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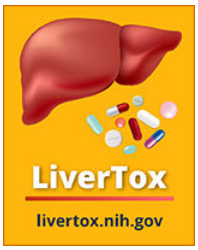


Phentermine-Topiramate

Updated: June 5, 2020.

OVERVIEW

Introduction

The fixed combination of phentermine and topiramate has been developed as a weight loss agent and was approved for use in the United States in 2012. This combination has not been linked to serum enzyme elevations or clinically apparent liver injury, but has had limited general use. Topiramate by itself is used as an anticonvulsant and has been implicated in rare instances of acute liver injury.

Background

Phentermine (fen' ter meen) has been available for many years as an over-the-counter weight loss aid, acting largely by sympathetic stimulation. Topiramate (toe pyre' a mate) was developed as an anticonvulsant, but studies of its efficacy in patients with seizures noted mild weight loss. Because both agents are fairly well tolerated, the combination was studied as an approach to weight loss using lower doses than employed with either as monotherapy. First in small pilot studies and later in sponsored, large randomized controlled trials, these studies showed that fixed combinations of these two agents led to weight loss that was significantly greater than occurred with placebo. The combination of phentermine and topiramate was approved for use in the United States in 2012 as a weight loss agent for patients with obesity (BMI >30) or who are overweight (BMI=27-30) and have an obesity related condition. There is only limited information on general clinical use of the combination. Fixed doses of phentermine (3.75, 7, 11.25 and 15 mg) with topiramate (23, 46, 69 and 92 mg) are available as capsules under the brand name of Qsymia. Common side effects include paresthesias, dizziness, dry mouth, constipation, insomnia and change in taste. Uncommon side effects may include depression, anxiety and nephrolithiasis. Topiramate therapy during pregnancy has been associated with oral cleft defects in newborns and this combination is contraindicated in women of child bearing potential who cannot practice birth control.

Hepatotoxicity

In premarketing clinical trials, serum aminotransferase elevations were no more common among patients receiving the combination of phentermine and topiramate than placebo. Clinically apparent liver injury due to this combination has not been reported, but several instances of acute liver injury have been linked to topiramate monotherapy of other conditions. Case reports of liver injury attributed to topiramate have occurred largely in patients with seizure disorders who were receiving other anticonvulsants with known hepatotoxic potential. Topiramate is metabolized by the cytochrome P450 system and is known to induce CYP 3A4 activity and alter the levels of other anticonvulsants, thus predisposing to hepatic injury. By itself, topiramate has not been linked to severe hepatic injury.

Likelihood score: E* (suspected but unproven rare cause of clinically apparent liver injury).

Outcome and Management

No instances of acute liver failure or chronic liver injury have been linked to phentermine/topiramate, but it has had limited general clinical use.

References on the hepatotoxicity and safety of phentermine and topiramate separately are given in the sections on the individual agents.

- Phentermine
- Topiramate

Drug Class: Weight Loss Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Phentermine-Topiramate – Qsymia®

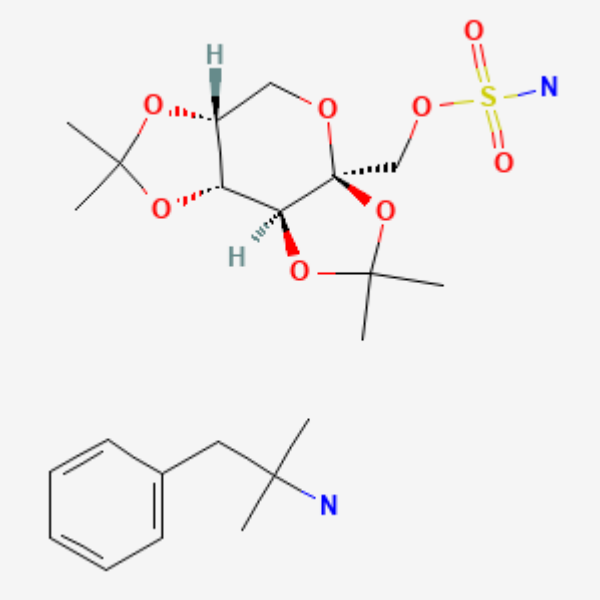
DRUG CLASS

Weight Loss Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Phentermine-Topiramate	960078-81-3	C12-H21-N-O8-S.C10-H15-N	

ANNOTATED BIBLIOGRAPHY

References updated: 06 June 2020

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

(Review of hepatotoxicity published in 1999, well before the availability of phentermine/topiramate).

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 phentermine or topiramate).

Diet, drugs and surgery for weight loss. Treat Guidel Med Lett. 2011;9(104):17–22. PubMed PMID: 21436767.

(Concise review of approved and unapproved medical and surgical approaches to obesity; the sympathomimetic amines are the oldest weight loss drugs, but are approved for short term use only; no mention of hepatotoxicity in discussion of side effects of phentermine).

Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, Day WW. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377:1341–52. PubMed PMID: 21481449.

(Randomized controlled trial of 56 weeks of two doses of phentermine-topiramate vs placebo in 2487 overweight or obese patients; no mention of ALT levels or hepatotoxicity).

Powell AG, Apovian CM, Aronne LJ. The combination of phentermine and topiramate is an effective adjunct to diet and lifestyle modification for weight loss and measures of comorbidity in overweight or obese adults with additional metabolic risk factors. Evid Based Med. 2012;17:14–5. PubMed PMID: 21937501.

(Commentary on Gadde [2011] pointing out that this regimen "is more efficacious than anything currently on the market"; no discussion of adverse events).

Lauer MS. Lemons for obesity. Ann Intern Med. 2012;157:139–40. PubMed PMID: 22801677.

(Editorial criticizing the decision to approve phentermine-topiramate for general use in the US, expressing concerns of potential long term adverse effects which have not been adequately evaluated in premarketing studies).

Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr. 2012;95:297–308. PubMed PMID: 22158731.

(Controlled extension to two years of a randomized controlled trial of phentermine-topiramate vs placebo in 676 obese patients; weight loss was sustained and common side effects were similar with longer therapy: "No dose related changes were observed in shift summaries of selected laboratory values").

Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, Tam PY, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity (Silver Spring). 2012;20:330–42. PubMed PMID: 22051941.

(Randomized controlled trial of two dose regimens of phentermine-topiramate vs placebo in 1267 obese subjects; common side effects were paresthesias, dry mouth, constipation, headache, change in taste, insomnia and depression; no mention of ALT levels or hepatotoxicity).

Kang JG, Park CY. Anti-Obesity Drugs: A Review about Their Effects and Safety. Diabetes Metab J. 2012;36:13–25. PubMed PMID: 22363917.

(Review of the safety and efficacy of current and potentially future medications for obesity; mentions that phentermine has been available for 50 years, but there is little data on its long term efficacy and safety).

2 new drugs for weight loss. Med Lett Drugs Ther. 2012;54(1398):69–71. PubMed PMID: 22992487.

(Concise review of phentermine-topiramate and lorcaserin for weight loss shortly after their approval for use in the US; in discussion of side effects, no mention of hepatotoxicity).

Smith SM, Meyer M, Trinkley KE. Phentermine/topiramate for the treatment of obesity. Ann Pharmacother. 2013;47:340–9. PubMed PMID: 23482732.

(Review of the pharmacology, efficacy and safety of phentermine/topiramate focusing on 3 phase 3 trials which found a dose related effect on weight loss that was sustained for over 2 years while adverse events included paresthesia, dizziness, dysgeusia, insomnia, constipation and dry mouth; no mention of ALT elevations or hepatotoxicity, although recommended caution and monitoring in patients with preexisting liver disease).

Kim HO, Lee JA, Suh HW, Kim YS, Kim BS, Ahn ES, Roh YJ, et al. Postmarketing surveillance study of the efficacy and safety of phentermine in patients with obesity. Korean J Fam Med. 2013;34:298–306. PubMed PMID: 24106582.

(Among 795 obese Korean patients enrolled in a prospective surveillance program and treated with phentermine [37.5 mg daily], the mean weight loss at 12 weeks was 3.8 kg and 30% of patients reported adverse events, but none were serious and there was no mention of ALT elevations or hepatotoxicity).

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.

(Population based prospective analysis of cases of drug induced liver injury seen over a two year period in Iceland identified 96 cases, none of which were attributed to weight loss agents).

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 1996-2012 identified 176 cases, none of which were attributed to phentermine or topiramate, separately or together).

Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA. 2014;311:74–86. PubMed PMID: 24231879.

(Systematic review of the literature on the efficacy of long term use of drugs for obesity that were FDA approved [at the time of the analysis] mentions that phentermine, diethylpropion and phendimetrazine are approved for short term use only, but that orlistat, lorcaserin and phentermine/topiramate are approved for long term use although their efficacy is modest; no discussion of hepatotoxicity).

Hainer V, Aldhoon-Hainerová I. Tolerability and safety of the new anti-obesity medications. Drug Saf. 2014;37:693–702. PubMed PMID: 25096956.

(Review of the safety of two recently approved [2012] drugs for obesity [phentermine/topiramate and lorcaserin] based upon large, randomized controlled trials mentions that adverse events were common but usually mild-to-moderate in severity and decreasing with continued usage beyond 1 year; no mention of ALT elevations or hepatotoxicity).

Alfaris N, Minnick AM, Hopkins CM, Berkowitz RI, Wadden TA. Combination phentermine and topiramate extended release in the management of obesity. Expert Opin Pharmacother. 2015;16:1263–74. PubMed PMID: 25958964.

(Review of the history of development, chemistry, mechanism of action, clinical efficacy and safety of phentermine/ topiramate in the management of obesity, discusses the common adverse events and the special concerns regarding heart rate, depression, and fetal abnormalities associated with long term use, but no mention of ALT elevations or hepatotoxicity).

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, two cases were attributed to topiramate separately and not as a combination and another unlikely case was attributed to phentermine given by itself).

Aagaard L, Hallgreen CE, Hansen EH. Serious adverse events reported for antiobesity medicines: postmarketing experiences from the EU adverse event reporting system EudraVigilance. Int J Obes (Lond). 2016;40:1742–7. PubMed PMID: 27478924.

(Analysis of adverse event reports from antiobesity medications to the European pharmacovigilance database [EudraVigilance] between 2007 and 2013 identified 4941 reports detailing 13,957 individual adverse events, 90% serious, only 15 attributed to phentermine with 2 deaths, but none were classified as hepatobiliary).

Halpern B, Mancini MC. Safety assessment of combination therapies in the treatment of obesity: focus on naltrexone/ bupropion extended release and phentermine-topiramate extended release. Expert Opin Drug Saf. 2017;16:27–39. PubMed PMID: 27732121.

(Review of the mechanism of action, clinical efficacy and safety of fixed combination therapies for obesity discusses the common adverse events of phentermine/topiramate as well as psychiatric, cardiovascular, renal, ophthalmologic and pregnancy-fetal toxicity, but discussion of hepatic safety is limited to the issue of increased drug levels in patients with hepatic impairment).

Diet, drugs, devices, and surgery for weight management. Med Lett Drugs Ther. 2018;60(1548):91–8. PubMed PMID: 29913463.

(Concise review of the medical and surgical therapies for obesity mentions that for orlistat "severe liver injury has been reported rarely, but no cause-and-effect relationship has been established"; discussions of adverse events due to other weight loss agents [phentermine/ topiramate, naltrexone/bupropion, lorcaserin and liraglutide] do not mention ALT elevations or hepatotoxicity).

Saunders KH, Umashanker D, Igel LI, Kumar RB, Aronne LJ. Obesity pharmacotherapy. Med Clin North Am. 2018;102:135–48. PubMed PMID: 29156182.

(Review of the pharmacotherapy of obesity focusing upon the 6 most commonly used medications, discusses the common side effects of phentermine/topiramate, but does not discuss hepatotoxicity).

Patel DK, Stanford FC. Safety and tolerability of new-generation anti-obesity medications: a narrative review. Postgrad Med. 2018;130:173–82. PubMed PMID: 29388462.

(Review of the history of approval and indications, efficacy and long term safety of major currently available weight loss agents including orlistat, phentermine/topiramate, lorcaserin, liraglutide and naltrexone/bupropion; does not discuss hepatotoxicity).

Lewis KH, Fischer H, Ard J, Barton L, Bessesen DH, Daley MF, Desai J, et al. Safety and effectiveness of longer-term phentermine use: clinical outcomes from an Electronic Health Record Cohort. Obesity (Silver Spring). 2019;27:591–602. PubMed PMID: 30900410.

(Among 13,972 adults who initiated therapy with phentermine between 2010-15 identified by electronic health records, those who remained on long term therapy [n=144] lost an average of 7.5% of weight vs none of those in

follow up after short term therapy, and there were no differences in composite adverse cardiovascular outcomes with long term continuous or intermittent therapy; no mention of hepatotoxicity or ALT elevations).

Safer DL, Adler S, Dalai SS, Bentley JP, Toyama H, Pajarito S, Najarian T. A randomized, placebo-controlled crossover trial of phentermine-topiramate ER in patients with binge-eating disorder and bulimia nervosa. Int J Eat Disord. 2020;53:266–77. PubMed PMID: 31721257.

(Among 22 adults with binge eating disorder or bulimia treated with phentermine-topiramate [escalating dose to 15/92 mg] or placebo for 12 weeks followed by wash-out and cross over, weight loss was -5.8 kg on drug vs +0.4 kg on placebo; there were no serious adverse events and no mention of ALT elevations or hepatotoxicity).

Hsia DS, Gosselin NH, Williams J, Farhat N, Marier JF, Shih W, Peterson C, et al. A randomized, double-blind, placebo-controlled, pharmacokinetic and pharmacodynamic study of a fixed-dose combination of phentermine/topiramate in adolescents with obesity. Diabetes Obes Metab. 2020;22:480–91. PubMed PMID: 31696603.

(Among 42 obese adolescents treated with phentermine/topiramate [7.5/46 mg or 15/92 mg] or placebo once daily for 56 days, weight loss of at least 5% was achieved in 13% and 50% on the drug combination vs none on placebo and side effects were usually mild, 2 patients stopped drug early because of adverse events; no mention of ALT elevations or hepatotoxicity).

Tak YJ, Lee SY. Anti-obesity drugs: long-term efficacy and safety: an updated review. World J Mens Health. 2020 Mar 9. Epub ahead of print. PubMed PMID: 32202085.

(Review of currently available agents for long term therapy of obesity with specific discussion of mechanism of action, dosing regimen, efficacy and safety, mentions that phentermine/topiramate has the highest rates of weight loss compared to other agents, but also has a high rate of discontinuation because of side effects such as insomnia, paresthesia, dizziness, dry mouth, dysgeusia and constipation and has embryo-fetal toxicity; no mention of ALT elevations or hepatotoxicity).