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Phentermine-Topiramate

Updated: January 15, 2014.

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 been in general use for a short time only. 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, 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.

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 therapy 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.

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®

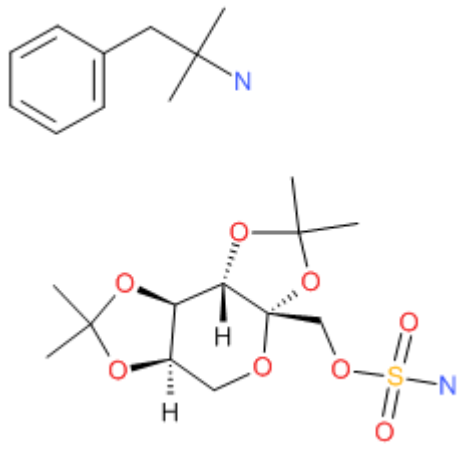
DRUG CLASS

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: 15 January 2014

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: 2363917.

(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).