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EXPERT OPINION

Two anti-obesity hopefuls and their safety

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Obesity is a worldwide health problem. One obstacle faced by health care professionals is the lack of available medications. As discussed in the recent review by Derosa and Maffioli [1], the development of anti-obesity drugs is a delicate balance between efficacy and safety. Approval and use of a medication relies on a risk–benefit assessment. Regarding efficacy with anti-obesity drugs, there is a clear distinction between significant weight loss and clinically effective weight loss. The primary clinical effective endpoint at 52 weeks for anti-obesity medications, as stipulated by FDA (USA) and NICE (UK), is based on *mean efficacy* or *categorical efficacy*. Mean efficacy is defined as a medication-associated (i.e., greater than placebo) weight reduction of 5%. Categorical efficacy is defined as a significantly greater proportion, at least 35% and double the number of individuals receiving placebo, maintaining a 5% weight loss from their initial weight and statistically significant [2,3]. Derosa and Maffioli [1] determined that orlistat (120 mg, TID), a gastrointestinal lipase inhibitor, was the best choice for the long-term treatment of obesity. Their conclusion was limited to the fact that orlistat is the only available long-term medication available in US and European markets. Notwithstanding, orlistat is a fairly safe medication. Most adverse events are limited to some minor to moderate gastrointestinal disturbances with rare cases of severe liver injury. The primary endpoints for weight loss with orlistat are modest. A meta-analysis combining 13 studies of 6,196 obese subjects revealed that orlistat has a mean efficacy of 2.9% weight loss (placebo-subtracted) with 54% of individuals achieving a 5% weight loss compared with 33% receiving placebo [4]. Treatment options for obesity, however, are likely to soon change in the next year. Currently, there are two potential anti-obesity medications that have completed Phase III clinical trials and are under review by the FDA for approval in the US.

Lorcaserin [(1R)-8-Chloro-2,3,4,5 tetrahydro-1-methyl-1H-3-benzazepine] is structurally similar to β-phenylethylamine compounds, such as serotonin (5-hydroxytryptamine; 5HT) and dexfenfluramine [5]. Lorcaserin is a centrally acting novel compound and selectively activates $5HT_{2C}$ receptors on POMC neurons in the hypothalamus to promote reductions in food intake and body weight. Completed Phase III clinical trials assessed lorcaserin (10 mg) twice a day (BID) or once a day (QD) in three separate randomized controlled studies in a total of 7597 overweight and obese subjects. One of these studies (n = 687) examined weight loss and secondary glycemic endpoints in obese subjects with type 2 diabetes mellitus. After 52 weeks, the combined mean efficacy weight loss for the BID dose was 3.2% (placebo-subtracted) and 2.4% (placebo-subtracted) for the QD dose. While this does not meet the mean efficacy criteria for the FDA, categorical efficacy was achieved with the 10 mg BID dose. That is, in non-diabetic overweight/obese subjects a 5% weight loss was observed with lorcaserin in 47.3% compared with 25% receiving placebo, whereas categorical efficacy in

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diabetic overweight/obese subjects was in 37.5% compared with 16.1% receiving placebo at 52 weeks [6]. As noted in Derosa and Maffioli [1] the previously FDA-withdrawn serotonergic anorectic drug, dexfenfluramine, was associated with a significant increased risk of valvular heart disease. Pre-clinical findings have indicated that the dexfenfluramine-induced valvulopathy and other cardiac-related issues are mediated by peripheral $5HT_{2B}$ receptor [7,8]. In *in vitro* assays using human receptor, lorcaserin has a 10-fold greater affinity for $5HT_{2C}$ compared with $5HT_{2B}$ receptors (i.e., K_i of 13 nM for $5HT_{2C}$ compared with K_i of 147 for $5HT_{2B}$). Subsequent functional *in vitro* assays have also supported the claim that lorcaserin is highly selective for the $5HT_{2C}$ receptors [6]. Clinical data collected by echocardiogram during the Phase III trials, on the other hand, have suggested that lorcaserin increases the risk of valvulopathy after 52 weeks. The percentage of individuals receiving lorcaserin (10 mg BID) with FDA-defined valvulopathy was 2.5% compared with 1.6% in the placebo group. The data resulted in a pooled relative risk of 1.16 with a 95% CI of 0.87 – 1.67, which exceed the FDA upper bound of 1.5 to suggest a potential risk of valvular heart disease. Interestingly, when the data were stratified based on whether subjects had a lorcaserin-induced 5% weight loss (i.e., responders) the relative risk of FDA-defined valvulopathy was 0.86 with a 95% CI of 0.49 – 1.5, suggesting that the valvulopathy risk is related to the weight loss response of the drug. Further testing is needed with a large number of subjects to adequately address the risk of lorcaserin on valvular heart disease. In May 2012, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) voted 18-4 in favor of approval of lorcaserin (10 mg BID) stating that the benefits of lorcaserin to treat obesity outweigh the potential risks.

In February 2012, Qnexa, another potential anti-obesity drug received a favorable (20-2 vote) endorsement by the FDA EMDAC. This drug is a novel formulation combining two already FDA-approved centrally acting medications phentermine (2-methyl-1-phenylpropan-2-amine) and topiramate [2 3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate] [9]. As noted in Derosa and Maffioli [1], phentermine is an amphetamine analog stimulant approved since 1959 for the short-term (i.e., up to 3 months) treatment of obesity. Currently, it is the most prescribed weight loss treatment in the US [1]. Phentermine is not available for prescription in European markets because of concerns about tolerance and abuse potential, though there is little evidence supporting concerns about the abuse of phentermine [10]. Topiramate is a sulfamate-substituted monosaccharide, although not completely understood, the mechanism of action is related to augmenting GABAergic activity. Topiramate was approved in 1997 to treat partial onset seizures and is also labeled to treat migraines [9]. One of the adverse effects of the drug is weight loss. Accordingly, topiramate (64 – 384 mg, QD) has been demonstrated to produce significant weight loss in obese subjects in a 6-month trial [11]. Qnexa formulation contains doses of phentermine that are 1/10 to 1/2 the doses used for obesity, whereas the doses of topiramate are 1/16 to 1/4 the doses used as an anticonvulsant [9]. Phase III clinical trials used two randomized controlled studies to assess three Qnexa (phentermine/topiramate) doses (QD), which included a low (3.75 mg/23 mg), mid (7.5 mg/46 mg), and top dose (15 mg/92 mg), in 3674 obese subjects. An additional 6-month randomized controlled Phase III study in 726 obese subjects was conducted to determine the efficacy of weight loss in the mid and top dose of Qnexa compared with doses of phentermine alone and topiramate alone. After 56 weeks, the mean efficacy weight loss for the low dose was 3.5% (placebo-subtracted), mid dose was 6.6% (placebo-subtracted), and top dose was 8.9% (placebo-subtracted) [9]. The proportion of subjects achieving a 5% weight loss, categorical efficacy, was 44.9% for the low dose, 62.1% for the mid dose, 68.3% for the top dose, and 19.4% for placebo. The 6-month randomized controlled study in obese individuals revealed that Qnexa produced significantly greater weight loss than individual doses of phentermine or topiramate [9]. Two safety concerns of Qnexa are the potential teratogenic risk and effects on the cardiovascular system. While phentermine has Pregnancy Category X [12] designation, the focus of the teratogenicity risk possibly associated with Qnexa has been directed toward topiramate. The drug topiramate, Pregnancy Category D, is associated with an increased risk to develop oral cleft malformations in infants. In a FDA drug safety communication [03-04-2011] using data gathered from North American Antiepileptic Drug pregnancy drug registry, which currently has 8500 women enrolled, the relative risk of oral clefts in topiramate-exposed pregnancies was 21.3 with a 95% CI of 7.9 – 57.1. Data from a similar designed pregnancy registry in the UK reported a 16-fold increase in risk of oral clefts with topiramate compared with the general population [13]. During all the clinical trials (Phase I, II, and III) with Qnexa there were 34 pregnancies reported, 29 were in active treatment and 6 placebo treatment. Of the 19 live births, all were associated healthy newborns without congenital malformation on physical examination [9]. Further extensive testing and registry data are needed with a large number of subjects to adequately address the risk of Qnexa on congenital malformation and could result in prescribing restrictions. The other safety issue related to the cardiovascular risk, Qnexa, increased heart rate at the mid dose of 0.6 beats per minute (bpm) and 1.6 bpm in the top dose. A higher proportion of Qnexa-treated subjects also experienced a categorical significant increase in heart rate > 20 bpm compared to placebo-treated subjects (13.5% mid, 19.6% top, and 11.9% placebo). The FDA has required further details for a comprehensive Risk Evaluation and Mitigation Strategy (REMS) to assess both teratogenic potential and cardiovascular risks of Qnexa.

Expert opinion

Despite not approving an anti-obesity drug since 1999, there is a strong likelihood the FDA will approve both (or at least

one) of the anti-obesity hopefuls in the next few months. The fact that these two potential medications differ in their mechanisms of action, efficacy, and safety profiles, can be seen as an asset to the treatment for obesity. Even though lorcaserin is marginally effective for weight loss, satisfying only one of the two FDA-efficacy criteria, patients could be placed on the medication for several weeks to determine if they are responders or non-responders for 5% weight loss. Combined data from the Phase III trials indicate at 8 – 12 weeks responders show an approximate 3 – 4% weight loss [6]. In a meta-analysis of 10 studies examining dexfenfluramine it was determined that prevalence rate for FDA-defined valvulopathy was 10.8% when the drug was given more than 90 days of treatment, but dropped to 6.9% when treatment was less than 90 days. In addition, the prevalence odds ratio for valvulopathy dropped from 2.0 with a 95% CI of 1.4 – 2.7 to an odds ratio of 1.5 with a 95% CI of 0.8 – 2.7 with a less than 90-day treatment [14]. Taken in the context of the stratified data indicating lorcaserin responders had a relative risk of valvulopathy of less than 1, it is likely that the risk of lorcaserin-induced valvulopathy could be further reduced by half with an 8- to 12-week responder trial period. Although the efficacy data for Qnexa is stronger, the teratogenic potential certainly possesses limitation for women of childbearing age. A retrospective large-scale Denmark study examined in uterine exposure to newer epileptic drugs in 837,795 live births indicated that topiramate taken only the first trimester result in 4.6% with a prevalence odds ratio of 1.44 with a 95% CI of 0.58 – 3.58 of a major birth defect (inclusive of oral clefts). The unexposed rate of major birth defect in the Denmark population was 2.4% [15]. Such data suggest halting Qnexa treatment in the first trimester could limit the teratogenic risk. However, the potential teratogenic risk of topiramate combined with phentermine has not been addressed to date.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Derosa G, Maffioli P. Anti-obesity drugs: a review about their effects and their safety. Expert Opin Drug Saf 2012;11(3):459-71
2. FDA. Guidance for the clinical evaluation of weight-control drugs. Crit Rev Food Sci Nutr 2001;41(1):91-4
3. Mayor S. NICE requires primary care trusts to tackle prevention and management of obesity. Bmj 2006;333(7581):1239
4. Rucker D, Padwal R, Li SK, et al. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. Bmj 2007;335(7631):1194-9

•• . **Meta-analysis of 30 randomized controlled studies of orlistat, sibutramine, and rimonabant. In addition to providing mean and categorical efficacy for each drug, results are stratified based on secondary metabolic endpoints and adverse events.**

5. Bello NT, Liang NC. The use of serotonergic drugs to treat obesity–is there any hope? Drug Des Devel Ther 2011;5:95-109
6. FDA. NDA 22529 Lorcaserin Hydrochloride Tablets, 10 mg Briefing Document, 2012 (10-May-2012)
7. Launay JM, Herve P, Peoc'h K, et al. Function of the serotonin 5-hydroxytryptamine 2B receptor in pulmonary hypertension. Nat Med 2002;8(10):1129-35
8. Nebigil CG, Hickel P, Messaddeq N, et al. Ablation of serotonin 5-HT(2B) receptors in mice leads to abnormal cardiac structure and function. Circulation 2001;103(24):2973-9
9. FDA. NDA 22580 VI-0521 (Qnexa) Briefing Document 2012(22-Feb-2012)
10. Rothman RB, Hendricks EJ. Phentermine cardiovascular safety. Am J Emerg Med 2009;27(8):1010-13
11. Bray GA, Hollander P, Klein S, et al. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. Obes Res 2003;11(6):722-33

• . **A 24-week placebo controlled study to examine the effects of topiramate on weight loss in obese subjects. Doses of topiramate (64-384 mg/d) resulted in 2.4-3.6% placebo-subtracted weight loss.**

12. Lannett Company I. Phentermine Hydrochloride tablet (37.5 mg), Revised 04/2012, Revision 2. Package Insert 2012
13. FDA. Risk of oral clefts in children born to mothers taking Topamax (topiramate)[03-04-2011] Drug Safety Communication, 2011 (07-March-2011)
14. Sachdev M, Miller WC, Ryan T, et al. Effect of fenfluramine-derivative diet pills on cardiac valves: a meta-analysis of observational studies. Am Heart J 2002;144(6):1065-73

• . **Meta-analysis of 10 clinical trials to determine the fenfluramine and dexfenfluramine effects on FDA-derived valvulopathy. The estimated prevalence of drug-induced valvulopathy was 12% for > 90 day treatment.**

15. Molgaard-Nielsen D, Hviid A. Newer-generation antiepileptic drugs and the risk of major birth defects. JAMA 2011;305(19):1996-2002

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