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Temazepam

Updated: June 22, 2023.

OVERVIEW

Introduction

Temazepam is an orally available benzodiazepine used in the therapy of insomnia. As with most benzodiazepines, temazepam has not been associated with serum aminotransferase or alkaline phosphatase elevations during therapy, and clinically apparent liver injury from temazepam has not been reported and must be very rare, if it occurs at all.

Background

Temazepam (tem az' e pam) is a benzodiazepine that is used as a sleeping aid in the therapy of insomnia. The soporific 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. Temazepam was approved in the United States in 1981 and is still widely used with more than 2 million prescriptions written yearly. Current indications are limited to the short term treatment of insomnia. Temazepam is available in capsules of 7.5, 15, 22.5 and 30 mg in several generic forms and under the brand name Restoril. The recommended initial dose for insomnia is 7.5 mg before bedtime, increasing as needed to a maximum dose of 30 mg. The most common side effects of temazepam are dose related and include daytime drowsiness, lethargy, ataxia, dysarthria and dizziness. Tolerance develops to these side effects, but tolerance may also develop to the effects on insomnia. Rare but severe adverse events include hallucinations, restlessness, agitation, and hypersensitivity reactions including angioedema. Temazepam like all oral benzodiazepines has a boxed warning in its product label stressing the risks of severe sedation and potentially fatal respiratory depression when combined with opiates, the risks of abuse, misuse, and addiction with prolonged use which can lead to overdose and death, and the risks of dependence with continued use and severe potentially life-threatening withdrawal symptoms if discontinued suddenly.

Hepatotoxicity

Temazepam, like other benzodiazepines, is rarely associated with serum ALT elevations, and clinically apparent liver injury from temazepam is extremely rare, if it occurs at all. There have been no case reports of symptomatic, acute liver injury from temazepam. Isolated single cases of clinically apparent liver injury have been reported with other benzodiazepines including alprazolam, chlordiazepoxide, clonazepam, diazepam, flurazepam, lorazepam, and triazolam. The clinical pattern of acute liver injury from benzodiazepines is typically cholestatic and mild-to-moderate in severity with a latency of 1 to 6 months and rapid resolution with discontinuation. Fever and rash are uncommon as is autoantibody formation.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

Temazepam is metabolized by the liver to inactive metabolites. Liver injury from benzodiazepines is probably due to the toxic effects of 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 temazepam have been described. There is no information about cross reactivity with other benzodiazepines, but some degree of cross sensitivity may occur.

Drug Class: Sedatives and Hypnotics, Benzodiazepines

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Temazepam – Generic, Restoril®

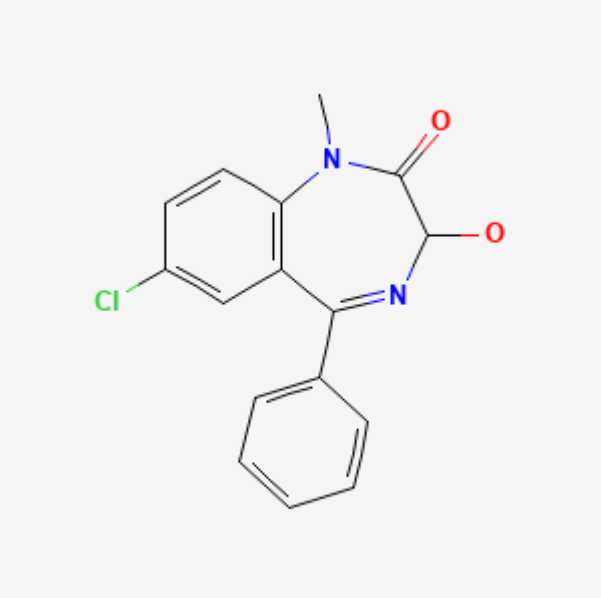
DRUG CLASS

Sedatives and Hypnotics

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Temazepam	846-50-4	C16-H13-Cl-N2-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 22 June 2023

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. Benzodiazepines. 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. 517.

(Review of drug induced liver injury published in 2007; rare instances of acute liver injury [usually cholestatic] have been reported with alprazolam, chlordiazepoxide, diazepam, flurazepam, and triazolam; a hepatitis-like pattern has been reported with clonazepam and clorazepate).

Mihic SJ, Mayfield J, Harris RA. Hypnotics and sedatives. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 339-53.

(Textbook of pharmacology and therapeutics).

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

Lewis JH, Zimmerman HJ. Drug- and chemical-induced cholestasis. Clin Liver Dis. 1999;3:433–64. vii. Erratum in: Clin Liver Dis 1999; 3: 917. 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").

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").

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 temazepam or any other benzodiazepine, despite the fact millions of prescriptions for them 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.e7. 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 temazepam or any other benzodiazepine).

Drugs for chronic insomnia. Med Lett Drugs Ther. 2023;65:1–6. PubMed PMID: 36630579.

(Concise review of drugs for chronic insomnia mentions that tolerance and dependence can occur with use of benzodiazepines and their use should be discouraged, and that benzodiazepines are CNS suppressants and can impair next day performance including driving and cause complex behavior disorders, retrograde amnesia, dependence, tolerance, abuse and rebound insomnia; no mention of ALT elevations or hepatotoxicity).