Management of obesity

George A Bray, Gema Frühbeck, Donna H Ryan, John P H Wilding

A modern approach to obesity acknowledges the multifactorial determinants of weight gain and the health benefits to be derived from weight loss. Foundational to any weight loss effort is lifestyle change, diet, and increased physical activity. The approach should be a high quality diet to which patients will adhere accompanied by an exercise prescription describing frequency, intensity, type, and time with a minimum of 150 min moderate weekly activity. For patients who struggle with weight loss and who would receive health benefit from weight loss, management of medications that are contributing to weight gain and use of approved medications for chronic weight management along with lifestyle changes are appropriate. Medications approved in the USA or European Union are orlistat, naltrexone/bupropion, and liraglutide; in the USA, lorcaserin and phentermine/topiramate are also available. Surgical management (gastric banding, sleeve gastrectomy, and Roux-en Y gastric bypass) can produce remarkable health improvement and reduce mortality for patients with severe obesity.

Lancet 2016; 387: 1947–56

Published Online February 8, 2016 http://dx.doi.org/10.1016/S0140-6736(16)00271-3

Pennington Biomedical Research Center/LSU, Baton Rouge, LA, USA (Prof G A Bray MD, Prof D H Ryan MD); **Department of Endocrinology and Nutrition, Clínica Universidad de Navarra, University of Navarra, CIBEROBN, IdiSNA, Spain** (Prof G Frühbeck MD); **and Department of Medicine (Obesity) University of Liverpool, Liverpool, UK** (Prof J P H Wilding MD)

Correspondence to: Prof George A Bray, Pennington Biomedical Research Center/LSU, Baton Rouge, LA 70808, USA **brayga@pbrc.edu**

See Online for appendix

Introduction

In the past 50 years, obesity has become an international public health issue that affects the quality of life, increases the risk of illness, and raises health-care costs in countries in all parts of the world (appendix).[1–6]

Measurement of obesity in these surveys[1–6] is done with the body-mass index (BMI; weight in kg/height in m²), which has a good correlation with body fat.[7] The BMI has the advantage of simplicity in epidemiological studies, but it has deficiencies because it does not distinguish between fat and lean body mass.[8] Thus, BMI should be considered as a screening measurement rather than a diagnostic method. Additional measurements to complement the BMI and should include waist circumference (or waist-to-height ratio).[9,10] Both variables are strong predictors of health risk.[9,10] The physician should take ethnicity into consideration when assessing the waist circumference of a particular patient.[11] In addition to measures of central adiposity, blood pressure, glucose, and lipids (HDL and triglycerides) should also be measured.

Obesity management is expensive[12,13] and, along with diabetes, obesity is a disease that needs to be defused.[14] Medical costs rise progressively as BMI increases[15] and are expected to continue to rise in the next 15 years.[16,17] Obesity is second only to depression in its cost to employers.[18]

Obesity has a multifactorial nature resulting from genetic, epigenetic, physiological, behavioural, socio-cultural, and environmental factors that lead to an imbalance between energy intake and expenditure during an extended time period. The importance of less sleep, endocrine disruptors—such as some chemicals in food packaging and foods—increased time in climate-controlled areas, cessation of smoking, weight gain that is associated with some medications, older parental age at birth, and intrauterine and inter-generational effects have been reported as contributors to the obesity epidemic.[19,20]

Obesity shortens life span[21] and affects the function of many organ systems[21–23] (appendix). Mortality results from several diseases that are associated with obesity, including diabetes, chronic kidney disease, gastrointestinal disease, and cardiovascular disease and maintaining weight loss is often difficult or unsuccessful.[24,25]

Management of the patients with obesity

The rising prevalence of obesity worldwide calls for preventive strategies to defuse the future health and economic costs of this problem Economic and technological changes in the environment have driven the obesity epidemic,[26] and many studies have tested strategies in schools, work-sites, and the community that might prevent the rise of BMI, but so far these efforts have had little effect,[27,28] and the evidence for use of effective economic policies to prevent obesity remains limited.[26]

When prevention of obesity does not work, as occurs for many people, treatment is indicated. To guide health-care professionals in treating obesity effectively, several guidelines have been developed in the USA,[29–31] in the UK,[32] and in Europe.[33,34] We use these guidelines as the

Search strategy and selection criteria

We searched for original articles and reviews published between Jan 1, 1990, and Aug 31, 2015, focusing on obesity management in PubMed and MEDLINE using the following search terms (or combination of terms): "obesity", "weight loss", "management", "treatment", "guidelines", "recommendations", "costs", "outcomes", "comorbidity or comorbidities", "body composition", "life-style intervention", "physical activity", "exercise", "pharmacotherapy", "medication", "anti-obesity drugs", "bariatric surgery", and "metabolic surgery". Only full-text articles written in English were included. References published after September, 2015, were also identified and selected. Articles in journals with explicit policies governing conflicts of interest and stringent peer-review processes were favoured. Data from larger replicated studies with longer periods of observation when possible were systematically chosen to be presented. More weight was given to randomised controlled trials, prospective case-control studies, meta-analyses, and systematic reviews.

basis for outlining therapy for obesity, which can include lifestyle changes, dietary modification, increased physical activity, the use of medications, and in some cases the recommendation for surgery.

Lifestyle changes

The cornerstone for treatment of a patient with obesity in the USA, UK, and Europe, and many other countries is a comprehensive, or multicomponent lifestyle intervention.[29,30,32,35] The term comprehensive refers to simultaneous implementation of three strategies: lifestyle or behavioural training, dietary change to reduce energy intake, and an increase in physical activity. The evidence supporting the efficacy of lifestyle intervention or behavioural modification is supported, partly, by data from two large randomised clinical trials: the Look AHEAD[36] and the Diabetes Prevention Program.[37] Three variables, including number of behavioural sessions attended, number of meal replacements used ,and the weekly minutes of physical activity all predicted weight loss at 1, 4, and 8 years in the Look AHEAD study and these are summarised for the 8 year data (figure 1). A systematic review[29] of evidence showed that if these components are delivered in at least 14 face-to-face (group or individual) sessions over 6 months with treatment continuing to 1 year, the average reported weight loss would be 8 kg. Although this might seem small, it translates into clinically significant improvements in blood pressure, triglycerides, HDL, measures of glycaemic control, and reduction in risk for progression to type 2 diabetes.[29] On the basis of these and other findings, the US Preventive Services Task Force[38] has recommended that individuals with obesity and cardiovascular disease risk factors should be referred for lifestyle treatment, and the US Center for Medicare and Medicaid Services promote policies to reimburse providers for intensive behavioural therapy for the patient with obesity.[39] In the UK, the National Institute for Health and Care Excellence recommends progressively intensive interventions on the basis of the degree of overweight and obesity and presence of comorbidities.

The initial rate of weight loss in the first and second months predicted weight loss at 4 and 8 years in the Look AHEAD study (figure 1). Individuals losing less than 3% of their bodyweight at 2 months were 2·5% below the average baseline weight at 8 years, whereas those losing 3–6% of their bodyweight were about 4·5% below baseline at 8 years, and those losing more than 6% were roughly 7% below baseline on average at 8 years, data which suggests that larger early weight losses are beneficial.[40] Commercial programmes of many types can provide a useful strategy for some individuals to lose weight.[41] The costs and methods of delivering treatment vary which might affect compliance and real-world applicability. These commercial programmes provide on average a weight loss of about 3% per year, but long-term compliance is generally poor. Studies longer than 1 year are sparse. A meta-analysis[42] comparing these named diets identified that differences between them were not significant.

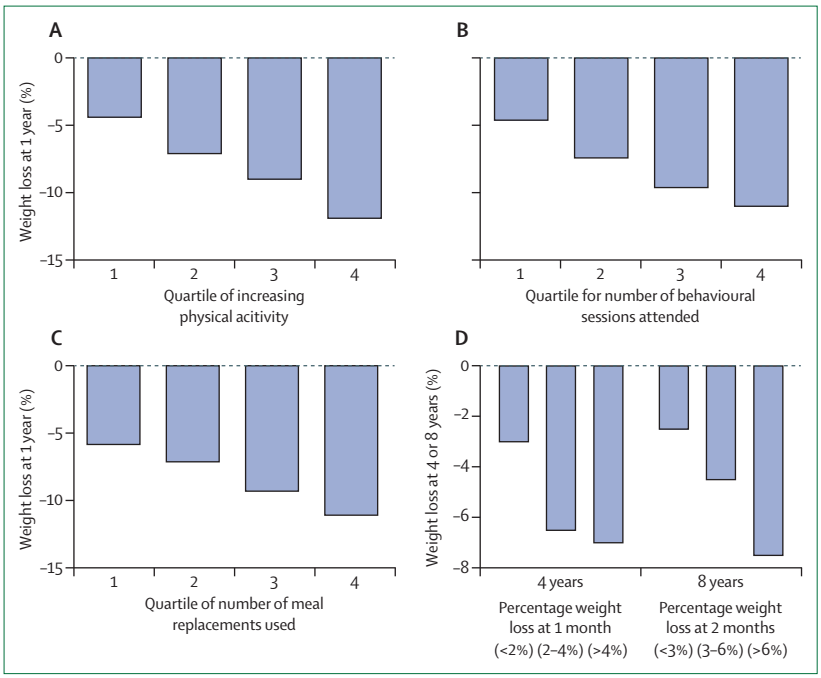

Figure 1: **Factors that predict weight loss in the Look AHEAD study**[36,40]
Effect of physical activity (A), behaviour sessions (B), meal replacements (C) on weight loss. (D) Weight loss at years 4 and 8 after beginning the study is shown relative to percentage weight loss at 1 month and 2 months. Greater weight loss at 1 year is associated with greater proportion of visits attended, minutes per week of physical activity, and greater meal replacement use (A, B, C). The tertiles of weight ranges are shown below each set of bars.

Diets for weight loss

Several considerations enter into selecting a diet for weight loss. It must have less energy than is required for daily maintenance[29,43,44] and be one to which the patient will adhere and possibly provide other health benefits. A reduction of energy by 500 kcal/day below energy requirements or by using a dietary plan that has 1200–1500 kcal/day for women or 1500–1800 kcal/day for men (increased by a further 300 kcal/day for each sex if weight exceeds 150 kg) will accomplish the first goal. In addition to reducing calories, some dietary patterns seem to offer other health benefits.[45–47] Some believe that there is a magic weight loss diet (one that gets you to your ideal weight and allows you to eat as much as you want, with only the need to eat the right foods). This belief has stimulated many studies that have focused on different amounts of dietary fat, protein, or carbohydrate. These low-fat, low-carbohydrate or high-protein, low glycaemic-index, and balanced deficit diets have been compared in many studies and summarised in a few meta-analyses. One of the largest studies with 811 patients who were obese or overweight, the POUNDS Lost study,[48] compared diets with 20% or 40% fat and 15% or 25% protein and

reported no difference in weight loss at 6 months or 2 years. A meta-analysis[49] of low-carbohydrate versus low-fat diets was in agreement stating that low-carbohydrate diets are at least as effective as low-fat diets at reducing weight and improving metabolic risk factors. A systematic review[29] of evidence from 17 diets also showed that no one diet was better. Similarly, a meta-analysis[42] of named diets showed no significant difference in weight loss between them. Thus, the best advice is to provide low energy diets that are likely to be adhered to by the patient and provide health benefits.

A slightly more favourable picture emerges for the Mediterranean style diet. In a meta-analysis[50] of nine studies with 1178 patients, Mediterranean style diets were associated with a significant decrease in bodyweight and BMI and reductions in haemoglobin A_{1c}, fasting plasma glucose, and fasting insulin. Along with this effect on bodyweight, one version of this dietary pattern can reduce cardiovascular disease risk.[47]

The jury is still out about low-glycaemic index or low-glycaemic load diets. A 5 week randomised trial showed no significant effect of these diets on insulin resistance or markers of cardiovascular disease risk.[51] A meta-analysis of 14 studies,[52] however, raised concerns. Although C-reactive protein and fasting insulin did benefit from the low-glycaemic index or low-glycaemic diets, there was a significant loss of fat-free mass, leading to caution in recommending the use of low-glycaemic index diets for weight loss.

Very low-calorie diets or very low-energy diets, defined as having 200 and 800 kcal/day, provide a lower energy intake that might result in more rapid loss of body fat and weight. Some studies have shown that such an approach can rapidly normalise blood glucose and other risk factors in people with type 2 diabetes. Systematic reviews,[32,53] however, suggested that although initial weight loss is more rapid with these diets, weight change after 1 year or more does not differ much from comprehensive or multicomponent approaches and does not recommend their routine use, although they might be considered if rapid weight loss is clinically necessary. In their analysis of commercial programmes, Gudzune and colleagues[41] showed that very low-calorie programmes, which are usually medically monitored (Health Management Resources, Medifast, and OPTIFAST) resulted in at least 4·0% greater short-term weight loss than counselling, but some attenuation of effect occurred after 6 months.

Physical activity

Increased physical activity is an essential component of comprehensive lifestyle intervention for obesity management. The recommendations in US and UK guidelines typically prescribe gradually increasing aerobic physical activity (such as brisk walking) to reach a goal of more than 150 min/week (equal to >30 min/day, for at least 5 days each week).[29,32,54] This has benefits for general health that are independent of weight loss.[55] Meta-analysis[32,56] of trials indicated that this results in an additional 1–1·5kg weight loss over 12 months in addition to dietary intervention alone. There is evidence[29,57] that a greater amount physical activity (30–45 min/day) is needed to prevent obesity and that for long-term weight maintenance in those who have lost weight, 60–90 min/day is required, but this is likely to require close supervision as part of an intensive programme, which might not be practical or sustainable in many clinical settings.[58–60] However, although physical activity is effective in the short term in controlled settings, the activities and their benefits are not readily sustained, as was found comparing the

	Weight gain	Weight neutral	Weight loss
Antidiabetics	Insulin; sulfonylureas (many); meglitinides (nateglinide, repaglinide); glitazones (pioglitazone, rosiglitazone)	Dipeptidyl peptidase-4 inhibitors (many)	Metformin; pramlintide GLP-1 agonists (exenatide, liraglutide, others); sodium-glucose co-transporter-2 inhibitors (canagliflozin, others)
Antidepressants or mood stabilisers	Monoamine oxidase inhibitors (many); tricyclics (some—ie, doxepin); serotonin reuptake inhibitors (some—ie, paroxetine); mirtazapine; lithium	Citalopram; fuvoxamine; vortionzetine; duloxetine; venlafaxine; nefazodone; sertraline (<1 year) psychotherapy	Venlafaxine; bupropion; fluoxetine (short term)
Antipsychotics	Clozapine; risperidone; olanzapine; quetiapine; haloperidol; perphenazine; quetiapine	Ziprasidone; aripiprizole psychotherapy	..
Anticonvulsants	Carbamazepine; gabapentin; valproate	Lamotrigine	Topiramate; zonisamide
Antihistamines	Cycloheptadine; diphenhydramine; doxepin	Steroid inhalers; decongestants	..
Adrenergic blockers	Propranolol; doxazosin	Angiotensin converting enzyme inhibitors; angiotensin receptor blockers; calcium channel blockers	..
Adrenal steroids	Corticosteroids	Non-steroidal anti-inflammatory drugs	..
Oral contraceptives	..	..	..

Table 1: **Medications affecting weight gain and alternative approaches**

	Mechanism of action	Available for chronic use		Mean percentage weight loss		Advantages	Disadvantages
		USA	European Union	Placebo	Drug		
Phentermine; 15–30 mg orally	Sympathomimetic	For short-term use	No	Not stated in label	Not stated in label	Inexpensive	Side-effect profile; no long-term data*
Orlistat; 120 mg orally three times a day before meals	Pancreatic lipase inhibitor	Yes	Yes	−2·6%†	−6·1%†	Not absorbed; long-term data*	Modest weight loss; side-effect profile
Lorcaserin; 10 mg orally twice a day	5-HT_{2c} serotonin agonist with little affinity for other serotonergic receptors	Yes	No	−2·5%	−5·8%	Mild side-effects; long-term data*	Expensive; modest weight loss
Phentermine/ topiramate ER; 7·5 mg/46 mg or 15 mg/92 mg orally indicated as rescue (requires titration)	Sympathomimetic anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)	Yes	No	−1·2%	−7·8% (mid-dose) −9·8% (full dose)	Robust weight loss; long-term data*	Expensive; teratogen
Naltrexone SR/ bupropion SR; 32 mg/360 mg orally (requires titration)	Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor	Yes	Yes	−1·3%	−5·4%	Reduces food craving; long-term data*	Moderately expensive; side-effect profile
Liraglutide; 3·0 mg Injection (requires titration)	GLP-1 receptor agonist	Yes	Yes	−3%	−7·4% (full dose)	Side-effect profile; long-term data*	Expensive; injectable

Information is from US product labels, except where noted. The data supporting these tables are derived from the prescribing information labelling approved by the US Food and Drug Administration.[64–69] ER=extended release. SR=sustained release. *Data from randomised controlled trials lasting more than 52 weeks. †Assuming the average patient in the orlistat and placebo groups weighed 100 kg at baseline.

Table 2: **Medications for weight management with mechanism of action, availability, and dosing**

1 and 4 year results in the Look AHEAD study.[36] The type of physical activity (eg, aerobic *vs* resistance or high intensity *vs* low intensity) does not seem to affect overall weight loss, but as more intensive activity produces similar weight loss with a reduced time commitment, this might be preferable to some; it would therefore seem appropriate to recommend programmes that are acceptable to patients.[55,61]

Pharmacotherapy

A systematic review and clinical guidance[29] sponsored by the Endocrine Society promotes the concept that, for patients with obesity, medicating for chronic diseases should be with a weight centric focus. Many medications in use for common chronic diseases produce weight gain, and others are associated with weight loss, albeit those medications do not have an obesity indication. Whenever possible, patients with obesity should avoid medications associated with gain and use weight neutral medications or those associated with loss (table 1).[31,62,63]

The indications for adding pharmacotherapy to a weight loss effort are history of failure to achieve clinically meaningful weight loss (>5% of total bodyweight) and to sustain lost weight, for patients who meet regulatory prescribing guidelines (BMI ≥27 kg/m² with one or more comorbidities or a BMI >30 kg/m² with or without associated metabolic effects).[29,31,32]

Five medications have been approved in the USA for chronic weight management, and three of these have also been approved in the European Union (table 2, figure 2).

Several guiding principles should be followed when prescribing drugs for weight loss.[31] First, effective lifestyle support for weight loss should be provided during their use. These medications work to reinforce the patient's attempts to change eating behaviours and produce an energy deficit. Second, the prescriber and patient should be familiar with the drug and its potential side-effects. Third, unless clinically meaningful weight loss occurs after 3 to 4 months, (generally defined as loss of more than 4–5% of total bodyweight in patients without diabetes; in patients with obesity and diabetes, loss of more than 3% of total bodyweight can be considered satisfactory) a new treatment plan should be implemented. No one medication is effective in every patient just as not every patient is appropriate for every medication.

Phentermine is a sympathomimetic drug with cardiostimulatory properties.[64] It has only been studied in short-term trials and is a controlled substance in the USA. It has misuse potential (albeit small) and small risk of primary pulmonary hypertension, thus making its use for managing a chronic disease less than ideal. Orlistat is a pancreatic lipase inhibitor that blocks absorption of 30% of ingested fat when eating a 30% fat diet.[70] It is available in most countries worldwide. Orlistat is one of the safest drugs in this category[64] and is approved for use in adolescents.[71] Additionally, a study[72] of 4 years duration supports its long-term safety and efficacy and shows that it reduces the development of diabetes mellitus in people with prediabetes. However the drug's gastrointestinal side-effects[65] limit its popularity with patients.

Since 2012, four medications have reached the market in the USA: lorcaserin,[73–75] a combination of phentermine/topiramate extended release (ER),[76–78] a combination of naltrexone sustained release (SR)/bupropion SR,[79–82] and liraglutide 3·0 mg.[83–86] These drugs are required by regulatory agencies in the USA and European Union to

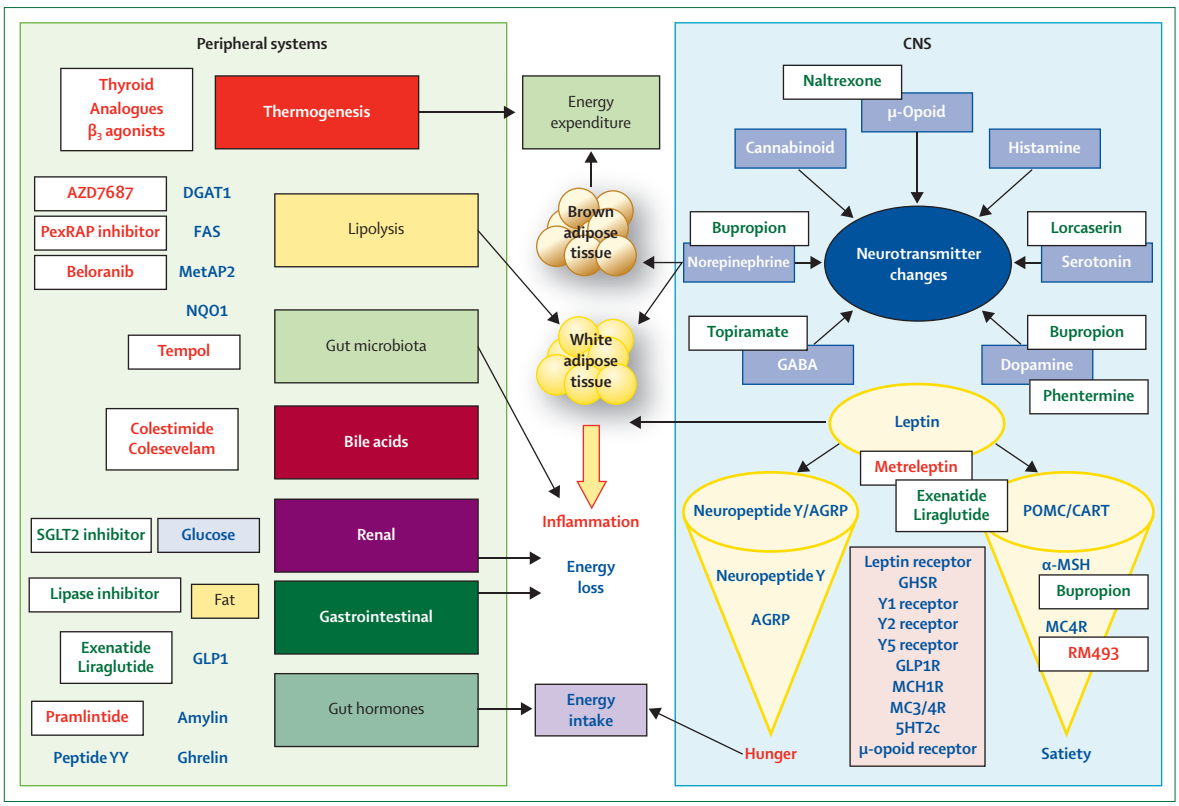

Figure 2: **Targets for anti-obesity drugs**

White boxes indicate specific drugs located next to the target upon which they are acting. Inside the white boxes green names stand for already approved drugs, whereas red names represent drugs in phase 1–3 development. The right hand panel summarises the neurotransmitters and pathways in the CNS in energy homoeostasis, whereas the left hand panel represents the mechanisms operative in the periphery. The intermediate area represents where the effects of both central and peripheral actions converge—namely, on the two main components of the energy balance equation: energy intake and expenditure. Most of the approved drugs are working centrally where stimulation of the POMC/CART pathway has anorexigenic effects, whereas the NPY/AGRP pathway exerts orexigenic effects. The interaction with the several receptors present in neurones of the hypothalamus determines the balance between orexigenic and anorexigenic effects. Most of the drugs tested in clinical trials are aimed at peripheral systems. Thus, thyroid analogues and β_3 adrenergic agonists induce thermogenesis by activation of brown adipose tissue, thereby increasing energy expenditure. Enzymes involved in lipid metabolism, such as DGAT, FAS, MetAP2, and NQO1 are also being targeted. The gut microbiome and the regulation of bile acids represent further targets to combat obesity. The lipase and SGLT2 inhibitors favour energy loss by the gastrointestinal and renal elimination of fat and glucose, respectively. Agonism of pancreatic and intestinal hormones like amylin and GLP-1 has also been shown to be useful for weight loss. DGAT1=diacylglycerol O-acyltransferase aminotransferase 1. PexRAP=peroxisomal reductase activating PPARγ. FAS=fatty acid synthase. MetAP2=methionyl aminopeptidase 2. NQO1=NAD(P)H dehydrogenase: quinone oxidoreductase 1. SGLT2=sodium-glucose-linked transporter 2. AGRP=agouti-related peptide POMC=proopiomelanocortin C. CART=cocaine amphetamine-related transcript. GHSR=growth hormone secretagogue receptor. GLP1R=glucagon-like peptide 1 receptor. α-MSH=α-melanocyte-stimulating hormone. MCH1R=melanin-concentrating hormone 1 receptor. MC3/4R=melanocortin receptor type 3/4. 5HT2c=serotonin receptor type 2c.

present data for more than 2500 patients and to approximate or exceed 5% greater weight loss than placebo and to show positive effects on various risk factors and disease markers. All drugs must show evidence of no increase in cardiovascular risk, which is likely to require a cardiovascular outcome trial either before or after marketing. Furthermore, all of these drugs were studied with a suicidality rating scale.[87] These medications have an indication for chronic weight management, indicating long-term usage, along with diet and physical activity in individuals with BMI of 30 kg/m² or greater or a BMI 27 kg/m² or greater with one or more comorbidities. They are to be used in the long term not only to produce weight loss but also to sustain weight loss.

Lorcaserin is a specific serotonin 2c receptor agonist.[73] Lorcaserin is remarkable for its tolerability and low rate of adverse events.[73–75] Echocardiograms done in phase 3 studies on more than 5200 participants showed no statistically significant increase in Food and Drug Administration defined valvulopathy.[66] The drug should not be used with monoamine oxidase inhibitors because of the risk of serotonin syndrome.[66] It has not been studied with serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or other serotonergic drugs and extreme caution should be used in combining it with those drugs.[66]

The combination of phentermine and topiramate as an ER formulation uses lower doses of both drugs (7·5 mg of phentermine and 46 mg of topiramate at the recommended

	Change in BMI after 3 years (kg /m²)	Effects on type 2 diabetes remission	Mortality at less than 30 days	Mortality at more than 30 days	Re-operation rate	Complications
Adjustable gastric banding	−11·43 (−18·14 to −4·72)	67·58% (49·51 to 82·83)	0·07% (0·02 to 0·12)	0·21% (0·08 to 0·37)	7·01% (3·99 to 11·24)	7·80% (3·90 to 13·00)
Sleeve gastrectomy	−16·78 (−20·57 to −12·99)	85·53% (72·69 to 94·07)	0·29% (0·11 to 0·63)	0·34% (0·14 to 0·60)	2·96 (1·70 to 4·71)	8·90 (5·60 to 13·00)
Roux-en-Y gastric bypass	−21·88 (−27·96 to −15·79)	92·83% (85·29 to 97·21)	0·38% (0·22 to 0·59)	0·39% (0·01 to 0·86)	5·34 (4·48 to 6·48)	12·00 (7·30 to 17·00)

Data are n or n% (95% CI). Data in table are from Chang (2014).[102] For this analysis, surgical procedures were grouped: adjustable gastric banding included laparoscopic gastric banding and swedish band; sleeve gastrectomy included sleeve gastrectomy and vertical banded gastroplasty; and Roux-en-Y gastric bypass included laparoscopic and open procedures and biliopancreatic diversion with or without duodenal switch. BMI=body-mass index.

Table 3: **Surgical procedures for treatment of obesity**

dose) than are usually prescribed when either drug is used as alone.[76–78] This medication is associated with greater mean weight loss than other available medications. Topiramate is associated with fetal toxic effects (oral clefts)[88] and a pregnancy test before initiation of therapy, and monthly thereafter, is recommended.[67] The most common side-effects include paraesthesias, dizziness, dysgeusia, insomnia, constipation, and dry mouth.[67] A rare side-effect of topiramate is acute myopia with glaucoma and the drug is contraindicated in glaucoma.[67] The combination of phentermine and topiramate ER is also contraindicated in hyperthyroidism and within 14 days of treatment with monoamine oxidase inhibitors.[67] Other rare potential adverse risks include kidney stones (associated with topiramate) and increased heart rate (associated with phentermine) in patients susceptible to sympathomimetic drugs.[67]

The combination of naltrexone SR/bupropion SR was approved in the USA in 2012 and in the European Union in 2015.[79–82] Bupropion is a mild reuptake inhibitor of dopamine and norepinephrine. Naltrexone, an opioid antagonist has minimum effect on weight loss on its own. Naltrexone is thought to block the inhibitory effects of opioid receptors activated by the β-endorphin released in the hypothalamus that stimulates feeding, thus allowing the inhibitory effects of α-melanocyte stimulating hormone to reduce food intake. Naltrexone SR/bupropion SR can increase blood pressure, and therefore the combination should only be prescribed to patients with controlled hypertension and the patient's blood pressure should be monitored in the early weeks of therapy.[68] Despite these signals, no increased events were noted in the interim analysis of a cardiovascular outcome trial[68] done before marketing allowed approval. Another cardiovascular outcome trial was needed post-marketing. Tolerability issues, chiefly nausea on initiating the drug mandate a dose escalation over four weeks. All antidepressants in the USA are required to carry a black box warning of suicidality and the combination's label includes this.[68] However, there was no signal for suicidality in phase 3 studies.[78–81,83]

Liraglutide is a GLP-1 agonist with a 97% homology to GLP-1 which extends its circulating half-life. It has been used for management of diabetes at doses of up to 1·8 mg, given by injection. It is now approved in the USA and European Union for chronic weight management at a dose of 3·0 mg.[83–86] Nausea has been one of the principal complaints in patients injecting this drug and a slow dose escalation over 5 weeks is prescribed.[69] There is also a small, but significant increase in heart rate, but blood pressure tends to fall.[69] GLP-1 agonists are associated with thyroid C cell tumours in animals, but this has not been shown with certainty in humans.[69] Liraglutide should not be prescribed in patients with family or personal history of medullary thyroid cancer or multiple endocrine neoplasia.[69] Acute pancreatitis, gall bladder disease, and hypoglycaemia in diabetics are safety issues that require managing if they occur.

Surgical procedures to treat obesity

Bariatric surgery has rapidly become used as a treatment option for severe obesity, particularly since the advent of lower risk laparoscopic procedures, with nearly half a million procedures done worldwide in 2013.[89] A range of procedures are now well established, which result in varying degrees of weight loss; each procedure has its own risks and benefits which need to be considered carefully with each patient (table 3).[90]

Long term studies of outcomes after bariatric surgery have generally shown favourable results. The Swedish Obese Subjects study[91–93] followed up 2000 patients for up to 20 years after surgery including banded gastroplasty, gastric banding, and Roux-en-Y gastric bypass done by open techniques, which have since been replaced by laparoscopy. A 24% reduction in mortality was reported, mainly because of the reduced risk of myocardial infarction and cancer (in women), compared with an observational control group.[91,92] Many other comorbidities, such as type 2 diabetes and sleep apnoea were also improved, and patients reported consistent improvements in quality of life.[93]

Particularly striking and rapid improvements in glucose control have been seen in patients with type 2 diabetes, especially after gastric bypass, suggesting that part of the metabolic improvement is independent of weight loss.[94] Head to head randomised controlled trials against medical treatment for type 2 diabetes consistently show greater improvements in glucose control and other risk factors in the surgical group.[95–99] Observational data also suggest that the future risk of diabetes-related microvascular and

macrovascular complications are also reduced.[99] This has led to the concept of metabolic surgery, and revision of guidelines and recommendations to lower thresholds for considering surgery in people with type 2 diabetes, particularly of recent onset, to include patients with a BMI between 30 kg/m² and 35 kg/m² and a move away from BMI as the main criterion used to assess eligibility for surgery.[32,100,101] These encouraging data need to be put into the context of potential risks and side-effects of surgery, which for some patients can be distressing or disabling. Although mortality is low for modern laparoscopic surgery, re-operation rates for surgical complications are high, particularly for gastric banding (table 3).[102] Some patients find it hard to adapt to the profound changes in the amount and type of food they can eat once they have had the procedure and lifelong replacement therapy and monitoring is required for nutritional vitamin and mineral deficiencies, particularly after malabsorptive surgery. Dumping syndrome gastro-oesophageal reflux and hypoglycaemia can be very distressing and a challenge to treat.[103] Weight regain can also be a substantial issue, and revisional surgery carries greater risks and no guarantee of success;[104] there is an increasing focus on lifestyle programmes after bariatric surgery to reduce the risk of this occurring.[32]

From a clinical perspective, patients and clinicians considering referral for bariatric surgery should be made fully aware of the risks and benefits; good practice might include provision of a detailed education session, attendance at patient support groups, and detailed lifestyle advice and psychological support both before and after surgery.[105]

Controversies

As with other areas of medicine, not all issues have been resolved and several controversies are still being debated. Should the topic of obesity be a strong focus of undergraduate medical education or should it be taught mainly at the post graduate level?[106] Weight bias is commonly reported in medical students and experienced doctors to stigmatise patients.[107] This stigma might be reduced if the complexities of obesity were introduced earlier. This stigma might also partly explain why obesity is an underdiagnosed and undertreated condition despite its high prevalence.[108]

Who needs to lose weight and what is the best way to decide? Is BMI an appropriate measure to decide who should lose weight?[109] If not appropriate in itself, what will improve clinical decision making? Is the percentage of weight reduction acceptable as a primary endpoint given that several additional benefits not requiring weight loss can be of equal clinical relevance? Should a weight- or BMI-centric approach should be abandoned in favour of a wider array of endpoints such as improvements in cardiometabolic variables? Introduction of additional criteria for identifying patients at high risk should be discussed.

Another controversy revolves around whether there are people who are obese and metabolically healthy, so-called metabolically healthy obesity. Individuals with metabolically healthy obesity might not improve their cardiometabolic risk factors significantly after weight loss interventions and might therefore not benefit to the same extent as patients who are obese with metabolic comorbidities. Controversy also exists as to whether individuals labelled as metabolically healthily obese are really healthy, especially because no general agreement exists about accepted criteria to define those with metabolic healthy obesity.[110,111] Moreover, controversy still exists as to whether metabolic healthy obesity can be considered an established phenotype or rather represents a transient stage toward ill-health with ageing, behavioural, and environmental factors. Metabolically healthy obesity seems to be a transient condition with a substantial percentage of these individuals having similar metabolic derangements to those reported in patients who are obese with metabolic comorbidities as time passes.[112,113] Conversely, non-obese individuals according to BMI but obese based on body fat distribution have elevated cardiometabolic risk factors,[114,115] and should be identified and treated irrespective of BMI.

One of the major uncertainties for patients with obesity is whether current pharmacological treatments increase, reduce, or are neutral with respect to cardiovascular events. This topic is currently under investigation in the Cardiovascular outcomes study of naltrexone SR/bupropion SR in overweight and obese subjects with cardiovascular risk factors (the light study; NCT01601704) and liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results—a long term evaluation (LEADER; NCT01601704).

The question of whether obesity should be treated in primary care or by specialists with training in obesity is one that will have major effects on health services. Several studies (NCT00991640, NCT01967797, and NCT01606813) are due to report on this issue in the next few years.

Obesity raises several societal controversies. Government taxes on unhealthy foods has been tried in some countries (Denmark for example) but with variable results. Should the next step be for governments to subsidise commercial weight loss programmes that have proven to be successful?[116]

Contributors

GAB was invited to develop the review and invited DHR, GF, and JPHW to contribute. GAB drafted the initial manuscript, which was substantially revised by each author. All authors contributed to the literature search and to the figures and tables.

Declaration of interests

GAB is a consultant to Herbalife International and Medifast; a member of the Speakers Bureau for Novo Nordisk Pharmaceuticals and Takeda Pharmaceuticals; and receives royalties from Up-to-Date and Handbook of Obesity. GF is a consultant to Novo Nordisk Pharmaceuticals. DHR is a consultant to Novo Nordisk Pharmaceuticals, Takeda Pharmaceuticals, Eisai Pharmaceuticals, Vivus Pharmaceuticals, Janssen Pharmaceuticals, Amgen Pharmaceuticals, Real Appeal, Gila Therapeutics, Tulip Medical, and Scientific Intake; is on the speakers' bureau for Novo Nordisk

Pharmaceuticals, Takeda Pharmaceuticals, Eisai Pharmaceuticals, and Vivus Pharmaceuticals; and has equity ownership in Scientific Intake. JPHW received grant funding from Novo Nordisk and AstraZeneca, and is a consultant to Novo Nordisk, Janssen Pharmaceuticals, AstraZeneca Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals, and Pfizer Pharmaceuticals.

References

1 WHO. WHO obesity and overweight fact sheet no 311, March 2013. http://who.ubt.neduacebter.factsheet.fs311/en (accessed Jan 7, 2015).

2 CDC. Overweight and obesity. http://www.cdc.gov/obesity/adult/defining (accessed Jan 7, 2015).

3 Health and Social Care Information Centre. Statistics on obesity, physical activity and diet: England 2015. March, 2015. http://www.hscic.gov.uk/catalogue/PUB16988/obes-phys-acti-diet-eng-2015.pdf (accessed April 15, 2015).

4 WHO regional office for Europe. Data and statistics. http://www.euro.who.int/en/health-topics/noncommunicable-diseases/obesity/data-and-statistics (accessed Jan 7, 2015).

5 Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384:** 766–81.

6 Scully T. Public health: society at large. *Nature* 2014; **508:** S50–51.

7 Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *Am J Clin Nutr* 2000; **72:** 694–701.

8 Romero-Corral A, Lopez-Jimenez F, Sierra-Johnson J, Somers VK. Differentiating between body fat and lean mass-how should we measure obesity? *Nat Clin Pract Endocrinol Metab* 2008; **4:** 322–23.

9 Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev* 2012; **13:** 275–86.

10 Cerhan JR, Moore SC, Jacobs EJ, et al. A pooled analysis of waist circumference and mortality in 650,000 adults. *Mayo Clin Proc* 2014; **89:** 335–45.

11 Staiano AE, Bouchard C, Katzmarzyk PT. BMI-specific waist circumference thresholds to discriminate elevated cardiometabolic risk in white and African American adults. *Obes Facts* 2013; **6:** 317–24.

12 Tsai AG, Williamson DF, Glick HA. Direct medical cost of overweight and obesity in the USA: a quantitative systematic review. *Obes Rev* 2011; **12:** 50–61.

13 Finkelstein EA, Graham WC, Malhotra R. Lifetime direct medical costs of childhood obesity. *Pediatrics* 2014; **133:** 854–62.

14 Bray GA. Diabetes and obesity—time bombs to be defused. *Diabetes Care* 2015; **38:** 1997–99.

15 Cawley J, Meyerhoefer C. The medical care costs of obesity: an instrumental variables approach. *J Health Econ* 2012; **31:** 219–30.

16 Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet* 2011; **378:** 815–25.

17 Finkelstein EA, Khavjou OA, Thompson H, et al. Obesity and severe obesity forecasts through 2030. *Am J Prev Med* 2012; **42:** 563–70.

18 Loeppke R, Taitel M, Haufle V, Parry T, Kessler RC, Jinnett K. Health and productivity as a business strategy: a multiemployer study. *J Occup Environ Med* 2009; **51:** 411–28.

19 Keith SW, Redden DT, Katzmarzyk PT, et al. Putative contributors to the secular increase in obesity: exploring the roads less traveled. *Int J Obes (Lond)* 2006; **30:** 1585–94.

20 Janesick AS, Shioda T, Blumberg B. Transgenerational inheritance of prenatal obesogen exposure. *Mol Cell Endocrinol* 2014; **398:** 31–35.

21 Whitlock G, Lewington S, Sherliker P, et al, and the Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; **373:** 1083–96.

22 Li C, Ford ES, Zhao G, Croft JB, Balluz LS, Mokdad AH. Prevalence of self-reported clinically diagnosed sleep apnea according to obesity status in men and women: National Health and Nutrition Examination Survey, 2005–2006. *Prev Med* 2010; **51:** 18–23.

23 Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010; **363:** 2211–19.

24 Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med* 1995; **332:** 621–28.

25 Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. *Int J Obes (Lond)* 2015; **39:** 1188–96.

26 Sturm R, An R. Obesity and economic environments. *CA Cancer J Clin* 2014; **64:** 337–50.

27 Bray GA. Prevention of obesity. In: De Groot LJ, Beck-Peccoz P, Chrousos G, et al, eds. Endotext. South Dartmouth: MDText.com, 2000–12: 1–28.

28 Wang Y, Wu Y, Wilson RF, et al. Childhood obesity prevention programs: comparative effectiveness review and meta-analysis. Comparative effectiveness review no 115. Rockville: Agency for Healthcare Research and Quality, 2013.

29 Ryan D, Heaner M. Guidelines (2013) for managing overweight and obesity in adults. Preface to the full report. *Obesity (Silver Spring)* 2014; **22** (suppl 2)**:** S1–3.

30 Garvey WT, Garber AJ, Mechanick JI. AACE Advanced framework for a new diagnosis of obesity as a chronic disease. https://www.aace.com/files/2014-advanced-framework-for-a-new-diagnosis-of-obesity-as-a-chronic-disease.pdf (accessed Jan 15, 2015).

31 Apovian CM, Aronne LJ, Bessesen DH, et al, and the Endocrine Society. Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2015; **100:** 342–62.

32 National Institute for Health and Clinical Excellence: Guidance. Obesity: identification, assessment and management of overweight and obesity in children, young people and adults: partial update of CG43. National Clinical Guideline Centre (UK). London: National Institute for Health and Care Excellence (UK), 2014.

33 Yumuk V, Frühbeck G, Oppert JM, Woodward E, Toplak H. An EASO position statement on multidisciplinary obesity management in adults. *Obes Facts* 2014; **7:** 96–101.

34 Frühbeck G, Toplak H, Woodward E, Halford JC, Yumuk V, and the European Association for the Study of Obesity. Need for a paradigm shift in adult overweight and obesity management - an EASO position statement on a pressing public health, clinical and scientific challenge in Europe. *Obes Facts* 2014; **7:** 408–16.

35 Eckel RH, Jakicic JM, Ard JD, et al, and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63** (25 Pt B)**:** 2960–84.

36 Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity (Silver Spring)* 2014; **22:** 5–13.

37 Knowler WC, Fowler SE, Hamman RF, et al, and the Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; **374:** 1677–86.

38 LeFevre ML, and the U.S. Preventive Services Task Force. Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2014; **161:** 587–93.

39 Anon. Decision memo for intensive behavioral therapy for obesity. (CAG-00423N). http://www.cms.gov/medicare-coverage-database/shared/handlers/highwire.ashx?url=http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx (accessed Jan 15, 2015).

40 Unick JL, Neiberg RH, Hogan PE, et al, and the Look AHEAD Research Group. Weight change in the first 2 months of a lifestyle intervention predicts weight changes 8 years later. *Obesity (Silver Spring)* 2015; **23:** 1353–56.

41 Gudzune KA, Doshi RS, Mehta AK, et al. Efficacy of commercial weight-loss programs: an updated systematic review. *Ann Intern Med* 2015; **162:** 501–12.

42 Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA* 2014; **312:** 923–33.

43 Thomas DM, Weedermann M, Fuemmeler BF, et al. Dynamic model predicting overweight, obesity, and extreme obesity prevalence trends. *Obesity (Silver Spring)* 2014; **22:** 590–97.

44 Hall KD, Sacks G, Chandramohan D, et al. Quantification of the effect of energy imbalance on bodyweight. *Lancet* 2011; **378:** 826–37.

45 Siervo M, Lara J, Chowdhury S, Ashor A, Oggioni C, Mathers JC. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a systematic review and meta-analysis. *Br J Nutr* 2014; **113:** 1–15.

46 Appel LJ, Moore TJ, Obarzanek E, et al, and the DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997; **336:** 1117–24.

47 Estruch R, Ros E, Salas-Salvadó J, et al, and the PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013; **368:** 1279–90.

48 Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 2009; **360:** 859–73.

49 Hu T, Mills KT, Yao L, et al. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. *Am J Epidemiol* 2012; **176** (suppl 7): S44–54.

50 Huo R, Du T, Xu Y, et al. Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: a meta-analysis. *Eur J Clin Nutr* 2014; **69:** 1200–08.

51 Sacks FM, Carey VJ, Anderson CA, et al. Effects of high vs low glycemic index of dietary carbohydrate on cardiovascular disease risk factors and insulin sensitivity: the OmniCarb randomized clinical trial. *JAMA* 2014; **312:** 2531–41.

52 Schwingshackl L, Hoffmann G. Long-term effects of low glycemic index/load vs. high glycemic index/load diets on parameters of obesity and obesity-associated risks: a systematic review and meta-analysis. *Nutr Metab Cardiovasc Dis* 2013; **23:** 699–706.

53 Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity (Silver Spring)* 2006; **14:** 1283–93.

54 Jakicic JM, Egan CM, Fabricatore AN, et al, and the Look AHEAD Research Group. Four-year change in cardiorespiratory fitness and influence on glycemic control in adults with type 2 diabetes in a randomized trial: the Look AHEAD Trial. *Diabetes Care* 2013; **36:** 1297–303.

55 Scottish Intercollegiate Guidelines Network. 115 management of obesity. http://www.sign.ac.uk/pdf/sign115.pdf (accessed Aug 21, 2015).

56 Wu T, Gao X, Chen M, van Dam RM. Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: a meta-analysis. *Obes Rev* 2009; **10:** 313–23.

57 Slentz CA, Houmard JA, Kraus WE. Exercise, abdominal obesity, skeletal muscle, and metabolic risk: evidence for a dose response. *Obesity (Silver Spring)* 2009; **17** (suppl 3): S27–33.

58 McTiernan A, Sorensen B, Irwin ML, et al. Exercise effect on weight and body fat in men and women. *Obesity (Silver Spring)* 2007; **15:** 1496–512.

59 Jakicic JM, Marcus BH, Gallagher KI, Napolitano M, Lang W. Effect of exercise duration and intensity on weight loss in overweight, sedentary women: a randomized trial. *JAMA* 2003; **290:** 1323–30.

60 Jakicic JM, Marcus BH, Lang W, Janney C. Effect of exercise on 24-month weight loss maintenance in overweight women. *Arch Intern Med* 2008; **168:** 1550–59, discussion 1559–60.

61 Ross R, Hudson R, Stotz PJ, Lam M. Effects of exercise amount and intensity on abdominal obesity and glucose tolerance in obese adults: a randomized trial. *Ann Intern Med* 2015; **162:** 325–34.

62 Leslie WS, Hankey CR, Lean ME. Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review. *QJM* 2007; **100:** 395–404.

63 Blumenthal SR, Castro VM, Clements CC, et al. An electronic health records study of long-term weight gain following antidepressant use. *JAMA Psychiatry* 2014; **71:** 889–96.

64 Anon. Adipex-P (phentermine) prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/088023s037lbl.pdf (accessed Feb 22, 2015).

65 Anon. Xenical (orlistat) prescribing information. http://www.gene.com/download/pdf/xenical_prescribing.pdf (accessed Feb 22, 2015).

66 Anon. Belviq (lorcaserin) prescribing information. https://www.belviq.com/pdf/Belviq_Prescribing_information.pdf (accessed Feb 22, 2015).

67 Anon. Qsymia (phentermine/topiramate ER) prescribing information. https://qsymia.com/pdf/prescribing-information.pdf (accessed Feb 22, 2015).

68 Anon. Contrave (naltrexone SR/bupropion SR) prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/200063s000lbl.pdf (accessed Feb 22, 2015).

69 Anon. Saxenda (liraglutide 3.0 mg) prescribing information. http://novo-pi.nnittest.com/saxenda.pdf (accessed Jan 18, 2015).

70 Sjöström L, Rissanen A, Andersen T, et al, and the European Multicentre Orlistat Study Group. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet* 1998; **352:** 167–72.

71 Chanoine JP, Hampl S, Jensen C, Boldrin M, Hauptman J. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA* 2005; **293:** 2873–83.

72 Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; **27:** 155–61.

73 Smith SR, Weissman NJ, Anderson CM, et al, and the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010; **363:** 245–56.

74 O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)* 2012; **20:** 1426–36.

75 Fidler MC, Sanchez M, Raether B, et al, and the BLOSSOM Clinical Trial Group. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab* 2011; **96:** 3067–77.

76 Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; **377:** 1341–52.

77 Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity (Silver Spring)* 2013; **21:** 2163–71.

78 Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring)* 2012; **20:** 330–42.

79 Apovian CM, Aronne L, Rubino D, et al, and the COR-II Study Group. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)* 2013; **21:** 935–43.

80 Hollander P, Gupta AK, Plodkowski R, et al, and the COR-Diabetes Study Group. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care* 2013; **36:** 4022–29.

81 Greenway FL, Fujioka K, Plodkowski RA, et al, and the COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010; **376:** 595–605.

82 Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)* 2011; **19:** 110–20; published online June 17, 2010. DOI:10.1038/oby.2010.147.

83 Astrup A, Carraro R, Finer N, et al, and the NN8022-1807 Investigators. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)* 2012; **36:** 843–54.

84 Wadden TA, Hollander P, Klein S, et al, and the NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)* 2013; **37:** 1443–51.

85 Pi-Sunyer X, Astrup A, Fujioka K, et al, and the SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med* 2015; **373:** 11–22.

86 Davies MJ, Bergenstal R, Bode B, et al, and the NN8022-1922 Study Group. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. *JAMA* 2015; **314:** 687–99.

87 Giddens JM, Sheehan KH, Sheehan DV. The Columbia Suicidality severity rating scale (C-SSRS): has the gold standard become a liability? *Innov Clin Neurosci* 2014; **11:** 66–80.

88 Margulis AV, Mitchell AA, Gilboa SM, et al, National Birth Defects Prevention Study. Use of topiramate in pregnancy and risk of oral clefts. *Am J Obstet Gynecol* 2012; **207:** 405 (e1–7).

89 Angrisani L, Santonicola A, Iovino P, Formisano G, Buchwald H, Scopinaro N. Bariatric Surgery Worldwide 2013. *Obes Surg* 2015; **25:** 1822–32.

90 Mechanick JI, Youdim A, Jones DB, et al, the American Association of Clinical Endocrinologists, Obesity Society, American Society for Metabolic & Bariatric Surgery. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient–2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Endocr Pract* 2013; **19:** 337–72.

91 Sjöström L, Narbro K, Sjöström CD, et al, and the Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007; **357:** 741–52.

92 Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. *JAMA* 2012; **307:** 56–65.

93 Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. *J Intern Med* 2013; **273:** 219–34.

94 Dixon JB, le Roux CW, Rubino F, Zimmet P. Bariatric surgery for type 2 diabetes. *Lancet* 2012; **379:** 2300–11.

95 Kashyap SR, Bhatt DL, Wolski K, et al. Metabolic effects of bariatric surgery in patients with moderate obesity and type 2 diabetes: analysis of a randomized control trial comparing surgery with intensive medical treatment. *Diabetes Care* 2013; **36:** 2175–82.

96 Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the diabetes surgery study randomized clinical trial. *JAMA* 2013; **309:** 2240–49.

97 Schauer PR, Bhatt DL, Kirwan JP, et al, and the STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes--3-year outcomes. *N Engl J Med* 2014; **370:** 2002–13.

98 Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 2015; **386:** 964–73.

99 Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 2014; **311:** 2297–304.

100 Frühbeck G. Bariatric and metabolic surgery: a shift in eligibility and success criteria. *Nat Rev Endocrinol* 2015; **11:** 465–77.

101 Fried M, Yumuk V, Oppert JM, et al, and the International Federation for Surgery of Obesity and Metabolic Disorders-European Chapter (IFSO-EC), and the European Association for the Study of Obesity (EASO), and the European Association for the Study of Obesity Obesity Management Task Force (EASO OMTF). Interdisciplinary European guidelines on metabolic and bariatric surgery. *Obes Surg* 2014; **24:** 42–55.

102 Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. *JAMA Surg* 2014; **149:** 275–87.

103 Tack J, Deloose E. Complications of bariatric surgery: dumping syndrome, reflux and vitamin deficiencies. *Best Pract Res Clin Gastroenterol* 2014; **28:** 741–49.

104 Brethauer SA, Kothari S, Sudan R, et al. Systematic review on reoperative bariatric surgery: American Society for Metabolic and Bariatric Surgery Revision Task Force. *Surg Obes Relat Dis* 2014; **10:** 952–72.

105 Stegenga H, Haines A, Jones K, Wilding J, for the Obesity Guideline Development Group (GDG). Identification, assessment and management of overweight and obesity: summary of NICE guidance. *BMJ* 2014; **349:** g6608.

106 Dietz WH, Baur LA, Hall K, et al. Management of obesity: improvement of health-care training and systems for prevention and care. *Lancet* 2015; **385:** 2521–33.

107 Phelan SM, Burgess DJ, Yeazel MW, Hellerstedt WL, Griffin JM, van Ryn M. Impact of weight bias and stigma on quality of care and outcomes for patients with obesity. *Obes Rev* 2015; **16:** 319–26.

108 Frühbeck G. Obesity: screening for the evident in obesity. *Nat Rev Endocrinol* 2012; **8:** 570–72.

109 Blundell JE, Dulloo AG, Salvador J, Frühbeck G, EASO SAB Working Group on BMI. Beyond BMI—phenotyping the obesities. *Obes Facts* 2014; **7:** 322–28.

110 Ahima RS, Lazar MA. Physiology. The health risk of obesity—better metrics imperative. *Science* 2013; **341:** 856–58.

111 Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. *Ann Intern Med* 2013; **159:** 758–69.

112 Chang Y, Ryu S, Suh BS, Yun KE, Kim CW, Cho SI. Impact of BMI on the incidence of metabolic abnormalities in metabolically healthy men. *Int J Obes (Lond)* 2012; **36:** 1187–94.

113 Gómez-Ambrosi J, Catalán V, Rodríguez A, et al. Increased cardiometabolic risk factors and inflammation in adipose tissue in obese subjects classified as metabolically healthy. *Diabetes Care* 2014; **37:** 2813–21.

114 Gómez-Ambrosi J, Silva C, Galofré JC, et al. Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. *Int J Obes (Lond)* 2012; **36:** 286–94.

115 Lavie CJ, De Schutter A, Milani RV. Healthy obese versus unhealthy lean: the obesity paradox. *Nat Rev Endocrinol* 2015; **11:** 55–62.

116 Thow AM, Downs S, Jan S. A systematic review of the effectiveness of food taxes and subsidies to improve diets: understanding the recent evidence. *Nutr Rev* 2014; **72:** 551–65.