Phentermine-topiramate: First combination drug for obesity

Jagjit Singh, Rajiv Kumar

Department of Pharmacology, Government Medical College and Hospital, Chandigarh, India

Abstract

Obesity is spreading globally at an alarming speed. The management of obesity is multifaceted and includes lifestyle modifications as the cornerstone. Until only orlistat was approved for long term use in obesity. The US Food and Drug Administration granted approval to a fixed dose mid 2012 combination of phentermine immediate release and topiramate extended release in 2012 for treatment of obese patients or overweight patients with comorbid conditions. The new drug has shown significant weight loss compared with placebo for a period up to 2 years.

Key words: Diabetes, obesity, phentermine-topiramate, risk evaluation and mitigation strategy

Submission: 21-04-2014 **Accepted:** 28-11-2014

The problem of obesity is spreading at a fast pace globally and is posing a public health problem. The worldwide prevalence of obesity has nearly doubled between 1980 and 2008.[1] It is assumed that at least 2.8 million people die each year as a result of being overweight or obese. The management of obesity is multipronged, which mainly involves management of diet and regular exercise.[2] Pharmacotherapy using drugs is used as an adjunct to lifestyle measures. However, the success with drugs has been far from satisfactory. Besides not being very effective in reducing weight in the long-term, many drugs have been withdrawn from the market as more and more data on adverse events emerged from post-marketing studies. The fate of sibutramine and rimonabant are glaring examples. Until the mid of 2012, orlistat was the only drug approved for long-term use in weight loss.[3]

The fixed dose combination of phentermine immediate release and topiramate extended release was approved by the US Food and Drug Administration (FDA) on 17th July 2012.[4] This formulation is suggested to have a longer duration of action and better tolerability profile compared with regular topiramate.[5]

Phentermine is a centrally acting sympathomimetic agent, which acts as an appetite suppressant.[6] Since it is pharmacologically related to amphetamine, it has a potential for drug dependence and abuse.[7] It may also cause a number of side-effects on the cardiovascular system.[8] Topiramate is an antiepileptic drug marketed since 1996. The exact mechanism for weight loss is not clear. Topiramate modulates voltage-activated sodium channels and calcium channels. It mediates GABA receptor–mediated inhibitory currents and antagonizes alpha-amino 3-hydroxyl-4 isoxazole-propionic acid kainite receptors.[9] It is a potent inhibitor of carbonic anhydrase enzyme and thought to reduce appetite by altering the taste. Animal studies suggest decreased energy intake coupled with increased energy expenditure with topiramate that may contribute to weight loss.[10]

The combination of phentermine-topiramate is well absorbed orally. Phentermine is not bound significantly to plasma proteins. It is metabolized primarily by cytochrome P4503A4, though not extensively. About 70–80% of the dose is excreted unchanged in the urine, when administered alone. The half-life of phentermine is about 20 h. Topiramate is 15–41% plasma protein bound and is not extensively metabolized. The half-life of topiramate is about 65 h. There is no need of dose adjustments in patients with mild renal impairment and in patients with mild hepatic impairment.[11]

Address for correspondence: Dr. Jagjit Singh,
Department of Pharmacology, Government Medical College ans Hospital, Chandigarh - 160 030, India.
E-mail: drjagjitsingh1@gmail.com

Access this article online	
Quick Response Code:	Website: www.ijabmr.org
	DOI: 10.4103/2229-516X.157177

Three phase III randomized, placebo-controlled trials evaluated the safety and efficacy of phentermine-topiramate combination in the treatment of obesity. The EQUIP trial evaluated 1267 obese patients with BMI >35Kg/m^2 over a period of 56-week.[12] Patients were divided into 3 treatment arms: One receiving 3.75/23 mg Phentermine-topiramate and the second 15/92 mg combination and the third received placebo. Mean percentage weight loss from baseline (in maximum dose group) was 14.4%, while 67% patients lost at least 5% weight and 47% lost at least 10% body weight. The CONQUER trial estimated safety and efficacy of the combination on 2487 patients with BMI ≥27 and ≤45 kg/m^2.[13] Patients received either 7.5/46 mg or 15/92 mg phentermine-topiramate or placebo over a 56-week period. Mean percentage weight loss from baseline (in maximum dose group) was 12.4%, while 70% patients lost at least 5% weight, and 48% lost at least 10% body weight. The EQUATE trial demonstrated the superiority of this combination over either component alone.[14] SEQUEL study, a two year extension of the CONQUER trial confirmed the sustained weight loss over this period alongwith improvement in cardio-metabolic profile.[13a]

The drug is approved for use in adults with a BMI ≥30 or adults with a BMI ≥27 who have at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. The recommended daily dose of phentermine-topiramate contains 7.5 mg of phentermine and 46 mg of topiramate extended-release.[4] In the clinical trials with the combination therapy, the most common and important side-effects observed were paraesthesias, dizziness, dysguesia, insomnia, constipation and dry mouth.[13-15]

Concomitant use of oral contraceptives may cause irregular bleeding but not increased risk of pregnancy. Nonpotassium sparing diuretics may potentiate hypokalemia. The combination is contraindicated during pregnancy due to its teratogenic potential. The FORTRESS (Fetal Outcome Retrospective TopiRamate Exposure Study) has estimated that women taking this combination had a two times increased risk of giving birth to children with oral clefts when compared to nonusers.[16] Owing to this risk the drug has been approved with a risk evaluation and mitigation strategy (REMS) recommendation by the FDA.

References

1. World Health Organization. Global Health Observatory. Geneva: World Health Organization. Available from: http://www.who.int/gho/ncd/risk_factors/obesity_text/en/index.html. [Last accessed on 2013 Sep 13].
2. Khan A, Raza S, Khan Y, Aksoy T, Khan M, Weinberger Y, *et al*. Current updates in the medical management of obesity. Recent Pat Endocr Metab Immune Drug Discov 2012;6:117-28.
3. Ioannides-Demos LL, Piccenna L, McNeil JJ. Pharmacotherapies for obesity: Past, current, and future therapies. J Obes 2011;2011:179674.
4. US Food and Drug Administration. FDA Approves Weight-Management Drug Qsymia. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312468.htm. [Last accessed on 2013 Sep 15].
5. Lexicomp. Topiramate; Drug Information. Uptodate®. Available from: http://www.uptodate.com. [Last accessed on 2013 Sep 15].
6. Bray GA. Drug Insight: Appetite suppressants. Nat Clin Pract Gastroenterol Hepatol 2005;2:89-95.
7. Alexander M, Rothman RB, Baumann MH, Endres CJ, Brasic JR, Wong DF. Noradrenergic and dopaminergic effects of (+)-amphetamine-like stimulants in the baboon *Papio anubis*. Synapse 2005;56:94-9.
8. Rothman RB, Hendricks EJ. Phentermine cardiovascular safety. Am J Emerg Med 2009;27:1010-3.
9. Bray GA, Hollander P, Klein S, Kushner R, Levy B, Fitchet M, *et al*. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. Obes Res 2003;11:722-33.
10. Dodgson SJ, Shank RP, Maryanoff BE. Topiramate as an inhibitor of carbonic anhydrase isoenzymes. Epilepsia 2000;41 Suppl 1:S35-9.
11. Tremblay A, Chaput JP, Bérubé-Parent S, Prud'homme D, Leblanc C, Alméras N, *et al*. The effect of topiramate on energy balance in obese men: A 6-month double-blind randomized placebo-controlled study with a 6-month open-label extension. Eur J Clin Pharmacol 2007;63:123-34.
12. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, *et al*. Controlled-release phentermine/topiramate in severely obese adults: A randomized controlled trial (EQUIP). Obesity (Silver Spring) 2012;20:330-42.
13. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, *et al*. 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.
14. Garvey WT, Ryan DH, Look 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.
15. Aronne LJ, Peterson C, Troupin B. Weight Loss with V1-0521 (Phentermine/Controlled Release Topiramate) Stops Progression Towards Type 2 Diabetes in Obese Non-Diabetic Subjects. Poster PO. 22. Presented at: Obesity Society Meeting and the Abstract Included in Obesity Facts; 2010.
16. VIVUS Reports Topline Findings from FORTRESS. [media release on the Internet]. 21 December, 2011. Available from: http://www.ir.vivus.com/releasedetail.cfm?ReleaseID=634920. [Last assessed 2013 Dec 21].

How to cite this article: Singh J, Kumar R. Phentermine-topiramate: First combination drug for obesity. Int J App Basic Med Res 2015;5:157-8.

Source of Support: Nil. **Conflict of Interest:** None declared.