Obesity Surgery (2019) 29:4095–4104
https://doi.org/10.1007/s11695-019-04206-7

REVIEW

Review of Advances in Anti-obesity Pharmacotherapy: Implications for a Multimodal Treatment Approach with Metabolic Surgery

Alexis C Sudlow[1] · Carel W le Roux[2] · Dimitri J Pournaras[1]

Published online: 24 October 2019

Abstract

There is a growing need for treatments for patients who would benefit from further weight loss following bariatric surgery or weight loss maintenance/long-term disease remission. Currently, therapeutic options are limited. Although largely dismissed previously, advances in weight loss pharmacotherapy now offer the possibility of achieving clinically significant weight loss. Historical comparisons drawn between the effects of medications vs surgery are generally inaccurate as novel classes of anti-obesity pharmacotherapy have since been developed and moreover, reflect an outdated approach in comparing medicine with surgery. Herein, we provide an overview of the most recently developed anti-obesity medications which may not only present a potentially innovative approach to medical treatment of obesity but may also inspire renewed enthusiasm for investigating what can be achieved through multimodal care.

Keywords Obesity · Type 2 diabetes · Bariatric surgery · Anti-obesity drugs · Weight loss drugs · Weight regain

Introduction

Obesity is a complex, multifactorial disease a fact which is reflected in the challenges of developing adequate treatment options and strategies for long-term management. A wide range of safe and effective treatment modalities are required in order to successfully treat this disease and the growing worldwide health epidemic it represents. Currently, the best treatment approach with good evidence showing long-term benefit in terms of both improved morbidity and mortality has been bariatric surgery [1]. Although anti-obesity pharmacotherapy has long been available, its use remains limited as it is perceived as costly, of limited efficacy and associated with significant side effects. Compounding this view, drugs such as rimonabant, sibutramine and flenfluramine have been withdrawn from the market in the past as a result of safety concerns while bariatric surgery has grown in popularity given the low procedural morbidity and mortality. For many years, the only widely available drug licensed for long-term use has been orlistat; however, evidence of its efficacy is limited with a systematic review reporting the use of orlistat led to a 3% weight loss relative to placebo [2]. The development of several new classes of medications may present the opportunity for a revolutionary change in the approach to the treatment of obesity. Herein, we review the recent developments in pharmacotherapy for weight management and discuss the relevance and future implications for those involved in the provision of bariatric surgery.

Lifestyle Modification

Irrespective of the intervention—bariatric surgery, lifestyle modification or anti-obesity pharmacotherapy, significant weight loss is achievable but what remains the real challenge is long-term weight loss maintenance. Although there have been promising RCTs investigating various lifestyle interventions demonstrating clinically significant weight loss, there is no long-term data at present to support that weight loss is maintained with a resultant improvement in mortality or cardiovascular end points. The Look AHEAD trial was the largest RCT to date examining the effects of intensive lifestyle intervention on weight loss in patients with obesity and T2DM. Although patients in the intensive lifestyle modification

✉ Dimitri J Pournaras
dpournaras@doctors.org.uk

[1] Department of Upper GI Surgery, Southmead Hospital, Bristol, UK

[2] Department of Experimental Pathology, University College Dublin, Dublin, Ireland

group had a 6% weight loss at 10-year follow-up, the primary end point of reducing the cardiovascular disease event rate was not met and the trial stopped due to futility after a median follow-up of 9.6 years. A systematic review and meta-analysis of 11 RCTs found that in all aside from two, at 12 months, weight loss was < 5% with no evidence for benefit with regards to metabolic outcomes [3]. There have been several RCTs investigating the effect of weight loss medications using lifestyle intervention as the control group which have demonstrated a clinically significant weight loss > 5% with lifestyle intervention alone. In all of these studies, the combination of pharmacotherapy in conjunction with lifestyle intervention produced a significantly greater weight loss.

Weight Loss Pharmacotherapy

Given the limited efficacy of currently available drugs and the growing obesity crisis, there has been significant research into the development of a new generation of anti-obesity medications (AOMs). A number of novel agents have recently undergone phase three clinical trials and have demonstrated good tolerability and safety while producing clinically significant weight loss in patients with obesity as compared with placebo (Table 1).

Liraglutide

Initially prescribed for the management of type 2 diabetes (T2DM), liraglutide is a GLP-1 analogue which has been licensed for use as an AOM, given as a 3 mg once daily subcutaneous injection. GLP-1 analogues have both central and peripheral action. The primary action of GLP-1 analogues and the reason they are used in treatment of diabetes mellitus is the inhibition of glucagon secretion, accompanied by a concomitant increase in insulin secretion which occurs in a glucose-dependent manner, thereby reducing the risk of associated hypoglycaemia [4, 5]. Additionally, liraglutide decreases the rate of gastric emptying. Within the CNS, they are thought to promote satiety, acting on receptors within the arcuate nucleus in the hypothalamus and nucleus of the solitary tract [6]. GLP-1 analogues produce powerful anti-diabetic effects as well as play a significant role in moderating appetite and satiety, mimicking the early neurohormonal changes resulting in raised GLP-1 within days of RYGB [7, 8]. In patients with a poor GLP-1 response following RYGB or after procedures associated with a lower GLP-1 response, SG or LAGB, GLP-1 analogues may play a role in improving weight loss. The SCALE trial was a 56-week double-blind, placebo-controlled trial of 3731 patients 18 years or older without T2DM and a BMI of at least 27 kg/m^2 given 3.0 mg liraglutide. At the trial conclusion, 33.1% of the patients taking liraglutide vs 10.6% of the patients in the placebo group

Table 1 Characteristics of available weight loss agents

Drug	Dosing	Mechanism of action	Expected weight loss	Common side effects
Liraglutide	3 mg OD via SC injection	↑GLP-1 analogue—insulin secretion, satiety ↓Gluconeogenesis, gastric emptying	> 10% weight loss in 1/3 of patients	Nausea (39.3%) Diarrhoea (21%) Constipation (19%) Vomiting (15%)
Semaglutide	1 mg weekly via SC injection or	↑GLP-1 analogue—insulin secretion, satiety ↓Gluconeogenesis, gastric emptying	− 4.9 kg after 104 weeks of treatment	Nausea (24%) Diarrhoea (11%)
Phentermine/topiramate	7.5 mg phentermine/46 mg topiramate or 15/92 mg daily	Phentermine—centrally acting sympathomimetic Topiramate—anti-convulsant ↓Appetite via hypothalamus	> 10% weight loss in 48% of patients on high dose	Upper respiratory tract infection (15%) Constipation (4%) Headache (5%)
Lorcaserin	10 mg BD 20 mg extended release OD	5-HT$_{2c}$ agonist ↓Appetite via hypothalamus	> 10% weight loss in 22.6% of patients	Nasopharyngitis (16%) Upper respiratory tract infection (15%) Headache (7%) Diarrhoea (6%)
Naltrexone/bupropion	180 mg naltrexone/ 8 mg bupropion BD	Naltrexone—μ-opiod receptor antagonist Bupropion—norepinephrine and dopamine reuptake inhibitor ↓Appetite via hypothalamus	>10% weight loss in 28.3% of patients	Nausea (29%) Constipation (19%) Headache (18%) Insomnia (10%)
Canagliflozin	300 mg OD	SGLT-2 inhibitor ↓Renal glucose reabsorption	> 5% weight loss in 33% of patients	Genital mycotic infection (22%) Urinary tract infection (8%)
Metformin	Up to 2 mg daily	Biguanide ↓Appetite via hypothalamus, modulates insulin and leptin sensitivity	1.1 kg weight loss—protective against insulin-associated weight gain	Abdominal pain Nausea Diarrhoea

lost > 10% of their body weight and 14% of patients lost > 15% vs 3.5% in the placebo group with an associated improvement in cardiovascular and metabolic outcomes [9]. A follow-up study using the initial SCALE data found that > 4% weight loss at 16 weeks was the strongest predictor of > 10% weight loss at 56 weeks [10]. Furthermore, the LEADER trial which was a double-blinded, placebo-controlled trial of 9340 patients > 50 years old with T2DM and an HbA1c>7% in addition to at least one cardiovascular comorbidity and 3.8-year median follow-up demonstrated a statistically significant 6.0% reduction in mortality secondary to cardiovascular events as compared with placebo in patients with T2DM [11].

Semaglutide

Similar to liraglutide, semaglutide is also a GLP-1 analogue; however, one of its potential benefits is that it is longer acting, requiring once weekly dosing as opposed to once daily. Further increasing its acceptability as a treatment for patients, an oral preparation of semaglutide has recently been approved by the FDA, unlike liraglutide which is only available in an injectable form. In comparison with placebo, the SUSTAIN-1 trial demonstrated a weight loss of 4.53 kg with 1.0 mg of semaglutide (estimated treatment difference from placebo—3.5 kg) [12]. The subsequent SUSTAIN-6 trial looking at cardiovascular end points in patients > 50 years and an HbA1c>7% demonstrated a statistically significant 26% lower risk of death from cardiovascular causes in the semaglutide 1 mg once weekly group vs placebo over a 2.1-year follow-up period in patients with T2DM [13]. The results of a recent double-blinded, placebo and active-controlled, phase two trial suggest that semaglutide given at a dose of 0.05–0.4 mg daily may be an even more potent agent for promoting weight loss than liraglutide [14]. The trial involved 957 patients randomised to either placebo, 3.0 mg liraglutide or variable doses of semaglutide. At 52 weeks, the patients in the semaglutide groups given 0.2–0.4 mg daily experienced a significant weight loss from 11.2 to 13.8% as compared with 7.8% in the group of patients taking liraglutide.

Phentermine/Topiramate

Phentermine promotes suppression of hunger as a centrally acting sympathomimetic drug, part of the amphetamine class of drugs. The second agent, topiramate, is used widely as an anti-convulsant and is thought to promote weight loss through reduced hunger and may affect energy balance; however, the exact mechanisms remain unclear [15]. The combination of phentermine/topiramate in the randomised blinded placebo-controlled trial, CONQUER, included nearly 2500 patients between 18 and 70 years with a BMI of 27–45 kg/m^2 over a 56-week period. Two different doses of phentermine/topiramate were compared with placebo (PhT-7.5/46 mg or 15/92 mg) with 37% of the patients on the lower dose and 48% on the higher dose achieving > 10% weight loss as compared with 7% in the placebo group [16]. The follow-up SEQUEL trial was an extension of the original and followed-up participants continuing on the dose of phentermine/topiramate or placebo from the initial phase for a further 52 weeks. The trial concluded at 108 weeks and found patients sustained a 9.3% and 10.5% weight loss from baseline in the low- and high-dose groups respectively as compared with 1.8% weight loss in the placebo arm [17].

Lorcaserin

Lorcaserin is a selective 5-HT$_{2c}$ agonist which stimulates proopiomelanocortin receptors (POMC) in the arcuate nucleus of the hypothalamus, resulting in suppression of hunger [18]. It was tested in the BLOOM and BLOSSOM studies which investigated the use of variable doses of lorcaserin. In the BLOOM study, 3182 patients aged 18–65 and a BMI 30–45 kg/m^2 were assigned to either 10 mg lorcaserin twice daily or placebo for 52 weeks [19]. At the conclusion of the trial, those in the treatment arm were then randomised either to continued lorcaserin at the same dose or placebo. All patients had diet and exercise counselling. At the completion of the trial, 22.6% in the lorcaserin group vs 7.7% in the placebo group had lost more > 10% of their body weight. Of those in the lorcaserin group who received a further 52 weeks of treatment, 67.9% of the patients who had achieved an initial > 5% weight loss maintained this weight loss as compared with 50.3% who were re-randomised to placebo in year two. In the BLOSSOM study, 4008 patients aged 18–65 with a BMI 30–45 kg/m^2 were assigned to variable doses of lorcaserin (10 mg OD, 10 mg BD) as compared with placebo. At 52 weeks, significantly more patients treated with lorcaserin, either 10 mg OD or 10 mg BD lost > 10% of their body weight, 22.6% and 17.4%, respectively as compared with 9.7% in the placebo group [20]. A recent RCT of 12,000 patients with a BMI > 27 and established atherosclerotic disease in women > 55 years old or men > 50 receiving 10 mg bd lorcaserin vs placebo looking primarily at cardiovascular safety and efficacy found at 1 year, 14.6% of the lorcaserin group had lost > 10% weight vs 4.8% in the placebo group with a similar cardiovascular risk at 3.3-year median follow-up [21]. Lorcaserin belongs to the same class of drugs as fenfluramine which is no longer available due to concerns of significant cardiovascular risks, specifically the rapid development of pulmonary hypertension and valvular defects. Locaserin differs in that its activity is selective at the 5-HT$_{2c}$ receptor whereas fenfluramine is predominantly a 5-HT$_{2b}$ receptor agonist where it is thought to mediate its adverse effect through stimulating increased mitotic activity and subsequent cell overgrowth within the valve leaflets [22].

Naltrexone/Bupropion

Naltrexone as monotherapy is commonly used in the treatment of opioid addiction as its mechanism of action is primarily mediated by its effect as an antagonist at the μ-opioid receptor. Similarly, bupropion is also most well-known for its alternative use as a smoking cessation aide and is a dual norepinephrine and dopamine reuptake inhibitor. The combination is thought to work synergistically. Buproprion acts centrally, activating POMC neurons in the arcuate nucleus of the hypothalamus, resulting in α-MSH release which in turn reduces appetite. Buproprion binding also results in activation of an auto-regulatory, negative feedback mechanism, stimulating β-endorphin release and suppressing further activity of POMC neurons by binding to inhibitory opioid receptors. Co-administration of naltrexone which is an opioid antagonist is thought to attenuate this effect by blocking the effect of β-endorphin at the POMC opioid receptors [23]. Given the mechanism of action, neither drug is licensed for use as monotherapy for weight loss; however, a randomised, placebo-controlled trial, COR-II, examined the combination of naltrexone/bupropion in patients aged 18–65 years with a BMI of 30–45 kg/m^2 or 27 kg/m^2 in those with HTN or dyslipidaemia and found at 56 weeks 28.3% of the patients receiving naltrexone/bupropion achieved > 10% weight loss as compared with 5.7% taking placebo [24]. A randomised, double-blind, placebo-controlled, non-inferiority study looking at major cardiovascular end points in 8910 patients aged 50 years or older in men or 45 and over in women with increased cardiovascular risk and a BMI 27–50 kg/m^2 showed an interim analysis HR of 0.59 (95% CI 0.39–90) after 25% of the major cardiac events of interest had been accrued and 0.88 (99.7% CI 0.57–1.34) at 50%; however, the trial was terminated early after confidential interim data was released publicly by the sponsor. A final analysis of the available data once the trial had been stopped after 64% of the end points had accrued showed a much less favourable cardiovascular risk profile than the interim analysis with an HR of 0.95 (99.7% CI 0.95–1.38) [25].

Canagliflozin

Although not specifically licensed for use as an AOM, canagliflozin, an SGLT-2 inhibitor used in the treatment of patients with T2DM has been shown in multiple studies to produce clinically significant weight loss. SGLT-2 inhibitors act by decreasing renal glucose reabsorption, promoting urinary excretion. A 12-week phase 2b study involving 376 patients without diabetes aged 18–65 years old and a BMI between 27 and 50 kg/m^2 found that there was a dose-dependent, statistically significant reduction in weight compared with placebo with a least squares mean percent change from baseline of − 2.2%, − 2.9% and − 2.7% for canagliflozin doses of 50, 100 and 300 mg respectively as compared with − 1.3% with placebo [26].

Metformin

Treatment of patients suffering from both obesity and T2DM is inherently challenging given the most effective treatment for regulating glycaemic control, insulin also promotes significant weight gain. As a result, a joint guideline produced by the Endocrine Society, the European Society of Endocrinology and the Obesity Society recommends that in patients with T2DM requiring insulin, a second anti-diabetic agent associated with weight loss be prescribed to counteract the weight gain associated with insulin [27]. Metformin is thought to promote weight loss primarily as a result of decreased food intake mediated through its central effects in the hypothalamus regulating appetite as well as modulating leptin and insulin sensitivity [28]. Metformin is a common first-line choice given its well-known safety profile and relative low cost with evidence from a Cochrane Review to support its efficacy in limiting weight gain when given in conjunction with insulin [29]. A systematic review and meta-analysis found that metformin was associated with a 1.1 kg weight loss although this was lower than other medications given in conjunction with insulin such as GLP-1 analogues. Data from the Diabetes Prevention Programme suggested that although metformin was associated with only a modest weight loss, this effect was maintained over 10 years whereas the more substantial initial weight loss through lifestyle modification was not [30]. Evidence to support the use of metformin in patients who do not have diabetes is lacking although some small studies have suggested it can be safely used to promote weight loss.

Pharmacotherapy for Obesity as an Adjunct to Bariatric Surgery

A Cochrane review of 22 trials found bariatric surgery was more effective in promoting weight loss, resulting in an improvement in associated comorbid conditions irrespective of the type of surgery as compared with any non-surgical intervention [31]. Moreover, the landmark Swedish Obese Subjects (SOS) study, a 20-year prospective case-control series, demonstrated a reduction in all-cause mortality and decreased rates of fatal and non-fatal cardiovascular events in patients undergoing bariatric surgery compared with matched controls receiving usual care [1]. Despite the demonstrated efficacy of bariatric surgery as a treatment for obesity and related disease, there are well-recognised limitations to what can be achieved and sustained in the long term. The introduction of the concept of using medication as an adjunct to surgery allows us to identify several logical applications for pharmacotherapy: neo-adjuvant treatment for preoperative optimisation, pharmacotherapy combined with surgery to improve overall weight loss/weight loss maintenance and finally as

rescue therapy in patients with suboptimal weight loss or significant weight regain.

Patients undergoing bariatric surgery are routinely instructed to adhere to a diet and lifestyle programme preoperatively and may be asked to reach certain weight loss targets which can present a significant challenge. A retrospective analysis of patients prescribed a 4-week low-calorie diet presurgery found weight loss of 8% was associated with greater weight loss at 12 months and shorter mean hospital length of stay [32]. The difficulty in achieving this goal however was illustrated by the fact that nearly 37% of patients on the diet were unable to reach the 8% weight loss threshold. This is unsurprising given the overall reticence to prescribe AOMs that their role in the preoperative management of patients is rarely considered and limited evidence is available to justify their use for this indication. Recent advances in pharmacotherapy present a potentially beneficial application that should be considered. There is only one controlled trial currently published looking at the use of preoperative orlistat administration to help patients achieve a target 10% weight loss prior to Roux-en-Y gastric bypass (RYGB) [33]. The trial compared the use of 60 mg orlistat up to three times daily vs placebo and did not find that there was a statistically significant difference between the groups at 3 months for BMI, excess weight loss or percent excess weight loss. A second trial investigated the use of mood stabilising medications in 75 patients giving either fluoxetine, topiramate or a combination of the two and found a statistically significant reduction in weight with the use of either topiramate as monotherapy or topiramate coadministered with fluoxetine after six months [34]. Although no longer licensed for use, a trial investigating the use of sibutramine to aid preoperative weight loss prior to RYGB in 20 patients found a mean weight loss of 4.6 kg over six weeks compared with the group given dietary advice alone who gained a mean of 7.0 kg [35]. A recently completed phase two trial investigated the use of extended release phentermine/topiramate in patients undergoing sleeve gastrectomy (SG). The study involved 13 patients with a BMI > 50 kg/m^2 who were given phentermine/topiramate for at least 3 months preoperatively and continued in the postoperative period for a further 2 years. In comparison with matched controls undergoing SG but given no additional weight loss medications, those in the treatment arm had an 11.2% greater weight loss at 2 years and a mean BMI of 33 kg/m^2 compared with 42 kg/m^2 in the control group [36].

Long-term weight regain or weight loss plateau in patients undergoing bariatric surgery is well recognised in a significant proportion of patients, the reasons for which are complex and multifactorial. Although the definition of 'significant' weight regain varies from study to study, it is crucial to look beyond the simple numbers to recognise whether it is weight regain associated with the reappearance or new development of obesity-related comorbidity. Despite this heterogeneity in terms of quantifying weight regain, a recent meta-analysis of patients undergoing RYGB reported that weight regain when measured as a percentage of maximum weight lost was the most closely correlated with clinical outcomes including progression of diabetes, hypertension and dyslipidaemia which may serve as a guide for future studies [37]. At present, treatment options are limited, including revisional bariatric surgery which is infrequently considered as it is associated with higher complication rates when performed out-with centres with significant experience [38]. What remains to be established is the role of 'rescue' pharmacotherapy in patients who have already undergone bariatric surgery and have experienced weight regain with associated recurrence of comorbidity. Research thus far has for the most part been limited to retrospective studies or very small prospective studies using a wide variety of agents. The largest study to date comes from Stanford et al. in 2017 which was a retrospective, multicentre review of 319 patients [39]. They included patients following RYGB or SG receiving any form of weight loss pharmacotherapy (15 agents in total evaluated) following inadequate weight loss or weight regain at least 1 year after surgery. More than 50% of patients achieved a clinically significant weight loss of > 5% of total weight. Topiramate was the only agent shown to result in a statistically significant weight loss with patients twice as likely to lose > 10%. Positive predictive factors identified for weight loss included patients undergoing RYGB vs SG, higher BMI preoperatively and a history of psychiatric comorbidity. Similarly, another retrospective study of 209 patients following bariatric surgery using four different agents (phentermine, phentermine/topiramate, locaserin and naltrexone/bupropion) was carried out by Nor-Hanipah et al. in patients who had experienced suboptimal weight loss or weight regain [40]. Overall, 37% of patients lost > 5% of their total weight after 1 year of medical treatment. There was a statistically significant difference in weight loss observed between operative procedures with patients undergoing RYGB and adjustable gastric banding (AGB) losing 2.8% and 4.6% respectively vs 0.3% in patients undergoing SG. The authors also found patients with a higher BMI at the initiation of medical treatment had a significantly greater amount of total weight lost at 1 year. A recent prospective study investigating the use of 3 mg liraglutide in 2092 patients with obesity, 188 of whom had already undergone bariatric surgery, found that in those completing > 16 weeks of treatment, 23% lost > 10% of their weight from baseline and there was no observed difference between the groups who were postmetabolic surgery and those managed with medications alone [41].

The availability of prospective trials investigating the use of rescue pharmacotherapy following bariatric surgery is limited with only four published studies to date, only one of which included a control arm and all involved very small numbers of patients. The agents used in each study were different and one included fenfluramine which has since been

withdrawn. It is difficult to draw conclusions from these studies due to their significant limitations. The larger retrospective studies while unable to necessarily account for the indication for prescribing AOMs in the postoperative period would suggest that these medications are well tolerated with only mild-moderate GI side effects, warranting the development of larger RCTs to investigate their potential for use in the wider population [42–52].

Although there is limited evidence for lifestyle intervention as a method for long-term weight loss in its own right, it remains an important component in the overall management of obesity. AOMs work via several distinct pathways; however, they are most effective in conjunction with lifestyle modification involving decreased caloric intake. These changes are difficult to maintain in the long term; however, in conjunction with bariatric surgery, we may see a more sustained reduction in intake and improved efficacy. As highlighted by an earlier review looking at anti-obesity pharmacotherapy, even in patients who have undergone surgery, nearly 25% have difficulty adhering to postoperative nutritional guidelines; however, the addition of appetite suppressing medications may prove to be beneficial [53].

Initiating and Stopping Pharmacological Treatment

It is essential prior to considering the addition of weight loss pharmacotherapy following bariatric surgery that there is a thorough MDT evaluation whereby any surgical, medical or lifestyle/behavioural causes for poor weight loss or regain are identified. In the absence of any modifiable factors, AOMs should be considered. Given the relative novelty of most of the newly developed AOMs and longstanding low prescribing rates within primary care, it is worth considering whether these medications should be initiated by the MDT with the primary care physician to monitor ongoing use. There is a significant amount of debate regarding the timing of treatment and indication, i.e. should the clinician prescribe for primary poor weight loss, weight loss plateau or weight regain. Moreover, the indications for bariatric surgery are gradually widening in recognition that BMI/weight alone is a poor proxy indicator for the severity of the disease process and the profound metabolic changes as a result of obesity. In light of this, clinicians should be perhaps even more concerned by the reappearance or persistence of the secondary effects of obesity such as diabetes and should consider this as a further indication to prescribe AOMs. Given the relative lack of high-quality data investigating the use of AOMs in the postoperative period, there is no clear consensus; however, it has been observed in one of the larger retrospective studies that patients appeared to have a better response in the context of weight loss plateau rather than when treatment was initiated for weight regain [39].

A trial period of 3 to 4 months is essential in determining if a patient is likely to experience a clinically significant weight loss at 1 year. A lack of response in the early phase of treatment should prompt the clinician to consider discontinuing the medication to reduce the risk of experiencing unnecessary side effects given the low likelihood of weight loss. In the USA and Europe, newly approved AOMs are usually accompanied by 'stopping rules' provided by the FDA and EMA to help clinicians identify those who are most likely to achieve a weight loss of > 5% within 1 year. There is some variability between drugs; however, the general guideline is that a weight loss of < 5% after 12 weeks of treatment on full-dose should be an indication for stopping treatment. These stopping rules are supported by data demonstrating early weight loss with any medical intervention albeit lifestyle or pharmacotherapy is a strong predictor of long-term outcomes [54–56]. The finding that patients in most studies can be classified as responders or non-responders after a relatively short period on a given medication raises the question whether a patient who does not respond to one class of drug can be universally considered a 'non-responder' or whether a trial of another medication acting via a different pathway may be beneficial. These novel agents work via distinct pathways and the development of an individualised approach based on neuroendocrine/hormone profiles may be on the horizon. Central to our understanding of the mechanisms which may contribute to the development obesity and the effects of bariatric surgery is the recognition and understanding of the complex neurohormonal pathways involved. The identification of a number of target pathways which appear to be implicated in obesity but vary from patient to patient such as GLP-1 and PYY introduces the possibility of developing an individualised approach in terms of delivering pharmacotherapy. Identifying patients who may be deficient or resistant to the effects of certain hormones may allow for a targeted, personalised treatment which we may see developed in the future.

Discussion

Although bariatric surgery remains the most effective treatment for obesity, it is evident that there are still limitations to what can be achieved and significant improvements to be made with regards to long-term management. The increasing recognition of the possibility of using pharmacotherapy to improve or maintain weight loss presents a potential new direction in obesity care. Understandably, given the concerns regarding the safety and efficacy of previously available AOMs, it is not surprising that there is widespread reluctance amongst primary and secondary care physicians to prescribe these medications. In spite of this, it should be appreciated that the newly developed agents show promise for use either as

monotherapy or in conjunction with surgery, prompting clinicians to rethink their role in the management of patients suffering from obesity. The majority of the current trials looking at these newer agents are not used in the context of bariatric surgery; however, as monotherapy, achieving a clinically significant 10% reduction in weight has been demonstrated in responders. It is worth noting that a significant proportion of patients will be classified as non-responders and this may be a contributory factor in the relative slow uptake of these medications in comparison with those for other chronic illnesses. As a result of this observation in a subset of patients, guidance on AOM prescribing is accompanied by stopping rules based on percentage weight loss to prevent ongoing treatment in patients who will not benefit from ongoing treatment. Critically, studies investigating the secondary effects of AOMs have shown benefit in terms of improving cardiovascular risk factors including blood pressure and triglyceride levels and promisingly, trials involving liraglutide have demonstrated a long-term reduction in cardiovascular mortality in patients with T2DM. Although newly used for weight loss, several medications including topiramate, naltrexone and bupropion have been used previously for other indications with well-studied side effect profiles. A recent systematic review of these agents, including orlistat, found that the main side effects tended to be gastrointestinal disturbances with an overall withdrawal rate of 10% due to adverse effects, the exception being naltrexone/bupropion which was significantly higher at 24.5% [57].

In spite of the advantages associated with surgical treatment of patients with obesity in terms of efficacy and safety as well as the recent promising developments in pharmacotherapy, access to appropriate care remains problematic. Antiquated attitudes pertaining to the understanding of obesity as a disease, recognition of the need for treatment and the perceived efficacy of available therapies continue to restrict patients receiving adequate care. This is evidenced in terms of numbers of bariatric procedures performed as well as prescribing patterns for weight loss medication. Despite the increasing prevalence of obesity and related burden of disease, the number of bariatric procedures performed in the UK has paradoxically fallen in recent years. In 2016/2017, there were a total of 6760 bariatric procedures recorded, down 23% from a peak in 2011/2012. It is estimated that less than 1% of patients who would qualify and benefit from bariatric surgery receive any treatment [58]. The prescribing of medications for the treatment of obesity in England has seen an even sharper decline, down 82% from a peak of 1.45 million items in 2009 to 450,000 in 2016 [59]. In the USA where there are a number of AOMs available, prescribing is on the rise with regard to agents indicated for short-term use but those for prolonged use have fallen markedly [60]. Further evidence of the general reluctance to prescribe AOMs was demonstrated by a study comparing prescribing patterns of AOMs vs anti-diabetes medications which found that only 2% of American patients with obesity were prescribed AOMs in contrast to 86% of those with T2DM, a disease predominantly affecting those with obesity [61]. A SGLT-2 inhibitor introduced at a similar time to a new weight loss medication showed a nearly exponential adoption rate in comparison with the linear uptake for the AOM, suggesting reluctance by general practitioners to prescribe AOMs in contrast to anti-diabetic medications. Given the inextricable link between T2DM and obesity, this clearly presents a missed opportunity to recognise the potential to treat obesity as a significant contributory factor in the development of T2DM and reduce the long-term effects of poor disease control. Shifting the focus beyond traditional end points such as glucose, BP and lipids and including active weight control represents a possible additional treatment target in the management of T2DM. Interestingly, an anecdotal observation from the same study found a cyclical prescribing pattern with respect to AOMs, describing a low in December followed by a dramatic increase in prescribing in January each year. This trend may suggest that prescribing is possibly largely patient driven and moreover may be motivated by a desire to lose weight for reasons other than health improvement.

Increasing use and prescribing of AOMs is a challenge as it requires moving beyond long-held perceptions of being an unsafe and inefficacious in the treatment for obesity. Moreover, in order to use AOMs to the greatest possible benefit to patients, we must consider their role in addition to surgery which would require a reconsideration of the current approach to managing patients with obesity [62]. The current view of adopting a stepwise approach to the management of obesity is problematic. Patients are offered one treatment modality, i.e. lifestyle modification/pharmacotherapy followed by bariatric surgery in the face of apparent treatment failure with previous interventions often being discontinued. The widely accepted dogma that obesity should be treated with either medical or surgical intervention alone rather than a multimodal approach is reflected not only in clinical practice but the majority of the current research as well. Furthermore, bariatric surgery is often seen as the final treatment option in this pathway and that no further therapeutic options are available following weight regain or recurrence of comorbidity which occurs in a significant proportion of patients in the postoperative period. Rather than accepting weight regain as an inevitability, we must consider moving to a multidisciplinary, long-term approach to treating obesity as a disease whereby patients are offered both a surgical and medical intervention if required in order to facilitate weight loss, improving associated morbidity and mortality. Parallels can be drawn between bariatric surgery and other domains such as the treatment of breast cancer where multimodal therapy is the standard of care with surgery forming just one element in the overall approach to management. Similarly, in the treatment of other complex multisystem diseases such as peripheral vascular disease, joint

surgical and medical treatment is universally recognised as a requirement to improve long-term outcomes, i.e. anti-platelet medications are routinely given to help maintain graft patency in the postoperative period. While evidence for the use of adjuvant or rescue pharmacotherapy in the context of bariatric surgery is not yet available, further research is warranted given the promising results and demonstrated safety/tolerability thus far using novel agents as monotherapy for weight loss and control of comorbidities. There is good evidence that these newer agents do result in a clinically significant weight loss with acceptable side effect profiles; however, in order to increase their use in the treatment of obesity, further trials are required. What can be drawn from previous trials comparing the use of pharmacotherapy vs bariatric surgery is limited given the AOMs now come from a variety of new classes and cannot be compared with historically available agents. Moreover, the shifting attitude towards the adoption of a multimodal treatment approach should be reflected in the direction of research with a move away from a direct comparison of medicine vs surgery to investigate what can be achieved using medicine as an adjunct to surgery. In order to achieve the greatest effect of a combinational approach, further research investigating the timing of initiating medical therapy in conjunction with surgery is required. Bariatric surgery is associated with changes in the absorption of some drugs [63, 64]. While pharmacokinetic studies of weight loss medications after bariatric surgery have not been done, changes in drug absorption could result in decreased efficacy and differing patterns of weight loss in comparison with non-operated patients. In addition to the newer agents currently available and those in development, there is also the possibility of offering patients individualised AOMs based on neurohormonal profiles delivering targeted therapy to optimise weight loss and minimise unnecessary side effects, thereby providing precision treatment. Furthermore, we may in the future consider the use of multiple agents for weight loss, targeting several different pathways as our understanding of the multifactorial causes of obesity improve, just as we have seen in diabetes where glycaemic control is optimised through a combinational approach to pharmacotherapy.

The recent developments in pharmacotherapy offer the possibility of rethinking our approach to the treatment of obesity as a disease requiring lifelong management strategies. Patients suffering from obesity are frequently undertreated for this disease; however, the use of AOMs opens up the possibility of a number of new treatment targets. Although it may be proven in the long term to be highly effective as monotherapy for some patients, given the evolution in thought towards treating obesity as a chronic disease, we must also consider that rather than seeing pharmacotherapy as a replacement for surgery, it may be seen in a complimentary role to improve or enhance what can be achieved with surgery.

Compliance with Ethical Standards This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study, informed consent is not required and does not apply to our work.

Conflict of Interest ACS has no conflict of interest to declare. CWlR reports grants from Science Foundation Ireland, grants from Health Research Board, grants from AnaBio during the conduct of the study; other from NovoNordisk, other from GI Dynamics, personal fees from Eli Lilly, grants and personal fees from Johnson and Johnson, personal fees from Sanofi Aventis, personal fees from Astra Zeneca, personal fees from Janssen, personal fees from Bristol-Myers Squibb, personal fees from Boehringer-Ingelheim, outside the submitted work and shares in Keyron. DJP reports receiving honoraria from NovoNordisk and Johnson and Johnson for lectures.

References

1. Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish Obese subjects. N Engl J Med. 2007;357(8):741–52.
2. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA. 2014;311(1):74–86.
3. Franz MJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. J Acad Nutr Diet. 2015;115(9):1447–63.
4. Drucker DJ, Philippe J, Mojsov S, et al. Glucagon-like peptide 1 stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line. Proc Natl Acad Sci U S A. 1987;84(10):3434–8.
5. Nauck MA, Heimesaat MM, Behle K, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycaemic clamp experiments in healthy volunteers. J Clin Endocrinol Metab. 2002;87(2):1239–46.
6. Navarro M, De Fonseca R, Alvarez E, et al. Colocalization of glucagon-like peptide-1 (GLP-1) receptors, glucose transporter GLUT-2, and glucokinase mRNAs in rat hypothalamic cells: evidence for a role of GLP-1 receptor agonists as an inhibitory signal for food and water intake. J Neruochem. 1996;67(5):1982–91.
7. Pournaras DJ, Osborne A, Hawkins SC, et al. Remission of type 2 diabetes after gastric bypass and banding: mechanisms and two year outcomes. Ann Surg. 2010;252(6):966–71.
8. Pournaras DJ, Aasheim ET, Bueter M, et al. Effect of bypassing the proximal gut on gut hormones involved with glycemic control and weight loss. Surg Obes Relat Dis. 2012;8(4):371–4.
9. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomised, controlled trial of 3.0mg of liraglutide in weight management. N Engl J Med. 2015;373(7):11–22.
10. Fujikoa K, O'Neil P, Davies M, et al. Early weight loss with liraglutide 3.0mg predicts 1-year weight loss and is associated with improvements in clinical markers. Obesity. 2016;24(11):2278–88.
11. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311–22.
12. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy vs placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol. 2017;5(4):251–60.
13. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–44.

14. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose ranging, phase 2 trial. Lancet. 2018;392(10148):637–49.
15. Ben-Menachem E, Axelsen M, Johanson EH, et al. Predictors of weight loss in adults with topiramate-treated epilepsy. Obesity. 2012;11(4):556–62.
16. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9774):1341–52.
17. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomised, placebo-controlled, phase 3 extension study. Am J Clin Nutr. 2012;95(2):297–308.
18. Gustafson A, King C, Rey JA. Lorcaserin (Belviq): a selective serotonin 5-HT2C agonist in the treatment of obesity. PT. 2013;38(9):525–34.
19. Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med. 2010;363(3):245–56.
20. Fidler MC, Sanchez M, Raether B, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab. 2011;96(10):3067–77.
21. Bohula EA, Wiviott SD, McGuire DK, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. N Engl J Med. 2018;379(12):1107–17.
22. Rothman RB, Baumann MH, Savage JE, et al. Evidence for possible involvement of 5-HT(2B) in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. Circulation. 2000;102(23):2836–41.
23. Greenway FL, Whitehouse MJ, Guttadauria M, et al. Rational design of a combination medication for the treatment of obesity. Obesity. 2008;17(1):30–9.
24. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/ bupropion SR on weight and obesity-related risk factors (COR-II). Obesity. 2013;21(5):935–43.
25. Nissen SE, Wolski KE, Prcela L, et al. Effect of naltrexone-bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomised clinical trial. JAMA. 2016;315(10):990–1004.
26. Bays HE, Weinstein R, Law G, et al. Canagliflozin: Effects in overweight and obese subjects without diabetes mellitus. Obesity. 2014;22(4):1042–9.
27. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(2):342–62.
28. Malin SK, Kashyap SR. Effects of metformin on weight loss. Curr Opin Endocrinol Diabetes Obes. 2014;21(10):323–9.
29. Goudswaard AN, Furlong NJ, Rutten GE, et al. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2004;18(4):CD003418.
30. Diabetes Prevention Programme Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Programme Outcomes Study. Lancet. 2009;374(9702):1677–86.
31. Colquitt JL, Pickett K, Loveman E, et al. Surgery for weight loss in adults. Cochrane Database Syst Rev. 2014;8:CD003641.
32. Hutcheon DA, Hale AL, Ewing JA, et al. Short-term preoperative weight loss and postoperative outcomes in bariatric surgery. J Am Coll Surg. 2018;226(4):514–24.
33. Malone M, Alger-Mayer SA, Lindstrom J. Use of orlistat 60 mg in the management of weight loss before bariatric surgery. Ann Pharmacother. 2012;46(6):779–84.
34. Guisado-Macias JA, Mendez-Sanchez F, Baltasar-Tello I, et al. Fluoxetine, topiramate, and combination of both to stabilize eating behaviour before bariatric surgery. Actas Esp Psiquiatr. 2016;44(3):93–6.
35. Aberle J, Freier A, Busch P, et al. Treatment with sibutramine prior to Roux-en-Y gastric bypass leads to an improvement of metabolic parameters and to a reduction of liver size and operative time. Obes Surg. 2009;19(11):1504–7.
36. Ard JD, Beavers DP, Hale E, et al. Use of phentermine/topiramate extended release in combination with sleeve gastrectomy in patients with BMI 50kg/m^2 or more. Surg Obes Relat Dis. 2019; Article in press available from https://www.soard.org/article/S1550-7289(19)30159-5/abstract. Accessed 4/6/19
37. King WC, Hinerman AS, Belle SH, et al. Comparison of the performance of common measures of weight regain after bariatric surgery for association with clinical outcomes. JAMA. 2018;320(15):1560–9.
38. Brethauer SA, Kothari S, Sudan R, et al. Systematic review on reoperative bariatric surgery: American Society for Metabolic and Bariatric Surgery Revision Task Force. Surg Obes Relat Dis. 2014;10(5):952–72.
39. Stanford FC, Alfaris N, Gomez G, et al. The utility of weight loss medications after bariatric surgery for weight regain or inadequate weight loss: a multi-centre study. Surg Obes Relat Dis. 2017;13(3):491–500.
40. Nor-Hanipah Z, Nasr EC, Bucak E, et al. Efficacy of adjuvant weight loss medication after bariatric surgery. Surg Obes Relat Dis. 2018;14(1):93–8.
41. Suliman M, Buckley A, Al-Tikriti A, et al. Routine clinical use of liraglutide 3mg for the treatment of obesity: outcomes in non-surgical and bariatric surgical patients. Diabetes Obes Metab. 2019;21(6):1498–501.
42. Gorgojo-Martinez J, Feo-Ortega G, Serrano-Moreno C. Effectiveness and tolerability of liraglutide in patients with type 2 diabetes mellitus and obesity after bariatric surgery. Surg Obes Relat Dis. 2016;12(10):1856–65.
43. Shehadeh N, Zaid WA, Zuckerman Levin N, et al. Liraglutide treatment in post-bariatric surgery patients who failed to maintain weight reduction. Surg Obes Relat Dis. 2017;13(10):S144.
44. Pajecki D, Halpern A, Cercato C, et al. Short-term use of liraglutide in the management of patients with weight regain after bariatric surgery. Rev Col Bras Cir. 2013;40(5):191–5.
45. Rye P, Modi R, Cawsey S, et al. Efficacy of high-dose liraglutide as an adjunct for weight loss in patients with prior bariatric surgery. Obes Surg. 2018;28(11):3553–8.
46. Shwartz J, Chaudhry UI, Suzo A, et al. Pharmacotherapy in conjunction with a diet and exercise program for the treatment of weight recidivism or weight loss plateau post-bariatric surgery: a retrospective review. Obes Surg. 2016;26(2):452–8.
47. Jester L, Wittgrove AC, Clark W. Adjunctive use of appetite suppressant medications for improved weight management in bariatric surgical patients. Obes Surg. 1996;6(5):412–5.
48. Zilberstein B, Pajecki D. Garcia de Brito A, Gallafrio ST, Eshkenazy R, Andrade CG. Topiramate after adjustable gastric banding in patients with binge eating and difficulty losing weight. Obes Surg. 2004;14(6):802–5.
49. Toth AT, Gomez G, Shukla A, et al. Weight loss medications in young adults after bariatric surgery for weight regain or inadequate weight loss: a multi-centre study. Children. 2018;5(9)
50. Zoss I, Piec G, Horber FF. Impact of orlistat therapy on weight reduction in morbidly obese patients after implantation of the Swedish adjustable gastric band. Obes Surg. 2002;12(1):113–7.
51. Stanford FC, Toth AT, Shukla AP, et al. Weight loss medications in older adults after bariatric surgery for weight regain or inadequate

weight loss: a multicentre study. Bariatr Surg Pract Patient Care. 2018;13(4):171–8.
52. Creange C, Lin E, Ren-Fielding C, et al. Use of liraglutide for weight loss in patients with prior bariatric surgery. Surg Obes Relat Dis. 2016;12(7):S157.
53. Gutt S, Schraier S, Gonzalez Bagnes MF, et al. Long-term pharmacotherapy of obesity in patients that have undergone bariatric surgery: pharmacological prevention and management of body weight regain. Expert Opin Pharmacother. 2019;20(8):393–947.
54. Hanjieva-Darlenska T, Handjiev S, Larsen TM, et al. Initial weight loss on an 800-kcal diet as a predictor of weight loss success after 8 weeks: the Diogenes study. Eur J Clin Nutr. 2010;64(9):994–9.
55. Rissanen A, Lean M, Rössner S, et al. Predictive value of early weight loss in obesity management with orlistat: an evidence-based assessment of prescribing guidelines. Int J Obes Relat Metab Disord. 2003;27(1):103–9.
56. Fujioka K, Plodkowski R, O'Neil PM, et al. The relationship between early and weight loss at 1 year with naltrexone ER/bupropion ER combination therapy. Int J Obes. 2016;40(9):1369–75.
57. Patel DK, Stanford FC. Safety and tolerability of new-generation anti-obesity medications: a narrative review. Postgrad Med. 2018;130(2):173–82.
58. Welbourn R, le Roux C, Owen-Smith A, et al. Why the NHS should do more bariatric surgery; how much should we do? BMJ. 2016;353:i1472.
59. Baker C. Obesity statistics. House of Commons Library Briefing Paper No 3336; 2018. https://researchbriefings.parliament.uk/ResearchBriefing/Summary/SN03336. Accessed 4/6/19
60. Xia Y, Kelton CM, Guo JJ, et al. Treatment of obesity: pharmacotherapy trends in the United States from 1999-2010. Obesity. 2015;23(8):1721–8.
61. Thomas CE, Mauer EA, Shukla AP, et al. Low adoption of weight loss medications: a comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT2s. Obesity. 2016;24(9):1955–61.
62. Pournaras DJ, le Roux CW. Type 2 diabetes: multimodal treatment of a complex disease. Lancet. 2015;386(9):936–37.
63. Gesquiere I, Steenackers N, Lannoo M, et al. Predicting iron absorption from an effervescent iron supplement in obese patients before and after Roux-en-Y gastric bypass: a preliminary study. J Trace Elem Med Biol. 2019;52(3):68–73.
64. Arzan C, Porat D, Fine-Shamir N, et al. Oral levothyroxine therapy post bariatric surgery: biopharmaceutical aspects and clinical effects. Surg Obes Relat Dis. 2019;15(2):333–41.