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Medical Management of Obesity

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Scientific Evidence Supporting the Potential Efficacy of Medical Treatment of Obesity

It is generally believed in the scientific community that medical (nonsurgical) treatments alone have not been effective in achieving a significant long-term weight loss in obese adults. The situation is even less optimistic in regard to patients with obesity class II (moderate) and III (morbid obesity). However, very few studies have specifically examined the effects of nonsurgical treatment in these morbidly obese patients, so conclusions about nonsurgical therapy in this population are based on inference. In studies of class I (minimal) and class II obesity, medical therapy can achieve about 10 % body weight loss in 10–40 % of patients depending on study design, use of medications, and duration of the intervention. Duration of the weight loss response increases with duration of treatment and with use of medications and behavior modification.

Some studies have demonstrated the beneficial effect that dietary plans, behavior therapy programs, and physical activity have in helping to lose weight and to improve the comorbidities associated to obesity [19, 20]. Also, some clinical trials have shown the beneficial effect that drugs such as sibutramine and orlistat have had in reducing weight and improving the glycemic and lipid profiles in obese patients. The subjects participating in these clinical trials also received dietary advice. Their BMI was between 30 and 35 kg/m^2 and the average duration of these studies was only 1 year [20, 21].

It is very important to set realistic expectations before starting medical treatments of obesity. Both physician and the patient should be aware that a weight loss of 5–15 % reduces obesity-related health risks significantly. There are a substantial number of patients who respond to weight loss interventions with important changes in their lifestyle, which translates in long-term weight loss. Identifying the patients who will respond to nonsurgical interventions would be very important to maximize resources and avoid unnecessary surgeries. We need to keep in mind that bariatric surgery treats less than 1 % of the eligible morbid obese population, and that already implies waiting lists averaging more than 1 year. Should all the obese patients with the current indications ask for surgery, we simply would not have either the economical and infrastructure resources or the health professionals necessary to operate on 3–5 % of the Western population. Therefore, it is important to count with effective comprehensive interdisciplinary medical therapies alternative (and complementary) to bariatric surgery.

Setting unrealistic goals concerning the weight loss is frequently associated with weight management failure. Recent studies have shown the short efficacy of lifestyle interventions for the treatment of severe obesity and related comorbidities [22, 23].

Dietary Modifications

The macronutrient composition of different weight loss diets is a topic of great interest, and several clinical trials have attempted to compare their effectiveness [24–34] (Table 1). Most studies have indicated that hypocaloric diets, low in calories from carbohydrates, help patients to achieve a greater weight loss in the short term than low-fat diets [24–29]. In line with these observations, a Cochrane review confirmed that low-carbohydrate diets are associated with a greater weight loss than others [35]. Below are presented some of latest evidence and recommendations available [36].

Changes in Total Calorie Intake

The Balanced Hypocaloric Diet

Evidence:

A caloric restriction between 500 and 1,000 kcal daily induces weight loss ranging between 0.5 and 1.0 kg/week, equivalent to a weight loss of 8 % for an average period of 6 months (evidence level 1+).

S.A. Brethauer et al. (eds.), *Minimally Invasive Bariatric Surgery*,
DOI 10.1007/978-1-4939-1637-5_3, © Springer Science+Business Media New York 2015

Table 1. Some common diets

Type	Description	Average weight loss, kg (95 % CI)
Mediterranean diet	Fruits, nuts, red wine, fiber, whole grains, fish, and vegetable fat (extra virgin olive oil)	−4.4 kg (−5,9 to −2,9 kg)
Weight watchers	Moderate energy deficit Portion control	−2.8 kg (−5.9 to −0.7 kg)
LEARN	Moderate energy deficit (lifestyle, exercise, attitude, intensive lifestyle, relationships, nutrition) modification	−2.6 kg (−3.8 to −1.3 kg)
Ornish	Vegetarian based Fat restricted (<10 % of total calories)	−2.2 kg (−3.6 to −0.8 kg)
Zone	Low carbohydrate Carbohydrate/protein/fat 40/30/30	−1.6 kg (−2.8 to −0.4 kg)
Atkins	Very low carbohydrate Minimal fat restriction	−4.7 kg (−6.3 to −3.1 kg)

- Measures such as reducing portion sizes or reducing the energy density of the diet can facilitate compliance with a reduced-calorie diet and weight loss in obese patients (evidence level 3).

Recommendations:

- In obese adults, a caloric deficit of 500–1,000 kcal/day vs. caloric requirements is enough to induce a weight loss of 8 % in the first 6 months of therapy (grade A recommendation).
- The reduction on the portion sizes of serving and the energy density of the diet are effective measures to reduce the weight via dietary management (grade D recommendation).

Dietary Modifications Based on Different Combinations of Macronutrients

Modified-Fat Diets Versus Modified-Carbohydrate Diets

Evidence:

- Short term (6 months): a low-carbohydrate diet allows people to achieve greater weight loss than a low-fat diet (evidence level 1++).
- Long term (12 months or more): a low-carbohydrate diet allows people to achieve similar weight loss than a low-fat diet (evidence level 1+).
- Long term (12 months or more): a low-carbohydrate diet can help patients to achieve a further increase in the concentration of high-density cholesterol (HDL-Cl) and a greater reduction in the concentration of triglycerides than a low saturated fat diet (evidence level 1+).
- Long term (12 months or more): a low saturated fat diet can help patients to achieve a further decrease in the concentration of low-density cholesterol (LDL-Cl) than a low-carbohydrate diet (evidence level 2+).
- Low-carb diets cause more adverse effects than low-fat diets (evidence level 2++).
- Low-carb diets can increase long-time mortality if the fat contained is, mostly, from animal origin.

Recommendations:

- The reduction in the proportion of carbohydrates, with an increase in fats, is not helpful to enhance the effects of diet on weight loss (grade A recommendation).
- In an obese patient, a low-fat diet is useful to control the levels of LDL cholesterol, whereas a low-carb diet allows to achieve better triglyceride and HDL cholesterol control (grade B recommendation).
- Low-carb diets may not contain a high proportion of animal fats (grade D recommendation).

Modified-Carbohydrate Diets

Fiber-Enriched Diets

Evidence:

- There are not enough data to establish evidence on the role of a diet enriched with dietary fiber or whole grains on weight loss.
- Glucomannan supplements added to the diet may have a modest (satiating) effect, which encourages weight loss (level of evidence 1+).
- Fiber supplements (different than glucomannan) added to the diet can contribute minimally to weight loss (level of evidence 2+).
- The treatment of obesity with a diet enriched or supplemented with glucomannan, plantago ovata, and β-glucan lowers LDL cholesterol levels of obese patients (evidence level 1+).

Recommendations:

- In the treatment of obesity, fiber supplements (mainly glucomannan) may increase the effectiveness of the diet on weight loss (grade C recommendation).
- The prescription of diets enriched with fiber or fiber supplements (mainly glucomannan) may benefit obese people with lipid abnormalities (grade B recommendation).

Low Glycemic Index Diets

- The glycemic index (GI) is a system for quantifying the glycemic response of a food containing the same amount of carbohydrates with that of a reference food [37]. The glycemic load (GL) is the product of the GI and the amount of ingested carbohydrates and provides an indication of

the amount of glucose available to metabolize or store after ingestion of food containing carbohydrates [38].

Evidence:

- In the treatment of obesity, dietary modifications in GI or GL have no persistent effect on weight loss (evidence level 1+).
- There are not enough data to establish evidence on the role of low-GI diets or low GL on maintenance of weight loss after a low-calorie diet.

Recommendations:

- As a specific strategy for the dietary management of obesity, the decrease in GL and GI, can't be recommended (grade A recommendation).

High-Protein Diets

Evidence:

- A high-protein diet can induce greater weight loss in the short term (less than 6 months) than a conventional diet, rich in carbohydrates (evidence level 2+).
- A high-protein diet does not induce greater weight loss in the long term (over 12 months) than conventional diet, rich in carbohydrates (evidence level 1+).
- There are insufficient data to establish the effectiveness of high-protein diets in the maintenance of weight loss after an initial phase of weight loss with other diets.
- A high-protein diet helps to preserve lean mass, better than a diet rich in carbohydrates (evidence level 2+).
- A high-protein diet can increase (in the long term) the risk of total mortality and cardiovascular mortality, mainly when the protein is of animal origin (evidence level 2+).

Recommendations:

- In the treatment of obesity, it is not recommended to induce changes in the proportion of dietary protein (grade A recommendation).
- To ensure the maintenance or the increase of the lean mass during a low-calorie diet, it is effective to increase the protein content of the diet above 1.05 g/kg (grade B recommendation).
- When a high protein is prescribed, the intake of animal protein in the diet should be limited, to prevent an increased risk of mortality in the very long term (grade C recommendation).

Meal Replacement Diets

Evidence:

- The use of commercial meal replacements for one or more meals a day may facilitate the monitoring of a hypocaloric diet more effectively, promoting, in this case, both weight loss and maintenance of weight loss (evidence level 1−).
- This benefit is greater when those meal replacements are used in the context of structured treatments that include physical activity, education, and food behavior modification (evidence level 3).
- There have not been clinically significant adverse effects associated with the use of meal replacements in the context of low-calorie diets (evidence level 3).

Recommendations:

- In obese or overweight adults, replacing some meals for meal replacements (in the context of low-calorie diets) can be useful for weight loss and its maintenance (grade D recommendation).

Very-Low-Calorie Diets

Evidence:

- In the short term (less than 3 months), very-low-calorie diets (VLCD) (400–800 kcal/day) result in a greater weight loss than low-calorie diets (>800 to <1,200 kcal/day) (evidence level 1+).
- In the long term (over 1 year), these diets do not result in a greater weight loss than low-calorie diets (evidence level 1+).
- The use of a VLCD before bariatric surgery, in patients with hepatic steatosis and increased surgical risk, can reduce surgical risk (evidence level 1+).
- At the moment, there are no data available to establish whether VLCD with commercial products help patients to reach an adequate protein intake.
- The VLCD presents a higher risk of adverse effects than the low-calorie diet (evidence level 1−).
- The evidence available does not support that the VLCD are associated with a greater lean mass loss in relation to fat mass loss, compared to less restrictive calorie diets.

Recommendations:

- The VLCD can be used in the treatment of obese patients, following a specific clinical indication and a close medical monitoring (grade D recommendation).
- The VLCD can't be used in patients who don't meet the guidelines, requirements, and criteria (grade A recommendation).
- Under medical supervision, and considering the possible adverse effects that can be observed, the use of VLCD can be justified in the preoperative bariatric surgery in patients with hepatic steatosis and increased surgical risk (grade B recommendation).
- Using VLCD with commercial products could be justified in the immediate postoperative of bariatric surgery to help the patient reach an adequate protein intake (grade D recommendation).

Mediterranean Diet (MedDiet)

Evidence:

- Studies point to a possible role of MedDiet in the prevention of overweight and obesity, although there are inconsistent results (evidence level 2–).
- The available evidence suggests that greater adherence to the MedDiet could prevent the increase of the abdominal circumference (evidence level 2+).

Recommendations:

- Increased adherence to the MedDiet could prevent overweight and obesity and prevent the increase of the abdominal circumference (grade C recommendation).

Benefits of the Mediterranean Diet:

Most prospective studies researching the association between dietary quality and risk of obesity found that an overall dietary pattern based on the traditional Mediterranean diet was inversely associated with the risk of obesity or weight gain [39–42]. The inverse association between the MedDiet and adiposity indices has also been reported in some studies [43–47]. Some clinical trials have added support for this association [48–50].

Nutrigenetic studies [51–53] have analyzed the biological and statistical interactions between the Mediterranean diet and its components and variations in key genes in lipid metabolism, inflammation, adipocytokines, obesity, diabetes, and cardiovascular disease (APOA1, APOA2, ABCA1, LIPC, COX-2, FTO, TCF7L2, PRKAG3, PRKAA2, ADIPOQ, CD36, NR1H3, etc.). There have been many statistically significant interactions in which greater adherence to the MedDiet, or some of its typical foods, is able to reverse the adverse effects that have risk allelic variants in these genes on their specific phenotypes, being able to modulate the adverse effects of certain genetic variants, dyslipidemia, hyperglycemia, and/or obesity.

This evidence suggests that the typical MedDiet pattern, based on whole foods, minimally processed, which includes fruits, nuts (walnuts), vegetables, legumes, whole grains, red wine, fiber, fish, vegetable protein, and vegetable fat (from extra virgin olive oil), has qualitative elements that promote weight loss and glycemic control and enhances the management of the metabolic syndrome [54]. It has recently been demonstrated a further reduction in the incidence of cardiovascular events in people at high risk who consumed a Mediterranean diet supplemented with extra virgin olive oil or nuts [55].

Physical Activity

Increased physical activity is an important component in the medical treatment of obesity; it represents an increase in energy expenditure. A class A evidence indicates that, with or without diet associated, the impact of physical activity has good results for weight loss and its maintenance [56, 57]. However, subsequent recommendations of the American College of Sports Medicine indicate that physical activity in itself has a limited effect on weight loss [58].

Since the publication in 1999 of the report "A one year follow-up to Physical Activity and Health: A report of the Surgeon General" [59] in the USA, a large amount of evidence-based knowledge has been accumulated on the benefits of physical activity in overweight and obese individuals, although not so much in the morbidly obese.

In order to update the scientific knowledge, an Experts Committee reviewed new research and classified the degree of evidence of the benefits of physical activity on health. The results of this review were published in the report Physical Activity Advisory Committee Report, 2008 [60]. These guidelines suggest that the health benefits of physical activity include the prevention of disease and the reduction of multiple risk factors associated with many diseases and chronic conditions, becoming part of the treatment recommendations of some of these, as in the case of obesity.

Benefits of Physical Activity

The benefits of physical activity include reduced risk of premature death of any cause, CVD, T2DM, some cancers (breast cancer and colon cancer), depression, prevention of weight gain, weight loss (in combination with caloric restriction), and improvement of physical fitness and musculoskeletal fitness [61, 62]. Inactivity and low cardiorespiratory fitness are as important as overweight and obesity as mortality predictors [63].

In elderly people there is strong evidence supporting the improvement of cognitive function in people who are physically active and moderate evidence in regard to overall improvement in well-being [64] and functional health, reduction of abdominal obesity, reduced risk of developing hip fracture, risk reduction of lung cancer, and weight loss maintenance. In a recent systematic review and meta-analysis, Hobbs et al. [65] found that interventions in adults aged 55–70 years led to long-term improvements in physical fitness at 12 months; however, maintenance beyond this is unclear. Interventions which involved individually tailoring with personalized activity goals or provision of information about local physical activity opportunities in the community may be more effective in this population [65], and the benefits associated with regular exercise and physical activity contribute to a more healthy, independent lifestyle, greatly improving the functional capacity and quality of life in this population [66].

Recommendations for Physical Activity

Best practices:

1. All adults should avoid inactivity and all those who participate in physical activity should obtain some health benefits.

2. In order to obtain significant benefits of physical activity in adults, its duration should be at least 2.5 h/week (150 min) of moderate-intensity activity or 75 min of vigorous activity or a combination of both (category: "active").
3. To obtain additional benefits, adults should increase their aerobic activity to 300 min of moderate activity, or 150 of vigorous activity, or a combination of both (considered as "highly active") [60, 67].

The guidelines also recommend that adults should get involved in physical activity, increasing gradually its duration, frequency, and intensity, with the aim of minimizing the risk of injury.

As for the type of exercise recommended, muscle-strengthening activities involve all muscle groups 2 or more days a week. The elderly at risk of falling should also practice exercises to maintain and/or improve their balance.

There appears to be a linear relation between physical activity and health status, such that a further increase in physical activity and fitness will lead to additional improvements in health status. In addition to the recommendations from the guidelines, different studies provided data underlying the importance of avoiding a sedentary lifestyle as a key tool in health promotion [68, 69]. These recommendations are mainly addressed to obese people who are fairly inactive, encouraging them to reach gradually higher levels of physical activity in order to obtain the maximum benefit from its protective effects.

Some studies have focused attention on the sedentary profile of patients, in order to observe the benefit that certain dose of physical activity (in intensity and duration) would produce greater benefit in terms of weight loss and cardiovascular function. These studies concluded that the duration of exercise (150 min) is more important than the intensity (moderate vs. vigorous), but these studies did not include patients with BMI > 40 kg/m^2 [70].

The rise of new technologies on the development and marketing of instruments to measure the amount of physical activity (pedometers, accelerometers) will undoubtedly help to better determine the amount of physical activity needed to optimize the dose–response results on physical activity-based interventions [71].

There are few randomized controlled clinical trials evaluating the impact of physical activity in a lifestyle intervention in morbidly obese patients. Goodpaster et al. [22] conducted a trial designed specifically to evaluate the effects of an intensive lifestyle intervention on weight loss, abdominal fat, hepatic steatosis, and other cardiovascular risk factors in people with obesity (degrees II and III, BMI >35 and >40 kg/m^2, respectively) without T2DM. They concluded that, among patients with severe obesity, a lifestyle intervention involving diet combined with initial or delayed initiation of physical activity resulted in clinically significant weight loss and favorable changes in cardiometabolic risk factors.

In summary, the available evidence suggests that physically active people live longer than sedentary people and do so with a greater quality of life by improving their rest, reducing the risk of cardiovascular disease, type 2 diabetes, hypertension, dyslipidemia, and colon cancer. In relation to obesity, physical activity appears to help weight loss (although not induce weight loss by itself) and, in a dose sufficient, help in the maintenance of weight loss [57, 72–74].

Behavioral Therapy

Behavioral therapy is a key tool to help overweight and obese patients make long-term changes in their behavior by modifying and monitoring their food intake, increasing their physical activity, and controlling cues and environmental stimuli that trigger overeating [56, 57, 75–78].

Different eligibility criteria, target population, and inclusion criteria (T2DM and BMI) have been used in the most important clinical trials (Table 2). Two of the most cited studies involving behavioral therapy in the context of a lifestyle modification targeted diabetic and/or nondiabetic persons with elevated fasting and post-load plasma glucose concentrations: the Diabetes Prevention Program (DPP) [79] and the Action for Health in Diabetes (Look AHEAD) [80–82]. DPP participants (overweight, sedentary, and nondiabetic persons with elevated fasting and post-load plasma glucose concentrations) were randomly assigned to a metformin group, a lifestyle modification group, and a placebo group. The research team hypothesized that modifying these risk factors with a lifestyle intervention program or the administration of metformin would prevent or delay the development of diabetes. This program was based on 16 individual education sessions during the first 24 weeks and bimonthly the rest of the period. A low-fat, hypocaloric diet was prescribed (1,200–2,000 kcal/day depending on the degree of overweight), composed of conventional foods, and 150 min/week of physical activity (generally brisk walking), with a goal of losing 7 % of their initial body weight.

In the Look AHEAD study, more than 5,100 overweight participants with DM2 were randomized to a Diabetes Support and Education group (DSE) or an Intensive Lifestyle Intervention (ILI) with a weight loss goal of 7 % of their baseline weight and an increase of the time spent in physical activity to an average of 175 min a week. In the first 6 months, the patients attended to three group sessions and one individual visit. They used two meal replacement products a day, with a 1,200–1,800 kcal/day caloric intake goal. Between months 7–12, patients had a single and a group session per month, using one meal replacement product every day. From years 2–4, participants attended a single visit to the hospital and received a telephone call or an e-mail every month, with regular group sessions to help maintain a 7 % initial weight loss and/or neutralize possible weight regain.

Table 2. Eligibility criteria, population targeted, and inclusion criteria (T2DM and BMI) in the clinical trials Look AHEAD, DPP, LOSS, and TRAMOMTANA

	Ages eligible for study	Ethnically diverse population	Inclusion criteria: T2DM	Inclusion criteria: BMI
Look AHEAD	45–74	Yes	Yes	25 or higher (27 or higher if on insulin)
DPP	25 at least	Yes	No (ADA 1997 criteria) Impaired glucose tolerance (WHO 1985 criteria)	24 or higher (22 or higher in Asians)
LOSS	20–60	Yes	No	40 or higher
TRAMOMTANA	18–65	No	No	40 or higher

These two examples illustrate the wide range of approaches (Table 3) in regard to the number and configuration of individual visits, group sessions, dietary changes, exercise programs as well as patterns in weight loss and weight loss maintenance through these changes in lifestyle. The literature suggests that the current weight loss programs usually achieve a reduction of 7–10 % of the initial body weight [75, 83] after 6–9 months of intervention, and the combination of diet, physical activity, and behavioral changes can obtain even better results if anti-obesity agents are added to the therapy [84].

One of the biggest challenges is to maintain this weight loss over the medium- and long-term periods [77]. It is important to make these changes durable enough to allow a significant improvement in their comorbidities, quality of life [85, 86], and body composition [87].

One of the few clinical trials focused on the treatment of morbid obesity was the Louisiana Obese Subjects Study (LOSS Study) [23] (Table 4). The main objective of the study was to test whether, with brief training, primary care physicians could effectively implement weight loss for individuals with a BMI of 40–60 kg/m^2. In this 2-year randomized, controlled, clinical trial, the recommendations for patients in the Intensive Medical Intervention (IMI) group included a 900 kcal liquid diet for 12 weeks or less, group behavioral counseling, structured diet, and choice of pharmacotherapy (sibutramine hydrochloride, orlistat, or diethylpropion hydrochloride) during months 3–7 and continued use of medications and maintenance strategies for months 8–24.

Ryan et al. [23] obtained data indicating that severely obese patients randomized to an intensive weight loss program in primary care lost a significant amount of weight, compared to those receiving usual care (21 % of patients lost 10 % or more of the initial weight). The authors reported a weight loss of 5 % or higher in 31 % of the analyzed patients and a 10 % weight loss in 21 % of cases, with a significant improvement in many metabolic parameters. These results suggest that, with minimal training, primary care professionals could treat, successfully, a high percentage of morbidly obese patients. However, retention (retention rate in IMI group = 51 %) and weight loss maintenance were two key points to improve, according with the researchers.

In a 1-year non-randomized controlled trial, Johnson et al. [88] compared changes in the dietary patterns of morbidly obese patients undergoing either laparoscopic gastric bypass surgery or a comprehensive lifestyle intervention program. Lifestyle intervention was associated with more favorable dietary 1-year changes than gastric bypass surgery in morbidly obese patients, as measured by intake of vegetables, whole grains, dietary fiber, and saturated fat.

A Spanish randomized clinical trial, performed in Mallorca (multidisciplinary treatment of morbid obesity—TRAMOMTANA) [89, 90], was designed to examine the effects of an Intensive Lifestyle Intervention (ILI) on the therapy of morbid obesity in comparison with a conventional obesity therapy group (COT) and with a third group consisting of patients already included in the bariatric surgery waiting list (SOG). The ILI group received behavioral therapy and nutritional/physical activity counseling. These morbidly obese patients attended weekly group meetings from weeks 1 through to 12 and biweekly from weeks 13 to 52. Meetings included 10–12 subjects, lasted 90 min, and were led by a registered nurse, who mastered in nutrition. The group sessions were focused on the qualitative aspects of the dietary habits, such as the distribution of energy intake, frequency of consumption, and food choices. The research team provided information on the benefits of the Mediterranean diet and encouraged the patients to follow this diet. There were no restrictions in calorie intake. A sport medicine physician prescribed daily home-based exercise (led by a physiotherapist), with gradual progression toward a goal of 175 min of moderate-intensity physical activity per week. Patients could receive treatment with weight loss medicines, such as orlistat or antidepressants at the endocrinologist discretion. Forty percent of the patients included in this group received treatment with sibutramine for a period of 1–2 months until it was withdrawn from the market in January of 2010.

The COT group received the standard medical treatment available for these patients (one visit with the endocrinologist every 6 months). Patients who received ILI achieved a significant weight loss compared with COT group (Fig. 1). The weight loss effect was already obtained after 6 months of ILI intervention. These results seriously question the efficacy of the COT approach to morbid obesity. Furthermore, they underscore the use of ILI programs to effectively treat morbidly obese patients which might help to reduce the number of candidate patients for

TABLE 3. Comparison of different lifestyle interventions: (1) Look AHEAD vs. DPP

	Frequency of sessions/visits	Format	Weight loss goal	Physical activity goal	Special features	Weight loss drugs	Meal replacements
Look AHEAD phase 1.1 (months 1–6)	Weekly	Three groups, one individual	Lose 7 % of initial weight	Exercise #175 min/ week by month 6	Treatment toolbox	No	Two meal replacement products, one portion-controlled snack, and a self-selected meal each day
Look AHEAD phase 1.2 (months 7–12)	Three per month	Two groups, one individual		Increase minutes per week of activity; 10,000 steps/day goal			One meal replacement per day and two meals of self-selected foods are allowed
Look AHEAD phase 2 (months 13–48)	Two per month	One on site, one by mail or telephone Additional: refresher groups are offered three times a year	Continued weight loss or weight maintenance		Advanced treatment toolbox orlistat		One meal replacement per day
Look AHEAD phase 3 (month 49+)	Two per year	On site. Additional phone calls and/or e-mail contacts. Participants may also join refresher groups			Additional support through newsletters, phone, or e-mail contact		
Diabetes Prevention Program (DPP), initial structured core curriculum (months 1–6)	16 in 24 weeks + 4 supervised phisic physical activity. Supervised sessions	Individual and group sessions	Lose 7 % of initial weight	150 min/week	Toolbox: adherence strategies, local and national network of training, feedback, and clinical support	No	Structured meal plans and meal replacement products were provided as an option for participants
Diabetes Prevention Program (DPP), maintenance program (months 7–12)	Face to face at least once every 2 months and by phone at least once between visits				Motivational campaigns Small incentives (T-shirts, magnets, weight graphs. newsletters		

Table 4. Comparison of different lifestyle interventions: (2) LOSS vs. TRAMOMTANA

	Frequency of sessions/ visits	Format	Weight loss goal	Physical activity goal	Special features	Weight loss drugs	Meal replacements
LOSS phase 1 (12 weeks or less)	No	No	Lose 10 % of initial weight	Exercise 150 min/ week	Flexibility		Low-calorie liquid diet (900 kcal/day), 5 shakes per day
LOSS phase 2 (months 3–7)	4 weekly, then every 2 weeks	Group sessions + individual monthly physician visit			Individualized treatment strategies	Sibutramine	Two daily meal replacements
	Monthly physician visit					Orlistat	
LOSS phase 3 (months 8–24)	Monthly	Group sessions			$100 gift card rewarded attendance at month 24	Diethylpropion	One daily meal replacement, low-calorie liquid diet in 4- to 12-week episodes
TRAMOMTANA phase 1 (months 1–3)	Weekly	Four group sessions + 1 individual visit with specialist every 3 months	Lose 10 % of initial weight	Exercise 150 min/ week by month 12	Social toolbox Rockport test Healthy cooking show Small incentives (umbrellas, magnets)	Sibutramine until withdrawal (40 % patients during 1–2 months)	No
TRAMOMTANA phase 2 (months 4–24)	Two per month	Two group sessions + 1 individual visit with specialist every 3 months			Social toolbox Rockport test Workshop: eat slowly and chew	No	

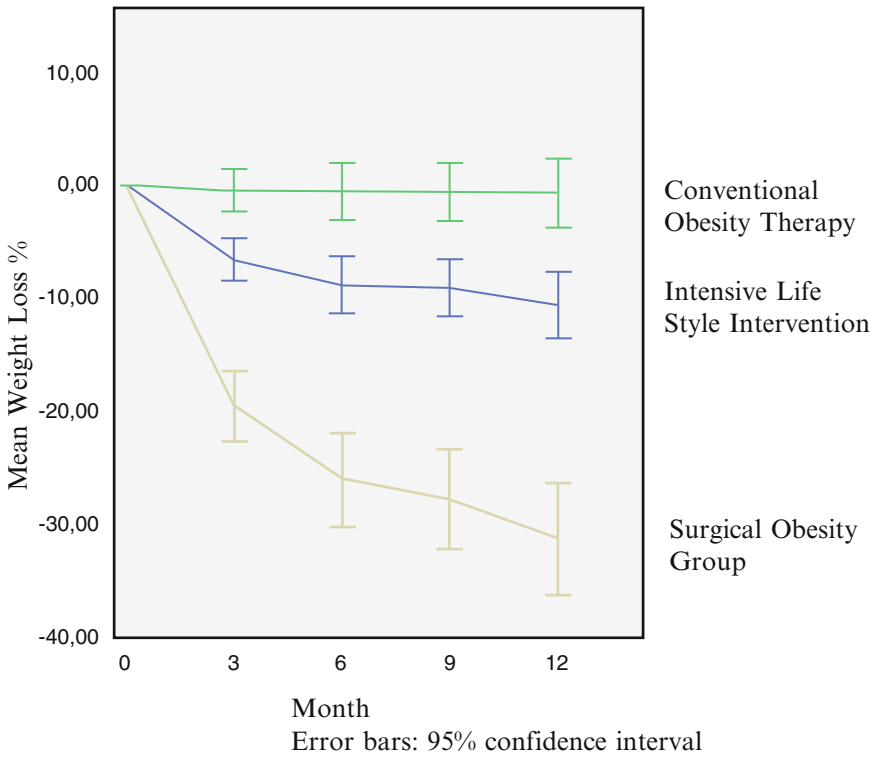

FIG. 1. One-year weight loss in the TRAMOMTANA study.

bariatric surgery, at a lower cost (evaluating medical visits, surgery, sessions, and meds).

Non-pharmacological strategies for weight reduction have reported 10 % losses that have been difficult to maintain [91]. Changes in dietary behavior, the stimulation of physical activity, and emotional support continue to be the mainstays for the management of obesity in adults, children, and adolescents.

Sustained caloric restriction (to 1,500 kcal/day for women and 1,800 for men), regardless of dietary macronutrient composition or regimen [19], has fairly similar effects on weight loss, ranging from 3 to 5 kg over 2 years [20]. The addition of physical exercise facilitates weight loss by increasing energy expenditure and increasing basal metabolic rate through an increase in muscle mass.

Unfortunately, lifestyle interventions alone rarely result in long-term weight loss and the majority of dieters return to baseline weight within 3–5 years. This even holds true for participants in weight loss trials who are offered education and intensive support to help prevent weight regain [21, 22].

The improvements described in morbidly obese patients using behavioral therapy as an element of an intensive lifestyle intervention could benefit a huge number of people: those who will undergo bariatric surgery and those who are not interested in surgery and just need to lose 5–10 % of the bodyweight. These interventions must be provided by multidisciplinary, academic, or clinical groups and can be provided at the hospital or primary care setting, to groups of 10–15 patients with an optimal duration of 20–26 weeks and a follow-up period of monitoring and maintenance (also 20–26 weeks) [57].

Overview of Current Obesity Medications

Lifestyle measures are the cornerstone of prevention and treatment of obesity. However, there is general agreement in the scientific community that the use of anti-obesity drugs should also be considered (after careful considerations of the pros and cons), in patients who did not have an optimal response to lifestyle interventions. Weight loss medications could also be considered in some cases as "jump-start" intervention, acting as coadjutant therapy to lifestyle interventions. In many circumstances adding medications to behavioral interventions helps to accomplish the recommended 10 % weight loss and also reinforces adherence to these lifestyle/behavioral interventions.

FDA guidance for the approval of new weight loss therapies intended for long-term use recommends a 5 % placebo-corrected weight reduction that should be maintained for at least 12 months after treatment initiation. Small, sustained reductions in weight can significantly improve CVR factors, particularly glycemia and BP, in overweight and obese individuals. The target adult population for drug therapy is set at BMI > 30 (or a BMI >27 plus a comorbidity such as HTA or T2DM). This opens up a potentially huge market for the development of new weight loss drugs. Despite the great strides in the understanding of the mechanisms involved in the hypothalamic regulation of appetite and energy balance, we still have a very limited armamentarium of drugs useful for the treatment of obesity.

Table 5. Drugs approved for treatment of obesity

Drug	Mechanism of action	Effect	Daily dosage	Average weight loss (kg)
Phentermine[a] (Adipex)	Augments central NE release	Decreases appetite	5–37.5 mg QD[b]	3.6 kg (12 weeks)
Diethylpropion[a] (Tenuate)	Augments central NE release	Decreases appetite	25 mg TID[c]	10 kg (12 weeks)
Orlistat[d] (Xenical)	Pancreatic and gastric	Decreases fat	120 mg TID	6 kg (1 year)
Orlistat[d,e] (Alli)[b]	Lipase inhibitor	Absorption	60 mg TID	
Lorcaserin (Belviq)	Agonist serotonin receptor 5-HT2C	Decreases appetite	10 mg BID	3.6 kg (1 year)
Phentermine and	Augments central NE and GABA release	7.5 mg/46 mg	8.1 kg (56 weeks)	
Topiramate CR (Qsymia®)	15 mg/92 mg	10.2 kg (56 weeks)		

[a]Approved only for short-term use (a few weeks)
[b]Usually taken mid-morning
[c]Taken 1 h before meals
[d]Taken with fatty meals or up to 1 h later; omit dose if meal is skipped; approved for up to 2 years' use. Diet should contain <30 % fat
[e]Available OTC

Given the previous history of several obesity medications that have been removed from the market due to significant side effects (HTA, depression, cardiac valvular abnormalities) and the current obesity-related health crisis, the need to identify safe and efficacious weight loss drugs is more than evident. Unfortunately, the medications currently available for obesity therapy are limited in number and efficacy (Table 5).

Sympathomimetic Amines

The oldest weight loss drugs still approved by the US FDA as weight loss adjuncts are sympathomimetic (amphetamine-like drugs) such as methamphetamine, phentermine, and diethylpropion. These medications act centrally as adrenergic stimulants, reducing appetite and increasing energy expenditure through generalized sympathetic activation.

Phentermine (Adipex®)

Phentermine (a central norepinephrine-releasing drug) is an approved anti-obesity agent, indicated as an adjunct to appropriate nutrition and physical exercise for short-term (up to 12 weeks) treatment of obesity. In the 1970s, phentermine hydrochloride was developed, with doses ranging from 8 to 37.5 mg [92].

Phentermine remains as the most widely prescribed weight loss drug in the USA. The phentermine hydrochloride salt easily dissociates in the GI tract, resulting in immediate release of the phentermine drug causing a significant appetite suppressant effect. Phentermine is classified by the FDA as a Schedule IV drug. It carries a risk for addiction and/or habituation, though its abuse potential is considered very low [93]. Short-term use of phentermine was associated with a mean weight loss of about 3 kg more than with placebo. No long-term (>1 year) randomized controlled trials of phentermine have been reported. Phentermine was widely used in combination with fenfluramine ("phen-fen"). Unfortunately, dexfenfluramine, a related drug, was found to cause valvular heart abnormalities and primary pulmonary hypertension and was removed from the market in 1997 [94].

Data on adverse events in weight loss trials that used sympathomimetic amines are limited but include increases in HR and BP, dry mouth, nervousness, insomnia, and constipation. Phentermine is contraindicated in patients with CAD, congestive heart failure (CHF), stroke, and uncontrolled HTA. There are no long-term data suggesting that treatment with this agent reduces CVD. Given the fact that phentermine is just approved for short-term use, this medication has very limited use in the management of obesity, as a chronic disease. However, as previously mentioned, it could be a helpful tool to use as a jump start to get patients motivated to participate in a lifestyle intervention program and start making small improvements in their daily habits, which could translate in long-term weight loss.

Diethylpropion (Tenuate®)

Diethylpropion is another amphetamine-like analogue, with fewer stimulant side effects, which has been approved by the US FDA for treatment of obesity since 1959. Diethylpropion is used as part of a short-term plan, along with a low-calorie diet, for weight reduction. Although most studies evaluating the efficacy of diethylpropion for weight loss were short term (less than 20 weeks), obese patients treated with diethylpropion lost an average of 3.0 kg of additional weight compared to placebo [95].

A report evaluated the efficacy of diethylpropion 50 mg BID or placebo for 6 months. After this period, all participants received diethylpropion in an open-label extension for an additional 6 months [96]. The study included 69 obese healthy adults who received a hypocaloric diet. After the initial 6 months, the diethylpropion group lost an average of 9.8 % of initial body weight vs. 3.2 % in the placebo group (Fig. 2). From baseline to month 12, the mean weight loss produced by diethylpropion was 10.6 %. Participants in the

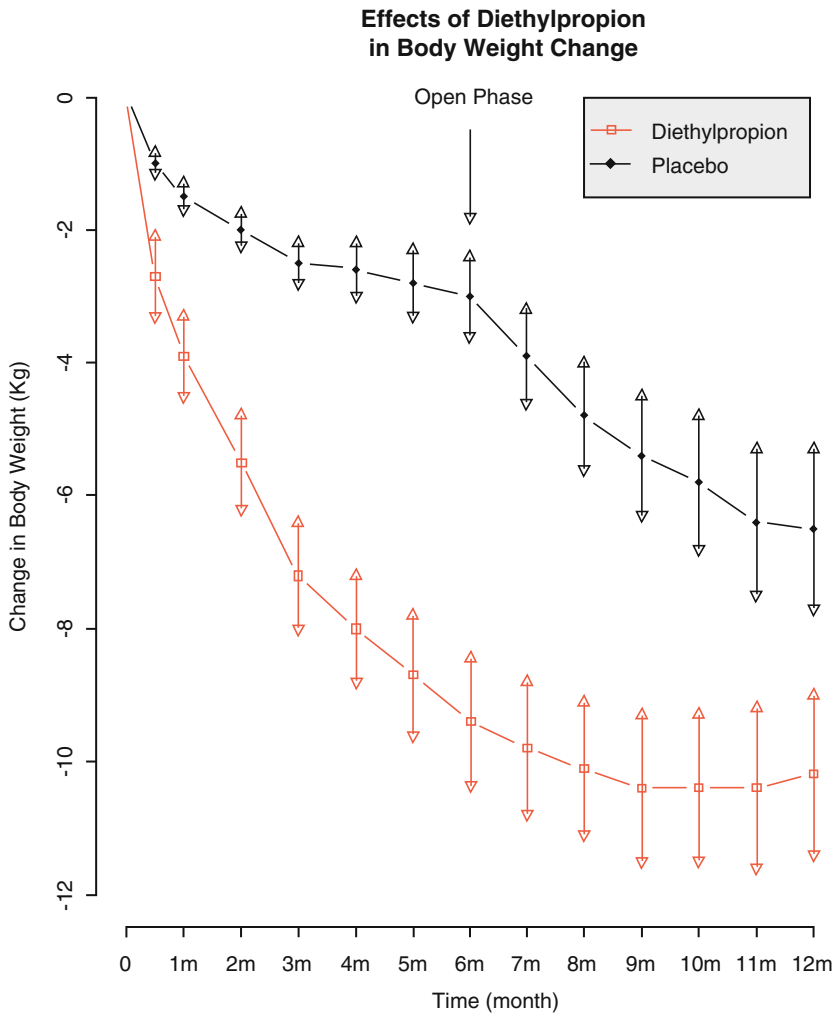

FIG. 2. Effects of diethylpropion in body weight change.

placebo group who were switched to diethylpropion after 6 months lost an average of 7.0 % of their initial body weight. No differences in BP, pulse rate, EKG, and psychiatric evaluation were observed. As with phentermine, common side effects of diethylpropion included insomnia, dry mouth, dizziness, headache, mild increases in BP, and palpitations. Very few studies have evaluated the long-term use of diethylpropion.

Orlistat (Xenical®)

Orlistat is currently the only medication approved by the European Medicine Agency (EMEA) for the treatment of obesity [97]. Xenical acts by inhibiting the intestinal lipase, which translates into a reduction up to 30 % of ingested fat absorption. The recommended dosage is 1 capsule TID with meals. It has a dose-dependent effect: 120 mg decreases up to 30 % fat intake, whereas a dose of 60 mg decreases up to 25 %. In 2007, GlaxoSmithKline, under license from Roche, launched a low dose of orlistat (Alli®) which is not a necessary prescription.

The XENDOS study (XENical in the prevention of Diabetes in Obese Subjects) assessed the effect of the treatment with orlistat in 3,300 obese patients with impaired glucose tolerance [21], a 4-year, prospective, randomized, double-blind, placebo-controlled study; it demonstrated that orlistat (plus lifestyle modification) significantly reduced the incidence of T2DM and improved weight loss, when compared with placebo plus lifestyle changes. Mean weight loss after 4 years was significantly greater with orlistat (5.8 vs. 3.0 kg with placebo). The 3.0 kg weight loss achieved by the placebo plus lifestyle changes group over 4 years was comparable with that in the intensive lifestyle intervention arms of the DPS (3.5 kg) and DPP (3.5 kg). XENDOS was the first study to show that a weight loss agent such as orlistat in combination with lifestyle changes was more powerful than lifestyle changes alone helping patients to obtain long-term weight loss and improvements in their CVR factors. After 4 years' treatment, the cumulative incidence of diabetes was 9.0 % with placebo and 6.2 % with orlistat, corresponding to a risk reduction of 37.3 %. A meta-analysis of studies with orlistat [98] showed a drop of average weight of 2,39 kg.

Other benefits of orlistat include a reduction of LDL cholesterol more than expected by the drop in body weight.

Fat-soluble vitamin supplements should be taken 2 h before or after taking orlistat. The most common adverse effects included flatulence with discharge and fecal urgency, which occurred especially after high-fat dietary indiscretions, and were responsible for a significant rate of drug discontinuation. Serious, but very uncommon (only 12 cases), adverse effects have been reported such as liver damage, which were thought to be cases of individual hypersensitivity. Liver function should be monitored while doing Xenical therapy.

A study [99] warned of a possible link between reported cases of acute renal damage in orlistat users (incidence of 2 %). The authors hypothesized that the nonabsorbed dietary fat binds enteric calcium and reduces their ability to bind and sequestrate oxalate in the intestine that leads to excessive absorption of free oxalate with the consequent deposit in the renal parenchyma.

Xenical continues to be a useful therapy which could help obese patients to modified their dietary habits and lose weight.

Sibutramine (Meridia®, Reductil®)

Sibutramine was approved on November 1997 for weight loss and maintenance of weight loss in obese people, as well as in certain overweight people with other risks for CAD. Sibutramine induces weight loss by selectively inhibiting the neuronal reuptake of serotonin and norepinephrine within the hypothalamus. To a smaller degree, it also inhibits the reuptake of dopamine. Treatment with sibutramine resulted in an increase in satiety and a reduction in appetite [100, 101].

In a meta-analysis of randomized placebo-controlled trials of at least 1 year in duration (10 studies with 2,623 patients), sibutramine reduced body weight 4.3 kg more than placebo [102]. There was also a greater reduction in BMI in the sibutramine group and a 4 cm decrease in waist circumference with sibutramine therapy.

Sibutramine also prevented weight regain when administered after a dietary intervention. In the Sibutramine Trial of Obesity Reduction and Maintenance (STORM) study [103], 605 obese patients were treated with sibutramine (10 mg QD) and followed a low-energy diet for 6 months. Patients achieving >5 % weight loss after 6 months ($n=467$) were randomly allocated to continue sibutramine (10 mg QD uptitrated to 20 mg QD if weight regain occurred, or placebo for 18 months. The sibutramine group had less weight regain than the placebo group. In a subgroup of patients in STORM study, computed tomography showed a preferential reduction in visceral fat.

Sibutramine therapy was associated with an increase in BP and heart rate in some patients. As expected with any therapy for a chronic disease, significant weight regain was frequently observed after sibutramine therapy was discontinued. In the year 2010 both the EMA and FDA requested market withdrawal of sibutramine after reviewing data from the Sibutramine Cardiovascular Outcomes Trial (SCOUT) [104]. SCOUT was part of a post market requirement to look at cardiovascular safety of sibutramine after the European approval of the drug. It is important to emphasize that in this study patients participated for over 55 years with high CVR and that, in the vast majority of cases, they did not correspond with the type of patients for which this drug was originally approved for. After 6 years of treatment, the individuals who took sibutramine showed an increased risk of serious heart events, including nonfatal heart attack, nonfatal stroke, and death of 11.4 %, compared to 10.0 % in a placebo control group.

The results of the SCOUT were not surprising, if we take into account that most of the patients included in the SCOUT did not meet criteria for treatment with sibutramine. The odds were against sibutramine, because CVR is embedded in its mechanism of action and the study sample consisted of older obese patients, deliberately selected for high CVR, and exposed to sibutramine for 5 years (five times the maximum licensed duration of treatment) [105]. A large number of investigators and Scientific Societies felt that the SCOUT study was flawed as it only covered high-risk patients and did not consider obese patients who did not have cardiovascular complications or similar contraindications, especially considering that those were the patients who could really benefit from this medication.

Recently Approved Drugs for the Treatment of Obesity

Lorcaserin (Belviq®)

Lorcaserin is a new agonist of the 5-hydroxytryptamine (5-HT, or serotonin) receptor 5-HT2C. It binds selectively to the central 5-HT2C receptors, with poor affinity for 5-HT2A and 5-HT2B, respectively. Nonselective serotonergic agents, including fenfluramine and dexfenfluramine, were withdrawn from the market in 1997, after they were reported to be associated with valvular heart abnormalities [106]. Due to its selective agonist effect on 5-HT2C receptors, lorcaserin theoretically should not have similar cardiac adverse effects as fenfluramine.

Lorcaserin was approved by the FDA in June 2012, and it marked the end of a long era without any new drugs to treat obesity. The indication for lorcaserin is an addition to a reduced-calorie diet and exercise for patients who are obese or overweight with at least one medical comorbidity, such as T2DM, HTA, high cholesterol, or OSA. The mechanism by which lorcaserin results in weight loss appears to be by reducing appetite, which in turn reduces total energy intake. Three important phase 3 randomized clinical trials have eval-

uated the efficacy of lorcaserin helping obese patients to lose weight [107].

The BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) was a 104-week, clinical trial to assess the safety and efficacy of lorcaserin in obese patients. The primary outcome measure at year 1 was the proportion of patients achieving >5 % weight loss from baseline. At year 2 the primary outcome measure was the proportion of patients maintaining >5 % weight loss at week 104. In this study 3,182 obese adults (BMI >36 kg/m^2) were randomly assigned to lorcaserin (10 mg) or placebo BID for 1 year, followed by a 1-year extension period. All subjects participated in a behavioral modification program which included dietary and physical activity counseling. Obese patients treated with lorcaserin lost 3.6 kg more than controls at the end of the first year. Approximately 50 % of participants remained in the trial during year 2. Additionally, the weight reduction was maintained in more patients who continued to receive lorcaserin during the second year (68 %) than in patients who received a placebo (50.3 %) [108].

A second phase 3 Lorcaserin clinical trial was the BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management) [109]. In this 52-week clinical trial, 4,008 patients were treated with lorcaserin 10 mg QD or BID compared to placebo. The study was designed to assess the efficacy and safety of a dose range of lorcaserin when administered in conjunction with a nutritional and physical exercise program to promote weight loss, in obese patients and at-risk overweight patients. The primary outcome measure was again the proportion of patients achieving >5 % weight loss from baseline to week 52. Significantly more patients treated with lorcaserin 10 mg BID and QD lost at least 5 % of baseline body weight (47.2 % and 40.2 %, respectively) as compared with placebo (25.0 %). Weight loss of at least 10 % was achieved by 22.6 and 17.4 % of patients receiving lorcaserin 10 mg BID and QD, respectively, and 9.7 % of patients in the placebo group. Thus, the weight losses seen with lorcaserin were slightly greater than that seen in the orlistat studies, which provided 2–3 kg of placebo-subtracted weight loss. Headache, nausea, and dizziness were the most common lorcaserin-related adverse events.

A third lorcaserin trial BLOOM-DM (Behavioral Modification and lorcaserin for Overweight and Obesity Management in Diabetes Mellitus) [110] was carried out in 604 T2DM obese and overweight patients. The BLOOM-DM's purpose was to assess the weight loss effect of lorcaserin during and at the end of 1 year of treatment in patients treated with metformin, sulfonylurea (SFU), or either agent in combination with other oral hypoglycemic agents. Patients were randomized to lorcaserin 10 mg BID ($n=256$), lorcaserin 10 mg dosed QD ($n=95$), or placebo ($n=253$). Lorcaserin 10 mg BID met the three primary efficacy endpoints by producing statistically significant weight loss compared to placebo. At week 52, the data showed that weight loss was 4.5 % of total body weight with lorcaserin BID and 5 % with lorcaserin QD vs. 1.5 % with placebo. Also 37.5 % of patients treated with lorcaserin 10 mg twice daily achieved at least 5 % weight loss, more than double the 16.1 % of patients taking a placebo. Additionally, 16.3 % of lorcaserin 10 mg BID patients achieved at least 10 % weight loss compared to 4.4 % of patients taking a placebo. HgA1C decreased by 0.9 % with lorcaserin BID, 1.0 % with lorcaserin QD, and 0.4 % with placebo. Symptomatic hypoglycemia occurred in 7.4 % of patients on lorcaserin BID, 10.5 % on lorcaserin QD, and 6.3 % on placebo.

Lorcaserin produced side effects in human clinical trials, but at rates not significantly different than placebo and mostly with mild and transient severity. The most common side effect was headache, experienced by about 18 % of drug arm participants compared to 11 % of placebo participants. Other reported side effects and their rates for lorcaserin and placebo patients, respectively, were as follows: upper respiratory tract infection (14.8 % vs. 11.9 %), nasopharyngitis (13.4 % vs. 12.0 %), sinusitis (7.2 % vs. 8.2 %), and nausea (7.5 % vs. 5.4 %). Lorcaserin has been associated with perceptual disturbances, and because lorcaserin has the potential to bind 5-HT2A receptors, it has been evaluated and found to have low abuse potential. Adverse events of depression, anxiety and suicidal ideation were infrequent and were reported at a similar rate in each treatment group. In agreement with the FDA, Arena conducted regular echocardiograms of the phase III participants. At the 3-, 6-, and 12-month intervals, the echocardiograms of participants of the BLOOM trial did not show any significant increase in valvulopathy over baseline.

Thus, lorcaserin is a new therapeutic tool to treat obesity and is a well-needed addition to an area where therapeutic agents are sparse. Lorcaserin has also been shown to improve glycemic control and it has modestly beneficial effects on lipids and BP as well. This data justifies the proposed indications for the use of lorcaserin as an adjunct to diet and physical activity for weight management, including weight loss and maintenance of weight loss in obese patients and overweight patients with at least 1 weight-related comorbidity.

Phentermine and Topiramate Controlled Release (Qsymia®)

The scientific literature and clinical experience tell us that anti-obesity drugs that specifically target just one area within the brain may have a limited effect inducing weight loss in obese patients; consequently the idea of targeting more than one circuit in the regulatory pathways of energy balance has become a popular and potentially efficient strategy to treat patients with obesity.

The FDA recently approved a combination of low doses of controlled-release (CR) phentermine and the anticonvulsant agent topiramate (in one capsule) for adults with a BMI ≥30 kg/m^2 or with a BMI ≥27 kg/m^2 and at least one weight-related comorbidity such as HTA, T2DM, and dyslipidemia

(July 2012). Several trials had evaluated the efficacy of this combination inducing weight loss in obese patients [111–115].

In the CONQUER clinical trial [111], 2,487 overweight and obese patients with HTA, high cholesterol or T2DM participated. Patients received a combination of phentermine-topiramate CR (7.5/46 or 15/92 mg) compared with placebo over 56 weeks [49]. At 56 weeks, change in body weight was −1.4, −8.1, and −10.2 kg in the patients assigned to placebo, phentermine-topiramate 7.5/46 mg, and phentermine-topiramate CR 15/92 mg, respectively. 21 % of the patients achieved at least 5 % weight loss with placebo, 62 % with phentermine-topiramate CR 7.5/46 mg, and 70 % with phentermine-topiramate CR 15/92 mg; for ≥10 % weight loss, the corresponding numbers were 7, 37, and 48 %.

In an extension of the CONQUER (the SEQUEL study) [112], investigators addressed the longer-term efficacy and safety of lifestyle intervention and two doses of phentermine-topiramate CR for an additional 52 weeks (total treatment duration of 108 weeks) in overweight and obese subjects with cardiometabolic disease. Overall, 84 % of subjects completed the study, with similar completion rates between treatment groups. At week 108, phentermine and topiramate CR was associated with significant, sustained weight loss compared with placebo. Mean percentage changes from baseline in body weight were −1.8, −9.3, and −10.5 % for placebo, 7.5/46, and 15/92, respectively. Phentermine-topiramate CR improved cardiovascular and metabolic variables and decreased rates of incident T2DM in comparison with placebo. Phentermine-topiramate CR was well tolerated over 108 weeks. Of note, phentermine-topiramate CR was less effective causing weight loss in the second year of use, although most individuals were able to maintain the weight they lost achieved in year 1.

In a third clinical trial (EQUIP) [113], 1,267 morbidly obese patients (BMI >35 kg/m^2) were included into three arms: placebo, phentermine-topiramate CR 3.75/23 mg, and phentermine-topiramate CR 15/92 mg with a total treatment duration of 56 weeks. Both doses of phentermine-topiramate CR yielded significantly greater 1-year weight loss compared with placebo, with a greater proportion of patients losing more than 5, 10, or 15 % of baseline body weight. Patients treated with phentermine-topiramate CR 15/92 and 3.75/23 lost 10.9 % and 5.1 % of body weight, respectively, when analyzed as ITT-LOCF, compared with 1.6 % weight loss on placebo and 14.4 and 6.7 % weight loss in completers-only analyses compared with 2.1 % weight loss with placebo. Of importance was that weight loss induced by phentermine-topiramate CR was accompanied by improvements in several cardiovascular and metabolic risk factors, such as waist circumference, systolic BP, and total cholesterol/HDL cholesterol ratio in both doses. As previously shown Phentermine-topiramate CR 15/92 treatment was also associated with significant improvements in diastolic BP, fasting glucose, LDL cholesterol, HDL cholesterol, and total cholesterol.

The most common adverse events were dry mouth (2, 13, and 21 %) in the groups assigned to placebo, phentermine-topiramate CR 7.5/46 mg, and phentermine-topiramate CR 15/92 mg, respectively, paraesthesia (2 %, 14 %, and 21 %, respectively) and constipation (6 %, 15 %, and 17 %, respectively) none of these events caused study discontinuation in more than 1 % of patients [116]. There was a dose-related increase in the incidence of psychiatric (e.g., depression, anxiety) and cognitive (e.g., disturbance in attention) adverse events in the active treatment group. Although BP improved slightly with active therapy, there was an increase in heart rate (0.6–1.6 beats/min) compared with placebo.

The FDA does not recommend the use of this drug combination in patients with recent stroke, unstable heart disease, HTA or CAD, glaucoma, hyperthyroidism or in patients who have taken monoamine oxidase inhibitors within 14 days. Women of child-bearing age should have a pregnancy test before starting this therapy and monthly thereafter. Because topiramate can produce renal stones, this combination preparation should be used cautiously in patients with a history of kidney stones.

A recommendation for the use of phentermine-topiramate CR was recently presented [115]. This algorithm titrates the dose starting with a phase-in dose of phentermine-topiramate CR 3.75/23 mg QD for 2 weeks. The dose then is increased to a half dose of 7.5/46 mg QD for 12 weeks. Patients are evaluated at that point for weight loss, and "responders" (patients with weight loss >3 %) are maintained on that dose. "Nonresponders" (those with weight loss <3 %) are either discontinued or receive increased doses. Those receiving increased doses are stepped up to an intermediate dose of 11.25/69 mg QD for 2 weeks, then the treatment is increased to a final full dose of 15/92 mg QD for 12 weeks. At the end of the full-dose period, responders with weight loss of 5 % or more are maintained on their doses. If an individual does not lose 5 % of body weight after 12 weeks on the highest dose, phentermine-topiramate CR should be discontinued gradually, as abrupt withdrawal of topiramate could cause seizures.

Phentermine-topiramate CR may be considered for obese postmenopausal women and men without CVD, particularly those who do not tolerate orlistat or lorcaserin [116]. The possibility of adding this combination therapy to orlistat should also be considered. Clinicians who prescribe and pharmacists who dispense the drug must be enrolled in a Risk Evaluation and Mitigation Strategy, which includes a medication guide, a patient brochure, and a formal training program for prescribers, detailing safety information [114].

In Europe, the combination of phentermine-topiramate CR has not been approved yet. The EMA's Committee for Medicinal Products for Human Use first rejected the product in October of 2012. In February of 2013 the EMA refused again to grant approval for this drug combination in the European Union.

TABLE 6. Effect of GLP-1 analogues on body weight compared to other T2DM therapies

Drug	Mechanism of action/effect	Daily dosage	Average weight change (kg)
Liraglutide (Victoza)	GLP-1 receptor agonist. Decreases appetite	1.8 mg (3 mg)	−4.8 to −7.2 kg (dose dependent; 20 weeks)
Exenatide (Byetta)	GLP-1 receptor agonist. Decreases appetite	5–10 μg	−2.8 to −4.4 kg (dose dependent, 30–82 weeks)
Exenatide ER (Bydureon)	GLP-1 receptor agonist. Decreases appetite	0.8–2 mg	−2.8 to −4.0 kg (dose dependent, 15–30 weeks)
Metformin (Glucophage)	Increases FA oxidation Decreases glucose absorption	2,000 mg	1–2 kg
DpP-4 inhibitors	(sitagliptin) Increase incretin (GLP-1 and GIP) levels (Vildagliptin, Saxagliptin, Linagliptin, Alogliptin)	VBF[a]	Weight neutral
Alpha-glucosidase	(acarbose, miglitol) Inhibit the breakdown and inhibitors	25, 50, 100 mg	Weight neutral
	Absorption of carbohydrates in the GI tract		
Sulfonylurea	Stimulate insulin secretion	VBF[a]	+ 1 to +5 kg
Non-sulfonylurea	(meglitinides) Stimulate insulin secretion	0.5–1–2 mg	+0.7 to +2.4 kg
	Secretagogues		
Thiazolidinediones	Enhancing of muscle/adipose tissue insulin sensitivity	15–30–45 mg	+ 1 to +5 kg
Insulin	Glucose uptake. Decreases appetite by inhibiting NPY/AgRP-secreting neurons	VBF[a]	+ 1 to +5 kg

[a]Varies by formulation (VBF)

Incretins as Potential Anti-obesity Drugs: GLP-1 Analogues

Glucagon-like peptide 1 (GLP-1) is an incretin hormone secreted from the L-cells in the lower gut in response to meal ingestion, which stimulates endogenous insulin secretion in a glucose-dependent manner. GLP-1 reduces appetite in lean and normal-weight individuals, as well as in obese individuals [117], and it has been shown to reduce body weight in overweight individuals with T2DM [118, 119] (Table 6). The underlying mechanism mediating the weight reducing effects of GLP-1 is most likely a combination of effects on the gastrointestinal tract and the central nervous system. GLP-1 also decreases blood glucagon levels and has been shown to promote B-cell growth and proliferation in animal models [120].

The combination of these mechanisms makes GLP-1 receptor stimulation, an interesting target to investigate for obesity therapy. However, a major drawback with endogenous GLP-1 with regard to administration as medical treatment is the short elimination half-life of <1.5 min after IV administration, due to rapid degradation by dipeptidyl peptidase (DPP-4) present on the capillary endothelium [121]. Hence, GLP-1 treatment has limited clinical value, and alternative therapeutic strategies have already been developed. A successful approach that has been employed to prolong the in vivo half-life of GLP-1 is to protect the peptide from cleavage by DPP-4 by exchanging amino acids at the second and third N-terminal positions of the peptide; cleavage by this enzyme is reduced [122].

Liraglutide (Victoza®)

Liraglutide is a long-acting GLP-1 analogue, with a 97 % structural homology to human GLP-1 and recently approved for the treatment of T2DM in the USA, EU, Japan, and other countries worldwide under the brand name Victoza® (Novo Nordisk) (1.2 or 1.8 mg QD) [123, 124]. Because GLP-1 decreases appetite and causes a dose-dependent weight loss in obese individuals [125], it could be an attractive treatment option for both T2DM and obesity. To explore the mechanism behind the observed weight loss with liraglutide, the effect of this drug on various body weight-related parameters known to be affected by native GLP-1 has been investigated. Results from various trials have shown that liraglutide 1.8 mg seems to exert a mild suppression of hunger ratings and increase postprandial fullness, as indicated by appetite rating endpoints [126].

More than 50 clinical trials with liraglutide have been completed (with doses up to 3.0 mg). Out of 10,000 subjects included, more than 7,000 subjects were exposed to liraglutide. A total of 986 obese subjects without T2DM (<9 % of all subjects) have been included to date in the obesity clinical development program for liraglutide. The first of three confirmatory phase 3 trials within the liraglutide obesity development program (NN8022-1923, o SCALE-Maintenance) was recently completed. Reporting is ongoing. The trial was a 56-week randomized, double-blind, placebo-controlled trial investigating treatment of liraglutide 3.0 mg vs. placebo as an adjunct to diet and exercise in overweight/obese subjects with comorbidities who had already lost at least 5 % of their body weight during a 4- to 12-week run-in period on a low-calorie diet. The mean weight loss for subjects in the run-in period was approximately 6 kg. From a body weight of approximately 100 kg at randomization, treatment with liraglutide for 56 weeks provided an additional estimated mean weight loss of 5.7 kg, compared to weight neutrality or maintenance in the placebo group (+0.16 kg vs. baseline). Treatment with liraglutide maintained and in some instances further improved beneficial effects on markers of glycemic control and CVR.

An important study including obese patient (BMI 30–40 kg/m^2) without T2DM was conducted by Astrup et al. [125]. This placebo-controlled 20-week clinical trial included 564 obese individuals. They used one of four liraglutide doses (1.2, 1.8, 2.4, or 3.0 mg) compared to placebo-administered QD s.c. or to orlistat (120 mg) p.o. TID. Weight change analyzed by intention to treat was the primary endpoint. An 84-week open-label extension followed. Patients on liraglutide lost significantly more weight than did those on placebo or orlistat. Mean weight loss with liraglutide 1.2–3.0 mg was 4.8, 5.5, 6.3 g, and 7.2 kg compared with 2.8 kg with placebo and 4.1 kg with orlistat [127].

Treatment with liraglutide was generally well tolerated, with high completion rates in groups (75 % in liraglutide group, 70 % in placebo group). Serious adverse events were relatively uncommon, but were more frequent in liraglutide-treated subjects (4.2 %) compared to placebo (2.4 %). There were no events of pancreatitis or medullary thyroid cancer, and no treatment-related increases in blood calcitonin levels. The most commonly reported adverse events were from the gastrointestinal system, with nausea reported by 47 % of subjects in the liraglutide group compared to 17 % in the placebo groups and vomiting by 17 % vs. 2 %, respectively. It will be important to see the results from the studies currently conducted evaluating the efficacy and safety of liraglutide for the treatment of obesity and its impact on CVD disease.

Exenatide (Synthetic Exendin-4) (Byetta®)

Exenatide, an exendin-based GLP-1 receptor agonist, is a synthetic 39-amino acid peptide which was discovered in a search for biologically active peptides in venom from the Gila monster (Heloderma suspectum). It is currently available in the USA and EU (Eli Lilly). This reptilian protein shares 53 % amino acid homology to human GLP-1 [128] and is resistant to DPP4-mediated degradation.

Exenatide 5 or 10 μg administered twice daily s.c. was associated with a dose-dependent mean weight loss of up to 2.8 kg at 30 weeks, which increased to 4.4 kg at week 82 in an open-label trial extension [127, 129, 130]. Weight reductions were greatest in persons with the highest baseline BMI and in those taking metformin, with lesser reductions occurring in those patients taking an SU or a combination of metformin and SU.

At a dose of 10 μg BID, exenatide reduced HbA1c concentrations by 0.8–1.5 % [128–130]. In particular, exenatide lowered postprandial glucose levels after breakfast and dinner to a much greater degree than after lunch. A pooled analysis of three trials of adjunctive treatment with exenatide 5 or 10 μg BID showed a mean decrease in SBP and DBP of 2.6 and 1.9 mmHg, respectively, at week 104, suggesting sustained improvement in BP. Changes in lipid parameters at 82 weeks included decreased triglyceride (−38.6 mg/dL), LDLC (−1.6 mg/dL), and apolipoprotein B (−1.1 mg/dL) levels and an increase in HDL-C (+4.6 mg/dL). The most frequently reported adverse effects of exenatide were nausea and vomiting, which occurred in 40–60 % and ≤10 % of patients, respectively. Antibodies against exenatide were detected in 40–60 % of patients treated with the drug [128–130]. The clinical relevance of these antibodies cannot be known with certainty, but in the majority of patients, their presence does not seem to impair the efficacy of exenatide. Several additional GLP-1 agonists, including lixisenatide, albiglutide, and taspoglutide, are in various stages of clinical trials and have been modified to increase their half-lives.

Exenatide Long-Acting Release (Bydureon®)

The long-acting formulation exenatide LAR was developed to maintain a constant plasma level of the drug with once-weekly (QW) administration. Exenatide is incorporated into a matrix of poly(d,l-lactide-*co*-glycolide) (PLG), which previously has been used as a biomaterial in sutures and in extended release preparations. Once injected subcutaneously the compound breaks down over time and allows a controlled rate of drug delivery resulting in the longer duration of exenatide release [131]. Once released, exenatide is eliminated via the kidneys. Exenatide LAR exhibits a median half-life of 2 weeks and reaches steady-state plasma concentrations in approximately 6–10 weeks. Absorption is similar when given subcutaneously in the abdomen, thigh, or upper arm. When exenatide LAR 2 mg was given once weekly by injection, the concentration reached 50 pg/mL by end of week 2. This level has been associated with reduced fasting and postprandial plasma glucose in previous studies using continuous infusion of exenatide. Exenatide LAR was approved for marketing in the USA in 2011 and in Europe in 2013.

A small randomized, placebo-controlled, double-blinded phase 2 study compared exenatide LAR (0.8 or 2 mg) administered subcutaneously QW [132] in patients with T2DM during 15 weeks. From baseline to week 15, exenatide LAR reduced mean HbA_{1c} by −1.4 % (0.8 mg) and −1.7 % (2 mg) compared to +0.4 % with placebo. In the exenatide LAR 2 mg treatment arm, body weight reductions of 3.8 kg were seen, while no change was noted in either the 0.8 mg exenatide LAR and placebo arms. All results were clinically significant. No participants receiving exenatide withdrew from the study; adverse events reported included mild to moderate nausea, gastroenteritis, and hypoglycemia.

Several clinical trials including the DURATION Program (*D*iabetes therapy *U*tilization: *R*esearching changes in Hb*A*1c, weight and other factors *T*hough *I*ntervention with exenatide *ON*ce weekly) have evaluated the efficacy of exenatide LAR, compared to placebo and other antidiabetic drugs to improve body weight and metabolic parameters [133–136].

The clinical trial DURATION-1 studied the effect of exenatide QW in a head to head comparison against BID exenatide, over 30 weeks, in 295 patients with T2DM.

Treatment with exenatide LAR resulted in significantly greater improvements in HgA1C compared to exenatide BID (HgA1C changed from baseline, −1.9 %±0.08 vs. 1.5 %±.0.08). The weight loss did not differ between the two groups by 30 weeks (−3.7 kg for QW vs. −3.6 kg for BID), and about 75 % of the patients lost weight. Both treatments were associated with reduction in triglycerides and blood pressure. As previously seen, nausea was predominantly mild and transient and occurred less frequently with exenatide LAR. The size of the needle required for subcutaneous injection of exenatide LAR is bigger than that required for administration of exenatide (23 gauge [0.64 mm] vs. 29–32 gauge [0.24–0.34 mm]). Injection site reactions, such as erythema, nodules, or pruritus, are more common with exenatide LAR and have been reported in 10–15 % of patients [133]. By contrast, injection site reactions have been found in less than 2 % of patients treated with exenatide. The DURATION-1 study illustrates that exenatide QW is more effective in reducing HbA1c and fasting plasma glucose than BID, while the reduction in weight did not differ.

Most patients with T2DM often begin pharmacotherapy with metformin but eventually need additional treatment. In DURATION-2, exenatide QW (2 mg) was compared with pioglitazone (45 mg) and sitagliptin (100 mg) to assess the potential differences between these antidiabetic drugs as add-on therapy to metformin during a period of 26 weeks. In this study exenatide LAR produced superior HbA1c reduction (1.5 %) and weight loss (2.3 kg) compared to results obtained with sitagliptin (−0.9 % HgA1C, −1.5 kg weight loss) or pioglitazone (−1.2 % HgA1C, +2.8 kg weight gain) in a head to head study of patients with T2DM not achieving adequate glycemic control (starting HgA1C of 8.5 %) on metformin therapy [134]. The reduction in SBP was significantly greater with exenatide (−4 mmHg) compared with sitagliptin, but not pioglitazone. About 24 and 10 % registered nausea with exenatide and sitagliptin, while diarrhea was observed in 18 % and 10 %, respectively. Fewer patients withdrew from treatment with sitagliptin (13 %) than with exenatide (21 %) or pioglitazone (21 %). No major hypoglycemia occurred in any group.

In the open-label DURATION-3 trial [135], exenatide QW (2 mg) was compared with insulin glargine QD. Exenatide QW treatment resulted in greater HbA1c reduction (−1.5 %) after 26 weeks than insulin glargine (−1.3 %). Insulin glargine produced greater reduction in fasting glucose than did exenatide, while significantly greater reductions in postprandial glucose excursions were obtained with exenatide LAR.

Mean weight changes were −2.6 kg in the exenatide group and +1.4 kg in the insulin glargine-treated patients. Mean heart rate at week 26 was raised compared with baseline in the exenatide but not in the insulin glargine group. No other CVR factors including lipid concentrations differed between the groups. Risk of hypoglycemia was reduced with exenatide. One patient taking exenatide developed pancreatitis. The number of patients who discontinued treatment because of adverse effects was 5 % (exenatide group) vs. 1 % (insulin glargine group). More patients discontinued exenatide QW than insulin glargine due to nausea and inject reactions.

The DURATION-4 study [136] assessed the relative efficacy of exenatide LAR head to head with metformin (2.5 g QD), pioglitazone (45 mg QD), or sitagliptin (100 mg QD). After 26 weeks of treatment, exenatide LAR produced an average weight loss of 2 kg, which was statistically significantly greater than the average 0.8 kg that patients lost with sitagliptin and the average 1.5 kg patients gained with Actos. Patients receiving metformin experienced an average weight loss of 2 kg. Patients randomized to exenatide LAR experienced a reduction in HgA1C of 1.5 % from baseline, which was significantly greater than the reduction of 1.2 % for sitagliptin in drug-naive subjects with T2DM. The most frequently reported adverse events among exenatide LAR users were nausea (11.3 %) and diarrhea (10.9 %) [136].

A recent article by Visboll et al. [137] presented a systematic review with meta-analyses of all randomized controlled trials of adult participants with a BMI of 25 or higher, with or without T2DM, and who received exenatide BID, exenatide QW, or liraglutide QD at clinically relevant doses for at least 20 weeks. They showed that GLP-1R agonist groups achieved a greater weight loss than control groups (weighted mean difference −2.9 kg). They recorded weight loss in the GLP-1R agonist groups for patients without T2DM (−3.2 kg) as well as patients with T2DM (−2.8 kg). In the overall analysis, GLP-1R agonists had beneficial effects on systolic and diastolic BP, plasma concentrations of cholesterol, and glycemic control. GLP-1R agonists were associated with nausea, diarrhea, and vomiting, but not with hypoglycemia.

Anti-obesity Medications in the Late Phase of Development

Naltrexone-Bupropion Extended Release (Tentatively Named Contrave)

This combination of naltrexone-bupropion extended release (SR) is not yet approved for marketing in the USA. Naltrexone is an opioid receptor antagonist that is approved for the treatment of alcohol and opioid dependence [138]. Bupropion is a dopamine and norepinephrine reuptake inhibitor that was first approved for the treatment of depression [139] and later for smoking cessation [140].

The safety and efficacy of this combination were studied by the Contrave Obesity Research (COR) program which consists of four randomized, double-blind, placebo-controlled, phase III clinical studies of 56-week duration (COR-I [141], COR-II [142], COR-BMOD (COR-Behavior MODification) [143], and COR-Diabetes), assessing the efficacy, safety, and tolerability of naltrexone SR-bupropion SR combination therapy in obese patients with or without T2DM.

In *COR-I trial* 1,742 obese patients were randomly assigned in a 1:1:1 ratio to a fixed oral (p.o.) of naltrexone-bupropion 32/360 mg SR (8 + 90 mg in each tablet, two tablets taken BID), naltrexone-bupropion 16/360 mg SR (4 + 90 mg in each tablet, two tablets taken BID), or matching placebo for 56 weeks [141]. Weight loss was significantly greater in the combination treatment groups compared with placebo. In the study population that completed 56 weeks of treatment, weight loss was −8.1 %, −6.7 %, and −1.8 % in the naltrexone-bupropion 32/360 SR, naltrexone-bupropion 16/360 SR, and placebo groups, respectively. Waist circumference, TG, CRP, and HOMA-IR were significantly reduced, and HDL-C levels were significantly increased in the combination treatment groups compared with placebo. COR-I investigators also reported greater improvements in the quality of life, eating behavior, and food craving in participants on naltrexone-bupropion SR compared with placebo.

The percentage of participants achieving weight loss of ≥10 % in the COR-II trial was also significantly higher in the naltrexone-bupropion 32/360 mg SR group compared with the placebo group (32.9 % vs. 5.7 %, respectively) as was the proportion of those achieving weight loss of ≥15 % (15.7% vs. 2.4 % in the naltrexone-bupropion 32/360 mg SR group vs. placebo. The most frequently reported side effects were nausea, constipation, and headache.

In the COR-BMOD trial, 793 obese patients were randomly assigned in a 3:1 ratio to a fixed p.o. dose of naltrexone-bupropion 32/360 mg SR or placebo. All participants were on an energy-reduced diet and attended group behavioral modification sessions. At week 56 a significantly greater weight loss was observed in the naltrexone-bupropion SR group compared with placebo (−11.5 % vs. −7.3 %, respectively). Participants in both groups attended a similar number of BMOD sessions; the more sessions attended, the higher the percentage of weight reduction. The data showed that reductions in mean SBP and DBP were greater in the placebo group compared with the combination treatment group. Pulse rate was slightly increased in patients treated with naltrexone-bupropion SR, whereas it remained unchanged in the placebo group. This finding suggests that naltrexone-bupropion SR may attenuate the favorable effects of weight loss on BP. The smaller reduction in BP (as well as the small increase in pulse) in the naltrexone-bupropion SR group is consistent with the pharmacological properties of bupropion [144]. As previously shown, quality of life, as assessed by the IWQOL-Lite total score and subscales, was improved significantly more in the naltrexone-bupropion SR group compared with placebo.

Significantly more participants in the combination treatment group reported adverse events compared with placebo (nausea, 34.1 % vs. 10.5 %; constipation, 24.1 % vs. 14 %; dizziness, 14.6 % vs. 4.5 %; dry mouth, 8 % vs. 3 %; tremor, 5.8 % vs. 1 %; upper abdominal pain, 5.5 % vs. 1.5 %; and tinnitus, 5.3 % vs. 0.5 %, respectively) [143]. These adverse events were mostly mild to moderate in severity and occurred during the first weeks of the study. There were two serious cases of cholecystitis (followed by successful surgery) in patients on naltrexone-bupropion SR who had achieved weight loss >15 kg.

In the COR-Diabetes trial, 505 overweight or obese T2DM patients with a mean HbA1c = 8.0 % and on several oral hypoglycemic drugs were randomized in a 2:1 ratio to either naltrexone-bupropion 32/360 mg SR or placebo [145]. More patients on combination treatment lost >5 % of their initial weight compared with the placebo group (44.5 % vs. 18.9 %, respectively). Furthermore, reductions in mean HbA1c values were greater in the naltrexone-bupropion SR group compared with placebo (−0.6 % vs. −0.1 %, respectively), leading to a higher proportion of T2DM patients achieving HbA1c target levels of <7 % in the combination treatment group compared with placebo (44 % vs. 26 %, respectively).

Diabetic patients on naltrexone-bupropion SR showed significantly greater improvements in various cardiometabolic risk factors compared with placebo (waist circumference, −5 vs. 2.9 cm; TG, −11.2 % vs. −0.8 %; HDL-C, −3 % vs. −0.3 %). Mean reductions in LDL-C, fasting glucose, insulin, HOMA IR, and CRP levels were also greater in the combination group compared with placebo, although they did not reach significance. As previously shown the most frequently reported adverse events were nausea, vomiting, constipation, and dizziness. Discontinuation usually occurred due to nausea.

Even though the mechanisms by which the naltrexone-bupropion induces weight loss are not entirely understood, this combination deserves further evaluation because it can be an important new tool in the therapy of obesity. The combination of bupropion and naltrexone was favorably reviewed by an FDA Advisory Panel in 2012. The FDA has required a pre-marketing study of the combination drug with assessment of cardiovascular outcomes. There will be an interim analysis of the trial and the FDA may allow the marketing of the combination as Contrave as early as 2014, provided the cardiovascular outcomes are acceptable [146].

Cetilistat

Cetilistat (Norgine, Amsterdam, the Netherlands) is a lipase inhibitor and, while similar to the currently FDA-approved Roche's anti-obesity drug orlistat, may have a more tolerable side-effect profile due to a different molecular structure.

To determine the efficacy, safety, and tolerability of cetilistat in obese patients, a phase II, multicenter [147], randomized, placebo-controlled, parallel group study was developed. The 442 enrolled patients were advised a hypocaloric diet for a 2-week run-in period before they were randomized to either placebo or one of three different doses of cetilistat (60 mg TID, 120 mg TID, and 240 mg TID) for 12 weeks. Treatment with cetilistat reduced mean body weight to similar extents at all doses, which were statistically significant

compared with placebo (60 mg TID 3.3 kg, 120 mg TID 3.5 kg, 240 mg TID 4.1 kg). Total serum and LDL cholesterol levels were likewise significantly reduced by 3–11 % at all doses of cetilistat. Cetilistat was well tolerated. The frequency of withdrawal owing to treatment-emergent adverse events was similar between cetilistat-treated groups (5.3–7.6 %) and placebo (7.6 %).

The incidence of GI adverse events was increased in the cetilistat-treated groups compared to placebo. However, those GI adverse events, such as flatus with discharge and oily spotting, only occurred in 1.8–2.8 % of subjects in the cetilistat-treated groups. Cetilistat produced a clinically and statistically significant weight loss in obese patients in this short-term 12-week study. This was accompanied by significant improvements in other obesity-related parameters.

Kopelman et al. [148] carried out a clinical trial to determine the efficacy and safety of cetilistat and orlistat relative to placebo in obese patients with T2DM, on metformin. Patients were randomized to placebo, cetilistat (40, 80, or 120 mg TID), or orlistat 120 mg TID, for 12 weeks. Similar reductions in body weight were observed in patients receiving cetilistat 80 or 120 mg TID or 120 mg TID orlistat (3.85, 4.32, 3.78 kg, respectively); and these reductions were significant vs. placebo. Statistically significant reductions in glycosylated hemoglobin were also noted. Discontinuation in the orlistat group was significantly worse than in the 120 mg cetilistat and placebo groups and was entirely due to gastrointestinal AEs.

Since successful management of obesity is likely to require long-term compliance with prescribed medication, cetilistat may have benefits over currently marketed anti-obesity drugs such as orlistat, with respect to better toleration. Takeda submitted a New Drug Application (NDA) to the Ministry of Health for cetilistat for the treatment of obesity with complications, based on data obtained from three phase III clinical trials in Japan in October of 2012. The three studies included a 52-week placebo-controlled study that evaluated the efficacy and safety of cetilistat and 24- and 52-week open-label safety studies that were conducted on obese patients with T2DM and dyslipidemia.

Conclusions

Obesity is a very serious global public health problem responsible for diseases such as CVD, T2DM, and hypertension, and it should be tackled by health-care providers as well as by health policy authorities. Obesity treatment should be individually tailored and the health risks and metabolic and psycho-behavioral characteristics of each patient should be taken into account before deciding what medical therapy could be more appropriate. Drugs must be prescribed over the long term for chronic weight management; they do not produce permanent weight loss. It is also very important to set up realistic expectations before starting the treatment of obesity. Both physician and the patient should know that a weight loss of 5–10 % reduces obesity-related health risks significantly.

There are emerging data in the literature suggesting the possible effectiveness of medical, intensive, and interdisciplinary weight loss programs in subjects with morbid obesity. Behavioral therapy especially in the context of group therapy can be effective helping an important number of obese and morbidly obese patients to lose weight and to keep it off. The use of medications should be seriously considered as adjuvant therapy early in the course of the therapy. The current armamentarium to combat the obesity epidemic is very limited, and what is more worrisome, the list of new medications to treat this condition is also slim.

Unfortunately the history of significant side effects of some of these medications, and the fact that many health-care legislators still feel that obesity is not a disease, has limited the effort of many governments to develop effective obesity prevention as well as obesity therapeutic programs. Also both socialized medicine and private insurance have put very limited effort in financing behavioral or pharmacological obesity therapies. These circumstances have also impacted in the general interest of pharmaceutical companies to develop new weight loss medications, which usually suffer exaggerated scrutiny by health regulatory agencies. In consequence, a large part of the drug development efforts have been switched to identify new T2DM treatments which interestingly cause weight loss as a side effect.

It is important to keep in mind that in addition to phentermine, diethylpropion, and orlistat, we have two new drugs, lorcaserin and the combination of phentermine and topiramate, approved for the treatment of the obesity, which could be useful tools to help treat our obese patients. Interesting new anti-obesity drugs are in the pipeline and hopefully some will reach the market in the near future. Meanwhile we should also take advance of the new GLP-1 analogues, which in some circumstances can be helpful to treat obese patients with T2DM.

New studies combining these medications and the ones to come in the context of lifestyle interventions will hopefully help to develop successful weight loss programs which bring some optimism to the field of obesity in the near future.

Review Questions and Answers

1. It is very important to set realistic expectations before starting medical treatments of obesity. What would be a realistic weight loss goal known to reduce the cardiovascular risk of patients?
   (a) 5–15 %
   (b) 3–10 %
   (c) 5–7 %
   (d) None of the above

CORRECT ANSWER (A): A −5 to −15% weight loss reduces obesity-related health risks significantly. There are a substantial number of patients who respond to weight loss interventions with important changes in their lifestyle, which translates in long-term weight loss.

2. Which of the following sentences would be false when we speak of the benefits of physical activity?
   (a) Reduced risk of premature death of any cause.
   (b) Reduced risk of diabetes mellitus.
   (c) Weight loss (without caloric restriction).
   (d) In elderly people there is strong evidence supporting the improvement of cognitive function in people who are physically active.

   CORRECT ANSWER (A): The benefits of physical activity include reduced risk of premature death of any cause, cerebrovascular disease, diabetes mellitus, some cancers (breast cancer and colon cancer), depression, prevention of weight gain, weight loss (in combination with caloric restriction), improvement of physical fitness, and musculoskeletal fitness. Inactivity and low cardiorespiratory fitness are as important as overweight and obesity as mortality predictors.

   In elderly people there is strong evidence supporting the improvement of cognitive function in people who are physically active and moderate evidence in regard to overall improvement in well-being, functional health, reduction of abdominal obesity, reduced risk of developing hip fracture, risk reduction of lung cancer, and weight loss maintenance.

3. Which of the following sentences is false when we speak of lifestyle modifications?
   (a) Changes in dietary behavior, the stimulation of physical activity, and emotional support continue to be the mainstays for the management of obesity in adults, children, and adolescents.
   (b) Lifestyle interventions alone result in long-term weight loss and the majority of dieters do not return to baseline weight within 3–5 years.
   (c) The improvements described in morbidly obese patients using behavioral therapy as an element of an intensive lifestyle intervention could benefit a huge number of people.
   (d) Lifestyle interventions can be provided at the hospital or primary care setting

   CORRECT ANSWER (B): Lifestyle interventions alone rarely result in long-term weight loss and the majority of dieters return to baseline weight within 3–5 years.

4. Which of the following sentences is correct?
   (a) Phentermine is an approved anti-obesity drug for short-term therapy.
   (b) GLP-1 analogues are effective weight loss drugs.
   (c) Topiramate is an antiepileptic drug with a weight loss side effect.
   (d) Lorcaserin, in addition to a reduced-calorie diet and exercise, could be a potential useful drug to treat obesity.
   (e) All of the above.

   CORRECT ANSWER (E).

5. Which of the following sentences is correct?
   (a) Bydureon is an exenatide long-acting release without weight loss effect.
   (b) Naltrexone is a dopamine reuptake inhibitor with weight loss effect.
   (c) Topiramate in combination with bupropion extended release is effective in causing weight loss.
   (d) Bupropion is an effective smoking cessation tool.
   (e) Cetilistat has central as well as gastrointestinal weight loss mechanism.

   CORRECT ANSWER (D). Bupropion is a dopamine and norepinephrine reuptake inhibitor that was first approved for the treatment of depression [139] and later for smoking cessation [140].

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