has been reported. In alprazolam related cases of acute liver injury, the latency has been within a few weeks and the typical pattern of liver enzyme elevations has been cholestatic or mixed (Case 1). The injury is usually mild-to-moderate in severity and self-limited. Fever and rash have not been described nor has autoantibody formation.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

### Mechanism of Injury

Alprazolam is metabolized by the liver via the cytochrome P450 system, predominantly by CYP 3A4. Concurrent use of CYP 3A4 inhibitors, such as cimetidine or ketaconazole, can cause an increase in alprazolam

plasma levels. The liver injury from the benzodiazepines is probably due to a rarely produced intermediate metabolite.

## Outcome and Management

The case reports of hepatic injury due to benzodiazepines were followed by prompt and complete recovery upon stopping the medication, without evidence of residual or chronic injury. No cases of acute liver failure or chronic liver injury due to alprazolam have been described. There is little information about cross reactivity with other benzodiazepines, but some degree of cross sensitivity should be assumed and patients with clinically apparent liver injury due to alprazolam should be monitored if they are switched to related agents.

Drug Class: Benzodiazepines

# CASE REPOT

**Case 1. Mild acute liver injury due to alprazolam.**

[Modified from: Judd FK, Norman TR, Marriott PF, Burrows GD. A case of alprazolam-related hepatitis. Am J Psychiatry 1986; 143: 388-9. PubMed Citation]

A 32 year old woman with a long history of panic attacks developed fatigue and abdominal pain 2 weeks after starting alprazolam (1 mg daily increasing to 8 mg daily), and she became jaundiced one week later. She had no history of liver disease and was known to have had normal serum liver tests before starting alprazolam. On examination, she was jaundiced but had no fever or rash. Laboratory results showed elevations in serum enzymes and bilirubin (Table). Tests for hepatitis A and B and for mononucleosis were negative. Alprazolam was stopped and diazepam (which she had received in the past) substituted. She improved rapidly and all tests were normal when she was seen one month after stopping alprazolam.

## Key Points

| | |
|---|---|
| Medication: | Alprazolam (8 mg daily) |
| Pattern: | Cholestatic (R=1.8) |
| Severity: | 2+ (jaundiced) |
| Latency: | 2 weeks to symptoms, 3 weeks to jaundice |
| Recovery: | Complete in one month |
| Other medications: | None mentioned |

## Laboratory Values

| Time After Starting | Time After Stopping | ALT (U/L) | Alk P (U/L) | Bilirubin (mg/dL) | Other |
|---|---|---|---|---|---|
| Pre | | Normal | Normal | Normal | |
| 3 weeks | 0 | 156 | 241 | 2.6 | Albumin 4.0 g/dL |
| | 4 days | 124 | 187 | 1.8 | |
| 7 weeks | 4 weeks | Normal | Normal | Normal | |
| **Normal Values** | | **<35** | **<95** | **<1.2** | |

## Comment

A convincing case of alprazolam induced liver injury characterized by a mild cholestatic hepatitis arising 2 to 3 weeks after starting the medication and resolving rapidly with stopping. There were no signs of hypersensitivity. Interestingly, she tolerated other benzodiazepines without problems, indicating lack of cross sensitivity to the injury.

# PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Alprazolam – Generic, Xanax®

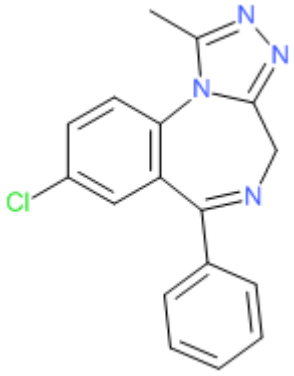
**DRUG CLASS**

Benzodiazepines, Antianxiety Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

# CHEMICAL FORMULA AND STRUCTURE

| DRUG | CAS REGISTRY NUMBER | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Alprazolam | 28981-97-7 | C17-H13-Cl-N4 |  |

# ANNOTATED BIBLIOGRAPHY

References updated: 24 January 2017

Zimmerman HJ. Benzodiazepines. Psychotropic and anticonvulsant agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 491-3.

*(Expert review of benzodiazepines and liver injury published in 1999; mentions rare instances of cholestatic hepatitis have been reported due to alprazolam, chlordiazepoxide, diazepam, flurazepam, and triazolam, and hepatocellular injury with clorazepate and clotiazepam, but no reports of hepatic injury with lorazepam, oxazepam or temazepam).*

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.

*(Review of sedative induced liver injury mentions that rare instances of acute liver injury [usually cholestatic] have been reported with alprazolam, bentazepam, clotiazepam, chlordiazepoxide, diazepam, flurazepam and triazolam; a hepatitis-like pattern has been reported with clonazepam and clorazepate).*

Mihic SJ, Harris RA. Hypnotics and sedatives. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 457-80.

*(Textbook of pharmacology and therapeutics).*

Roy-Byrne P, Vittone BJ, Uhde TW. Alprazolam-related hepatotoxicity. Lancet. 1983; 2: 786-7. PubMed PMID: 6137615.

*(Patient was found to have elevated ALT [96 U/L] 2 weeks after starting alprazolam, with prompt resolution upon stopping; rechallenge led to asymptomatic rise of ALT [28 to 70 U/L] within 9 days).*

Davion T, Capron-Chivrac D, Andrejak M, Capron JP. [Hepatitis due to antiepileptic agents] Gastroenterol Clin Biol 1985; 9: 117-26. PubMed PMID: 3920108.

*(Review of hepatotoxicity of anticonvulsants; among benzodiazepines, cases of cholestatic hepatitis have been linked to chlordiazepoxide and diazepam, but liver injury from this class of drugs is exceptionally rare).*

Judd FK, Norman TR, Marriott PF, Burrows GD. A case of alprazolam-related hepatitis. Am J Psychiatry 1986; 143: 388-9. PubMed PMID: 2869702.

*(32 year old woman had onset of lethargy 2 weeks after starting alprazolam followed by jaundice [bilirubin 2.6 mg/dL, AST 156 U/L, Alk P 241 U/L], resolving within 4 weeks of switching to diazepam: Case 1).*

Noyes R, DuPont RL, Pecknold JC, Rifkin A, Rubin RT, Swinson RP, Ballenger JC, et al. Alprazolam in panic disorder and agoraphobia: results from a multicenter trial. Arch Gen Psychiatry 1988; 45: 423-8. PubMed PMID: 3358644.

*(Controlled trial of alprazolam vs placebo in 525 patients with panic disorder; side effects were sedation, ataxia, fatigue, slurred speech, amnesia and increased appetite; 2 patients on alprazolam developed liver disease, one with jaundice at 4 weeks resolving quickly on stopping and a second with abnormal laboratory values that returned to normal with lowering the dose; details not given).*

Lewis JH, Zimmerman HJ. Drug- and chemical-induced cholestasis. Clin Liver Dis 1999; 3: 433-64. PubMed PMID: 11291233.

*(Review of drug induced cholestatic syndromes, listing many causes including chlordiazepoxide and flurazepam; "Benzodiazepines may cause cholestatic injury, although this is rare").*

Gil-Martin A, Saez-Royuela F, Arias L, Angulo ML, Nogal B. [Hepatic fibrosis after antidepressant treatment] Rev Esp Enferm Dig 2005; 97: 461-2. Spanish. PubMed PMID: 16048430.

*(Case report of patient developing fatigue, pruritus and jaundice after 1-2 months of therapy with sertraline, alprazolam and clorazepate, resolving with stopping sertraline, but with minor ALT elevations and biopsy showing mild bridging fibrosis 4 months later).*

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, 20 were attributed to benzodiazepines including 5 for clorazepate, 5 alprazolam, 6 lorazepam and 4 diazepam, but compared to controls, the relative risk of injury was increased only for clorazepate [8.3 and frequency 3.4 per 100,000 person-year exposures]).*

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, none were attributed to a benzodiazepine).*

Björnsson E. Hepatotoxicity associated with antiepileptic drugs. Acta Neurol Scand 2008; 118: 281-90. PubMed PMID: 18341684.

*(Review of hepatotoxicity of all anticonvulsants focusing upon phenytoin, valproate, carbamazepine; "Furthermore, hepatoxicity has not been convincingly shown to be associated with the use of benzodiazepines").*

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 were attributed to a benzodiazepine).*

Drugs for insomnia. Treat Guidel Med Lett 2012; 10 (119): 57-60. PubMed PMID: 22777275.

*(Guidelines for therapy of insomnia mentions that benzodiazepines are controlled substances and, when used for sleep, may impair next day performance).*

Björnsson ES, Bergmann OM, Björnsson 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, but none were attributed to alprazolam or any other benzodiazepine, despite the fact that more than 1 million prescriptions for alprazolam are filled yearly).*

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 on drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, none of which were attributed to a benzodiazepine).*

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: 1340-1352. PubMed PMID: 25754159.

*(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, no cases were attributed to alprazolam or any other benzodiazepine).*