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Editorial

Anti-Obesity Drugs of the Twenty-First Century: Hope or Hype?

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Obesity has now been officially accorded the tag of a 'disease', it is no longer just another 'risk factor'. Recently the US Food and Drug Administration (FDA) gave regulatory nod to two new anti-obesity drugs in quick succession, in a hope to keep up the fight against the growing epidemic of obesity. Globally, obesity is associated with a host of chronic diseases, especially diabetes, hypertension and ischaemic heart disease. Lifestyle modifications, including diet and exercise, are the mainstays of non-pharmacological management of obesity. Surgical management being a costly and invasive procedure is usually reserved for the morbidly obese patients. Pharmacotherapy for obesity is an attractive option, although the results have been disappointing so far. Agents like sibutramine and rimonabant have been banned due to their association with severe adverse effects, and most drugs available are approved for short-term use only. Currently, orlistat is the only drug approved for long-term management of obesity. Lorcaserin (Belviq^{TM}) and a combination of phentermine and topiramate (Qysma^{TM}) were approved by the FDA in June and July 2012, respectively.

Lorcaserin is an oral agent used as adjunct to diet and exercise in obese patients (Body-mass index (BMI)>30 kg/m^2) or overweight patients, i.e. BMI>28 kg/m^2, with at least one co-morbid condition (diabetes mellitus, hypertension, dyslipidemia, etc.).[1] The proposed mechanism of action of lorcaserin is via activation of the serotonergic $5HT_{2C}$ receptors in the brain. It induces a state of satiety without increasing the energy expenditure. In a study by Smith *et al*.,[2] lorcaserin produced a weight loss of 1.8, 2.6 and 3.6 kg at dosages of 10 mg once daily, 15 mg once daily and 10 mg twice daily, respectively, compared with placebo weight loss of 0.3 kg ($P < 0.001$ for each group). In the BLOSSOM trial, lorcaserin, at doses of 10 mg once or 10 mg twice daily, caused a significant decrease in at least 5% of the baseline body weight, as compared with the placebo.[3] In the BLOOM DM trial involving type 2 diabetic patients, loss of ≥5% body weight was seen in more patients in both the lorcaserin groups (10 mg once or twice daily) than with the placebo.[4] There was a statistically significant fall in the glycosylated haemoglobin levels (HbA (1c)) in both the lorcaserin groups compared with the placebo. The most frequent adverse events reported were transient headache, nausea and dizziness, back ache and nasopharyngitis, while there was no report of drug-related effects on the heart valves or on the pulmonary artery pressure, as shown on echocardiograms. In diabetic patients, hypoglycaemia was seen more commonly in the lorcaserin groups. The recommended dose of lorcaserin is 10 mg twice daily. It is not recommended during pregnancy.

Phentermine-topiramate is a fixed-dose combination of phentermine immediate release and topiramate extended release preparation, approved by the FDA.[5] The recommended daily dose is of 7.5 mg of phentermine and 46 mg of topiramate extended release preparation. Phentermine is a centrally acting sympathomimetic agent used since long as an appetite suppressant. Topiramate is a well-established anti-epileptic drug. However, its tendency to induce weight loss was noticed in patients undergoing trials for epilepsy and migraine. While the exact mechanism of weight loss in obesity is still unclear, animal experiments suggest that topiramate causes increased energy expenditure, decreased energetic efficiency and decreased energy intake. Three clinical studies evaluated the safety and efficacy of the combination. The EQUIP trial evaluated 1267 obese patients with BMI >35 kg/m^2, amongst whom 67% patients lost at

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least 5% weight and 47% lost at least 10% body weight.[6] The CONQUER trial evaluated the combination on 2487 patients with BMI ≥ 27 and ≤ 45 kg/m^2, of whom 70% patients lost at least 5% weight and 48% lost at least 10% body weight.[7] The SEQUEL study, which was a 2-year extension study on 676 participants of the CONQUER study, showed that the weight loss sustained for 2 years.[8] FORTRESS (Fetal Outcome Retrospective TopiRamate ExpoSure Study) was a retrospective study to identify the risk of birth defects with phentermine–topiramate combination, which estimated that women taking this combination had a two times increased risk of giving birth to children with oral clefts, as compared with non-users.[9] Hence, this drug has been approved with a risk evaluation and mitigation strategy (REMS) by the FDA.

With obesity being labelled as a disease in itself, the race for effective and safe treatments of this disease seems to be heating up. Though the initial trials have shown promising results with the two newly approved drugs, the prescribers need to act with caution. Long-term clinical studies and effective pharmacovigilance through phase IV studies will be required to shed more light on the effectiveness as well as the long-term safety of these drugs in real-life situations. Till then, let us hope that these new medicines may not prove to be just hype for the treatment of obesity.

REFERENCES

1. FDA approves Belviq™ to treat some overweight or obese adults. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309993.htm [Assessed on August 2013]
2. Smith SR, Prosser WA, Donahue DJ, Morgan ME, Anderson CM, Shanahan WR; APD356-004 Study Group. Lorcaserin (APD356), a selective 5-HT(2C) agonist, reduces body weight in obese men and women. Obesity 2009; 17(3): 494-503.
3. Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, et al.; BLOSSOM Clinical Trial Group. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab 2011; 96(10): 3067-77.
4. O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity 2012; 20(7): 1426-36.
5. FDA approves weight-management drug Qsymia (News & Events). Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312468.htm [Assessed on August 2013].
6. 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 2012; 20(2): 330–42.
7. 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(9774): 1341–52.
8. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, 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(2): 297–308.
9. VIVUS reports topline findings from FORTRESS [media release on the Internet]; 21 December 2011. Available at: http://ir.vivus.com/releasedetail.cfm?ReleaseID=634920 [Assessed on August 2013].

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