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Obesity medications in development

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Abstract

Introduction—Obesity is compounded by a neurobiology that is resistant to weight loss. Therefore, the development of pharmacotherapies to address the pathology underlying the dysregulation of energy homeostasis is critical.

Areas Covered—This review examines selected clinical trial evidence for the pharmacologic treatment of obesity and provides an expert opinion on anti-obesity drug development. The article includes the outcomes of anti-obesity medications that have been evaluated in clinical trials but have not yet received approval from the U.S. Food and Drug Administration. The mechanisms of action of glucagon-like peptide-1 agonists and co-agonists, diabetes medications being investigated for weight loss, and medications acting on the central nervous system as well as peripherally are reviewed. A search was conducted on PubMed using the terms 'Obesity AND Medications' restricted to clinical trials reported in English. Using similar terms, a search was also conducted on ClinicalTrials.gov.

Expert Opinion—The goal of anti-obesity therapy is finding compounds that are effective and have minimal side effects. Combining medications targeting more than one of the redundant mechanisms driving obesity increases efficacy. However, targeting peripheral mechanisms to overcome the trickle down effects of centrally acting drugs may be the key to success in treating obesity.

Keywords

Diabetes; Metabolic Syndrome; Incretin; Sirt-1/AMPK; FGF-21; MetAP2 Agonists; SGLT-2; DGAT-1; neurotransmitter reuptake inhibitors

1. Introduction

Over the last 150 years, global life expectancy has risen steadily. We have either eradicated or reduced the incidence of infectious diseases such as small pox and polio that once afflicted society.[1] With falling mortality rates in all groups, it is seemingly incongruous that we still fall short of health expectations. However, with the rise in chronic and

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degenerative diseases, fueled in part by obesity and the new and pressing challenges it poses, living longer may simply mean an increase in years of disability.[2] Approximately, 13% of the world's population have obesity.[3] Since 1980, the prevalence of obesity has doubled in more than 70 countries and has continued to rise in most other countries. [4]

Body weight is under homeostatic control and maintained relatively constant through a complex array of central nervous system circuitry that integrates peripheral metabolic feedback signals of either energy abundance or deficit.[5] In an environment where there is no dearth of readily available energy dense food choices and little incentive to engage in physical activity, a mismatch between physiology and the environment results in a chronic energy surplus and the development of obesity. To compound the issue, we are endowed with a biological resistance to weight loss and a predisposition to weight gain prompted by counter-regulatory mechanisms. Postprandial decreased activation of reward-related cues and the impact of cognitive functions such as memory, attention, and emotions have been implicated. These environmental, central, and peripheral mechanisms interacting with genetic, epigenetic, and other mechanisms contribute to the complexity of obesity.[5]

Pharmacotherapies seek to alter the interplay of hormones, receptors, and cells that coordinate to shape our body and its response to environmental factors. The task seems Herculean, nevertheless, the development of novel medical therapies to address the pathology underlying the dysregulation of energy homeostasis is ongoing. Centrally acting drugs that directly manipulate neurotransmission to target feeding circuitries have the potential to affect other physiologic systems, particularly psychiatric effects such as mood disorders. As a result drug combinations with synergistic actions which permit reduced dosage, and the development of novel compounds with less systemic effects are being explored.[6]

Our understanding of the anorexic effect of peripheral signals such as adipocyte-derived leptin, its downstream effectors, and the gut hormones has led to pointed investigation of these targets for obesity treatment. Signals derived from peripheral organs are being pharmacologically leveraged, with the development of several classes of peptide-based multi-agonists and peptide small-molecule conjugates with robust preclinical evidence. Coordinated targeting of multiple signaling pathways including food intake, energy expenditure and glucose metabolism have become the therapeutic focus, and novel hormonal-based combination pharmacotherapies to address obesity are under development. [7]

The discovery and elucidation of the anorexic effects of the gut hormone glucagon-like peptide 1 (GLP-1) precipitated the development of long-acting pharmacologic GLP-1 receptor (GLP1R) agonists that result in meaningful weight loss. [8–10] Synergistic effects of GLP-1 with other gut hormones, and the finding that the sodium-glucose transporter 2 (SGLT2) and metformin developed for glycemic control produce weight loss are driving the advancement of obesity medications.[11–15]

This review will examine selected clinical trial evidence for the treatment of obesity. However, the primary objective is to provide an opinion on the state of the science as it

relates to the pipeline of emerging treatments for obesity. A search was conducted on PubMed using the terms 'Obesity AND Medications' restricted to clinical trials reported in English. Using similar terms a search was also conducted on ClinicalTrials.gov. The United States (US) is at the forefront of anti-obesity drug development. Other nations such as Japan (mazindol and cetilistat), China (orlistat), or Europe (orlistat, the combination of naltrexone with bupropion, and liraglutide) have few approved anti-obesity medications, Therefore, this paper will present the US perspective.

2. Incretin Agonists in Drug Development

2.1. Peptide YY and Analog

Peptide YY (PYY) which is released post-prandially is a well-characterized mediator of satiety and exerts its effects through the Y family of receptors. It is released from the L cells of the GI tract throughout the gut but is present in highest concentrations in the distal regions. The most effective form is the amino-terminally truncated version, $PYY_{3–36}$, since the full form binds with little affinity to the Y receptors.[16] The preferred Y2 receptor is highly expressed in orexigenic neuropeptide Y neurons in the hypothalamic arcuate nucleus. Peripheral administration of $PYY_{3–36}$ reduces food intake in rodents and humans.[17,18] The results in rodents could not be replicated[19] and in humans the anorectic effect was evident only at pharmacologic doses.[20]

Novo Nordisk recently completed a clinical trial to evaluate the safety, tolerability, and pharmacokinetics of single and multiple doses of a subcutaneously delivered PYY analog. The drug was delivered twice weekly for five months, and compared with semaglutide, (, ClinicalTrials.gov). However, $PYY_{3–36}$ is present in the saliva of rodents and humans, and its anorectic effect appears to be mediated through activation of the specific Y2 receptor expressed in the lingual epithelial cells. In rodents, increase in salivary $PYY_{3–36}$ over eight weeks resulted in a significant reduction in food intake and body weight.[21] Gila Therapeutics completed a safety, tolerability, and pharmacokinetics study of $PYY_{3–36}$ applied directly to the tongue mucosa (, ClinicalTrials.gov), No results have been posted for the two clinical trials of $PYY_{3–36}$. Thus, the clinical trials of sublingual $PYY_{3–36}$ are in the early stages, and the results of these studies will determine its therapeutic potential in the treatment of obesity.

2.2. Glucagon-like Peptide 1 Receptor Agonists

Glucagon-like peptide 1 secreted from the L cells in the small and large intestine and from neurons in the nucleus tractus solitarius of the caudal brain stem, exhibits pleiotropic effects including increased insulin secretion, suppression of appetite and food intake, and delay in gastric emptying. Native GLP-1 has a circulating half-life of 1 – 2 minutes in humans as a result of degradation by dipeptidylpeptidase-IV (DPP-IV).[22] Substitution of the native alanine at position 2 confers protection from degradation by DPP-IV, or other modifications such as non-covalent attachment to serum albumin extend the plasma circulation time.[23–25] The development of longer acting subcutaneously delivered GLP1R agonists have resulted in weight loss and improvements in type 2 diabetes management. The GLP1R

agonists exenatide, lixisenatide, dulaglutide, and albiglutide have a half-life ranging from 2.4 hours to five days because of amino acid substitutions at position 2.

Liraglutide was developed with enhanced sequence similarity to native GLP-1 by retaining the alanine at position 2 but with modifications to provide protection against degradation.[26] Liraglutide, dulaglutide and albiglutide therapy are approved by the US Food and Drug Administration (FDA) for diabetes, but result in weight loss of 1.3 to 8.7 kg, 2.3 to 3 kg, and 1.1 to 1.7 kg respectively, compared to baseline.[27–29] Semaglutide is a GLP-1 analog similar to liraglutide but has an amino acid substitution for alanine at position 2 and a non-covalent association to provide a half-life of 165 hours.[30] Semaglutide therapy (0.05 mg or 0.1 mg) produces similar weight loss from baseline (8.5 kg) as liraglutide 3.0 mg treatment that is approved for obesity. However, at doses greater than 0.2 mg semaglutide produces greater weight loss with a similar adverse event (nausea and vomiting) profile as liraglutide 3.0 mg.[31]

Semaglutide is the only GLP-1 analog that has been developed as an oral formulation with an absorption enhancer to overcome low bioavailability observed with oral peptides. At 14 mg once daily semaglutide produces a greater weight loss than subcutaneous liraglutide at its highest approved dose for diabetes (1.8 mg). Safety and tolerability of oral semaglutide is consistent with subcutaneous liraglutide and the GLP1R agonist class of drugs.[32] Semaglutide holds promise as an anti-obesity treatment and Novo Nordisk has sought approval from the U.S. Food and Drug Administration (FDA) for oral semaglutide as a treatment for diabetes, but is expected to submit for an obesity indication at a higher does in the future.

3. Incretin - Co-Agonists in Drug Development

The adverse gastrointestinal effects and acute tachycardia induced by GLP1R agonists precludes achieving the maximal efficacy that could be achieved through activation of GLP1R signaling. Combinations with other hormones to potentiate the weight loss effect permits the activation of GLP1R signaling at lower than maximal doses for enhanced tolerance and efficacy.[33] Combinations of GLP-1 with gastrointestinal hormones having known effects on suppression of appetite, improvements in glycemic control, or stimulation of energy expenditure being a natural corollary, dual agonists with finely tuned mixed agonism have been developed and evaluated in clinical trials. Biochemical signaling through triple agonists has the potential to achieve comparable metabolic benefits while minimizing the risks of undesirable effects but as yet has no documented evidence of efficacy in humans.

3.1. Glucagon-like Peptide 1 + Glucagon Receptor Agonists

The central nervous system responds to a suppression of appetite and food intake by decreasing energy expenditure which is counteractive to inducing weight loss. Glucagon's established role is to oppose insulin action and increase blood glucose concentrations, lipolysis, and thermogenesis.[34] Thus, the biochemical and physiologic mechanisms by which glucagon enhances energy expenditure complement the actions of GLP-1 and would be the appropriate choice for co-agonism. Although seemingly counterintuitive in patients with impaired glucose metabolism, striking a fine balance between glucagon agonism and

GLP-1-induced anorexia has the effect of buffering the hyperglycemic risk of unopposed glucagon pharmacology with weight loss induced by GLP-1.[35] In clinical trials of GLP1R and glucagon receptor co-agonists, bodyweight reduced by 2.14 kg in 42 days with MED10382 (Medimmune), compared to placebo.[36] The GLP1R and glucagon receptor co-agonist SAR425899 (Sanofi) therapy for 21 days produced a weight loss of 5.32 kg in healthy subjects and in subjects with type 2 diabetes, SAR425899 produced a weight loss of 3.09 kg in 28 days.[37] Although these studies support the potential of GLP1 and glucagon receptor dual agonism for inducing weight loss, the sample sizes were small and further trials are needed to confirm the results in larger and longer-term trials.

3.2 Glucagon-like Peptide 1 + Glucose-dependent Insulin-tropic Peptide Receptor Agonists

Glucose-dependent insulin-tropic peptide (GIP) is an incretin hormone released by the K-cells of the gastrointestinal tract, and together with GLP-1 are largely responsible for the enhanced postprandial insulin secretion in healthy adults. Inhibition of DPP-IV increases the half-life of GLP-1 and GIP, suggesting a commonality in the consequences of their actions. Animal studies suggesting that GIP promotes obesity and impairs lipid metabolism quelled enthusiasm for GIP agonism.[38–41] However, studies showing that in patients with type 2 diabetes hyperglycemia blunts the incretin effect of GIP and that sensitivity to GIP is regained following therapy to control hyperglycemia, revived interest in GIP.[42,43] Further, GIP may modulate β-cell survival through signaling pathways independent of GLP-1.[44]

The two incretins may act through different mechanisms but the actions of GIP are dependent on control of hyperglycemia by GLP-1. Therefore, the likelihood of a synergistic effect on glucose metabolism and body weight held promise. The GLP-1/GIP dual agonists do not bind simultaneously to two different receptors in the same target cell. They are unimolecular and bind to either the GLPIR or the GIP receptor (GIPR). [35] The relative levels of occupancy proportionately reduces binding to GLP1R and is expected to reduce the adverse events associated with GLP1R agonism. The dual agonist NNC0090–2746 (Novo Nordisk) has balanced GLP1R and GIPR agonism; whereas, LY3298276 (Eli Lilly) is balanced toward GIPR agonism.[45,46]

The proof-of-concept clinical trial of NNC0090–2746 therapy in patients with type 2 diabetes inadequately controlled with metformin, significantly reduced body weight compared to placebo at eight weeks, but not at the end of the 12-week trial. Although treatment with NNC0090–2746 was determined to be safe and well-tolerated, further investigation is warranted.[46] In the phase II trial of LY3298276 5 mg, 10 mg, and 15 mg therapy, body weight reduced in a dose dependent manner compared to placebo and with clinically meaningful differences compared with 1.8 mg of dulaglutide. More subjects treated with 5 mg, 10 mg, and 15 mg doses of LY3298276 reached weight loss targets (> 5%, > 10%, and > 15% from baseline) than did subjects treated with placebo or dulaglutide with similar treatment-related adverse events.[45] The GLP1R/GIPR dual agonists have the potential to produce clinically relevant reductions in body weight and broaden the therapeutic window of GLP-1 receptor agonists but have yet to be evaluated in large

confirmatory studies to determine their superiority compared to selective GLP-1 receptor agonist class of agents.

4. Energy Consumption Activators in Drug Development

Fibroblast growth factor 21 (FGF21) has garnered substantial interest because of its profound metabolic benefits in animal models of type 2 diabetes and obesity. In obese rodents, it causes weight loss and increases insulin sensitivity without hypoglycemia or reductions in food intake.[47–49] Although FGF21 has similar metabolic effects in monkeys, it does not decrease food intake, which underscores its differing mechanisms of action across species.[50–54] FGF21 binds to a cell surface receptor complex comprised of the FGF receptor (FGFR) and a co-receptor protein named β-klotho, to activate FGFR signaling activity.[55] Long-acting FGF21 analogs have been evaluated in human studies with inconsistent results on weight loss.[52,56–58]

An engineered FGF21 protein (LY2405319 [Eli Lily]), 10 mg and 20 mg doses for four weeks significantly reduced body weight in obese subjects with type 2 diabetes compared to baseline (−1.75 kg and −1.49 kg respectively), but was not different from the placebo.[57] Pegbelfermin (BMS-986036, Briston-Myers Squibb) is a polyethylene glycol-modified recombinant human FGF21 analog with a prolonged half-life to support weekly administration. Over 12 weeks Pegbelfermin therapy did not result in a significant change in body weight or glycemic control in obese subjects with type 2 diabetes.[56]

PF-05231023 is a long-acting FGF21 analog consisting of two molecules linked to a humanized immunoglobulin 1 monoclonal antibody backbone. In overweight or obese subjects with type 2 diabetes, PF-05231023 therapy at 100 mg and 140 mg doses intravenously administered twice weekly significantly reduced body weight over four weeks compared to the placebo. There was no change in glycemic control and significant changes in markers of bone turnover.[52] However, intravenous administration of PF-05231023 at 100 mg and 150 mg doses once weekly had no effect on body weight with minimal effects on markers of bone turnover.[58] Novo Nordisk recently completed a safety, tolerability, and pharmacokinetic study of an FGF21 analog (, ClinicalTrials.gov), but no results have been posted. Whether FGF21 analogs will prove to be effective in the treatment of obesity remains to be established.

5. Inhibitors of Fat Absorption in Drug Development

Dietary triacylglycerol (TAG) is cleaved by lipases in the lumen of the gut to monoacylglycerol and free fatty acids which are taken up by the intestinal epithelial cells and re-esterified into TAG inside the epithelial cells. The TAG assembled in enterocytes are then incorporated into chylomicrons and enter the lymphatic system. Diacylglycerol acyltransferase 1 (DGAT1) plays a key role in the absorption of dietary fat as it catalyzes the final step in the biosynthesis of TAG [59] DGAT1 is most highly expressed in the small intestine and adipose tissue and the deletion of *DGAT1* or inhibition of DGAT1 in rodents reduces body weight and adiposity, increases the secretion of GLP-1 and PYY, and slows

gastric emptying.[60–64] Animal studies suggest that DGAT1 inhibition has therapeutic potential in the treatment of obesity.

AZD7687 (Astrazeneca) is a potent and selective small molecule DGAT1 inhibitor that was evaluated in clinical trials. In the single dose study, gastrointestinal intolerability limited the dose escalation over 20 mg once daily.[65] In the trial with multiple dosing over one week there was a significant reduction in TAG excursion. However, severe gastrointestinal adverse events at doses just above the dose that effectively inhibited gut DGAT1, caused participants to discontinue the medication suggesting that AZD7687 lacks a sufficient therapeutic window for safe treatment. The development of AZD7687 has been halted.[66] A modified benzimidazole DGAT1 inhibitor reduced body weight by 11% over 21 days, in high-fat fed dogs without any gastrointestinal adverse effects; but, a single dose of the inhibitor caused diarrhea and nausea in humans challenged with a high-fat meal.[67] Whether DGAT1 inhibitors can be tolerated by humans remains to be established.

6. Inhibitors of Glucose Absorption in Drug Development

Selective sodium glucose co-transporter (SGLT) 2 inhibitors approved for the treatment of diabetes reduce glycated hemoglobin (Hb_{A1C}) by 1%.[68,69] Additionally, in patients with diabetes, SGLT2 inhibitors reduce body weight by 1 – 3 kg and this effect reaches a plateau in nine months of the treatment.[70] [71,72] The function of SGLT 2 is to reabsorb 80 – 90% of filtered glucose in the proximal convoluted tubule of the kidney, and the remainder is reabsorbed through the actions of SGLT 1 in the S2/S3 segment of the kidney. Following inhibition of SGLT 2, SGLT 1 prevents 30% - 40% of the filtered glucose from being excreted which may be due to compensatory reabsorption by SGLT 1.[73] In addition to the kidney, SGLT 1 is expressed in the intestines and its inhibition has been shown to reduce intestinal glucose and galactose absorption.[74] Inhibition of SGLT 1 and SGLT 2 has the potential to reduce both renal and intestinal glucose absorption and enhance weight loss.

Licogliflozin (Novartis) is an SGLT 1/2 dual agonist. In subjects with obesity, Licogliflozin (150 mg/day) treatment for 12 weeks resulted in a reduction in body weight by 5.7% (6.16 kg) compared to placebo which is superior to the effects of SGLT 2 inhibitors. The gastrointestinal adverse events were more frequent in the treated groups compared with the placebo, and increased with the dose. However, the adverse events were mild and did not impact quality of life.[75] Sotagliflozin is another SGLT 1/2 agonist (400 mg/day) which taken in conjunction with insulin in patients with type 1 diabetes, produced weight loss of 2.98 kg in 24 weeks compared to placebo. The gastrointestinal adverse events were of low incidence.[76] Thus, SGLT 1/2 inhibitors may be a safe treatment for obesity, but the weight loss effect of Licogliflozin was not sufficient for the sponsor (Novartis) to want to proceed with its development [77].

7. Activators of Lipid and Energy Metabolism in Drug Development

AMP-activated protein kinase (AMPK) and mammalian sirtuin 1 (Sirt1) regulate lipid and energy metabolism via reciprocal activation to stimulate muscle and hepatic mitochondrial biogenesis and fatty acid oxidation.[78–80] While a high-fat diet and positive energy

balance decrease AMPK and Sirt1 activity, their activation reduces lipid accumulation in response to excess energy intake.[81–86] Leucine, metformin, and sildenafil are activators of Sirt1 each acting through different pathways of Sirt1 activation. NS-0200 (NuSirt) is a combination of leucine (1100 mg), metformin (500 mg), and sildenafil (0.5 or 1.0 mg) that was evaluated for its effects on body weight after 16 weeks of treatment. The combination with 1.0 mg sildenafil caused weight loss of 2.4 kg. However, in subjects with elevated triglycerides (n = 22), the weight loss was 5 kg. The adverse gastrointestinal effects were consistent with metformin treatment.[87] The combination of Sirt1 activators holds promise as an anti-obesity treatment and further development will enable a more clear determination of its safety and efficacy.

8. Triple Re-uptake Inhibitors in Drug Development

Tesofensine (Saniona) is an inhibitor of the presynaptic uptake of noradrenaline, dopamine, and serotonin that was originally developed for the treatment of Parkinson's and Alzheimer's diseases, but it did not meet the efficacy criteria.[88–91] However, the unintended weight loss caused by Tesofensine treatment led to its development as an anti-obesity medication. Tesofensine causes a small increase in metabolic rate but it appears to induce weight loss primarily through a reduction in food intake.[92,93]

Tesofensine 0.5 mg/day and 1 mg/day taken orally produced a weight loss of 9.2% and 10.6% respectively in 24 weeks. The most common adverse events resulting from tesofensine therapy were of gastrointestinal origins and were mainly reported in the 1 mg group. Sleep disturbances and mood changes occurred more frequently in the 1 mg group compared to placebo. There was no change in blood pressure at the 0.5 mg/day dose but an increase in blood pressure occurred at the 1.0 mg dose compared to placebo. Pulse rate increased by 7.4 bpm in the 0.5 mg treatment group.[91] In rodents, the rise in blood pressure is reversed by a beta-adrenergic response inhibitor suggesting that tesofensine may increase sympathetic activity.[94] The phase III trial of 0.25 and 0.5 mg doses has been completed, and resulted in average weight loss of 10% over 6 months according to a press release from the trial sponsor. The trial was done in Mexico by Saniona's Mexico partner Medix. The commercialization plan is to submit the new drug application in Mexico and Argentina in 2019, anticipating a product launch in those countries in 2020.[95] The peer-reviewed publication of the phase III trial results will provide more information of the safety and efficacy of tesofensine.

9. Inhibitors of Protein Translation in Drug Development

Eukaryotic proteins are synthesized on the ribosome with an N-terminal methionine that in most cellular proteins is removed cotranslationally.[96] Removal of the N-terminal methionine is essential for ensuring proper functioning of these proteins many of which are important for metabolism, growth, and proliferation.[97] This processing of the N-terminal methionine is accomplished by the enzyme methionine aminopeptidase (MetAP) 2.[98] In rodent models, MetAP2 inhibition produces reductions in body weight and body fat.[99,100]

The MetAP2 inhibitor beloranib (ZGN-440, Zafgen), consistently produced clinically significant weight loss in patients with obesity, type 2 diabetes and Prader Willi syndrome, with 13% weight loss over 26 weeks in patients with diabetes.[101–105] However, adverse events of venous thromboembolism including two fatal pulmonary emboli in patients with Prader Willi syndrome led to the demise of the development of beloranib.[102] ZGN −1061 (Zafgen) was developed with an improved safety profile and similar metabolic efficacy as ZGN-440, and in rodent models it had an enhanced safety profile with similar efficacy.[106] A Phase II study of ZGN-1061 was initiated (, ClinicalTrials.gov); however, the FDA has placed a clinical hold on further development of ZGN-1061. The obesity medications in the pipeline, their mechanisms of action, stage of development, and sponsor are presented in Table 1.

10. Conclusion

There are numerous pharmaceuticals exploring the manipulation of central and peripheral mechanisms involved in energy homeostasis that are being developed to treat obesity. Some of these medications such as the GLP-1 receptor agonists approved as diabetes medications fortuitously caused weight loss and are now being investigated as anti-obesity medications. In this class of drugs, semaglutide holds promise but has yet to be approved for weight loss. To mitigate adverse effects of the doses required to promote weight loss, low dose synergistic combinations such as GLP1R + glucagon or GIP are being investigated but have yet to be evaluated in large confirmatory trials. Despite the unequivocal metabolic benefits in rodent studies, FGF21 analogs have so far failed to live up to expectations in humans. SGLT 1/2 inhibitors and AMPK/Sirt1 activators produce weight loss with mild adverse events but have yet to be investigated in large trials of long duration. The 10% weight loss in 24 weeks induced by the centrally acting drug Tesofensine is promising, but at this time the product launch is anticipated only in Mexico and Argentina. The potential for venous thromboembolism with MetAP2 inhibitors has led to a clinical hold on its development. Thus, most of the anti-obesity drugs in development have a long way to go before they are likely to be available in the US.

11. Expert Opinion

The anorexic effects of gut hormone-derived agents such as the GLPIR agonists have garnered substantial interest in the development of drugs for obesity. The resulting weight loss, particularly of new orally active GLP-1 agonists such as semaglutide is substantial, but is accompanied by gastrointestinal disturbances such as nausea, vomiting, diarrhea and dyspepsia which limits maximization of the dose. To enhance the metabolic effects of GLP-1 agonists, combinations with other gut hormones such as GIP or glucagon to induce synergistic or complementary actions have been explored. Combination therapy produces tolerable symptoms but does not reduce gastrointestinal disturbances. In contrast, sublingual therapy targeting the cell receptors for PYY on the tongue rather than the hypothalamic arcuate nucleus holds promise because the anatomic location of the Y2 receptors in the oral mucosa reduces the adverse systemic effects of a centrally acting drug.

The path followed in the development of gut-hormone derived agents for obesity treatment has parallels in the development of other anti-obesity medications. Tesofensine is a triple neurotransmitter re-uptake inhibitor that acts on the central nervous system to increase efficacy compared to single re-uptake inhibitors such as bupropion and rimonabant. Similarly, the combination of three Sirt1 and AMPK agonists (Sildenafil, leucine, and metformin) uses a small dose of metformin to enhance the weight reducing effect of metformin alone while minimizing the gastrointestinal effects it commonly induces. At this dose, metformin does not produce sufficient weight loss to gain approval as a stand alone therapy.

FGF-21 agonists and DGAT-1 inhibitors are interesting targets that are still at such an early stage that their outcome is difficult to predict. FGF-21 appears to increase metabolic rate rather than regulate appetite, as is the case with several other anti-obesity medications. Thus, if FGF-21 is shown to be safe and effective, it could potentially be easily combined with other obesity medications. The DGAT-1 mechanism is attractive because it works in the periphery at the level of triglyceride reassembly in the enterocytes which one might postulate would have few side effects. Unfortunately, the compounds tested to this point in humans have caused significant gastrointestinal adverse events, which precludes a clear determination of the success of the DGAT-1 inhibition as a treatment for obesity.

Drugs that act on peripheral receptors may have greater specificity than those that act on the central nervous system. For instance, angiotensin receptor blockers act on the blood vessels and are effective in treating hypertension. They also have few side effects presumably because they avoid the potential trickle-down adverse events that are common in drugs that act on the brain. Similary, SGLT2 inhibitors and MetAP-2 are interesting from that perspective. SGLT2 inhibitors seem to be well-tolerated and have beneficial cardiovascular effects. [107] The weight loss induced by SGLT2 inhibition is modest; however, a dual antagonist of SGLT1 and SGLT2 produces greater weight loss. Moreover, the gastrointestinal effects that would ordinarily be anticipated by the influx of unabsorbed sugars fermented by microorganisms in the colon,[108] are surprisingly minimal.

Methionine aminopeptidase-2 agonists appeared to be a particularly promising approach to treat obesity. They act in the periphery and are effective in treating the obesity associated with hypothalamic injury and the Prader Willi Syndrome. In these two types of obesity the hypothalamus where centrally acting anti-obesity agents exert their effects is damaged. Obesity resulting from hypothalamic damage is very difficult to treat. The efficacy of the MetAP-2 agonists appeared to be outstanding, and they initially appeared to be very well-tolerated. Unfortunately, during phase 2 trials, a problem with pulmonary emboli was identified causing the company to evaluate an alternate compound. Now, there are problems with toxicity in the animal studies and the future of this drug is in doubt.

The most sensible approach to mitigating the side effects of centrally acting drugs is combining these medications at low doses. For the most part, using more than one of redundant mechanisms driving obesity reduces side effects by dose reduction. The ultimate goal in developing anti-obesity drugs is finding a compound that is effective and has minimal side effects. The disappointing experience with MetAP2 agonists and discontinuing

of a seemingly promising SGLT-1 and 2 inhibitors notwithstanding, peripherally acting drugs seem to fit the bill due to a lack of trickle-down adverse events. Hypertensive drugs such as the angiotensin receptor blocker provides the perfect example of a peripherally acting drug with minimal or no side effects. The development of anti-obesity drugs appears to be headed in a similar direction and we can expect success in the years ahead. It will probably take learning more about the peripheral mechanisms and synergistic combinations to reach the goal of safe and effective anti-obesity drugs, but the journey should certainly be interesting and intellectually stimulating.

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Declaration of interest

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Article Highlights

1. Gut hormones are an active area of anti-obesity drug research. The area is moving from single to dual agonist compounds like GLP-1 agonists with glucagon or GIP agonists
2. The concept of targeting more than one of the redundant mechanisms controlling obesity and using low doses of the drugs to reduce side effects is a prominent strategy in anti-obesity drug development. Tesofensine, a triple reuptake inhibitor and the triple Sirt-1 and AMPK agonist combination of leucine, sildenafil and metformin are examples.
3. Early work with novel targets like FGF-21 which increases metabolic rate and DGAT-1 that inhibits the last step in triglyceride reassembly prior to release from the enterocytes into the lymphatic system are promising, but it is too early to judge their potential success or failure.
4. SGLT-2 inhibitors and MetAP2 agonists work on peripheral targets, but these medications have challenges with efficacy and safety respectively.
5. Anti-obesity medications of the future are likely to address peripheral mechanisms that are less likely to have the side-effects that trickle down from drugs targeting the central nervous system.

Table 1.

Obesity Medications in the pipeline, their mechanism of action, stage of development, and sponsor

Drug	Mechanism	Stage of Development	Sponsor	References
NNC0165–1562	PYY analog	Phase I	Novo Nordisk	*
Semaglutide	GLP-1 receptor agonist	Phase III	Novo Nordisk	31, 32
MED10382	GLP-1 and glucagon receptor agonists	Phase II	MedImmune	36
SAR425899	GLP-1 and glucagon receptor agonists	Phase I	Sanofi	37
NNC0090–2746	GLP-1 and GIP receptor agonists	Phase I	Novo Nordisk	45
LY3298276	GLP-1 and GIP receptor agonists	Phase II	Eli Lilly	46
LY2405319	FGF21 protein	Phase I	Eli Lilly	57
Pegbelfermin	FGF21 analog	Phase II	Briston-Myers Squibb	56
PF-05231023	FGF21 analog	Phase I	Pfizer	52, 58
GT-001	$PYY_{3–36}$	Phase I	Gila Therapeutics	*
AZD7687	DGAT-1 inhibitor	Phase I	Astrazeneca	65, 66
Licogliflozin	SGLT 1/2 inhibitor	Phase II	Novartis	75
Leucine-Metformin-Sildenafil	Sirt1 activators	Phase II	NuSirt	87
Tesofensine	Noradrenaline, dopamine, serotonin uptake inhibitor	Phase III	Saniona	91
ZGN -1061	MetAP2	Phase II	Zafgen	*

PYY: Peptide YY; GLP-1: glucagon-like peptide 1; GIP: Glucose-dependent insulin tropic peptide:FGF21: Fibroblast growth factor 21; DGAT1: Diacylglycerol acyltransferase 1;SGLT 1/2: Sodium glucose co-transporter 1/2; Sirt1: Sirtuin 1; MetAP2: Methionine Aminopeptidase 2

* ClinicalTrials.gov identifier