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New Drug Update

Phentermine and topiramate combination for chronic weight management: a review

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ABSTRACT

Obesity is a major public health concern and one of the leading preventable causes of death worldwide. It has manifold adverse health consequences, potentially involving all major organ systems thus leading to a reduced life expectancy. The long-term successful management of obesity remains a herculean task and invariably requires a multifaceted approach including lifestyle and behavioral modification, increased physical activity, and adjunctive pharmacotherapy and bariatric surgery. However, effective pharmacological options are limited because of the previous history of several failed agents as well as the fact that presently available agents are few, and utilized only as monotherapy. The recent Food and Drug Administration (FDA) approval of the fixed drug combination of phentermine and extended release topiramate marks the first FDA approved combination pharmacotherapeutic agent for obesity. This review details the various pharmacological aspects of the use of phentermine and topiramate combination along with the results of clinical trials done so far and also the present role of this combination in the management of obesity. Beyond the significant improvement in weight, the findings from various clinical trials also show improvement in metabolic and glycemic parameters, blood pressure, and lipid profile suggesting its added utility in cardiovascular risk modification. The acceptability of this combination would usher in a new era in the pharmacotherapy of obesity that utilizes combination therapy to improve efficacy, enhance synergism and concurrently minimize the risk of adverse effects. As with any newly marketed drug, there may be yet-unknown benefits and risks associated with this combination, which would be known only after its long-term use.

Keywords: Obesity, Pharmacotherapy, Phentermine, Topiramate

INTRODUCTION

Obesity is one of the leading preventable causes of death worldwide.[1] It has been formally recognized as a global epidemic by World Health Organization (WHO) in the year 1997.[2] By 2008, as per WHO, 1.4 billion adults (20 and older) were overweight.[3] Of these, over 200 million men and 300 million women were obese. It has been predicted by WHO that the more traditional public health concerns like under nutrition and infectious diseases may soon be replaced by overweight and obesity as the most important cause of poor health.[4] According to some estimates, if the epidemic of obesity keeps growing as per the recent trends, up to 57.8% of the world's adult population (3.3 billion people) could be either overweight or obese by 2030.[5] Obesity predisposes to various diseases including obstructive sleep apnea, cardiovascular diseases, diabetes mellitus, malignancies and asthma; thus leading to a reduced life expectancy and also a heavy burden on health care systems. The management of obesity is multi-modal in which both pharmacological as well as non-pharmacological approaches are helpful. The non-pharmacological modalities include lifestyle modification, dietary alterations and changes in physical activity patterns. In extreme cases, surgery may be required. However, effective pharmacological options are limited. Numerous drugs for obesity have come and gone because of the potential to cause serious or unacceptable adverse effects for example valvulopathy with fenfluramine and dexfenfluramine, stroke with phenylpropanolamine and increased suicidal tendency with rimonabant, and recently there has been evidence of myocardial infarction and stroke with sibutramine. As of June 2012, only three Food and Drug Administration (FDA) approved drugs were available

for the management of obesity: orlistat, phentermine and lorcaserin.

As obesity is a chronic medical ailment, the long term success of monotherapy has been somewhat limited.[6] Hence, combination pharmacotherapy that targets multiple pathways regulating energy homeostasis will achieve more robust and sustained weight loss, especially in complicated obesity.[7] Rational drug combination therapy may also have improved safety and tolerability. Search for novel therapies has led to the development of combination of phentermine and topiramate extended release. Phentermine hydrochloride is a sympathomimetic amine approved by FDA in 1959 for short-term obesity treatment (dose up to 37.5 mg/day). Topiramate was initially approved by the FDA for treatment of epilepsy in 1996. During clinical trials as an anti-epileptic agent, incidentally it was found to be efficacious in treating migraine and hence it was consequently approved for prophylaxis of migraine as well in 2004. FDA approved this new drug combination in July 2012, and the drug is available in United States since September 2012.

CHEMICAL STRUCTURE AND MECHANISM OF ACTION

Topiramate is chemically described as [(1R,2S,6S,9R)-4,4,11,11-tetramethyl-3,5,7,10,12-pentaoxatricyclo[7.3.0.0^{2,6}] dodecan-6-yl]methyl sulfamate. Its empirical formula is C12H21NO8S. Its structural formula[8] is shown in Figure 1.

Phentermine is chemically described as 2-methyl-1-phenylpropan-2-amine. Its empirical formula is C10H15N. Its structural formula[9] is shown in Figure 2.

The exact mechanism of action of both components of this combination is not known. However, it is believed that phentermine has amphetamine like anorectic action in the brain because of its ability to release catecholamines in the hypothalamus leading to a decrease in appetite and decreased food intake.[10] On the other hand, topiramate is thought to be helpful in chronic weight management because of its multiple actions in the central nervous system which include augmentation of the inhibitory gamma-aminobutyric acid receptor, inhibition of AMPA/kainite excitatory glutamate receptors, and inhibition of carbonic anhydrase and modulation of voltage gated ion channels.[10] By virtue of its multiple effects, it has dual action of suppression of appetite as well as satiety enhancement.[10]

PHARMACOKINETICS

Phentermine

When a single 15 mg/92 mg capsule of this combination is administered orally, the resulting mean plasma maximum concentration (Cmax) of phentermine is 49.1 ng/ml and the time to maximum concentration (Tmax) is 6 hrs. A high fatty meal does not affect its pharmacokinetics. Its pharmacokinetics is approximately dose-proportional from doses of 3.75 mg/23 mg to that of 15 mg/92 mg. Phentermine is metabolized by two metabolic pathways, which are p-hydroxylation on the aromatic ring and N-oxidation on the aliphatic side chain. On an average 70-80% of the dose is excreted unchanged in the urine. The mean terminal half-life of phentermine is about 20 hrs. Its estimated oral clearance (CL/F) is 8.79 L/h.[10]

Topiramate

When a single 15 mg/92 mg capsule of this combination is administered orally, the resulting Cmax of topiramate is 1020 ng/ml, and the Tmax is 9 hr. A high fatty meal does not affect its pharmacokinetics, which is approximately dose-proportional from the doses of 3.75 mg/23 mg to that of 15 mg/92 mg. It is 15-41% plasma protein bound over the blood concentration range of 0.5-250 g/mL. The bound fraction decreases as its blood levels increase. Topiramate

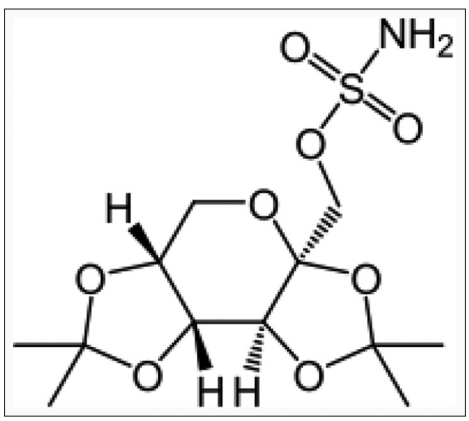

Figure 1: Structural formula of topiramate.

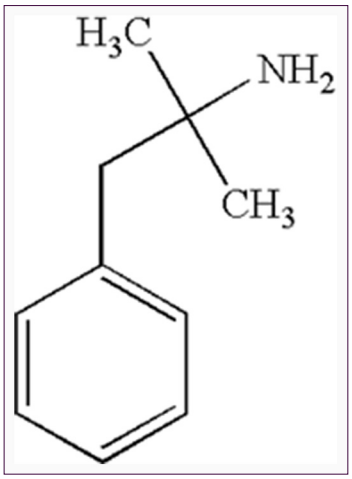

Figure 2: Structural formula of phentermine.

does not undergo extensive metabolism. About 70% of the drug is excreted unchanged in the urine. Its mean terminal half-life is about 65 hrs.[10]

INDICATIONS AND DOSAGE

The combination therapy of phentermine and topiramate has been approved by FDA for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related co morbidity such as dyslipidemia, type 2 diabetes mellitus or hypertension.

The combination has been approved as an adjunct to a reduced calorie diet and increased physical activity. The recommended dosage of this combination at the initiation of therapy is 3.75 mg/23 mg (3.75 mg phentermine/23 mg topiramate). After 14 days, dose has to be increased to 7.5 mg/46 mg once daily. This dose has to be continued for 12 weeks. However, if the reduction of >3% of basal body weight is not achieved in 12 weeks, escalation of the dose to up to 15 mg/92 mg/day can be done gradually. In those cases in which even with this high dose, reduction of >5% of basal body weight is not seen in 12 weeks, the drug has to be discontinued because any benefit from the continuation of therapy becomes highly unlikely.[10] The aim of dose titration is optimization of clinical response and minimization of adverse effects. The drug is taken once daily in the morning. In order to prevent insomnia, evening dosing should be avoided. In patients with moderate (creatinine clearance ≥30 to <50 mL/mins) or severe renal impairment (<30 mL/mins) or moderate hepatic impairment, the dose should not exceed 7.5 mg/46 mg.[10]

CLINICAL TRIALS

Among the various clinical trials conducted for the evaluation of this combination, those which deserve a necessary mention include:

EQUIP

It was a randomized, double-blind, placebo-controlled Phase III clinical trial to evaluate the safety and efficacy of controlled-release combination of phentermine and topiramate (PHEN/TPM CR) for weight loss and improvement in metabolic parameters. Males and females with Class II and III obesity (BMI ≥35 kg/m^2) were randomized to placebo, PHEN/TPM CR 3.75/23 mg, or PHEN/TPM CR 15/92 mg, along with a low calorie diet. In categorical analysis, 17.3% of placebo patients, 44.9% of PHEN/TPM CR 3.75/23 patients, and 66.7% of PHEN/TPM CR 15/92 patients lost at least 5% of baseline BW at 56 weeks ($p<0.0001$). The 15/92 group showed significantly greater metabolic improvement including BP, fasting glucose, triglycerides, total cholesterol, low density lipoprotein and high density lipoprotein. To conclude, PHEN/TPM CR demonstrated dose-dependent significant weight loss and improvement in the metabolic variables without any evidence of serious adverse events.[11]

CONQUER

In another 56 weeks long, randomized, double-blind, placebo-controlled Phase III clinical trial done in 93 centers in USA, 2487 overweight or obese adults (aged 18-70 years), with a BMI of 27-45 kg/m² and two or more comorbidities (hypertension, dyslipidemia, diabetes or prediabetes, or abdominal obesity) were randomly divided into 3 groups; 1st group received placebo, 2nd group received once-daily phentermine 7·5 mg plus topiramate 46 mg, and 3rd group received once-daily phentermine 15 mg plus topiramate 92 mg. Significant reduction in weight and comorbid risk was seen with both the doses of the CR formulation of phentermine plus topiramate when combined with a slight lifestyle intervention. Only 7% of placebo-treated patients achieved 10% weight loss, as compared to 48% of those treated with the higher dose of phentermine plus topiramate ($p<0.0001$), and 37% of those treated with the lower dose ($p<0.0001$), thus proving the efficacy of this combination. The trial also demonstrated that the weight loss was sustained for a period of 56 weeks and was accompanied by improvements in BP, lipid profile, glycemia, and inflammatory markers.[12]

SEQUEL

This was an extension study of the subjects who completed CONQUER trial where the blinded treatment was given for additional 72 weeks. The trial concluded that the beneficial therapeutic effects of the combination were sustained during the 2 year period.[13] In addition, this trial showed a 76% reduction in new onset type 2 diabetes in the maximum dose treatment group.

EQUATE

It was a randomized, double-blind, placebo-controlled Phase III trial conducted for 28 weeks and confirmed the superiority of the phentermine/topiramate combination over the individual components alone.[14] The treatment arms were 7.5/46 mg and 15/92 mg of the combination as well as 7.5 mg and 15 mg alone of phentermine, 46 and 92 mg alone of topiramate and a placebo arm. The mean weight loss achieved for the maximum dose combination was 9.21% compared to 6.06% in the maximum dose phentermine alone and 6.44% in the maximum dose topiramate alone groups and these findings were statistically significant. The 7.5/46 mg group was associated with 8.46% weight loss from baseline. An additional benefit of improvement in glycemic profiles was also reported.

Fetal outcome retrospective topiramate exposure study

It was a retrospective study of existing electronic health care database to evaluate the potential teratogenicity risk with exposure to the phentermine/topiramate combination during pregnancy in humans.[15] To estimate the relative risk for orofacial clefts and other congenital malformations, the prevalence rates were compared in women who were exposed to topiramate during pregnancy, but who discontinued its use (previously exposed cohort) to a cohort of pregnant women with similar clinical profiles, but no topiramate exposure. Exposed women had nearly 2 times greater risk for having children with oral clefts with estimated prevalence rates amongst those actively using topiramate of 0.29%, compared to 0.16% among previously exposed women and prevalence ratio of 1.88 between continuous pregnancy exposed to previously exposed groups. However, in women with similar clinical profiles who had no history of topiramate exposure, the prevalence rate of oral cleft was 0.07%.

ADVERSE DRUG REACTIONS

The observed adverse effects are as would be expected based on the clinical profile of the individual components of the combination. The most common adverse effects with the combination were paraesthesia, dizziness, dysguesia, insomnia, constipation and dryness of mouth. All the adverse reactions were dose related and were mild to moderate. Post marketing, the adverse effects, which have been attributed to the phentermine include urticaria, increase in BP, ischemic events, psychosis, tremor, euphoria, decrease in libido, and impotence. On the other hand, the adverse effects like dermatological reactions (Steven Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis), pemphigus, pancreatitis, hepatic disorders, hyperammonemia, glaucoma and maculopathy have been thought to be due to the topiramate component. Apart from these, increase in heart rate and mood and sleep disorders have been seen with this combination. Increased tendency of suicidal behavior and thoughts has also been reported with topiramate and might require discontinuation of the combination.[10] Topiramate component can lead to increase in the incidence of oral clefts when administered during pregnancy; hence, it should not be prescribed to pregnant women.[16] In order to minimize the risk of teratogenicity, women of childbearing age should have a negative pregnancy test before starting the drug, and every month afterwards. There is insufficient data regarding its safety in lactating mothers. Hence, caution is generally advised regarding breast feeding while taking the medication.

CONTRAINDICATIONS

The absolute contra-indications include pregnancy, glaucoma, hyperthyroidism, and known hypersensitivity to individual components.[10]

Adequate precautions must be taken while prescribing the drug in the following conditions:[10]

Elevated heart rate

The drug can cause an increase in resting heart rate from baseline of more than 5, 10, 15, and 20 beats/min. Hence, regular measurements of the resting heart rate should be done, particularly in patients with cardiac or cerebrovascular disease.

Suicidal behavior and ideation

Topiramate can increase the risk of suicidal thoughts or behavior. If a patient shows such tendency, treatment must be stopped.

Acute-angle closure glaucoma

There were reports of acute myopia associated with secondary angle-closure glaucoma due to topiramate component.

Cognitive impairment

Cognitive dysfunction such as difficulty in concentration, memory, or speech, has been reported. Chances are higher if the initial dose used is higher. Hence, caution is necessary for patients who are operating automobiles or hazardous machinery.

Metabolic acidosis

The drug has been associated with elevated levels of serum creatinine. To avoid the risk of metabolic acidosis, periodic electrolyte monitoring should be done.

DRUG INTERACTIONS

- Concomitant administration of monoamine oxidase inhibitors with this combination can lead to hypertensive crisis, so there should be a gap of at least 14 days between the two therapies.
- This combination can further accentuate the potassium wasting action of non-potassium sparing diuretics; hence, the patients who are on both the therapies should be monitored for hypokalemia.
- Concomitant administration of topiramate and Valproate has been associated with hyperammonemia and hypothermia (with and without hyperammonemia). Hence, blood ammonia levels should be assessed in patients in whom the onset of hypothermia or encephalopathy has been reported.
- As topiramate component of this combination has carbonic anhydrase inhibitory action, the concomitant

use of this combination with other carbonic anhydrase inhibitors like acetazolamide can increase the risk of metabolic acidosis and kidney stones.[10]

SUMMARY

In the clinical trials, the combination has achieved significant weight loss in the overweight patients. The 2 year follow-up data suggests that this combination therapy has an important place to occupy in the armamentarium for chronic obesity management. Beyond the significant improvement in weight, the findings from various clinical trials also show improvement in metabolic and glycemic parameters, blood pressure, and lipid profile suggesting its added utility in cardiovascular risk modification. As the complete information about the safety profile of the individual components of this combination is available because of the considerable period of clinical experience with both components, this combination will have its advantages over the other upcoming agents which will need a considerable period of post-marketing experience before their complete safety profile can be revealed. However, the answer to the question of the safety of this combination when taken along with other products intended for weight loss has not yet been established. Further experience with this combination is needed to throw light on this issue. The results of trials in special populations such as children are also awaited. The combination is in Phase II clinical trials for the treatment of diabetes mellitus Type 2 and obstructive sleep apnoea.[17]

The drug got FDA approval in July, 2012. European Medicines Agency; however, rejected its approval in the European Union in October 2012 due to concerns over potential long-term cardiovascular and central nervous system effects, teratogenic potential, and the possibility of use by patients for whom this combination therapy is not indicated. The drug is currently not available in India. The acceptability of this combination would hopefully bring a new era in the pharmacotherapy of obesity that utilizes combination therapy to improve efficacy, enhance synergism and concurrently minimize the risk of adverse effects.

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