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EDITORIAL

Novel Oral Anti-Obesity Agents: New Perspectives with Lorcaserin?

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The incidence and prevalence of obesity is increasing worldwide due to changes in lifestyles, with a shift to less physical activity and an increase in caloric intake. This development has led to an increased burden on healthcare systems and societies, as obesity is associated with severe co-morbidities (e.g. type 2 diabetes mellitus, hypertension, dyslipidaemia, sleep apnoea and many more) often leading to invalidity and psycho-social problems. Furthermore, obesity is associated with an increased mortality [1, 2]. The treatment strategies for obesity include lifestyle modifications, either as a single strategy or in conjunction with pharmacological treatments [3]. In recent years, different methods of bariatric surgery have also gained importance for the treatment of obesity [4–6], although surgery is unlikely to solve the widespread obesity problem. Since lifestyle modifications are often ineffective and difficult to implement, pharmacological treatment of obesity seems very attractive. There are limited options for medical therapy of obesity at present; in most countries, only orlistat (a lipase inhibitor) is available as oral medication. Sibutramine (an amphetamine derivative) and rimonabant (a cannabinoid receptor blocker) have been removed from the market due to the increased cardiovascular risk associated with sibutramine and the association of depression, anxiety and suicidal ideation with rimonabant [7–9]. Glucagon-like-peptide (GLP)-1 receptor agonists also have potential as weight-loss agents, but so far they are only approved for the treatment of type 2 diabetes and not yet for obesity. Apart from that, they are injectable agents [10, 11], and gastrointestinal adverse events (fullness, nausea, vomiting or diarrhoea) occur in approximately 20–30 % of patients, although usually only transiently at the initiation of therapy [11]. In this context, the development of novel oral anti-obesity agents seems necessary and prudent.

Recently, lorcaserin, a serotonin 5-HT_{2C} receptor agonist, has been approved in the USA for the treatment of obesity as an adjunct to lifestyle modifications in obese adults (body mass index [BMI] $\geq$30 kg/m^2), or overweight adults (BMI $\geq$27 kg/m^2) with at least one weight-related co-morbid condition (e.g. dyslipidemia, hypertension, type 2 diabetes). The approval has been based on a clinical study programme with lorcaserin that includes studies with a duration of 2 years. A comprehensive overview of this agent, including its clinical profile regarding efficacy and safety is given in the article by Hoy in this issue [17].

The efficacy and safety of lorcaserin was investigated in large clinical trials (BLOOM-DM [12], BLOSSOM [13] and BLOOM [18]), using doses of 10 mg lorcaserin twice daily in a randomized, multicentre, placebo-controlled, double-blind fashion. Significantly more patients receiving lorcaserin achieved a bodyweight reduction from baseline of $\geq$5 % and $\geq$10 % compared with the placebo group after 12 months. At 24 months, the least square mean bodyweight reductions from baseline (at randomization) were 6.0 kg in patients receiving lorcaserin treatment for 24 months ($n = 426$), 3.8 kg in patients who had received lorcaserin for 12 months before switching to placebo for 12 months ($n = 195$) and 2.6 kg in patients in the placebo-only group ($n = 507$), with no statistical analysis reported on these data [14]. In a pooled analysis, a significant ($p < 0.001$) placebo-subtracted change from baseline in bodyweight in favour of lorcaserin ($n = 3098$) was observed compared with placebo ($n = 3038$) (−3.3 kg [95 % CI −3.6, −2.9]). Significant ($p < 0.001$) placebo-subtracted differences favouring lorcaserin over placebo

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were also observed in the proportion of patients achieving a ≥5 % (24.5 % [95 % CI 22.2–26.8]) and ≥10 % (13.8 % [95 % CI 12.0–15.5]) reduction from baseline in their bodyweight [14]. However, patients who did not achieve a ≥5 % reduction from baseline in their bodyweight after 12 weeks of therapy were unlikely to achieve such a reduction after 52 weeks of treatment. For this reason, the US prescribing information states that the drug should be discontinued if this initial weight loss is not achieved [14]. It should be noted that 45–50 % of patients in the above-mentioned studies did not complete the study programme, with patient decision and loss to follow-up being the most frequent reasons for study discontinuation [12, 13].

Regarding safety and tolerability, lorcaserin was well tolerated, with headache and hypoglycaemia in patients with diabetes receiving sulfonylurea or insulin therapy being the most frequently reported adverse events. Even though non-inferiority of lorcaserin to placebo for US FDA-defined valvulopathy was not established, lorcaserin is most likely not associated with the degree of risk of US FDA-defined valvulopathy that was previously observed with the weight-loss agents dexfenfluramine and fenfluramine [15]. Lorcaserin, as a serotonin 5-HT_{2C} receptor agonist, should be used with extreme caution in combination with other serotonergic or antidopaminergic agents, and agents acting on the serotonergic neurotransmitter systems, due to its possible interaction with these drugs and the theoretical potential for serotonin syndrome [14].

For obese patients and individuals who are overweight with simultaneous cardiovascular risk factors, reducing bodyweight lowers the overall mortality, cardiovascular and cancer risk. Since a considerable proportion of individuals will not be able to implement sustained lifestyle changes necessary to lose bodyweight, pharmacological anti-obesity therapy may be an alternative provided it is efficacious and safe. Lorcaserin may offer a novel alternative for treatment of obesity. The amount of weight loss is comparable to that with other compounds that have been developed so far. For patients with extreme obesity, it will not be possible to achieve a near-normal BMI with this new drug, but the treatment may help to achieve some reduction in bodyweight and therefore other obesity-related risk factors. Since, in clinical studies, patients not showing a response to the drug after the first 12 weeks of treatment did not profit later on during therapy, the drug can be withdrawn fairly early in individuals who do not respond to lorcaserin after this short timeframe.

Another new drug combination, phentermine plus topiramate extended release, has been recently approved [16]. Phentermine acts as an appetite suppressant, while topiramate is an antiepileptic. The combination, for once-daily dosing, is designed to produce weight loss by decreasing appetite and increasing satiety. The product is also in clinical development for sleep apnoea syndrome and type 2 diabetes, two conditions that are often associated with obesity. Head-to-head studies comparing the phentermine and topiramate combination with lorcaserin are not available, and the weight-loss data available for the two agents are very difficult to compare and to translate into a real-world setting, given the different study populations and study protocols in clinical studies. The safety and tolerability of these novel anti-obesity medications need to be closely monitored and compared between agent classes under everyday clinical practice conditions.

The developmental pipeline for anti-obesity drugs is not empty and, in the future, we will perhaps see even more compounds reaching approval, such as tesofensine, or bupropion in combination with either naltrexone or zonisamide. Among those developments are peptide analogues of neurotransmitters and gut hormone-based peptides acting on satiety as injectable therapies, with particular focus on ghrelin, peptide YY, pancreatic polypeptide, amylin and oxyntomodulin [11, 12].

Hence, the approval of lorcaserin may be one further step towards the development of more diversified options in pharmacological obesity therapy.

References

1. Pi-Sunyer X. The medical risks of obesity. Postgrad Med. 2009; 121:21–33.
2. Abdullah A, Wolfe R, Stoelwinder JU, de Courten M, Stevenson C, Walls HL, Peeters A. The number of years lived with obesity and the risk of all-cause and cause-specific mortality. Int J Epidemiol. 2011;40:985–96.
3. Hussain SS, Bloom SR. The pharmacological treatment and management of obesity. Postgrad Med. 2011;123:34–44.
4. Picot J, Jones J, Colquitt JL, Loveman E, Clegg AJ. Weight loss surgery for mild to moderate obesity: a systematic review and economic evaluation. Obes Surg. 2012;22:1496–506.
5. Bradley D, Magkos F, Klein S. Effects of bariatric surgery on glucose homeostasis and type 2 diabetes. Gastroenterology. 2012;143:897–912.
6. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Agren G, Carlsson LM, Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357:741–52.
7. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, Torp-Pedersen C, Sharma AM, Shepherd GM, Rode RA, Renz CL, SCOUT Investigators. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med. 2010;363:905–17.
8. Scheen AJ. Cardiovascular risk-benefit profile of sibutramine. Am J Cardiovasc Drugs. 2010;10:321–34.
9. Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean ME, Niskanen L, Rasmussen MF, Rissanen A, Rössner S, Savolainen MJ, Van Gaal L, NN8022-1807 Investigators. Safety, tolerability

and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes (Lond). 2012;36:843–54.
10. Derosa G, Maffioli P. Anti-obesity drugs: a review about their effects and their safety. Expert Opin Drug Saf. 2012;11:459–71.
11. Gallwitz B. Anorexigenic effects of GLP-1 and its analogues. Handb Exp Pharmacol. 2012;209:185–207.
12. O'Neil P, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, Raether B, Anderson CM, Shanahan WR. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring, Md). 2012; 20: 1426–36.
13. Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, Anderson CM, 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;96:3067–77.
14. Eisai Inc. Belviq (lorcaserin hydrochloride) tablets, for oral use. 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022529lbl.pdf. Accessed 11 Dec 2012.
15. Coleman E. FDA briefing document. 2012. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022529Orig1s000SumR.pdf. Accessed 11 Dec 2012.
16. Cameron F, Whiteside G, McKeage K. Phentermine and topiramate extended release (Qsymia™): first global approval. Drugs. 2012;72(15):2033–42.
17. Hoy SM. Locaserin: a review of its use in chronic weight management. Drugs. 2013;73(5). doi:10.1007/s40265-013-0035-1.
18. Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, Bays H, Shanahan WR, Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med. 2010;363(3):245–56.