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LEADING ARTICLE

The New Era of Drug Therapy for Obesity: The Evidence and the Expectations

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Abstract There is an urgent need for effective pharmacological therapies to help tackle the growing obesity epidemic and the healthcare crisis it poses. The past 3 years have seen approval of a number of novel anti-obesity drugs. The majority of these influence hypothalamic appetite pathways via dopaminergic or serotoninergic signalling. Some are combination therapies, allowing lower doses to minimize the potential for off-target effects. An alternative approach is to mimic endogenous satiety signals using long-lasting forms of peripheral appetite-suppressing hormones. There is also considerable interest in targeting thermogenesis by brown adipose tissue to increase resting energy expenditure. Obesity pharmacotherapy has seen several false dawns, but improved understanding of the pathways regulating energy balance, and better-designed trials, give many greater confidence that recently approved agents will be both efficacious and safe. Nevertheless, a number of issues from preclinical and clinical development continue to attract debate, and additional large-scale trials are still required to address areas of uncertainty.

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Key Points

For the first time in over a decade, several new drugs have been licensed for long-term weight management.

Weight reduction can be achieved pharmacologically by reducing appetite, increasing energy expenditure or both.

Improved understanding of energy homeostasis has provided novel therapeutic targets.

1 Introduction

The increasing global prevalence of obesity threatens to reverse the improvements in life expectancy seen over the past several decades. Currently, 600 million adults, 13 % of the global population, are obese, defined as having a body mass index (BMI) of ≥ 30 kg/m^2 [1]. A substantial increase in childhood obesity is a particular cause for concern, as childhood BMI often persists into adulthood [2, 3]. Current projections anticipate that 20 % of adults will be obese by 2030 [4].

Obesity increases the risk of cardiometabolic disease, dementia, kidney disease, cancer, respiratory disease and osteoarthritis. This presents enormous healthcare challenges for the future. Preventative measures to tackle environmental determinants of obesity on a population level are essential, but so far they have been insufficiently applied to reverse the trend. Effective treatments for individuals are therefore urgently required. Lifestyle interventions can be effective, but inadequate responses are seen in a significant proportion of patients. Despite the

gold-standard programme used in the Look AHEAD trial, only 46 % of patients achieved 5 % weight loss [5]. Furthermore, weight regain is common when the intensive aspect of lifestyle programmes finishes [6]. Bariatric surgery leads to sustained weight loss and long-term health benefits [7] but carries with it a small but significant perioperative mortality rate and a risk of long-term complications, and many patients choose not to undergo an invasive procedure to help them lose weight.

There is therefore a clear incentive to develop effective pharmacological treatments to aid weight loss. In this review, we summarize the physiology of energy homeostasis to reveal pharmacological targets for weight reduction, before discussing past and current treatments, novel agents in the pipeline, the regulatory hurdles they face and their position in the overall management of obesity.

2 Strategies for Pharmacological Weight Loss

Environment, behaviour and genetic traits all influence body weight. The final common pathway for each of these disparate factors, however, is changes in energy intake or energy expenditure. Obesity results from energy imbalance sustained over several years, and obesity treatments can work only by reversing this. Accordingly, all anti-obesity agents have at least one of the following effects:

1. Reduce food intake or nutrient absorption.
2. Increase resting or activity-related energy expenditure.

Appetite reduction is the primary weight loss mechanism for the majority of current agents. The arcuate nucleus of the hypothalamus plays a critical role in appetite regulation (see Fig. 1). It contains two key populations of neurons, which project to other hypothalamic nuclei and distant brain regions to alter feeding behaviour—one coexpresses agouti-related peptide (AgRP) and neuropeptide Y (NPY), which increase food intake, and the other coexpresses pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which inhibit food intake. Because of the semipermeable blood–brain barrier in this region, peripheral signals indicative of energy balance—including glucose, insulin, leptin, a number of gut-derived factors including glucagon-like peptide-1 (GLP-1), peptide YY (PYY), oxyntomodulin and ghrelin—can directly interact with these neurons and influence feeding behaviour [8]. POMC neuronal activity is also modulated by dopaminergic and serotoninergic signalling from other brain regions and is therefore affected by a number of central nervous system (CNS) drugs that act on these neurotransmitters [9–11]. Of course, appetite is regulated not just by physiological energy status but also
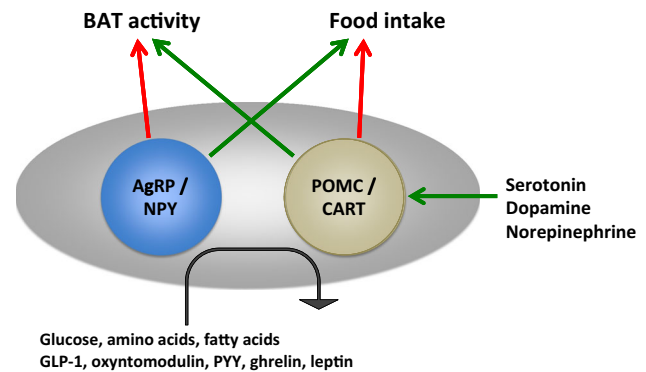
Fig. 1 Simplified schematic of hypothalamic energy regulatory pathways. Other pathways, including the reward circuitry, are involved in appetite and energy expenditure, but an understanding of the central role of the hypothalamus is useful in order to appreciate the mechanisms of action of several weight loss agents. *AgRP* agouti-related peptide, *BAT* brown adipose tissue, *CART* cocaine- and amphetamine-regulated transcript, *GLP-1* glucagon-like peptide-1, *NPY* neuropeptide Y, *POMC* pro-opiomelanocortin, *PYY* peptide YY

by environmental and emotional cues, such as the sight and smell of food. These reward-associated stimuli are integrated by the mesocorticolimbic reward system, with dopaminergic neurons originating in the ventral tegmental area (VTA) projecting to the nucleus accumbens and the prefrontal cortex, where they influence feeding behaviour [12]. Modulation of signalling in the dopaminergic reward system is also suggested as an additional mechanism for the action of some appetite suppressants [13, 14].

Interest has surged over recent years regarding the potential to increase resting energy expenditure by pharmacological activation of brown adipose tissue (BAT) [15]. Well known as a source of non-shivering thermogenesis in human infants, it was assumed not to persist into adulthood, until review of positron emission tomography (PET) images from adult cancer patients revealed extensive glucose-avid areas in the neck and thorax, subsequently identified as brown fat [16, 17]. BAT expresses high levels of uncoupling protein-1 (UCP-1), which uncouples mitochondrial substrate utilization from ATP production, causing energy wastage [18]. The best-known activator of BAT activity is cold exposure; under thermoneutral conditions, human BAT is unlikely to play a significant role in energy homeostasis. Nevertheless, a variety of peripheral factors directly increase BAT activity, such as catecholamines, thyroid hormone, glucagon and fibroblast growth factor-21 (FGF-21) [19], raising the possibility of pharmacological manipulation. Furthermore, AgRP/NPY and POMC neurons control sympathetic innervation of BAT, revealing a central role for this system in various aspects of energy homeostasis [20–22]. This is relevant from a therapeutic point of view, as compensatory physiological and behavioural responses limit the weight

loss that is achievable by any one mechanism [23]. Consequently, treatments that target both sides of the energy equation have the potential for greater effectiveness [24, 25]. Some studies have hinted at a possible minor role for BAT in mediating the effects of some newer anti-obesity agents [26, 27], but its current status is primarily as an area of active research with potential future therapeutic application.

3 How Are Weight Loss Drugs Judged?

For most obese patients, losing enough weight to return to a 'normal' BMI is unrealistic, even with bariatric surgery. Instead, the focus should be on health benefits resulting from more modest weight loss. A reduction in body weight of 5–10 % is enough for significant improvements in cardiovascular risk factor profiles [28–32], kidney disease [33] and osteoarthritis [34]. Consequently, the 5 % weight loss threshold features prominently in the current US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidances for approval of weight management drugs [35, 36]. While the absolute proportions of patients achieving this degree of weight loss in clinical trials are an important metric for regulatory bodies, differences in lifestyle programmes between trials can make comparisons difficult. Therefore, 5 % weight loss remains a useful target in clinical practice, but, in this review, we focus on average placebo-subtracted percentage body weight reduction as the key indicator of weight loss efficacy. Nevertheless, inferring positive health outcomes purely from weight loss is ill advised, as shown by the post-approval withdrawal of a number of agents—most recently, sibutramine due to increases in major adverse cardiac events [37]. All anti-obesity agents seeking regulatory approval now require pre-specified cardiovascular safety data as a minimum; improvements in surrogate cardiovascular risk biomarkers are also considered favourably by regulatory bodies.

4 A Brief History of Anti-Obesity Pharmacotherapy

In spite of a potentially lucrative market for effective pharmacological treatments for obesity, at the end of the 2000s, just one agent (orlistat) was approved for long-term use in North America and Europe. This reflected not any difficulty in producing drugs that caused weight loss, but concerns about safety, which, in many cases, were highlighted only after the drugs were brought to market. In the first half of the last century, popular 'diet pills', such as thyroxine and the respiratory chain uncoupler 2,4-dinitrophenol, were effective in producing weight loss but

exposed users to thyrotoxicosis and potentially fatal hyperthermia, respectively [38]. Subsequently, amphetamine-mimetic anorectic agents, such as desoxyephredine and diethylproprion, which enhance norepinephrine and dopaminergic stimulation of anorexogenic POMC neurons, enjoyed several years of popularity before the perceived addiction risk led to changes in their licences to allow short-term use only. However, in 1992, a well-publicized study demonstrated impressive results from combined use of two of these older drugs, phentermine and fenfluramine [39]. The ensuing 'phen–fen craze' came to an abrupt end in 1997, when reports emerged of valvular abnormalities in young patients taking these agents [40]. Shortly afterwards, the FDA approved sibutramine, a serotonin–noradrenaline reuptake inhibitor with an unimpressive antidepressant action but a powerful anorectic effect [41]. Use of sibutramine was terminated in Europe and the USA in 2010 after adverse cardiovascular outcomes were revealed in a post-marketing study [37]. In this study, the risk was observed only in patients with prior cardiovascular disease, and not in those at high cardiovascular risk (due to diabetes) but without prior cardiovascular disease, but the signal was sufficient for regulatory bodies to request withdrawal from the market. The well-known role of the endocannabinoid system in appetite was the target of the cannabinoid-1 (CB1) receptor antagonist rimonibant [42], licensed in Europe (but not in the USA) in 2006. The realization that some patients suffered significant psychiatric morbidity while taking this drug [43], including an increased risk of suicide, led to its rapid withdrawal from the market in 2008. In fact, the reason that FDA approval for rimonibant had been refused related to a signal of increased suicidality in the pre-marketing submission. However, the endocannabinoid system may yet prove a viable target, with non-CNS-penetrating forms of these agents believed to be less likely to lead to psychiatric morbidity [44].

5 Anti-Obesity Agents in Current Use

In spite of an inauspicious history, the recognition of future health crises posed by the obesity epidemic, and better understanding of the physiological mechanisms underpinning appetite and energy homeostasis, have driven significant progress in the obesity pharmacotherapy field. The past 4 years have seen approval of a number of new agents. Not all have been met with universal acclaim though; two agents (lorcaserin and phentermine/topiramate) have failed to gain approval for use in Europe. In general, both the FDA and EMA have recognized some uncertainties relating to safety and efficacy with the novel agents; however, the FDA considered the risk to benefit balance acceptable for specific issues to be addressed with post-marketing

trials, whereas the EMA demanded that further data be obtained prior to licensing.

5.1 Orlistat

The only survivor from the pre-2010 era is orlistat (marketed as Xenical), an intestinally active lipase inhibitor, which reduces absorption of fat by 30 % [45]. Pooled estimates from long-term studies indicate sustained weight loss of 2.9 % over placebo when given at the standard dose of 120 mg three times daily [46]. Reduced progression to diabetes [47] and improved glycaemic control in patients who already have diabetes [48] have also been noted. Fat malabsorption can give rise to side effects, including oily stools, faecal urgency and spotting if patients continue to consume a diet rich in fat, but these can be avoided with appropriate dietary restraint. Indeed, it is hypothesized that the effectiveness of orlistat likely reflects enforced dietary changes rather than a direct reduction in calorie absorption [49].

5.2 Lorcaserin

In 2012, lorcaserin (Belviq) was the first new anti-obesity agent to be granted an FDA licence for long-term weight management. Like fenfluramine, lorcaserin stimulates 5-HT (serotonin) receptors on anorectic POMC neurons. However, it was developed as a selective agonist of the 5-HT$_{2C}$ receptor to avoid 5-HT$_{2B}$-mediated valvulopathies, which afflicted the earlier agent. In phase 3 trials, lorcaserin achieved average weight loss of 3.0–3.6 % better than placebo [50, 51], with 2.3 times as many patients losing at least 5 % body weight in the treatment groups. Glycaemic improvements to the tune of a 0.5 % reduction in glycosylated haemoglobin (HbA$_{1c}$) were seen in patients with type 2 diabetes [52]. Lorcaserin is well tolerated by most patients, with few withdrawals during phase 3 trials due to adverse events. It is currently not clear, however, whether long-term use of lorcaserin has the potential to cause valve abnormalities, despite selectivity for 5-HT$_{2C}$ receptors. Pooled echocardiographic data from 5249 trial participants indicated a non–statistically significant risk ratio of 1.16 (95 % confidence interval [CI] 0.81–1.67) for incident valvulopathy [53]. A post-marketing clinical trial of major adverse cardiac events, including valvular assessment, is intended to answer this question more conclusively. The results of this study might, however, come too late for lorcaserin to be licensed in Europe. The manufacturer withdrew its application in 2013 when it became clear that it would be unable to address the safety concerns expressed by the EMA, which pertained to the potential for psychiatric morbidity, valvulopathy and carcinogenesis.

5.3 Phentermine/Topiramate

Soon after lorcaserin was licensed, the FDA approved a second anti-obesity agent for long-term use: a fixed dose combination of phentermine and topiramate extended release (marketed as Qsymia). Individually, these agents were already marketed for different indications and at higher doses, as a short-term adjunct for weight loss (phentermine) and for epilepsy and migraine (topiramate). As a centrally acting appetite suppressant with a mode of action similar to that of amphetamine, phentermine's short-term-only license reflected concerns regarding the potential for addiction [54]. Weight-lowering properties of topiramate had been noted in its initial trials as an antiseizure agent [55], but dose-limiting neuropsychiatric effects precluded its further development as an obesity monotherapy. The mechanism for topiramate-induced weight loss may involve both inhibition of orexigenic glutamate signalling [56] and increased energy utilization [57]. Combining different weight loss agents with different mechanisms of action is appealing for two reasons: first, it is less likely to be hindered by redundancy and compensation in appetite regulatory pathways; and second, it enables each component to be given at lower dose to reduce side effects. Weight loss data for phentermine/topiramate are impressive, with a placebo-subtracted body weight reduction of 6.6 % at the approved dose of 7.5 mg phentermine/46 mg topiramate [58]. Modest reductions in systolic and diastolic blood pressure of 2.3 and 0.7 mmHg, respectively, were also observed. A higher dose of 15 mg phentermine/92 mg topiramate showed enhanced weight lowering of 9.3 % better than placebo [59], but it is only recommended in selected patients who lose insufficient weight on the standard dose, because of increased adverse effects, including paraesthesia, dizziness, altered taste sensation, insomnia, constipation and xerostomia. In clinical practice, titration from an initial dose of 3.75 mg phentermine/23 mg topiramate is employed to limit side effects. However, safety concerns, particularly with regard to teratogenicity, neuropsychiatric morbidity and cardiovascular effects, have not been addressed to the satisfaction of the EMA, which has refused to grant a license for use of Qsymia in Europe. Some of the safety worries reflected previous experience with higher doses of the individual components of Qsymia rather than direct evidence of harm from trial data, although some signals were present at the 15/92 dose, including elevated heart rate and depression. On the same evidence, the FDA took the view that careful prescribing measures and ongoing patient monitoring were adequate to sway the risk to benefit balance in favour of Qsymia. These include, in particular, a risk evaluation mitigation strategy (REMS) for the teratogenic potential of topiramate,

requiring adequate contraception and regular pregnancy testing for ongoing use.

5.4 Bupropion/Naltrexone

A second combination therapy, consisting of bupropion and naltrexone (marketed as Contrave in the USA; approved name Mysimba in Europe), gained FDA and EMA approval in 2014 and 2015, respectively. Again, these agents were repurposed from existing indications. Bupropion, an aminoketone which acts as a mixed dopamine/norepinephrine reuptake inhibitor [60], is used as an antidepressant and in smoking cession, and has previously been evaluated as monotherapy in the treatment of obesity [61]. Naltrexone is an opioid receptor antagonist, which is used to treat alcohol dependence, reducing cravings by inhibiting the action of β-endorphins on dopaminergic reward pathways [62]. Combining these two agents leads to enhanced appetite reduction, as bupropion stimulates POMC neurons and naltrexone counteracts the autoinhibitory effects of endogenous opioids they secrete [63]. Data from phase 3 trials have indicated 3.2–5.2 % greater weight loss at 1 year over placebo [64–67], with an associated 0.5 % HbA_{1c} advantage in patients with type 2 diabetes. Interestingly, despite superior weight loss in the treatment groups, blood pressure reductions were actually better in the placebo groups, suggesting a treatment-related blood pressure increase. Indeed, concerns regarding cardiovascular safety were the primary reason why approval was not granted following the initial application in 2010. However, interim analysis of a subsequent cardiovascular outcomes trial provided reassurance for the regulatory bodies. Hypertension should nonetheless be controlled before treatment is initiated, and blood pressure should be carefully monitored thereafter, particularly in the first 3 months, when an adverse response is most likely to occur. When bupropion is used as monotherapy for depression or smoking cessation, it carries a black box warning stating the potential for increased suicidality. While there was no signal of psychiatric adverse events in the bupropion/naltrexone trials, the same boxed warning is included, and patients should be carefully monitored to ensure these do not develop.

5.5 Liraglutide

Liraglutide is the first of the GLP-1 mimetics to be granted an obesity indication (as Saxenda). GLP-1 is an endogenous incretin, released by intestinal L cells in response to nutrient ingestion, which enhances glucose-stimulated insulin release by pancreatic β cells and acts on satiety pathways, including hypothalamic POMC neurons, to reduce food intake [68]. A possible role for GLP-1 in

stimulating energy utilization via BAT [27] requires further investigation. Several analogues of GLP-1 are already marketed for type 2 diabetes, where their anorectic effect is well established [69]. A higher dose of liraglutide (3 mg, versus 1.8 mg for type 2 diabetes) led to treatment-related weight loss of 6 % over placebo [70]. Additional as-yet unpublished phase 3 data submitted by the manufacturer indicated 4.0–5.4 % weight loss over and above placebo at 1 year with liraglutide 3 mg [71]. As expected from its pharmacology, significant improvements in glycaemic control for patients with type 2 diabetes were noted (0.9 % reduction in HbA_{1c}), associated with improvements in measures of both β cell function and insulin resistance. Like other GLP-1 agents [72, 73], liraglutide increases heart rate, an observation that has not been satisfactorily explained, but evidence suggests it is not associated with an increase in arrhythmias or hypertension. The question of whether GLP-1-based agents can increase the risk of pancreatitis has attracted considerable debate [74–77]. The increased rate of pancreatitis in diabetes and obesity [78], as well as the inherent risk of over-reporting in pharmacoepidemiological studies, makes it difficult to unequivocally identify a treatment-related adverse effect. In 2014, the FDA and EMA concluded that assertions of a causal link between incretin use and pancreatic pathology were inconsistent with current data [79]. Nevertheless, an imbalance in the incidence of pancreatitis (but not pancreatic cancer) was noted in the liraglutide weight management trials; the small numbers (2.4 versus 0.6 per 1000 patient years) make it difficult to draw conclusions about causality, but larger trials must be performed to address this important question. Furthermore, Saxenda, like other GLP-1 receptor agonists, carries a boxed warning regarding a possible risk of medullary thyroid cancer. This stems from preclinical studies in which an excess of medullary thyroid cancer and C cell hyperplasia was noted in rodents [80]; to date, there has been no evidence suggesting this is also a human phenomenon.

6 Likely Future Developments

The recognition of persistence of thermogenic BAT into adulthood has led to intense interest in possible ways to exploit this pharmacologically. Beyond cold exposure, sympathetic activity is the best-known activator of BAT; pheochromocytoma patients have extensive BAT deposits [81]. To be useful clinically, a sympathomimetic agent would need to be relatively specific for BAT to avoid cardiovascular sequelae. The most promising target might therefore be the β3 adrenoreceptor, which is expressed at high levels in BAT [82], although it is also found in white adipose tissue, the gastrointestinal tract, prostate and

Table 1 Characteristics of pharmacological agents currently licensed for long-term weight loss

Drug	Dosage	Mechanism of action	Placebo-subtracted weight loss in phase 3 trials	Key adverse effects[a]	Contraindications
Orlistat (Xenical)	120 mg three times daily (immediately before, during or after meals)	Intestinal lipase inhibitor	3.0 % [46]	Common/mild: oily stools, malabsorption of fat-soluble vitamins (multivitamins are recommended) Rare/severe[b]: may reduce absorption of some medications such as ciclosporin and some antiretrovirals, cholelithiasis	Malabsorption syndromes, cholestasis, pregnancy/breastfeeding
Lorcaserin (Belviq)	10 mg twice daily	5-HT$_{2C}$ agonist	3.0–3.6 % [50, 51]	Common/mild: headache, nausea, dry mouth, dizziness, fatigue, constipation Rare/severe[b]: serotonin syndrome, valvular heart disease, cognitive impairment, priapism, hypoglycaemia	SSRIs/SNRIs and related drugs, coexisting congestive cardiac failure, valvulopathy, pregnancy
Phentermine/topiramate (Qsymia)	Starting dose 3.75 mg/23 mg daily, standard maintenance dose 7.5 mg/46 mg daily, highest dose 15 mg/92 mg daily	Norepinephrine + dopamine release/GABA modulation	6.6 % at standard dose, 8.6–9.3 % at highest dose [58, 59]	Common/mild: paraesthesia, dizziness, altered taste, insomnia, constipation, dry mouth Rare/severe[b]: teratogenic, tachycardia, acute myopia and secondary angle-closure glaucoma, cognitive impairment, metabolic acidosis, creatinine elevation, hypoglycaemia	Pregnancy, recent or unstable cardiovascular disease, glaucoma, hyperthyroidism, MAO inhibitors or sympathomimetic amines
Bupropion/naltrexone (Contrave, Mysimba)	16 mg/180 mg twice daily, titrated over 4 weeks	Dopamine + norepinephrine reuptake inhibitor/opioid antagonist	3.2–5.2 % [64–67]	Common/mild: nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhoea Rare/severe[b]: suicidal thoughts, seizures, hypertension, hepatotoxicity, angle-closure glaucoma, hypoglycaemia	Seizure disorder, uncontrolled hypertension, anorexia nervosa, alcohol or opiate withdrawal, bipolar disorder, end-stage renal disease, MAO inhibitors
Liraglutide 3 mg (Saxenda)	3 mg daily by subcutaneous injection, titrated over 5 weeks	GLP-1 receptor agonist	4.0–6.0 % [70, 71]	Common/mild: nausea, vomiting Rare/severe[b]: acute pancreatitis, thyroid C cell tumours, gall bladder disease, tachycardia, renal impairment, hypoglycaemia	Medullary thyroid carcinoma, multiple endocrine neoplasia, gastroparesis, pregnancy

5-HT serotonin, *GABA* gamma-aminobutyric acid, *GLP-1* glucagon-like peptide-1, *MAO* monoamine oxidase, *SNRI* serotonin/norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

[a] We have not listed all reported adverse effects

[b] We have included adverse events not conclusively proven to be treatment related in the 'rare/severe' category

bladder [83, 84]. A β3 agonist, mirabegron, was recently found to stimulate energy expenditure in humans [85]. In this case, however, increases in heart rate and blood pressure were noted, likely indicating action at other adrenoreceptors. The success of this approach may therefore depend on generation of agents with better selectivity for the β3 adrenoreceptor, or alternative methods of activating BAT. A further development is the possibility that a subpopulation of white adipocytes have the potential to be 'browned', forming thermogenically active 'beige' adipose tissue and increasing the capacity for therapeutic energy wastage [86].

Another approach uses gut-derived peptides. As well as GLP-1, the endogenous counterpart of liraglutide, several other satiety hormones are released after a meal and trigger cessation of food intake. Two of particular interest are PYY and oxyntomodulin. PYY is a high-affinity agonist of the Y2 receptor, which inhibits the activity of orexigenic AgRP/NPY hypothalamic neurons [87]. Oxyntomodulin is derived from the same precursor as both glucagon and GLP-1, and is a dual agonist of both of these receptors [88, 89]. Administration of both of these peptides to humans reduces food intake [90], and, in addition to this, oxyntomodulin is able to stimulate energy expenditure, although the receptor responsible for this effect is a matter of debate [24, 91, 92]. Like GLP-1, both of these endogenous peptides last for only minutes in the circulation because of rapid enzymatic degradation, and their potential clinical use as weight loss agents relies on the development of long-lasting analogues. As enhancement of gut hormone release is suggested as a possible mechanism for the large weight reductions seen with Roux-en-Y gastric bypass, combined use of two or more of these gut-derived peptides has been suggested as a way to mimic the effect of bariatric surgery without the need for a surgical procedure [49, 93].

7 The Position of Pharmacotherapy in the Management of Obesity

Lifestyle measures are an essential part of any treatment plan for obesity and provide health benefits independent of weight loss. The best evidence for their effectiveness is with intensive programmes addressing diet, activity and behavioural factors [33, 94, 95]. The most powerful intervention for weight loss is bariatric surgery, which leads to an average 25–33 % body weight reduction, depending on the surgical procedure. Bariatric surgery is superior to non-surgical approaches with regard to weight loss and diabetes remission, at least in the short-to-medium term [96]. However, patients are at risk of the usual surgical complications, including perioperative death, anastomotic leak and infection, as well as longer-term issues reflecting altered gastrointestinal physiology, such as dumping syndrome, hypoglycaemia, micronutrient malabsorption and cholelithiasis [97–99]. Resource implications and risks of complications mean that surgery is generally restricted to patients with a BMI ≥40 kg/m^2, or ≥35 kg/m^2 in those with an obesity-associated comorbidity [100, 101].

For individuals who do not wish to undergo (or do not meet the criteria for) bariatric surgery but are unable to lose sufficient weight by lifestyle alone, pharmacotherapy is a useful adjunct. Weight loss agents are generally licensed for use in patients with a BMI ≥30 kg/m^2, or ≥27–28 kg/m^2 in those with an obesity-associated comorbidity [102]. The choice of agent should reflect patient preference, relative co-indications (such as diabetes for liraglutide) and contraindications (such as seizure disorders for bupropion/naltrexone), and relative efficacy (see Table 1). Weight loss should be assessed at 3 months, and the treatment should be discontinued or substituted if at least 5 % weight loss has not been achieved.

In addition to surgery and pharmacotherapy, non-surgical interventional procedures for obesity are an exciting new development, which may widen options for weight loss management in the future. For example, the EndoBarrier system is an endoscopically inserted sleeve, which replicates some aspects of Roux-en-Y gastric bypass by accelerating nutrient delivery to the distal small intestine [103]. Implantable vagal nerve blockade devices are designed to exploit vagally mediated satiety signals to reduce food intake [104] and have been recently approved by the FDA. While these less invasive approaches are more easily reversible and less likely to cause long-term complications than bariatric surgery, they can be performed only in specialist centres; consequently, the continued role of pharmacotherapy in weight management is assured.

8 Conclusion

The past few years have witnessed the introduction of novel anti-obesity therapies for the first time in over a decade. Some represent refinements of older agents, some are rationally devised combinations, and some are entirely new approaches. Advancing understanding of energy homeostatic mechanisms has been essential to signposting development and continues to provide novel pharmacological targets yet to be exploited. However, our knowledge of the off-target effects of some of these agents remains incomplete, with outstanding safety concerns leading to disagreement between the major regulatory bodies regarding whether to grant approval. Research should focus on understanding the potential for adverse effects, not just the primary therapeutic aim. It remains to be seen whether medical therapy can achieve the robust

weight loss of bariatric surgery. Currently, approved weight loss medications are not licensed for use in combination (apart from the fact that some are already polytherapies). Given the multiplicity of pathways regulating food intake and energy expenditure, however, it may be that combination therapy with more than one agent, possibly at lower doses than those licensed at present, will be a viable treatment strategy to safely maximize weight loss in the future.

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