Antiobesity Pharmacotherapy for Patients with Type 2 Diabetes: Focus on Long-Term Management

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Type 2 diabetes and obesity have a complex relationship; obesity is linked to insulin resistance, the precursor to type 2 diabetes. The management of obesity is an important method to delay onset of diabetes and improve the glycemic durability of antidiabetic agents. However, insulin and some of the oral hypoglycemic agents used to treat diabetes cause significant weight gain, and it is difficult for patients with diabetes to reduce and maintain their weight by life-style changes alone. Thus, antiobesity medications or bariatric surgery may be a necessary adjunct for certain obese patients with diabetes. In 2012, the U.S. Food and Drug Administration (FDA) approved lorcaserin and phentermine/topiramate extended-release for the management of chronic weight, and approval for naltrexone/bupropion sustained-release as an adjunct to exercise and reduced caloric intake followed in 2014. Liraglutide is pending FDA approval for antiobesity drug. Here we review the efficacy of approved and new promising drugs for the management of obesity.

Keywords: Obesity; Drug therapy; Diabetes

INTRODUCTION

The proportion of individuals with obesity and type 2 diabetes has increased rapidly worldwide [1]. Several epidemiological studies have confirmed the close relationship between diabetes and obesity [2,3]; more than 80% of patients with type 2 diabetes are estimated to be overweight or obese [4]. As the prevalence of obesity increases, the risk of type 2 diabetes is likely to increase [5]. Between 1980 and 1990, the majority of Korean patients with diabetes were nonobese; however, as the prevalence of obesity has increased in Korea, the majority of patients with diabetes are now obese. According to the Diabetes Fact Sheet in Korea 2012, the prevalence of type 2 diabetes was 10.1% in 2010, and 75% of diabetic patients were overweight or obese (i.e., a mean body mass index [BMI] of 25.2 kg/m²).

Type 2 diabetes and obesity have a complex relationship, and obesity is linked to insulin resistance, the precursor to type 2 diabetes [2,3]. Obese adults are at increased risk of several chronic diseases, including cardiovascular disease, stroke, cancer, and type 2 diabetes [6-8]. Furthermore, the risk of death is increased 20% to 40% in overweight adults and 2- to 3-fold in obese compared with normal weight adults [9]. Thus, treatment of obesity is crucial for the prevention of several health problems and for delayed onset of diabetes.

The management of obese patients with diabetes must include significant and sustained weight loss [10]. Moreover, weight reduction may affect the incidence of diabetes. Accord-
ing to the Diabetes Prevention Program study [11], every kilogram of weight loss is correlated with a 16% reduction in the development of type 2 diabetes. Moderate weight reduction in obese patients with type 2 diabetes is associated with a decrease in insulin resistance, improved glycemic parameters, and reductions in diabetic complications and several cardiovascular disease-related risk factors [12]. The Action for Health Diabetes (Look AHEAD) study found that an 8.6% weight loss together with intensive lifestyle intervention was associated with significant improvements in cardiovascular risk factors in 5,145 overweight or obese participants with type 2 diabetes [13,14].

It is difficult for patients with diabetes to reduce and maintain their weight with lifestyle changes alone. Several oral hypoglycemic agents used to treat diabetes, such as sulfonylureas, glinides, and thiazolidinediones, and insulin are associated with significant weight gain that may impair metabolic conditions [15]. Thus, alternative antiobesity medications or bariatric surgery may be a necessary adjunct for obese patients with diabetes. Several placebo-controlled studies have shown that various medications help promote weight loss in obese patients with type 2 diabetes.

The focus of our review is antiobesity medications for the long-term treatment of obese patients with type 2 diabetes.

FDA-APPROVED MEDICATIONS FOR LONG-TERM TREATMENT OF OBESITY

The US Food and Drug Administration (FDA) approved the following drugs for use in adults with a BMI ≥30 (obese) or ≥27 (overweight) who had at least one weight-related condition such as type 2 diabetes, hypertension, or dyslipidemia.

Orlistat
Orlistat is a gastrointestinal lipase inhibitor that reduces the absorption of dietary fat. The recommended dose is 120 mg three times daily before meals. A lower dose (60 mg) is available as an over-the-counter preparation in the United States. One- and 2-year studies evaluating orlistat treatment for obesity have shown significant improvements in glycemic control and in blood pressure and lipid profiles [16]. In a large 4-year prospective study of 3,305 participants with BMI of ≥30 kg/m² and normal or impaired glucose tolerance (the Xenical in the Prevention of Diabetes in Obese subjects study), the orlistat-treated group exhibited significant mean weight loss (5.8 kg vs. 3.0 kg in the placebo group; \( P<0.001 \)) and reduced progression to type 2 diabetes (risk reduction of 37.3% in the orlistat group; \( P=0.0032 \)) [17]. A Korean study in which patients were administered orlistat for 24 weeks reported a modest but significant mean weight loss of –2.73 kg (mean weight change, –3.50%±0.38%) and significant improvements in lipid profiles, fasting insulin, waist circumference, blood pressure, fasting plasma glucose (–10.41±4.62 mg/dL), and glycosylated hemoglobin (HbA1c, –0.87%) [18].

The most common adverse effects of orlistat include flatus with discharge and oily spotting or fecal urgency, and the drug interferes with the absorption of fat-soluble vitamins, although not tremendously [17,19]. Thus, subjects receiving orlistat are instructed to take vitamin supplements.

Lorcaserin
Lorcaserin is a selective serotonin 2C (5-HT2C) receptor agonist that suppresses appetite via stimulation of melanocortin receptor 4. The drug has low affinity for the 5-HT2B receptor, which is associated with the development of valvular heart disease and the cause of the withdrawal of agents such as dexfenfluramine [20].

In 2012, the FDA approved lorcaserin 10 mg twice daily based on the findings of the pivotal randomized, placebo-controlled trials: Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM), Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM), and BLOOM-diabetes mellitus (BLOOM-DM) [21-23]. The BLOOM and BLOSSOM trials investigated the effect of lorcaserin on overweight or obese nondiabetic patients and found a ~3% placebo-corrected weight change in the group treated with lorcaserin (20 mg/day) (BLOOM, –3.6%; BLOSSOM, –2.9%; both \( P<0.05 \)). Moreover, a significantly higher proportion of patients in the lorcaserin group lost ≥5% of their baseline body weight compared with the placebo group (approximately 47% vs. 20%, respectively in the BLOOM; 47% vs. 25%, respectively in the BLOSSOM trials). Furthermore, improvements in fasting glucose and triglyceride levels and blood pressure were observed in the lorcaserin groups.

The BLOOM-DM study included 604 overweight and obese patients with type 2 diabetes who were treated with metformin and/or sulfonylurea and randomized to lorcaserin 10 or 20 mg/day or placebo groups for 52 weeks [23]. Consistent with the results of the BLOOM and BLOSSOM trials, the lorcaserin-treated groups achieved weight losses of –3.4% (10 mg) and –3.1% (20 mg). A significantly higher proportion of patients
in the lorcaserin groups lost ≥5% of their initial body weight (10 mg, 44.7%; 20 mg, 37.5%) compared with patients administered placebo (16.1%). The reduction in mean HbA1c was significantly greater in the lorcaserin-treated groups than in the placebo group (10 mg, −1.0% change from baseline; 20 mg, −0.9% change; and placebo, −0.4% change; P<0.001). A significantly higher proportion of patients in the lorcaserin groups achieved HbA1c ≤7% compared with patients treated with placebo (10 mg, 52.2%; 20 mg, 50.4%; and placebo, 26.3%). However, symptomatic hypoglycemia was more frequent in the lorcaserin groups (10 mg, 10.5%; 20 mg, 7.4%) than in the placebo group (6.3%).

The adverse events associated with lorcaserin include headache, dizziness, fatigue, nausea, dry-mouth, and constipation. No statistically significant difference in the occurrence of FDA-defined valvular disease was found between the lorcaserin and placebo groups. However, the postmarketing trials were required to evaluate the long-term cardiovascular effects of lorcaserin.

**Phentermine/topiramate extended-release**

Phentermine/Topiramate (PT) extended-release (ER) is a combination of the FDA-approved medications phentermine and topiramate in an ER formulation. Phentermine is indicated for short-term weight loss in overweight or obese adults who exercise and eat a reduced calorie diet. Topiramate is indicated for the treatment of certain types of seizures in people who have epilepsy and to prevent migraine headaches. The weight loss effect of phentermine is mediated by catecholamine release in the hypothalamus. The exact mechanism underlying the weight loss action of topiramate is not known; however, it may be associated with a combination of features such as an effect on sodium channels, enhancement of GABA-activated chloride channels, and inhibition of carbonic anhydrase isoenzymes [24]. The recommended daily dose of PT is 7.5 mg phentermine/46 mg topiramate ER. PT is available at a higher dose (15 mg phentermine/92 mg topiramate ER) for select patients. Discontinuation or an increase in dosage is recommended for patients who have not lost 3% of their baseline weight. Treatment should be discontinued if a weight loss >5% of baseline is not achieved with 15/92 mg per day.

FDA approval of PT was based on three phase III clinical trials performed to evaluate the efficacy of the drug (EQUIP, CONQUER, SEQUEL) [25-27]. In the EQUIP trial, 1,276 obese adults without diabetes were assigned randomly to a low- (3.75/23 mg/day) or high- (15/92 mg/day) dose PT or placebo group for 56 weeks. At the conclusion of the study, the patients in the low- and high-dose PT and placebo groups lost 5.1%, 10.9%, and 1.6% of their baseline body weight, respectively (P<0.0001). Moreover, the results revealed improvements in waist circumference, triglyceride levels, and blood pressure.

The CONQUER trial included 2,487 overweight and obese patients with two or more weight-related comorbidities such as hypertension, prediabetes, type 2 diabetes, dyslipidemia, and abdominal adiposity. The participants were assigned to PT (7.5/46 or 15/92 mg) or placebo groups for 56 weeks. At the conclusion of the trial, the subjects in the 7.5/46 mg group achieved a −8.1 kg change in body weight (mean change −7.8%), those in the 15/92 mg group a −10.2 kg change (mean change −9.8%), and those in the placebo group a −1.4 kg change (mean change −1.2%). A higher percentage of subjects in the PT groups achieved a ≥5% weight loss after 1 year compared with those receiving placebo (62%, 70%, and 21% in the 7.5/46, 15/92 mg, and placebo groups, respectively; P<0.001 for both groups vs. placebo). Moreover, weight loss was maintained for a second year in the SEQUEL trial, a 52-week extension of the CONQUER trial. The CONQUER trial revealed an overall significant improvement in HbA1c (% change from baseline: 0%, −0.1%, and 0.1% in the 7.5/46, 15/92 mg, and placebo groups, respectively; P<0.0001 for both groups vs. placebo) and in fasting glucose levels (% change from baseline: −0.01%, −0.07%, and 0.13% in the 7.5/46, 15/92 mg, and placebo groups, respectively; P=0.0047 for 7.5/46 mg vs. placebo and P<0.0001 for 15/92 mg vs. placebo) at week 56. The progression to type 2 diabetes among participants without diabetes was lower in the PT-treated patients (2.8% in the 7.5/46 mg and 1.7% in the 15/92 mg) compared with those receiving placebo (3.6%). The relative risk of type 2 diabetes versus placebo was 0.78 (95% confidence interval [CI], 0.40 to 1.50) for the 7.5/46 mg and 0.47 (95% CI, 0.25 to 0.88) for the 15/92 mg doses of PT.

An improvement in glycemic control was observed in the SEQUEL trial. At the conclusion of the trial (108 weeks), fasting glucose levels were significantly reduced from baseline in the 15/92 mg dose group (the least-squared change in fasting glucose was 0.1 in the 7.5/46 mg, −1.2 in the 15/92 mg, and 3.7 in the placebo groups; P=0.0048 for 15/92 mg vs. placebo).

In the participants without type 2 diabetes at baseline, the progression of type 2 diabetes decreased during the 1-year extension. The annualized incidence rates for progression to type 2 diabetes were 0.9%, 1.7%, and 3.7% in the 7.5/46, 15/92
mg, and placebo groups, respectively, among the study participants without diabetes at baseline. These results revealed a 54% reduction in the progression to type 2 diabetes in the low-dose (7.5/46 mg) and a 76% reduction in the high-dose (15/92 mg) groups compared with the placebo group [28]. Among participants with type 2 diabetes at baseline, HbA1c did not change markedly from baseline in the placebo group (0%), whereas treatment with 7.5/46 and 15/92 mg PT led to 0.4% and 0.2% reductions in HbA1c, respectively. However, the results of the SEQUEL trial should be interpreted with caution because, as an extension of the CONQUER trial, it may be subject to selection bias.

Common drug-related side effects include paresthesias, nausea, dizziness, constipation, and dry mouth. The reported neuropsychiatric adverse events include depression, anxiety, insomnia, and disturbances in attention. PT is contraindicated in pregnancy because of concerns about the teratogenicity of topiramate. Furthermore, PT may increase heart rate by two beats per minute; however, the FDA judged that the potential risk posed by an elevated heartbeat was outweighed by improvements in cardiovascular risk factors such as blood pressure [29].

Naltrexone/bupropion sustained-release
In September 2014, the FDA approved Naltrexone/bupropion (NB) sustained-release (SR) tablets as a treatment option for chronic weight management. Naltrexone was approved previously to treat alcohol and opioid dependence, and bupropion was approved for the treatment of depression or as an aid for smoking cessation. Naltrexone is an opioid receptor antagonist, and bupropion acts on adrenergic and dopaminergic receptors in the hypothalamus. Bupropion reduces energy intake and increases expenditure through neuronal effects. The combining of bupropion and naltrexone was based on the theory that naltrexone may block the compensatory mechanisms associated with bupropion that prevent sustained weight loss.

The efficacy of NB was evaluated by the Contrave Obesity Research (COR) program consisting of the COR-I, COR-II, COR trial with intensive behavior modification (COR-BMOD), and COR-Diabetes trials (Table 1) [30-33]. The COR-I, COR-II, and COR-BMOD trials evaluated overweight/obese patients without diabetes. Following treatment for 1 year, the group receiving naltrexone 32 mg/bupropion 360 mg lost 4 to 5 kg (approximately −4% weight loss from baseline body weight) more than the placebo group, and 48% to 66% of the patients in the NB group lost ≥5% of their baseline body weight.

The COR-Diabetes trial evaluated the safety and efficacy of NB in 505 overweight or obese patients with type 2 diabetes over a 56-week period [34]. Participants were assigned to the naltrexone 32 mg SR/bupropion 360 mg SR or placebo group. Compared with the placebo group, the patients treated with NB lost significantly more weight (−5.0% vs. −1.8%; P < 0.001), and a higher proportion lost ≥5% of their body weight (44.5% vs. 18.9%; P < 0.001). Furthermore, baseline HbA1c was significantly reduced in the patients receiving NB compared with the placebo group (−0.6% vs. −0.1%, respectively; P < 0.001), and 44.1% of patients receiving NB achieved <7% HbA1c compared with 26.3% in the placebo group (P < 0.001). The incidence of hypoglycemia did not differ between groups. The cardiovascular safety of naltrexone 32 mg SR/bupropion 360 mg SR is currently under investigation (Clinical trial reg No. NCT01601704, clinicaltrials.gov).

The most common adverse events include nausea, constipation or diarrhea, headache, vomiting, dizziness, insomnia, and dry mouth. The NB provides a boxed warning to alert users to the increased risk of suicidal thoughts and behaviors associated with bupropion. The NB has a dose-related risk of seizures and may elevate blood pressure and heart rate.

Liraglutide
Liraglutide is a human glucagon-like peptide 1 analog that may be administered once a day because of its prolonged half-life of 13 hours [35]. Liraglutide was developed to improve glycemic control in patients with type 2 diabetes. The efficacy of the drug was well established in the Liraglutide Effect and Action in Diabetes (LEAD) studies, a series of phase III randomized, controlled trials [36,37]. The approved doses for the treatment of diabetes are 1.2 and 1.8 mg in the United States and 0.6 and 0.9 mg in Japan [38]. The LEAD-3 trial comprised 746 patients with type 2 diabetes assigned to liraglutide (1.2 or 1.8 mg) or glimepiride (8 mg) treatment groups for 52 weeks [36]. The HbA1c reductions from baseline were −0.84% and −1.14% in the 1.2 and 1.8 mg groups, respectively, and body weight was reduced by −2.05 kg from baseline in the 1.2 mg group and −2.45 kg in the 1.8 mg group, whereas a significant weight gain (1.12 kg) was observed in patients treated with glimepiride. A consistent reduction in body weight was observed across the LEAD trials.

Liraglutide is pending FDA approval for the treatment of obesity. The recommend dose is 3 mg in contrast to 1.2 or 1.8 mg for diabetes. The Satiety and Clinical Adiposity-Liraglu-
tide Evidence in Nondiabetic and Diabetic Subjects (SCALE) trial consists of four clinical trials designed to demonstrate the safety and efficacy of liraglutide 3 mg for weight management. The SCALE Obesity and Prediabetes phase IIIa trial involving 3,731 patients found that patients treated with liraglutide lost an average of 8% of their body weight in 56 weeks compared with 2.6% in the placebo group. Moreover, significantly more patients in the liraglutide group lost ≥5% of their baseline body weight compared with those taking the placebo (63.5% vs. 26.6%, respectively), and 32.8% of the liraglutide group lost >10% of their baseline body weight (10.1% in the placebo group).

The SCALE-Diabetes trial was a 56-week randomized, placebo-controlled trial designed to investigate the potential of liraglutide 3 mg in obese or overweight patients with type 2 diabetes. In this trial, 846 overweight or obese patients with diabetes were assigned randomly to liraglutide 3 mg or 1.8 mg or placebo groups. After 56 weeks, the 3 and 1.8 mg liraglutide groups achieved weight loses of 6% and 5%, respectively, compared with 2% in the placebo group. Furthermore, 50% of the patients in the 3 mg group and 35% of those in the 1.8 mg group achieved ≥5% weight loss compared with 13% in the placebo group, and approximately 69% of the patients treated with liraglutide 3 mg achieved the HbA1c target of <7% (Clinical trial reg No. NCT01272232, clinicaltrials.gov).

Concerned by the lack of long-term data for liraglutide in the treatment of obesity and a variety of safety issues, such as gallbladder disease, pancreatitis, breast and thyroid cancers, and increased heart rate, the FDA advisory panel recommended that these issues be addressed in postmarketing studies. However, the panel agreed that the ongoing cardiovascular outcomes trial of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results study would be sufficient to characterize the cardiovascular risk of the liraglutide.

CONCLUSIONS

It is clear that weight management is essential for obese patients with diabetes. Exercise and monitoring food intake are
important components of a weight loss regime; however, it is difficult for patients to reduce and maintain their weight by lifestyle changes alone; thus, safe and effective long-term antiobesity drugs may be a necessary adjunct to lifestyle modification. The five drugs currently approved or pending FDA approval for long-term treatment of obesity are orlistat, lorcaserin, PT, NB, and liraglutide (Table 2). These medications have been shown to reduce weight by 5% to 10%, improve glycemic profiles significantly, and reduce cardiovascular risk in patients with diabetes. However, possible adverse events should be monitored, and these medications must be considered as part of a comprehensive management regime for obese patients with diabetes. Further study of neuropeptide-Y, β3-adrenergic receptors, oxyntomodulin, and amylin analogues are warranted for the development of future antiobesity medications.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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