

## Obesity Prevention

# Weight maintenance: challenges, tools and strategies for primary care physicians\*

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### Summary

Obesity is recognized as a chronic disease and one of the major healthcare challenges facing us today. Weight loss can be achieved via lifestyle, pharmacological and surgical interventions, but weight maintenance remains a lifetime challenge for individuals with obesity. Guidelines for the management of obesity have highlighted the role of primary care providers (PCPs). This review examines the long-term outcomes of clinical trials to identify effective weight maintenance strategies that can be utilized by PCPs. Because of the broad nature of the topic, a structured PubMed search was conducted to identify relevant research articles, peer-reviewed reviews, guidelines and articles published by regulatory bodies. Trials have demonstrated the benefit of sustained weight loss in managing obesity and its comorbidities. Maintaining 5–10% weight loss for  $\geq 1$  year is known to ameliorate many comorbidities. Weight maintenance with lifestyle modification – although challenging – is possible but requires long-term support to reinforce diet, physical activity and behavioural changes. The addition of pharmacotherapy to lifestyle interventions promotes greater and more sustained weight loss. Clinical evidence and recently approved pharmacotherapy has given PCPs improved strategies to support their patients with maintenance of weight loss. Further studies are needed to assess the translation of these strategies into clinical practice.

**Keywords:** Maintenance, obesity, primary care, weight loss.

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### Introduction

Obesity is now widely recognized as a disease (1–3) and its increasing prevalence makes it one of the major global health challenges of our time (4–6). In 2008, more than 200 million men and nearly 300 million women were estimated to be obese, which represents more than 10% of the world's adult population (4). An additional 1.4 billion adults are overweight (4), and both overweight and obesity are increasing in children (7). Obesity is associated with high morbidity and mortality; complications include cancer, cardiovascular disease, depression, dyslipidaemia, hypertension, obstructive sleep apnoea, osteoarthritis and type 2 diabetes (8–11). The World Health Organization

estimates that overweight and obesity are the fifth leading cause of death globally (4). This disease, therefore, represents a critical health challenge.

Consequently, there is an emphasis on public health campaigns aimed at the primary prevention of obesity, but these must be complemented by strategies to manage the disease in individuals who are already obese. Patients with overweight and obesity require secondary prevention and treatment, or tertiary interventions if there are associated weight-related complications (3), as is the case with other diseases such as type 2 diabetes and hypertension.

Currently, patients with overweight or obesity can be treated with lifestyle interventions alone, or with such interventions in combination with weight-loss medications or

with bariatric surgery. However, even when therapy involves medications or surgery, lifestyle intervention continues to be critically important for achieving treatment goals (1,12–15). Following weight loss, weight maintenance is a challenge, regardless of the initial modality used for weight loss. Behavioural interventions are successful at delivering 5–10% weight loss, but maintaining this weight loss is challenging, over the longer term (16–18).

### New tools and the role of primary care providers

Primary care providers (PCPs) play a critical role in supporting individuals attempting to lose weight and in maintaining their weight loss for long-term (19). This important role is acknowledged in the American Heart Association (AHA)/American College of Cardiology (ACC)/The Obesity Society (TOS) obesity guidelines, which are aimed at PCPs and designed to aid treatment decisions to support weight loss and maintenance (1,12,13). Patients often seek and trust the advice of PCPs on weight management (20). PCPs, therefore, have the opportunity and credibility to educate their patients on the negative health outcomes associated with obesity, the treatment options available to them, the challenges of weight maintenance and the various approaches to successful weight-loss maintenance. As with other chronic diseases, such as diabetes and hypertension, it is important that PCPs discuss obesity with their patients and how this disease can negatively impact health. However, it must also be acknowledged that it is challenging for PCPs to balance time constraints and competing demands in order to treat obesity effectively (21). Questions still remain on the effectiveness of obesity treatment in primary care and the optimal role of PCPs in the maintenance of weight loss (22). A team-based approach that includes dietitians, exercise trainers and behaviourists could assist in the time-efficient and comprehensive management of patients with overweight or obesity.

Several effective and well-tolerated pharmacotherapies are now available that complement both the weight-loss and weight-maintenance efforts of an individual, and other pharmacotherapies are under development (23). These new treatment options have enabled the development of more robust approaches to medical care that not only optimize the benefit–risk balance and improve outcomes but also are cost-effective (1,12–15).

This article overviews the various strategies for weight maintenance, based upon a review of what we know from clinical trials, and examines how these strategies can be applied in real-world settings.

### Methods

A PubMed search was conducted for articles related to the review topic and published in the English language prior to

28 February 2015. The search method employed was a structured rather than a systematic approach; this strategy was judged to be more appropriate because of the broad nature of the review topic. The search terms included '(weight) AND (loss OR reduc\* OR decreas\*) AND (maintenance OR maintain\* OR sustain\* OR control\*) AND (manag\* OR treat\* OR therap\*) AND (obesity) AND (benefit)'. This search provided 825 articles. The search was further refined by adding more specific search terms to the string. Additional terms included: 'metabol\*', 'disease', 'cardiovasc\*', 'diabet\*', 'risk', 'chronic', 'vascul\*', 'complications', 'primary care provider/specialist/multidisciplin\*', 'educat\*', 'pharmacother\*', 'lifestyle', 'diet', 'exercise/physical activity', 'behavio\*', 'gene/genetics', 'mechanism', 'regain', 'guideline' and 'surg\*'. Articles were scanned for relevance to the review topic and included if they were considered to be related to weight-loss maintenance. Selected articles included peer-reviewed reviews and original research articles, guidelines and articles published by regulatory bodies. The bibliographies of selected articles were also searched for any additional relevant literature. Article selection was based upon the author's own judgement, clinical experience and knowledge of the literature. The following types of articles were excluded: those considered not relevant to the topics covered by the review, single case studies, short commentaries, letters and interviews.

### Weight maintenance: definition, benefits and potential drawbacks

The initial weight-loss goal is 5–10% – a reduction that is sufficient to improve health and prevent or ameliorate many weight-related complications (18,24,25). Currently, there is no consensus on a definition of 'effective' or 'sufficient' weight-loss maintenance (Box 1) (25). Although such a definition should be based upon the degree of sustained weight loss needed to optimize health outcomes, there is a lack of evidence on the minimum weight loss needed to achieve these outcomes over the long term (25). Nevertheless, the data suggest that maintaining weight loss for at least 1 year can be sufficient to ameliorate many of the complications of obesity (18,24,25).

The evidence base for the benefits of weight loss and maintenance is substantial. Such benefits include improvements in cardiometabolic disease (cardiovascular disease risk, diabetes, dyslipidaemia, hypertension, metabolic syndrome, non-alcoholic fatty liver disease and prediabetes) (12,26), depression (27), gastroesophageal reflux disease (28), osteoarthritis (9), polycystic ovary syndrome (29), sleep apnoea (30), urinary incontinence (31) and others. Sustained weight loss (3 kg lost over 2–3 years) leads to reductions in blood pressure (32,33). Long-term weight loss is also associated with a reduced risk of developing

**Box 1 Descriptions that have been used to define weight-loss maintenance (25)**

- Maintaining 'new weight' for 2 years after weight loss (34)
- Gaining no more than 5 lb (2.27 kg) or 5% of weight after weight loss (4 years) (35)
- Maintaining weight loss of 5–10% (36)
- Remaining within  $\pm 5$  lb (2.27 kg) of goal weight (37)
- A weight change of less than  $\pm 3\%$  of a designated body weight under standardized conditions

type 2 diabetes and improved glucose control in patients with type 2 diabetes (38). In men with obesity with a waist circumference  $>100$  cm, weight maintenance ( $-4.8$  kg after 23 months) is associated with decreased glucose and insulin concentrations (39). Some studies have suggested that intentional long-term ( $>2$  years) weight loss may reduce the risk of all-cause mortality for women and people with diabetes (40). In a retrospective cohort study, 2,500 patients (74% men) undergoing bariatric surgery had significantly lower mortality than matched controls after 1–5 years (hazard ratio [HR]: 0.45; 95% confidence interval [CI]: 0.36–0.56) and after 5–14 years (HR: 0.47; 95% CI: 0.39–0.58) (41). Furthermore, a 23-year follow-up study showed that a 6-year lifestyle intervention programme (diet or exercise, or both) for Chinese subjects with impaired glucose tolerance had reduced the incidence of all-cause mortality (HR: 0.71; 95% CI: 0.51–0.99) and diabetes (HR: 0.55; 95% CI: 0.40–0.76), in comparison with controls (42).

Many people with obesity, however, struggle to maintain their weight, following weight loss (43). A variety of effects following weight regain have been reported. There is evidence that some benefits are sustained following transient weight loss, despite weight regain. For example, if patients with diabetes, hypertension or sleep apnoea are able to sustain lower glycosylated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) (44), lower blood pressure (33), and alleviate apnoea (10) over the period of weight loss, this can lower the health risks these diseases exert on patients over their lifetime. With better glycaemic control, fewer microvascular complications (45,46), and reduced cardiovascular disease (47) have been observed. In the Diabetes Prevention Program (DPP), subjects randomized to intensive lifestyle therapy experienced a 4–7% weight loss over the 4 years of the study, but continued to exhibit decreased rates of progression to type 2 diabetes after 10 years, despite regaining weight to a level equal to that in the control (placebo) group (44). Thus, there was a residual effect of preventing future type 2 diabetes, even though subjects had long regained the weight they had lost during the earlier intervention.

However, evidence also indicates that some benefits may be lost. Minimal weight regain (i.e. 2–6%) has been reported to cause metabolic risk factors (e.g. plasma lipids, blood pressure, fasting glucose and insulin concentrations) to revert to baseline levels (48). For postmenopausal women, partial weight regain following intentional weight loss is associated with an increased cardiometabolic risk (49). Serum triglycerides and low-density lipoprotein-cholesterol levels typically decrease with weight loss, but return to former levels after weight regain (38,50,51). Therefore, PCPs are in a unique position to educate their patients about the challenges of weight maintenance and the positive residual effect of weight loss, and to emphasize the need to maintain weight loss over the long term.

**Lifestyle modification and weight maintenance**

Lifestyle modification is effective in achieving weight loss. Landmark studies on the maintenance of weight loss with lifestyle modification are reviewed in this section. When reviewing these data, it is important to consider factors such as duration and intensity of treatment, as these can influence outcome. Overall, these studies demonstrate that weight maintenance with lifestyle modification – although challenging – is possible, and this message should be clearly communicated to patients.

The National Weight Control Registry (NWCR), a US database founded in 1993, has provided evidence in relation to specific strategies for achieving and maintaining weight loss. This registry has identified the lifestyle modifications practiced by those individuals who were able to successfully maintain weight loss. It is important that PCPs are aware of this information so that they can better educate and support their patients in their weight maintenance journey (Box 2). For inclusion of patients in this database as weight maintainers, their weight loss had to be  $\geq 13.6$  kg and their new weight sustained for  $\geq 1$  year. A 10-year observational study of 2,886 participants found that mean weight loss was  $23.1 \pm 0.4$  kg at 10 years and that  $\geq 87\%$  of participants maintained a weight loss of  $\geq 10\%$  (52). A decrease in leisure-time physical activity, dietary restraint and frequency of self-weighing and an increase in the proportion of energy intake derived from fat were associated with a greater weight regain (52). Participants with  $\geq 2$  years of weight loss maintenance at enrolment continued to maintain larger weight losses at 5 and 10 years (52). Longer duration of weight maintenance was associated with better long-term weight loss outcomes. The study concluded that most weight loss can be maintained over 10 years, but that it requires a sustained behaviour change (52). The NWCR found that characteristics common to successful weight-loss maintainers included eating breakfast (53), high levels of volitional physical activity (54), reduced fat intake (54), self-monitoring of

**Box 2 NWCR key patient data (55)**

- Registry members lost an average of 30 kg (66 lb) and maintained their reduced weight for 5.5 years
- 45% lost weight by themselves; 55% lost weight with the help of some type of programme
- 98% modified their food intake to lose weight
- 94% increased their physical activity – walking being the most frequent activity
- Most kept their weight off by continuing to maintain a low-calorie (1,360 kcal d<sup>-1</sup>), low-fat diet (24% of calories from fat) and by high levels of physical activity (–2,786 kcal week<sup>-1</sup>) (56)
- Most self-monitored their dietary intake and physical activity (56)
- 78% ate breakfast every day
- 75% weighed themselves once-weekly or more frequently
- 62% watched ≤10 h of television per week
- 90% exercised, on average, about 1 h per day of physical activity

dietary intake and physical activity, consumption of low or no calorie-sweetened beverages to limit total energy intake (57), greater dietary restraint (54), regular self-monitoring of weight, and limited television viewing time (≤10 h week<sup>-1</sup>; Box 2) (58).

The Look AHEAD (Action for Health in Diabetes) study assessed the effects of intensive lifestyle intervention (ILI) on clinically important health outcomes in people with overweight or obesity with type 2 diabetes (59–61). Participants were randomly assigned to one-on-one ILI or conventional diabetes support and education (DSE) (59). ILI included diet modification and physical activity to induce and maintain ≥7% weight loss at 1 year and beyond (59,60). ILI participants had goals of 1,200–1,800 kcal d<sup>-1</sup>, based upon initial weight, and physical activity of >175 min week<sup>-1</sup> (60). At 1 year, the ILI group, compared with the DSE group, had lost a greater percentage of their initial weight (–8.6% vs. –0.7%); had improved fitness (assessed by treadmill test); had improvements in HbA<sub>1c</sub>, systolic and diastolic blood pressure, triglyceride, high-density lipoprotein (HDL)-cholesterol and urine albumin/creatinine; and had a reduced need for type 2 diabetes, hypertension and lipid-lowering medications (59). Although the greatest benefits were often seen at 1 year, the ILI group still had greater improvements than the DSE group in terms of weight reduction (–6.15% vs. –0.88%), fitness, HbA<sub>1c</sub> levels, systolic blood pressure and HDL-cholesterol levels at 4 years (61). Factors indicative of the long-term success of ILI included use of meal replacements, high levels of exercise, self-monitoring and individualized

diets using ‘healthy meal plans’ that worked with personal and cultural food preferences (61). The study also found that participants who maintained their weight loss after 4 years reported more favourable physical activity and food intake, and attended more treatment sessions than those who had not maintained their weight loss – indicating the importance of a sustained lifestyle change in successful weight-loss maintainers (62).

The DPP evaluated if modest weight loss through dietary changes and increased physical activity or treatment with metformin could prevent or delay the onset of type 2 diabetes. Participants were randomized into three groups as follows: (i) the lifestyle intervention group received intensive training in diet, physical activity and behaviour modification (24-week curriculum), with the aim of losing ≥7% of their body weight and maintaining that weight loss; (ii) a second group received 850 mg of metformin twice daily, and (iii) a third group received placebo (44,63). The metformin and placebo groups both received information on diet and exercise but received no intensive or individualized counselling (63). Half of the lifestyle intervention group achieved the 7% weight reduction goal after 24 weeks (63). After 2.8 years, participants assigned to the lifestyle intervention group had shown a greater increase in physical activity and greater weight loss (–5.6 kg) than those on metformin (–2.1 kg) or placebo (–0.1 kg) ( $P < 0.001$  for both) (63). Compared with placebo, lifestyle intervention and treatment with metformin had reduced the incidence of type 2 diabetes by, respectively, 58% and 31% (63), and had reduced the incidence of metabolic syndrome by 41% and 17% (64). These findings demonstrate that intense lifestyle intervention can be effective in long-term weight loss, weight maintenance and in risk associated with comorbidities. In the 10-year follow-up (44), the lifestyle group had lost, on average, 7 kg by year 1 and then had partly regained weight (although still 2 kg less than at randomization), while the metformin group had maintained a modest weight loss of 2.5 kg. An additional analysis of the lifestyle intervention arm found that the overall 2-year weight loss (from baseline) was the strongest predictor of a reduced incidence of type 2 diabetes and improved cardiometabolic risk (65). Furthermore, the early rapid weight loss (and its subsequent maintenance for 2 years) had also provided the additional benefit of a reduction in the risk of developing type 2 diabetes (65).

A 3.5-year observational study of 110 women with obesity who had received an initial 6-month lifestyle intervention, followed by a 1-year extended-care phase (comprising face-to-face counselling, telephone counselling or mail-only contact) with no further treatment until follow-up, found that 41.8% of ‘successful’ participants had maintained weight reductions of ≥5% from baseline to follow-up (66). These subjects reported that they had planned meals in advance and selected lower calorie foods,



and had self-monitored their food intake, calories and weight. The intensive weekly group sessions emphasizing behaviour skills – particularly self-monitoring – were a key component of successful long-term weight management (66).

In the 2-year ‘Keep It Off’ trial, in participants who lost  $\geq 10\%$  of their body weight, sustained, supportive phone- and mail-based intervention was shown to have improved weight maintenance (defined as a regain of  $< 2.5\%$  baseline body weight), compared with brief intervention alone (67,68). The probability of successfully maintaining a reduced body weight at 2 years was 1.37 times higher in the group receiving intervention than in the group not receiving it, showing the benefit of sustained, supportive intervention over self-directed support (67).

In the weight-loss maintenance trial, adults with overweight or obesity (body mass index [BMI]  $25\text{--}45\text{ kg m}^{-2}$ ) who lost  $\geq 4\text{ kg}$  in a 6-month behaviour weight-loss intervention (phase I) were randomized to one of three 30-month maintenance interventions (phase II) (69–71). In phase II, participants received behaviour intervention via interactive internet-based technology (IT), monthly personal counselling (PC) or no further intervention (self-directed control, SD) (71). Mean weight changed range from  $-2.3\%$  (African-American women) to  $-4.5\%$  (Caucasian men) after 36 months. Although participants regained some weight during phase II, mean weight at the end of the study was significantly lower than entry weight in phase I ( $P = 0.0002$ ) (71). Participants in both the IT- and the PC-based groups regained significantly less weight than the SD group over a period of up to 24 months ( $P < 0.05$ ) (69). The PC group maintained significantly higher weight loss than the SD- ( $P = 0.003$ ) and IT-based groups ( $P = 0.03$ ) (69).

Some clinical trials and commercial weight-loss programmes have shown that meal replacements are highly effective in producing significant sustainable weight loss (62,72–74). Other studies have found that behaviour changes involving diet (e.g. increased consumption of fruits, vegetables and whole grains), self-monitoring of caloric intake, self-weighing, planning meals in advance and moderate-intensity physical activity ( $150\text{--}250\text{ min week}^{-1}$ ) are important factors in maintaining a reduced body weight over the long term (66,75–78). A staged approach to weight management – including monitoring weight fluctuations and having a clear signal for weight regain that triggers immediate action – is also a common characteristic of successful weight maintainers (79).

The clinical trials described previously provide ample evidence that lifestyle interventions can successfully produce clinically meaningful weight loss and weight maintenance, and also identify those components or practices within lifestyle modification programmes that are the most

### Box 3 Components of a weight maintenance lifestyle intervention programme of proven efficacy in clinical trials

#### Diet

- Individualized calorie goals, based upon an individual’s desire to maintain or lose more weight (61,62)
- Use of meal replacements for one or more meals or snacks per day (61)
- Planning meals in advance (66)
- Individualized healthy meal plans that accommodate personal and cultural food preferences (61,62)
- Self-monitoring of food intake and calories (66)

#### Exercise

- High levels of physical activity: achieve  $\geq 175\text{ min week}^{-1}$  and advance to  $\geq 200\text{ min week}^{-1}$  (61)
- Physical activity for weight maintenance after weight loss:  $200\text{--}300\text{ min week}^{-1}$  (78)
- Self-monitoring of physical activity (78)

#### Behaviour

- Monthly one-on-one (20–30 min) of lifestyle counselling sessions focusing on an individual’s specific treatment needs, followed by telephone or email contact after 2 weeks; monthly lifestyle modification group sessions (61)
- Self-monitoring of weight, weekly or more frequently (61)

effective (Box 3). The US Preventive Services Task Force Recommendation Statement calls for patients with BMI  $\geq 30\text{ kg m}^{-2}$  to receive intensive, multicomponent behaviour interventions, e.g. involving weight-loss goals, improving diet or nutrition and increasing physical activity, addressing barriers to change, self-monitoring and strategizing how to maintain lifestyle changes (80). Over the long term, however, people with obesity will need additional ongoing support to reinforce diet and physical activity changes.

### Pathophysiology of obesity and the physiological responses to weight loss that promote weight regain

Obesity susceptibility genes constitute an important determinant of body weight and act to influence the homeostatic processes that regulate food intake and energy balance (81). These genetic factors interact with the environment and behaviour to determine the degree of obesity and whether or not the excess adiposity is associated with



**Figure 1** The balance between weight loss and weight regain and the associated physiological and psychological changes involved. Physiological and psychological changes that occur as a result of weight loss are shown in blue, and the pathway to overcome the propensity for weight regain in green. This pathway, which may involve pharmaceutical and behavioural interventions that improve adherence, counteracts the physiological and behavioural adaptations and re-establishes the intake–expenditure balance. (Adapted, with permission, from MacLean *et al.* (82).

complications (81). Evidence indicates that, following weight loss, there are compensatory changes in the homeostatic processes that result in increased hunger and energy storage, favouring weight regain (43,83–86). These changes are part of the pathophysiology that characterizes obesity as a disease – namely, the exaggerated compensatory mechanisms that work to return the patient back to the original (high) body weight. They include changes in the levels of circulating appetite-related hormones – such as increases in orexigenic hormones (e.g. ghrelin), which make you feel hungry, and decreases in anorexigenic hormones (e.g. leptin, cholecystokinin, glucagon-like peptide-1 [GLP-1], amylin and peptide YY), which make you feel satiated, with the net result that appetite is increased (83,86,87). Clearly, increased hunger in an environment that promotes the availability of energy-dense foods makes it challenging for people to maintain a healthy weight. If individuals do not self-monitor and revert to disinhibited or unhealthy eating habits, they will not be able to overcome these regulatory changes, and weight regain occurs (52). Furthermore, in response to weight loss, resting energy expenditure rates are decreased, and the energy that muscles use for any given amount of work is also decreased (i.e. increased muscle energy efficiency). These energetic changes also promote weight regain (Fig. 1) (86,88). To maintain weight loss, individuals must adhere to behaviours that oppose these physiological adaptations and the other factors favouring weight regain. However, it is difficult for people with obesity to overcome physiology with behaviour over the long term. Common reasons for weight regain include decreased caloric expenditure, decreased self-weighing frequency, increased caloric intake, increased fat intake and

eating disinhibition over time (52). As a sustained change in behaviour can be challenging, patients need help, which can be provided by prescribing medications as an adjunct to lifestyle modification.

## Pharmacotherapy

Since 2012, there have been four new weight-loss medications approved for the chronic treatment of obesity by the US Food and Drugs Administration (FDA). These medications are in addition to orlistat (120 mg), approved in 1999 (89). The newer medications include lorcaserin, phentermine/topiramate extended release (ER), naltrexone ER/bupropion ER, and high-dose liraglutide (3.0 mg), which is the most recently approved weight-loss medication (US FDA, December 2014; European Medicines Agency, March 2015) (90,91). All these medications are approved in the US as adjuncts to lifestyle modification in patients with overweight with BMI 27–29.9 kg m<sup>-2</sup> having ≥1 weight-related comorbidity – generally taken to be type 2 diabetes, hypertension or dyslipidaemia – or in patients with obesity (BMI ≥30 kg m<sup>-2</sup>) whether or not comorbidities are present (90,92–94). Orlistat is the only approved long-term drug for adolescents ≥12 years of age with obesity (95), while all others have been approved only for adults. With the exception of orlistat, these medications act on the mechanisms regulating appetite and satiety, and help combat the pathophysiological adaptations that drive weight regain (13). These effects help patients sustain weight loss and help them comply with calorie-reduced diets. Clinical trials have shown that the addition of pharmacotherapy to lifestyle interventions promotes greater

**Table 1** Anti-obesity medications currently approved for use by the US FDA

Drug (dose)	Mechanism of action	Weight loss	AEs
Phentermine/topiramate extended release (ER) (96,97) (3.75 mg/23 mg [phentermine 3.75 mg/ topiramate 23 mg ER] daily for 14 d; then increase to 7.5 mg/46 mg daily (92))	Appetite suppressant; other central nervous system actions or metabolic effects also involved (92)	Up to -10.9% vs. placebo (1.6%) after 56 weeks (98)	Paraesthesia, dizziness, dysgeusia, dry mouth, constipation (92)
Lorcaserin (99,100) (10 mg twice daily (93))	Selective serotonin 2C receptor agonist; increases feelings of satiety (93)	-4.5% to -5.8% vs. placebo (-1.5% to -2.5%) in obese patients with/without diabetes after 1 year (99,100)	Headache, dizziness, fatigue, nausea, dry mouth and constipation, and in diabetic patients hypoglycaemia, headache, back pain, cough and fatigue (93)
Naltrexone/bupropion ER (8 mg naltrexone HCl/90 mg bupropion HCl; escalation dose up to week 4 (94))	Opioid receptor agonist/noradrenaline and dopamine uptake inhibitor; dual action: reduces appetite/ enhances control of eating behaviour (94)	-5.0% to -9.3% vs. placebo (-1.2 to 5.1%) after 56 weeks (101-103)	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhoea (94)
Orlistat (104) (120 mg three times daily (105))	Gastrointestinal lipase inhibitor; induces dietary fat malabsorption (106)	-5.8 kg vs. -3.0 kg with placebo after 4 years; $P < 0.001$ (104) Meta-analysis (8 trials, $n = 1,738$ ): -1.80 kg (-2.54 to -1.06) vs. placebo after 1 year (107)	Higher frequency of gastrointestinal AEs vs. placebo: oily spotting, flatus with discharge, faecal urgency, fatty/oily stool, oily evacuation, increased defaecation and faecal incontinence (105)
Liraglutide (3.0 mg once daily) (108) Lower doses of liraglutide (1.2-1.8 mg once daily) produce less weight loss and are approved to treat type 2 diabetes (109)	GLP-1 analogue that stimulates insulin secretion/inhibits glucagon output in a glucose-dependent manner, slows gastric emptying and promotes satiety/decreases appetite (110-112)	-6.2 to -8.0% vs. placebo (-0.2 to -2.6%) after 56 weeks (113,114)	Side effects are consistent with the known effects of GLP-1 receptor agonists (115). Nausea, hypoglycaemia, diarrhoea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain and increased lipase (108,113,114)

AEs, adverse events.

ER, extended release.

GLP, glucagon like peptide.

weight loss and sustains weight loss for a longer period of time than lifestyle interventions alone (13,96,97,99,100, 116). The available data, while only encompassing  $\leq 2$  years of follow-up, demonstrate that these pharmacotherapies sustain weight loss while patients randomized to lifestyle interventions plus placebo are regaining weight (Table 1) (13,96,97,99,100,116).

Of the new anti-obesity medications in the pipeline (23), many target the endogenous endocrine circuits regulating energy homeostasis, including central neuropeptide signalling (melanocortin receptor, neuropeptide Y), intestinal peptide hormone signalling (GLP-1, oxyntomodulin), pancreatic hormone signalling (pancreatic polypeptide, amylin), adipose tissue hormone signalling (leptin) and inhibition of pancreatic lipase (23). These future drugs offer the potential for replacing currently used drugs or combining them, with possible synergistic effects, and of improved safety and efficacy.

It is important to consider that obesity is a chronic disease and requires long-term management, which calls

for long-term efficacy and safety data on the use of the newly approved medications. Indeed, longer-term data (over 2 years) are available for several approved agents (97,104,117) and further studies are ongoing (118,119). Given the need to maintain weight loss, clinical experience needs to be developed for the use of medications to sustain weight loss over the patient's lifetime. The options include long-term use of medication and combination therapy, but there are only sparse data to support or guide their use in therapy intended for prolonged time periods. Furthermore, although these new anti-obesity medications have been approved, several cardiovascular outcome trials are pending or ongoing and may take several years to complete (120).

## Surgery

Bariatric surgery is the most effective method for the treatment of severe obesity (121-123). Referral is considered for patients with a BMI  $\geq 35$  kg m<sup>-2</sup> and associated

comorbidities, or a BMI of  $40 \text{ kg m}^{-2}$ , after failure of lifestyle modification and pharmacotherapies (124). Bariatric surgery can result in substantial weight loss of  $>28 \text{ kg}$  (121–123), but losses vary depending upon the procedure used (e.g. laparoscopic Roux-en-Y gastric bypass [RYGB], adjustable gastric banding, sleeve gastrectomy, biliopancreatic diversion with or without duodenal switch) (125,126). Many, although not all, patients achieve long-term weight loss following surgery (127). However, sustained weight loss also depends upon the re-education of patients in terms of active lifestyle changes, and long-term medical follow-up (122,126).

Adams and colleagues examined the association of RYGB surgery with weight loss, type 2 diabetes and other health risks 6 years after surgery (127). Weight-loss maintenance was superior in patients with severe obesity (BMI  $\geq 35 \text{ kg m}^{-2}$ ) receiving RYGB surgery compared with non-surgical controls, with 76% of patients who had received RYGB surgery maintaining  $\geq 20\%$  weight loss over 6 years (127). RYGB was also associated with higher rates of diabetes remission, and with lower cardiovascular disease risk and other health outcomes over 6 years (127). The Swedish Obese Subjects (SOS) study reported a 10-year follow-up that compared patients with obesity who had undergone bariatric surgery with matched conventionally treated obese controls (non-standardized care; lifestyle intervention, behaviour modification or no treatment) (121). In total, 73.5% of the gastric bypass subgroup maintained  $\geq 20\%$  weight loss over 10 years compared with only 3.8% of the control group (121). The authors also reviewed the key SOS study results published between 2004 and 2012, with follow-up periods of 10–20 years. The mean reported body weight changes after 2, 10, 15 and 20 years were, respectively,  $-23\%$ ,  $-17\%$ ,  $-16\%$  and  $-18\%$  in the surgery group, and  $0\%$ ,  $1\%$ ,  $-1\%$  and  $-1\%$  in the conventionally treated care group (123). Compared with standard care, bariatric surgery reduced overall mortality and decreased the incidence of diabetes, cardiovascular disease events and cancer. Study results have shown that, provided a 10–30% weight loss is maintained, the effects on risk factors remain for over 10 years (123). However, Cooper and colleagues demonstrated that weight regain is a common complication following RYGB surgery. In their study, the mean weight regain following surgery ( $6.9 \pm 4.9$  years [mean  $\pm$  SD]) for all patients was 23.4% (128). Furthermore, over one-third of patients experienced excessive weight regain ( $\geq 25\%$  of lost weight) (128). To counteract this weight regain, weight-loss medication could be considered as an adjunct to lifestyle intervention in this population (1,12,129,130).

### Medical models and guidelines

Individuals seeking medical care usually do so in the primary care setting, so PCPs are the first line of defense to

support patients with their weight loss and its maintenance. Once lifestyle intervention is initiated, patients typically achieve maximum weight loss at 6 months followed by plateau and gradual weight regain. PCPs should acknowledge and educate their patient on the challenges of weight maintenance. It is difficult to prevent weight regain in an environment where palatable and energy-dense foods are readily available and sedentary behaviour is prevalent. PCPs should encourage long-term follow-up,  $\geq 1$  year of monthly, or more frequent visits, in person or by phone to improve weight maintenance success. The long-term follow-up will give the PCP an opportunity to address small weight gains by reinstating the lifestyle intervention and to assess the need for weight-loss medications or bariatric surgery (12). Several models have been developed to help PCPs manage obesity and provide behaviour support to promote sustained weight loss (Box 4) (1,14,15).

These models advocate the involvement of effective multidisciplinary healthcare teams, although such teams are not a standard component of many healthcare systems. The team approach should include PCPs, registered dietitians, psychologists, or other counselling professionals and exercise specialists (131). If the supporting professionals (dietitians, exercise trainers, etc.) are not available to the PCP, patients should be referred to a wellness centre, obesity medicine specialist or an online programme. In a recent review of the best role for primary care in the management of obesity in the US, Ard suggested that there should be a stepped approach to interventions, such that therapy is intensified in those patients who respond partially to initial treatment. However, in those patients with serious weight-related complications, it may be beneficial to initiate therapy with aggressive weight-loss management (22). Evidently, however, it appears that patients are not usually offered these therapeutic options, which increases the likelihood for weight regain. Ko and colleagues reported that only 39% of 1,873 obese adults surveyed had been advised to lose weight. The authors concluded that patients should receive more weight-loss counselling from allied health professionals as follow-up advice to lose weight (132).

Guidelines for the management of obesity have been proposed by several professional organizations, including the American Association of Clinical Endocrinologists (AAACE) (1,13), AHA/ACC/TOS, and the Endocrine Society (12). The AHA/ACC/TOS guidelines were specifically developed for PCPs. Multiple guidelines can be confusing, but it is important to consider their points of consensus that are relevant to weight loss and prevention of weight regain. All guidelines agree on the following:

1. Obesity is a chronic disease that requires long-term management. It is important to approach patients with information regarding the health implications.



#### Box 4 Models to guide primary care providers in managing obesity

Relatively BMI-centric: AHA/ACC/TOS (12,13)

- Evaluate and stage patients, decide who needs treatment based upon BMI, and explain the possible health benefits
- Begin with comprehensive lifestyle intervention to achieve 5–10% weight loss
- Consider medications if 5–10% weight loss is not achieved by lifestyle intervention within 6 months
- Pharmacotherapy: BMI 27–29.9 kg m<sup>-2</sup> with comorbidity, BMI ≥30 kg m<sup>-2</sup>
- Counsel patients on weight-loss effects on cardiovascular risk factors
- Continue to provide dietary strategies, lifestyle intervention, and counselling
- Consider bariatric surgery in patients with BMI ≥35 kg m<sup>-2</sup> with comorbidity or ≥40 kg m<sup>-2</sup> who are motivated to lose weight but do not respond to non-surgical treatments

Relatively complications-centric: AACE (1,13)

- Evaluate and stage patients according to cardiometabolic or mechanical or functional obesity-related complications plus BMI
- Initiate weight-loss programme with sufficient intensity to achieve weight-loss goals (primary treatment)
- Prevent further weight gain and appearance of complications (secondary treatment or prevention)
- Treat existing weight-related complications (tertiary treatment)
- Employ lifestyle intervention, with or without medications as needed, to achieve degree of weight loss required to attain therapeutic goals. Refer for bariatric surgery in select patients
- Assess degree of improvement in complications after equilibrium weight loss is achieved and intensify weight-loss therapy and/or use complications-specific medication if goals of weight loss therapy are not achieved

2. The goal of obesity treatment is to improve the health of the patient, and it is not intended for cosmetic purposes.

3. The cornerstone of therapy is comprehensive lifestyle intervention from informed PCPs or other healthcare professionals.

4. The initial goal of therapy is a weight loss of 5–10% in most patients, as this is sufficient to ameliorate many weight-related complications. However, weight loss of ≥10% may be needed to improve certain weight-related complications, such as obstructive sleep apnoea.

5. Consideration should be given to the use of a weight-loss medication or possible bariatric surgery, as the addition of these treatment modalities to lifestyle therapy can promote greater weight loss and maintain the weight loss for a longer period of time.

6. It is important for clinicians to evaluate the patient for weight-related complications, that can be improved by weight loss, and to consider such patients for more aggressive treatment. The AACE guidelines represent a more ‘complications-centric’ approach (1), where the risk or presence of weight-related complications is a primary indication for weight-loss therapy. Similarly, the impact of weight loss and the need to prevent weight regain are considered in relationship to the prevention or improvements in weight-related complications.

#### What can primary care providers do?

Weight loss and maintenance are critical for managing obesity and its associated weight-related complications (133). PCPs need to address the problem of obesity in their patients, just as they would with any other chronic condition such as hypertension or type 2 diabetes, and to ensure that their patients are aware of the health risks of obesity. While no consensus exists for defining weight maintenance (25), the most commonly used definition is an initial weight loss of 5–10% and maintaining that loss for at least 1 year (18,24,25). Clinical trials have shown that many of the positive benefits of weight loss are sustained only if weight loss is maintained over the long term. However, it is clear that additional research is needed to better define how PCPs can be more effective in treating overweight and obesity (22). In the real-world setting, PCPs should evaluate their patients for the risk or presence of weight-related complications, both initially and during longer-term therapy, as these patients may derive the greatest benefits from weight loss and the prevention of weight regain.

The cornerstone of obesity treatment is lifestyle modification, and this is best achieved by structured intervention programmes that involve a multidisciplinary team of healthcare professionals. PCPs should aim to develop programmes or refer patients to programmes featuring lifestyle intervention practices that are known to sustain weight loss for longer periods of time as a strong component. However, through our improved knowledge of the mechanisms regulating energy balance, we know that pathophysiological processes promote weight regain, and that other therapeutic modalities will often be necessary to help patients sustain weight loss. New medications are now available to help combat these processes, and they may be used as adjuncts to lifestyle therapy. However, longer-term efficacy and safety data beyond 2 years are required for these medications.

Obesity is one of the major healthcare challenges facing us today. Clinical trials have demonstrated the benefit of sustained weight loss in managing the disease and its various comorbidities. Advances in our knowledge of the pathophysiology of obesity, and the new therapy options now available, mean that we are better equipped than ever before to manage the disease effectively over the long term. It now remains for us to translate such advances into standard clinical practice, and this is where PCPs have a critical role.

### Conflict of interest statement

W. Timothy Garvey, MD, FACE; Advisory Boards: Astra Zeneca, Boehringer-Ingelheim, Daiichi-Sankyo, Eisai, Janssen, Liposcience, Novo Nordisk, Takeda, Vivus; Research: Astra Zeneca, Eisai, Lexicon, Merck, Sanofi, Pfizer, Weight Watchers; Stocks/shares: Affymetrix, Bristol-Myers Squibb, Isis, Lilly, Merck, Novartis, Pfizer. Sunil Daniel, MD; Speakers bureau and Advisory Boards: Novo Nordisk. Taraneh Soleymani, MD; no disclosures to declare.

### Authors' contributions

TS, SD and WTG wrote and revised the manuscript. All authors gave final approval of the manuscript.

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