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Review

Pharmacotherapy of obesity: An update

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ABSTRACT

Several pharmacological approaches to controlling body weight have been developed over the last decades, albeit with limited success. Currently available agents include centrally acting appetite suppressants and peripherally acting compounds. Efficacy and safety of these agents in the clinical setting require a difficult balance. Further strategies including multiagonists able to simultaneously target multiple actors involved in obesity initiation and expansion such as the glucagon receptor family are under investigation. The results of recent clinical trials are encouraging and highlight emerging compounds as potential game changers. In view of the rising prevalence of obesity and the associated burden of comorbidities worldwide, and compared with other areas of pharmacological intervention, we feel that the field of obesity has been affected by therapeutic inertia. Of note, obesity may also affect the response to concomitant medications such as low-dose aspirin. Lessons from withdrawn agents such as the cannabinoid receptor antagonist rimonabant include developing compounds with a more targeted action profile (i.e., central vs peripheral, or antagonist versus inverse agonist) as well as careful selection of patients based on individual risk factors. We anticipate that the expanding knowledge base and clinical testing will result in improved outcomes for patients with obesity in the near future.

1. Introduction

Obesity is a chronic disease affecting millions of people world-wide, and is often associated with numerous co-morbidities, including type 2 diabetes, liver disease and cardiovascular disease. As the prevalence of obesity continues to sharply increase at a global level, it is crucial to develop strategies to prevent this chronic condition at a population level and at the individual level. Emerging research on the gut/brain axis including the microbiota has made transformational steps in our understanding of obesity etiology, as well as in treatment. There is strong evidence that the gut/brain axis is important not just for appetitive behavior but also energy homeostasis, blood glucose and even emotional state [1,2]. Connecting scientists in basic, transitional, clinical and pharmaceutical research will be crucial to moving the field forward.

2. Pharmacological Approaches to Obesity

The first weapons in the fight against obesity are diet and exercise [3]. Unfortunately, these often fail or show only short-term efficacy, leaving surgical techniques or drug therapy as feasible alternatives. Bariatric surgery is much more effective than currently licensed drugs. In fact, the attempt to control body weight with drugs has had a long and largely unremarkable history. Pharmacological approaches to obesity therapy require altering the balance between energy intake and expenditure and/or the partitioning of nutrients between lean tissue and fat [4]. Currently available agents include centrally acting appetite suppressants and peripherally acting compounds (Table 1). Further strategies are under investigation. For instance, metabolic cycles that spend energy not only create heat during cold exposure, but could also be harnessed to help treat obesity, where energy intake and output are often mismatched [5]. Combination therapies targeting complex

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Table 1
Currently approved medicines for obesity treatment.

Drug	Target and mechanism of action	Dose and route of administration	Regulatory status
Phentermine / topiramate	Phentermine: SLC6A2 transporter Topiramate: unclear mechanism	Oral capsule, extended release (11.25–69 mg; 15–92 mg; 3.75–23 mg; 7.5–46 mg)	Approved by FDA
Naltrexone / bupropion	Naltrexone: antagonist of opioid receptors in the brain Bupropion: inhibitor of noradrenaline and dopamine transporters	Extended release tablets (8–90 mg)	Approved by FDA and EMA
Setmelanotide	Agonist of melanocortin-4 receptor (MC_4R)	10 mg, subcutaneous injection	Approved by FDA Orphan designations by EMA
Liraglutide	GLP-1 receptor agonist	Maximum dose 3 mg/die, subcutaneous injection	Approved by FDA and EMA
Orlistat	Inhibitor of gastric and pancreatic lipases, diacylglycerol lipase (DAGL) and αβ-hydrolase 12 (ABHD12)	Oral capsule; 120 mg prescription, 60 mg over-the-counter Maximum dose: 120 mg three times a day	Approved by FDA and EMA

pathways involved in appetite regulation [6] as well as innovative polypharmacological treatments able to simultaneously target multiple actors involved in obesity initiation and expansion [7] also appear to be promising approaches.

Benefits of weight loss therapies are not limited to the control of cardiometabolic risk. Because *in utero* exposure to obesity is associated with altered gene expression and metabolic abnormalities in offspring [8], reducing obesity among women before they become pregnant could contribute to lower incidence of childhood obesity. With regard to approved medications, there is neither specific consideration for women of reproductive age nor safety information during pregnancy and breastfeeding. Thus, if women plan to pursue pregnancy, the anti-obesity medication should be discontinued prior to conception [9].

The mechanism(s) of action of anti-obesity drugs will be only briefly mentioned in the following sections. Additional details may be found in other qualified articles [10,11].

3. Agents approved for use in the United States and/or European Union

3.1. Centrally acting appetite suppressants

Despite improved understanding of the biochemical signals that regulate appetite, there has been little translation of this research into effective and safe pharmacological agents in clinical practice. Among centrally acting drugs to control appetite that have been developed and used for decades, dexfenfluramine, fenfluramine and sibutramine showed benefit on weight loss and glycemic control e.g. in patients with obesity and diabetes [12], but were withdrawn because of the increased risks of valvular heart disease and pulmonary hypertension. The selective cannabinoid type 1 (CB_1) receptor antagonist rimonabant, which suppresses appetite by acting in the hypothalamus, gained European Medicines Agency (EMA) approval in 2007 but was withdrawn in January 2009 due to psychological disturbances. While in clinical use, rimonabant induced an array of metabolic effects not limited to weight loss, but was probably prescribed to patients with underlying subclinical or clinical conditions affecting mood and behavior more likely to experience side effects [13]. Despite limited success and marketing authorization withdrawals for several agents in different countries, however, the development of centrally acting appetite suppressants is still being actively pursued.

3.1.1. Phentermine / topiramate

The amphetamine analogue phentermine suppresses appetite by inhibiting noradrenaline reuptake by the transporter *SLC6A2* in the hypothalamus, while the exact mechanisms of action of the anticonvulsant topiramate are not fully understood. Topiramate is a multifunctional compound, and has weight-loss as a side-effect primarily due to a reduction in body fat mass. The phentermine / topiramate combination stimulates the synaptic release of serotonin, noradrenaline and dopamine, and enhances GABA action. According to a recent systematic review, phentermine/topiramate has shown the most robust body weight reduction compared to other anti-obesity agents [14]. While licensed in the United States since 2012, this combination was refused authorization for use in the European Union in 2013 due to concerns about long-term effects on the heart related to phentermine, as well as depression, anxiety and cognitive impairment due to topiramate [15].

3.1.2. Naltrexone / bupropion

A fixed-dose combination of the opioid-receptor antagonist naltrexone and the noradrenaline–dopamine uptake–reuptake inhibitor bupropion, which are licensed individually in the European Union for other uses, is used for treating obesity [16]. Though possibly acting as a non-competitive nicotinic receptor antagonist, bupropion inhibitory action of dopamine and noradrenaline reuptake accounts for its indication to aid smoking cessation [17,18]. This agent undergoes extensive liver metabolism and is converted to three active metabolites mainly by CYP2B6; it is also an inhibitor of CYP2D6, which may cause clinically relevant interactions with e.g. tamoxifen. Bupropion has also relevant interactions with several CYP2D6 substrates including some antidepressants, antipsychotics, beta-blockers, and antiarrhythmics. There is a risk of pharmacodynamic interactions if bupropion is taken concomitantly with linezolid, tramadol or MAO-inhibitors; extreme caution should be applied when prescribing bupropion with drugs that lower the seizure threshold. Although the mechanism of action is not fully understood, naltrexone 8 mg / bupropion 90 mg in combination reduce appetite and food intake, and increase energy expenditure, helping patients to stick to a calorie-controlled diet and to reduce their body weight. In the main studies [19,20], the average weight loss in patients treated with naltrexone / bupropion was 3.7–5.7%, compared with 1.3–1.9% with placebo; the proportion of treated patients who achieved 5% weight loss was 28–42% compared with 12–14% with placebo. About 13–22% of those taking the combination achieved at least a 10% reduction in weight compared with 5–6% with placebo. Of note, the cardiovascular safety of this treatment among overweight or obese patients at increased cardiovascular risk remains uncertain [21]. Thus, the EMA requested a post-authorization multicenter, randomized, double-blind, placebo-controlled, phase 4 study to assess the effect of naltrexone extended release (ER) / bupropion ER on the occurrence of major adverse cardiovascular events in subjects with overweight and obesity to be completed by 2022.

3.1.3. Setmelanotide

Melanocortins transduce hormonal signals regulating appetite. Defects in melanocortin-4 receptor (MC_4R) signaling are prevalent in obesity, and MC_4R mutations can result in early-onset syndromic obesity. Setmelanotide is a cyclic peptide, able to cross the blood-brain barrier when administered peripherally, acting as a MC_4R agonist [22]. The US Food and Drug Administration (FDA) approved setmelanotide for chronic weight management (weight loss and weight maintenance for at least 1 year) in patients aged 6 years and older with obesity due to 3 rare genetic conditions: pro-opiomelanocortin (POMC) deficiency, proprotein subtilisin/kexin type 1 (PCSK1) deficiency, and leptin

receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes considered pathogenic, likely pathogenic or of uncertain significance. This is the first FDA-approved treatment for these genetic conditions. While leading to weight loss in patients with obesity associated with these conditions, setmelanotide does not treat the genetic defects that cause the conditions or other symptoms or signs. The effectiveness of setmelanotide was assessed in 21 patients. In this study, 80% of patients with POMC or PCSK1 deficiency and 46% of patients with LEPR deficiency lost ≥ 10% of their body weight [23]. The most common side effects of setmelanotide included injection site reactions, skin hyperpigmentation, headache and gastrointestinal side effects. Darkening of the skin and hair is likely due to off-target activation of melanocortin receptors (MC_1R) in peripheral melanocytes.

In Europe, setmelanotide was granted orphan designation for treatment of a number of conditions including Prader-Willi syndrome, pro-opiomelanocortin deficiency, Bardet-Biedl syndrome, leptin receptor deficiency and Alström syndrome. The drug is expected to restore appetite control in patients, thereby reducing their food intake and weight gain.

3.2. Agents with mixed central and peripheral action: liraglutide

The glucagon-like peptide-1 receptor agonist liraglutide, which is used for treating type 2 diabetes, also has anorexic actions [24] and is approved to help manage weight in adults both in the United States and in the European Union. While the dose can be increased up to 1.8 mg/die to improve glycemic control in patients with insufficiently controlled type 2 diabetes mellitus, the maximum dose for weight management is 3 mg/die. Evidence from trials of liraglutide in adults suggests that weight loss is mediated primarily by reduced appetite and energy intake [25]. Liraglutide treatment at 3 mg for up to 1 year has been shown to be effective in landmark studies involving over 5800 obese or overweight patients, leading to a 7.5% reduction in body weight compared with a 2.3% reduction in patients taking placebo [26–28]. Treatment should be stopped if patients have not lost at least 5% of their initial body weight after 12 weeks of treatment with 3 mg liraglutide per day. Beneficial effects of liraglutide plus lifestyle therapy compared with placebo on weight reduction were also reported in 251 adolescents with obesity [29]. The estimated treatment difference in the mean reduction in the BMI standard-deviation score observed in this trial was –0.22, which is considered to be clinically meaningful. Gastrointestinal adverse events were more common with liraglutide than with placebo (65% vs. 37%; $p < 0.001$). Of note, the weight loss effects of liraglutide offer a unique opportunity to expand the treatment options available to polycystic ovary syndrome patients [30–32], who in many cases are overweight or obese [33]. Liraglutide is commonly associated with gastrointestinal adverse effects (nausea, diarrhoea, and vomiting), which are dose-dependent and are markedly reduced with proper dose titration [34]. Other rare safety concerns may include hypoglycemia, vomiting and diarrhea, dehydration, altered renal function, allergic reactions, gallstones and acute pancreatitis.

Intensive behavioral therapy combined with liraglutide can produce clinically meaningful weight loss in patients who receive the treatment in primary care settings. In a 56-week study, all participants received 15-minute individual counselling sessions of behavioral therapy delivered by registered dietitians following a detailed treatment protocol. Participants were also randomized to receive either liraglutide 3 mg (n = 142) or placebo (n = 140). Significantly more individuals taking liraglutide 3 mg than placebo achieved ≥ 5%, > 10% and > 15% weight loss [35].

3.3. Peripherally acting agents: orlistat

Orlistat is an irreversible inhibitor of gastric and pancreatic lipase that prevents triglyceride hydrolysis and decreases absorption of dietary fat by ~30%. In a meta-analysis of 11 long-term placebo-controlled trials including over 6000 patients, orlistat was found to produce a 2.9% greater reduction in body weight than in the control group, and 12% more patients lost 10% or more weight compared with controls [36]. In an updated meta-analysis including 17 trials of duration longer than 1 year, these findings were essentially unchanged [37]. Only negligible amounts of orlistat or metabolites thereof are absorbed [38], which accounts for its good safety record. Orlistat is generally well tolerated, with gastrointestinal adverse events being most commonly reported [39].

The drug formulated as 60-mg capsules has recently been licensed for inclusion in over-the-counter medicines, whereas the 120-mg capsules are available as prescription medicines. Malabsorption of fat-soluble vitamins and drugs has been reported. The most clinically relevant drug interactions of orlistat occur with cyclosporin [40,41] and antiretroviral agents such as tenofovir and emtricitabine [42]. Such interactions significantly reduce absorption of co-administered victim drugs. Orlistat can also reduce the absorption of antiepileptic drugs [43].

4. The rise and fall of the selective serotonin (5-HT)$_{2C}$ receptor agonist lorcaserin

A modest benefit in terms of weight loss was observed in the main studies of the 5-HT_{2C} receptor agonist lorcaserin, which acts by increasing levels of the anorexigenic peptide pro-opiomelanocortin in the hypothalamus [44]. However, concerns were raised about the potential risk of tumors, particularly with long-term use, psychiatric disorders such as depression and valvulopathy [45]. The latter side effect is due to off-target activation of cardiac 5-HT_{2B} receptors [46]. In a large trial of 12,000 patients who were overweight or obese (BMI ≥27) with established atherosclerotic cardiovascular disease or multiple cardiovascular risk factors, lorcaserin (10 mg twice daily) induced weight loss of ≥ 5% in 38.7% of patients compared with 17.4% of patients in the placebo group at 1 year (odds ratio [OR] = 3.01, 95% confidence interval [CI] = 2.74–3.30, $P < 0.001$) with no evidence of increased cardiovascular risk [47]. However, a trend towards increased rates of valvulopathy and pulmonary hypertension was observed in the lorcaserin group, along with marked hypoglycemia (13 vs. 4 patients; $P = 0.04$), mainly in those with diabetes at baseline. This medication was approved by the US FDA in 2012 and withdrawn in February 2020, because the 5-year follow-up of the above safety trial revealed increased cancer occurrence associated with lorcaserin therapy. One additional cancer per 470 patients treated with lorcaserin for one year was observed. In particular, pancreatic, colorectal and lung cancers occurred more frequently in treated patients [48]. Lorcaserin never gained approval in Europe.

5. Investigational anti-obesity agents: spotlight on the pipeline

5.1. Tesofensine

Tesofensine is a novel triple monoamine reuptake inhibitor that induces weight loss primarily by reducing food intake with a slight effect on energy expenditure [49]. A phase 2 clinical trial reported significant weight loss in the tesofensine group compared with placebo along with a significant increase in heart rate [50]. Expression of concerns about underreporting of adverse effects and the blinding procedure have been expressed [51]. A new drug application has been submitted for approval of tesofensine as a treatment of patients with obesity in Mexico.

The combination of tesofensine plus the β_1 adrenoceptor blocker metoprolol has been reported to induce a hypophagic response in preclinical models with no increase in heart rate or blood pressure due to adrenergic overdrive [52]. In a recent study in patients with hypothalamic obesity [53], the fixed-dose formulation of tesofensine plus metoprolol (tesomet) resulted in an additional mean weight loss of 6.3% at week 24 ($P = 0.017$) compared with placebo (weight loss 0.3%) and a

significant increase in the proportion of patients with 5% reduction in body weight (61.5 vs 12.5%; $P = 0.046$). Significant positive correlations were seen between tesomet-induced weight loss and reductions in fat mass ($P = 0.0001$), waist circumference ($P = 0.002$), triglycerides ($P = 0.05$), and lean tissue mass ($P = 0.03$). This combination was generally well tolerated without effects on blood pressure and heart rate.

5.2. Semaglutide

Evidence of body weight loss in large cardiovascular outcome trials was also found in patients treated with the GLP-1 receptor (GLP-1R) agonist semaglutide compared with placebo [54–56]. The very recent STEP 1 study involving almost 2000 patients worldwide showed that about 75% of those who received semaglutide 2.4 mg weekly via subcutaneous injection using a prefilled pen lost more than 10% of their body weight, and 35% lost more than 20% [57]. On average, the change in body weight from baseline to week 68 was − 15.3 kg in the semaglutide group as compared with − 2.6 kg in the placebo group. Such an effect is larger than that observed with liraglutide, and did not appear to have reached a plateau at the end of follow-up. Weight loss in high responders in this study was comparable to that observed following bariatric surgery. Semaglutide is approved at a lower dose for treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise, and is available for both parenteral (up to 1 mg once a week s.c.) and oral (3 mg, 7 mg and 14 mg tablets, maximum recommended single daily dose 14 mg) administration. This is the first GLP-1R agonist treatment developed for oral use, but has not been licensed for weight management in obese or overweight patients yet. Following the STEP1 trial, semaglutide has been submitted for regulatory approval as a treatment for obesity in the United Kingdom, the European Union and the United States.

5.3. Dual GLP-1/GIP receptor agonist

The glucagon family of receptors are activated by endogenous peptides comprising growth hormone-releasing hormone, gastric inhibitory polypeptide (GIP), glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), glucagon and secretin. Among these, GLP-1Rs [58] attracted much interest from the pharmaceutical industry as targets for further effective antidiabetic anti-obesity medications.

Based on the hypothesis that combined treatment with GLP-1 and GIP receptor agonists would induce additive effects on glucose and body weight regulation, the dual GLP-1/GIP receptor agonist tirzepatide (LY3298176) has been developed as a treatment for type 2 diabetes. This 39-amino acid synthetic peptide is suitable for once-weekly subcutaneous administration. A recent elegant pharmacological investigation revealed the unique profile for tirzepatide as an imbalanced agonist due to higher affinity and potency at the GIP receptor (GIP-R) versus GLP-1R as well as a biased agonist at the GLP-1R while retaining full agonism at the GIP-R [59]. The degree of HbA_{1c} reduction and weight reduction observed in pre-clinical, phase 1 and 2 clinical trials has not previously been observed in diabetes clinical trials. In a phase 2b study, treatment of type 2 diabetes patients with tirzepatide for 26 weeks resulted in a statistically significant and clinically meaningful control of HbA_{1c} with greater weight loss and an acceptable tolerability profile with respect to treatment with the GLP-1R agonist dulaglutide alone [60]. Three different 8-week dose-escalation regimens followed by 4-week dosing of 12 or 15 mg have been tested in order to select therapeutic doses and dose-escalation steps for investigation within the phase 3 studies of tirzepatide [61]. The phase 3 SURPASS clinical trial programme including ten studies is testing the hypothesis that tirzepatide treatment provides comparable efficacy, safety and cardiovascular outcomes in the management of type 2 diabetes [62]. The SURPASS trials will also provide insight into understanding of incretin hormones, particularly the role of GIP in energy metabolism. The SURPASS-1 trial is due to be completed soon and results are eagerly awaited. Dose-related gastrointestinal events and decreased appetite have been the most common adverse events so far. It is as yet unknown how tirzepatide will compare with the best-in-class HbA_{1c}-lowering provided by semaglutide.

5.4. Dual GLP-1/glucagon receptor agonists

Glucagon receptor agonism may appear counterintuitive as a treatment for diabetes, which often complicates obesity. However, glucagon can suppress appetite, increase energy expenditure, delay gastric emptying time and even enhance insulin secretion under certain circumstances [63]. Phase IIa data for MEDI0382/cotadutide, a dual GLP-1-glucagon receptor agonist, in 51 overweight to obese type 2 diabetic patients reported improved glycemic responses in mixed-meal tolerance tests after once-daily dosing of up to 200–300 μg for 3–6 weeks [64]. The reduction in body weight was significantly greater with MEDI0382 than with placebo (mean difference of 2.14 kg). A subsequent study with once-daily subcutaneous 50–300 μg cotadutide or placebo administration to 65 patients for 49 days confirmed a significant reduction in body weight in cotadutide-treated patients versus placebo [63]. Compared with the previous trial, use of a starting dose of 50 μg resulted in a lower incidence of gastrointestinal adverse events. However, a significant increase from baseline to day 49 in pulse rate was reported with cotadutide compared with placebo. Longer term studies are required to better assess the clinical utility of this compound.

The results of the first in-human trials with SAR425899, another dual GLP-1-glucagon receptor agonist, show significant reductions in fasting plasma glucose and HbA_{1c} levels along with body weight loss in overweight healthy volunteers and in overweight/obese patients with type 2 diabetes. SAR425899 showed a favourable pharmacokinetics/pharmacodynamic profile in these subjects including a long half-life (11–18 h), which makes it suitable for a once-daily regimen [65]. Of note, a PET study in 6 type 2 diabetes patients aimed to assess target occupancy at glucagon receptor in liver and GLP-1R in pancreas after 17 and 20 days of treatment with SAR425899, respectively. The study demonstrated strong SAR425899 binding to the GLP-1R, but low occupancy at the glucagon receptor [66]. The high dropout rate along with unclear glucagon receptor-mediated effects in the latter study warrant further investigation.

Finally, balanced GLP-1/GIP/glucagon receptors triagonists are under preclinical development. The conceptual framework of this approach entails that GLP-1R agonism supports weight loss and insulin secretion, glucagon receptor agonism triggers independent complementary weight loss mechanisms, and GIP receptor agonism would further buffer glucagon-mediated hepatic glucose production through enhanced insulin secretion [67]. Phase 1 studies of a few such multireceptor agonists are under way.

Peripheral CB_1 receptor blockade activates multiple anti-obesity mechanisms [68–70], and peripheral CB1 receptor blockers are being investigated for therapeutic purposes being devoid of the neuropsychiatric adverse effects observed with centrally acting CB_1 receptor blockers [71]. A recent preclinical study reported that administration of a peripheral CB_1 receptor antagonist together with semaglutide to diet-induced obese mice led to greater reduction in body weight and fat mass than either agent alone [71], suggesting a functional cross talk between GLP-1 and CB_1 receptor signalling.

6. Obesity as a risk factor for drug toxicity or impaired responsiveness

An often-overlooked aspect in clinical practice is the impact of increased body weight on the pharmacokinetics, efficacy and safety of drug treatments [72]. This can be especially challenging for the pediatric population, due to the current gap of knowledge and the lack of dosing guidelines [73]. For instance, decreased sensitivity for effects on certain receptors, especially acetylcholine, and increased psychomotor

response to benzodiazepines has been reported in patients with obesity [74]. A potential association of body mass index and cardiotoxicity was examined using prospective data from a study including 929 patients with stage I to III breast cancer who were treated with anthracyclines and/or trastuzumab. Compared with the normal-weight group, the group with obesity was more prone to cardiotoxicity, regardless of other predictors of cardiotoxicity. In addition, cardiotoxicity was independently associated with obesity (OR = 3.02; 95% CI, 1.10–8.25; $P = 0.03$) and trastuzumab administration (OR = 12.12; 95% CI, 3.6–40.4; $P < 0.001$) [75].

In people with obesity, various mechanisms affect the pharmacodynamics and pharmacokinetics of aspirin [76]. Obesity has been found to be associated with higher residual thromboxane B_2 levels and higher on-treatment platelet reactivity after the 24–hour drug-dosing interval of once-daily low-dose aspirin in a cohort of otherwise-healthy subjects with moderate-to-severe obesity [77]. Pharmacokinetics observations disclosed reduced aspirin peak concentrations already at 4 h after intake, probably as a result of reduced drug bioavailability [77]. A recent meta-analysis of cardiovascular prevention trials showed that patients with a body weight of more than 70 kg may have lower cardiovascular protection by once-daily low-dose aspirin, suggesting that higher daily doses or a twice daily regimen of aspirin might be necessary in these subjects [78]. Thus, current antiplatelet drug regimens require adjustments in patients with obesity to improve outcomes.

7. Conclusions

There is considerable scientific and financial interest in developing pharmacologic therapy for obesity. Despite improved understanding of the neurochemical signals that regulate food intake, translation of this research into effective and safe pharmacological agents in clinical practice has been limited. Pharmacological research has been successful in identifying specific ligands that modulate signaling systems in the brain involved in food intake, satiety and energy homeostasis. Delivering these agents specifically to the brain regions, specific cells and subcellular structures where such signaling events take place, however, remains challenging. This is why the benefits of current anti-obesity medications do not necessarily outweigh risks. Peripherally acting agents appear to be safer, but limited efficacy with orlistat and lack of long-term safety data with GLP-1R agonists are to be considered.

At variance with type 2 diabetes and hypertension, we feel that the field of obesity pharmacotherapy has been affected by therapeutic inertia. Careful selection of patients for pharmacological treatment appears to be a priority and may result in improved outcomes with acceptable safety. A blend of nonpharmacological and pharmacological approaches may provide incremental benefit over current strategies. Of note, recent trials of investigational agents have yielded encouraging results. Thus, exciting developments are poised to expand the therapeutic armamentarium for obesity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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