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Anorectic state of obesity medications in the United States. Are leaner times ahead?

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Abstract

Introduction: Obesity is considered to be a chronic disease. Currently there are five prescription-only medications on the US market for the long-term management of obesity. However, these medications are underutilized by obese or overweight individuals seeking medical assistance for weight management.

Areas covered: This special report provides an overview of the emerging obesity pharmacotherapies based on the data available from recruiting and active phase II/III trials from a registry of clinical trials. The authors also give their expert opinion and provide their future perspectives on the treatment of obesity based on what is known.

Expert opinion: Despite obesity being a chronic condition affecting 40% of the US population, there is a low demand for obesity medications in the US market. Although the potential obesity medications that are currently being investigated in phase II/III clinical trials are promising, it is unclear whether the future pharmacotherapies will be enough to meet the health care need.

Keywords

orlistat; phentermine/topiramate; naltrexone/bupropion; lorcaserin; liraglutide; setmelanotide; semaglutide; dapagliflozin; MEDI0382; tesofensine

1. Introduction

Obesity is recognized as a chronic disease. In the US, there are currently five pharmacotherapies approved by the FDA for the long-term management of obesity, four of which were approved between 2012 to 2014. From a disease management perspective, all the current medications are generally well tolerated and achieve significant weight loss in

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overweight or obese populations (see Table). However, the clinical application of these weight-loss medications on the management of obesity in the US has not been fully realized. Specifically, these pharmacotherapies are not being prescribed. Data compiled from 2012 to 2015 indicated that diabetes pharmacotherapies (excluding insulin) were prescribed 15 times more often than obesity pharmacotherapies [1]. Continuation of new obesity pharmacotherapies was also prescribed approximately one third as frequent as subtype 2 sodium-glucose transporters (SGLT2) inhibitors, a novel class of diabetes pharmacotherapies [1]. The discrepancies between the prescription data are more troublesome considering that the US adult prevalence of obesity is approximately 5 times higher than that for type II diabetes mellitus [2, 3]. Obesity pharmacotherapies are underutilized even in patients participating in a comprehensive behavioral weight-management program [4, 5]. In a recent retrospective study (2013–2016) of overweight or obese veterans ($n = 153,393$) enrolled in a behavioral weight management program through the Veteran Health Administration (VHA), only 1.1% received an initial prescription of an obesity pharmacotherapy [5]. The prescribed medications were orlistat (70%), phentermine/topiramate (11.2%), bupropion/naltrexone (9.7%), lorcaserin (8.9%), liraglutide (1.5%), and phentermine (short-term; 5.4%) [5]. Most notably, in this study, these medications were prescribed within a weight-loss program administered by the VHA, meaning that these medications were available at no cost or relatively low out-of-pocket cost to the veterans [5]. Although the most prescribed obesity pharmacotherapy was orlistat, these findings suggest that cost or lack of insurance coverage is not the primary reason for the underutilization of obesity pharmacotherapies. Possible reasons for the underutilization of obesity pharmacotherapies have been a topic of other editorials and reviews [6–8]. These reasons range from pharmacotherapies not meeting weight loss expectations, underdiagnosis of obesity, “built-in” patient apprehension resulting from the negative history associated with withdrawn obesity medications (i.e. withdrawal of sibutramine in 2010), associated adverse effects, as well as abuse potential of some medications [6–9].

2. Forecast for potential obesity pharmacotherapies

The underutilization of currently available obesity medications has likely impacted the pursuit of future pharmacotherapies. A search on clinicaltrials.gov (31 October 2019) using the term “obese” and using the filters for not yet recruiting, recruiting, active (not recruiting), drug, interventional studies, phase II/III, and adult (18–64 yrs old) revealed 116 studies. Excluding studies of already FDA-approved obesity pharmacotherapies and short-term studies (< 6 months), there were only five pharmacotherapies (2 monotherapies, 3 combinational therapies) in phase II/III trials.

Semaglutide, currently FDA-approved for type II diabetes mellitus (2017; Ozempic® Novo Nordisk), is a monotherapy currently under active investigation for the long-term management of obesity (, , ,). Semaglutide is a subcutaneous injectable glucagon-like peptide-1 (GLP-1) receptor analogue, like liraglutide (see table). In contrast to liraglutide, which is a daily formulation, semaglutide has a longer duration of action and is a weekly formulation [10]. In a phase II trial (NTC02453711), five doses of semaglutide (0.05–0.4 mg/day) were compared with liraglutide (3.0 mg/day) in obese individuals (body mass index; BMI ≥ 30 kg/m²; $n = 957$; 65% female) without type II diabetes mellitus for 52

weeks [11]. Weight reductions from baseline after 52 weeks of semaglutide ranged from 6.0% (0.05 mg/day) to 13.8% (0.4 mg/day), compared with 7.8% for liraglutide (3.0 mg/day) and 2.3% for placebo [11]. Treatment-emergent adverse events (TEAEs) with semaglutide or liraglutide were mild (69%) or moderate (28%). The most common TEAEs associated with semaglutide were nausea (31%–48%), diarrhea (19%–38%), and constipation (19%–25%), which were similar in occurrence and frequency to liraglutide [11]. One of the TEAEs associated with semaglutide and liraglutide is injection-site reactions (approximately 7–10%), however, oral formulations of semaglutide are under investigation for the management of diabetes mellitus [12].

Setmelanotide (RM-493; Rhythm Pharmaceuticals) is a novel melanocortin-4 receptor (MC4R) agonist monotherapy currently under investigation (NTC02896192, NTC03287960, , ,). All currently active trials with setmelanotide are using patient populations with rare genetic forms of obesity, such as pro-opiomelanocortin (POMC) and leptin receptor (LEPR) deficiencies. Hence, the estimated enrollment for each trial ranges from 10 to 100 participants. A completed phase 1B randomized cross-over trial () evaluated the effects of setmelanotide on energy expenditure (EE) in non-genetic obese individuals (BMI 35.7 ± 2.9 kg/m²; n = 12; 50% female). Subjects received 72 h subcutaneous infusion of setmelanotide (1 mg/24 h) or placebo and treatment cross-over occurred at the end of the 72 h infusion period [13]. Resting EE was increased during the setmelanotide infusion when compared with placebo (1856 ± 369 kcal/day vs. 1745 ± 369 , $p < 0.03$) [13]. The most commonly reported TEAE was headache (n = 3) and 83.3% (10 out of 12) subjects were able to correctly identify treatment order [13]. In studies reported so far, setmelanotide does not appear to produce cardiovascular-associated TEAEs that were reported with first generation MC4 agonists [13–16].

Dapagliflozin is a selective SGLT2 inhibitor FDA-approved for type II diabetes mellitus in 2014 (Farxiga® Bristol-Meyers Squibb and AstraZeneca). There is currently a clinical trial () investigating the combination of dapagliflozin and metformin on weight loss in pre-diabetic and diabetic obese (type III; BMI ≥ 40 kg/m²) patients. In a retrospective study of a large electronic records database containing 30 million patients, data from type II diabetes mellitus patients receiving metformin were stratified into those who received an initial prescription of dapagliflozin with/without other oral anti-diabetic medications (OAD; other than metformin) (n = 1093; 45.4% female) or OAD alone (n = 1093; 44.8% female)[17]. Baseline characteristics of metformin patients, including BMI, hemodynamic measures and hemoglobin A1C, were matched and data were compiled 12 months before (i.e., pre-index) and 12 months after (i.e., post-index) the initial prescription of dapagliflozin or OAD alone [17]. Patients taking dapagliflozin + metformin compared with those taking OAD alone + metformin had reduced body weight from baseline (-1.8 kg vs. -0.7 kg, $p < 0.01$), as well as improved A1C levels (-1.0% vs. 0.7% , $p < 0.01$) [17]. Hemodynamic measures were also improved with dapagliflozin + metformin compared to OAD alone + metformin [17]. One limitation to the interpretation of these findings, however, was that an unspecified number of patients also received one or more OAD in the dapagliflozin group [17]. The current recruiting clinical trial () is more straightforward in the stated design and plans to compare dapagliflozin + metformin combination with metformin only in weight-loss outcomes.

A novel anti-diabetic medication under investigation is MEDI0382 (MedImmune, LLC), a dual GLP-1 and glucagon agonist. Currently there are several active or recruiting clinical trials of MEDI0382 to investigate its potential for weight loss and management of type II diabetes in overweight or obese populations (,). A phase I trial () indicated a favorable safety profile of MEDI0382 in non-obese male healthy subjects (n = 48) over a range of doses (5–300 µg)[18]. The most common TEAEs were nausea, dizziness, and headache and were more frequently reported in subjects who received the higher doses (150 and 300 µg) [18]. In a phase IIa study (), overweight or obese diabetic subjects received up to 200 µg of MEDI0382 (once-daily subcutaneous; n = 25; 48% female) or placebo (n = 26; 42% female) for 41 days [19]. Subjects receiving MEDI0382 had a significant reduction in body weight (–3.84 kg from baseline) compared with placebo (–1.70 kg from baseline, $p < 0.0008$), and 41% of MEDI0382-treated individuals had 5% weight loss [19]. Hemoglobin A1C levels were significantly reduced with MEDI0382 treatment (–0.9% from baseline) compared with placebo (–0.6% from baseline; $p < 0.0004$). In addition, MEDI0382 reduced the blood glucose (AUC) response to mixed meal tolerance test (–32.78% from baseline) in comparison to placebo (–10.16% from baseline; $p < 0.0001$). Unlike GLP-1 analogues, MEDI0382 also significantly reduced fasting plasma glucose levels (–2.8 mmol/L from baseline) compared with placebo (–1.1 mmol/L from baseline; $p < 0.0001$)[19]. No serious or severe TEAEs were reported with MEDI0382, and the most common TEAEs were nausea (52%), vomiting (32%), headache (36%), dyspepsia (28%), abdominal distention (24%), reduced appetite (20%), and fatigue (20%)[19].

Another combinational therapy under investigation is tesofensine/metoprolol for the management of hypothalamic injury-induced obesity () and Prader-Willi syndrome (). Tesofensine is a novel monoamine reuptake inhibitor (dopamine> norepinephrine> serotonin) that was developed by NeuroSearch A/S in collaboration with Boehringer Ingelheim [20]. A 24-week phase II trial () in obese patients (BMI 30 kg/m²; n = 203; 68–74% female) compared three doses of tesofensine (oral daily) with placebo [21]. The placebo-subtracted mean weight loss was 4.5% for 0.25 mg, 9.2% for 0.5 mg, and 10.6% for 1.0 mg ($p < 0.0001$ for all doses from placebo)[21]. All doses of tesofensine significantly increased heart rate (placebo-subtracted): +4.3 bpm for 0.25 mg ($p < 0.0018$ from placebo), +7.4 bpm for 0.5 mg ($p < 0.0001$ from placebo), and 8.1 bpm for 1.0 mg ($p < 0.0001$ from placebo) [21]. Despite the promising weight loss reported in the phase II trial, an audit by the Danish Health and Medicine Authority revealed that subjective TEAEs and reasons for discontinuation were underreported [22]. There were also some questions regarding the integrity of the blinding procedure and the process of informed consent [23]. Nonetheless, preclinical studies have suggested that metoprolol blocks the adverse cardiovascular effects of tesofensine while preserving the feeding-suppressive effects of the drug in rats [24].

3. Conclusion

Currently, there are five FDA-approved pharmacotherapies for the long-term management of obesity. An additional five potential pharmacotherapies are in phase II/III clinical trials. These include two monotherapies and three combinational therapies. Semaglutide is a monotherapy that is a long acting GLP-1 receptor agonist and is currently FDA approved for the management of type II diabetes. Another monotherapy, setmelanotide, is a novel MC4

agonist and the current trials are restricted to genetically obese populations. Two combination therapies, dapagliflozin/metformin and GLP-1/glucagon agonists (MEDI0382) are being investigated in diabetic obese populations for the management of weight loss. Another combinational therapy, tesofensine/metoprol is under investigation in hypothalamic-injured obese and Prader Willi populations.

4. Expert opinion

Based on the current demands of the health care field, and in contrast to 10 years ago, pharmaceutical companies have decreased their appetite for continuing or developing novel pharmacotherapies for obesity. Contributing to the decreased appetite for pharmaceutical companies is the discrepancies in guidelines and requirements between governmental agencies for obesity medication approval. For instance, although approved by the FDA, lorcaserin and phentermine/topiramate failed to be approved in Europe for the management of obesity [25]. From the currently available clinical trial information, there are only five pharmacotherapies with the potential to hit the US market for the management of obesity in the next several years. Setmelanotide is the only potential pharmacotherapy that is being tested in both adults and children (birth – 17 yrs). Of the five potential medications currently in clinical trials for adult populations, only one of these potential medications, semaglutide, would treat the same population as the currently available pharmacotherapies (see Table). The possibility of semaglutide being available as a longer-acting GLP-1 analogue in oral formulation would certainly help to improve patient compliance and treatment efficacy. In addition, a more expanded use of GLP-1 receptor analogues to treat obesity earlier in life is another therapeutic strategy for the long-term management of obesity. Currently, there is a 52-week phase II trial () investigating the effects of an GLP-1 analogue, an injectable exenatide extended-release (Bydureon®;Astra Zeneca), in obese (BMI ≥ 35 kg/m²) adolescent (12– 17 yrs old). Notably, a search of clinicaltrials.org expanded to include children (birth –17 yrs) in phase II/III trials (> 6 months) revealed an additional 11 studies with setmelanotide and exenatide as novel pharmacotherapies. Because even a 5% weight loss has been suggested to improve the medical management of type II diabetes mellitus [26], two medications, dapagliflozin/metformin and MEDI0382, would target weight loss in those obese or overweight patients with type II diabetes mellitus. Approximately 8% of the US population has type II diabetes with approximately 90% of those patients being overweight or obese [2, 3]. Since diabetic pharmacotherapies are more readily prescribed than obesity pharmacotherapies [1], dapagliflozin/metformin and MEDI0382 will likely be more appealing to patients and health care providers. Tirzepatide (LY3298176; Eli Lilly & company), a dual GLP-1 and gastric inhibitory peptide (GIP) receptor agonist, is currently in phase III trials (, , , , ,) for the management type II diabetes. Given the mechanisms of action and reported weight loss with other hormonal combinations [27], tirzepatide is potentially promising for the management of weight loss in this population. Of the five currently investigated medications in clinical trials in adults, tesofensine/metoprolol is likely the least promising. The current clinical trials investigating tesofensine/metoprolol for hypothalamic injury-induced obesity would have to demonstrate a favorable weight loss and cardiovascular safety profile before it could be considered by the FDA as a potential pharmacotherapy to treat the same obese/overweight clinical population as the currently

available pharmacotherapies. One reason for unfavorable endorsement of tesofensine/metoprolol is the questionable history associated with tesofensine [22, 23]. Based on the underutilization rate from data collected from the VHA patients receiving low-cost or no-cost obesity medications [5], cost of medication or lack of insurance coverage are not the only barriers to the utilization of obesity medication by the general population. Several other factors, such as underdiagnosis of obesity, “built-in” negative history, and lower than expected medication-induced weight loss are more likely to contribute to the underutilization of obesity pharmacotherapies. As such, currently available medications will have to change their current demand trajectory to revitalize the health care hunger for future obesity pharmacotherapies.

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Article Highlights Box

- Several safe and effective obesity medications are on the US market and these medications have failed to stem the rising obesity epidemic.
- There are five potential new pharmacotherapies under phase II/III clinical trials.
- Currently approved for type II diabetes mellitus, semaglutide is a long-acting GLP-1 receptor agonist being investigated for the management of obesity.
- Setmelanotide and tesofensine/metoprolol are being investigating in rare genetic and hypothalamic-injured obese populations, respectively.
- Two other potential pharmacotherapies, dapagliflozin/metformin and MEDI0382, for the management of weight loss in obese/overweight patients with type II diabetes mellitus.

Table of currently FDA-approved obesity pharmacotherapies in adults

Obesity Medication	FDA-Approval Year	Brand Name	Mean Efficacy (placebo-subtracted % weight loss)	Categorical Efficacy (differences between treatment and placebo)	Treatment-Emergent Adverse Effects (% occurrence)
Orlistat	Prescription: 1999 Over-the-counter (OTC); 2007	Prescription: Xenical® (Roche Pharmaceuticals) OTC: Alli® (GlaxoSmithKline)	~2.9% (2.5–3.4%, 13 studies)[28]	~21% (54 vs. 33%) [28]	1 gastrointestinal event: 91% vs. 65% (1 st year) and 36% vs. 23% (4 th year) [29] Loose stool: 58% vs. 16.4% [30] Increased defecation: 17.9% vs. 5.4% [30] Uncontrolled oily discharge: 16.1% vs. 0.9% [30]
Phentermine/topiramate	2012	Qsymia® (Vivus)	8.6–9.3% [31–33]	~49% (66.9–79.3% vs. 17.3–30.0%) [31–33]	Paresthesia: 18.8% vs. 1.9% [31] Dry mouth: 17.0% vs. 3.7% [31] Constipation: 14.1% vs. 6.8% [31] Dysgeusia: 8.4% vs. 1.0% [31] Depression: 4.7% vs. 1.2% [31] Irritability: 4.5% vs. 0.6% [31] Alopecia: 4.3% vs. 1.0% [31] Anxiety: 3.7% vs. 1.2% [31] Disturbance in attention: 3.5% vs. 0.6% [31] Hypoesthesia: 3.3% vs. 0.8% [31] May increase mean heart rate [31] Infants born to women taking Qsymia may be at greater risk of developing cleft palate [34]
Lorcaserin	BELVIQ: 2012 BELVIQ XR: 2016	BELVIQ® and BELVIQ XR® (Eisai)	3–3.65% [35, 36]	22.2–27.2% (47.2–47.5% vs. 20.3–25.0%) [35, 36]	Off-target activation of cardiac 5-HT 2B receptors may increase risks for cardiac valvulopathy: 2.37% vs. 2.04% [37] Upper respiratory infection: 14.8% vs. 11.9% [36] Headache: 18.0% vs. 11.0% [36] Dizziness: 8.2% vs. 3.8% [36] Nasopharyngitis: 13.4% vs. 12.0% [36] Nausea: 7.5% vs. 5.4% [36]
Naltrexone/bupropion	2014	Contrave®, (Nalpropion Pharmaceuticals)	4.2–5.2% [38–40]	23.9–33.4% (48–66.4% vs. 17.1–42.5%)	Nausea: 29.2% vs. 6.9% [38] Constipation: 19.1% vs. 7.1% [38] Headache: 17.5% vs. 8.7% [38] Dry mouth: 9.1% vs. 2.6% [38] Vomiting: 8.5% vs. 2.0% [38] Dizziness: 6.9% vs. 3.7% [38]
Liraglutide	Lower doses for type-2 diabetes treatment: 2010 Higher dose for weight management: 2014	Lower dose: Victoza® (Novo Nordisk) Higher dose: Saxenda® (Novo Nordisk)	5.4– 6.0% [41, 42]	28.7–45% (50.5–73% vs. 21.8–28%) [41–43]	Nausea: 40.2% vs. 14.7% [41] Diarrhea: 20.9% vs. 9.3% [14] Constipation: 20.0% vs. 8.7% [41] Vomiting: 16.3% vs. 4.1% [41] Gallbladder-related events: 2.5% vs. 1.0% [41] Pancreatitis: 0.4% vs. <0.1% [41] May increase mean resting pulse [41]