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Review

New Medications for Treatment of Obesity: Metabolic and Cardiovascular Effects

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ABSTRACT

The management of obesity remains a major challenge. Dietary therapy often fails, whereas bariatric surgery, although successful, is demanding and applicable to a limited number of patients. Drug therapy has had many setbacks over the past 20 years because of serious adverse effects; however, several new drugs for the treatment of obesity are either licensed in some parts of the world, submitted for registration, or completing phase III trials. These include combinations (at low dose) of existing drugs, eg, bupropion + naltrexone (Contrave), phentermine + topiramate (Qsymia), higher doses of existing drugs licensed for other indications (liraglutide, 3 mg), and new entities (lorcaserin).

We discuss the challenges and opportunities for obesity pharmacotherapy and review in detail the efficacy of the new drugs regarding weight loss and both desirable and potential undesirable cardiovascular (CV) and metabolic risk factors. Substantial barriers remain, even if the drugs are approved, in successfully integrating these agents into weight management practice, largely related to cost, patient acceptability, and clinician willingness to be engaged in obesity treatment. Although hard clinical outcome benefit (at least for CV outcomes) has yet to be established, obesity pharmacotherapy may soon address many of the challenges in the clinical management of obesity, although newer and better drug combinations and more evidence of benefit from appropriately designed outcome trials is needed.

RÉSUMÉ

La prise en charge de l'obésité demeure un enjeu majeur. La thérapie nutritionnelle échoue souvent, tandis que la chirurgie bariatrique, malgré son succès, est exigeante et praticable que chez un nombre limité de patients. La pharmacothérapie a subi plusieurs revers au cours des 20 dernières années en raison d'effets indésirables sérieux. Cependant, plusieurs nouveaux médicaments pour le traitement de l'obésité sont soit homologués dans certaines parties du monde, soit soumis à l'homologation ou en cours d'achèvement d'essais cliniques de phase III. De ce nombre, citons les combinaisons (à faible dose) de médicaments existants, par exemple le bupropione + la naltrexone (Contrave), la phentermine + le topiramate (Qsymia), des doses plus élevées de médicaments existants homologués pour d'autres indications (le liraglutide, 3 mg) et de nouvelles substances (la lorcasérine).

Nous discutons des enjeux et des possibilités de la pharmacothérapie contre l'obésité et passons minutieusement en revue l'efficacité des nouveaux médicaments quant à la perte de poids, aux facteurs de risque cardiovasculaire (CV) et métabolique désirables et indésirables potentiels. Même si les médicaments sont approuvés, il reste d'importants obstacles à surmonter pour réussir l'intégration de ces agents à la pratique pour la prise en charge du poids, en grande partie liés au coût, à l'acceptabilité des patients et à la bonne volonté du clinicien de s'impliquer dans le traitement de l'obésité. Bien que les avantages tangibles des résultats cliniques (du moins en ce qui concerne les résultats CV) n'aient pas encore été établis, la pharmacothérapie contre l'obésité pourra bientôt relever les nombreux défis de la prise en charge clinique de l'obésité. Cependant, de plus récentes et de meilleures combinaisons de médicaments et plus de données probantes sur les avantages provenant d'essais cliniques bien conçus sont nécessaires.

The rising tide of obesity is an increasing threat to the health of populations globally. According to a recent systematic analysis, in 2013, > 2.1 billion of people were overweight worldwide, defined by body mass index (BMI) ≥ 25 kg/m^2, or obese (≥ 30 kg/m^2) compared with 857 million in 1980. The prevalence of overweight and obesity combined rose by 27.5% for adults and 47.1% for children during the same period. This trend has been true both in developed and developing countries, although it now appears to be slowing down in the former.[1] The high burden of comorbidities (such as type 2 diabetes mellitus [T2D], cardiovascular [CV] disease, and certain cancers) associated with obesity heighten the severity of this obesity crisis.[2] In 2010, overweight and

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obesity were estimated to cause 3.4 million deaths worldwide.[3] There is a close relationship between obesity, metabolic disturbances, and CV risk (so-called cardiometabolic [CM] risk), which involves a number of mechanisms, including increased inflammation, dyslipidemia, hypertension (HTN), and insulin resistance, as well as alterations in sympathetic nervous system activity. Most deaths attributable to overweight and obesity are CV deaths,[3] and this trend is true even when starting from a BMI > 23 kg/m^2.[2] Data from the 1946 British birth cohort study showed that prolonged exposure to high adiposity in adulthood had a cumulative adverse effect on carotid intima media thickness and higher blood pressure (BP) affecting the overall CV risk,[4] although weight loss at any time appeared to be protective.

Therefore, obesity is associated with very high preventable costs, and this economic burden is beginning to raise global political awareness.[5] Although prevention of obesity is the strategic imperative, treatment of obese patients, preferably at a stage before end-organ damage has occurred, should also be an urgent priority. Lifestyle modification is the first step in weight management. Intervention programs focusing on diet or exercise, or both, are effective in inducing weight loss and weight loss maintenance in the short to medium term but lose efficacy in the long term; despite this patients may retain clinical benefits in the long term from reduced CV and all-cause mortality and reduced T2D incidence.[6-11] In most guidelines, bariatric surgery is reserved for patients with severe or complicated obesity (BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 in the presence of at least 1 obesity-related comorbidity) and is the most effective treatment regarding weight loss achieved and maintained and amelioration of obesity-related comorbidities.[12-14] A recent meta-analysis of 11 trials that included 796 participants and was randomized to either bariatric surgery or nonsurgical treatment found that bariatric surgery resulted in greater weight loss, remission of T2D and metabolic syndrome, and lipid profile improvement.[15] Bariatric surgery also reduces all-cause and CV mortality.[13] However, surgery will never be able to be performed on a scale large enough to address the pandemic proportions of obesity, and it is also subject to an increasing number of recognized medical and surgical complications and weight regain.[16,17] Clearly, effective alternative approaches are required, and it is appropriate that pharmacologic treatment should be considered as a treatment option.[18,19] In this review, we discuss the CV and metabolic benefits and risks of new antiobesity drugs.

Dichotomies in Obesity Pharmacotherapy

Past experience

Despite efficacy in producing weight loss and CM improvement, previous antiobesity drugs have also had serious adverse CV side effects. The fenfluramines, developed in the 1980s, were effective satiety-enhancing drugs that acted mainly through enhancing central serotoninergic neuronal transmission (by both release and reuptake inhibition of serotonin) but were found to cause (fatal) pulmonary HTN and cardiac valve abnormalities (especially when combined with phentermine) and were withdrawn from use in 2004.[20] Sibutramine, a selective serotonin and norepinephrine uptake inhibitor had been licensed and in use worldwide since the 1990s. Concerns that the drug had unwanted, and potentially dangerous, sympathomimetic effects that could raise BP and pulse led to a demand from the European Medicines Agency (EMA) for a CV outcome trial. The findings from the **S**ibutramine **C**ardiovascular **Out**comes (SCOUT) trial of an increased incidence of nonfatal myocardial infarction and stroke led to its withdrawal in the United States and Europe (although it is still licensed in some Latin American countries).

From the Clinician to the Patient

Patient and clinician expectations of antiobesity drugs differ. The clinician expects an antiobesity drug to normalize deranged factors involved in the pathogenesis of obesity, reduce body fat stores, ameliorate obesity-related comorbidities, reduce mortality, and improve quality of life with minor or acceptable side effects; yet the Look AHEAD: Action for Health in Diabetes study, an intensive diet and lifestyle intervention trial based on that used in the Diabetes Prevention Program but that also included the use of meal replacements and orlistat, suggested that 8% weight reduction in obese patients with T2D was insufficient to reduce CV disease.[21] Patients, however, often focus on weight loss alone and often have unrealistic expectations and may not wish to remain on a drug long term.[22-25] Thus, although lifestyle and pharmacologic interventions can reverse metabolic syndrome, the lack of data on whether these benefits are sustained and translate into longer term prevention of T2D or CV disease, or both,[26] may undermine confidence in this approach by both clinicians and patients.

From Europe to the United States

The US Food and Drug Administration (FDA) and the EMA differ in the criteria they set for efficacy of antiobesity drugs.[27] Efficacy is determined by mean and categorical weight losses at 1 year:

1. Mean efficacy is defined as the percentage of placebo-subtracted weight reduction.
2. Categorical efficacy requires that the significantly greater proportion receiving the medication doubles the placebo loss and maintains weight loss from their initial weight.

The FDA requires that mean efficacy is a $\geq 5\%$ difference in mean weight loss and that $\geq 35\%$ of drug-treated patients lose $\geq 5\%$ of body weight from baseline.[28] The EMA regards weight reduction from baseline as being more clinically relevant than placebo-subtracted weight loss and requires evidence for a mean weight loss $\geq 10\%$ at 1 year, which must also be $\geq 5\%$ greater than that achieved on placebo. Few drugs previously approved, or being considered for approval, have met both agencies' criteria. None of the weight-loss medication most recently approved by the EMA (orlistat, sibutramine, rimonabant) met the 10% criterion but were approved as meeting an alternative efficacy target, namely, a significantly greater proportion of patients losing more than 10% of their baseline body weight in the active treatment group compared with those in the placebo group at the end of a 12-month period.

Although both agencies consider weight reduction the primary efficacy criterion, and indicative of clinical benefit, they also seek treatment-related improvements in CV risk factors. Precipitated by the findings of the SCOUT trial,[29] which showed a higher frequency of nonfatal myocardial infarction and stroke in the active treatment arm of the study, sibutramine was withdrawn in Europe and the United States.[30] Although these findings were incontrovertible, subsequent prespecified analyses of SCOUT showed that this morbidity was likely driven by continued exposure of weight-loss–unresponsive patients to the sympathomimetic effects of sibutramine and that those achieving modest weight loss had a lower CV mortality over 4-5 years of follow-up.[31,32]

After the withdrawal of several previously approved pharmacotherapies,[33] regulatory agencies now require preapproval exclusion of CV risk for a CV outcome trial (CVOT), in general along the FDA guidelines for antidiabetic medications,[34] unless there is no adverse CV safety signal from phase III studies, in which case the CVOT can be performed after approval (Supplemental Table S1). Conventionally in outcome trials, participants receive treatment throughout the trial, regardless of whether or not they lose weight, therefore exposing patients who do not lose weight for several years to potential unwanted drug effects—a situation that would not be likely to occur in clinical practice.[35] New CV outcome trials of obesity pharmacotherapy have been designed to allow withdrawal from the drug in nonresponders to circumvent these limitations.[36] Although there is currently no regulatory pathway to license a drug for "weight loss maintenance" or "prevention of weight regain," traditionally, randomization to withdrawal of active drug during a second year of treatment has formed part of drug efficacy assessment.

The costs and practicalities of a preapproval CVOT can be a substantial barrier to drug development. Currently, outcome events are low, requiring very large numbers of participants to be recruited (~15,000-20,000) to achieve sufficient power over a 3- to 4-year period. Enrichment with older, sicker, and more obese patients can reduce the numbers of participants needed but risks failing to reflect the target population for such drugs—namely, younger often medically uncomplicated overweight/obese patients with a BMI < 35 kg/m^2.

Divergent Interpretation of Trial Data

The divergence between different regulatory authorities' interpretation of the same body of trial data is also illustrated by the fact that in the United States, the FDA has approved both lorcaserin and extended-release topiramate + phentermine (Qsymia), whereas both were rejected primarily on safety grounds by the EMA, a stance that has been criticized.[37] The main stumbling block appeared to be concerns about efficacy and preclinical toxicology for lorcaserin and CV and psychiatric safety for topiramate + phentermine.

Attrition Rates in Trials and Clinical Practice

All modalities of obesity treatment show very high attrition rates, both in trials and in clinical practice. Diet and lifestyle and pharmacotherapy trials lose up to 50% of patients within the first year,[38-40] up to one third of patients are lost to follow-up by 4 years in surgery trials, and more than 50% of patients discontinue follow-up in clinical practice.[41] The reasons for these high rates of withdrawal are complex, do not solely result from unwanted effects, and may in part be driven by the status or perception of obesity as a disease or not.[42] Within a clinical trial setting, the reasons for withdrawal are often unbalanced between different arms. The patient is not blinded to the primary outcome of weight loss so that dissatisfaction with weight loss is higher in those receiving placebo, whereas unwanted effects of treatment will be higher in those receiving active drug. However, increasingly in evaluating efficacy of drugs, responder populations can be defined early and may serve to limit exposure of nonresponsive patients to drug and selectively enhance outcomes.[43] Regulatory authorities increasingly require a weight loss threshold for continued medication as part of the product license.

Novel Obesity Pharmacotherapies

Current approaches have focused on central pathways involved with body weight regulation, ie, appetite suppressants or satiety enhancers (Fig. 1). Currently phentermine and diethylpropion (with similar amphetamine derivatives) are approved only for short-term ($<$ 12 weeks) treatment, although neither is recommended in any European guideline. New drugs have targeted central serotonin (lorcaserin), dopamine and GABAergic (phentermine + topiramate) and pro-opiomelanocortin (POMC) and opioid (bupropion + naltrexone) pathways. High-dose glucagon-like peptide-1 receptor (GLP-1) agonism with liraglutide has also been investigated, with evidence that this too has direct central effects.[44] In this review, we summarize important findings from recent randomized controlled trials that investigated the weight loss associated with these 4 agents and focus on the CM improvements and unwanted effects that these drugs may have.

The findings from these trials may not warrant direct translation to clinical practice. Clinical trials of pharmacotherapy represent a dual intervention (drug and lifestyle) with only 1 placebo (drug/placebo). This may confound results seen in clinical practice in which the lifestyle intervention is likely to be extremely varied and often of lower intensity and content. Furthermore, changes in CM parameters will also be influenced by baseline values and concomitant medications.

Lorcaserin

Lorcaserin (BELVIQ, Arena/Eisai, Tokyo, Japan) is a serotonin type 2C receptor (5HT2CR) agonist developed to exploit the 5HT2CR-specific hypophagic effects of fenfluramine while removing the unwanted effects of 5-HT2A and 5-HT2B receptor agonism.[45] Lorcaserin has been available in the United States since June 2013.

Weight loss. The efficacy and safety of lorcaserin were established in 3 pivotal randomized double-blind, placebo-controlled phase III trials (Table 1).[46-48] The 2-year **B**ehavioral Modification and **L**orcaserin for **O**verweight and **O**besity **M**anagement (BLOOM) trial randomized patients with either a BMI of 30-45 kg/m^2 or 27-45 kg/m^2 with at least 1 comorbidity to receive placebo or lorcaserin 10 mg twice daily (BID) for 1 year; participants who completed the trial were

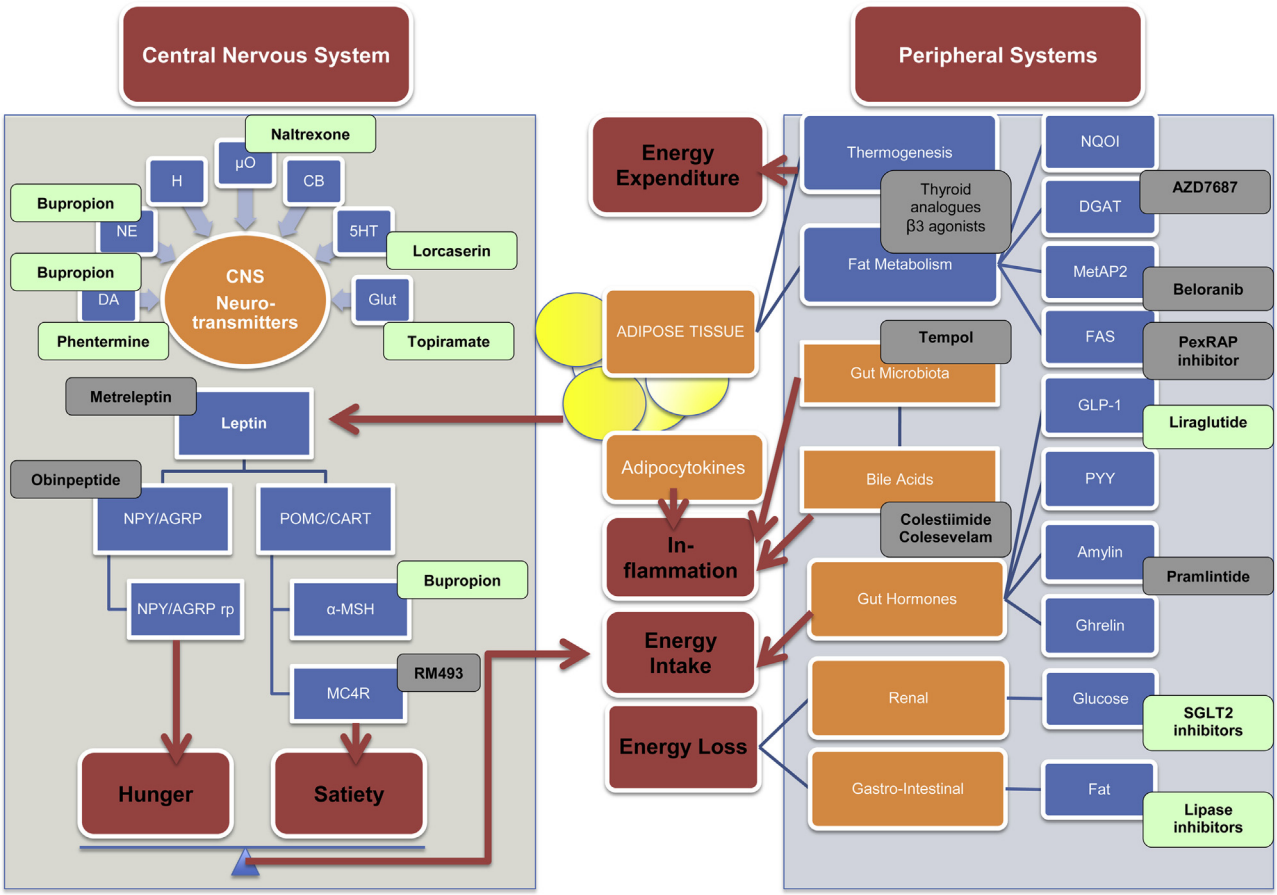


Figure 1. Targets for antiobesity drugs. Green boxes denote drugs approved (not all for obesity indications). Grey boxes denote drugs in phase I-III development.

then randomized 1:1 to remain on lorcaserin treatment or be switched to placebo.[46] **B**ehavioral Modification and **L**orcaserin for **O**besity and **O**verweight **M**anagement in **D**iabetes **M**ellitus (BLOOM-DM) had a similar design but included patients with T2D.[47] The **B**ehavioral Modification and **Lo**rcaserin **S**econd **S**tudy for **O**besity **M**anagement (BLOSSOM) trial randomized patients with a of BMI 30-45 kg/m^2 or a BMI of 27-29.9 kg/m^2 and at least 1 comorbidity to receive placebo or lorcaserin 10 mg daily or BID for 1 year.[48] A recent meta-analysis found a mean placebo-subtracted weight loss of 3.2 kg at 1 year and a BMI reduction of 1.2 kg/m^2.[59] In the BLOOM trial, weight regain was seen during the second year despite continued active treatment, raising the possibility that tolerance to lorcaserin may have developed. On the basis of

Table 1. Summary of weight loss data in randomized placebo-controlled antiobesity drug trials (1 year data only)*

Drug	Study	Participants (% T2D)	BMI (mean)	Age (mean)	1-year Δ% WL (mean)	Percent with > 5% WL (vs placebo)
Phentermine	Randomised controlled trials: no 1-year data, none since 1980s					
Orlistat (120 mg TID)	XENDOS[49]	3305 (0%)	37.3	43.3	4.0%	72% vs 45%
Lorcaserin (10 mg BID)	BLOOM[46]	3182 (0%)	36.2	44.1	3.6	45% vs 20%
Lorcaserin (10 mg BID)	BLOSSOM[48]	4408 (0%)	35.9	43.8	3.0%	47% vs 25%
Lorcaserin (10 mg daily)	BLOOM-DM[47]	604 (100%)	36.0	52.4	3.5%	45% vs 16%
Phentermine/topiramate (15/92 mg)	EQUIP[50]	1267 (0%)	42.2	42.6	9.3%	67% vs 17%
Phentermine/topiramate (15/92 mg)	CONQUER	2487 (15.8%)	36.6	51.1	8.6%	70% vs 21%
Bupropion/naltrexone (32/360 mg)	COR-I[51,52]	1742 (0%)	36.2	44.2	4.8%	48% vs 16%
Bupropion/naltrexone (32/360 mg)	COR-II[53]	1496 (0%)	36.1	44.3	5.2%	67% vs 17%
Bupropion/naltrexone (32/360 mg)	COR-BMOD[54]	793 (0%)	36.6	45.7	4.2%	54% vs 41%
Bupropion/naltrexone (32/360 mg)	COR-D[55]	505 (100%)	36.4	53.7	3.2%	44% vs 19%
Liraglutide (3 mg)	Phase II[56]	398 (5.3%)	34.8	45.9	5.9%	73% vs 28%
Liraglutide (3 mg)	SCALE Maintain[57]	422 (0%)	35.6	46.2	6.1%	50% vs 22%
Liraglutide	SCALE Obesity[58]	3731 (0%)	—	—	5.4%	64% vs 27%

BID, twice daily; BMI, body mass index; 2TD, diabetes mellitus, type 2; TID, 3 times daily; WL, weight loss.
*Some changes have been derived from reported data.

the trial data, the product licence requires that if after 12 weeks (W12) of treatment with lorcaserin, a patient has not lost at least 5% of the baseline body weight, it should be discontinued. Under such circumstances, patients with a W12 response achieved mean 1-year weight losses of 10.6 kg (without T2D) and 9.3 kg (with T2D), with proportions achieving $\geq$ 5% and $\geq$ 10% weight loss of 85.5% and 49.8% (without T2D), and 70.5% and 35.9% (with T2D).[43]

CM effects. A meta-analysis on secondary outcomes showed that compared with placebo, lorcaserin decreased mean waist circumference by 2.51 cm, systolic BP (SBP) by 0.61 mm Hg, diastolic BP (DBP) by 0.49 mm Hg, with no significant difference in heart rate (HR). Significant percentage reductions in total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were also found.[59] In the BLOOM-DM trial, both fasting blood glucose and hemoglobin A1C (HbA1c) levels were improved.[47] No statistically significant differences in the incidence of cardiac valvulopathy between the placebo and lorcaserin groups were found (Table 2).[61]

Side effects. The most common adverse events associated with lorcaserin were consistent with its serotonergic agonist mechanism of action and included blurred vision, dizziness, somnolence, headache, gastrointestinal disturbance, and nausea. Lorcaserin is contraindicated in pregnancy because of a risk of teratogenicity. The Committee on Human Medicinal Products had concerns about the finding of a variety of tumors in animal studies, particularly with long-term use, and the potential risk of psychiatric disorders and valvulopathy.[62] The cancer risk in animal studies had been a FDA concern when it rejected lorcaserin the first time around, but they ultimately concluded that the incidence of mammary adenocarcinoma was increased only at plasma exposures 87 times the daily human clinical dose and were therefore not relevant to therapeutic doses in humans.[63] Notwithstanding the approval by the FDA, the manufacturers (Arena Pharmaceuticals) withdrew their European application, where the development strategy remains "under evaluation."

Phentermine/topiramate extended release capsules

Phentermine and extended-release topiramate (PHEN/TPM-ER: Qnexa/Qsiva/Qsymia) (VIVUS, Mountain View, CA) exploit the principle of a synergistic combination of 2 drugs at a lower dose to obtain efficacy with less toxicity. After approval by the FDA, the drug was launched in the United States in September 2012. Phentermine is an atypical amphetamine analogue that suppresses appetite by norepinephrine agonism in the central nervous system.[64] It has been widely used (mainly outside of Europe) since the 1960s.[65] Topiramate is an atypical anticonvulsant drug previously evaluated as a potential antiobesity drug after anecdotal reports of weight loss occurring in epileptic patients taking this drug.[66] The mechanisms by which topiramate induces a weight loss are unknown and may include carbonic-anhydrase inhibition of taste or influences on GABA transmission, thus reducing appetite.[67,68] Topiramate produced a substantial weight reduction in obese patients, particularly when administered after initial weight loss induced with a very low energy diet,[69] but indication as an antiobesity agent was abandoned because of dose-dependent neuropsychiatric and cognitive adverse events.[70,71] The combination includes lower doses than used for either drug alone in an extended-release formulation to give an equivalent duration of action for each component.[50,51,72]

Weight loss. PHEN/TPM-ER has been evaluated in clinical trials at low (3.75 phentermine/23 extended-release topiramate mg), intermediate (7.5/46 mg), and full (15/92 mg) doses. The EQUIP trial enrolled 1267 participants (BMI $\geq$ 35 kg/m^2) and the CONQUER trial enrolled 2487 adults (BMI, 27-45 kg/m^2 with no lower BMI limit in those with T2D) and also required patients to have at least 2 comorbidities (HTN, hypertriglyceridemia, impaired fasting glucose levels, impaired glucose tolerance, T2D, or visceral adiposity, or a combination).[50,51] In EQUIP, patients in the placebo, low-dose, and high-dose groups lost 1.6%, 5.1%, and 10.9% of baseline body weight, respectively, at 56 weeks. In categorical analysis, 17.3% of patients who received placebo, 44.9% of patients who received low-dose treatment, and 66.7% of patients who received the full dose lost at least 5% of baseline body weight at 56 weeks. In the higher risk population in the CONQUER trial, all participants received a lifestyle modification program based on the LEARN Program for Weight Management.[51,73] Seventy percent of patients receiving high-dose PHEN/TPM-ER lost at least 5% of their body weight compared with 21% of patients receiving placebo. Mean weight loss was 9.8% in the high-dose group and 1.2% in the placebo group. The proportions of patients achieving at least a 10% weight loss were 48% in the drug treatment group compared with 7% in the placebo group. Although there are no head-to-head studies, this combination medication produced much larger weight loss than previously seen in clinical trials of other obesity medications. The CONQUER study was extended for a second year of observation, with patients keeping their treatment assignment. This has been published as the SEQUEL study (676 participants).[72] At the end of the second year of treatment, participants who completed high-dose treatment maintained a 10.7% weight loss from baseline. In a fourth study, adults with T2DM evaluated in a 28-week extension of a 28-week double-blind, placebo-controlled phase II trial, achieved a 9.4% weight loss on high-dose treatment compared with 2.7% in the placebo group.[74] The 28-week EQUATE trial was designed to compare the weight loss effect of PHEN/TPM-ER with that of its individual constituents.[75] Seven hundred fifty-six obese participants were randomized to receive phentermine alone (7.5 mg or 15 mg), topiramate ER alone (46 mg or 92 mg), PHEN/TPM-ER (mid or high dose), or placebo. At the end, those receiving the combination had a significantly greater weight loss when compared with any monotherapy or placebo; the mid dose demonstrated greater weight loss efficacy than either phentermine 15 mg or topiramate ER 92 mg when used individually.

CM effects. In a pooled analysis of a 1-year data cohort, significant reductions in SBP and DBP ($P < 0.0001$) were seen for the intermediate and full doses but not for the low dose compared with placebo.[76] Reductions in BP occurred in parallel with slight increases in HR in all PHEN/TPM-ER

Table 2. Summary of percent changes in cardiovascular and metabolic risk factors*

Drug	Reference	SBP (mm Hg)	DBP (mm Hg)	FG (mg/dL)	HbA1c (%)	LDL (%)	TGL (%)
Phentermine	Randomized controlled trials: no 1-year data, none since 1980s						
Orlistat	XENDOS[49]	7.3† (5.2)	−3.6† (−2.6)	1.8† (3.6)	NA	−11.4† (−1.6)	−6.2 (−6.3)
Lorcaserin (10 mg BID)	BLOOM[46]	1.4† (0.8)	−1.1† (−0.6)	−0.8† (1.1)	−0.04† (0.03)	2.87† (4.03)	−6.15† (−0.14)
Lorcaserin (10 mg BID)	BLOSSOM[48]	1.9 (1.2)	−1.9 (−1.4)	NA	0.19 (-0.14)	0.3 (1.7)	−4.3 (−0.9)
Lorcaserin (10 mg BID)	BLOOM-DM[47]	0.8 (0.9)	−1.1 (−0.7)	−27.4† (−11.9)	−0.9† (−0.4)	4.2 (5.0)	−10.7 (−4.8)
Phentermine/Topiramate (15/92 mg)	EQUIP[50]	2.9† (0.9)	−1.5† (0.4)	−0.6† (1.9)	NA	−8.4† (−5.5)	−5.2† (9.1)
Phentermine/Topiramate (15/92 mg)	CONQUER[51]	5.6† (2.4)	−3.8† (−2.7)	−1.26† (0.54)	−0.1† (0.1)	−6.9† (−4.1)	−10.6† (4.7)
Bupropion/naltrexone (32/360 mg)	COR-I[52]	0.1† (1.9)	0.0 (−0.9)	−3.24† (−1.26)	NA	−2.0 (−0.5)	−12.7† (−3.1)
Bupropion/naltrexone (32/360 mg)	[77] COR-II[53]	0.6† (0.5)	0.4 (0.3)	−2.8 (−1.3)	NA	−6.2† (−2.1)	−9.8† (−0.5)
Bupropion/naltrexone (32/360 mg)	COR-BMOD[54]	1.3† (3.9)	−1.4† (−2.8)	−2.4 (−1.1)	NA	7.1 (10.0)	−16.6† (−8.5)
Bupropion/naltrexone (32/360 mg)	COR-D[55]	0.0 (1.1)	−1.1 (−1.5)	−11.9 (−4.0)	−0.6† (−0.1)	−1.4 (0.0)	−11.2† (−0.8)
Liraglutide (3 mg)	Phase II[56]	4.9 (1.6)	−2.8 (−0.2)	−5.77† (1.44)	−0.26† (0.01)	−0.43§† (−0.28) mmol/L	−0.14†,‡ (0.01) mmol/L
Liraglutide (3 mg)	SCALE Maintain[57]	0.2† (2.8) −2.7	1.4 (1.2) −0.3	−9.0† (−3.6) −7.2	−0.1† (0.1) −0.3	0.2‡ (0.3) −0.09 mmol/L	0.0‡ (0.1) −0.11 mmol/L
Liraglutide	SCALE Obesity[60]	Estimated treatment differences: SBP, −2.8, DBP, −0.9 mm Hg† Low-density lipoprotein cholesterol −2%,† high -density lipoprotein cholesterol 2%,† triglyceride levels, 9%† Progression to prediabetes: liraglutide 3 mg, 6.9%; placebo,19.9%†					

Effects in placebo group in parentheses.

BID, twice daily; BMI, body mass index; DBP, diastolic blood pressure; FG, fasting glucose; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; SBP, systolic blood pressure; TGL, triglycerides.

*Some changes have been derived from reported data.

† Absolute change.

‡ Significant active vs placebo.

groups (mean change ± SD of 1.3 ± 10.3 beats per minute (bpm), 0.6 ± 10.2 bpm, and 1.6 ± 10.3 bpm for PHEN/TPM-ER 3.75/23 mg, 7.5/46 mg, and 15/92 mg groups, respectively), which was significant vs placebo (0.0 ± 10.2 bpm) only in the PHEN/TPM-ER 15/92 mg group. However, among patients with the highest HR at baseline (>90 bpm), most showed reductions in HR at the 1-year end point. These findings were despite a significant reduction in concomitant antihypertensive medication use in PHEN/TPM-ER–treated patients compared with net increase in antihypertensive medication use in the placebo group ($P = 0.0012$ for between-group differences). Within the 1-year safety cohort, the percentage of patients in the low–, moderate–, and high–CV-risk groups were 19.8%, 65.6%, and 14.6%, respectively, according to modified Adult Treatment Panel III criteria.[77] There were too few CV events to allow conclusive CV safety determination, with a major adverse cardiovascular event (MACE) end point hazard ratio of 0.84 (95% confidence interval [CI], 0.26-2.64). To fulfil FDA requirements, a postregistration CV outcomes trial is under way; licensing in Europe will await the outcome of this trial (Table 2).[78]

Side effects. Given the proven teratogenic effect of topiramate (orofacial cleft), even in the absence of fetal adverse outcomes in 15 births with an exposure to the drug during the trials, the FDA requires a negative pregnancy test before PHEN/TPM-ER treatment is started and at monthly intervals thereafter. Adverse events associated with PHEN/TPM-ER treatment were dry mouth, constipation, insomnia, palpitations, dizziness, paraesthesia, disturbances in attention, metabolic acidosis and renal calculi, headache, dysgeusia (distortion of sense of taste), alopecia, and hypokalemia.

Bupropion/naltrexone

Bupropion/naltrexone (Contrave, Orexigen, La Jolla, CA), which combines 2 centrally acting medications that are already FDA approved is being assessed for the treatment of obesity by both the US and European drug agencies. Bupropion is used for treating depression and to aid smoking cessation. It is a nonselective inhibitor of the dopamine and norepinephrine transporters.[79] The use of bupropion alone as an antiobesity agent compared with placebo showed very modest weight loss.[80,81] Naltrexone is an opioid receptor antagonist widely used to treat alcohol and opiate dependence syndromes. Most studies have failed to demonstrate weight loss with conventional doses of naltrexone alone,[82] and at higher doses hepatotoxicity occurred.[83] The anorectic effect of the bupropion/naltrexone combination is believed to result from activation of POMC neurons in the arcuate nucleus. POMC neurons release a-melanocyte–stimulating hormone (a-MSH), which is a potent anorectic feeding neuropeptide, and these neurons project to other hypothalamic areas involved in feeding and body weight control. The combination of the 2 drugs has an additive effect in stimulating the release of a-MSH compared with the individual drugs taken alone.[84]

Weight loss. The efficacy and safety of bupropion/naltrexone have been determined in 4 randomized studies named

Contrave Obesity Research (COR)-I,[52] COR-II,[53] Contrave Obesity Research—Behavior Modification (COR-BMOD),[54] and Contrave Obesity Research-Diabetes (COR-D)[55] including 4536 overweight or obese participants. The first 3 trials included obese or overweight/obese patients with controlled HTN or dyslipidemia, or both. In COR-BMOD, the efficacy of bupropion/naltrexone was determined when used as an adjunct to intensive diet, exercise, and lifestyle modification. COR-D included more complicated overweight and obese participants (T2D, HTN, and dyslipidemia). Naltrexone 32 mg/bupropion 360 mg was the dose used for all the studies except COR-I, which also evaluated naltrexone 16 mg/bupropion 360 mg. At week 56, the placebo-subtracted weight reductions produced by the higher dose of bupropion/naltrexone were 4.8 and 5.2 kg in COR-I and COR-II, respectively. Participants achieving > 5% weight loss with the higher dose were 48% and 50.5%, respectively. In COR-BMOD, all the participants adhered to an intensive program that included dietary, behavioural, and exercise support. In this study, bupropion/naltrexone produced 4.2 kg weight loss; 54.3% of participants lost > 5% of their baseline weight. Mean weight loss in obese participants with T2D, the group most resistant to weight loss, was 3.2%, with 44.5% achieving > 5% weight loss. In comparison with other already marketed antiobesity drugs, bupropion/naltrexone ranks below phentermine/topiramate regarding weight loss efficacy but above lorcaserin and orlistat (Table 2).

CM effects. COR-I and COR-II showed significant improvements in CM parameters, which included decreased waist circumference (WC), triglyceride levels and C-reactive protein (CRP) levels, and increased high-density lipoprotein levels for the lower dose and an additional r decrease in fasting plasma insulin and glucose levels and Homeostatic Model Assessment of Insulin Resistance levels for the higher dose.[52,53] COR-BMOD showed improvements in CRP and fasting blood glucose values also.[54] In the COR-D, patients with T2D showed a decreased HbA1c level without hypoglycemia and an increased likelihood of reducing HbA1c to < 7% (Table 2).[55]

Some concerns regarding HR and BP emerged from these trials. In the COR-I study, there was an initial increase (1.5 mm Hg during the first 8 weeks of treatment) in SBP, followed by a subsequent reduction. At the same time, those receiving placebo showed a greater decrease in BP.[52] In the COR-II study, there was an increase of about 1 bpm in HR in the treated participants compared with those receiving placebo.[53] A smaller fall in in BP was seen in the COR-BMOD study, similar to that in COR-I; 0.7% of treated patients had to discontinue treatment because of BP increases. The HR was not different at the end of the study, but during the first 20 weeks there was an average placebo-subtracted increase of 3.4 bpm.[54] In the COR-D study, the BP-related adverse event in treated participants was higher than that in those receiving placebo (12% vs 6.5%). In this case also, there were no differences between groups regarding SBP, DBP, or HR at the end of the study.[55] For these reasons, the FDA declined the application in January 2011 to await the outcome of a long-term CV outcome trial (Light study: clinical Trials ID: NCT01601704). In November 2013, Orexigen Therapeutics (La Jolla, CA) announced the results of a prespecified interim analysis of the Light study, excluding a hazard ratio of 2.0, using the upper bound of the 95% CI, for excess risk of MACE in patients receiving Contrave compared with those receiving placebo.[85] In addition to meeting the prespecified criteria for excluding CV risk, no new safety signals were observed. Currently, the drug is under review by both the FDA and EMA.

Side effects. The most common reported adverse event was nausea, which in most cases was transient for the first few weeks of treatment. Along with nausea, headache, dizziness, insomnia, and vomiting were the most common adverse events that led to discontinuation. Constipation, upper abdominal pain, and migraine were also reported.

GLP-1 receptor agonists

GLP-1R agonists and incretin therapies are established options for the treatment of T2D.[86] A meta-analysis on the effects of GLP-1R agonists on weight in clinical trials of overweight or obese patients with or without T2D showed a greater weight loss in GLP-1R—treated patients,[87] suggesting a role for the appetite-suppressant properties as an antiobesity drug.[88] Liraglutide (Victoza; Novo Nordisk, Plainsboro, NJ) is a long-acting GLP-1R agonist designed to resist rapid metabolism by dipeptidyl peptidase-IV.[89] Licensed for treatment of T2D at doses of 0.6-1.8 mg daily, it has no current indication as a weight loss agent. It has undergone full phase III trials at higher doses than used for T2D: 2.4 and 3.0 mg daily.

Weight loss. The effects of liraglutide in groups of obese nondiabetic adults were studied in a randomized phase II dose-ranging trial that included orlistat as an active comparator.[90] Participants were advised on increased physical activity and a 500-kcal daily energy deficit diet. Mean weight loss with liraglutide at doses of 1.2, 1.8, 2.4, and 3.0 mg was 4.8, 5.5, 6.3, and 7.2 kg, respectively, compared with 2.8 kg with placebo and 4.1 kg with orlistat. The percentage of individuals who lost more than 5% of their baseline weight with liraglutide 3.0 mg was 76% compared with 30% in those receiving placebo and 44% in those receiving orlistat. A largely open continuation of the trial, in which participants who continued or crossed over to liraglutide 2.4/3.0 mg maintained the lost weight, which was 3.0 kg more than lost by those who received orlistat.[56] Preliminary results from the phase III **S**atiety and **C**linical **A**diposity—**L**iraglutide **E**vidence in Non-Diabetic and Diabetic Subjects (SCALE) trial in obese or overweight people without T2D, but with comorbidities, were reported at the American Diabetes Association meeting in June 2014.[91] Patients achieved a significantly greater mean weight loss of 5.9% of baseline body weight vs 4.6% with liraglutide 1.8 mg ($P < 0.01$) and 2.0% with placebo ($P < 0.0001$). In the trial, 49.9% of participants lost at least 5% of baseline weight when treated with liraglutide 3 mg vs 35.0% of participants who were treated with liraglutide 1.8 mg ($P < 0.001$) and 12.7% of patients who were treated with placebo ($P < 0.0001$). The proportion of participants losing more than 10% body weight was significantly greater with liraglutide 3 mg (22.1 %) vs liraglutide 1.8

mg (13.3 %) and placebo (3.8%) ($P < 0.01$ and $P < 0.0001$, respectively).

Another randomized phase III trial included individuals (BMI $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 with comorbidities) who achieved $\geq$ 5% weight loss during an initial diet and exercise run-in period.[57] After the run-in period, liraglutide treatment not only maintained the weight loss achieved but also resulted in an additional 6% weight loss over 56 weeks compared with 0.2% in the placebo group. Thus, liraglutide treatment could represent a therapeutic strategy for successful weight loss. Another recent trial in overweight and obese patients with prediabetes[92] found that patients taking liraglutide 1.8 mg daily lost twice as much weight as those receiving placebo (Table 2).

CM effects. CM effects of liraglutide 2.4/3.0 mg included a decrease in WC of 6.2 cm compared with 4.5 cm with orlistat at 2 years as well as greater falls in SBP after 20 weeks compared with placebo and orlistat,[90] changes that were maintained at 2 years.[56] Liraglutide-treated individuals had a higher probability of having normal glucose tolerance at week 20,[90] albeit while still receiving treatment. HbA1c levels were reduced with liraglutide. Up to 62% of prediabetic individuals at baseline achieved normal glucose tolerance after 2 years compared with 26% of those receiving orlistat,[56] results that were confirmed in the SCALE study: significantly fewer individuals with obesity and normal blood glucose levels at baseline progressed to prediabetes with liraglutide 3 mg treatment (6.9%) at 56 weeks compared with those receiving placebo (19.9%).[91] Lipid levels were also improved: liraglutide 2.4/3.0 mg induced a higher LDL level, a decreased LDL level, and lower triglyceride levels compared with orlistat after 2 years.[56] The proportion of individuals with metabolic syndrome at week 20 decreased by > 60% in the liraglutide group compared with 38% and 13% in the placebo and orlistat groups, respectively.[90] Liraglutide-treated participants also achieved greater decreases in WC and glycemic parameters at week 56 in the Wadden et al. trial and in another trial specifically conducted in those with prediabetes (Table 2).[57] Concerns have been raised, however, over the finding of increased HR with liraglutide.[56] The clinical relevance of this on overall CV risk or benefit is being investigated in patients with T2D in the **L**iraglutide **E**ffect and **A**ction in **D**iabetes: **E**valuation of Cardiovascular Outcome **R**esults—A Long-Term Evaluation (LEADER) trial.[93]

Side effects. Liraglutide is generally well tolerated. Nausea and vomiting are the main, usually transient, side effects,[56] but they may actively contribute to weight loss.[94] As with all GLP-1R agonists, long-term safety data are not yet established; however, cardioprotective properties of incretin therapies have been already demonstrated.[95] Concerns about GLP-1 agonists and pancreatitis or pancreatic cancer have been raised,[96,97] but according to the EMA "no new data has emerged that implies that this risk is higher compared with what has previously been concluded."[98]

Conclusions

It appears that there are a number of new pharmacologic agents either approved or being evaluated by regulatory authorities that may have a role in managing the growing number of patients with clinical needs for weight loss as a result of the current obesity epidemic. Currently, all these drugs are centrally acting agents. Although they have all shown efficacy in weight loss, some may regard the amount of loss insufficient. It is important to recognize that clinical trials report means derived from intention-to-treat populations, whereas in clinical practice it is "responder" populations that better reflect the target population. Furthermore, significant metabolic, and in the main CV, risk factors are improved, which is probably related to weight loss rather than independent effects of the drugs. Even if the drugs are approved, substantial barriers remain in successfully integrating these agents into weight management practice, largely related to cost, patient acceptability, and clinician willingness to be engaged in adjunctive lifestyle management. Hard clinical outcome benefit has not yet been established. Although bariatric surgery is effective and very effective in selected patients, albeit requiring highly developed skills and follow-up, it is likely able to address only a small part of the overall clinical problem. Thus, newer and better drug combinations and more evidence of benefit from appropriately designed outcome trials is needed. If these deficiencies can be overcome, obesity pharmacotherapy may ultimately offer the best opportunity to address the enormity of the clinical challenge in managing the disease of obesity.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2014.11.010.