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REVIEW ARTICLE

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Evidence-based weight loss interventions: Individualized treatment options to maximize patient outcomes

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Abstract

Against the backdrop of obesity as a major public health problem, we examined three questions: How much weight loss is needed to benefit patients with obesity? How well do current therapies do in producing weight loss? What strategies can be used to improve patient outcomes using evidence-based studies. This paper reviews literature on the outcomes of lifestyle, diet, medications and surgical treatments for obesity using literature searches for obesity treatments. Current treatments, including lifestyle, diet and exercise, produce a weight loss of 5% to 7% on average. Despite continued attempts to identify superior dietary approaches, most careful comparisons find that low carbohydrate diets are not significantly better than low fat diets for weight loss. The four medications currently approved by the US Food and Drug Administration for long-term management of obesity are not as effective as surgery, adding about 5% on average to lifestyle approaches to weight loss. Two new medications that are under investigation, semaglutide and tirzepatide, significantly improve on this. For all treatments for weight loss, including lifestyle, medications and surgery, there is enormous variability in the amount of weight lost. Examination of this literature has yielded evidence supporting baseline and process predictors, but the effect sizes associated with these predictors are small and there are no prospective studies showing that a personalized approach based on genotype or phenotype will yield uniform success. Because obesity is a chronic disease it requires a 'continuous treatment model' across the lifespan.

KEYWORDS

bariatric/metabolic surgery, comprehensive lifestyle programme, diet, medications for obesity, personalized obesity management

1 | INTRODUCTION

In this review, we will try to answer three questions. First, how much weight loss is needed to provide benefit to individuals with obesity? Second, how much weight loss do the current interventions, including lifestyle, diet, pharmacotherapy and surgery, provide? And third, what information can we give to patients with obesity to personalize their treatment and to focus more precisely on their individual needs based on this evidence?

Obesity is a chronic, relapsing, stigmatized disease process that is increasing in prevalence worldwide and affecting both children and adults.[1–3] Using the body mass index (BMI; kg/m^2) as a criterion, the prevalence of obesity began rising about 1975,[3] and since then the prevalence of obesity worldwide has nearly tripled. In 2016 there were more than 1.9 billion adults, aged 18 years and older, who were overweight, and more than 650 million of them were obese. In addition, 38 million children under the age of 5 years were overweight or obese in 2019, and in 2016 over 340 million children and adolescents aged 5-19 years were overweight or obese.[4]

Excess body fat mass can cause disease by several mechanisms[5–8]; first, from the burden of excess fat (e.g. osteoarthritis

and sleep apnea); second, by the metabolic and inflammatory consequences of abnormal fat deposition in ectopic sites and the cytokines and adipokines released from these fat tissues (e.g. diabetes, cardiovascular diseases, fatty liver disease, some cancers); and third, by the psychological response resulting from the stigma of obesity[6] and psychological problems attributable to disease burden and reduced physical function that impact the quality of life. Determining a personalized treatment plan requires an assessment of mechanical, metabolic and psychosocial health, so that more intensive approaches are directed at those with greater health risk. Personalized treatment plans may also help navigate the variability in response to treatment experienced by individual patients, that we describe later.

2 | OBESITY: HOW MUCH WEIGHT LOSS IS NEEDED TO PROVIDE BENEFIT?

How much weight loss is needed to reduce risk and improve health? It is not necessary for patients to achieve an ideal body weight or even a BMI less than 30 kg/m^2 to achieve health benefits. Modest weight loss (5%-10%) improves glycaemia, blood pressure, lipids, the need for medications, mobility and quality of life.[9] The benefit of 5% or more weight loss is elegantly shown with data from the Diabetes Prevention Program (DPP; Figure 1).[10] Over the first 2.8 years, weight loss averaged 5.5 kg and reduced the risk of conversion from impaired glucose tolerance to type 2 diabetes by 58%.[11] When these data were modelled it was clear that the reduction in risk had a curvilinear relation to the degree of weight loss: more weight loss equated to greater risk reduction, but after 10 kg of loss (equivalent to ~10% in this study) there was little incremental benefit in reduction of conversion to type 2 diabetes.[10] Of course, for more advanced dysglycaemia, as in those with established type 2 diabetes, more weight loss brings more benefits. In the British DiRECT study,[12,13] a weight loss of 15 kg achieved by patients with type 2 diabetes was associated with normoglycaemia and requiring no diabetes medications, called diabetes remission. In DiRECT participants, if weight was regained, diabetes reoccurred.[5,12,13]

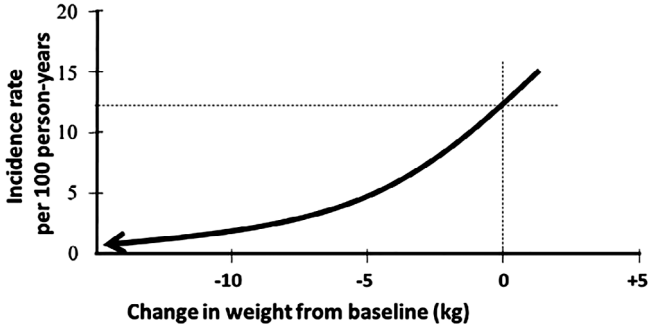


FIGURE 1 Relationship of weight loss to the incidence of diabetes in the Diabetes Prevention Program. Redrawn from[10]

While improvements in glycaemia and triglycerides begin at 3% and improvements in lipid and blood pressure at 5%, larger weight losses may be needed to produce benefits in some conditions such as obstructive sleep apnoea and non-alcoholic steatotic hepatitis.[14] Magkos et al.[14] examined clinical endpoints at each of three levels of weight loss, namely, 5%, 11% and 16%. They found that a weight loss of 5% significantly decreased plasma concentrations of glucose, insulin, triglycerides, alanine transaminase and leptin, but did not affect free fatty acids, low- and high-density lipoprotein cholesterol, or adiponectin. It was only after a weight loss of 16% that plasma-free fatty acid and c-reactive protein (CRP) concentrations decreased, and plasma adiponectin concentration increased. The loss of fat in critical depots was disproportionately greater than weight loss.[14] The message to healthcare professionals is that significant improvements in health can occur with a modest weight loss of 5% while others need a larger weight loss of 10% or more. If we can obtain and sustain a weight loss of 15% or more, we are probable to produce a much greater health benefit, as well as make patients with obesity more satisfied with the outcome. Furthermore, significant weight loss may reduce mortality. For US adults, those who lost weight from obesity in early adulthood to overweight in midlife had 54% reduced mortality compared with those who remained with obesity.[15]

For patients with more co-morbidities, treatments that produce more weight loss are indicated. This is a fundamental way to personalize therapy. The decision to employ medication or bariatric surgery is always based on health risk assessment, usually a combination of higher BMI and presence of co-morbidities.

3 | EVIDENCE-BASED LIFESTYLE INTERVENTIONS FOR WEIGHT LOSS: HOW MUCH WEIGHT LOSS DO THE CURRENT INTERVENTIONS PROVIDE?

3.1 | Lifestyle

Most guidelines for health professionals who manage patients with obesity recommend a comprehensive lifestyle programme as the first step.[6,16–18] 'Comprehensive' refers to counselling about changing behaviours related to both diet and physical activity. This recommendation is derived from the large lifestyle intervention studies that developed programmes around changing behaviours based on changing food intake and physical activity.[19] Behavioural techniques encompass self-monitoring of food intake and physical activity, stimulus control of the food environment, goal-setting, reinforcement and shaping of behaviours, problem-solving and social support.[6] During active weight loss the emphasis is usually on diet and the emphasis to maintain weight loss is on physical activity. To achieve weight loss with increasing physical activity is inefficient because of the time commitment required to create significant negative energy balance solely through increasing physical activity. Guidelines for physical activity during a lifestyle intervention recommend gradually increasing it to 150 minutes of moderate physical activity per week. For weight

loss maintenance, where physical activity is a significant predictor of success,[20] this recommendation is usually increased to 250 minutes per week.

With all non-surgical treatments for obesity there is gradual slowing of weight loss, followed by a high frequency of weight regain when treatment is slowed or stopped. There is also considerable variability in the amount of weight lost along with variability in patient satisfaction with their weight loss. Patterns of weight loss are illustrated in Figure 2 using data from two large randomized clinical trials, one called Look AHEAD, in which adults with diabetes were treated with the best lifestyle programme that could be designed,[21] and the second, depicting the DPP, which used lifestyle to prevent the onset of diabetes.[11] The left panel of Figure 2 shows that at the end of the first year, the top 90th percentile had lost nearly 18% of their baseline weight, in contrast to the loss of less than 1% in the bottom 10th percentile. By the end of the first year all but the top 90th percentile had stopped losing weight and this group was also approaching a plateau.[22] Weight regain is shown on the right-hand side of Figure 2 using 10-year data from the DPP Outcomes Study (DPPOS).[24] Note that between 6 and 12 months there was a plateau, but that after 1 year there was steady weight regain even although the lifestyle groups received ongoing treatment. The lifestyle group remained parallel to, but 1 to 2 kg lower than the placebo-treated control group over the next 5 years, in part because of the continuing lifestyle booster sessions. The conclusion from these studies is that a well-designed lifestyle programme can provide individuals with the tools they need to lose on average 8% and in some cases more than 15% of their weight, which is a very satisfactory outcome. However, there are an equal number of people who receive little or no benefit in terms of weight loss from this intensive therapy.

3.2 | Diet

The idea that there is an 'ideal' diet that could 'cure' obesity has driven the writing of an increasing number of diet books. Banting's *Letter on Corpulence Addressed to the Public* published in 1863 is the granddaddy of these books in English.[25] Over the last 150 years, countless books have been written, each claiming to possess a magic formula for both losing and maintaining weight loss. Each year, a new crop of new books are purchased by individuals who have regained the weight they lost the previous year, and who venture forth with the frequently 'false hope' that they will succeed this year where they failed last year and the year before.[26]

Two recent meta-analyses have examined the effect of many popular diets.[27,28] The data summarized in Table 1 show the mean weight losses for some of these diets. A key message from comparing weight-loss diets is that each one works if followed.[27,28,34–37] Table 1 shows that low carbohydrate diets do not produce significantly more weight loss than low fat diets.[27,28] In one meta-analysis, the Mediterranean, dietary approaches to stop hypertension (DASH) and vegetarian diets were significantly better than comparable diets. By contrast, low glycaemic index diets were not significantly better than high glycaemic index diets, nor were low carbohydrate diets better than high carbohydrate diets.[28]

Dietary protein can have a confounding effect when comparing diets. To compare low fat and low carbohydrate diets, Hall and Guo selected those studies where protein was held constant.[38] They found a small statistically significant effect favouring the low fat diet, but it was probably not clinically significant.[38] Gardner et al.[36] reported a large well-designed randomized controlled trial, in which a healthy low fat or healthy low carbohydrate diet were compared over 2 years, with both groups losing the same amount of weight. Another large randomized clinical trial comparing 20% versus 40% fat and 15% versus 25% protein also found no significant differences in weight loss with any of the four diets.[37] Of interest was the strikingly similar distribution of weight loss from more than 15% to a small gain for each diet, as shown in Figure 3.[37,39]

The DIOGENES study, a large family-based dietary intervention in the European Union, examined diet composition effect on weight regain after individuals had lost weight with a formula diet before being randomized. Over 26 weeks, a modest increase in protein and a modest reduction in glycaemic index improved the maintenance of weight loss.[40] The PREDICT study (clinicaltrials.gov identifier: NCTO3983733) is underway in the United States and the UK to determine if the glycaemic response to foods, microbiome profiles and other characteristics can help determine the response to diet.[41] Further, the US National Institutes of Health (NIH) announced a US $155 million project targeting nutrition in preventive health powered

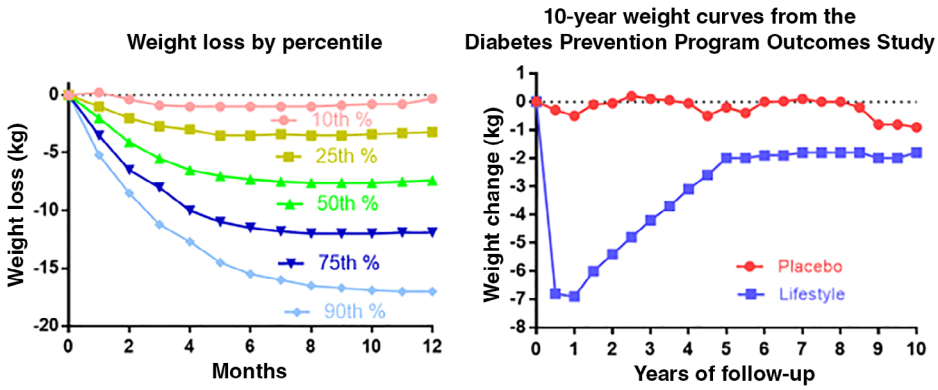


FIGURE 2 Weight change over time with lifestyle interventions in two large trials: (left) weight loss by percentiles during the first year of the Look AHEAD Trial[21]; (right) weight change over 10 years in the Diabetes Prevention Program Outcomes Study comparing the intensive lifestyle and control groups[22]

TABLE 1 Weight loss with various treatment options for obesity

Treatment		Amount of weight loss
Comprehensive lifestyle intervention: reduced calorie diet, increased physical activity and structured behavioural counselling with >14 sessions in 6 mo and monthly thereafter (high intensity)	Delivered on-site by trained interventionist in individual or group sessions	Average 8 kg loss achieved in 6 mo and sustained at 1 y, compared with usual care or no treatment[6]
	Delivered electronically or by telephone	Average 5 kg loss at 6 mo and sustained for 1 y, compared with usual care or no treatment[6]
Diets for weight loss	For weight loss, there was no one clearly superior dietary approach. (Jensen[6])	
	14 popular named diet programmes and macronutrient approaches evaluated (low carbohydrate diets included: Atkins, South Beach and Zone diets; low-fat diets included: Ornish, Rosemary Conley; moderate macronutrient diets included: Mediterranean diet, DASH diet, Volumetrics, Weight Watchers, Biggest Loser, Portfolio, Slimming World, Jenny Craig)[27]	For weight loss had similar results[27] Low carbohydrate 4.63 kg Low fat diet 4.37 kg at 6 mo Moderate macronutrient diets 3.06 kg at 6 mo
Pharmacotherapy with or without lifestyle intervention	Currently in the United States, four drugs are approved for long-term management of obesity; several others are approved for short-term use, usually considered less than 12 wk.	Pharmacotherapy addition showed greater weight loss or less weight regain compared with placebo groups at 12 to 18 mo (range, −0.6 to −5.8 kg; no meta-analysis)[29] All active agents were associated with significant excess weight loss compared with placebo at 1 y[30] phentermine-topiramate, 8.8 kg (95% CI −10.20, −7.42) liraglutide, 5.3 kg (95% CI, −6.06, −4.52); naltrexone-bupropion, 5.0 kg (95% CI, −5.94, −3.96); orlistat, 2.6 kg (95% CI, −3.04, −2.16)
Bariatric surgery	Sleeve gastrectomy (63% of US cases in 2015)[31]	Weight loss 3 y[32] 7 y 18.8% N/A
	Gastric bypass (30% of US cases in 2015)[31]	Weight loss 3 y[32] 7 y[33] 25.5% 24.8%
	Adjustable laparoscopic band (2% of US cases in 2015)[31]	Weight loss 3 y[32] 7 y[33] 11.7% 14.9%

by the All of Us research programme, which will use artificial intelligence, machine learning, computational and mathematical modelling of complex biological systems in an attempt to understand how genes, microbiome, metabolome and other measures can be used to predict response to diet.[42]

Finally, there are other important aspects of diet besides weight loss. In fact, only one diet has been shown to reduce cardiovascular events in a randomized controlled trial.[43] That diet, the Mediterranean diet, reinforces the concept that diet quality is an important consideration, especially for those individuals with increased cardiovascular risk.

3.3 | Pharmacotherapy

At present there are four drugs, orlistat and liraglutide and two combination drugs, topiramate-phentermine and bupropion-naltrexone, which were approved by the US Food and Drug Administration (FDA) after 1973 for use in the chronic management of obesity. Marked variability in weight loss exists for these drugs (Figure 4),[44–47] just as it does for weight loss with lifestyle (Figure 2), diet (Figure 3) and surgery (Figure 5). In a review of drug treatment for obesity, weight loss with orlistat was 2.94 kg with a confidence range from 1.27 to 5.82 kg; for naltrexone/bupropion it was 6.15 kg with a confidence range from 3.25 to 9.78 kg; for phentermine/topiramate it was 7.45 kg with a confidence range from 3.88 to 9.76 kg; and for liraglutide it was 5.50 kg with a range from 2.97 to 10.62 kg.[48] In addition, there are four drugs that were approved before 1973 for short-term use in treating obesity, phentermine (the most widely prescribed weight loss drug in the United States), phendimetrazine, diethylpropion and benzphetamine. A recent meta-analysis used mathematical modelling to assess weight loss efficacy and identify the maximum weight loss.[48] All drugs (orlistat, phentermine/topiramate, naltrexone/bupropion and liraglutide 3.0 mg) produced significantly greater weight loss than placebo. None of these medications have been studied in head-to-head comparisons. Currently, the personalized choice of a medication is determined by what a patient's

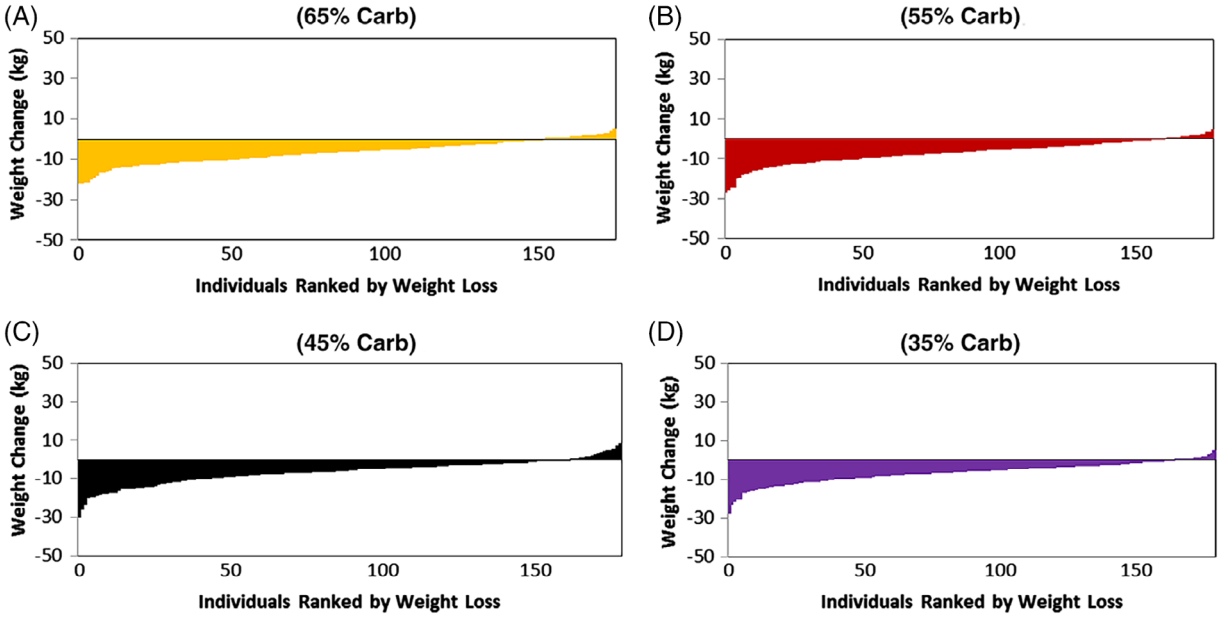
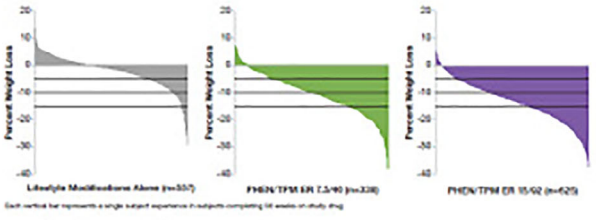
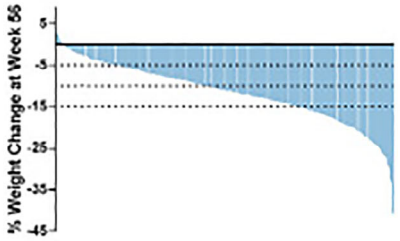


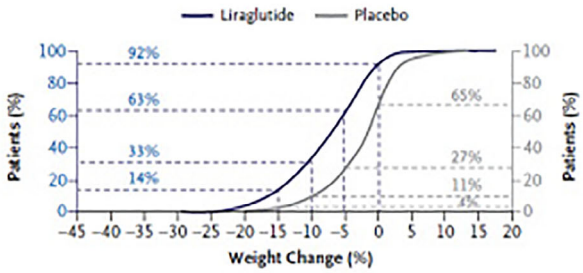
FIGURE 3 Weight loss by diet group in the POUNDS Lost study. Each panel shows the distribution of highest to lowest weight loss for individual participants[38]



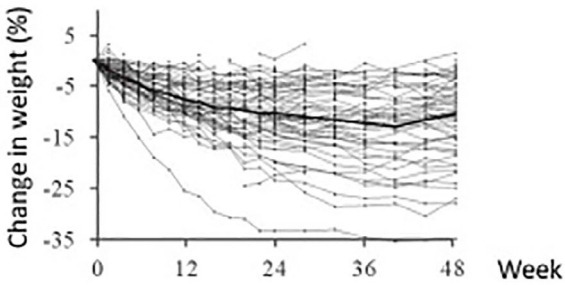
Placebo and Phentermine/Topiramate
McCullough PA, *et al.* Poster AANP 2013.



Naltexone/Bupropion (data shown for those who lost 5% at week 16)
Fujioka K, *et al.* IJO 2016; 40:1369-75



Placebo and Liraglutide 3.0 mg
Pi Sunyer X, *et al.* N Engl J Med 2015; 373:11-22.



Orlistat plus low-fat, reduced-calorie diet
Yancy *et al. Arch Intern Med* 2010;170:136–45

FIGURE 4 Variability of weight loss with four antiobesity medications including (top left) phentermine/topiramate,[43] (top right) naltrexone/bupropion orlistat,[44] (lower left), liraglutide[45] and (lower right) orlistat[45]

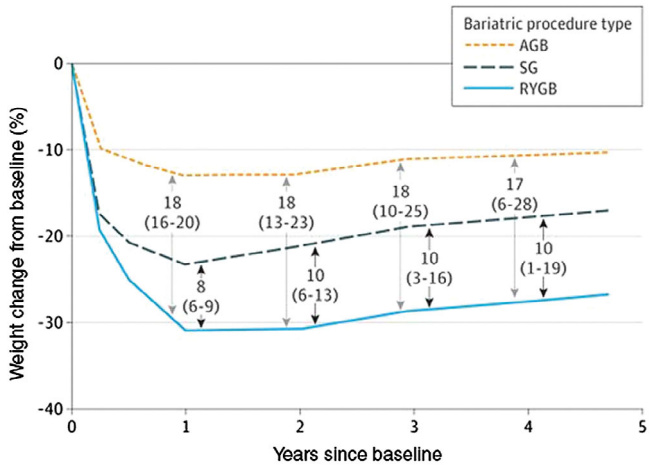


FIGURE 5 Variability of weight loss with sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB) and adjustable gastric banding (AGB). Numbers and arrows in the centre of the figure represent the differences and 95% CIs of the differences between (top) the AGB (N = 246), (middle) SG (N = 379) and (bottom) RYGB (N = 1785) groups at years 1, 2, 3 and 4[23]

insurance coverage permits, whether a drug might pose a safety issue and the patient's preference. This choice is generally made as a shared decision by prescriber and patient. Labelling for all drugs recommends stopping at 12 to 16 weeks if there is not a 4% to 5% weight loss. Identification of craving and binge eating may aid in selecting treatments. Some acute food intake studies show that semaglutide is associated with reduced craving, although currently semaglutide is not on the market. The phase 3 data from natltrexone/bupropion showed that greater control of craving was associated with greater weight loss, but there was no difference in drug and placebo.[49] Certain drugs (lisdexamphetamine and topiramate and second generation antidepressants such as citalopram, fluoxetine and sertraline) have been shown to reduce binge eating and to produce weight loss.[50]

Gelesis 100 has recently been approved. Gelesis is a transient, space-occupying, gel-like product for oral use that is approved by the US FDA for individuals with a BMI from 25 to 40 kg/m^2. In clinical trials it produced a modest weight loss of 6.4% compared with 4.6% in the placebo-control group.

Although none of the currently available drugs produced a placebo-subtracted weight loss that exceeded 10% on average, there are three examples where medications for managing obesity do produce more than 10% weight loss. The first is historical and comes from a report using the combination of phentermine and fenfluramine (when it was still available) that showed a mean weight loss from baseline of ~17%, with many individuals maintaining their lower weight for the 2-year duration of the trial.[51]

The other two examples concern drugs on the horizon. On 13 May 2020, Novo Nordisk issued a press release reporting that in a period of 68 weeks (including a 20-week run-in period), individuals receiving semaglutide, a second generation glucagon-like peptide-1 (GLP-1) agonist, at a dose of 2.4 mg subcutaneously once a week, lost 17.4% from baseline.[52] We have not seen this reported in peer-reviewed journals, but semaglutide is currently in phase 3 trials and will be reviewed by the FDA in 2021.[53] Another drug in phase 3 clinical trials is tirzepatide, a single molecule with a dual action given as a once-weekly injection that targets both the GLP-1 receptor and the glucose-insulin peptide receptor. In a phase 2 trial it produced a mean weight loss of ~12% at 26 weeks at a dose of 15 mg per day and also had potent effects on glycaemia.[54]

Finally, setmelanotide is a new drug that is a melanocortin 4 receptor agonist.[55] It is being developed for individuals with rare genetic disorders (proopiomelanocortin [POMC] obesity, leptin receptor deficiency obesity, Bardet-Biedl syndrome and Alström syndrome). The drug is in phase 3 trials, after showing efficacy in two patients with POMC obesity.[56]

3.4 | Surgery

Surgical treatment of obesity produces the largest weight losses and the best maintenance of weight loss of any currently available treatment. There are three major surgical procedures in wide use, with sleeve gastrectomy (SG) being most common, followed by Roux-en-Y gastric bypass (RYGB) and laparoscopic adjustable gastric band (LAGB) (Table 1). In the multicentre, NIH-funded longitudinal study of bariatric surgery, the median weight loss after 3 years for the 1513 patients undergoing RYGB was 31.5% (IQR: 24.6%-38.4%). For the 509 patients undergoing LAGB, the weight loss was about half as much at 16.0% (IQR: 8.1%-23.1%).[57] As depicted in Figure 4, there is a large variation in weight loss with surgical procedures, just as there is for all other treatments for obesity. However, the weight loss with surgery exceeded the weight loss produced by lifestyle, by diets and by pharmacotherapy, which led Müller et al. to suggest that bariatric surgery was a 'benchmark for efficacy' in the management of obesity.[23] But like all other treatments for obesity, there is considerable variability between SG, RYGB and LAGB procedures (Figure 4).[58] This again emphasizes the need to provide as much personalized advice for management of the patient with obesity as can be supported by evidence.

4 | TREATMENT OPTIONS TO HELP PATIENTS MAXIMIZE THEIR OUTCOMES

4.1 | Patient anticipation of weight loss outcomes

An important issue is how patients view their outcomes of treatment for obesity. If patients are to seek and accept treatments for obesity, then they must value the weight loss outcomes. Two groups have provided similar answers about how much weight loss individuals want when they begin a lifestyle treatment programme (Figure 6). In a study of 60 women with a BMI of 36.3 kg/m^2, Foster et al. asked participants to define their weight goals before treatment by one of four

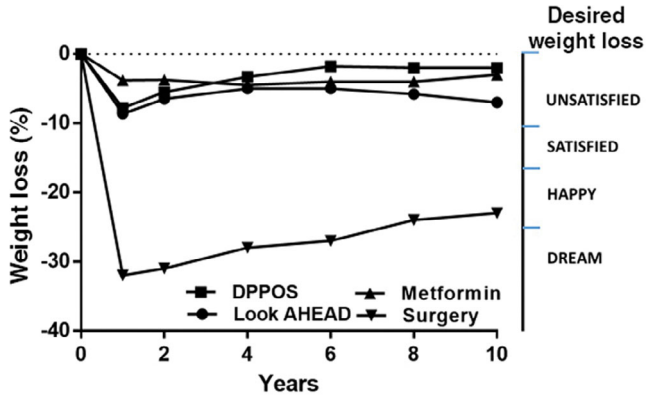


FIGURE 6 Comparison of weight loss over 10 years for Roux-en-Y gastric bypass, the DPP lifestyle arm, the DPP metformin arm and the Look AHEAD lifestyle arm against the level of patient satisfaction related to weight loss

categories, a 'dream weight', 'happy weight' or 'acceptable weight' loss, or a weight loss that would leave them 'disappointed'.[59] A weight loss of less than 17 kg was a disappointed outcome and one of 25 kg was acceptable. After 48 weeks of treatment, the average weight loss was 16 kg in 47% of patients, who had not even achieved their disappointed weight target. Despite achieving the positive effects they had expected, patients still reported not being satisfied with their weight. A similar study from 2015 surveyed 634 women with obesity.[60] Dream, happy, acceptable or disappointing weights would require losses of 34%, 28%, 23% or 16%, respectively, in individuals who dropped out of the trial compared with losses of 32%, 25%, 19% or 11%, respectively, in those who completed the trial.[60] The implication for clinicians is that patients are highly desirous of larger amounts of body weight loss, almost certainly reflecting cultural norms.

These weight loss goals can be compared with the results of several long-term (lasting 10 years or longer) clinical trials of weight loss (Figure 5). The weight loss data were from the intensive lifestyle intervention in the DPPOS,[61] the metformin arm of the DPPOS,[62] the Look AHEAD (Action for Health in Diabetes)[63] and a Swedish obese subjects subgroup who underwent RYGB.[64] It was evident that only the average weight loss achieved with bariatric/metabolic surgery with RYGB would provide a happy or dream weight loss outcome for patients.

4.2 | Optimizing outcomes: key treatment options to help maximize weight loss

It would be wonderful if there were sufficient data available to help us predict, with precision, who would and would not respond to each individual treatment that could be used for the patient with obesity. Unfortunately (with exceptions), that day is still in the future. The ongoing personalized response to dietary composition (PREDICT) study from the UK provides data on the challenges of designing personalized messages.[41] The authors measured differences in response of plasma glucose and triglycerides following a mixed meal using 1002 twins and unrelated healthy adults and found that genetic and environmental contributions to variability were about the same (~50%). If environment has that much of an impact upon something as tightly controlled as glucose, it will be more difficult to identify markers that are highly predictive of success with weight loss and efforts to maintain weight loss.[41]

4.2.1 | Lessons learned from prior weight loss programmes

Several components of a comprehensive weight loss programme provide data identifying successful participants. The first factor is the degree of adherence to the programme. Adherence to behavioural recommendations has long been noted to predict weight loss success in a number of studies, including Look AHEAD,[65] POUNDS Lost[37,66] and the DPP.[24] In Look AHEAD, attendance at clinic visits, minutes of physical activity and the number of meal replacements used all predicted the amount of weight loss.[66] In a sub-study of Look AHEAD participants, completeness of the food diary at baseline was also a strong predictor of weight loss success at 1 year.[67]

Another important lesson is that initial weight loss is a powerful predictor of ultimate weight loss.[40] In Look AHEAD, weight loss at 1 month predicted weight loss at 8 years. A greater initial rate of weight loss is associated with more weight loss at 1 and 4 years in the intensive lifestyle programme used in Look AHEAD.[22,68] Encouraging patients in efforts to lose weight in the early stages can thus be rewarding to them. Self-weighing on a regular basis produces a significantly better maintenance of weight loss.[69] This is obviously a tool that can be used to provide continuing feedback to help weight-conscious individuals adhere to their personal programme. Self-monitoring of foods eaten and the when and where of eating along with self-weighing can facilitate weight loss. The use of smartphones as mobile devices to help monitor steps taken, foods eaten and other behavioural strategies is rapidly developing to help patients achieve their goals, although data are contradictory on the value of these strategies. Like many other strategies, this one is only as good as the user makes it.

Weight control registries of individuals who have lost weight provide another source of information on better practices in weight control.[20] A recent meta-analysis identified five such registries, with The National Weight Control Registry from the United States by far the largest. This analysis found factors of importance for both weight loss and maintenance of weight loss. There were several strategies that reported success more than 80% of the time they were used for weight loss and maintenance. Among these were having healthy foods available at home, eating breakfast regularly, increased vegetable consumption, engaging in physical activity/exercise as well as restricting the consumption of sugary and fatty foods, having a regular meal frequency and reducing fat in meals. Increased physical activity was the

most consistent positive correlate of weight loss maintenance. Fewer than 20% of participants reported taking weight loss medication, using meal substitutes or consuming weight loss supplements.

Despite these limitations, there is still plenty of information that the healthcare provider can transmit to individuals who want to lose weight or maintain weight loss based on what we have learned from previous studies. To guide this discussion, we have prepared Table 2, which provides information about how well people during their weight loss programme or after the programme has finished, along with information that can be obtained prior to initiating treatment for an individual patient.

4.2.2 | Baseline assessment and process predictors

Table 2 lists information obtained during weight loss from studies that are associated with greater weight loss. Several factors are associated with successful weight loss, which are defined individually in each study. Success in maintaining weight loss is defined as regaining 25% or less of initial weight loss during maintenance based on comparing data from both the DPP and Look AHEAD studies.[77] A major problem with these measurements of success is that they are post hoc, that is, you do not know who will succeed until after the treatment starts. But we do know that people who adopt them increase their chances

TABLE 2 Process predictors and baseline assessments that are associated with more weight loss or maintenance of weight loss and can be used to personalize management of obesity

Measurement	Predictor outcome	Action
Programme components		
Adherence to programme[37,66]	More adherence, greater weight loss	Encourage adherence
Initial rate of weight loss[22,68]	More early weight loss, greater weight loss	Encourage early adherence
Physical activity[20,65]	More physical activity, greater weight loss	Encourage activity
Self-weighing[69]	More self-weighing, greater weight loss	Encourage self-weighing
Self-monitoring of diet and activity[70]	More self-monitoring, greater weight loss	Encourage self-monitoring
Use of antiobesity medications[18]	More weight loss than placebo	Depending on the specific drug, the product label recommends 4%-5% weight loss in 12-16 wk as a benchmark for success. Change therapy if needed
Eating patterns		
Regular breakfast intake[19]	Weight loss and better weight maintenance	Eat breakfast regularly
Healthy foods at home[19]	Better weight loss and maintenance	Have healthy foods at home
Increasing vegetable intake[19]	Better weight loss and maintenance	Increase vegetable intake
Sugary drinks and foods[19]	Better weight loss and maintenance	Restrict sugary foods
Healthy Food Diversity Index[71]	Higher values, greater weight loss	Encourage healthier and diverse choices
Protein intake[39]	High protein, greater weight loss	Encourage >15% protein intake
Selection of low-fat high fibre foods[19,20,72]	Low fat diet, better maintenance	Encourage low fat diet for maintenance
Circadian rhythms—sleeping and eating		
	Short sleep time[73]	Sleep 8 h or more
	Duration of eating[74]	Less than 10 h and earlier in the day
	Timing of meals[75]	Eat earlier in the day
Endocrine-prediabetes		
Glucose	Fasting glucose >5.5 mM (100 mg/dL), including people with diabetes[72]	More weight loss with lower carb./high fibre diet
Medication profile[a]		
	Using antidepressant drugs[17,76]	Select, if possible, those with least adverse effect on weight
	Using anticonvulsant drugs[17,76]	Select, if possible, those with least adverse effect on weight
	Using antipsychotic drugs[17,76]	Select, if possible, those with least adverse effect on weight
	Using antidiabetic drugs[17,76]	Select, if possible, those with least adverse effect on weight

[a]For a detailed list of medications affecting body weight see[17,76].

of success. Thus, it is valuable to provide them to all patients with obesity.

4.3 | Eating patterns

Higher protein intake has been associated with more weight loss in some studies[39] and this can be a useful strategy for some people. As noted above, successful eaters in the National Weight Control Registry select a lower fat diet, advice that can be relayed to patients. Finally, people who have higher scores on the Healthy Food Diversity Index lose more weight and this can be a useful teaching tool.[71]

4.4 | Circadian rhythms: eating and sleeping

Mammals, including human beings, have a biological clock that functions in most cells in the body. This system is synchronized in the brain by light that hits the retina in the eye and whose messages are transmitted to the suprachiasmatic nucleus. This brain centre is, in turn, synchronized by temperature and to some extent by food. When human beings eat *ad libitum*, they consume food over a period of nearly 14 hours on average.[74] If the feeding time is reduced to 10 to 12 hours, food intake declines and so does body weight. Eating earlier in the day is associated with less food intake and with leaner people. Sleep duration has also been associated with differences in body weight. Individuals with a short sleeping time tend to weigh more than those who sleep more than 8 hours at night.[73] These studies in biological rhythms give us lessons for the patient with obesity that can be part of their personalized armamentarium.[75]

4.4.1 | Behavioural measures

Behavioural measures, including assessment of eating behaviour and the answers to questionnaires, have provided further useful guidance for individuals wanting to lose weight. In the POUNDS Lost study, every one-point increase in baseline craving score for high fat foods was associated with a −1.62 kg weight loss (P = .0004), which was probably accounted for by the associated highly significant decrease in energy intake and fat intake.[78] This emphasizes the value of decreasing fat intake in people with a craving for fatty foods. By contrast, a craving for carbohydrates and starches was associated with significantly less weight loss in the first year and more weight regain in the second year. Using the three-factor eating inventory, the cognitive restraint score predicted less weight loss and more weight regain during the second year of the POUNDS Lost study. Although the effect sizes are small, the authors suggest that interventions targeting different psychological and behavioural variables can lead to greater success in weight loss.[71] A meta-analysis showed that reactivity to food cues and food craving only accounted for 11% of the variance in weight change, indicating a positive, albeit small, effect.

4.4.2 | Endocrine (dysglycaemia and hyperinsulinaemia)

Elevated fasting glucose and insulin are markers of insulin resistance and may indicate prediabetes. Retrospective examination of several large European and American prospective weight loss studies shows that individuals with glucose levels that indicate prediabetes or diabetes lose more weight with a low carbohydrate, high fat diet that is enhanced by increased intake of fibre.[72] In an interesting statistical approach, a study comparing the average Danish diet to a new Nordic diet with high fibre and whole grain was analysed based on baseline fasting plasma glucose and fasting insulin.[79] The study showed that individualized predictions of the efficacy of the new Nordic diet were reliable, with those at the highest baseline glucose levels having a 95% probability of 8 kg more weight loss than with the average Danish diet. Further, those with the lowest glucose and insulin levels at baseline had no difference in effect.[79] This novel statistical approach may help us to better understand predicting response from existing randomized controlled trials.

4.4.3 | Medication profile

Some medications are well known to produce weight gain, including antidiabetic and antidepressant drugs.[17] In the Look AHEAD study, if patients were exposed to one or more of these obesogenic medications then the probability of achieving a weight loss of greater than 5% was reduced by 32%.[80] If the patient interview identifies one or more of the drug classes listed in Table 2 then the healthcare provider can review the possibility of switching to drugs that have the least adverse effect on weight.[17]

4.4.4 | State of the art in personalizing therapies for weight loss

The intriguing evidence of great variability of weight loss response has not yielded any markers that might direct healthcare providers in the clinic. Yet every patient's weight gain and weight loss history are different. The healthcare provider must operate without a detailed map, using only broad guideposts when recommending treatments. Because the patient is the one who must make the lifestyle changes, follow the diet, take the medication and undergo surgery, it is wise to make treatment decisions by including the patient. The healthcare provider's knowledge of risk and benefit can inform the patient in determining the treatment path. Many times, treatments are tried and, if they do not work, another approach is deployed. The enormous interest in personalizing medical care will eventually extend to weight management and phenotyping and genotyping will be important pretreatment assessments.

5 | FUTURE DIRECTIONS FOR INDIVIDUALIZED TREATMENT

5.1 | Genetic information

Human obesity has a strong genetic basis, with heritability estimated to be between 40 and 70. There are a few major genes that have major effects on body weight, including the leptin gene and its receptor, the melanocortin-4 gene and its receptor.[81,82] In the rare individual who is leptin-deficient, treatment with leptin will reverse almost all features of the disease. This is obviously one example where medicine can be precise and personal. A second is in individuals with deficiency of the POMC gene. POMC is cleaved in the brain into several peptides, including adrenocorticotrophic hormone, α-melanocyte stimulating hormone (MSH), β-MSH and β-lipotropin. The α-MSH acts on the melanocortin-4 receptor to reduce food intake. In the absence of POMC there is no α-MSH to act on this receptor and obesity results. Setmelanotide is a synthetic melanocortin-4 receptor agonist that is being evaluated for treatment of POMC deficiency and which represents another focused 'personalized obesity therapy'.[55,56]

The most common forms of obesity, however, are polygenic, meaning that they result from small contributions of many genes.[81] The fat mass and obesity associated gene (FTO) was the first of these to be clearly characterized and it has the largest effect of the many polygenes, which when aggregated account for less than 5% of the variance of human obesity. The possibility of predicting future obesity was examined by Khera et al.[83] in a study where 2.1 million common variants were examined. The authors showed that there was a gradient of 13 kg between the lowest and highest decile of the polygenic risk score. However, the ability of this score to accurately predict future obesity increased with increasing age through childhood.

A review by Tan et al.,[84] however, was pessimistic about the use of genetic data for predicting weight loss. In their review of 36 studies conducted in 13 different countries with a total of 15 931 participants aged between 19 and 70 years of age, 26 genes and 64 single nucleotide polymorphism (SNPs) were examined for their relation to the reduction of body weight and improvement in metabolic risk factors in response to diet, exercise and lifestyle interventions. The authors concluded that gene-lifestyle interaction studies on the same candidate gene in different populations reported data that were challenging to interpret, stating that 'it is difficult to arrive at a particular model for a strategy on weight management at this point in time'.

Between the small group of genes with major effects and low prediction for even a very large number of polygenes, genetic information is used to predict differences in response to specific diets. In the POUNDS Lost study, 811 individuals were randomly assigned to either a 20% or 40% fat diet or either a 15% or 25% protein diet. Some of the genes measured at baseline provided guidance in selecting one diet over the other.[85] Several genes suggested that a low fat diet would produce more weight loss (TT genotype of transcription factor 7-like 2, T allele of glucose-dependent insulinotropic polypeptide and the G allele of melatonin receptor 1B). Another group of genes predicted more weight loss with a high fat diet (T allele of hepatocyte nuclear factor 1 homeobox A, C allele of protein phosphatase, Mg2+/Mn2+ dependent 1K and baseline methylation of nuclear factor of activated T cells 2 interacting protein). Weight loss was higher with a protein diet in individuals with the A allele of FTO. Finally, carbohydrate diets were favoured by two genes. Individuals with the TT genotype of fibroblast growth factor-21 lost more weight eating a low carbohydrate diet and those with the CC genotype of insulin receptor substrate-1 lost more weight eating a high carbohydrate diet.[85]

5.2 | Metabolomic signatures

Interest in the microbiome and its relation to obesity has been growing for several years.[86] In ongoing studies of two microbiome species, prevotella and bacteroides, Hjorth et al.[87] found that individuals with a high prevotella to bacteroides ratio lost significantly more weight when eating a high fibre weight loss diet compared with a low fibre diet.

In a meta-analysis of prebiotics, probiotics and mixtures (synbiotics) that can influence the microbiome, Ferrarese et al.[88] found that some of the synbiotics, particularly those with *Lactobacillus gasseri*, produced weight loss in randomized controlled trials. Prebiotics on their own were unimpressive, as were the probiotics; it was the synbiotics that had effects in some trials.

5.3 | Thyroid

Baseline hormone levels may predict weight change, although their current value in advising patients with obesity is unclear. In the POUNDS Lost study, Liu et al.[89] found that higher baseline levels of free triiodothyronine (T3) and free thyroxine (T4) levels predicted greater weight loss during the first 6 months and were positively associated with changes in body fat mass, blood pressure, glucose, insulin, triglycerides and leptin at 6 and 24 months.

6 | CONCLUSION

In this review we have examined three questions. First, we reviewed obesity and its associated problems then addressed the question of how much weight loss was needed to reverse these problems and concluded that optimal weight loss should be defined by the endpoint one is desiring to effect. Risk reduction for future diabetes could be achieved with as little as 3% to 5% weight loss, while improvement in obstructive sleep apnea requires weight loss of greater than 10%. If we can obtain and sustain a weight loss of 15% or more, we are probable to produce a much greater health benefit, as well as make patients with obesity more satisfied with the outcome. Next, we examined the various methods for achieving weight loss and concluded that most of them achieved an average of less than 10%, except for bariatric surgery, which was well in excess of 10%. We

then compared weight loss from diet, medication and surgery with the preferences that patients express when entering a weight loss programme, and concluded that only bariatric surgery currently provided sufficient weight loss to make most people with obesity happy with their outcome. Finally, we examined the question of whether there are techniques to personalize treatment for obesity and make it more precise. The lessons learned from previous clinical studies with weight loss were reviewed and many salient lessons identified. In addition, several baseline variables can provide information that can be used to steer decision-making during the weight loss process. Individualizing therapy based on patient phenotype or genotype is not yet a reality, but the future will probably bring advances in this arena.

CONFLICT OF INTEREST

GAB acknowledges membership on Medifast Scientific Advisory Board and the Herbalife Nutrition Advisory Committee; DHR reports personal fees from Novo Nordisk, Lilly, Boehringer Ingelheim, Sanofi, Amgen, Bausch Health, IFA Celtic, real appeal, ReDesign Health, Epitommee, Gila Therapeutics, Phenomix, Scientific Intake and Kintai, outside the submitted work.

AUTHOR CONTRIBUTIONS

GB prepared the first draft. GB and DR edited, revised, responded to reviewers and approved final manuscript.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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