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Pharmacotherapy of obesity: Available medications and drugs under investigation

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ABSTRACT

Obesity is a chronic disease with a continuously rising prevalence that currently affects more than half a billion people worldwide. Energy balance and appetite are highly regulated via central and peripheral mechanisms, and weight loss triggers a homeostatic response leading to weight regain. Lifestyle and behavioral modifications are the cornerstones of obesity management; however, they often fail to achieve or sustain long-term weight loss. Pharmacotherapy added onto lifestyle modifications results in an additional, albeit limited, weight reduction. Regardless, this weight reduction of 5–10% conveys multiple cardiovascular and metabolic benefits. In this review, evidence on the food and drug administration (FDA)-approved medications, i.e., orlistat, lorcaserin, phentermine/topiramate, liraglutide and naltrexone/bupropion, is summarized. Furthermore, anti-obesity agents in the pipeline for potential future therapeutic use are presented.

Contents

Abbreviations: Ach, acetylcholine; ACTH, adrenocorticotropic hormone; ADHD, attention-deficit hyperactivity disorder; AgRP, agouti-related peptide; AHI, apnea hypopnea index; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ARC, arcuate nucleus; AVP, arginine-vasopressin; BAT, brown adipose tissue; BDNF, brain-derived neurotrophic factor; BED, binge eating disorder; BID, twice daily; BMI, body mass index; BOTOX, botulinum toxin; BW, body weight; CART, cocaine- and amphetamine-regulated transcript; CB1, cannabinoid receptor type 1; CNS, central nervous system; CR, controlled release; CV, cardiovascular; CVD, cardiovascular disease; DA, dopamine; DBP, diastolic blood pressure; DIO, diet-induced obesity; FDA, Food and Drug Administration; eGFR, estimated glomerular filtration rate; FGF, fibroblast growth factor; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; GCG R, glucagon receptor; GI, gastrointestinal; GIP R, gastric inhibitory peptide receptor; GLP, Glucagon-like peptide; HbA1c, glycosylated hemoglobin; HCl, hydrochloric; HDL-C, high density lipoprotein-cholesterol; HR, heart rate; HT R, hydroxytryptamin receptor; K, potassium; LDL-C, low density lipoprotein-cholesterol; MC, melanocortin; MC4R, melanocortin 4 receptor; MSH, melanocyte-stimulating hormone; NA, not available; Na, sodium; NAFLD, nonalcoholic fatty liver disease; Nal-Bup, naltrexone-bupropion; NE, norepinephrine; NPY, neuropeptide Y; NS, non-significant; NTS, nucleus of the solitary tract; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome; PDE, phosphodiesterase; Phen-Top, phentermine/topiramate; POMC, proopiomelanocortin; PP, pancreatic polypeptide; PVN, paraventricular nucleus; PWS, Prader Willi syndrome; PYY, peptide YY; QD, once daily; RCT, randomized controlled trial; rhGH, recombinant human growth hormone; SBP, systolic blood pressure; sc, subcutaneous; SE, serotonin; SGLT, sodium-glucose cotransporter; TC, total cholesterol; T2D, type 2 diabetes; TC, total cholesterol; TG, triglyceride; TID, three times daily; TNF, tumor necrosis factor; TRH, Thyrotropin-releasing, ventromedial nucleus; WC, waist circumference; XR, extended release; y, year.

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1. Introduction

Obesity is a chronic, complex disease, characterized by excessive fat accumulation, which alters anatomy and physiology, thus resulting in unfavorable metabolic, biomechanical and psychosocial health consequences [1,2]. Obesity results from the interplay of genetic, epigenetic, biological, hormonal, microbial, behavioral, sociocultural, and environmental factors that disturb the balance between caloric intake and energy expenditure [3,4]. Body mass index (BMI) is the most practical diagnostic tool available, although it is a crude index, not distinguishing specific distribution of fat and lean body mass [5].

Four out of the ten leading causes of death in the United States (US), i.e., heart disease, cancer, cerebrovascular events and type 2 diabetes (T2D), are to a certain extent linked to obesity [6]. Indeed, obesity largely impacts health status through its associations with dyslipidemia, hypertension, metabolic syndrome, prediabetes and T2D, cardiovascular disease (e.g. coronary artery disease), nonalcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), female infertility and male hypogonadism, certain types of cancers (e.g. endometrial, colon, breast cancer), sleep disturbances, particularly obstructive sleep apnea (OSA), osteoarthritis, depression, and neurocognitive disorders (e.g. Alzheimer's disease) [7–14]. Obesity accounts for an estimated 0.8–13.7 lost years of life, mainly due to cardiovascular disease, T2D and cancer, depending on the severity and age of onset of obesity [15,16].

Currently, one-third of the adult population in the US is overweight and another one-third has obesity [17]. Worldwide, an estimated 650 million adults are affected, rendering this disease an epidemic and a major public health concern [17]. Furthermore, approximately $190 billion are spent annually for direct and indirect health care costs related to obesity in the US [18]. Prevalence of obesity is estimated to climb to 44% by 2030 with major health, social and financial consequences [19].

Lifestyle (e.g. diet and exercise) and behavioral modifications are the cornerstones of the management of obesity, but they are difficult to achieve and to sustain [20]. If they fail, pharmacotherapy is added, when BMI ≥ 30 or BMI ≥ 27 and at least one cardiovascular risk factor exists (e.g. hypertension, hyperlipidemia, T2D) [21]. This review focuses on the pharmacologic management of adult obesity, summarizing food and drug administration (FDA)-approved medications for obesity (Table 1) and introducing the drugs currently in the pipeline. Orlistat is the only FDA-approved medication for long-term management of obesity that can be prescribed to adolescents >12, while phentermine can be used for short-term in individuals >16 years of age [22].

2. Mechanisms of Obesity and Targets of Anti-obesity Drugs

Energy balance, eating and appetitive behaviors are highly regulated by central and peripheral hormones and neuropeptides that act on multiple brain areas and peripheral organs (Fig. 1) [5,23–26]. Several central nervous system (CNS) networks are implicated in the development and management of obesity in humans, including the hypothalamus, reward system, emotion and memory related brain areas along with attention related cortex and prefrontal cortex responsible for cognitive control [27]. Pathways controlling energy equilibrium and factors predisposing to obesity may vary among humans and other species and are described in detail in other articles of the current special issue for “Obesity”. FDA-approved medications and novel therapies under investigation in preclinical studies and clinical trials exert their anti-obesity effects via one or more of the following mechanisms: 1) decreasing appetite and caloric intake, 2) increasing energy expenditure, 3) decreasing fat absorption (Fig. 2) [7].

3. FDA-Approved Medications

3.1. Phentermine Hydrochloric (HCl), Diethylpropion, Benzphetamine, Phendimetrazine

3.1.1. Mechanism of Action

Phentermine hydrochloric (HCl) (Adipex-P®, Lomaira®), diethylpropion/amfepramone (Tenuate®, Tenuate dospan®), benzphetamine (Didrex®),

and phendimetrazine (Bontril®, Prelu-2®) are oral noradrenergic agonists that suppress appetite. They have been approved only as short-term (<12 weeks) anti-obesity medications since the 1950s (1959, 1950, 1956, 1956, respectively), due to the lack of long-term data [28]. They all exert their appetite suppressant effects through interaction with biogenic amine transporters in rodents [29], but their mechanism of action in humans has not yet been thoroughly understood [5]. Phentermine, the most frequently prescribed in this class, enhances mainly norepinephrine, but also serotonin and dopamine release in the CNS [29]. Adrenergic, serotoninergic and dopaminergic neurons are spread throughout the CNS both in rodents and humans [30]. Hypothesized sites of phentermine action, based on rodent studies, are the homeostatic-related hypothalamus and reward-related nucleus accumbens [31,32]. Benzphetamine and phendimetrazine are rarely prescribed nowadays and since they have not been assessed in randomized controlled trials since the 1960s, they will not be described in detail.

3.1.2. Dose, Side Effects and Position in Treatment Armamentarium

Phentermine resin was used as an anti-obesity drug the period 1959–1973, until phentermine HCl was released onto the market. Phentermine HCl is taken orally, before or right after breakfast in a dose that varies from 15 to 37.5 mg based on patient's response and tolerability (e.g. Adipex-P® capsules or tablets, Suprenza™ 15 mg, 30 mg, or 37.5 mg etc.); tablets of 8 mg (Lomaira®) can be taken at a maximum of three times daily (TID), if additional regulation of appetite in the late afternoon and evening is required. It is approved for individuals >16 years old [33]. The drug should be discontinued upon development of tolerance to the anorectic effect, which usually happens within a few weeks [33]. Diethylpropion is taken orally either TID, 1 h before meals (immediate-release tablets of 25 mg) or once per day (QD) (controlled-release tablets of 75 mg). Interestingly, diethylpropion has been withdrawn in Europe due to concerns about cardiotoxicity [34,35]. Benzphetamine should be initiated QD at a dosage of 25 to 50 mg and escalated up to TID, based on patient response. Phendimetrazine extended-release (105 mg) is taken QD 30 to 60 min prior breakfast and immediate-release formula (35 mg) twice per day (BID) or TID one hour prior to meals.

The most frequent placebo-subtracted adverse events of phentermine are: dry mouth (38.5%), insomnia (34.5%), dizziness (15.1%), palpitations (12.4%), flushing (13.8%), fatigue (11.6%) and constipation (5.5%), and of diethylpropion: constipation (13.5%), insomnia (7%), tremor (6.4%) and dry mouth (3.1%) [36,37]. Phentermine is contraindicated in patients with recreational drugs [31]. Before 2012, phentermine was the most frequently prescribed anti-obesity medication in the USA, but following the approval of more effective drugs with more favorable safety profiles, the prescription rates have fallen [31]. Nevertheless, these drugs remain relatively inexpensive compared to newer anti-obesity medications and thus are still prescribed.

3.1.3. Outcomes; Phentermine

Randomized, controlled trials (RCT) with phentermine were conducted between 1965 and 2010, but were typically of short duration. The longest RCT involved administration of phentermine HCl 30 mg in combination with a hypocaloric diet in overweight or obese women ($n = 108$) either continuously or intermittently (alternating between medication and placebo every 4 weeks) for 36 weeks, and resulted in a placebo-subtracted weight loss of 7.4 kg and 8.2 kg respectively [38]. Phentermine (7.5 mg and 15 mg) was also assessed in a 28-week phase 3 RCT study (EQUATE) with 756 obese participants in comparison to topiramate extended release (46 mg and 92 mg) monotherapy and to combination with topiramate (7.5 mg/46 mg and 15 mg/92 mg) [39]. Placebo subtracted weight loss was 3.8%, 4.4%, 3.4%, 4.7%, 6.8% and 7.5%, respectively without significant improvement in cardiometabolic parameters in the phentermine monotherapy groups [39]. In studies of shorter duration (12 weeks) daily phentermine 30–37.5 mg resulted in a mean placebo-subtracted weight loss of 3–6.4 kg [40,41]. Placebo-subtracted weight loss of 3.6 kg at 6 months was calculated in a meta-analysis of 6 RCTs with phentermine 15-30 mg daily for 2–24 weeks [42]. Total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), and waist circumference (WC) were also decreased (by 0.38 mmol/l, 0.59 mmol/l and 5.1 cm, respectively) after 12 weeks of phentermine [40]. Cravings for sweet and fatty foods (measured by the Food Craving Inventory and the General Food Cravings State and Trait Questionnaires) were also decreased after 12 weeks of treatment [41]. Participants with higher hunger scores and lower cognitive resistance to food consumption (rated by Three-Factor Eating Questionnaires) at baseline exhibited greater weight loss with phentermine at 8 weeks [43]. RCTs of >1 year duration are required to shed light on long-term efficacy and safety of these medications.

3.1.3.1. Diethylpropion. Mean placebo-subtracted weight loss with diethylpropion 50 mg for 6 months was 6.2 kg (6.6%), while reduction in WC 6.5 cm [37]. After 1 year on daily diethylpropion 75 mg, placebo-subtracted weight loss was 6.9 kg (8%), WC was reduced by 6.6 cm and triglycerides (TGs) by 6.48 mmol/l, while high density lipoprotein-cholesterol (HDL-C) was increased by 0.20 mmmol/l [44]. A meta-analysis of 9 RCTs with diethylpropion 75 mg daily for 6–52 weeks showed a placebo-subtracted weight loss of 3 kg at 6 months [42]. Interestingly, diethylpropion was inferior to phentermine in weight loss at 12 weeks in a comparative study [45]: phentermine 30 mg per day resulted in an additional weight loss of 2 kg compared with diethylpropion 75 mg at 12 weeks [45].

3.2. Orlistat

Orlistat 120 mg (Xenical®) has been approved since 1998 in Europe and 1999 in the USA, while orlistat 60 mg (Alli®) is an over-the-counter formulation, available since 2007 in the USA and 2010 in Europe.

3.2.1. Mechanism of action

Orlistat inhibits gastrointestinal and pancreatic lipases, thus hydrolysis of TGs is blocked and fatty acid absorption by intestinal endothelium is reduced [46]. Typically, this results in approximately one-third of fatty acids consumed with food not being absorbed [46].

3.2.2. Dose, Side Effects and Position in Treatment Armamentarium

Orlistat is administered TID with meals or at a maximum of 1 h after meals; patients should limit daily calories from fat to <30%. It is generally well tolerated, but may be associated with various gastrointestinal side effects due to its mechanism of action that results in steatorrhea. At least one gastrointestinal adverse event was reported by 91% and 36% of patients receiving orlistat at the 1st and 4th year of treatment, respectively [47], suggesting decreased gastrointestinal side effects with long-term use. Dropout rates due to side effects were up to 8% in clinical studies [47]. The most common side effects are oily stools (27.1%), oily spotting (13.7%), fecal urgency (9.0%), fecal incontinence (6.1%), hyper-defecation (5.3%) and flatus with discharge (4.1%) [25]. Orlistat prescriptions may need supplementation of fat-soluble vitamins (A, D, E, and K), in order to avoid their deficiency following its long-term use, especially in the elderly [48,49]. Moreover, in a recent case series, acute kidney injury, presumably due to oxalate crystal deposition, was observed in 2% of the 953 patients within one year of orlistat initiation, but has also been reported even after several years of orlistat (60 or 120 mg) initiation [50,51]. Therefore, renal function should be monitored periodically in all patients, but particularly in those with increased risk of renal insufficiency [50,52]. Urine collection is usually performed for identification of hyperoxaluria and kidney biopsy (showing tubular atrophy, acute tubular necrosis, interstitial fibrosis) has facilitated early diagnosis in some of the reported cases; however, it is not typically indicated [50,52,53]. Renal function was progressively improved in most of the reported cases upon drug discontinuation, renal replacement therapy and dietary modifications [52,54]. Nevertheless, there

Table 1
FDA approved drugs for obesity: Studies that established their safety and efficacy, mechanism of action, main health benefits, frequent side effects, contraindications and approximate monthly cost in the USA.

Drug (trade name(s))	Mechanism of action	Main phase 3 studies (duration)	Arms	Weight loss Change in kg (%)	HbA1c Change %	Lipids Change %*	SBP/DBP Change in mmHg	Main adverse effects	Contraindications	Cost/month ($)
Orlistat (Xenical, Alli)	GI and pancreatic lipase inhibitor; ↓lipid absorption	XENDOS (4 years)	120 mg or placebo	1y: - 4.4 (NA) 4y: - 2.8 (NA)	NA	1y: TC: - 7.5; LDL-C: - 9.8; HDL-C: - 5.1; TGs: NS 4y: TC: - 5.6; LDL-C: - 7.7; HDL-C: - 2.6; TGs: 0.1	1y: - 2.1/- 1 4y: - 1.5/- 0.7	oily stools, oily spotting, fecal urgency, fecal incontinence, hyper-defecation, flatus with discharge, A, D, E, K deficiency	pregnancy, cholestasis, malabsorption	519 (Xenical) 50 (Alli)
Lorcaserin (Belviq, Belviq XR)	5HT-2C R agonist; ↓food intake	BLOOM (104 weeks); reassignment of lorcaserin to lorcaserin or placebo, while placebo unchanged at 52 weeks	10 mg or placebo	1y: 4.6 (3.7)	1y: - 0.07%	1y: TC: - 0.3; LDL-C: - 1.12; HDL: NS; TGs: -0.01	- 0.6/- 0.5	headache, dizziness, fatigue, nausea, constipation, dry mouth	pregnancy, severe renal disease	215
		BLOSSOM (52 weeks)	10 mg QD or 10 mg BID or placebo	QD: - 1.8 (- 1.9) BID: - 2.9 (- 3)	NA	QD: TC: - 1.3; LDL-C: NS; HDL-C: 2.2; TGs: - 4.6 BID: TC: NS; LDL-C: NS; HDL-C: 2.4; TGs: - 3.4	NS			
		BLOOM-DM (52 weeks)	10 mg QD, 10 mg BID or placebo	QD: - 3.4 (3.5) BID: - 3.1 (4)	QD: - 0.6% BID: - 0.5	BID: TC: NS; LDL-C: NS; HDL-C: 3.6; TGs: NS	NS			
Phentermine/ Topiramate (Qsymia)	NE agonist/GABA agonist, glutamate antagonist; suppress appetite	EQUIP (56 weeks)	3.75 mg/23 mg, 15 mg/92 mg or placebo	3.75 mg/23 mg: NA (- 3.6) 15 mg/92 mg: NA (- 9.4)	NA	15 mg/92 mg: TC - 2.5; LDL-C: - 2.9; HDL-C: 3.5; TGs: - 14.3	3.75 mg/23 mg: - 2.7/NS 15 mg/92 mg: - 3.8/- 1.9	paresthesia, dry mouth, constipation, insomnia, dysgeusia, anxiety, depression	pregnancy, uncontrolled HTN, cardiovascular disease, chronic kidney disease, glaucoma, hyperthyroidism and in patients on MAOIs	160-220
		CONQUER (56 weeks)	7.5 mg/46 mg, 15 mg/92 mg or placebo	7.5 mg/46 mg: - 6.7 (- 6.6) 15 mg/92 mg: - 8.8 (- 8.6)	7.5 mg/46 mg: - 0.1 15 mg/92 mg: - 0.2	7.5 mg/46 mg: TC: - 1.6; LDL-C: NS; HDL-C: 4; TGs: - 13.3 15 mg/92 mg: TC: - 3; LDL-C: -2.8; HDL-C: 5.6; TGs: - 15.3	7.5 mg/46 mg: - 2.3/NS 15 mg/92 mg: - 3.2/- 1.1			
		SEQUEL (52-wk extension of the CONQUER)	7.5 mg/46 mg, 15 mg/92 mg or placebo	7.5 mg/46 mg: - 7.4 (- 8.5) 15 mg/92 mg: - 8.9 (- 8.7)	15 mg/92 mg: - 0.2	7.5 mg/46 mg: TC: NS; LDL-C: 3.8; HDL-C: NS; TGs: - 13.1 15 mg/92 mg: TC: NS; LDL-C: 5; HDL-C: 7.7; TGs: - 14.5	NS			
Liraglutide (Saxenda)	GLP-1 analogue; slows gastric emptying, ↑ satiety, ↓food reward	SCALE Obesity and Prediabetes (56 weeks)	3 mg or placebo	- 5.6 (- 5.4)	- 0.23	TC: - 2.3; LDL-C: - 2.4; HDL-C: 1.9; TGs: - 9.3	- 2.8/- 0.9	nausea, diarrhea, constipation, vomiting, dyspepsia	pregnancy, and personal or family history of medullary thyroid carcinoma or type 2	1000

(continued on next page)

Table 1 (*continued*)

Drug (trade name(s))	Mechanism of action	Main phase 3 studies (duration)	Arms	Weight loss Change in kg (%)	HbA1c Change %	Lipids Change %*	SBP/DBP Change in mmHg	Main adverse effects	Contraindications	Cost/month ($)
		SCALE Obesity and Prediabetes extension (160 weeks)	3 mg or placebo	- 4.6 (- 4.3)	- 0.21	TC: -2; LDL-C: NS; HDLD-C: NS; TGs: -6	- 2.8/NS		MEN	
		SCALE Diabetes (56 weeks)	1.8 mg, 3 mg or placebo	1.8 mg: NA (- 2.7)	1.8 mg: - 0.8	1.8 mg: TC: - 6; LDL-C: NS; HDL-C: NS; TGs: NS	- 3.1/NS (1.8 mg)			
				3 mg: NA (- 4)	3 mg: - 1	3 mg: TC: -4.3; LDL-C: NS; HDL-C: NS; TGs: -15.1	- 2.4/NS (3 mg)			
		SCALE Maintenance (4–12 weeks run-in period, 56 weeks)	3 mg or placebo	- 5.9 (- 6)	- 0.3	NS	- 2.7/NS			
		SCALE Sleep Apnea (32 weeks)	3 mg or placebo	- 4.9 (- 4.2)	- 0.2	NS	- 4.1/NS			
		LEADER (3.5-5 years)^	1.8 mg to maximum tolerated or placebo	- 2.3 (NA)	- 0.4	NA	- 1.2/+ 0.6			
Naltrexone/ Bupropion (Contrave)	Opioid receptor antagonist/DA and NE reuptake inhibitor; ↑ satiety, suppress appetite	CORI (56 weeks)	16 mg/360 mg, 32 mg/360 mg or placebo	16 mg/360 mg: -3.5 (- 3.7)	NA	16 mg/360 mg: TC: NS; LDL-C: NS; HDL-C: 6.8; TGs: - 1.4;	16 mg/360 mg: - 2.2/- 1	nausea, headache, constipation, dizziness, vomiting, dry mouth	uncontrolled HTN, seizure, anorexia or bulimia nervosa, abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs, other bupropion-containing drugs, opioids or opiate agonists, MAOIs, pregnancy	99
				32 mg/360 mg: -4.7 (- 4.8)		32 mg/360 mg: TC: NS; LDL-C: NS; HDL-C: 7.2; TGs: - 6.1	32 mg/360 mg: - 0.4/- 0.1			
		CORII (56 weeks)	32 mg/360 mg or placebo	- 4.9 (- 5.2)	NA	TC: NS; LDL-C: 0.03; HDL: 0.1; TGs: - 9.3	+ 1.1/NS			
		COR-BMOD (56 weeks)	32 mg/360 mg or placebo	- 4.1 (- 4.2)	NA	TC: NS; LDL-C: -2.9; HDL-C: 6.6; TGs: - 8.1	+ 2.6/+ 1.4			
		COR-DIABETES (56 weeks)	32 mg/360 mg or placebo	- 3.4 (- 3.2)	- 0.5	TC: NS; LDL-C: NS; HDL-C: 3.3; TGs: - 10.4	NS			

All values shown are placebo-subtracted. ^Analysis performed at 36 months.

BID, twice daily; DA, dopamine; DBP; DBP, Diastolic Blood Pressure; GABA, gamma-aminobutyric acid; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; HbA1c, glycosylated hemoglobin; HDL-C: high-density lipoprotein cholesterol; HT-2C R, hydroxytryptamine 2C receptor; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MAOI, monoamine oxidase inhibitors; MEN, multiple endocrine neoplasia; NA, not available; NE, norepinephrine; NS, non-significant; QD, once per day; SBP, systolic blood pressure; TC, total cholesterol; TGs, triglycerides; TID, three times daily; XR: extended release; y, year.

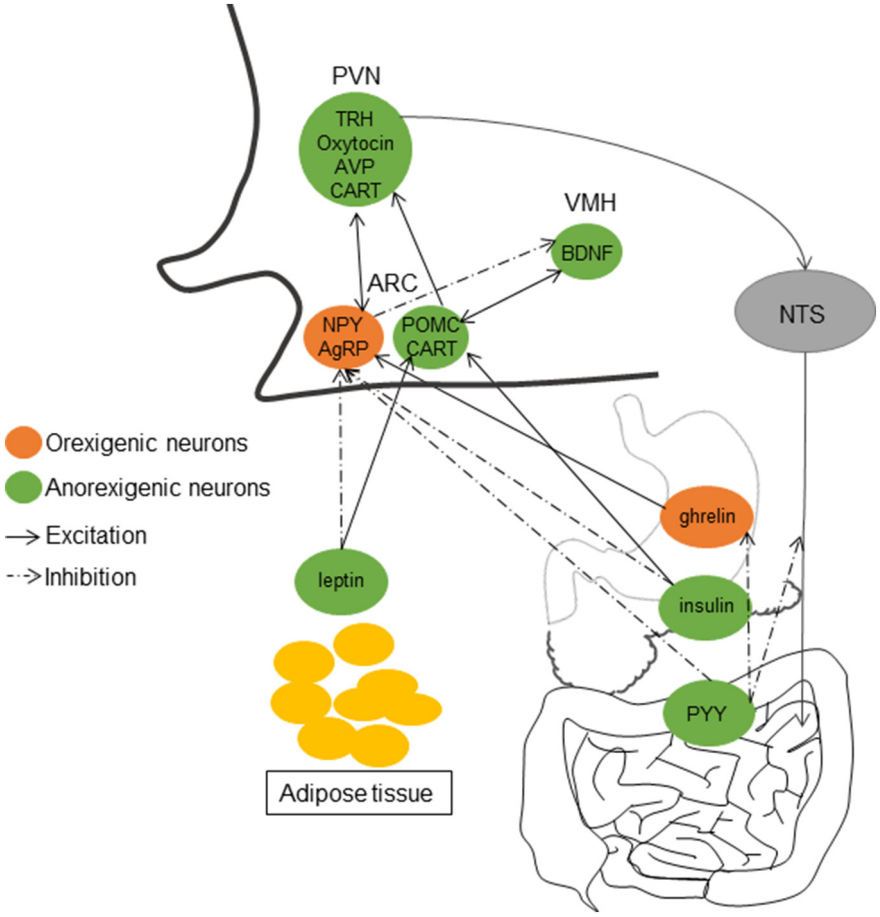

Fig. 1. Nuclei of the hypothalamus that control eating along with hormonal signaling from the periphery. The ARC contains NPY/AgRP neurons, which are orexigenic and POMC/CART neurons, which are anorexigenic. These neurons project to other nuclei and neurons resulting in release of other orexigenic (MSH, galanin, orexin) or anorexigenic (BDNF, oxytocin, AVP, TRH) peptides accordingly. Anorexigenic and orexigenic peptides are shown in groups for simplicity, but not all of them are released by a single neuron of a nucleus. *AgRP, agouti-related peptide; ARC, arcuate nucleus; AVP, arginine-vasopressin; BDNF, brain-derived neurotrophic factor; CART, cocaine- and amphetamine-regulated transcript; MSH,* melanocyte-stimulating hormone*; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; POMC, proopiomelanocortin; PVN, paraventricular nucleus; TRH; Thyrotropin-releasing hormone; PYY, peptide YY; VMH, ventromedial nucleus of hypothalamus.*

are no RCTs evaluating renal function with orlistat therapy, and therefore, specific guidelines are not currently available. Contraindications for orlistat are pregnancy, cholestasis and malabsorption [47]. Notably, it is the only FDA-approved medication for adolescents 12–16 years of age; however, clinicians typically try to manage adolescent obesity with non-pharmacologic means [55].

3.2.3. Outcomes

Long-term safety of orlistat was evaluated in the XENDOS (XENical in the Prevention of Diabetes in Obese Subjects) study that assigned obese individuals with or without impaired glucose tolerance to either orlistat plus lifestyle changes or lifestyle changes alone for a 4-year period. Placebo-subtracted weight reduction was 4.4 kg at 1 year and 2.8 kg at 4 years [47]. Placebo-subtracted percentages of participants losing >5% and >10% of their baseline weight by the end of the first year were 27.7% and 20.2%, respectively, and remained significant, albeit attenuated, over 4 years (15.5% and 10.6%, respectively) [47]. The placebo-subtracted decrease in WC was 2.6 cm at 1 year and 2 cm at 4 years [47]. Additionally, 60 mg orlistat for 24 weeks induced considerable reduction in abdominal visceral fat (placebo-subtracted 6.3%) in addition to total fat mass, liver fat and intramuscular fat [56]. In a meta-analysis of 12 RCTs with orlistat plus lifestyle modifications up to 12 months in patients with BMI ≥25 and T2D, the placebo-subtracted weight loss was 2.6 kg [57].

The benefit of orlistat on other components of metabolic syndrome is demonstrated by a 41% risk reduction in overall incidence of T2D and a 52% reduction in progression to T2D of individuals with obesity and impaired oral glucose tolerance after 4 years of treatment [47]. Additionally, the mean placebo-subtracted reduction in glycosylated hemoglobin (HbA1c) in patients with T2D was 6.1 mmol/l [57]. Orlistat was also associated with a mean reduction of 1.3 mmHg in systolic blood pressure (SBP) and 1.2 mmHg in diastolic blood pressure (DBP) independently of dose or duration, based on a meta-analysis [58]. This was somehow higher in patients with established hypertension (reduction of 2.9 mmHg in SBP and 2.3 mm in DBP at 1 year) [59]. Finally, orlistat was associated with a significant reduction in TC (7.5%), LDL-C (9.8%) and HDL-C (5.1%) at 1 year and 5.6, 7.7 and 2.6%, respectively at 4 years in the XENDOS trial [47]. Notably, the effect of orlistat on TGs was rather null [47].

3.2.4. Other Lipase Inhibitors

Cetilistat 120 mg has been marketed as OBLEAN® in Japan since 2013. It is also a lipase inhibitor that reduces absorption of ingested fat at least as efficiently as orlistat does, but with 30% fewer gastrointestinal side effects than orlistat [60,61]. A phase 2 RCT assigned 371 individuals with obesity to escalating doses of cetilistat (60 mg, 120 mg and 240 mg TID) and reported a significant body weight and WC reduction of 3.3 kg and 1 cm with 60 mg, 3.5 kg and 1.3 cm with 120 mg and 4.1 kg and 1.8 cm with 240 mg vs. placebo at 12 weeks. TC and LDL-C were also reduced vs. placebo (3–8% and 6–11%, respectively) with all doses [62]. Mild to moderate gastrointestinal adverse effects were noted [62]. Additionally, cetilistat as well as orlistat resulted in a significant placebo-

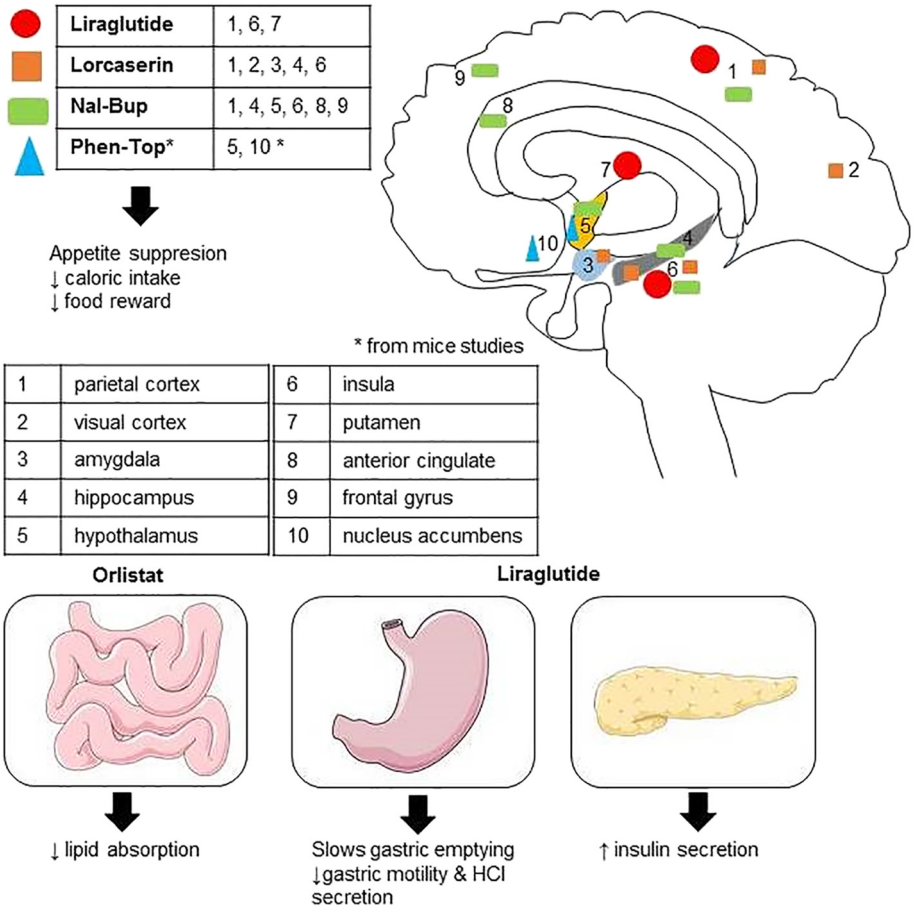

Fig. 2. FDA approved drugs for obesity: Site of action. Liraglutide, a GLP-1 analogue acts both in the periphery to stimulate insulin secretion and reduce gastric motility, gastric emptying and acid secretion as well as the CNS to control appetite. Lorcaserin decreases caloric intake and emotion- and saliency related activity of limbic system as well as the activity of parietal and visual cortices associated with the brain response to highly palatable food cues via 5-HT 2C receptors. Phentermine/topiramate exert noradrenergic and GABA agonism, glutamate antagonism and carbonic anhydrase inhibition respectively, suppressing appetite. Naltrexone, a mu- and kappa-opioid receptor antagonist and bupropion a weak norepinephrine and dopamine reuptake inhibitor and nicotinic acetylcholine receptor antagonist decrease food consumption synergistically. Orlistat decreases the amount of fatty acids absorbed by the gastrointestinal tract via inhibition of gastrointestinal and pancreatic lipases. Some of the illustrations were downloaded from *https://smart.servier.com/*. *CNS, central nervous system; FDA, food and drug administration; GABA, gamma aminobutyric acid; GLP, glucagon-like peptide; HCl, hydrochloric acid; HT, hydroxytryptamine; Nal-Bup, naltrexone-bupropion; Phen-Top, phentermine/topiramate.*

subtracted weight loss (1 kg with cetilistat 80 mg, 1.5 kg with cetilistat 120 mg and 0.9 kg with orlistat 120 mg) and a modest improvement in placebo subtracted HbA1c (0.17%, 0.14% and 0.16%, respectively) when administered in patients with obesity and T2D ($n = 600$) for 12 weeks [61].

3.3. Lorcaserin

Lorcaserin (Belviq® and Belviq XR®) has been approved in the USA since 2012. The European Medical Agency did not approve lorcaserin due to concerns about psychiatric side effects (depression, suicidal ideation, psychosis) and valvulopathy [phase 3 studies were underpowered to detect incidence difference between groups, thus the Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients–Thrombolysis in Myocardial Infarction (CAMELLIA-TIMI) study followed], as well as preclinical data about potential breast tumors [48].

3.3.1. Mechanism of Action

Lorcaserin is a selective 5-hydroxytryptamine 2C (5HT-2C) receptor agonist that decreases caloric intake but not energy expenditure in humans [63]. The proposed mechanism, based on rodent studies, is targeting hypothalamic proopiomelanocortin (POMC) neurons [63,64]. A functional magnetic resonance imaging (fMRI) study in humans has shown that lorcaserin decreases the emotion- and saliency-related activity of limbic system, and the activity of parietal and visual cortices in response to highly palatable food cues [65]. Thus, lorcaserin may be more effective in obesity associated with emotional eating, a hypothesis also supported by the maintenance of diet reduced emotion-and stress-related eating after 24 weeks on lorcaserin vs. placebo [65,66].

3.3.2. Dose, Side Effects and Position in Therapeutic Armamentarium

Lorcaserin can be taken 10 mg BID or 20 mg (extended release) QD. If body weight is reduced <5% at 12 weeks, the drug should be stopped [67]. The most frequent side effects are: headache (6.4%), dizziness (4.8%), fatigue (4.3%) and nausea (3.8%) [68,69]. Tolerability of the medication is high, as per the BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) study, a phase 3 RCT ($n = 3182$) that investigated the efficacy of lorcaserin 10 mg BID over 52 weeks and reported low withdrawal rates due to side effects, similar to those of placebo (7.1% in the lorcaserin vs. 6.7% in the placebo group) [70]. Lorcaserin binds with much less affinity to 5HT-2A and 5HT-2B receptors, and thus, did not seem to increase the incidence of hallucinations and valvulopathy as did previous similar drugs, such as dexfenfluramine, which affected more 5HT-2A and 5HT-2B receptors [70]. However, since the major phase 3 trials were underpowered to detect a difference in the incidence of valvulopathy between treatment groups, the CAMELLIA-TIMI 61 studied the association in 12,000 overweight or obese patients with atherosclerotic disease or cardiovascular risk factors that were randomized to lorcaserin 10 mg BID or placebo for a median duration of 3.3 years [71]. The study group reported a slight, but non-significant rise in the incidence of new or worsening subclinical

valvulopathy (1.4%) and pulmonary hypertension (1.9%) with lorcaserin vs. placebo [72]. Other side effects, including cancers, ductal carcinoma in situ, fibroadenoma, euphoria, psychosis, suicidal ideation and behavior, which concerned the European Medical Agency in the past, are not increased by lorcaserin vs. placebo as per the same trial [73]. Contraindications for lorcaserin are pregnancy and severe renal disease. Co-administration with other serotoninergic agents might potentially lead to serotonin syndrome, however both a retrospective analysis of the three main phase 3 trials and the CAMELLIA-TIMI study did not raise any concern [73].

3.3.3. Outcomes

At the extension of BLOOM study, the patients on lorcaserin were reassigned to receive lorcaserin on placebo, while the initial placebo group remained on placebo for another year [70]. At year 1, 47.5% of individuals in the lorcaserin group lost ≥5% of body weight vs. 20.4% of those in the control group, which corresponded to a mean reduction of 5.8 kg and 2.2 kg, respectively [70]. Among patients with ≥5% weight loss at the end of the first year, those that received lorcaserin for another year regained less weight compared to placebo by the end of the second year (2.8 kg vs. 4.6 kg, respectively) [70]. The BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management) study assigned 4008 patients to either lorcaserin 10 mg BID or lorcaserin 10 mg QD or placebo and showed a placebo-subtracted weight reduction of 2.9 kg (BID) and 1.8 kg (QD), thus suggesting greater efficacy with BID dosing [68]. In patients with T2D, similar results were observed with a placebo-subtracted weight loss of 3.1 kg with lorcaserin 10 mg BID and 3.4 kg with 10 mg QD at 52 weeks, while 37.5% of the former and 44.7% of the latter group lost ≥5% of their baseline body weight (vs. 16.1% in placebo) [69]. A meta-analysis of three RCTs demonstrated an additional weight reduction of 3.2 kg with lorcaserin compared to placebo at 1 year [74]. WC also decreased with lorcaserin by 2.5 cm according to the same meta-analysis [74]. In patients without T2D, fasting glucose and HbA1c improved significantly but modestly with lorcaserin at 1 year (placebo-subtracted reductions 1.9 mg/dl and 0.07%, respectively) [70]. In patients with T2D, placebo-subtracted HbA1c reduction was 0.5% and 0.6% with lorcaserin 10 mg BID and 10 mg QD, respectively, and fasting glucose reduction was 15.5 mg/dl and 16.5 mg/dl, respectively [69]. In the aforementioned meta-analysis, SBP and DBP decreased modestly with lorcaserin (0.6 mmHg and 0.5 mmHg, respectively) at 12 months, which however is of low clinical significance [74]. Furthermore, lorcaserin had a modest favorable effect on lipids vs. placebo at 1 year: −1.1% in TC, −1.3% in LDL-C, +1.8% in HDL-C and −4.7% in TGs [74].

Long-term effects of lorcaserin on the cardiovascular system were evaluated by the CAMELLIA-TIMI 61 trial [71]. Percentage of major cardiovascular events (cardiovascular death, myocardial infarction or stroke) did not increase with lorcaserin vs. placebo (2.0% vs. 2.1% per year, hazard ratio 0.99) during the 3.3 years of follow up [72]. However, lorcaserin was not proven superior in terms of extended major cardiovascular events (plus hospitalization for unstable angina, heart failure and coronary revascularization) (hazard ratio, 0.97). SBP, DBP, HR, LDL-C, TGs, HbA1c were slightly improved at 1 year, while annual rate of new-onset diabetes in patients with prediabetes was lower with lorcaserin vs. placebo (3.1% vs. 3.8%) [72].

Lorcaserin has also been assessed in combination with phentermine in a 12-week RCT consisting of 238 subjects with obesity or overweight and ≥1 related comorbidities (hypertension, dyslipidemia, T2D, sleep apnea) [75]. Lorcaserin 10 mg BID plus phentermine 15 mg QD or 15 mg BID achieved a significant subtracted weight loss of 3.5 kg (3.4%) and 4.1 kg (3.9%), respectively, in comparison to 10 mg BID lorcaserin monotherapy, with no significant increase in serotoninergic adverse events (e.g. dry mouth, insomnia, nausea, diarrhea, vomiting, anxiety) or vital signs [75]. Lorcaserin 10 mg BID, lorcaserin 10 mg BID plus phentermine 15 mg QD and lorcaserin 10 mg BID plus phentermine 15 mg BID decreased perceived food cravings and improved control of eating (assessed by the Food Craving Inventory and the Control of Eating Questionnaire) significantly compared to baseline, which was more effective with the combination treatments [76]. However, the combination phentermine/lorcaserin is not currently approved.

3.4. Phentermine and Topiramate

Qsymia®, a combination of phentermine and topiramate, was launched in the US in 2012, but it has not been approved in Europe, mainly due to the lack of long-term data on the cardiovascular effects (arrhythmia, ischemic heart disease, pulmonary hypertension, valvulopathy) of phentermine and abuse potential, psychiatric (such as anxiety, depression, sleep disorders, and suicide/self-injury) and cognitive (such as attention, language, memory impairment etc.) side effects of topiramate, since the main phase 3 trials were underpowered to detect differences between treatment groups [77].

3.4.1. Mechanism of action

This combination drug suppresses appetite via mechanisms that are still under investigation. As aforementioned, phentermine, a centrally acting sympathomimetic, enhances the release of serotonin, norepinephrine and dopamine [29]. Topiramate is a gamma-aminobutyric acid (GABA) agonist, glutamate antagonist and carbonic anhydrase inhibitor, whose primary approval was as antiepileptic [31]. CNS studies in humans have not yet been completed, but could clarify the effect of the medication on brain areas regulating energy balance and appetite.

3.4.2. Dose, Side Effects and Position in Treatment Armamentarium

The dose of phentermine/topiramate is progressively increased and adjusted based on individual needs using one of the four available controlled release oral combinations. Initially, phentermine/topiramate 3.75 mg/23 mg is given QD for 2 weeks, followed by 7.5 mg/46 mg QD for 12 weeks. If the weight reduction is <3%, the drug should be either discontinued or dose-escalated. If dose-escalated, phentermine/topiramate 11.25 mg/69 mg should be administered QD for the next 2 weeks, followed by 15 mg/92 mg QD for another 12 weeks [31]. Unless weight loss from baseline is ≥5%, the drug should be gradually discontinued [31]. Paresthesia (2–17%), dry mouth (3–13.3%), constipation (1.1–7.3%), dysgeusia (7%), insomnia (2.7%), depression (2.1–3.5%) and anxiety (1.7–2.5%) are the most common adverse events, which are dose-dependent [78,79]. Phentermine/topiramate increases heart rate, might affect renal function and may lead to development of metabolic acidosis and nephrolithiasis (due to cardonic anhydrase inhibition by topiramate) in a small percentage of patients, therefore heart rate, electrolytes and creatinine should be assessed in the beginning and periodically while on treatment, especially during dose adjustment [7,80]. Patients should also be monitored for depression and suicidal ideation [48]. Phentermine/topiramate is contraindicated in pregnancy, uncontrolled hypertension, cardiovascular disease, chronic kidney disease, glaucoma, hyperthyroidism and in patients on monoamine oxidase inhibitors (or within 14 days after their discontinuation) [81].

3.4.3. Outcomes

Efficacy and safety of phentermine/topiramate was assessed in three main phase 3 RCTs: EQUIP, CONQUER and SEQUEL [78,79,82]. In EQUIP, 1267 patients with BMI ≥ 35, without hypertension/T2D, were randomly assigned to receive placebo, phentermine/topiramate 3.75 mg/23 mg or 15 mg/92 mg, as addition on a hypocaloric diet for 56 weeks [78]. Placebo-subtracted percentage of patients losing ≥5% of their weight was 27.6% for the low and 49.4% for the high treatment dose, corresponding to an overall placebo-subtracted weight loss of 3.5% and 9.3%, respectively [78]. Evaluation of phentermine/topiramate in overweight or obese adults ($n = 2487$) with a BMI > 27 and ≥1 related comorbidities (hypertension, dyslipidemia, T2D) in the CONQUER study resulted in a placebo-subtracted weight reduction of 6.7 kg (6.6%) with the 7.5 mg/46 mg dose and 8.8 kg (8.6%) with the15 mg/92 mg dose [79].

The participants, achieving a weight reduction ≥5% compared to placebo were 41% and 49%, respectively [79]. SEQUEL, a 52-week extension of the CONQUER, reported a total placebo-subtracted weight loss of 7.5% (7.5 kg) with the 7.5 mg/46 mg and 8.7% (8.8 kg) with the 15 mg/92 mg dose at 108 weeks, thus beneficial effects of phentermine/topiramate are maintained but not amplified with treatment continuation [82]. As previously discussed, phentermine/topiramate (7.5 mg/46 mg and 15 mg/92 mg) resulted in significantly greater placebo subtracted weight reduction as compared to phentermine (7.5 mg and 15 mg) and topiramate extended release (46 mg and 92 mg) monotherapies (6.8% and 7.5% vs. 3.8%, 4.4%, 3.4%, 4.7% respectively) in the EQUATE study [39]. In patients with T2D, placebo-subtracted weight loss was 6.7% with the 15 mg/92 mg dose and the tolerability was good, with only one individual from the treatment arm withdrawing due to side effects [83]. Based on a meta-analysis of RCTs, phentermine/topiramate results in an overall placebo-subtracted weight loss of 8.8 kg (6.7%) at 56 weeks, which is currently the highest among all FDA-approved medications for obesity [84].

Placebo-subtracted WC was reduced by 2.5 cm and 7.8 cm with the 3.75 mg/23 mg and the 15 mg/92 mg dose, respectively, in obese without comorbidities (EQUIP), and 5.2 cm and 6.8 cm with the 7.5 mg/46 mg and the 15 mg/92 mg, respectively in obese with related comorbidities (CONQUER) [78,79]. Phentermine/topiramate was also found to improve glycemic control after 1-year treatment; placebo-subtracted reduction in HbA1c was 0.2% and 0.1% with the 15 mg/92 mg and the 7.5 mg/46 mg dose, respectively, in obese with ≥2 related comorbidities, and 0.4% with 15 mg/92 mg in patients with T2D [82,83]. Furthermore, treatment with 7.5 mg/46 mg and 15 mg/92 mg phentermine/topiramate in patients without T2D at baseline decreased the progression to T2D by 54% and 76%, respectively, as compared to placebo [82]. SBP and DBP were significantly but modestly reduced with the high dose of phentermine/topiramate (15 mg/92 mg) in patients without comorbidities (3.8 mm Hg and 1.9 mm Hg, respectively) and in patients with comorbidities (3.2 mm Hg and 1.1 mm Hg, respectively) compared to placebo [78,79]. Lower doses (3.75 mg/23 mg and 7.5 mg/46 mg) did not affect blood pressure [78,79]. In patients with hypertension, the beneficial effects of phentermine/topiramate on SBP and DBP were observed with both 15 mg/92 mg and 7.5 mg/46 mg doses (placebo-subtracted reduction 4.2/1.9 mmHg and 2.0/1.3 mmHg, respectively) [59]. Only high dose (15 mg/92 mg) phentermine/topiramate improved lipid profile, particularly TGs and HDL-C, while low dose did not change them. Placebo-subtracted changes in patients with and without comorbidities were similar at 1 year (reduction by 14.3% and 15.3%, respectively, in TGs, by 2.5% and 3.0%, respectively, in TC, by 2.9% and 2.8%, respectively, in LDL-C, and increase by 3.5% and 5.6%, respectively, in HDL-C) [78,79]. Interestingly, after 2 years of treatment, LDL-C was decreased by 5.1–6.2% less (ranges due to two dosages: 7.5 mg/46 mg and 15 mg/92 mg) as compared to placebo; however, concomitant medications for T2D, hyperlipidemia and hypertension might have confounded this effect [82].

Furthermore, phentermine/topiramate 15 mg/92 mg improved apnea-hypopnea index (AHI), a marker of OSA severity, in patients with obesity and moderate to severe OSA (31.5 less events/h compared to 16.6 less events/h with placebo) in a phase 2, 28-week RCT [85].

In addition, phentermine/topiramate 3.75 mg/23 mg daily followed by 7.5 mg/46 mg plus dietary counseling resulted in a body weight reduction of 4.9 kg at 12 weeks in an open-label, prospective study, in which overweight or obese patients with Binge Eating Disorder were recruited. This combination drug significantly improved frequency of binge-eating episodes, obsessive-compulsive characteristics and overall disorder severity, but RCTs are needed to reach safe conclusions [86].

3.5. Liraglutide

Liraglutide has been marketed as Saxenda® both in the USA and Europe since 2014 and 2015, respectively.

3.5.1. Mechanism of Action

Liraglutide is a GLP-1 analogue, originally approved for the treatment of T2D at doses up to 1.8 mg. GLP-1, an incretin hormone, is secreted by the L-cells of the distal ileum, proximal colon and the vagal nucleus of the solitary tract after meals and has multiple effects: 1) enhances insulin secretion by the pancreatic beta-cells and inhibits glucagon secretion in a glucose-dependent manner, thus it regulates blood glucose; 2) slows gastric emptying and increases postprandial satiety and fullness; and 3) decreases appetite and food consumption by acting in the hypothalamus, limbic/reward system and cortex [87–91]. In rodents, satiety is mediated via activation of POMC/cocaine- and amphetamine-regulated transcript (CART) and inhibition neuropeptide Y (NPY) neurons of arcuate nucleus (ARC) and decreased appetite by stimulation of paraventricular nucleus (PVN) of the hypothalamus to release oxytocin, an anorexigenic molecule [92,93]. Liraglutide also targets the ventral tegmental area and nucleus accumbens neurons of the reward system, thus reducing intake of highly palatable food in rodents [94,95]. In humans, CNS studies confirm the hypothesis that altered activation of areas responsible for appetitive behaviors (e.g. parietal cortex, insula and putamen) in response to images of highly desirable foods are responsible for decreased hunger and increased fullness observed with liraglutide [90,96].

3.5.2. Dose, Side Effects and Position in Treatment Armamentarium

The optimal dose of liraglutide for obesity management is 3 mg subcutaneously daily, but it should be initiated at 0.6 mg QD and escalated weekly by 0.6 mg up to 3 mg [31]. The most frequent placebo-subtracted side effects are: nausea (25.0%), vomiting (12.2%), diarrhea (11.6%), constipation (11.0%), and dyspepsia (6.4%) [97]. A meta-analysis reported that liraglutide has the highest probability of discontinuation due to side effects (13% of the patients) among all FDA-approved medications [84]. The area postrema, the center of the brain responsible for nausea and vomiting, contains GLP-1 receptors, and, therefore, are direct side effects of the GLP-1 analogues [96]. However, they are tolerated by most patients and the tolerability improves over time [96–98]. Presumably due to the rapid weight loss associated with liraglutide, the risk of cholelithiasis slightly increases. On the contrary, despite the initial considerations regarding the risk of acute pancreatitis, which is low in absolute numbers, long term trials suggest that the risk of pancreatitis does not seem to increase significantly [99,100]. More specifically, biomarkers of acute pancreatitis, amylase and mostly lipase, do rise in a non-dose-dependent fashion during therapy with GLP-1 receptor analogues, but their rise is not usually accompanied by symptoms, and monitoring them has not been proven to predict acute pancreatitis [101]. Contraindications for liraglutide are pregnancy, and personal or family history of medullary thyroid carcinoma or type 2 multiple endocrine neoplasia, based on rodent studies which showed a proliferative effect of liraglutide on thyroid C-cells [48]. Pancreatic, intestinal and breast neoplasms also developed more frequently in rodents on incretin-based medications, but these results are not consistent in human studies [102–106]. The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) study, a phase 3b RCT, showed no difference in calcitonin levels and in medullary thyroid carcinoma rates between liraglutide (≤1.8 mg) and placebo after 3.5–5 years of follow up [107]. Likewise, the total risk of malignant and benign neoplasms, including pancreatic cancer, did not increase in the liraglutide vs. placebo group [99,100,108]. However, these results should be cautiously interpreted because: 1) the LEADER trial was not designed to assess the cancer risk; and 2) the rarity of medullary thyroid carcinoma possibly renders LEADER underpowered to detect the risk of it. Thus, intensive post-market surveillance of liraglutide is considered to be important. Since evaluation of neuropsychiatric safety of liraglutide did not raise any concerns, this medication could probably be a good choice for obese patients with mental disorders [109].

3.5.3. Outcomes

The SCALE (Satiety and Clinical Adiposity Liraglutide Evidence in Nondiabetic and Diabetic people) Obesity and Prediabetes, the SCALE Diabetes and the SCALE Maintenance RCTs resulted in the approval of liraglutide as an anti-obesity medication [97,110,111]. In the SCALE Obesity and Prediabetes, obese without T2D ($n = 2487$) were assigned to liraglutide 3 mg QD or placebo for 56 weeks and a placebo-subtracted weight loss of 5.2% (5.6 kg) was reported, corresponding to placebo-subtracted 36.1% and 22.5% of the participants achieving ≥5% and ≥ 10% weight loss, respectively [97]. In the SCALE Diabetes, overweight or obese patients with T2D ($n = 846$) were assigned to liraglutide 3 mg QD or 1.8 mg QD or placebo for 56 weeks and a placebo-subtracted weight loss of 4% (4.2 kg) and 2.7% (2.3 kg), respectively, was reported [110]. Early (at 16 weeks) weight loss ≥4% with liraglutide 3 mg was associated with more weight loss at the end of the study [112]. In 422 obese without T2D, weight loss ≥5% with hypocaloric diet during a run-in period followed by liraglutide 3 mg QD for 56 weeks resulted in the maintenance of the previously lost weight in a placebo-subtracted 32.5% of the patients in the treatment group and an additional placebo-subtracted weight loss of 6% [111]. Considering the above, liraglutide 3 mg QD seems to have a similar effect on weight loss irrespective of previous diet-induced weight loss.

A meta-analysis showed that the placebo-subtracted WC reduction with liraglutide (1.2 mg–3 mg) was 4 cm (3 studies; duration 52–104 weeks) [113]. Glycemic control was also improved with liraglutide. Placebo-subtracted reduction in HbA1c was 0.2% with 3 mg in patients without T2D, and 0.9% and 0.7% with 3 mg and 1.8 mg, respectively, in patients with T2D [97,110]. Among patients with prediabetes at screening, 4% fewer progressed to T2D after 160 weeks on liraglutide [114]. Mean placebo-subtracted reduction in SBP was 2.7 mm Hg and 2.4 mm Hg in obese without and with T2D, respectively, and reduction in DBP was 0.7 mm Hg in those without T2D [97,110]. Lipid profile is also improved with liraglutide both in patients without and with T2D. Placebo-subtracted changes were: 1) TC: decrease by 5.3% and 2.1%, respectively; 2) LDL-C: decrease by 2% in patients without T2D, but not significant in T2D; 3) HDL-C: increase by 2.8% and 1.6%, respectively; and 4) TGs: decrease by 15.1% and 7.8%, respectively [97,110].

Patients with T2D and high cardiovascular risk that were randomized to liraglutide 1.8 mg (or maximum tolerated dose) plus standard care had a 22% decrease in cardiovascular mortality and a 15% decrease in all-cause mortality compared with placebo at 3.8 years [Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial] [115]. Similarly, hazard ratio of renal outcomes, mainly rate of new onset macroalbuminuria, was decreased in those on liraglutide vs. placebo [116]. Additionally, renal function deteriorated less in the liraglutide vs. placebo participants over time [116]. In patients with heart failure and ejection fraction ≤40% [Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT study] liraglutide resulted in a placebo subtracted weight loss of 2.1%, a reduction in HbA1c of 0.5% and in TGs of 33 mg/dl after 180 days [117].

Administration of liraglutide 3 mg for 16 weeks decreased body weight by 6% both in individuals with melanocortin (MC) 4 receptor mutations (6.8 kg) and normal controls (6.1 kg), indicating that GLP-1 receptors are effective in patients with this most common form of monogenic obesity [118]. In addition, WC was reduced by a placebo-subtracted 5.4 and 6.5 cm, total fat mass by 2.5 and 2.6% and fasting insulin by 0.25 and 0.4 mmol/l in the MC4 receptor mutation and control groups, respectively [118].

The effect of liraglutide in OSA was evaluated in a RCT (SCALE Sleep Apnea) that recruited patients ($n = 359$) with obesity and moderate or severe OSA, stratified by AHI. A placebo-subtracted decrease of 6.1 in AHI together with a weight loss of 4.1% was reported after 32 weeks on liraglutide 3 mg. Notably, improvement in OSA symptoms were associated with weight reduction [119].

Based on a recent meta-analysis of 23 RCTs of 12–26 weeks in overweight and obese women with PCOS ($n = 941$), liraglutide (1.2 mg–3 mg) produced the greater weight loss effect (5.2 kg), followed by orlistat (3.2 kg), liraglutide 1.2 mg plus metformin (3.0 kg) and metformin alone (1.34 kg) [120]. WC was also decreased more with liraglutide (5.7 cm) as compared to liraglutide plus metformin (4.7 cm) and metformin alone (2.7 cm) after 12–36 weeks of treatment [120]. However, when only studies of 12 weeks duration were included in the meta-analysis, statistical significance was achieved only for the weight (5.7 kg), but not the WC reduction [120].

3.6. Naltrexone and Bupropion

Contrave® and Mysimba® are the trade names of the combination of naltrexone 32 mg and bupropion 360 mg available in the US since 2014 and in Europe since 2015, respectively [48].

3.6.1. Mechanism of Action

Naltrexone is as a mu- and kappa-opioid receptor antagonist, primarily used in the management of drug and alcohol abuse [121]. Bupropion is a weak norepinephrine and dopamine reuptake inhibitor, and nicotinic acetylcholine receptor antagonist, primarily used in the management of depression and smoking cessation [121]. Since both had weight loss as a side effect, they were combined for the use as an anti-obesity medication [121]. Rodent studies have shown that bupropion acts on POMC neurons of the hypothalamic ARC and enhances secretion of α-melanocyte-stimulating hormone (α-MSH), which is an anorexigenic molecule that decreases food consumption and increases energy expenditure [122]. Beta-endorphins are also produced by POMC neurons to inhibit α-MSH release and counterbalance its anorexigenic effect, resulting in stimulation of hunger [122]. Naltrexone prevents inhibition of α-MSH by beta-endorphins, thus synergistically acts with bupropion to regulate appetite and decrease body weight [31]. In humans, based on an fMRI study, the anti-obesity effects of naltrexone/bupropion are exerted by changing the response to food of the hypothalamus (homeostatic control), and cortical and subcortical regions (anterior cingulate, superior frontal and superior parietal cortices, posterior insula, hippocampus) regulating self-control, internal awareness and memory [123].

3.6.2. Dose, Side Effects and Position in Treatment Armamentarium

Naltrexone/bupropion is available in sustained release tablets of 8 mg/90 mg. Dose should be escalated: one tablet every morning for one week, then one tablet twice daily for another week, followed by two tablets every morning and one every evening for a third week and finally two tablets twice daily from the 4th week [31]. Moderate and transient nausea (21.9–24.5%), headache (4.5–6.7%), constipation (10%), dizziness (5.1–6.8%), vomiting (3.8–7.3%) and dry mouth (5.5%) are the most common side effects [124,125]. The meta-analysis mentioned above showed that naltrexone/bupropion is the second most probable anti-obesity medication to discontinue due to side effects (12% of study participants) after liraglutide [84]. Contraindications to naltrexone/bupropion are uncontrolled hypertension, seizure, anorexia or bulimia nervosa, abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs, use of other bupropion-containing drugs, opioids or opiate agonists, use of monoamine oxidase inhibitors or their discontinuation within the previous 14 days, and pregnancy [48]. The patients receiving naltrexone/bupropion should be monitored for the development of depression or suicidal ideation.

3.6.3. Outcomes

COR-I (Contrave Obesity Research I), COR-II (Contrave Obesity Research II), COR-DIABETES (Contrave Obesity Research in Diabetes) and COR-BMOD (Contrave Obesity Research in adjunct to intensive Behavioral MODification) were the major studies that led to the approval of naltrexone/bupropion [124–127]. COR-I, which enrolled 1742 obese without T2D, reported a placebo-subtracted weight loss of 4.8% with 32 mg/360 mg and 3.7% with 16 mg/360 mg; ≥5% reduction in body

weight was achieved by 32% of the former and 23% of the latter group at 56 weeks [124]. COR-II evaluated naltrexone/bupropion 32 mg/360 mg daily in 1496 obese or overweight patients with dyslipidemia and/or hypertension. The placebo-subtracted weight loss was 4.6% at 28 weeks and 5.2% at 56 weeks [125]. The same dose was assessed in 505 obese with T2D in a 56-week RCT that resulted in a placebo-subtracted weight loss of 3.2%; 25.6% more participants from the treatment group lost ≥5% of their body weight [126]. Similarly, behavioral modification with naltrexone/bupropion 32 mg/360 mg in 793 individuals with obesity plus hypertension and/or dyslipidemia resulted in a mean placebo-subtracted weight loss of 4.2% at 56 weeks [127]. Similar findings derived from a recent phase 3b, 26-week, open-label RCT that showed a greater weight reduction in patients receiving naltrexone/bupropion 32 mg/360 mg plus lifestyle modification vs. lifestyle modification alone (9.5% vs. 0.9%, respectively) [128]. Subjects that lost ≥5% of their body weight continued treatment until week 78 and maintained the weight loss. However, one-fifth of the participants withdrew due to side effects, the more common of which was nausea (7%) [128]. In a recent meta-analysis, placebo-subtracted weight reduction with naltrexone/bupropion was 5 kg at 56 weeks [84]. Furthermore, patients on naltrexone/bupropion reported better quality of life and greater control over eating, assessed by the Impact of Weight on Quality of Life (IWQOL)-Lite and Control of Eating Questionnaire, respectively [125,129].

A meta-analysis also showed a placebo-subtracted reduction in WC of 3.5 cm at 56 weeks [84]. Improvement in glycemic control was also showed in patients with T2D receiving naltrexone/bupropion. More specifically, the placebo-subtracted reduction in HbA1c was 0.5% [126]. Naltrexone/bupropion increased SBP/DBP by 1.8/0.9 mm Hg in patients without T2D, but no changes in blood pressure were shown in patients with T2D [124,125]. TG and HDL-C levels were improved with naltrexone/bupropion regardless of T2D with a placebo-subtracted reduction of 8.1–10.4% and increase of 3.3–6.6%, respectively [124–127]. Naltrexone/bupropion 32 mg/360 mg did not affect the risk of major adverse cardiovascular events compared with placebo in overweight and obese patients with increased cardiovascular risk, as shown in an interim analysis of an RCT with early termination [130], thus requiring further investigation.

4. Anti-obesity Medications in the Pipeline

One of the goals of the ongoing research on anti-obesity medications is the development of more potent and more selective agents, thus multiplying effectiveness and reducing toxicity. Scientific endeavors are also focused on the discovery of novel molecules that act through different pathways than the existing drugs.

4.1. Anti-diabetic Medications as Potential Anti-obesity Agents

Some medications approved for the treatment of T2D, like GLP-1 analogues, result in weight loss, therefore they are currently being evaluated as anti-obesity agents in obese without T2D. Metformin, a first line drug for the management of T2D, and sodium-glucose cotransporter (SGLT)-2 inhibitors, a newer class of anti-diabetic medication, belong to this category.

4.1.1. GLP-1 Receptor Agonists (Exenatide and Semaglutide)

Exenatide, a short acting GLP-1 analogue, has completed a phase 3 RCT in obese patients without T2D and is currently in phase 3 for treatment of hypothalamic obesity after therapy for craniopharyngioma (NCT02860923). Results from a phase 2 RCT showed greater weight loss with exenatide vs. placebo (5.1 and 1.6 kg, respectively) and improvement in glucose tolerance in obese without T2D at 24 weeks [131]. Another RCT with 80 obese randomized to subcutaneous exenatide 10 μg BID or placebo reported a placebo subtracted decrease of 625 kcal/day in ad libitum absolute energy intake, but no significant difference in 24-hour energy expenditure and substrate oxidation at 3 days [132]. However, no significant changes in energy intake, 24-hour energy expenditure and body weight were observed at 24 weeks, rendering the use of exenatide as an anti-obesity medication questionable [132]. Nevertheless, based on a meta-analysis of 4 RCTs of obese without T2D, exenatide resulted in a placebo subtracted weight loss of 4.5 kg at 12–24 weeks [133]. Another meta-analysis of 21 trials showed that exenatide (5–10 μg BID or 2 mg/week) was at least as effective as liraglutide (1.2 or 1.8 mg QD) in reducing weight, with weight loss of 2.8 kg and 2.2 kg in obese with and without T2D, respectively, after 24–53 weeks of treatment [134]. However, exenatide was shown to increase heart rate more compared with other GLP-1 analogues [135]. Based on the aforementioned data, more studies are needed to definitely evaluate the efficacy and safety of exenatide as an anti-obesity medication.

Semaglutide, a long acting GLP-1 analogue, was administered once per week subcutaneously (0.25 mg up to 1.0 mg) in a 12-week cross-over RCT with 30 obese [136]. Placebo-subtracted weight loss was 6 kg, consisting of more fat than lean mass compared to placebo, while daily caloric intake was decreased by 24% (726 kcal less per day) with semaglutide compared to placebo [136]. Furthermore, hunger, duration and portions of meal, consumption of high fat food and craving were reduced with semaglutide [136]. Semaglutide, resulted in an average weight reduction of 3.2 kg (2.5–5.7 kg with 0.5 mg weekly and 2.0–7.9 kg with 1.0 mg weekly) at 30–104 weeks, greater compared to placebo or other comparators (sitagliptin, exenatide extended release or insulin glargine; 1.5 kg gain to 3.7 kg weight loss) across the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) trials which evaluated cardiovascular and other long-term outcomes with semaglutide in patients with T2D [137,138]. Similarly, a recent meta-analysis of 21 trials, including the SUSTAIN ones, reported a greater benefit in weight loss with semaglutide 0.5 mg (−2.28 kg) and semaglutide 1.0 mg (−3.78 kg) vs. other antidiabetic medications, as well as with semaglutide 1.0 mg (−2.79 kg) vs. other GLP-1 receptor agonists in patients with T2D [139]. In obese patients without T2D administration of escalating semaglutide doses (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg) or liraglutide 3 mg QD resulted in a placebo subtracted weight loss of 4.0%, 6.8%, 10.2%, 9.8%, 11.7% and 5% respectively (higher with semaglutide dose ≥0.1 mg vs. liraglutide) [140]. SBP and DBP decreased with ≥0.1 mg semaglutide doses as well as with liraglutide vs. placebo [140]. The most frequent side effects were gastrointestinal, but none was of considerable severity [136,140]. Notably, a recent meta-analysis of 12 trials in patients with T2D reported no significant increase in incidence of acute pancreatitis with semaglutide vs. placebo or active comparators [139]. The SELECT (semaglutide effects on cardiovascular outcomes in people with overweight or obesity) study will investigate semaglutide effect on incidence of fatal and non-fatal cardiovascular events in overweight or obese patients with co-existing cardiovascular disease over a period of 2.5–5 years (NCT03574597).

4.1.2. Metformin

Metformin is the first line agent for the management of T2D, since it reduces glucose synthesis in the liver and its absorption from the intestine, while increasing glucose uptake in the periphery, thus improving insulin sensitivity [141]. Metformin mediates its anti-diabetic effect via: 1) interfering with adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) signaling, thus suppressing glucose production and 2) changing gut microbiome [142]. Metformin does not increase body weight and might actually prevent weight gain from other anti-diabetic medications or even produce some weight loss (−1.1 kg) based on meta-analyses of RCTs [143,144]. Metformin also reduced weight in adults and children on anti-psychotic medications by 4.8% and 4.1%, respectively [145]. In obese or overweight women with PCOS metformin administration decreased body weight by 1 kg and WC by 1.7 cm at 24 weeks, but did not significantly affect BMI or waist-to-hip ratio [120]. Metformin administration in pregnant women with a BMI ≥ 30 reduced maternal weight gain by 1.4 kg, without affecting newborn birth weight and the incidence of maternal and

fetal adverse events in comparison to placebo [146]. Addition of metformin to dietary intervention resulted in the maintenance of diet-induced weight loss and decreased android fat distribution in overweight and obese women with normoglycemia and hyperinsulinemia [147]. A meta-analysis of 6 RCTs with metformin in children and adolescents reported a small, but significant reduction in body weight, as expressed by a placebo-subtracted decrease of 0.1 in BMI *z* score and 0.9 in BMI after 6–12 months [148]. In clinical terms, the position of metformin for the treatment of obesity is limited and is mostly used in obese patients with T2D [149]. It's combined use with specific anti-diabetic medications, including GLP-1 analogues, SGLT-2 inhibitors or dipeptyl-peptidase-4 inhibitors, may have additive weight reduction effect. In this regard, the combination of metformin with dapagliflozin, a SGLT-2 inhibitor, is on a phase 3 clinical trial in overweight/obese women with a history of gestational diabetes mellitus, thus at risk of T2D (NCT02338193).

4.1.3. SGLT-2 Inhibitors

SGLT-2 reabsorb up to 90% of glucose in the proximal convoluted tubule, while SGLT-1 reabsorb the rest [87]. SGLT-2 inhibitors prevent reabsorption of glucose at the nephron, inducing glycosuria, mild diuresis and natriuresis, thus improving glycemic control in an estimated glomerular filtration rate (eGFR) dependent fashion [150]. Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin are the FDA-approved medications for the treatment of T2D in patients with an eGFR>45 ml/min/1.73 m^2 [87]. Due to glycosuria, there is outflow of calories, which is the main mechanism SGLT-2 inhibitors decrease body weight in a dose-dependent manner (2.2–4.7 kg), albeit increase caloric intake [151–154]. Weight loss is more pronounced in patients with worse glycemic control at baseline and decreases as the latter improves [155]. Co-administration of canagliflozin 300 mg and phentermine 15 mg vs. placebo or canagliflozin or phentermine monotherapies in 335 overweight and obese without T2D resulted in a weight loss of 7.5%, 0.6%, 4.1% and 1.9%, respectively and a placebo-subtracted percentage of individuals on the combination of canagliflozin/phentermine losing ≥5% of 49.2% at 26 weeks [156]. In a phase 2 RCT, 50 obese adults without T2D were assigned to dapagliflozin 10 mg QD plus subcutaneous long-acting exenatide 2 mg once per week or placebo for 24 weeks. Placebo-subtracted weight loss was 4.1 kg and total adipose tissue decrease 4.1 L in dapagliflozin/exenatide group [157]. Furthermore, progression to prediabetes was 50.2% less and SBP was reduced by 6.7 mmHg in the treatment group, but nausea and injection site adverse events were most frequent in the treatment group vs. placebo [157]. The Dapagliflozin Plus Exenatide on Central REgulation of Appetite in diabeteS typE 2 (DECREASE) trial is currently investigating the effects of monotherapy and combinations of dapagliflozin and exenatide on caloric intake, body weight, appetite and brain activity in response to food-related stimuli with fMRI in patients with obesity and T2D (NCT03361098). Additional short- as well as long-term benefits of empagliflozin and canagliflozin based on phase 3 RCTs, meta-analyses and real world data include reno-protection (decreased albuminuria, progression of renal dysfunction and blood pressure), cardio-protection (reduced risk of cardiovascular disease and heart failure-related hospitalizations), but exact mechanisms are still under investigation [155,158–163]. More specifically, results from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) and The Health Improvement Network (THIN) databases have led to approval of empagliflozin as a cardiovascular risk reducing agent and revealed decreased mortality compared to other medications such as liraglutide (5.5 more deaths prevented per 1000 per year [164,165]. The Canagliflozin Cardiovascular Assessment Study (CANVAS-PROGRAM) highlighted an increased rate of amputations with canagliflozin in patients with high cardiovascular risk, most probably absent with empagliflozin, but also suggested maintenance of its cardiovascular and reno-protective benefits even in patients with eGFR>30 ml/min/1.73 m^2 [161,166,167]. Cardiovascular and renal outcomes of canagliflozin and dapagliflozin in patients with diabetic nephropathy and chronic kidney disease respectively are currently investigated by the CREDENCE and DAPA-CKD trials (NCT02065791, NCT03036150). The DECLARE-TIMI58 study (NCT01730534) is anticipated to shed light on the incidence of cardiovascular events with canagliflozin, while the Dapa-HF (NCT03036124) is specifically designed to include patients with chronic heart failure. The EMPEROR-Reduced (NCT03057977) and EMPEROR-Preserved (NCT03057951) trials will explore safety and efficacy of empagliflozin in patients with heart failure plus decreased or normal ejection fraction respectively.

Improved glycemic control and insulin sensitivity decrease fatty acid synthesis and inhibit de novo lipogenesis in the liver [168,169]. Therefore, weight loss with SGLT-2 inhibitors, which mainly results from fat mass loss, was thought to be accompanied by utilization of hepatic glycogen, thus decreasing steatosis, as well as visceral and subcutaneous adipose tissue to meet the bodily needs [155]. Indeed, the Effect of Empagliflozin on Liver Fat Content in Patients With Type 2 Diabetes (*E*-LIFT) trial reported a significant control (other anti-diabetic medications) subtracted reduction in liver far (−4%), measured with MRI proton density fat fraction, with empagliflozin 10 mg QD and a significant improvement in alanine aminotransferase in patients with T2D and NAFLD, highlighting an additional benefit of this medication for people with obesity and related comorbidities [170]. Side effects include vulvovaginal and urinary tract infections, dry mouth, nocturia, polyuria, thirst and increased urine output (due to osmotic diuresis) and postural dizziness, hypotension and syncope (due to intravascular volume reduction) [87]. Notably, monotherapy with any of the SGLT-2 inhibitors does not increase risk of hypoglycemia [171–174]. SGLT-2 inhibitors should not be used in Type 1 diabetes, as well as severe hepatic and renal impairment [87]. Combining SGLT2-inhibitors with GLP-1 agonists could potentially maximize HbA1c, SBP and body weight improvement as well as decrease rate of cardiovascular and renal disease progression [175].

4.2. Other Medications Under Investigation

4.2.1. Agents that Have Reached Phase 3 Clinical Trials

Potential anti-obesity drugs in phase 3 clinical trials are presented in Table 2 and discussed below.

4.2.1.1. Setmelanotide. The melanocortin system regulates body weight in the hypothalamus and consists of the melanocortins, agouti, agouti-related proteins, and their receptors (melanocortin receptors) [176]. Leptin and insulin stimulate POMC neurons to secrete POMC, which is cleaved by convertases to melanocortins (α-MSH, β-MSH, γ-MSH and adrenocorticotropic hormone [ACTH]) [176]. In the PVN, α-MSH binds to the MC4R and activates them leading in decreased caloric intake, increased energy expenditure and weight loss, as shown in rodent and non-human primate studies [177–180]. In humans, loss-of-function mutations in genes involved in the hypothalamic melanocortin network, such as POMC, leptin receptor or MC4R cause some forms of monogenic obesity that are more prevalent in specific populations, such as Pima Indian [181,182]. Setmelanotide (RM-493), a synthetic MC4R agonist, decreased weight in obese with MC4R deficiency by an average of 0.6 kg/week for 4 weeks [183]. Setmelanotide also reduced hunger and body weight (13.9-51 kg in 12–42 weeks) in individuals with obesity due to POMC deficiency or leptin receptor deficiency in phase 2 trials [184,185] and is currently undergoing phase 3 trials in subjects with: 1) POMC deficiency; 2) leptin receptor deficiency; and 3) other rare genetic syndromes of obesity, such as Bardet-Biedl and Alström syndrome (NCT03287960, NCT02896192, NCT03013543). However, since liraglutide has already demonstrated weight loss effect in patients with MC4R deficiency, as discussed previously, setmelanotide might be of limited use, especially if highly priced.

Table 2
Potential anti-obesity agents in phase 3 clinical trials.

Drug	Mechanism of action	Target population	Registration number
Centrally acting			
Methylphenidate	Dopamine reuptake inhibitor	Obese adults	NCT02754258
Setmelanotide	MC4R agonist	Obesity due to leptin receptor deficiency	NCT03287960
		Obesity due to POMC deficiency	NCT02896192
		Rare genetic obesity disorders[a]	NCT03013543
Tesofensine	Norepinephrine, dopamine and serotonin transporter inhibitor	Obesity	Not registered
Peripherally acting			
Exenatide	GLP- 1 analogue	Obese adults without T2D	NCT00856609
		Hypothalamic obesity	NCT02860923
Liraglutide (3 mg)	GLP- 1 analogue	Obese women with PCOS	NCT03480022
Semaglutide	GLP- 1 analogue	Obesity with T2D	NCT03552757, NCT03574597
Orlistat (60 mg)	Intestinal and pancreatic lipase inhibitor	Obese adults	NCT01755676

GLP-1, glucagon-like peptide 1; MC4R, melanocortin 4 receptor; PCOS, Polycystic Ovary Syndrome; POMC, pro-opiomelanocortin;T2D, Type 2 Diabetes.
[a] POMC deficiency, Leptin receptor deficiency, Bardet-Biedl syndrome, Alström syndrome.

Older synthetic MC4R agonists lacked significant weight loss effect or had cardiovascular and behavioral side effects in patients with common obesity [186,187]. However, short-term subcutaneous administration (over 72 h) of setmelanotide in individuals with common obesity increased resting energy expenditure by 6.4% and fat oxidation, while it did not affect blood pressure or heart rate [188].

4.2.1.2. Tesofensine. Dysregulated dopaminergic activity is associated with overeating [27]. Tesofensine inhibits the presynaptic transporter of norepinephrine, dopamine and serotonin, thus increasing their availability [86]. It reverses low dopamine levels in nucleus accumbens and prefrontal cortex and increases dopamine transporter binding capacity in dorsal striatum, which might account for the reduced food intake and body weight in diet-induced obese (DIO) rats and mice [189,190]. In overweight and obese individuals, tesofensine increased satiety and sense of fullness, 24-h fat oxidation and night energy expenditure, but not total energy expenditure [191,192]. The placebo-subtracted weight loss with tesofensine 0.25 mg, 0.5 mg or 1.0 mg QD was 2.5%, 7.2%, and 8.6%, respectively, at 24 weeks in a phase 2 RCT with 203 participants with obesity [193]. Dry mouth (11.6–47.7%), nausea (7.7–12.8%), diarrhea (7.7–12.6%), insomnia (1.9–24.6%) and constipation (1.9–8.6%) were the most frequent placebo-subtracted side effects, while heart rate increased by 7.4 and 8.1 beats per min in the tesofensine 0.5 mg and 1 mg groups, respectively. Among the participants, 2% and 10% of those receiving 0.25 mg and 1 mg, respectively, discontinued the study due to side effects [193]. Currently, tesofensine is in a 24-week, phase 3 trial, in which obese ($n = 372$) were randomized to tesofensine (0.25 mg or 0.5 mg) or placebo QD [194].

4.2.1.3. Methylphenidate. Methylphenidate inhibits dopamine transport and reuptake, therefore increasing both synaptic dopamine and norepinephrine levels in brain areas responsible for motivation, reward, attention and impulsivity [195,196]. Dopaminergic neurotransmission participates in food reward, thus low dopamine increases food consumption [197]. Methylphenidate was first used for Attention-Deficit Hyperactivity Disorder (ADHD), in which anorexia and weight loss were identified as side effects [198]. Methylphenidate robustly decreased BMI by 12.4 kg/m^2 in a 2-year-old boy with ADHD and MC4R gene mutation that led to early onset extreme obesity and by 4.4 kg/m^2 in an adolescent with hypothalamic obesity post craniopharyngioma therapy [199,200]. Administration of methylphenidate in patients with ADHD for 2 months resulted in 1 kg weight loss in 67% and loss of appetite in 70% of them in a case-control study [201]. In a prospective study with children treated with methylphenidate for ADHD, total fat was decreased by 1.4 kg and the ratio of central to total fat by 0.3 after 6 months [202]. However, at 3 years, total fat relapsed, but the ratio of central to total fat remained decreased (by 0.55). Notably, lean mass, including bone mineral density, decreased at 6 months, but increased slowly over 3 years of treatment [202]. Administration of methylphenidate in adults with obesity and ADHD resulted in a placebo-subtracted weight loss of 15.1% (18.3 kg) at 466 days [203]. Short-term administration of methylphenidate reduced energy intake and consumption of fatty foods in adults and teenagers with obesity [204,205]. In 9 men with obesity, a single dose of methylphenidate decreased energy intake by 34%, but did not alter hunger [205]. Furthermore, methylphenidate significantly increased resting and postprandial energy expenditure, with no effects on heart rate or blood pressure [206]. Healthy individuals who performed the stop-signal task, which assesses cognitive control, while on methylphenidate had increased saliency processing and enhanced activation in striatum (caudate nuclei), cortex (primary motor cortices, inferior parietal cortex) and the cerebellum, suggesting that methylphenidate may act through cognitive control networks to improve caloric intake [207]. Insomnia and sleep problems (17.9%), headache (14.4%) and abdominal pain (10.7%) were the most frequent side effects [207]. Serious adverse events, including psychotic disorders or arrhythmia, were also increased (relative risk 1.36 and 1.61, respectively) [208]. Methylphenidate is in a phase 3 RCT for effects on energy intake, energy expenditure, body weight and impulsivity in obese adults (NCT02754258).

4.2.2. Agents that Have Reached Phase 2 Clinical Trials

Potential anti-obesity drugs in phase 2 clinical trials are presented in Table 3 and summarized below.

4.2.2.1. Cannabinoid Type-1 Receptor Blockers. The endocannabinoid system has both central and peripheral components, comprised of: 1) cannabinoid type-1 receptors (CB1R) in the hypothalamus and limbic system as well as in the adipose tissue, liver, gastrointestinal tract, pancreas and muscles and 2) their endogenous ligands, anandamide and 2-arachidonoylglycerol [209]. Activation of CB1R increases caloric intake via orexigenic signals, while their antagonism has the opposite effect [209]. Therefore, CB1R antagonists have been investigated as appetite suppressants. Rimonabant, a central CB1R inhibitor, the first approved molecule in this class, resulted in weight loss (0.9–3.9 kg in 1 year) and improved cardiovascular and metabolic markers (WC, HDL-C, TGs, SBP) and glycemic control (decrease in HbA1c by 0.2–0.7%) in overweight or obese patients with or without T2D [210,211]. The RIO (Rimonabant In Obesity) Europe study, in which obese adults with or without comorbidities were assigned to placebo ($n = 305$), rimonabant 5 mg ($n = 603$) or rimonabant 20 mg ($n = 599$) QD for 1 year, reported a placebo-subtracted weight loss of 1.2 kg (5 mg) and 5.0 kg (20 mg) along with significant improvements in WC (7 cm decrease), TGs (8.3% decrease, adjusted for weight loss), HDL-C (3.6% increase, adjusted for weight loss) in the 20 mg group [212]. The most frequent

Table 3
Potential anti-obesity agents in phase 2 clinical trials.

Drug name	Mechanism of action	Indication	Registration number
Centrally acting			
Cannabidiol oral solution	CB1R antagonists; 5-HT 1 receptor agonist	Hyperphagia of PWS	NCT02844933
Setmelanotide	MC4R agonists	Obesity without T2D	NCT01749137
		PWS	NCT02311673
Oxytocin (intranasal)	Oxytocin receptor agonist	Hypothalamic obesity	NCT02849743
		Obesity	NCT03043053
		Sarcopenic obesity	NCT03119610
		Hyperphagia of PWS	NCT03197662
GSK1521498	Opioid mu receptor inverse agonist	Obesity with overeating behavior	NCT01195792
Lorcaserin	5-hydroxytryptamin 2C receptor agonist	Smoking cessation related weight gain	NCT02412631
Peripherally acting			
Efpeglenatide (HM11260C)	GLP-1 agonist	Obesity	NCT02075281
Exenatide		Hypothalamic obesity	NCT01484873
Licofliglozin (LIK066)	SGLT1/2 inhibitors	Obesity	NCT03320941
Canagliflozin (JNJ-28431754)		Overweight and obesity	NCT03100058, NCT00650806
HM12525A; JNJ-5111	Dual GLP-1R/GCGR agonists	Severe obesity	NCT03486392
MEDI0382		Obesity with T2D	NCT03244800, NCT02548585
GT 001- Peptide YY (3–36), nasal	PYY 3–36 analogue	Obesity	NCT00537420
rhGH	Somatotropin receptor agonist	Obesity in women	NCT01169103
BOTOX Type A (intragastric injection)	Ach release blocker in peripheral nerve endings	Obesity	NCT02035397, NCT03079557
Tadalafil	PDE-5 inhibitor	Obesity	NCT02819440
Sildenafil		Obesity	NCT03364335
Amlexanox	Mast cell stabilizer; PDE inhibitor	T2D, NAFLD, Obesity	NCT01842282
Diazoxide choline CR	K channel agonist	PWS	NCT00892073, NCT02034071
ISIS-FGFR4RX	Type 4 FGF R antagonist	Obesity	NCT02476019
RZL 012	Thermogenesis activator in sc fat	Obesity	NCT03171415
Combination therapies			
Phentermine/topiramate	Adrenergic receptor agonist	Binge eating disorder	NCT02659475
Extended release	AMPA receptor antagonist; Carbonic anhydrase inhibitor; GABA A receptor agonist		
Zonisamide-bupropion slow-release [Empatic]	Na channel modulators; carbonic anhydrase inhibitor/DA and SE transmission modulator	Obesity	NCT00709371, NCT00339014
Canagliflozin/phentermine	SGLT-2 inhibitor/noradrenergic agonist	Obesity	NCT02243202
Dapagliflozin/exenatide	SGLT 1/2 inhibitor/GLP-1 receptor agonist	Obesity	NCT02313220
Tesofensine/metoprolol	Biogenic monoamine uptake inhibitor/Beta 1 receptor antagonist	PWS	NCT03149445

Ach; Acetylcholine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CB1, cannabinoid receptor type 1; BOTOX; Botulinum toxin; CR, controlled release; DA, dopamine; FGF, Fibroblast growth factor; GABA, gamma- Aminobutyric acid; GCG R, glucagon receptor; GLP-1 R; glucagon-like peptide 1; H, histamine; HT 1 R, hydroxytryptamin 1 receptor; K, potassium; MC, melanocortin; Na, sodium; NAFLD, non-alcoholic fatty liver disease; PDE, phosphodiesterase; PWS, Prader Willi Syndrome; rhGH, recombinant human growth hormone; sc, subcutaneous; SE, serotonin; SGLT; Sodium glucose transporter protein; T2D; Type 2 diabetes.

side effects were nausea (8.6%), diarrhea (4.2%) and dizziness (3.8%), but serious side effects, being mainly psychiatric (1.2%), including depression and suicide ideation, were also recorded [212]. One death from uterine adenocarcinoma in the rimonabant group was also recorded, possibly being unrelated to rimonabant [212]. Even though rimonabant was approved as an anti-obesity agent in Europe in 2006, it was withdrawn one year later due to concerns about the psychiatric side effects [213]. Currently, there is an attempt to overcome some of these side effects through the development of peripherally acting CB1R inhibitors, like JD5037, a peripheral CB1R inverse agonist, and AM6545, a neutral antagonist with decreased ability to penetrate CNS [214]. Peripheral inhibition of CB1R with AM6545 decreases hyperphagia in DIO mice [215]. Intraperitoneal administration of AM6545 in rats significantly reduced food seeking behavior and especially intake of high-carbohydrate and high-fat foods [216]. AM6545 administered to mice with hypothalamic obesity managed to reduce body weight and intraperitoneal fat mass, improve TGs, TC, free fatty acids, LDL-C, glucose tolerance, insulin and circulating adipokines (leptin, asprosin, TNFα, adiponectin) at 3 weeks [217]. JD5037 administration in DIO mice decreased total fat mass and was more effective in reducing caloric intake and body weight compared to AM6545 [218]. JD5037 also corrected the hyperleptinemia observed in DIO mice by decreasing leptin expression and secretion by adipocytes, and by increasing leptin clearance [218]. Cannabidiol, a CB1R antagonist is currently in phase 2 trials for hyperphagia related to Prader-Will Syndrome (NCT02844933).

4.2.2.2. Dual GLP-1 and Glucagon Receptor Agonists. Hormones produced by the gastrointestinal tract, i.e., GLP-1, Peptide YY (PYY), glucose-dependent insulinotropic polypeptide (GIP), glucagon, cholecystokinin and oxyntomodulin increase right after meal and nutrient absorption and affect insulin secretion [219,220]. Glucagon, secreted by the alpha-pancreatic cells, increases satiety, energy expenditure, glucose production in the liver, insulin secretion and lipolysis [221]. Activation of GLP-1 receptors reduces caloric intake, while of glucagon increases energy expenditure [222]. It has been proposed that the ratio of GLP-1 to glucagon receptor activation should favor GLP-1 for avoidance of undesirable effects linked with activation of glucagon, e.g. hyperglycemia [222,223]. Oxyntomodulin is secreted by the L-cells of the intestine after cleavage of pre-proglucagon precursor by prohormone convertase 1/3 and activates both GLP-1 receptor and the glucagon receptor [224]. It decreases gastric emptying and ghrelin secretion, increases satiety and energy expenditure, thus decreasing food consumption and body weight in humans, and positively affects glucose levels [224]. Oxyntomodulin increases after bariatric surgery along with other gut-derived peptides and its levels correlate with weight loss and glycemic control [225,226]. Thirteen healthy individuals who received intravenous oxyntomodulin in a crossover RCT consumed 19.3% less energy during a meal and 11.3% less energy during a 12-h period, while reported less hunger during fasting and meal time [227]. Oxyntomodulin did not impact satiety, prospective food consumption or meal palatability, but decreased both fasting and postprandial ghrelin levels [227]. A

double-blind, parallel-group study assigned 29 healthy individuals to oxyntomodulin or saline injections subcutaneously for 4 weeks TID, 30 min before each meal [228]. The placebo-subtracted reduction in body weight was 1.8 kg and in caloric intake 170 ± 37 kcal and 250 ± 63 kcal in the first and last meals of the study, respectively [228]. Interestingly, oxyntomodulin did not affect palatability of the meal [228]. Furthermore, oxyntomodulin increased energy expenditure of activity by 143 ± 109 kcal/day and total energy expenditure by 9.4 ± 4.8%, but did not impact resting energy expenditure [229]. In a single-blinded, crossover study, 10 obese patients received an infusion of GLP-1, oxyntomodulin and PYY or placebo for 10.5 h a day that resulted in a 32% decrease in caloric intake without any significant changes in resting energy expenditure or hunger after 3 days [230]. MOD-6031, a long-acting reversibly pegylated oxyntomodulin analogue is undergoing a phase 1 trial (NCT02692781). MEDI0382, a synthetic GLP-1 and glucagon receptor dual agonist that has completed a phase 1 trial in healthy subjects, administered subcutaneously QD in overweight/obese with T2D, resulted in a placebo-subtracted weight loss of 2.1 kg and an HbA1c reduction of 0.3% at 41 days in a phase 2a study [231,232]. Gastrointestinal side effects occurred in 22% of patients and included (placebo subtracted) vomiting (32%), nausea (25%), abdominal distention (24%), headache (20%), fatigue (20%), dyspepsia (16%), eructation (14%) and constipation (13%) and decreased appetite in 20% of those on MEDI0382 [231]. Due to side effects, 12% of the patients in the MEDI0382 vs. 4% in the placebo group withdrew [231]. Other GLP-1 receptor and glucagon receptor dual agonists are also under evaluation: JNJ-64565111 is currently in a phase 2 trial and NN9277, with or without liraglutide, is in phase 1 trials in obese without T2D (NCT03486392, NCT02835235, NCT02870231, NCT02235961).

4.2.2.3. Sildenafil. Sildenafil is a phosphodiesterase (PDE) type 5 inhibitor, approved for the management of erectile dysfunction [233]. It acts via increasing cGMP levels and subsequently nitric oxide, thus achieving smooth muscle relaxation [234]. Impaired nitric oxide signaling has been associated with obesity and insulin resistance. In this regard, PDE5 inhibitors, which enhance endothelial nitric oxide synthase and nitric oxide, were found to improve energy balance and glycemic control in insulin resistant patients [235,236]. Leucine is an essential amino acid that can stimulate myofibrillar muscle protein synthesis [237]. It synergistically acts with PDE5 inhibitors to improve insulin sensitivity and enhance fat oxidation in skeletal muscle cells, adipocytes and hepatocytes in DIO mice [238]. Additionally, sildenafil, possibly by inducing browning of white adipose tissue, increased energy expenditure and decreased blood pressure in young, overweight adults [234]. An ongoing phase 2, 24-week RCT currently assesses the effects of two fixed-dose combinations of leucine and sildenafil (NS-0300) or two fixed-dose combinations of leucine, sildenafil and metformin (NS-0200) vs. placebo on body weight, cardiometabolic, glycemic and inflammatory markers in 267 adults with obesity (NCT03364335).

4.2.2.4. Oxytocin. Oxytocin, produced by the hypothalamus, is a multifunctional peptide, involved in food consumption [239]. Oxytocin producing neurons receive and send signals via multiple connections throughout the brain and especially areas responsible for reward and homeostatic regulation of feeding, such as hypothalamus, ARC, basal ganglia, ventral tegmental area, nucleus accumbens, frontal cortex, insula, nucleus of the solitary tract and spinal cord [239]. Additionally, oxytocin receptors are found in the periphery, such as anterior pituitary gland, pancreas, adipose tissue and gastrointestinal tract [239]. Oxytocin has a very short half-life, thus, since continuous intramuscular or intravenous administration is not practical, an intranasal formulation has been developed [240]. Oxytocin single dose (24 IU) administration in 20 healthy men decreased post-prandial snack consumption (reward-driven) by 25%, but did not alter caloric intake in the fasting state (hunger-driven) or energy expenditure [240]. In another study, oxytocin administration in 18 obese and 20 normal-weight young men decreased total food consumption after fasting only in the former, but reduced snack consumption in both groups, whereas energy expenditure remained unaffected [241]. Oxytocin also suppressed hypothalamic-pituitary-adrenal axis, as evident by the decreased levels of ACTH and cortisol and attenuated plasma glucose postprandial peak [240,241]. Additionally, oxytocin (24 IU) decreased total caloric intake (122 kcal), fat intake (8.7 g) and carbohydrate utilization (0.02 g/min), while increased fat utilization (0.01 g/min) as per indirect calorimetry and improved insulin sensitivity in 25 healthy men [242]. Appetite and resting energy expenditure remained unaffected [242]. Oxytocin ability to alter brain activity in response to high- vs. low-calorie food images in most areas regulating energy balance and appetite has been shown in fMRI studies, albeit in an inconsistent fashion [243–245]. A 13-year-old patient with hypothalamic obesity and hyperphagia after treatment for craniopharyngioma was given intranasal oxytocin for 10 weeks and intranasal oxytocin plus naltrexone for another 38 weeks [246]. He lost 4.4 kg (corresponding to 0.28 units in BMI z-score) at 10 weeks and 2.9 kg (corresponding to 0.67 units in BMI z-score) at 38 weeks; hyperphagia was decreased, but seeking of carbohydrate-rich foods remained unchanged [246]. A pilot clinical study reported weight loss of 8.9 ± 5.4 kg after 8 weeks of intranasal administration of 24 IU, 4 times daily [247]. Currently, there are three phase 2 trials assessing the effect of intranasal oxytocin on polygenic, hypothalamic and sarcopenic obesity (NCT03043053, NCT02849743, NCT03119610).

4.2.3. Agents that Have Reached Phase 1 Clinical Trials

Potential anti-obesity drugs in phase 1 clinical trials are presented in Table 4 and summarized below.

4.2.3.1. Amylin Analogues. Amylin is a peptide co-produced with insulin by pancreatic beta-cells that inhibits postprandial glucose secretion, slows gastric emptying and increases satiety, while decreasing caloric intake [248]. Therefore, amylin analogue pramlintide, approved as an adjunct medication for the management of type 1 diabetes and T2D, showed a modest weight loss effect (placebo-subtracted 2.3 kg at 16 weeks, 2.1 kg at 52 weeks) [249–251]. Amylin is also secreted in the CNS (hypothalamus) and mediates its satiety effect through area postrema and a pathway involving nucleus tractus solitarius, lateral parabrachial nucleus and possibly central amygdala [252]. Amylin also targets the ventral tegmental area and indirectly the nucleus accumbens, interfering with food reward [252]. Subcutaneous self- administration of pramlintide 15 min before meals in patients with obesity ($n = 88$) resulted in a placebo-subtracted weight reduction of 2.2 kg at 6 weeks and daily caloric reduction of 747 kcal on day 3 and 489 kcal on day 43 [253]. Furthermore, patients with obesity on pramlintide consumed smaller meal portions, less fast food and exhibited less binge eating episodes vs. those on placebo [253]. Another RCT assessed pramlintide (dose escalation up to 240 μg) TID before each meal in individuals with obesity ($n = 204$) for 16 weeks and reported a placebo-subtracted weight loss of 3.6 kg and WC reduction of 3.6 cm [254]. The most common side effect was mild, transient nausea, which was not associated with weight loss [254]. A long acting amylin analogue, AM833, is undergoing phase 1 trial in combination with semaglutide (NCT03600480).

4.2.3.2. Peptide YY (PYY). PYY belongs to the pancreatic polypeptide (PP) family, together with PP and NPY, and is co-secreted with GLP-1 by the L-cells of the gastrointestinal tract after meal [255]. Cholecystokinin, vasoactive intestinal polypeptide, gastrin and GLP-1 regulate its secretion in the form of PYY(1–36) (60% of circulating form) that is cleaved by dipeptidyl peptidase 4 into PYY(3–36) (40% of circulating form) [256]. PYY(3–36) levels increase 15 min after meal, plateau by 90 min and correlate with caloric intake; thus, PYY(3–36) is as a satiety signal to the brain [257]. There are four receptor subtypes in humans (Y1, Y2, Y4 and Y5), but PYY(3–36) specifically activates Y2 receptors in the ARC of hypothalamus, inhibiting NPY releasing neurons and activating

Table 4
Potential anti-obesity agents in phase 1 clinical trials.

Drug	Mechanism of action	Indication	Registration number
Peripherally acting			
NNC0174-0833	Long-acting amylin analogue	Overweight and obesity	NCT02300844, NCT02958085
NNC0194-0499	Fibroblast growth factor 21 analogue	Overweight and obesity	NCT03479892, NCT03015207
LLF580		Obesity	NCT03466203
Mirabegron/Pioglitazone	Beta-3 adrenergic agonist	Overweight and obesity	NCT02919176
Combination therapies			
NNC9204-1706 A	GLP-1R/GCGR/GIPR triple agonist	Overweight and obesity (men)	NCT03095807
HM15211		Obesity	NCT03374241, NCT03308721
NNC9204–1177	GLP-1R/GCGR dual agonist	Overweight and obesity	NCT03308721
BI 456906		Normal/Overweight	NCT03175211, NCT03591718
NNC9204–0530 and liraglitide	Glucagon and GLP-1 analogue	Overweight and obesity	NCT02835235, NCT02870231, NCT02235961
NNC0165–1562 and Semaglutide	Peptide YY and GLP-1 analogue	Overweight and obesity	NCT02568306
MOD-6031	Long-acting reversibly pegylated oxyntomodulin analogue	Overweight and obesity	NCT02692781
MEDI0382	Oxyntomodulin analogue	Obesity	NCT03625778

GLP-1 R, glucagon -like peptide 1 receptor; GCG R, glucagon receptor; GIP R, gastric inhibitory peptide receptor.

POMC neurons, thus suppressing appetite and enhancing weight loss [257]. Increased postprandial plasma levels of PYY and GLP-1 after bariatric surgery have been also associated with brain activation in food reward related areas [258]. Additionally, PYY inhibits gastric acid, exocrine pancreatic and insulin secretion, slows gastric emptying and increases time of food transit throughout the gastrointestinal tract [256]. Escalating doses of intravenous PYY(3–36) for 5 days increased satiety and decreased hunger, thirst and food intake in 24 overweight and obese men [259]. Co-administration of PYY(3–36) and oxyntomodulin in 12 overweight and obese individuals reduced energy intake more than either hormone alone (238 kcal less than saline, 192 kcal less than PYY monotherapy and 164 kcal less than oxyntomodulin monotherapy) [260]. A crossover RCT that evaluated food consumption after oral administration of GLP-1, PYY(3–36) or their combination vs. placebo reported 21.5% reduction in total energy intake and significant increase in satiety with the combination vs. placebo [261]. Decrease in total energy intake vs. placebo was also achieved with GLP-1 monotherapy, but not PYY(3–36) monotherapy [261]. PYY is currently being investigated as monotherapy and in combination with semaglutide for obesity in a phase 1 trial (NCT02568306).

4.2.3.3. GLP-1/Glucagon/GIP Receptor Triple Agonists. Bariatric surgery, an intervention that yields the most impressive and long-term weight loss effects, has been associated with rises of gastrointestinal hormones, including GLP-1, glucagon and GIP, as discussed above [219,220,262]. GIP is secreted by the K-cells of the intestine in response to meals [263]. It mainly enhances insulin secretion, but it also stimulates lipogenesis and decreases glucagon secretion [263]. Thus, GLP-1/glucagon/GIP receptor triple agonists were developed to enhance GLP-1 actions and combine the above-mentioned positive effects, aiming to promote weight loss and improving metabolic profile in individuals with obesity. HM15211, a GLP-1/glucagon/GIP receptor triple agonist, resulted in 29% and 25% more weight loss than liraglutide when administered once weekly and once monthly, respectively, for 4 weeks in DIO mice [264]. HM15211 is currently in a phase 1 trial in overweight and obese individuals (NCT03374241).

4.2.3.4. Fibroblast Growth Factor 21 Analogue. Fibroblast growth factor (FGF) 21 is primarily secreted by the liver and plays a role in energy balance, glucose and lipid homeostasis [265]. Obesity is considered a state of FGF21 resistance, which impairs FGF21 functionality [265]. Intravenous administration of a FGF21 long-acting analogue, PF-05231023, twice weekly for 25 days decreased food consumption and weight in obese monkeys [266]. PF-05231023 was also evaluated at 4 different intravenous doses (5, 25, 100, 140 mg) twice weekly in 50 overweight/obese patients with T2D [267]. >4% weight loss was observed in the 100 and 140 mg treatment groups after 25 days, along with improvement in lipid profile, but not in glycemic control [267]. The drug was generally well tolerated with the most frequent side effect being diarrhea, and a femoral neck fracture in one of the participants [267]. Another FGF21 analogue administered in 46 adults with obesity and T2D also reduced LDL-C and TGs and increased HDL-C at 1 month vs. placebo, but was not designed to assess weight loss [268]. FGF21 analogue NN9499 is currently in a phase 1 trial in overweight and obese individuals (NCT03479892).

4.2.4. β3 Adrenergic Receptor Agonist

Mirabegron, a β3 adrenergic receptor agonist approved for the treatment of overactive bladder [269], is in trials investigating its role in activation of brown adipose tissue (BAT) and resting energy expenditure in humans (NCT02919176). BAT, which is rich in mitochondria, has been suggested to contribute to energy expenditure through conversion of energy into heat and through glucose and lipid homeostasis [270–272]. In rodents and humans, stimulation of sympathetic system activated BAT through β3 adrenergic receptors, which are abundant in BAT [273]. β3 adrenergic receptors have been also located in brain areas, such as raphe pallidus, nucleus of the solitary tract, nucleus accumbens and hypothalamus of rats [274]. Central and peripheral injection of a β3 agonist in rats decreased food intake and increased insulin secretion, while only central injection decreased body weight after 24 h [274]. Mirabegron increased resting metabolic rate by 203 ± 40 kcal/day (13%) when administered orally in 12 healthy men [273]. However, it remains debatable whether inducing thermogenesis is a mechanism sufficient to produce weight loss in humans [275].

4.3. Vaccines Against Obesity

Vaccination has also been considered a potential weapon against obesity [186]. Ghrelin is an orexigenic hormone produced by the stomach in state to motivate food consumption; its levels decrease after the meal proportionately to caloric intake [265]. An anti-ghrelin vaccine consisting of a recombinant fusion protein of ghrelin and the pneumococcal surface protein A, as a carrier protein, was administered intranasally in obese mice [276]. Immunoglobulin G antibodies against ghrelin were formed and weight loss was observed, due to decrease in fat accumulation and increase in energy expenditure, probably via enhanced expression of mitochondrial uncoupling protein 1 in BAT [276]. Viral infections have also been linked with the development of obesity in humans and animals [277]. Infection by adenovirus 36 is strongly associated with increased adiposity and insulin resistance [277]. Obesity is also associated with other infections, but also with gut microbes [277].

Therefore, developing a multi-potent anti-viral vaccine might possibly offer prophylaxis against obesity in the future [278].

5. Closing Remarks

Years of research have shed light on the brain areas, pathways and molecules responsible for regulating energy balance and controlling eating and have led to progress in the management of obesity [31,279–281]. Lifestyle modification is the cornerstone of preventing and managing obesity, which has numerous health benefits; nevertheless, weight loss is difficult to achieve and possibly more difficult to maintain. Weight loss is followed by activation of energy balance and appetite regulatory mechanisms which tend to reset body weight to its previous status [282]. The Look AHEAD (Action for Health in Diabetes) study, which evaluated lifestyle modification in patients with T2D over 8 years, showed that only 39% of the participants who lost ≥10% of weight at year 1 maintained this weight loss at the end of the study [283]. On the other hand, medications result in an average weight loss of 3–12% depending on the agent, but also on specific patient characteristics [84]. Additionally, some of the approved medications improve glycemic control, cardiometabolic profile and management of obesity-related comorbidities, such as NAFLD and OSA (see Fig. 3) [284,285]. However, medications have side effects that influence patient adherence and persistence and in some cases have led to withdrawal of approved agents (Table 5) [34,84]. Bariatric surgery leads to the greatest weight loss (15–60%) and more permanent results compared with pharmacotherapy, in addition to favorable glycemic and cardiometabolic changes [281,286]. Nevertheless, it carries the limitations of a surgical procedure, being irreversible in most cases.

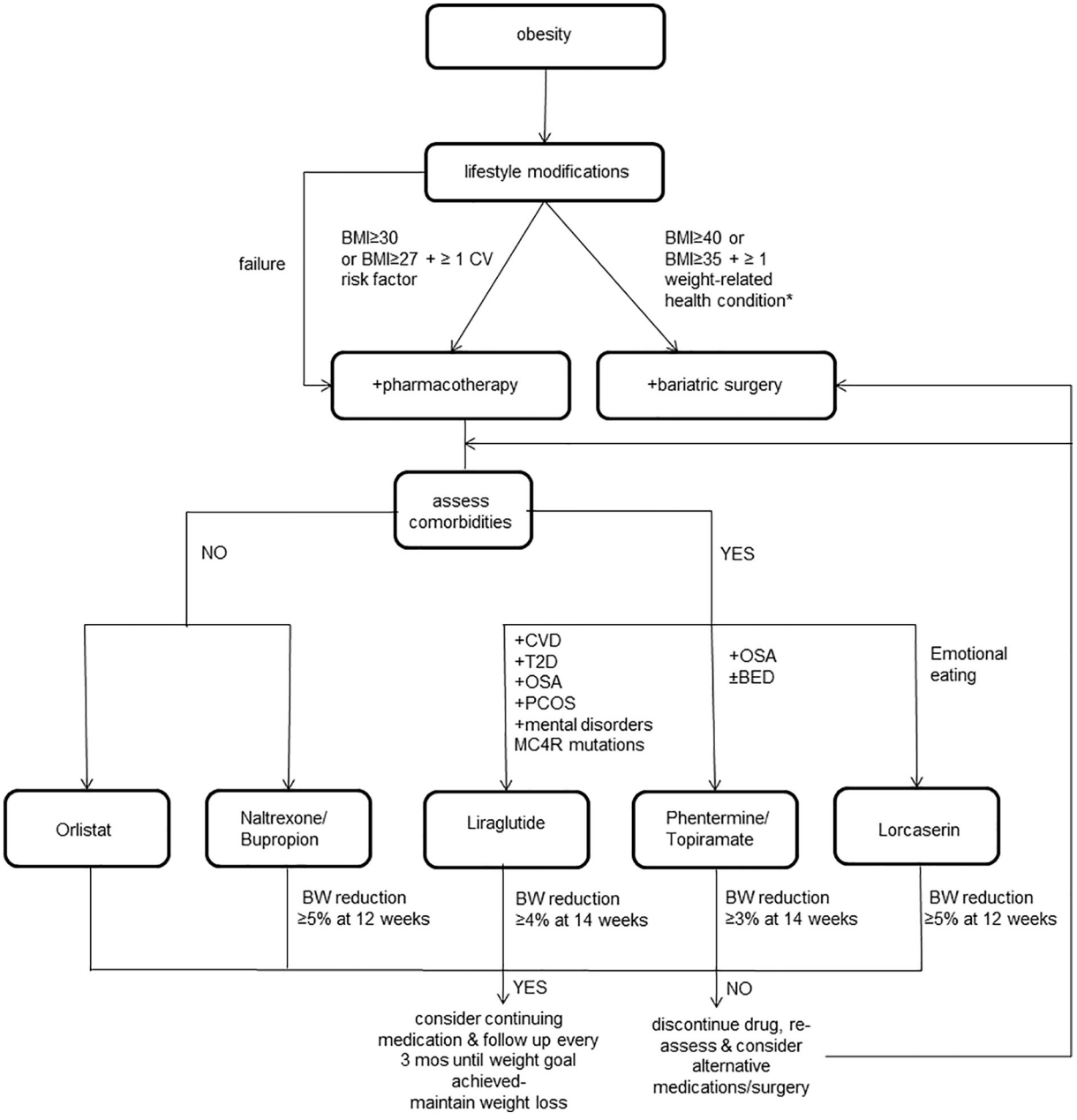

Fig. 3. Proposed flowchart for the long-term management of obesity. Lifestyle modification is always the first step. If lifestyle changes fail to control weight or if BMI ≥ 30 or BMI ≥ 27 plus at least one cardiovascular risk factor, an anti-obesity medication should be initiated. Ideal bodyweight target, patient's comorbidities, personal choices and insurance profile can guide the physician to select the appropriate among the FDA-approved medications. *BED, binge eating disorder; BMI, body mass index; BW, body weight; CV, cardiovascular; CVD, cardiovascular disease; FDA, food and drug administration; MC4R, melanocortin 4 receptor; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes.*

Table 5
Withdrawn anti-obesity medications.

Drug	Mechanism of action	Approval	Withdrawal	Reason for withdrawal
US market				
Amphetamine	SE-NE-DA releasing agent	1939	1979	Dependence and abuse
Clobenzorex	SE-NE-DA releasing agent	1966	2000	Abuse and psychiatric side effects
Levamphetamine	SE-NE-DA releasing agent	1944	1973	Dependence and abuse
Methamphetamine	SE-NE-DA releasing agent	1944	1973	Dependence and abuse
Phenylpropanolamine	NE-DA releasing agent	1947	1987	Hemorrhagic stroke
Sibutramine	SE-NE reuptake inhibitor	1997	2010	Myocardial infarction, stroke (nonfatal)
Dexfenfluramine	SE reuptake inhibitor	1995	1997	Valvular heart disease, pulmonary HTN
Fenfluramine	SE reuptake inhibitor	1973	1997	Valvular heart disease, pulmonary HTN
Pipradrol	NE-DA re-uptake inhibitor	1953	1982	Abuse
Iodinated casein strophanthin	Thyroxine analogue	1944	1964	Endocrine disturbance
European market				
Diethylpropion	SE-NE-DA releasing agent	1957	1975	Cardiotoxicity
Mefenorex	SE-NE-DA releasing agent	1966	1999	Abuse, psychiatric side effects
Fenbutrazate	NE-DA releasing agent	1957	1969	Abuse, psychiatric side effects
Fenproporex	NE releasing agent	1966	1999	Abuse, psychiatric side effects
Sibutramine	SE-NE reuptake inhibitor	2001	2002	Myocardial infarction, stroke (nonfatal)
Aminorex fumarate	serotonin re-uptake inhibitor	1962	1967	Cardiotoxicity
Benfluorex	SE reuptake inhibitor	1976	2009	Cardiotoxicity
Dexfenfluramine	SE reuptake inhibitor	1995	1997	Cardiotoxicity
Fenfluramine	SE reuptake inhibitor	1973	1997	Valvular heart disease, pulmonary HTN
Rimonabant	CB_1 antagonist	2006	2007	Depression and suicidality

SE, serotonin; NE, norepinephrine; DA, dopamine; CB1, cannabinoid receptor type 1, HTN; hypertension.

Since obesity is a multifactorial disease, combination treatment may be necessary, so as to target more than one pathogenetic factors, as it is the case in the management of T2D and as it has been proposed for the management of NAFLD, both diseases of multifactorial pathogenesis and closely associated with obesity [287]. Moreover, the multifactorial pathogenesis of obesity should render its management more personalized: different pathogenetic mechanisms contribute to obesity on an individual basis; therefore, the same medications are not similarly useful in all patients. New genetic methods and circulating biomarkers may possibly facilitate to decode the profile of each obese individual in the near future, thereby leading in a more personalized pharmacotherapy. Importantly, since obesity is a chronic disease, pharmacologic treatment should be long-term to sustain the pharmacologic effect, similar to the current management of T2D. In this regard, the efficacy and safety of existing and future medications should be evaluated in a long-term basis, possibly through multicenter trials. Medications that have been withdrawn from the market after approval due to safety concerns could possibly guide future research towards similar compounds with fewer side effects.

Among all the drugs that are currently in the pipeline, one would expect that those referring to gastrointestinal peptides have higher probabilities of reaching the market. This is based on observation of alterations in gastrointestinal hormones before and after bariatric surgery, as described previously, and correlations of their levels with weight loss and cardiovascular effects [262]. Novel biomedical engineering techniques are currently employed to facilitate production of oral peptides that will replace injectable medications in the future and thus, increase patient adherence, however the cost of these medications might be a limiting factor [288]. Based on the fact that multiple gastrointestinal peptides change after bariatric surgery, we would expect that activation of receptors regulating energy balance and weight loss in the ideal ratio could be more effectively achieved by the right combination of peptides designed specifically for each patient. Thus, designing multi-molecular medications tailored to the individual needs instead of fixed proportion or unimolecular ones might solve the problem of partial response with existing medications. Hopefully, such novel medications will alter both the peripheral and the central regulation of appetite and energy homeostasis, reduce body weight and improve cardiometabolic profile in a safer, more permanent, more effective and personalized fashion, paving the way towards precision medicine in obesity.

Credit Authorship Contribution Statement

Eleni Pilitsi: Investigation, Writing - original draft. **Olivia M. Farr:** Writing - review & editing. **Stergios A. Polyzos:** Writing - review & editing. **Nikolaos Perakakis:** Writing - review & editing. **Eric Nolen-Doerr:** Writing - review & editing. **Aimilia-Eirini Papathanasiou:** Writing - original draft. **Christos S. Mantzoros:** Writing - review & editing.

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