The Role of Anti-obesity Drugs in Patients with Type 2 Diabetes

Priscilla Hollander, MD, PhD

Medical Director, Ruth Collins Diabetes Center, Baylor University Medical Center, Dallas, Texas, US

Abstract

The prevalence of diabetes continues to rise, following the rising rates of obesity. Obesity is not only associated with an increased risk for developing type 2 diabetes but also an elevated probability of developing long-term complications associated with the disease. Weight gain is also an important concern as a potential side effect of therapies that improve glycemic control in diabetes, including insulin therapy. As a result, patients with type 2 diabetes are at risk for a vicious circle of increasing weight and increasing insulin resistance, thus requiring further intensification of glycemic treatment. It is therefore important to address the problem of obesity in patients with type 2 diabetes. In 2012, the US Food and Drug Administration (FDA) approved two new anti-obesity medications: lorcaserin and phentermine/topiramate extended-release. Both agents have demonstrated clinically meaningful weight reduction as well as significant improvements in glycemic control in obese patients with diabetes. Liraglutide has also shown weight loss and improvements in glycemic control in patients with diabetes. Anti-obesity drugs, in conjunction with lifestyle changes, may play a valuable role in the management of diabetes.

Keywords

Diabetes, liraglutide, lorcaserin, obesity, phentermine/topiramate extended-release

Disclosure: Priscilla Hollander, MD, PhD, has been a member of advisory boards for Genentech, Johnson & Johnson, Novo Nordisk, and Merck.
Acknowledgments: Editorial assistance was provided by Katrina Mountfort, PhD, at Touch Medical Media.
Received: November 18, 2013 **Accepted**: December 2, 2013 **Citation**: *US Endocrinology* 2013;9(2):101–7 *DOI: 10.17925/USE.2013.09.02.101*
Correspondence: Priscilla Hollander, MD, PhD, Baylor Endocrine Center, 3600 Gaston Ave, Dallas, TX 75246, US. E: priscilh@baylorhealth.edu

Support: The publication of this article was supported by Eisai. The views and opinions expressed are those of the author and not necessarily those of Eisai.

The prevalence of overweight and obesity among patients with type 2 diabetes is extremely high. Data from two national surveys indicate that 28 % of individuals with diabetes were overweight and 59 % were obese.[1] Furthermore, a rise in body mass index (BMI) is directly correlated to an increased risk for diabetes.[2–4] The prevalence of type 2 diabetes is three to seven times higher in obese adults than in those of normal weight, and adults with a BMI >35 kg/m^2 are 20 times more likely to develop diabetes than those with a BMI between 18.5 and 24.9 kg/m^2.[5,6] Prediabetes and the metabolic syndrome are also associated with obesity.[7] Obesity is not only associated with an increased risk for developing type 2 diabetes but also an elevated probability of developing microvascular,[8] neuropathic,[8,9] and cardiovascular[10,11] complications associated with the disease.

The incidence of type 2 diabetes has risen in parallel with the global increase in obesity, which can be illustrated by examining US data (see *Figure 1*). The prevalence of obesity is leveling out in the US population, but the prevalence of diabetes is rising. The presence of diabetes parallels the prevalence of obesity, but follows obesity by about 10 years.[12] This has important health and economic implications. The total number of people with diabetes worldwide is projected to rise from 366 million in 2012 to 552 million in 2030.[13] Projections also suggest that there will be 65 million more obese adults in the US by 2030, resulting in an additional 6–8.5 million cases of diabetes.[14] Obesity is also associated with elevated risk for long-term complications, such as cardiovascular disease (CVD), in people with type 2 diabetes.[15] Strategies to combat the increasing incidence of diabetes should therefore also focus on the obesity epidemic.

The transition from obesity to type 2 diabetes is characterized by a progressive deficiency in insulin secretion accompanied by a rise in insulin resistance.[16] Numerous mechanisms underlie these changes, including adipose tissue dysfunction, which results in impaired insulin sensitivity in adipocytes[17] and secretion of numerous factors that are involved in the development of insulin resistance, such as non-esterified or free fatty acids (FFAs), glycerol, hormones, and pro-inflammatory cytokines.[18] Chronic elevations in FFAs have also been implicated as a causative factor in pancreatic β-cell dysfunction.[19] This article aims to consider the role of pharmacologic therapies to control obesity in individuals with type 2 diabetes.

Effect of Type 2 Diabetes Therapy on Bodyweight

The current treatment goal in type 2 diabetes is to achieve the best possible glycemic control, since intensive glycemic control has been associated with a substantially decreased risk for microvascular complications.[20] Clinical evidence has also suggested a beneficial role for glycemic control on CVD, depending on patient characteristics, including age, diabetes duration, previous glucose control, and risk for hypoglycemia.[21] CVD is the major cause of death in patients with type 2 diabetes; more than 60 % of patients die of myocardial infarction (MI) or stroke.[22]

Table 1: Effect of Anti-diabetic Medications on Weight

Medication Class	Examples	Effect on Weight	Reference
Insulin	Insulin glargine, detemir	Most associated with weight gain, insulin detemir less so	20, 31
Thiazolidinediones	Pioglitazone	Weight gain often occurs but is not inevitable. Favorable shift in fat distribution from visceral to subcutaneous adipose depots	25
Sulfonylureas	Glyburide, glipizide, glimepiride	Mixed data though some studies have made associations with weight gain	28
Meglitinides	Repaglinide, nateglinide, mitiglinide	Weight gain of up to 3 kg in 3 months reported	29
Alpha-glucosidase inhibitors	Acarbose, miglitol, voglibose	No clinically relevant effect on bodyweight	32
Bile acid sequestrants	Colesevelam	No effect on bodyweight	34
Biguanides	Metformin	Some beneficial effects on weight/weight neutral	35–37
GLP-1 agonists	Exenatide, liraglutide, lixisenatide	Associated with modest weight loss	38
DPP-IV inhibitors	Sitagliptin, vildagliptin, saxagliptin, linagliptin	Neutral effects on bodyweight	33
SGLT-2 inhibitors	Dapagliflozin, canagliflozin	Associated with reduction in bodyweight	42

DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; SGLT-2 = sodium-glucose co-transporter 2.

Table 2: US Food and Drug Administration-approved Anti-obesity Medication—Clinical Data in Patients with Type 2 Diabetes and Obesity

Agent	Impact on Weight	Adverse Events	Reference
Orlistat	In a 1-year, multicenter RCT, patients with type 2 diabetes on metformin were given orlistat or metformin Orlistat-treated patients lost significantly more weight at 1 year compared with placebo (4.7 ± 0.3 kg versus 1.8 ± 0.3 kg, respectively)	Intestinal cramps, flatus, fecal incontinence, oily spotting, and flatus with discharge in up to a third of patients	68
PHEN/TPM ER	Sustained 2-year weight reduction of 6.8 % (7.5/46 mg) to 8.8 % (15/92 mg) was reported in the diabetic population versus 1.9 % in the placebo group	Paresthesia (14–21 %), constipation (15–17 %), dizziness (7–10 %), dysgeusia, depression-related and anxiety-related symptoms in 5–10 %	76
Lorcaserin	Results at 1 year showed that more patients lost ≥ 5 % bodyweight with lorcaserin BID (37.5 %; p<0.001) or lorcaserin QD (44.7 %; p<0.001) versus placebo (16.1 %). Mean (± SEM) weight reduction was 4.5 ± 0.35 % with lorcaserin BID and 5.0 ± 0.5 % with lorcaserin QD versus 1.5 ± 0.36 % with placebo (p<0.001 for each)	Headache (14.5–16.8 %), back pain (8.4–11.7 %), nasopharyngitis (11.3–23.2 %), and nausea, urinary tract infection, cough, fatigue, gastroenteritis, and dizziness in 5–10 %	74

BID = twice a day; PHEN/TPM ER = phentermine/topiramate extended-release; QD = daily; RCT = randomized controlled trial; SEM = standard error of the mean.

The American Diabetes Association (ADA) guidelines currently recommend a glycemic goal of glycated hemoglobin (HbA_{1c}) <7.0 %.[23] However, they recommend that glucose goals should be individualized for patient depending on various risk factors. Glycemic goals present a challenge to the obese patient with diabetes, as improvement in glycemic control has been linked to weight gain due to the reduction in glycosuria associated with diabetes therapy.[24] Weight gain has been associated with both insulin and oral anti-diabetic therapies (see *Table 1*).[20,25–29] As diabetes progresses, increasing β-cell dysfunction and insulin resistance necessitate the administration of higher dosages of insulin, or the addition of insulin to pharmacologic regimes that promote weight gain. A vicious circle may ensue. Strategies to overcome insulin-associated weight gain include increasing insulin sensitivity through diet and exercise, enabling dose reductions, or by the use of co-medications, such as pramlintide or metformin.[30] Newer, long-lasting basal insulin analogs, such as insulin detemir, are associated with lower levels of weight gain compared with shorter-acting insulin formulations.[31]

Most oral anti-diabetic agents have been associated either with weight gain (thiazolidinediones,[25] sulfonylureas,[28] meglitinides[29]) or are weight-neutral (alpha-glucosidase inhibitors;[32] dipeptidyl peptidase-IV inhibitors,[33] bile acid sequestrants[34]). Metformin has been associated with beneficial effects on weight in type 2 diabetes,[35,36] although a Cochrane review concluded that it is weight-neutral.[37] Modest weight loss has consistently been observed in clinical studies of glucagon-like peptide 1 (GLP-1) agonists in type 2 diabetes.[38] The addition of GLP-1 agonists to insulin therapy in obese patients with diabetes improves both glycemic control and weight.[39] The beneficial effect on weight is thought to be mediated by central regulation of feeding[40] and delayed gastric emptying, promoting early satiety.[41] Sodium-glucose co-transporter 2 (SGLT2) inhibitors, the newest class of diabetic medications, have also been associated with favorable effects on bodyweight,[42] resulting from an initial osmotic diuresis, and in the long term from increased urinary excretion of glucose.[43]

Impact of Treating Obesity in Diabetes

Numerous studies have demonstrated that weight loss in patients with diabetes results in improvement in glycemic control.[44,45] Moderate weight loss (5 % of bodyweight) can improve insulin action, decrease fasting blood glucose concentrations, and reduce the need for diabetes medications,[46] as well as preventing or delaying the development of type 2 diabetes in those with risk factors for the disease, such as impaired glucose tolerance.[47] In a 4-year, double-blind, prospective study, 3,305 patients were randomized to lifestyle changes plus either an anti-obesity drug (orlistat 120 mg) or placebo. Compared with lifestyle changes alone, orlistat plus lifestyle changes resulted in a greater reduction in the incidence of type 2 diabetes over 4 years and produced greater weight

loss in a clinically representative obese population.[48] There is therefore a strong rationale for the use of anti-obesity drugs in overweight and obese patients with type 2 diabetes.

Anti-obesity Treatment Options in Diabetes

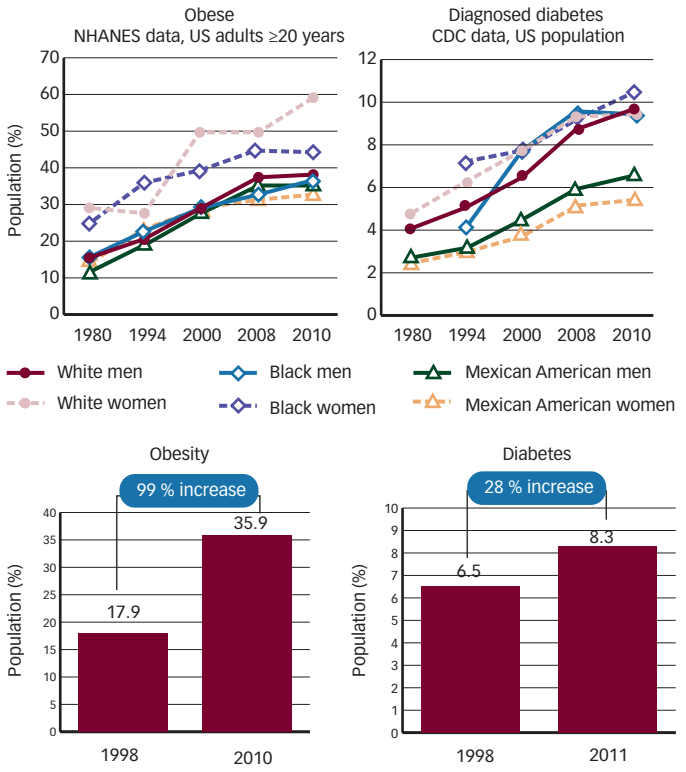
Lifestyle interventions should be undertaken before initiating drug therapy in obese patients with diabetes. These should include reductions in caloric intake of 500–1,000 calories per day, increases in physical activity, and changes in health behavior. Lifestyle interventions have proved successful in the prevention of diabetes,[47,49] as well as in achieving weight loss in patients with type 2 diabetes. The Look AHEAD trial randomly assigned 5,145 overweight or obese patients with type 2 diabetes to participate in an intensive lifestyle intervention or to receive diabetes support and education. After a median follow-up of 9.6 years, weight loss was greater in the intervention group than in the control group throughout the study (8.6 % versus 0.7 % at 1 year; 6.0 % versus 3.5 % at study end). The intensive lifestyle intervention also produced greater reductions in HbA_{1c}. However, the trial was stopped early for futility after failing to meet its primary endpoint of reduction in the rate of cardiovascular events.[50]

Although many lifestyle interventions may result in short-term weight loss, most are associated with poor long-term compliance and weight regain. In daily life settings, the implementation of lifestyle interventions is more difficult than in clinical studies. Long-term success with lifestyle modification for weight loss in diabetes is often poor: a systematic review of dietary interventions in obesity between 1931 and 1999 found a median success rate of 15 % in either maintaining all weight loss initially achieved or at least 9–11 kg of initial weight loss.[51] A Cochrane review concluded that lifestyle measures are effective but limited at producing sustained weight loss in patients with type 2 diabetes.[52]

Bariatric surgery is an effective treatment for obesity in the prevention[53] and management of diabetes, and has resulted in rapid improvements in glycemic parameters[54,55] but is associated with a risk for postoperative complications, including death, as well as being expensive and requiring specialist facilities. It is therefore unlikely to become a first-line treatment strategy for the majority of patients with diabetes and obesity. The ADA[23] and International Diabetes Federation[56] recommend that bariatric surgery should be considered in patients with type 2 diabetes with a BMI ≥35 kg/m^2. Recent recommendations from the American Society of Bariatric Physicians also suggest that it may be considered for patients with BMI ≥30 kg/m^2 with one or more adverse health consequences due to excessive body fat.[57]

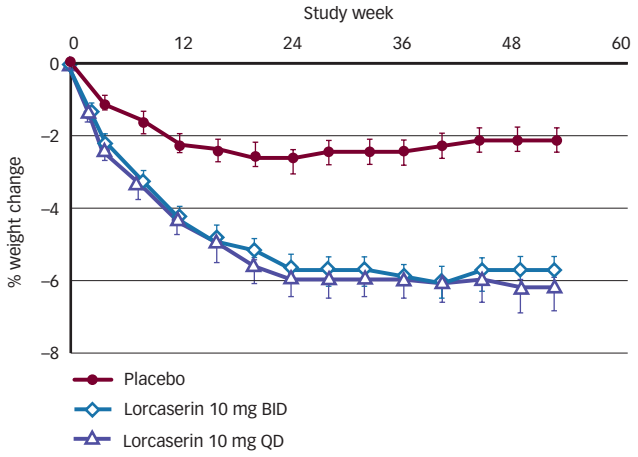
Both the American College of Physicians and the American Society of Bariatric Physicians recommend that drug therapy is part of an overall strategy for managing overweight and obesity, which should include appropriate recommendations for diet, physical activity, and behavior therapy.[57,58] Anti-obesity medications have been successfully employed in the management of obese patients with diabetes.[59] However, obesity is a complex disorder, and there is broad variability in the weight-loss response to all therapies for obesity including surgery, lifestyle interventions, and pharmacotherapy. Genome-wide association studies have identified numerous associated genes,[60,61] suggesting that multiple mechanisms are involved in obesity. Furthermore, inflammation plays a major role in obesity. Studies have identified an imbalance between the levels of proinflammatory cytokines, such as interleukins and tumor necrosis factors, and the levels of anti-inflammatory cytokines.[62,63] It is therefore unlikely that a single drug will be effective in all cases and there is a need for a range of anti-obesity therapies with differing mechanisms of action.

Figure 1: The Increase in Diabetes Parallels the Increase in Obesity in the US



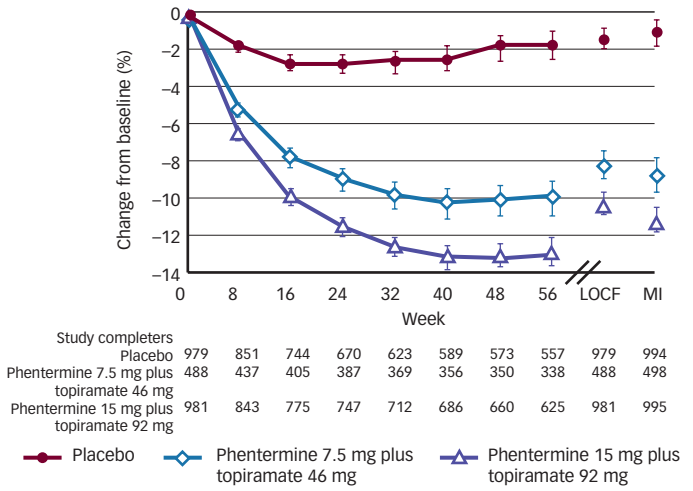
Sources: Flegal 1998,[97] Flegal 2002,[98] Flegal 2010,[99] Flegal 2012,[100] Harris 1998,[101] Centers for Disease Control and Prevention (CDC),[102,103] Mokdad 2000,[104] and Mokdad 1999.[105] NHANES = National Health and Nutrition Examination Survey.

Figure 2: Bodyweight Change in Patients with Type 2 Diabetes—The BLOOM-DM Study



Percent change in bodyweight from baseline to each study visit in those who completed the study. Values are mean ± standard error of the mean. BID = twice daily; QD = once daily. Source: O'Neill et al., 2012.[74]

Figure 3: Effect of Phentermine/Topiramate Extended-release on Bodyweight in the CONQUER Trial



LOCF = last observation carried forward; MI = multiple imputation. Source: Gadde et al. 2011.[76]

Throughout the past decade, many medications have been introduced and approved by the US Food and Drug Administration (FDA) for the treatment of obesity. However, most of them have subsequently been withdrawn following the postmarketing discovery of serious adverse events (AEs). The anti-obesity drug rimonabant showed clinically meaningful reductions in HbA_{1c} in obese patients with type 2 diabetes as an adjunct to oral anti-diabetic therapy,[64] as monotherapy,[65] and in insulin-treated individuals.[66] However, its use was suspended because of an associated risk for psychiatric problems. Silbutramine was withdrawn in 2010 due to cardiovascular risks, phenylpropanolamine was withdrawn in 2000 due to risk for hemorrhagic stroke and fenfluramine and dexfenfluramine were withdrawn after reports of valvular heart damage and primary pulmonary hypertension in 1997.

Prior to 2012, orlistat, (Xenical®, Roche) an inhibitor of pancreatic lipase, was the only weight-loss drug approved by the FDA for long-term use. Orlistat is associated with moderate weight loss[48] and confers additional HbA_{1c} reductions of 0.3–0.5 % at 1 year when given in combination with oral anti-diabetic drugs[67,68] or insulin,[69] but is associated with gastrointestinal side effects in up to a third of patients including intestinal cramps, flatus, fecal incontinence, oily spotting, and flatus with discharge.[67] More recently, rare cases of serious liver injury have been reported.[70] Cetilistat, a highly lipophilic benzoxazinone that inhibits lipases with a similar action to orlistat, is in clinical development in Japan. In a phase II study, it demonstrated significantly reduced bodyweight and improved glycemic control relative to placebo in obese patients with diabetes, with fewer discontinuations compared with orlistat.[71] Phase III studies have recently completed.

In 2012, the FDA approved two new drugs for chronic weight management in obese or overweight adults with one or more weight-related co-morbidities, to be used in conjunction with a reduced-calorie diet and increased physical activity.[72] Lorcaserin (Belviq®, Arena Pharmaceuticals) is a selective agonist of the serotonin (5-hydroxytryptamine) 2C (5-HT2c) receptor that is associated with the regulation of food intake, and therefore suppresses appetite.[73–75] Phentermine/topiramate extended-release (PHEN/TPM ER, Qsymia®, Vivus) is a fixed-dose combination of phentermine (an anorectic agent), and the anti-epileptic drug topiramate.[76]

Clinical trial data demonstrating the efficacy and safety of the FDA-approved anti-obesity medications in patients with type 2 diabetes is summarized in *Table 2*. Lorcaserin produces clinically meaningful weight reductions in obese individuals as well as improvements of glycemic control. The Behavioral modification and Lorcaserin for Overweight and Obesity Management (BLOOM) phase III clinical trial (n=3,182) showed significant weight reduction as well as nonsignificant reduction of HbA_{1c}.[75] In the Behavioral modification and LOrcaserin Second Study for Obesity Management (BLOSSOM) phase III study (n=4,008), significant weight reduction and statistically insignificant reductions in HbA_{1c} were noted.[73] The BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) clinical trial enrolled 604 patients with a BMI of 27–45 kg/m^2, a diagnosis of type 2 diabetes, and a HbA_{1c} of 7–10 %. Results at 1 year showed that more patients lost ≥5 % bodyweight with lorcaserin twice daily (BID) (37.5 %; p<0.001) or lorcaserin once daily (QD) (44.7 %; p<0.001) compared with placebo (16.1 %). The mean weight reduction was 4.5 % with lorcaserin BID and 5.0 % with lorcaserin QD versus 1.5 % with placebo (p<0.001 for each) (see *Figure 2*). There was a reduction in HbA_{1c} of 0.9 with lorcaserin BID, 1.0 with lorcaserin QD, and 0.4 with placebo (p<0.001 for each); fasting glucose decreased by 27.4 mg/dl, 28.4 mg/dl, and 11.9 mg/dl, respectively (p<0.001 for each).[74,75]

The most common AEs associated with lorcaserin are headache, nausea, dizziness, fatigue, dry mouth, and constipation.[75,77] In the BLOOM-DM study, headache was reported in 14.5 % and 16.8% of the BID and QD lorcaserin groups, respectively; back pain was reported in 11.7 % and 8.4 % of the BID and QD lorcaserin groups, respectively; however, most were mild and self-limiting.[75] Concerns have been expressed in terms of the risk for valvulopathy associated with activation of the serotonin 2B (5-HT2B) receptors on cardiac interstitial cells; an association with valvulopathy resulted in the withdrawal of fenfluramine and dexfenfluramine from the market.[72] However, data from *in vitro* assays indicated that lorcaserin at recommended doses is unlikely to activate the 5-HT2B receptor.[78] Furthermore, among 2,472 patients evaluated at 1 year and 1,127 evaluated at 2 years in the BLOOM study, the rate of cardiac valvulopathy was not increased with the use of lorcaserin.[75] In the BLOOM-DM study, higher rates of valvulopathy were seen in lorcaserin-treated patients (2.5 % on lorcaserin BID; 3.9 % on lorcaserin QD) versus placebo (1.9 %) group; however, this was considered to be due to the unusually low rate of valvulopathy in the placebo group. Prescribing information recommends discontinuation if 5 % weight loss is not achieved by week 12, or if signs or symptoms of valvular heart disease develop.[79]

The Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER) phase III clinical trial of PHEN/TPN ER (n=2,487) randomized patients to placebo, PHEN 7.5 mg/TPM ER 46 mg (7.5/46), or PHEN 15 mg/TPM ER 92 mg (15/92). Significant weight loss was demonstrated in all patient groups (see *Figure 3*). Among the patient population that had type 2 diabetes (16 %), the placebo-subtracted weight loss at 1 year was 4.9 % in the 7.5/46 group and 6.9 % in the 15/92 group.[76]

In the Longer-Term Safety, Efficacy of Phentermine + Topiramate for Weight Reduction Among Overweight or Obese Individuals with Cardiometabolic Disease (SEQUEL) extension study (n=676), a sustained 2-year weight reduction of 9 % was reported in patients with type 2 diabetes compared with 2 % in the placebo group (p=0.0003 for 7.5/46 and p<0.0001 for 15/92).[80] Improvements in glycemic parameters were also noted in the treatment group compared with placebo. In a recently published subanalysis of the SEQUEL study, 475 high-risk overweight or obese patients with prediabetes and/or the metabolic syndrome at baseline were monitored for progression to type 2 diabetes. Patients in the PHEN/TPM 7.5/46 and 15/92 treatment groups experienced reductions of 71 % and 79 % in the annualized incidence rate of type 2 diabetes, respectively, compared with placebo. This was related to degree of weight lost (10.9 % and 12.1 %, respectively versus 2.5 % with placebo; p< 0.0001).[81]

AEs reported in the CONQUER trial included paresthesia (14 % in the 7.5/46 group versus 21 % in the 15/92 group), constipation (15 % in the 7.5/46 group versus 27 % in the 15/92 group), and insomnia, dizziness, dysgeusia, depression-related symptoms, and anxiety-related symptoms in 5–10 %.[76] Safety concerns about PHEN/TPM ER include teratogenicity and elevation in resting heart rate.[82] However, a large population-based cohort study (n=837,795) did not find an increased incidence of birth defects.[83] Other concerns include the risk for metabolic acidosis, glaucoma, and psychiatric and cognitive AEs.[72]

The weight reduction associated with GLP-1 analogs in diabetes has led to studies investigating the efficacy and safety of liraglutide (Victoza®, Novo Nordisk) as an anti-obesity treatment. A 20-week clinical trial (n=564) provided evidence that higher doses of liraglutide than are usually indicated for glycemic control led to significant weight loss and may be used in the treatment of obesity.[84,85] As a result, the Satiety and Clinical Adiposity – Liraglutide Evidence in Non-Diabetic and Diabetic Subjects (SCALE) clinical development program was initiated. One of the phase III clinical trials in this program enrolled 846 patients with type 2 diabetes. Weight reductions of 6 % and 5 % have recently been reported in patients treated with liraglutide 3 mg and liraglutide 1.8 mg after 56 weeks were 6 % and 5 %, respectively, compared with a 2 % weight loss for people treated with placebo. The proportion of people achieving a weight loss of at least 5 % or 10 % was 50 % and 22 % for liraglutide 3 mg, 35 % and 13 % for liraglutide 1.8 mg, and 13 % and 4 % for placebo treatment, respectively.[86]

The safety profile of liraglutide is acceptable; the most common AEs were related to the gastrointestinal system and diminished over time.[86] In 2011, the FDA advisory panel issued a safety warning regarding the risk for thyroid C-cell tumors and pancreatitis with liraglutide,[87] following the discovery that long-term liraglutide exposure is associated with C-cell carcinoma and thyroid C-cell focal hyperplasia in rodents.[88] However, a recent study suggested that GLP1 receptor agonist-induced C-cell responses in rodents may not be relevant to primates.[89] Concern has also been raised about the potential for pancreatitis; however, liraglutide did not induce pancreatitis in mice, rats, or monkeys when dosed for up to 2 years and at exposure levels up to 60 times higher than in humans.[90] Other impediments to the widespread use of liraglutide include its relatively high cost and the fact that it administered by intramuscular injection, reducing its acceptability to patients.

Naltrexone plus buprion (Contrave) is a dopamine and noradrenaline reuptake inhibitor that has not yet been approved. The Contrave Obesity Research (COR) trials assessed the efficacy of naltrexone/buproprion in both patients with and without diabetes.[91,92] Reductions in weight and HbA_{1c} have been reported. The drug was previously rejected by the FDA who, in February 2011, stated that a large-scale study of CV risk would be needed before they could consider approval. The Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects With Cardiovascular Risk Factors (Light) Study is a randomized, double-blind, placebo-controlled cardiovascular outcomes trial evaluating the occurrence of major adverse cardiovascular events in patients participating in the study.[93] Other agents in late-stage clinical development include tensofesine, an inhibitor of the presynaptic uptake of noradrenaline, dopamine, and serotonin[94] Several additional gut hormone-based treatments for obesity are under clinical investigation, including peptide YY, pancreatic polypeptide, amylin, and oxyntomodulin.[95]

It is evident that new anti-obesity medications provide clinically meaningful weight reductions in patients with diabetes with acceptable safety profiles. There is a need for long-term safety data on these medications, in order to dispel fears associated with the safely of anti-obesity medications and increase their clinical utility. An analysis of data from the National Health and Nutritional Examination Survey in 2007–8 found that 45.4 % of the sample population were eligible for anti-obesity treatment. However, among these, only 0.6 % were taking anti-obesity drugs.[96] Reasons for this low usage may include concerns over the limited effectiveness and safety of previously available drugs.

Summary and Concluding Remarks

The twin epidemics of diabetes and obesity continue to rise and intervention is required to prevent a global public health crisis. A large body of clinical data supports the treatment of obesity as a management strategy in type 2 diabetes (see *Figure 1*).[97–105] Lifestyle modification focused on diet and physical activity should be an essential component of weight-management interventions. Anti-obesity medications also play a role in weight management, providing modest additional fat loss to that achieved by lifestyle modification alone, improving quality of life (QoL) and showing improvements in glycemic parameters in patients with type 2 diabetes. However, obesity is a heterogeneous condition: the genetic and pathophysiologic factors underlying obesity are highly variable between individuals and, therefore, the clinical response to anti-obesity medication may also vary. There is therefore a need for need for a variety of drugs with differing mechanisms in the management of obesity in type 2 diabetes in order to achieve individualized and optimized therapy.

The regulatory approval of the pharmacologic treatment of obesity has been characterized by repeated rejections of new agents and the withdrawal of previously approved agents due to serious AEs. The approval of lorcaserin and PHEN/TPM ER by the FDA reflect their favorable benefit: risk profile and may represent recognition of the enormity of the obesity problem and an increasing acceptance of the growing demand for effective and safe medications for the treatment of obesity. Both agents have demonstrated clinically meaningful weight reduction as well as significant improvements in glycemic control of obese patients with diabetes. The submission of liraglutide for FDA approval will hopefully further expand the treatment armamentarium.

It remains to be seen whether the performance of new anti-obesity medications in daily life matches that of controlled clinical settings. The patient's perception of how a new medication affects their QoL is crucial to compliance and ultimately treatment success. The QoL parameters reported in the BLOSSOM, BLOOM, and CONQUER clinical studies suggest that the effect of lorcaserin and PHEN/TRM ER on weight loss correspond to a meaningful improvement in QoL. However, the relatively high dropout rates observed in these trials suggest that compliance may be a limiting factor in day-to-day use of these therapies. Despite these concerns, evidence to date suggests that new anti-obesity medications have been well accepted by patients and, in conjunction with lifestyle modification, offer an effective alternative to bariatric surgery in patients with type 2 diabetes. ■

1. Bays HE, Chapman RH, Grandy S, et al., The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys, *Int J Clin Pract*, 2007;61:737–47.
2. Rodbard HW, Bays HE, Gavin JR, 3rd, et al., Rate and risk predictors for development of self-reported type-2 diabetes mellitus over a 5-year period: the SHIELD study, *Int J Clin Pract*, 2012;66:684–91.
3. Chan JM, Rimm EB, Colditz GA, et al., Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men, *Diabetes Care*, 1994;17:961–9.
4. Colditz GA, Willett WC, Stampfer MJ, et al., Weight as a risk factor for clinical diabetes in women, *Am J Epidemiol*, 1990;132:501–13.
5. Mokdad AH, Ford ES, Bowman BA, et al., Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001, *JAMA*, 2003;289:76–9.
6. Field AE, Coakley EH, Must A, et al., Impact of overweight on the risk of developing common chronic diseases during a 10-year period, *Arch Intern Med*, 2001;161:1581–6.
7. Grundy SM, Pre-diabetes, metabolic syndrome, and cardiovascular risk, *J Am Coll Cardiol*, 2012;59:635–43.
8. Tomic MP, Poljičanin T, Pavlic-Renar, et al, Obesity – a risk factor for microvascular and neuropathis complications in diabetes?, *Diabetologica Croatia*, 2003;2.
9. Smith AG, Singleton JR, Obesity and hyperlipidemia are risk factors for early diabetic neuropathy, *J Diabetes Complications*, 2013;27:436–42.
10. Masuo K, Rakugi H, Ogihara T, et al., Cardiovascular and renal complications of type 2 diabetes in obesity: role of sympathetic nerve activity and insulin resistance, *Curr Diabetes Rev*, 2010;6:58–67.
11. Serrano Rios M, Relationship between obesity and the increased risk of major complications in non-insulin-dependent diabetes mellitus, *Eur J Clin Invest*, 1998;28(Suppl. 2):14–17, discussion 7–8.
12. Bray GA, Obesity: a time bomb to be defused, *Lancet*, 1998;352:160–61.
13. International Diabetes Federation, IDF Diabetes Atlas. Update 2012. Available at: http://www.idf.org/diabetesatlas/5e/Update2012 (accessed October 21, 2013).
14. Wang YC, McPherson K, Marsh T, et al., Health and economic burden of the projected obesity trends in the USA and the UK, *Lancet*, 2011;378:815–25.
15. Meigs JB, Wilson PW, Fox CS, et al., Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease, *J Clin Endocrinol Metab*, 2006;91:2906–12.
16. Felber JP, Golay A, Pathways from obesity to diabetes, *Int J Obes Relat Metab Disord*, 2002;26(Suppl. 2):S39–45.
17. Bluher M, Adipose tissue dysfunction in obesity, *Exp Clin Endocrinol Diabetes*, 2009;117:241–50.
18. Kahn SE, Hull RL, Utzschneider KM, Mechanisms linking obesity to insulin resistance and type 2 diabetes, *Nature*, 2006;444:840–46.
19. Zraika S, Dunlop M, Proietto J, et al., Effects of free fatty acids on insulin secretion in obesity, *Obes Rev*, 2002;3:103–12.
20. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group, *Lancet*, 1998;352:837–53.
21. Giorgino F, Leonardini A, Laviola L, Cardiovascular disease and glycemic control in type 2 diabetes: now that the dust is settling from large clinical trials, *Ann N Y Acad Sci*, 2013;1281:36–50.
22. Fox CS, Coady S, Sorlie PD, et al., Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study, *Circulation*, 2007;115:1544–50.
23. Association AD, Executive summary: standards of medical care in diabetes–2011, *Diabetes Care*, 2011;34(Suppl. 1):S4–10.
24. Bagg W, Plank LD, Gamble G, et al., The effects of intensive glycaemic control on body composition in patients with type 2 diabetes, *Diabetes Obes Metab*, 2001;3:410–16.
25. Fonseca V, Effect of thiazolidinediones on body weight in patients with diabetes mellitus, *Am J Med*, 2003;115(Suppl. 8A):42S-8S.
26. Ohkubo Y, Kishikawa H, Araki E, et al., Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study, *Diabetes Res Clin Pract*, 1995;28:103–17.
27. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group, *N Engl J Med,* 1993;329:977–86.
28. Kahn SE, Haffner SM, Heise MA, et al., Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy, *N Engl J Med*, 2006;355:2427–43.
29. Black C, Donnelly P, McIntyre L, et al., Meglitinide analogues for type 2 diabetes mellitus, *Cochrane Database Syst Rev*, 2007;CD004654.
30. Russell-Jones D, Khan R, Insulin-associated weight gain in diabetes—causes, effects and coping strategies, *Diabetes Obes Metab*, 2007;9:799–812.
31. Rojas JM, Printz RL, Niswender KD, Insulin detemir attenuates food intake, body weight gain and fat mass gain in diet-induced obese Sprague-Dawley rats, *Nutr Diabetes*, 2011;1:e10.
32. Van de Laar FA, Lucassen PL, Akkermans RP, et al., Alpha-glucosidase inhibitors for type 2 diabetes mellitus, *Cochrane Database Syst Rev*, 2005;CD003639.
33. Karagiannis T, Paschos P, Paletas K, et al., Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis, *BMJ*, 2012;344:e1369.
34. Fonseca VA, Handelsman Y, Staels B, Colesevelam lowers glucose and lipid levels in type 2 diabetes: the clinical evidence, *Diabetes Obes Metab*, 2010;12:384–92.
35. Golay A, Metformin and body weight, *Int J Obes (Lond),* 2008;32:61–72.
36. Diabetes Prevention Program Research G, Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study, *Diabetes Care*, 2012;35:731–7.
37. Saenz A, Fernandez-Esteban I, Mataix A, et al., Metformin monotherapy for type 2 diabetes mellitus, *Cochrane Database Syst Rev*, 2005;CD002966.
38. Vilsboll T, Christensen M, Junker AE, et al., Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials, *BMJ*, 2012;344:d7771.
39. Thong KY, Jose B, Sukumar N, et al., Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit, *Diabetes Obes Metab*, 2011;13:703–10.
40. Turton MD, O'Shea D, Gunn I, et al., A role for glucagon-like peptide-1 in the central regulation of feeding, *Nature*, 1996;379:69–72.
41. Naslund E, Bogefors J, Skogar S, et al., GLP-1 slows solid gastric emptying and inhibits insulin, glucagon, and PYY release in humans, *Am J Physiol*, 1999;277:R910–6.
42. Scherrnthaner G, Gross JL, Rosenstock J, et al., Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial, *Diabetes Care*, 2013;36:2508–15.
43. Ghosh RK, Ghosh SM, Chawla S, et al., SGLT2 inhibitors: a new emerging therapeutic class in the treatment of type 2 diabetes mellitus, *J Clin Pharmacol*, 2012;52:457–63.
44. Horton ES, Silberman C, Davis KL, et al., Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort database, *Diabetes Care*, 2010;33:1759–65.
45. Feldstein AC, Nichols GA, Smith DH, et al., Weight change in diabetes and glycemic and blood pressure control, *Diabetes Care*, 2008;31:1960–5.
46. Williams KV, Kelley DE, Metabolic consequences of weight loss on glucose metabolism and insulin action in type 2 diabetes, *Diabetes Obes Metab*, 2000;2:121–9.
47. Tuomilehto J, Lindstrom J, Eriksson JG, et al., Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance, *N Engl J Med*, 2001;344:1343–50.
48. Torgerson JS, Hauptman J, Boldrin MN, et al., XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients, *Diabetes Care*, 2004;27:155–61.
49. Diabetes Prevention Program Research G, Knowler WC, Fowler SE, et al., 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study, *Lancet*, 2009;374:1677–86.
50. Look AHEAD Research Group, Wing RR, Bolin P, et al., Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes, *N Engl J Med*, 2013;369:145–54.
51. Ayyad C, Andersen T, Long-term efficacy of dietary treatment of obesity: a systematic review of studies published between 1931 and 1999, *Obes Rev*, 2000;1:113–9.
52. Norris SL, Zhang X, Avenell A, et al., Long-term non-pharmacological weight loss interventions for adults with prediabetes, *Cochrane Database Syst Rev*, 2005;CD005270.
53. Carlsson LM, Peltonen M, Ahlin S, et al., Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects, *N Engl J Med*, 2012;367:695–704.
54. Schauer PR, Kashyap SR, Wolski K, et al., Bariatric surgery versus intensive medical therapy in obese patients with diabetes, *N Engl J Med*, 2012;366:1567–76.
55. Buchwald H, Estok R, Fahrbach K, et al., Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis, *Am J Med*, 2009;122:248–56 e5.
56. Dixon JB, Zimmet P, Alberti KG, et al., Bariatric surgery: an IDF statement for obese Type 2 diabetes, *Diabet Med*, 2011;28:628–42.
57. Seger J DB, Westman EC, Lindquist R, et al., American Society of Bariatric Physicians, Obesity Algorithm:. ASBP Obesity Algorithm: Adult Adiposity Evaluation and Treatment 2013. http://www.asbp.org/images/ADV-COPY_ASBPObeistyAlgorithmOctober2013.pdf (accessed November 5, 2013).
58. Snow V, Barry P, Fitterman N, et al., Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American College of Physicians, *Ann Intern Med*, 2005;142:525–31.
59. Albu J, Raja-Khan N, The management of the obese diabetic patient, *Prim Care*, 2003;30:465–91.
60. Fox CS, Heard-Costa N, Cupples LA, et al., Genome-wide association to body mass index and waist circumference: the Framingham Heart Study 100K project, *BMC Med Genet*, 2007;8(Suppl. 1):S18.
61. Ciullo M, Nutile T, Dalmasso C, et al., Identification and replication of a novel obesity locus on chromosome 1q24 in isolated populations of Cilento, *Diabetes*, 2008;57:783–90.
62. Ziccardi P, Nappo F, Giugliano G, et al., Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year, *Circulation*, 2002;105:804–9.
63. Roytblat L, Rachinsky M, Fisher A, et al., Raised interleukin-6 levels in obese patients, *Obes Res*, 2000;8:673–5.
64. Scheen AJ, Finer N, Hollander P, et al., Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study, *Lancet*, 2006;368:1660–72.
65. Rosenstock J, Hollander P, Chevalier S, et al., SERENADE: the Study Evaluating Rimonabant Efficacy in Drug-naive Diabetic Patients: effects of monotherapy with rimonabant, the first selective CB1 receptor antagonist, on glycemic control, body weight, and lipid profile in drug-naive type 2 diabetes, *Diabetes Care*, 2008;31:2169–76.
66. Hollander PA, Amod A, Litwak LE, et al., Effect of rimonabant on glycemic control in insulin-treated type 2 diabetes: the ARPEGGIO trial, *Diabetes Care*, 2010;33:605–7.
67. Hollander PA, Elbein SC, Hirsch IB, et al., Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study, *Diabetes Care*, 1998;21:1288–94.
68. Miles JM, Leiter L, Hollander P, et al., Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin, *Diabetes Care*, 2002;25:1123-8.
69. Kelley DE, Bray GA, Pi-Sunyer FX, et al., Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: A 1-year randomized controlled trial, *Diabetes Care*, 2002;25:1033–41.
70. Derosa G, Maffioli P, Anti-obesity drugs: a review about their effects and their safety, *Expert Opin Drug Saf*, 2012;11:459–71.
71. Kopelman P, Groot Gde H, Rissanen A, et al., Weight loss, HbA1c reduction, and tolerability of cetilistat in a randomized, placebo-controlled phase 2 trial in obese diabetics: comparison with orlistat (Xenical), *Obesity (Silver Spring)*, 2010;18:108–15.
72. Colman E, Golden J, Roberts M, et al., The FDA's assessment of two drugs for chronic weight management, *N Engl J Med*, 2012;367:1577–9.
73. Fidler MC, Sanchez M, Raether B, et al., 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.
74. O'Neil PM, Smith SR, Weissman NJ, et al., Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study, *Obesity (Silver Spring)*, 2012;20:1426–36.
75. Smith SR, Weissman NJ, Anderson CM, et al., Multicenter, placebo-controlled trial of lorcaserin for weight management, *N Engl J Med*, 2010;363:245–56.
76. Gadde KM, Allison DB, Ryan DH, 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;377:1341–52.
77. Astrup A, Drug management of obesity—efficacy versus safety, *N Engl J Med*, 2010;363:288–90.
78. Thomsen WJ, Grottick AJ, Menzaghi F, et al., Lorcaserin, a novel selective human 5-hydroxytryptamine2C agonist: *in vitro* and *in vivo* pharmacological characterization, *J Pharmacol Exp Ther*, 2008;325:577–87.
79. Esai, Belviq prescribing information, 2012. Available at: http://www.belviq.com/pdf/Belviq_Prescribing_information.pdf (accessed October 22, 2013).
80. Garvey WT, Ryan DH, Look M, 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;95:297–308.
81. Garvey WT, Ryan DH, Henry R et al., Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended-release, *Diabetes Care*, 2013 [Epub ahead of print].
82. Hunt S, Russell A, Smithson WH, et al., Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register, *Neurology*, 2008;71:272–6.
83. Molgaard-Nielsen D, Hviid A, Newer-generation antiepileptic drugs and the risk of major birth defects, *JAMA*, 2011;305:1996–2002.
84. Astrup A, Rossner S, Van Gaal L, et al., Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study, *Lancet*, 2009;374:1606–16.
85. Astrup A, Carraro R, Finer N, et al., 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.
86. Novo Nordisk, Company announcement: Novo Nordisk reports 6% weight loss in phase 3a obesity trial with liraglutide 3 mg, 2013. Available at: http://www.novonordisk.com/include/asp/exe_news_attachment.asp?sAttachmentGUID=872441e7-92cb-4a08-9bd7-ef262e9c797b (accessed October 22, 2013).
87. FDA, Victoza (liraglutide [rDNA origin]) Injection: REMS - Risk of Thyroid C-cell Tumors, Acute Pancreatitis, 2011. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258826.htm (accessed October 22, 2013).
88. Bjerre Knudsen L, Madsen LW, Andersen S, et al., Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation, *Endocrinology*, 2010;151:1473–86.
89. Boess F, Bertinetti-Lapatki C, Zoffmann S, et al., Effect of GLP1R agonists taspoglutide and liraglutide on primary thyroid C-cells from rodent and man, *J Mol Endocrinol*, 2013;50:325–36.
90. Nyborg NC, Molck AM, Madsen LW, et al., The human GLP-1 analog liraglutide and the pancreas: evidence for the absence of structural pancreatic changes in three species, *Diabetes*, 2012;61:1243–9.
91. Hollander P, Gupta AK, Plodkowski R, et al., Effects of naltrexone sustained-release/bupropion sustained release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes, *Diabetes Care*, 2013;36:4022–9.
92. Greenway FL, Fujioka K, Plodkowski RA, et al., Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial, *Lancet*, 2010;376:595–605.
93. Cardiovascular outcomes study of naltrexone SR/bupropion SR in overweight and obese subjects with cardiovascular risk factors (The Light Study). Available at: http://clinicaltrials.gov/ct2/show/NCT01601704?term=contrave&rank=3 (accessed November 5, 2013).
94. Astrup A, Madsbad S, Breum L, et al., Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial, *Lancet*, 2008;372:1906–13.
95. Kenkre J, Tan T, Bloom S, Treating the obese diabetic, *Expert Rev Clin Pharmacol*, 2013;6:171–83.
96. Samaranayake NR, Ong KL, Leung RY, et al., Management of obesity in the National Health and Nutrition Examination Survey (NHANES), 2007-2008, *Ann Epidemiol*, 2012;22:349–53.
97. Flegal KM, Carroll MD, Kuczmarski RJ, et al., Overweight and obesity in the United States: prevalence and trends, 1960–1994, *Int J Obes Relat Metab Disord*, 1998;22:39–47.
98. Flegal KM, Carroll MD, Ogden CL, et al., Prevalence and trends in obesity among US adults, 1999–2000, *JAMA*, 2002;288:1723–7.
99. Flegal KM, Carroll MD, Ogden CL, et al., Prevalence and trends in obesity among US adults, 1999–2008, *JAMA*, 2010;303:235–41.
100. Flegal KM, Carroll MD, Kit BK, et al., Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010, *JAMA*, 2012;307:491–7.
101. Harris MI, Diabetes in America: epidemiology and scope of the problem, *Diabetes Care*, 1998;21(Suppl. 3):C11–14.
102. CDC, Age-Adjusted Percentage of Civilian, Noninstitutionalized Population with Diagnosed Diabetes, by Race and Sex, \United States, 1980–2011. Available at: http://www.cdc.gov/diabetes/statistics/prev/national/figraceethsex.htm (accessed November 4, 2013).
103. CDC, Age-Adjusted Percentage of Civilian, Noninstitutionalized Population with Diagnosed Diabetes, by Hispanic Origin and Sex, United States, 1997–2011. Available at: http://www.cdc.gov/diabetes/statistics/prev/national/fighispanicthsex.htm (accessed November 4, 2013).
104. Mokdad AH, Ford ES, Bowman BA, et al., Diabetes trends in the U.S.: 1990–1998, *Diabetes Care*, 2000;23:1278–83.
105. Mokdad AH, Serdula MK, Dietz WH, et al., The spread of the obesity epidemic in the United States, 1991–1998, *JAMA*, 1999;282:1519–22.