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Corresponding Author: Prof. George Bray,

Corresponding Author's Institution: Pennington Biomedical Research Center

First Author: George A Bray, MD

Order of Authors: George A Bray, MD; Donna H Ryan, MD; John P Wilding, MD; Gema Fruhbeck, MD

Abstract: -Fast Facts (abbreviated) [Words = 425]

Definition: Obesity is multifactorial, resulting from genetic, epigenetic, physiological, behavioural, sociocultural and environmental influences which produce an imbalance between energy intake and expenditure over an extended time period.

Etiology: Obesity occurs in genetically susceptible individuals under a variety of environmental influences.

Natural history: Physiologic processes resist weight loss and produce a "settled" weight within a given environment. Weight loss produces metabolic adaptation (lower energy expenditure) and alterations in appetite signals that promote food intake. Persons with obesity struggle to lose weight and regain is common.

Prevention: The environment of developed countries is obesogenic.

Environmental change is the responsibility of societies. For individuals with obesity and no associated health risk, advise self-help approaches.

Iatrogenic weight gain: Many medications have been associated with weight gain (insulin, sulfonylureas, antidepressants, antipsychotics and others). For patients at-risk, avoid them, or prescribe weight neutral alternatives.

In medical practices, weight management is indicated for individuals with BMI >30kg/m<sup>2</sup> or >25kg/m<sup>2</sup> with an obesity associated comorbidity, including increased waist circumference.

Lifestyle Change: For many patients, changing behaviours requires skill training and use of behavioural tools (self-monitoring of food intake, physical activity and body weight; environmental control; contingency planning).

Diet: Many diets have been shown to produce and sustain weight loss, if they are followed. There is no magic diet. Choose a diet that the patient will follow and which has health benefits.

Physical Activity: Give a specific prescription describing the frequency, intensity, time and type. For weight loss, recommend minimum goal of 150 min/week. For prevention and maintenance, recommend 250-300 minutes per week is recommended.

Medicating for weight loss is indicated for individuals with BMI >30kg/m<sup>2</sup> or >27kg/m<sup>2</sup> with an obesity associated comorbidity. Medications approved in the US/EU are orlistat, naltrexone/ bupropion and liraglutide. In the US, lorcaserin and phentermine/topiramate are also available. Use the following principles:

\*Medications work by enhancing adherence to diet.

- \*Lifestyle is the foundation. Don't prescribe medications alone.
- \*All medications have different safety profiles that must be matched to the patient's profile.
- \*Every medication will not work in every patient. Stop the medication and try another if 4-5% weight loss does not occur in 3-4 months [In obese diabetic patients >3% weight loss can be considered satisfactory].
- \*Use medications long term to sustain lost weight.

Surgical management is indicated for individuals with BMI >40kg/m<sup>2</sup> or >35kg/m<sup>2</sup> with an obesity associated comorbidity. The three most common procedures are gastric banding, sleeve gastrectomy, and Roux-en Y gastric bypass. These procedures have been shown to produce remarkable health improvement and to reduce mortality. Life-long care is indicated to address nutritional needs long-term.

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## Management of Obesity

George A. Bray<sup>1</sup>, Gema Frühbeck<sup>2</sup>, Donna H. Ryan<sup>1</sup> and John PH Wilding<sup>3</sup>

1. Pennington Biomedical Research Center/LSU, Baton Rouge, Louisiana
2. Department of Endocrinology & Nutrition, Clínica Universidad de Navarra, University of Navarra, CIBEROBN, IdiSNA, Spain
3. Department of Medicine (Obesity) University of Liverpool, Liverpool, United Kingdom

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Contact Information:

George A. Bray MD  
Pennington Biomedical Research Center/LSU  
Baton Rouge, Louisiana 70808  
Telephone: (225) 763-3176  
e-mail: brayga@pbrc.edu

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**Surgical management is indicated for individuals with BMI  $\geq 40\text{kg/m}^2$  or  $\geq 35\text{kg/m}^2$  with an obesity associated comorbidity.** The three most common procedures are gastric banding, sleeve gastrectomy, and Roux-en Y gastric bypass. These procedures have been shown to produce remarkable health improvement and to reduce mortality. Life-long care is indicated to address nutritional needs long-term.

### **Search strategy and selection criteria**

A search for original articles and reviews published between January 1990 and August 2015 focusing on obesity management was performed 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 English-language, full-text articles were included. Very recent references from 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 randomized controlled trials, prospective case–control studies, meta-analyses and systematic reviews.

## **Background/Introduction: (Word Count = 376)**

Over the past 50 years obesity has become an international public health problem that impacts the quality of life, increases the risk of illness and raises health care costs in countries in all parts of the world (Appendix **Figure 1**).<sup>1-6</sup>

### **Appendix Figure 1 Worldwide prevalence of Obesity in men**

Measurement of obesity in these surveys is done with the body mass index (BMI), [wt(kg)/Ht(m<sup>2</sup>)] which has a modestly good correlation with body fat.<sup>7</sup> The BMI has the advantage of simplicity in epidemiological studies, but it has deficiencies since it does not separate fat from lean body mass.<sup>8</sup> Thus, BMI should be considered a screening measurement rather than a diagnostic tool. Additional measurements are needed to complement the BMI and should include waist circumference (or Waist/Height ratio).<sup>9,10</sup> Both variables are strong predictors of health risk.<sup>9,10</sup> Ethnic differences in waist circumference need to be considered in its clinical use.<sup>11</sup> In addition to measures of central adiposity it is desirable to measure blood pressure, glucose and lipids (HDL-cholesterol and triglycerides).

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

Obesity has a multifactorial nature resulting from genetic, epigenetic, physiological, behavioural, sociocultural and environmental influences that lead to an imbalance between energy intake and expenditure over an extended time period. Recently, 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 (described in more detail later), older parental age at birth as well as intrauterine and intergenerational effects have been highlighted as contributors to the obesity epidemic.<sup>19, 20</sup>

Obesity shortens life span<sup>21</sup> and impacts the function of many organ systems<sup>21, 22, 23</sup> (Appendix **Figure 2**). This mortality results from several diseases that are associated with obesity, including diabetes, chronic kidney disease, gastro-intestinal disease and cardiovascular disease.

### **Appendix Figure 2 Mortality versus BMI**

Body weight is defended, meaning that maintaining weight loss is often difficult or unsuccessful.<sup>24</sup>

### **Management of the Patient with Obesity (Word count = 171)**

The rising prevalence of obesity worldwide cries out 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<sup>28</sup>, and many studies have tested strategies in schools, in work-sites and in the community that might prevent progression of BMI, but so far, these efforts have had limited impact<sup>26, 27</sup> and the evidence for effective economic policies to prevent obesity remains limited.<sup>28</sup>

When prevention fails, as it will for many people, treatment is indicated. To guide health care professionals in treating the problem effectively a number of guidelines have been developed both in the US,<sup>29, 30, 31</sup> in the UK<sup>32</sup> and in Europe.<sup>33, 34</sup> We will use these guidelines as the 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 (Word Count = 485):**

The cornerstone for treatment of the patient with obesity in the US, UK and Europe is a Comprehensive, or Multi-component Lifestyle Intervention.<sup>29, 30, 32, 35</sup>

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, in part, by data from 2 large randomized clinical trials: the Look AHEAD<sup>36</sup> and the Diabetes Prevention Program.

<sup>37</sup> 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 summarized for the 8 year data in 3 of the 4 panels in **Figure 1**. A systematic review of evidence showed that if these components are delivered in at least 14 face-to-face (group or individual) sessions over six months with treatment continuing to one year, average observed weight loss is 8 kg.<sup>29</sup> While this may seem modest, it translates into clinically significant improvements in blood pressure, triglycerides, HDL cholesterol, measures of glycaemic control and reduction in risk for progression to type 2 diabetes.<sup>29</sup> Based on these and other findings, the US Preventive Services Task Force<sup>38</sup> has recommended that obese individuals with cardiovascular disease (CVD) risk factors should be referred for lifestyle treatment and the US Center for Medicare and Medicaid Services promoted policies to reimburse providers for intensive behavioural therapy for the patient with obesity.<sup>39</sup> In the UK, NICE



recommends progressively intensive interventions based on degree of overweight and obesity and presence of co-morbidity(ies).

### **Figure 1 about here**

The initial rate of weight loss in the 1<sup>st</sup> month as well as the 2<sup>nd</sup> month also predicts weight loss at 4 and 8 years in the Look AHEAD study (**panel 4 of figure 1**). Those losing <3% at 2 months were 2.5% below baseline at 8 years, those losing 3-6% were about 4.5% below baseline at 8 years and those losing >6% were just over 7% below baseline on average at 8 years, data which suggests that larger early weight losses are beneficial.<sup>40</sup> Commercial programs of many types can provide a useful strategy for some individuals to lose weight<sup>41</sup>. There are several commercial weight loss programmes available, and some individuals may benefit from them. The costs and methods of delivering treatment vary which may affect compliance and real-world applicability. These programmes provide on the average about 3% weight loss over a year, but long-term compliance is generally poor. Studies of longer than a year are sparse. A meta-analysis comparing these “named” diets found not significant differences between them<sup>42</sup>.

### **Diets for Weight Loss (Words = 581).**

Several considerations enter into selecting a diet for weight loss. It must have less energy than is required for daily maintenance<sup>29, 43,44</sup> and one to which the patient with obesity will adhere and possibly provide other health benefits. Reducing energy by 500 kcal/d below energy requirements or by using a dietary plan which has 1200 to 1500 kcal/d for women or 1500 to 1800 kcal/d for men (increased by a further 300 kcal/d for each gender if weight exceeds 150 kg) will accomplish the first

goal. In addition to reducing calories, some dietary patterns appears to offer other health benefits.<sup>45, 46, 47</sup>

There is an entrenched belief that there is a “magic” weight loss diet. This belief has stimulated numerous studies that have focused on different amounts of dietary fat, protein or carbohydrate. These low-fat diets, low-carbohydrate/high-protein diets, low glycaemic-index diets, balanced deficit diets have been compared in many studies and summarized in a few meta-analyses. One of the largest studies with 811 patients who were obese or overweight, the POUNDS Lost study, compared diets with 20% or 40% fat and 15% or 25% protein and found no difference in weight loss at 6 months or 2 years.<sup>48</sup> A meta-analysis of low carbohydrate versus low fat diets was in essential agreement stating that low-carbohydrate diets are at least as effective as low-fat diets at reducing weight and improving metabolic risk factors.<sup>49</sup> A systematic review of evidence from 17 diets also found that no one diet was superior.<sup>29</sup> Similarly, a meta-analysis of “named” diets found no significant difference in weight loss between them.<sup>42</sup> Thus the best current advice is to provide low energy diets that are likely to be followed by the patient and provide health benefits.

A slightly more favourable picture emerges for the Mediterranean style diet. In a meta-analysis of nine studies with 1178 patients Mediterranean style diets were associated with a significant decline of body weight and BMI and reductions in hemoglobin A1c, fasting plasma glucose, and fasting insulin.<sup>50</sup> Along with this effect on body weight, one version of this dietary pattern can reduce CVD risk.<sup>47</sup>

The jury is still out about low glycaemic index/load diets. A 5 week randomized trial found no significant effect on insulin resistance or markers of CVD

risk.<sup>51</sup> A meta-analysis of 14 studies, however, raised concern. Although C-reactive protein and fasting insulin did benefit from the low GI/GL 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.<sup>52</sup>

Very low-calorie diets (VLCD) or very low-energy diets (VLED), 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 interesting work has shown that such an approach can rapidly normalize blood glucose and other risk factors in people with type 2 diabetes. Systematic reviews, however,<sup>32,53</sup> suggested that although initial weight loss is more rapid, weight change after one year or more is not much different from comprehensive or multi-component approaches and does not recommend their routine use, although they may be considered if rapid weight loss is clinically necessary. In their analysis of commercial programs, Gudzone et al found that very-low-calorie (VLCD) programs, 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 beyond 6 months when this duration of data was available.<sup>41</sup>

### **Physical Activity (Word Count = 247)**

Increased physical activity is an essential component of comprehensive lifestyle intervention for obesity management. The recommendations in recent US & UK guidelines typically prescribe gradually increasing aerobic physical activity (such as brisk walking) to reach a goal of >150 minutes/week (equal to >30 minutes/day, for at least 5 days each week).<sup>29, 32, 54</sup> This has benefits for general health that are independent of weight loss.<sup>55</sup> Meta-analysis of trials indicated that this results in an

additional 1 to 1.5kg weight loss over 12 months over and above dietary intervention alone.<sup>32, 57</sup> There is evidence that a greater amount physical activity (30-45 minutes per day) is required to prevent obesity and that for long-term weight maintenance in those who have lost weight, 60-90 minutes per day is required,<sup>29, 56</sup> but this is likely to require close supervision as part of an intensive programme, which may not be practical or sustainable in many clinical settings.<sup>58, 59, 60</sup> However, while this is effective in the short term in controlled settings, the activities and their benefits are not readily sustained, as was found comparing the 1 and 4 year results in the Look AHEAD study.<sup>36</sup> The type of physical activity (eg aerobic vs resistance; 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, they might be preferable to some; it would therefore seem appropriate to recommend programmes that are acceptable to patients.<sup>55, 61</sup>

### **Pharmacotherapy (Words = 1252)**

A recent systematic review and clinical guidance sponsored by the Endocrine Society<sup>29</sup> 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**).<sup>31, 62, 63</sup>

#### **Table 1 (Medications that Produce Weight Gain)**

The indications for adding pharmacotherapy to a weight loss effort are history of failure to achieve clinically meaningful weight loss (>5%) and to sustain lost

weight, for patients who meet regulatory prescribing guidelines (BMI  $\geq 27$  kg/m<sup>2</sup> with one or more co-morbidities or a BMI  $>30$  kg/m<sup>2</sup> with or without associated metabolic consequences).<sup>29, 31, 32</sup>

Five medications have been approved in the US for chronic weight management, and three of these have also been approved in the EU. [See **Table 2** for dosing, mechanism of action and efficacy, safety and tolerability of these drugs. The data supporting these tables is derived from the prescribing information labelling approved by the US FDA].<sup>64, 65, 66, 67, 68, 69</sup> **Figure 2** shows the sites of action for these medications.

**Figure 2 about here**

**Table 2. Medications Approved in EU and/or US: Mechanism of Action, Dosing, Efficacy, Tolerability and Safety**

Several guiding principles should be followed when prescribing drugs for weight loss.<sup>31</sup> 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 more than 4 to 5% in patients without diabetes (In patients with obesity and diabetes  $>3\%$  weight loss 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.<sup>64</sup> It has only been studied in short-term trials and is a controlled substance in the US. It has abuse 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.<sup>70</sup> It is available in most countries world-wide. Orlistat is among the safest drugs in this category<sup>64</sup> and is approved for use in adolescents.<sup>71</sup> Additionally, a study of 4 years duration<sup>72</sup> 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<sup>65</sup> limit its popularity with patients.

Since 2012, 4 medications have reached the market in the US – lorcaserin,<sup>73, 74, 75</sup> a combination of phentermine/topiramate ER,<sup>76, 77, 78</sup> a combination of naltrexone SR/bupropion SR<sup>79, 80, 81, 82</sup> and liraglutide 3.0 mg.<sup>83, 84, 85, 86</sup> These drugs are required by regulatory agencies in the US and EU to present data on >2500 patients and to approximate or exceed 5% greater weight loss than placebo and to demonstrate positive effects on a variety of risk factors and disease markers. All agents must show evidence of no increase in cardiovascular risk, which is likely to require a cardiovascular outcome trial either before or after marketing.. Further, all of these drugs were studied with a suicidality rating scale.<sup>87</sup> These medications have an indication for “chronic weight management” indicating long-term usage, along with diet and physical activity in individuals with BMI  $\geq 30$  kg/m<sup>2</sup> or a BMI  $\geq 27$  kg/m<sup>2</sup> with one or more comorbidities. They are to be used over the long term, not just to produce weight loss, but to sustain lost weight.

Lorcaserin is a specific serotonin 2c receptor agonist.<sup>73</sup> Lorcaserin is remarkable for its tolerability and low rate of adverse events.<sup>73, 74, 75</sup> Echocardiograms performed in phase III studies on more than 5200 subjects found no statistically significant increase in FDA defined valvulopathy.<sup>66</sup> The drug should not be used with monoamine oxidase inhibitors (MAOIs) because of the risk of serotonin syndrome.<sup>66</sup> It has not been studied with SSRIs, SNRIs or other serotonergic agents and extreme caution should be used in combining it with those agents.<sup>66</sup>

The combination of phentermine and topiramate as in extended release (ER) formulation (PHEN/TPM ER) uses lower doses of both (7.5/46 mg at the recommended dose) than are usually prescribed when either drug is used as single agent.<sup>76, 77, 78</sup> This medication is associated with greater mean weight loss than other available medications. Topiramate is associated with fetal toxicity (oral clefts)<sup>88</sup> and a pregnancy test prior to initiating therapy and monthly thereafter is recommended.<sup>67</sup> The most common side effects include paresthesias, dizziness, dysgeusia, insomnia, constipation and dry mouth.<sup>67</sup> A rare side effect of topiramate is acute myopia with glaucoma and the drug is contraindicated in glaucoma.<sup>67</sup> The combination of PHEN/TPM ER is also contraindicated in hyperthyroidism and within 14 days of treatment with monoamine oxidase inhibitors (MAOIs).<sup>67</sup> Other rare potential adverse risks include kidney stones (associated with topiramate) and increased heart rate (associated with phentermine) in patients susceptible to sympathomimetic drugs.<sup>67</sup>

The combination of naltrexone SR/bupropion SR was approved in the US in 2012 and in the EU in 2015.<sup>79, 80 81, 82</sup> Bupropion is a mild reuptake inhibitor of dopamine and norepinephrine. Naltrexone, an opioid antagonist has minimal effect

on weight loss on its own. Naltrexone is thought to block inhibitory influences of opioid receptors activated by the  $\beta$ -endorphin released in the hypothalamus that stimulates feeding, thus allowing the inhibitory effects of  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH) to reduce food intake. Naltrexone SR/ bupropion SR can increase blood pressure; 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.<sup>68</sup> Despite these signals, absence of increased events in the interim analysis of a cardiovascular outcome trial conducted before marketing allowed approval.<sup>68</sup> Another cardiovascular outcome trial was required post-marketing. Tolerability issues, chiefly nausea on initiating the drug mandate a dose escalation over four weeks. All antidepressants in the US are required to carry a black box warning of suicidality and the combination's label includes this.<sup>68</sup> However, there was no signal for suicidality in phase III studies.<sup>78, 79, 80, 81, 83</sup>

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 up to 1.8 mg, given by injection. It is now approved in the US and EU for chronic weight management at a dose of 3.0 mg.<sup>83, 84, 85, 86</sup> Nausea has been one of the principal complaints in patients injecting this drug and a slow dose escalation over 5 weeks is prescribed.<sup>69</sup> There is also a small, but significant increase in heart rate, but blood pressure tends to fall.<sup>69</sup> GLP-1 agonists are associated with thyroid C cell tumors in animals, but this has not been demonstrated with certainty in humans.<sup>69</sup> Liraglutide should not be prescribed in patients with family or personal history of medullary thyroid cancer or multiple endocrine neoplasia.<sup>69</sup> Acute pancreatitis, gall bladder disease and hypoglycemia in diabetics are safety issues that require managing if they occur.



## **Surgical Procedures in the Treatment of Obesity (Word Count = 509)**

Bariatric surgery has rapidly become adopted as a treatment option for severe obesity, particularly since the advent of lower risk laparoscopic procedures, with nearly half a million procedures performed worldwide in 2013.<sup>89</sup> 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**).<sup>90</sup>

### **Table 3 about here**

Longer term studies of outcomes following bariatric surgery have generally shown favourable results. The Swedish Obese Subjects study followed 2000 patients for up to 20 years after surgery including banded gastroplasty, gastric banding and Roux-en-Y gastric bypass performed by open techniques which have since been replaced by laparoscopy. There was a 24% reduction in mortality, mainly due to reduced risk of myocardial infarction and cancer (in women), compared to an observational control group.<sup>91, 92</sup> Many other co-morbidities, such as type 2 diabetes and sleep apnoea are also improved, and patients report consistent improvements in quality of life.<sup>93</sup>

Particularly striking and rapid improvements in glucose control have been seen in patients with type 2 diabetes, especially following gastric bypass, suggesting that part of the metabolic improvement is independent of weight loss.<sup>94</sup> 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.<sup>95, 96, 97, 99</sup> Observational data also suggest that future risk of

diabetes-related micro- and macrovascular complications are also reduced.<sup>99</sup> This has led to the concept of 'metabolic' surgery, and recent 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 and 35 kg/m<sup>2</sup>,<sup>32, 100, 101</sup> and a move away from BMI as the main criterion used to assess eligibility for surgery.<sup>100</sup> 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 significant, particularly for gastric banding (**Table 3**). 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.<sup>103</sup> Weight regain can also be a significant problem, and revisional surgery carries greater risks and no guarantee of success;<sup>104</sup> there is an increasing focus on lifestyle programmes after bariatric surgery to reduce the risk of this occurring.<sup>32</sup>

From a clinical perspective it is essential that patients and clinicians considering referral for bariatric surgery are fully aware of the risks and benefits; good practice might include provision of a detailed education session, attendance at patient support groups as well as detailed lifestyle advice and psychological support both before and after surgery.<sup>105</sup>

**Controversies: (words = 529)**

As with other areas of medicine, not all issues have been resolved to everyone's satisfaction. Below is a list of some of the controversies that are up for continuing debate and resolution.

Should obesity be a strong focus of undergraduate medical education or should it be taught primarily at the most graduate level? <sup>106</sup> Weight bias is commonly observed among medical students as well as experienced doctors to stigmatize patients.<sup>107</sup> This stigma might be reduced if the complexities of obesity were introduced earlier. This stigma might also partly explain why obesity is an under-diagnosed and under-treated condition despite its high prevalence. <sup>108</sup>

Who needs to lose weight and what is the best way to decide? Is BMI an appropriate measure to decide who should lose weight? <sup>109</sup> 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 favor 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.

A third controversy revolves around whether there are people who are obese and "metabolically healthy" the so-called Metabolic Healthy Obesity or MHO. Individuals with metabolically healthy obesity (MHO) may not improve their cardiometabolic risk factors significantly after weight loss interventions and may therefore not benefit to the same extent as obese patients with metabolic comorbidities. There is controversy as to whether individuals labeled as "metabolic-health-obese" are really healthy, especially since no general agreement exists on accepted criteria to define those with MHO.<sup>110, 111</sup> Moreover, there is still controversy as to whether MHO

can be considered an established phenotype or rather represents a transient stage toward ill-health with ageing, behavioural and environmental factors. MHO appears to be a relatively transient condition with a considerable percentage of these individuals exhibiting similar metabolic derangements to those observed in obese metabolically altered patients as time passes.<sup>112, 113</sup> Conversely, non-obese individuals according to BMI but obese based on body fat distribution exhibit elevated cardiometabolic risk factors<sup>114, 115</sup>, 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 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 impacts on health services. A number of studies (NCT00991640, NCT01967797 and NCT01606813) are due to report on this problem in the next few years.

Obesity raises a number of societal controversies. Government taxes on “unhealthy” foods has been tried in some countries (Denmark for example) but with variable results. Should governments subsidize commercial weight loss programs that have proven to be successful?<sup>116</sup>

## Legends:

**Figure 1.** Factors that predict weight loss in the Look AHEAD study (Refs 36, 40) The results in panels A, B and C indicate the greater weight loss at 1-year associated with greater proportion of visits, attended, minutes per week of physical activity, and greater meal replacement use. Black bars indicate the first quartile and light gray ones the 4<sup>th</sup> quartile. Panel D shows the weight loss at years 4 and 8 by percent weight loss at one month (left side) and 2 months (right side). The tertiles of weight ranges are shown below each set of bars.

**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 I-III development. The right hand panel summarizes the neurotransmitters and pathways involved in the central nervous system in energy homeostasis, while 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, i.e. energy intake and expenditure. Note that most of the currently approved drugs are working centrally where stimulation of the POMC/CART pathway has anorexigenic effects, while the NPY/AGRP pathway exerts orexigenic effects. The interaction with the multiple receptors present in neurones of the hypothalamus determines the balance between orexigenic and anorexigenic influences. Most of the drugs currently tested in clinical trials are aimed at peripheral systems. Thus, thyroid analogues and  $\beta_3$  adrenergic agonists induce thermogenesis via activation of brown adipose tissue (BAT), thereby increasing energy expenditure. Enzymes involved in lipid metabolism such as DGAT, FAS, MetAP2 and NQO1 are also being targeted. The gut microbiome as well as the regulation of bile acids represent further targets to combat obesity. The lipase and SGLT2 inhibitors favour energy loss via 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.

Abbreviations: DGAT1 = diacylglycerol O-acyltransferase aminotransferase 1; FAS = fatty acid synthase; MetAP2 = methionyl aminopeptidase 2; PexRAP inh = peroxisomal reductase activating PPAR $\gamma$  inhibitor; NQO1 = NAD(P)H dehydrogenase:quinone oxidoreductase 1; SGLT2 = sodium-glucose-linked transporter 2; inh = inhibitor; BAT = brown adipose tissue; WAT = white adipose tissue; GABA =  $\gamma$ -aminobutyric acid; DA = dopamine; NE = norepinephrine; CB = cannabinoid; H = histamine; 5HT = serotonin; ObR = leptin receptor; GHSR = growth hormone secretagogue receptor; AGRP = Agouti-related peptide; CART = cocaine amphetamine-related transcript; NPY = neuropeptide Y; Y1R = Y1 receptor; Y2R = Y2 receptor; Y5R = Y5 receptor; POMC = proopiomelanocortin C; GLP1R =

glucagon-like peptide 1 receptor;  $\alpha$ -MSH =  $\alpha$ -melanocyte-stimulating hormone; MCH1R = melanin-concentrating hormone 1 receptor; MC3R = melanocortin receptor type 3; MC4R = melanocortin receptor type 4;  $\mu$ -OR =  $\mu$ -opioid receptor; 5HT2c = serotonin receptor type 2c.

**Appendix figure 1.** The Global Pandemic of Obesity Illustrated by the Prevalence of Obesity by Country for Males over 20 Years of Age. (Ref 5).

**Appendix figure 2.** Relation of body mass index to mortality in pooled data sets with over 900,000 people and the effect of specific causes of death (Ref 21). All-cause mortality versus BMI for each sex in the range 15-50 kg/m<sup>2</sup> (excluding the first 5 years of follow-up) Relative risks at age 35-89 adjusted for age at risk, smoking and study, were multiplied by a common factor (i.e., floated) to make the weighted average match the PSC mortality rate at age 35-79 years. Area of the square is inversely proportional to the variance of the long risk.

#### **Tables:**

Table 1: Medications Affecting Weight Gain and Alternative Approaches

Table 2: Medications for weight management: Mechanism of action, availability and dosing. (Ref: US Product Label, except where noted)

Table 3: Effect of the Principal Surgical Procedures for Treatment of Obesity

Appendix Table: Common side effects and contraindications and warnings for medications used to treat patients who are overweight or obese.

### **Author Contributions to the Manuscript:**

George Bray was invited to develop the review and invited Dr. Donna Ryan, Dr. Gema Frühbeck and Dr. John Wilding to contribute. Bray drafted the initial manuscript which was substantially revised by each author. All 4 authors contributed to the literature search and to the development of figures and tables.

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## Management of Obesity

George A. Bray<sup>1</sup>, Gema Frühbeck<sup>2</sup>, Donna H. Ryan<sup>1</sup> and John PH Wilding<sup>3</sup>

1. Pennington Biomedical Research Center/LSU, Baton Rouge, Louisiana
2. Department of Endocrinology & Nutrition, Clínica Universidad de Navarra, University of Navarra, CIBEROBN, IdiSNA, Spain
3. Department of Medicine (Obesity) University of Liverpool, Liverpool, United Kingdom

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3 Tables, [1 Supplemental Table](#), [24 Figures in text](#), [2 figures in appendix](#) and [1166](#) References

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Contact Information:

George A. Bray MD  
Pennington Biomedical Research Center/LSU  
Baton Rouge, Louisiana 70808  
Telephone: (225) 763-3176  
e-mail: [brayga@pbrc.edu](mailto:brayga@pbrc.edu)

**Fast Facts** (abbreviated) [Words = 424]

**Definition:** Obesity is multifactorial, resulting from genetic, epigenetic, physiological, behavioural, sociocultural and environmental influences which produce an imbalance between energy intake and expenditure over an extended time period.

**Etiology:** Obesity occurs in genetically susceptible individuals under a variety of environmental influences.

**Natural history:** Physiologic processes resist weight loss and produce a “settled” weight *within a given environment*. Weight loss produces metabolic adaptation (lower energy expenditure) and alterations in appetite signals that promote food intake. Persons with obesity struggle to lose weight and regain is common.

**Prevention:** The environment of developed countries is obesogenic. Environmental change is the responsibility of societies. For individuals with obesity and no associated health risk, advise self-help approaches.

**Iatrogenic weight gain:** Many medications have been associated with weight gain (insulin, sulfonylureas, antidepressants, [antipsychotics](#) and others). For patients at-risk, avoid them, or prescribe weight neutral alternatives.

**In medical practices, weight management is indicated for individuals with BMI  $\geq 30\text{kg/m}^2$  or  $\geq 25\text{kg/m}^2$  with an obesity associated comorbidity, including increased waist circumference.**

**Lifestyle Change:** For many patients, changing behaviours requires skill training and use of behavioural tools (self-monitoring of food intake, physical activity and body weight; environmental control; contingency planning).

**Diet:** Many diets have been shown to produce and sustain weight loss, if they are followed. There is no magic diet. Choose a diet that the patient will follow and which has health benefits.

**Physical Activity:** Give a specific prescription describing the frequency, intensity, time and type. For weight loss, recommend minimum goal of 150 min/week. For prevention and maintenance, recommend 250-300 minutes per week is recommended.

**Medicating for weight loss is indicated for individuals with BMI  $\geq 30\text{kg/m}^2$  or  $\geq 27\text{kg/m}^2$  with an obesity associated comorbidity. Medications approved in the US/EU are orlistat, naltrexone/ bupropion and liraglutide. In the US, lorcaserin and phentermine/topiramate are also available.** Use the following principles:

- Medications work by enhancing adherence to diet.

- Lifestyle is the foundation. Don't prescribe medications alone.
- All medications have different safety profiles that must be matched to the patient's profile.
- Every medication will not work in every patient. Stop the medication and try another if 4-5% weight loss does not occur in 3-4 months [In obese diabetic patients >3% weight loss can be considered satisfactory].
- Use medications long term to sustain lost weight.

**Surgical management is indicated for individuals with BMI  $\geq 40\text{kg/m}^2$  or  $\geq 35\text{kg/m}^2$  with an obesity associated comorbidity.** The three most common procedures are gastric banding, sleeve gastrectomy, and Roux-en Y gastric bypass. These procedures have been shown to produce remarkable health improvement and to reduce mortality. Life-long care is indicated to address nutritional needs long-term.

### **Search strategy and selection criteria**

A search for original articles and reviews published between January 1990 and August 2015 focusing on obesity management was performed 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 English-language, full-text articles were included. Very recent references from 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 randomized controlled trials, prospective case-control studies, meta-analyses and systematic reviews.

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## Background/Introduction: (Word Count = 376)

Over the past 50 years obesity has become an international public health problem that impacts the quality of life, increases the risk of illness and raises health care costs in countries in all parts of the world ([Appendix Figure 1](#)) (1-6).

### [Appendix Figure 1](#) Worldwide prevalence of Obesity in men

Measurement of obesity in these surveys is done with the body mass index (BMI),  $[\text{wt}(\text{kg})/\text{Ht}(\text{m}^2)]$  which has a modestly good correlation with body fat (7). The BMI has the advantage of simplicity in epidemiological studies, but it has deficiencies since it does not separate fat from lean body mass (8). Thus, BMI should be considered a screening measurement rather than a diagnostic tool. Additional measurements are needed to complement the BMI and should include waist circumference (or Waist/Height ratio) (9, 10). Both variables are strong predictors of health risk (9, 10). Ethnic differences in waist circumference need to be considered in its clinical use (11). In addition to measures of central adiposity it is desirable to measure blood pressure, glucose and lipids (HDL-~~cholesterol~~C and triglycerides).

Obesity is expensive (12, 13) and along with diabetes 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, sociocultural and environmental influences that lead to an imbalance between energy intake and expenditure over an extended time period. Recently, 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 (described in more detail later), older parental age at birth as well as intrauterine and intergenerational effects have been highlighted as contributors to the obesity epidemic.<sup>19, 20</sup>

Obesity shortens life span (21) and impacts the function of many organ systems (22). ( [Appendix Figure 2](#)). (21, 23) This mortality results from several diseases that are associated with obesity, including diabetes, chronic kidney disease, gastro-intestinal disease and cardiovascular disease.

### **[Appendix Figure 2 Mortality versus BMI](#)**

Body weight is defended, meaning that maintaining weight loss is often difficult or unsuccessful (24).

### **Management of the Patient with Obesity (Word count = 171)**

The rising prevalence of obesity worldwide cries out 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 ([28Sturm-2014](#)), and many studies have tested strategies in schools, in work-sites and in the community that might prevent progression of BMI, but so far, these efforts have had limited impact<sup>26, 27</sup> and the evidence for effective economic policies to prevent obesity remains limited.<sup>28</sup>

When prevention fails, as it will for many people, treatment is indicated. To guide health care professionals in treating the problem effectively a number of guidelines have been developed both in the US,<sup>29, 30, 31</sup> in the UK<sup>32</sup> and in Europe.<sup>33, 34</sup> We will use these guidelines as the 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 (Word Count = 485):**

The cornerstone for treatment of the patient with obesity in the US, UK and Europe is a Comprehensive, or Multi-component Lifestyle Intervention.<sup>29, 30, 32, 35</sup> 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, in part, by data from 2 large randomized clinical trials: the Look AHEAD<sup>36</sup> and the Diabetes Prevention Program.<sup>37</sup> 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 summarized for the 8 year data in 3 of the 4 panels in **Figure 13**. A systematic review of evidence showed that if these components are delivered in at least 14 face-to-face (group or individual) sessions over six months with treatment continuing to one year, average observed weight loss is 8 kg.<sup>29</sup> While this may seem modest, it translates into clinically significant improvements in blood pressure, triglycerides, HDL cholesterol, measures of glycaemic control and reduction in risk for progression to type 2 diabetes.<sup>29</sup> Based on these and other findings, the US Preventive Services Task Force<sup>38</sup> has recommended that obese individuals with cardiovascular disease (CVD) risk factors should be referred for lifestyle treatment and the US Center for Medicare and Medicaid Services promoted policies to reimburse providers for intensive behavioural therapy for the patient with obesity.<sup>39</sup> In the UK, NICE

recommends progressively intensive interventions based on degree of overweight and obesity and presence of co-morbidity(ies).

**Figure 13** about here

The initial rate of weight loss in the 1<sup>st</sup> month as well as the 2<sup>nd</sup> month also predicts weight loss at 4 and 8 years in the Look AHEAD study (**panel 4 of figure 13**).

Those losing <3% at 2 months were 2.5% below baseline at 8 years, those losing 3-6% were about 4.5% below baseline at 8 years and those losing >6% were just over 7% below baseline on average at 8 years, data which suggests that larger early weight losses are beneficial.<sup>40</sup> Commercial programs of many types can provide a

useful strategy for some individuals to lose weight<sup>41</sup>. ~~In a meta-analysis of commercial programs in the US, found that at 12 months Weight Watchers participants achieved at least 2.6% more weight loss than the control/education group; the Jenny Craig program weight loss was at least 4.9% greater at 12 months than in the control/education and counselling group; the Atkins program resulted in 0.1% to 2.9% greater weight loss at 12 months than counselling; and the Nutrisystem weight loss program was at least 3.8% greater at 3 months than the control/education and counseling control groups.~~<sup>44</sup> There are several commercial weight loss programmes available, and some individuals may benefit from them. The costs and methods of delivering treatment vary which may affect compliance and real-world applicability. These programmes provide on the average about 3% weight loss over a year, but long-term compliance is generally poor. Studies of longer than a year are sparse. A meta-analysis comparing these “named” diets found not significant differences between them<sup>42</sup>.

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## **Diets for Weight Loss (Words = 582).**

Several considerations enter into selecting a diet for weight loss. It must have less energy than is required for daily maintenance<sup>29, 43, 44</sup> and one to which the patient with obesity will adhere and possibly provide other health benefits. Reducing energy by 500 kcal/d below energy requirements or by using a dietary plan which has 1200 to 1500 kcal/d for women or 1500 to 1800 kcal/d for men (increased by a further 300 kcal/d for each gender if weight exceeds 150 kg) will accomplish the first goal. In addition to reducing calories, some dietary patterns appears to offer other health benefits.<sup>45, 46, 47</sup>

There is an entrenched belief that there is a “magic” weight loss diet. This belief has stimulated numerous studies that have focused on different amounts of dietary fat, protein or carbohydrate. These low-fat diets, low-carbohydrate/high-protein diets, low glycaemic-index diets, balanced deficit diets have been compared in many studies and summarized in a few meta-analyses. One of the largest studies with 811 patients who were obese or overweight, the POUNDS Lost study, compared diets with 20% or 40% fat and 15% or 25% protein and found no difference in weight loss at 6 months or 2 years.<sup>48</sup> A meta-analysis of low carbohydrate versus low fat diets was in essential agreement stating that low-carbohydrate diets are at least as effective as low-fat diets at reducing weight and improving metabolic risk factors.<sup>49</sup> A systematic review of evidence from 17 diets also found that no one diet was superior.<sup>29</sup> Similarly, a meta-analysis of “named” diets found no significant difference in weight loss between them.<sup>42</sup> Thus the best current advice is to provide low energy diets that are likely to be followed by the patient and provide health benefits.

A slightly more favourable picture emerges for the Mediterranean style diet. In a meta-analysis of nine studies with 1178 patients Mediterranean style diets were associated with a significant decline of body weight and BMI and reductions in hemoglobin A1c, fasting plasma glucose, and fasting insulin.<sup>50</sup> Along with this effect on body weight, one version of this dietary pattern can reduce CVD risk.<sup>47</sup>

The jury is still out about low glycaemic index/load diets. A 5 week randomized trial found no significant effect on insulin resistance or markers of CVD risk.<sup>51</sup> A meta-analysis of 14 studies, however, raised concern. Although C-reactive protein and fasting insulin did benefit from the low GI/GL 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.<sup>52</sup>

Very low-calorie diets (VLCD) or very low-energy diets (VLED), 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 interesting work has shown that such an approach can rapidly normalize blood glucose and other risk factors in people with type 2 diabetes. ~~A s~~Systematic reviews, however, <sup>32,53</sup> suggested that although initial weight loss is more rapid, weight change after one year or more is not much different from comprehensive or multi-component approaches and does not recommend their routine use, although they may be considered if rapid weight loss is clinically necessary. In their analysis of commercial programs, Gudzone et al found that very-low-calorie (VLCD) programs, 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 beyond 6 months when this duration of data was available.<sup>41</sup>

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### **Physical Activity (Word Count = 247)**

Increased physical activity is an essential component of comprehensive lifestyle intervention for obesity management. The recommendations in recent US & UK guidelines typically prescribe gradually increasing aerobic physical activity (such as brisk walking) to reach a goal of >150 minutes/week (equal to >30 minutes/day, for at least 5 days each week).<sup>29, 32, 54</sup> This has benefits for general health that are independent of weight loss.<sup>556</sup> Meta-analysis of trials indicated that this results in an additional 1 to 1.5kg weight loss over 12 months over and above dietary intervention alone.<sup>32, 57</sup> There is evidence that a greater amount physical activity (30-45 minutes per day) is required to prevent obesity and that for long-term weight maintenance in those who have lost weight, 60-90 minutes per day is required,<sup>29, 565</sup> but this is likely to require close supervision as part of an intensive programme, which may not be practical or sustainable in many clinical settings.<sup>58, 59, 60</sup> However, while this is effective in the short term in controlled settings, the activities and their benefits are not readily sustained, as was found comparing the 1 and 4 year results in the Look AHEAD study.<sup>36</sup> The type of physical activity (eg aerobic vs resistance; 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, they might be preferable to some; it would therefore seem appropriate to recommend programmes that are acceptable to patients.<sup>556, 61</sup>

### **Pharmacotherapy (Words = 1232)**

A recent systematic review and clinical guidance sponsored by the Endocrine Society<sup>29</sup> 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**).<sup>31, 62, 63</sup>

### **Table 1 (Medications that Produce Weight Gain)**

The indications for adding pharmacotherapy to a weight loss effort are history of failure to achieve clinically meaningful weight loss (>5%) and to sustain lost weight, for patients who meet regulatory prescribing guidelines (BMI  $\geq 27$  kg/m<sup>2</sup> with one or more co-morbidities or a BMI >30 kg/m<sup>2</sup> with or without associated metabolic consequences).<sup>29, 31, 32</sup>

Five medications have been approved in the US for chronic weight management, and three of these have also been approved in the EU. [See **Table 2** for dosing, mechanism of action and efficacy, safety and tolerability of these drugs. The data supporting these tables is derived from the prescribing information labelling approved by the US FDA].<sup>643, 654, 665, 676, 687, 698</sup> **Figure 24** shows the sites of action for these medications.

**Figure 2 about here**

### **Table 2. Medications Approved in EU and/or US: Mechanism of Action, Dosing, Efficacy, Tolerability and Safety**

Several guiding principles should be followed when prescribing drugs for weight loss.<sup>31</sup> 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*

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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 more than 4 to 5% in patients without diabetes (In patients with obesity and diabetes >3% weight loss 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.<sup>643</sup> It has only been studied in short-term trials and is a controlled substance in the US. It has abuse 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.<sup>7069</sup> It is available in most countries world-wide. Orlistat is among the safest drugs in this category<sup>64</sup> and is approved for use in adolescents.<sup>710</sup> Additionally, a study of 4 years duration<sup>721</sup> 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<sup>654</sup> limit its popularity with patients.

Since 2012, 4 medications have reached the market in the US – lorcaserin,<sup>732, 743, 754</sup> a combination of phentermine/topiramate ER,<sup>765, 776, 787</sup> a combination of naltrexone SR/bupropion SR<sup>798, 8079, 80, 81, 82, 823</sup> and liraglutide 3.0 mg.<sup>834, 845, 856, 867</sup> These drugs are required by regulatory agencies in the US and EU to present data on >2500 patients and to approximate or exceed 5% greater weight loss than placebo (~~with the EU's interest in exceeding 10% weight loss~~) and to demonstrate positive effects on a variety of risk factors and disease markers. All ~~centrally acting~~ agents must [show evidence of no increase in cardiovascular risk, which is likely to](#)

~~require a cardiovascular outcome trial either before or after marketing.~~ ~~have a cardiovascular outcome trial, either before or after marketing.~~ Further, all of these drugs were studied with a suicidality rating scale.<sup>878</sup> These medications have an indication for “chronic weight management” indicating long-term usage, along with diet and physical activity in individuals with BMI  $\geq 30$  kg/m<sup>2</sup> or a BMI  $\geq 27$  kg/m<sup>2</sup> with one or more comorbidities. They are to be used over the long term, not just to produce weight loss, but to sustain lost weight.

Lorcaserin is a specific serotonin 2c receptor agonist.<sup>732</sup> Lorcaserin is remarkable for its tolerability and low rate of adverse events.<sup>732, 743, 754</sup> Echocardiograms performed in phase III studies on more than 5200 subjects found no statistically significant increase in FDA defined valvulopathy.<sup>665</sup> The drug should not be used with monoamine oxidase inhibitors (MAOIs) because of the risk of serotonin syndrome.<sup>665</sup> It has not been studied with SSRIs, SNRIs or other serotonergic agents and extreme caution should be used in combining it with those agents.<sup>665</sup>

The combination of phentermine and topiramate as in extended release (ER) formulation (PHEN/TPM ER) uses lower doses of both (7.5/46 mg at the recommended dose) than are usually prescribed when either drug is used as single agent.<sup>765, 776, 787</sup> This medication is associated with greater mean weight loss than other available medications. Topiramate is associated with fetal toxicity (oral clefts)<sup>889</sup> and a pregnancy test prior to initiating therapy and monthly thereafter is recommended.<sup>676</sup> The most common side effects include paresthesias, dizziness, dysgeusia, insomnia, constipation and dry mouth.<sup>676</sup> A rare side effect of topiramate is acute myopia with glaucoma and the drug is contraindicated in glaucoma.<sup>676</sup> The combination of PHEN/TPM ER is also contraindicated in hyperthyroidism and within

14 days of treatment with monoamine oxidase inhibitors (MAOIs).<sup>676</sup> Other rare potential adverse risks include kidney stones (associated with topiramate) and increased heart rate (associated with phentermine) in patients susceptible to sympathomimetic drugs.<sup>676</sup>

The combination of naltrexone SR/bupropion SR was approved in the US in 2012 and in the EU in 2015.<sup>798, 8079-80, 81, 823</sup> Bupropion is a mild reuptake inhibitor of dopamine and norepinephrine. Naltrexone, an opioid antagonist has minimal effect on weight loss on its own. Naltrexone is thought to block inhibitory influences of opioid receptors activated by the  $\beta$ -endorphin released in the hypothalamus that stimulates feeding, thus allowing the inhibitory effects of  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH) to reduce food intake.<sup>82</sup> Naltrexone SR/ bupropion SR can increase blood pressure; 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.<sup>687</sup> Despite these signals, absence of increased events in [the interim analysis of a-A cardiovascular outcome trial](#) conducted before marketing allowed approval.<sup>687</sup> [Another cardiovascular outcome trial was required post-marketing.](#) Tolerability issues, chiefly nausea on initiating the drug mandate a dose escalation over four weeks. All antidepressants in the US are required to carry a black box warning of suicidality and the combination's label includes this.<sup>687</sup> However, there was no signal for suicidality in phase III studies.<sup>78, 79, 80, 81, 83</sup>

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 up to 1.8 mg, given by injection. It is now approved in the US and EU for chronic weight management at a dose of 3.0 mg.<sup>834, 845, 856, 867</sup> Nausea has been one of the principal complaints in patients injecting this drug and a slow dose escalation over 5

weeks is prescribed.<sup>698</sup> There is also a small, but significant increase in heart rate, but blood pressure tends to fall.<sup>698</sup> GLP-1 agonists are associated with thyroid C cell tumors in animals, but this has not been demonstrated with certainty in humans.<sup>698</sup> Liraglutide should not be prescribed in patients with family or personal history of medullary thyroid cancer or multiple endocrine neoplasia.<sup>698</sup> Acute pancreatitis, gall bladder disease and hypoglycemia in diabetics are safety issues that require managing if they occur.

### **Surgical Procedures in the Treatment of Obesity (Word Count = 508)**

Bariatric surgery has rapidly become adopted as a treatment option for severe obesity, particularly since the advent of lower risk laparoscopic procedures, with nearly half a million procedures performed worldwide in 2013.<sup>8990</sup> 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**).<sup>904</sup>

#### **Table 3 about here**

Longer term studies of outcomes following bariatric surgery have generally shown favourable results. The Swedish Obese Subjects study followed 2000 patients for up to 20 years after surgery including banded gastroplasty, gastric banding and Roux-en-Y gastric bypass performed by open techniques which have since been replaced by laparoscopy. There was a 24% reduction in mortality, mainly due to reduced risk of myocardial infarction and cancer (in women), compared to an observational control group.<sup>912, 923</sup> Many other co-morbidities, such as type 2 diabetes and sleep apnoea are also improved, and patients report consistent improvements in quality of life.<sup>934</sup>



Particularly striking and rapid improvements in glucose control have been seen in patients with type 2 diabetes, especially following gastric bypass, suggesting that part of the metabolic improvement is independent of weight loss.<sup>945</sup> 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.<sup>956, 967, 978, 99</sup> Observational data also suggest that future risk of diabetes-related micro- and macrovascular complications are also reduced.<sup>999</sup> This has led to the concept of 'metabolic' surgery, and recent 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 and 35 kg/m<sup>2</sup>,<sup>32, 100400, 1014</sup> and a move away from BMI as the main criterion used to assess eligibility for surgery.<sup>100400</sup> 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 significant, particularly for gastric banding (**Table 3**). 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.<sup>1033</sup> Weight regain can also be a significant problem, and revisional surgery carries greater risks and no guarantee of success;<sup>1044</sup> there is an increasing focus on lifestyle programmes after bariatric surgery to reduce the risk of this occurring.<sup>32</sup>

From a clinical perspective it is essential that patients and clinicians considering referral for bariatric surgery are fully aware of the risks and benefits; good practice might include provision of a detailed education session, attendance at patient support groups as well as detailed lifestyle advice and psychological support both before and after surgery. <sup>1055</sup>

### **Controversies: (words = 529)**

As with other areas of medicine, not all issues have been resolved to everyone's satisfaction. Below is a list of some of the controversies that are up for continuing debate and resolution.

Should obesity be a strong focus of undergraduate medical education or should it be taught primarily at the most graduate level? <sup>1066</sup> Weight bias is commonly observed among medical students as well as experienced doctors to stigmatize patients. <sup>1077</sup> This stigma might be reduced if the complexities of obesity were introduced earlier. This stigma might also partly explain why obesity is an under-diagnosed and under-treated condition despite its high prevalence. <sup>1088</sup>

Who needs to lose weight and what is the best way to decide? Is BMI an appropriate measure to decide who should lose weight? <sup>1099</sup> 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 favor 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.

A third controversy revolves around whether there are people who are obese and “metabolically healthy” the so-called Metabolic Healthy Obesity or MHO. Individuals with metabolically healthy obesity (MHO) may not improve their cardio-metabolic risk factors significantly after weight loss interventions and may therefore not benefit to the same extent as obese patients with metabolic comorbidities. There is controversy as to whether individuals labeled as “metabolic-health-obese” are really healthy, especially since no general agreement exists on accepted criteria to define those with MHO.<sup>11049, 11114</sup> Moreover, there is still controversy as to whether MHO can be considered an established phenotype or rather represents a transient stage toward ill-health with ageing, behavioural and environmental factors. MHO appears to be a relatively transient condition with a considerable percentage of these individuals exhibiting similar metabolic derangements to those observed in obese metabolically altered patients as time passes.<sup>1122, 1133</sup> Conversely, non-obese individuals according to BMI but obese based on body fat distribution exhibit elevated cardiometabolic risk factors<sup>1144, 1155</sup>, 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 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 impacts on health

services. A number of studies (NCT00991640, NCT01967797 and NCT01606813) are due to report on this problem in the next few years.

Obesity raises a number of societal controversies. Government taxes on “unhealthy” foods has been tried in some countries (Denmark for example) but with variable results. Should governments subsidize commercial weight loss programs that have proven to be successful? <sup>1156</sup>

### Legends:

**Appendix f** Figure 1. The Global Pandemic of Obesity Illustrated by the Prevalence of Obesity by Country for Males over 20 Years of Age. (Ref 5).

**Appendix f** Figure 2. Relation of body mass index to mortality in pooled data sets with over 900,000 people and the effect of specific causes of death (Ref 21). All-cause mortality versus BMI for each sex in the range 15-50 kg/m<sup>2</sup> (excluding the first 5 years of follow-up) Relative risks at age 35-89 adjusted for age at risk, smoking and study, were multiplied by a common factor (i.e., floated) to make the weighted average match the PSC mortality rate at age 35-79 years. Area of the square is inversely proportional to the variance of the long risk.

**Figure 13.** Factors that predict weight loss in the Look AHEAD study (Refs 36, 40) The results in panels A, B and C indicate the greater weight loss at 1-year associated with greater proportion of visits, attended, minutes per week of physical activity, and greater meal replacement use. Black bars indicate the first quartile and light gray ones the 4<sup>th</sup> quartile. Panel D shows the weight loss at years 4 and 8 by percent weight loss at one month (left side) and 2 months (right side). The tertiles of weight ranges are shown below each set of bars.

**Figure 4.**

**Figure 24.** 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 I-III development. The right hand panel summarizes the neurotransmitters and pathways involved in the central nervous system in energy homeostasis, while 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, i.e. energy intake and expenditure. Note that most of the currently approved drugs are working centrally where stimulation of the POMC/CART pathway has anorexigenic effects,

while the NPY/AGRP pathway exerts orexigenic effects. The interaction with the multiple receptors present in neurones of the hypothalamus determines the balance between orexigenic and anorexigenic influences. Most of the drugs currently tested in clinical trials are aimed at peripheral systems. Thus, thyroid analogues and  $\beta_3$  adrenergic agonists induce thermogenesis via activation of brown adipose tissue (BAT), thereby increasing energy expenditure. Enzymes involved in lipid metabolism such as DGAT, FAS, MetAP2 and NQO1 are also being targeted. The gut microbiome as well as the regulation of bile acids represent further targets to combat obesity. The lipase and SGLT2 inhibitors favour energy loss via 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.

Abbreviations: DGAT1 = diacylglycerol O-acyltransferase aminotransferase 1; FAS = fatty acid synthase; MetAP2 = methionyl aminopeptidase 2; PexRAP inh = peroxisomal reductase activating PPAR $\gamma$  inhibitor; NQO1 = NAD(P)H dehydrogenase:quinone oxidoreductase 1; SGLT2 = sodium-glucose-linked transporter 2; inh = inhibitor; BAT = brown adipose tissue; WAT = white adipose tissue; GABA =  $\gamma$ -aminobutyric acid; DA = dopamine; NE = norepinephrine; CB = cannabinoid; H = histamine; 5HT = serotonin; ObR = leptin receptor; GHSR = growth hormone secretagogue receptor; AGRP = Agouti-related peptide; CART = cocaine amphetamine-related transcript; NPY = neuropeptide Y; Y1R = Y1 receptor; Y2R = Y2 receptor; Y5R = Y5 receptor; POMC = proopiomelanocortin C; GLP1R = glucagon-like peptide 1 receptor;  $\alpha$ -MSH =  $\alpha$ -melanocyte-stimulating hormone; MCH1R = melanin-concentrating hormone 1 receptor; MC3R = melanocortin receptor type 3; MC4R = melanocortin receptor type 4;  $\mu$ -OR =  $\mu$ -opioid receptor; 5HT2c = serotonin receptor type 2c.

#### **Tables:**

- Table 1: Medications Affecting Weight Gain and Alternative Approaches
- Table 2: Medications for weight management: Mechanism of action, availability and dosing. (Ref: US Product Label, except where noted)
- Table 3: Effect of the Principal Surgical Procedures for Treatment of Obesity

### **Author Contributions to the Manuscript:**

George Bray was invited to develop the review and invited Dr. Donna Ryan, Dr. Gema Frühbeck and Dr. John Wilding to contribute. Bray drafted the initial manuscript which was substantially revised by each author. All 4 authors contributed to the literature search and to the development of figures and tables.

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October 12, 2015

Dr. Stuart Spencer  
The Lancet  
125 London Wall  
London, EC2Y 5AS, UK

Dear Stuart

Manuscript: THELANCET-D-15-01286R4, Management of Obesity

Good morning. The four of us want to thank you for “sticking” with us while we complete the reworking of this paper. In this version we have:

Moved 2 figures (formerly Figure 1 and Figure 2) to the appendix.

Revised Table 1 to include the suggestions of the reviewer.

Included a search strategy.

Added a few references, removed a few others and aligned the numbering.

We hope that all of these changes will make the paper acceptable.

I have one questions about copyright for the figures. Both Appendix Figure 1 and 2 were originally published in Lancet, so I presume you hold the copyright. Figure 3 is a composite of 3 panels (left hand pair and top right) that have been redrawn and the lower right panel which was drawn from data in a different paper. If we send this figure to a journal it will be unrecognizable as one they have copyrighted. How should I proceed?

Below is the point-by-point response to the Editorial and Referee comments:

#### COMMENTS TO THE AUTHOR:

##### Editors

There are some specific points that editors raised in addition to those that are our standard requirements.

1. From our psychiatry editor: Why mention only antidepressants being associated with weight gain, and not antipsychotics? And why only pharmacological alternatives and not psychotherapy?

**RESPONSE:** We added “antipsychotics” to the examples of medication associated with gain in the fast facts section. Since we were targeting primary care provides, we limited Table 1 to medications they were most likely to prescribe and manage. However, this has been revised based on the comments above. We have inserted relevant medications for antipsychotics and anti-convulsants and expanded the antidepressants to include mood stabilizers. We have followed Endocrine Society guidelines based on a

systematic evidence review, and although psychotherapy was not mentioned in this document, we included it in the table as weight neutral.

2. Please include a conflicts of interest statement in the main text (this does not count towards your word count)

RESPONSE: Here is the conflict of interest statement:

The authors identify the following potential conflicts of interest: Dr. Bray is a consultant to Herbalife International and Medifast; a member of the Speakers Bureau for Novo Nordisk Pharmaceuticals and Takeda Pharmaceuticals; receives royalties from Up-to-Date and Handbook of Obesity; Dr. Frühbeck is a consultant to Novo Nordisk; Dr. Ryan 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 and is on the speakers bureau for Novo Nordisk Pharmaceuticals, Takeda Pharmaceuticals, Eisai Pharmaceuticals and Vivus Pharmaceuticals, and has equity ownership in Scientific Intake; Dr. Wilding 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.

3. We need a search strategy, please

RESPONSE: A search strategy was inserted just after FAST FACTS

4. At least 2 of the non-text items (tables or figures) need to go to the web appendix

RESPONSE: The group voted to move figures 1 and 2 to the appendix and leave only one figure and 3 tables which have been appropriately edited.

5. Please provide permission to use the recycled figures (except The Lancet figure)

RESPONSE: Appendix figure 1 is from Lancet; Appendix figure 2 is from Lancet PLUS the right hand box which uses data from the same paper; Figure 3 is a composite. The left 2 panels and the top right panel have been published several places and were redrawn from Obesity Supplement. The lower right hand panel is drawn from data in Ref 40. I am not sure how to get permission for a figure which doesn't exist per se. Please advise. Figure 4 is original

Reviewer #5: This SEMINAR paper is well crafted, reads well, and provides adequate and meaningful information to the practicing clinician.

A few suggestions that are not critically important:

Page 8 (of the merged PDF file): Suggest deleting the following text:

"In a meta-analysis of commercial programs in the US, found that at 12 months Weight Watchers participants achieved at least 2.6% more weight loss than the control/education group; the Jenny Craig program weight loss was at least 4.9% greater at 12 months than in the control/education and counselling group; the Atkins program resulted in 0.1% to 2.9% greater weight loss at 12 months than counselling; and the Nutrisystem weight loss program was at least 3.8% greater at 3 months than the control/education and counseling control groups."

RESPONSE: I made this deletion and inserted this wording"

"There are several commercial weight loss programmes, and some individuals may benefit from them. The costs and methods of delivering treatment vary which may affect compliance and real-world applicability. These programmes provide on the average about 3% weight loss over a year, but long-term compliance is generally poor. Studies of longer than a year are sparse."

Suggest replacing the above with a broad-stroke statement that several commercial weight loss programmes exist. Some individuals might benefit from these approaches, costs and treatment delivery methods vary thus affecting compliance and real-world applicability, and they provide on the average about 3% weight loss over a year, studies longer than a year are sparse, and long-term compliance is generally poor.

Reason for the suggestion: This was a much-criticised meta-analysis. Included studies had methodological limitations and varying sample sizes and high dropout rates. A concern is that some commercial programmes could use inclusion of numbers in this prestigious paper as an advertisement whereas a meta-analysis showed no differences among the 'named' diets.

Page 13: "These drugs are required by regulatory agencies in the US and EU to present data on >2500 patients and to approximate or exceed 5% greater weight loss than placebo (with the EU's interest in exceeding 10% weight loss) and to demonstrate positive effects on a variety of risk factors and disease markers."

EMA's June 2014 draft guidance does not insist on 10% total weight loss. Rather, it states: Demonstration of a clinically significant degree of weight loss of at least 5- 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs. Please revise your statement accordingly.

RESPONSE: Thank you for this comment. We thought that since the EU labels focus on providing results for 10% weight loss, this comment might be appropriate. However, it is better to simply omit it which we have done.

Page 13: "All centrally acting agents must have a cardiovascular outcome trial, either before or after marketing."

The above statement is not accurate.

In March 2012 the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) discussed and voted on CV risk assessment for weight loss drugs similar to requirements for diabetes drugs. EMDAC voted 17 to 6 to require pre-approval assessments to exclude some degree of CV risk for all weight loss drugs, even in the absence of a CV signal or theoretical risk. This requirement is not just for "centrally acting agents"; rather, it is a requirement for all weight loss drugs. However, FDA is yet to establish a clear guidance for CV risk assessment for weight management drugs.

RESPONSE: In order to address this comment and the fact that there was no CVOT for orlistat, we revised the statement to say that "All agents must show evidence of no increase in cardiovascular risk, which is likely to require a cardiovascular outcome trial, either before or after marketing.

Page 15: "Despite these signals, absence of increased events in a cardiovascular outcome trial conducted before marketing allowed approval.

Please note that this was based on an interim analysis. A full-size trial to rule out increased risk of MACE has not been completed yet.

RESPONSE: We edited this section as follows: "Despite these signals, absence of increased events in the interim analysis of a cardiovascular outcome trial conducted before marketing allowed approval.<sup>67</sup> Another cardiovascular outcome trial was required post-marketing."

References 75 and 77 are identical. I believe 77 should be: Allison DB et al, published in the journal Obesity, 2012.

RESPONSE: Thank you for picking up this duplication. Reference 77 in the older version should have been Allison et al and this correction has been made and the new reference inserted. All references have been appropriately renumbered and the text checked against them.

To keep it consistent, delete references of proof-of-concept and phase II trials of naltrexone/bupropion and keep only the phase III trials.

RESPONSE: Proof of concept trials were deleted.

Table 1: There are no consistent data with regard to the effects of antidepressants on body weight. A recently very large study of electronic medical records published in JAMA Psychiatry (Aug 2015) revealed less weight gain with two tricyclics - amitriptyline and nortriptyline, a finding that conflicts with generally held beliefs.

**RESPONSE:** We relied on the systematic evidence review conducted by the Endocrine Society for their Guidelines which were published in January 2015. There are no serious contradictions across review, so we added this citation: Blumentahl SR, Castro VM, Clements CC, Rosenfield HR, Murphy SN, Fava M, Weilburg JB, Erb JL, Churchill SE, Kohane IS, Smoller JW, Perlis RH. An electronic health records study of long-term weight gain following antidepressant use. JAMA Psychiatry 2014 Aug;71(8):889-896.

Lacking data from direct comparison trials, here is suggested placement for various antidepressants:

Weight gain:

Monoamine oxidase inhibitors, some tricyclics (e.g., doxepin), some SSRIs (most prominent being paroxetine), mirtazapine

Weight neutral:

Some SSRIs (e.g., citalopram, fluvoxamine, vortioxetine), duloxetine, venlafaxine

Weight gain: (We think you mean weight loss) Bupropion, fluoxetine (short-term)

**RESPONSE:** We resolved this issue of competing reviews by merging both and citing the JAMA Psychiatry review in addition to the ENDO Guidelines. Please note: the table has been expanded to address the Lancet Psychiatry Consultant.

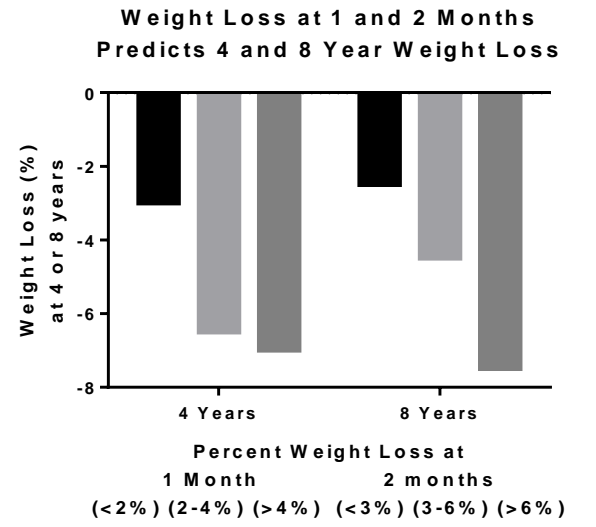
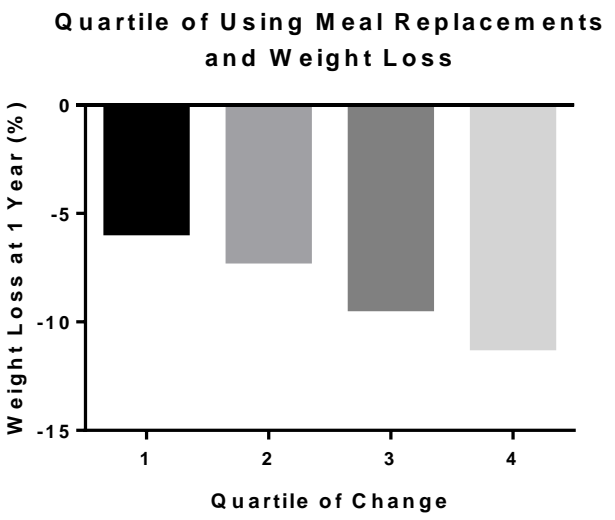
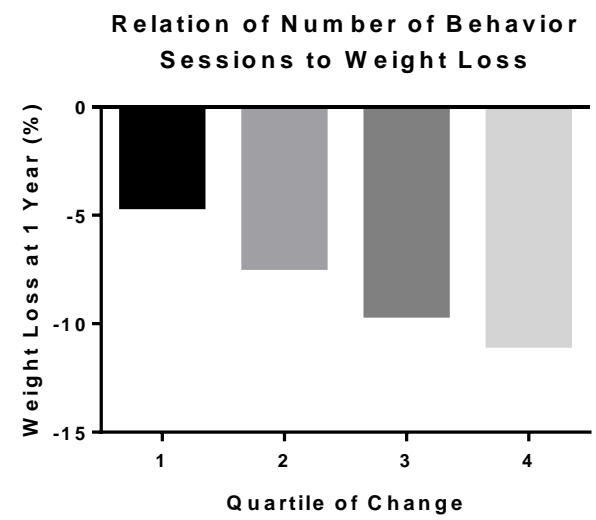
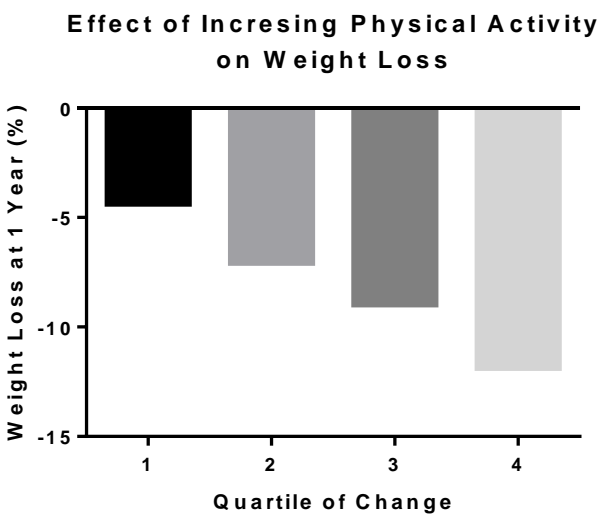
Table 2: Weight loss shown for phentermine (12% vs. 4.5% with placebo) is probably exaggerated and not in line with the results from the Haddock et al meta-analysis. This weight loss was based on the 1968 Munro et al study which enrolled 108 women who were placed on a 1000 kcal/d diet and assigned to 30 mg/d phentermine continuously, 30 mg/d of phentermine intermittently (on for a month and off for a month), or placebo for 9 months. The paper reported weight loss data for 64 completers only (17 continuous phentermine, 22 intermittent phentermine, and 25 placebo). Thus the reported weight loss of 12.2 kg for continuous phentermine was the average weight loss for 17 completers only. Hence, if you are showing these data, please describe the limitations of the Munro et al study.

**RESPONSE:** We agree with these comments. We had adapted this table from the Endocrine Society Guidelines and that is where the phentermine data was provided. For this purpose, since we are relying on data from product labels, we think it best to indicate that 1) phentermine is only indicated for short term use in the US, 2) there is NO efficacy data supplied in the Adipex label and that 3) we can't say anything about phentermine efficacy. See revision in the table.

Sincerely yours,

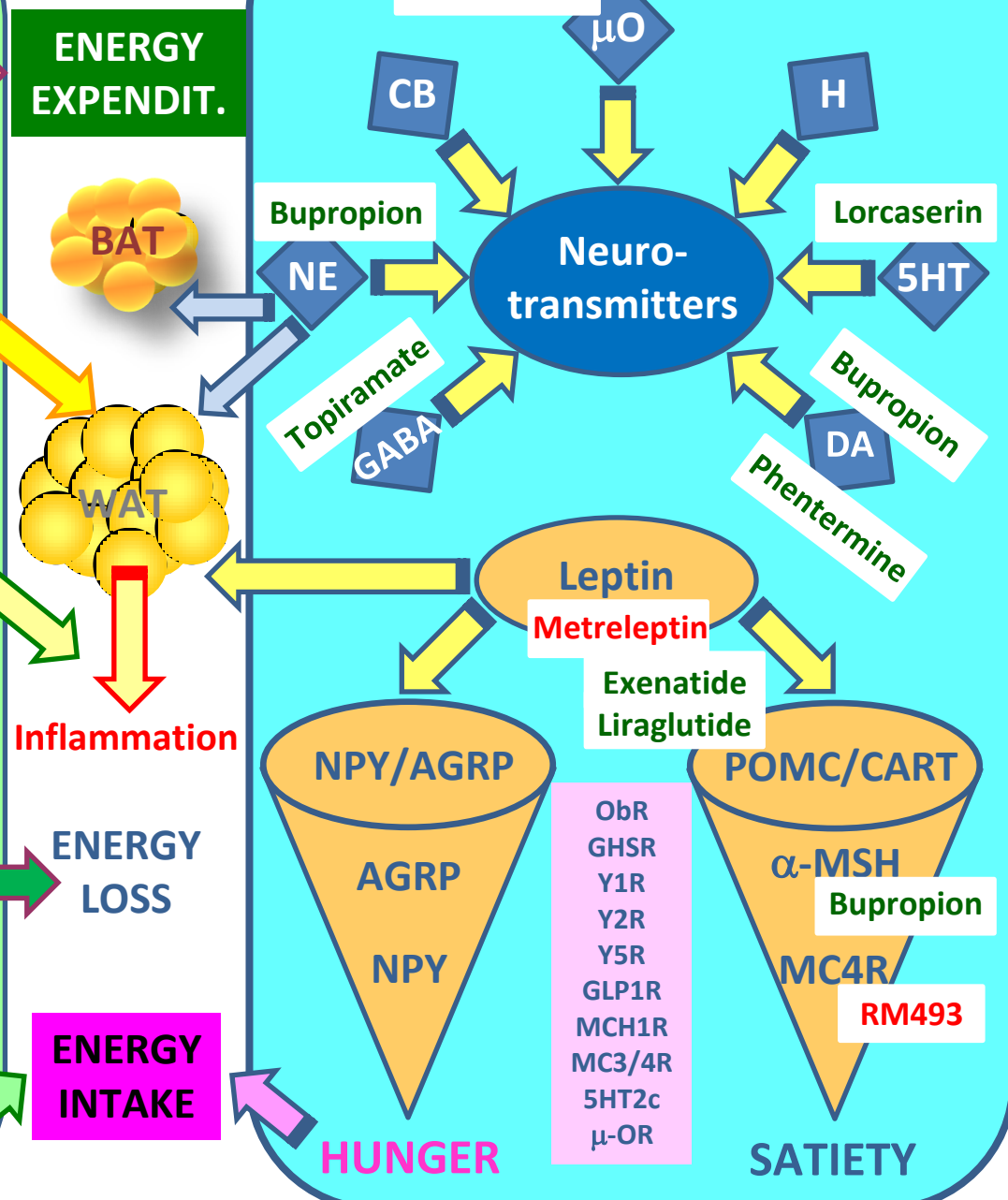
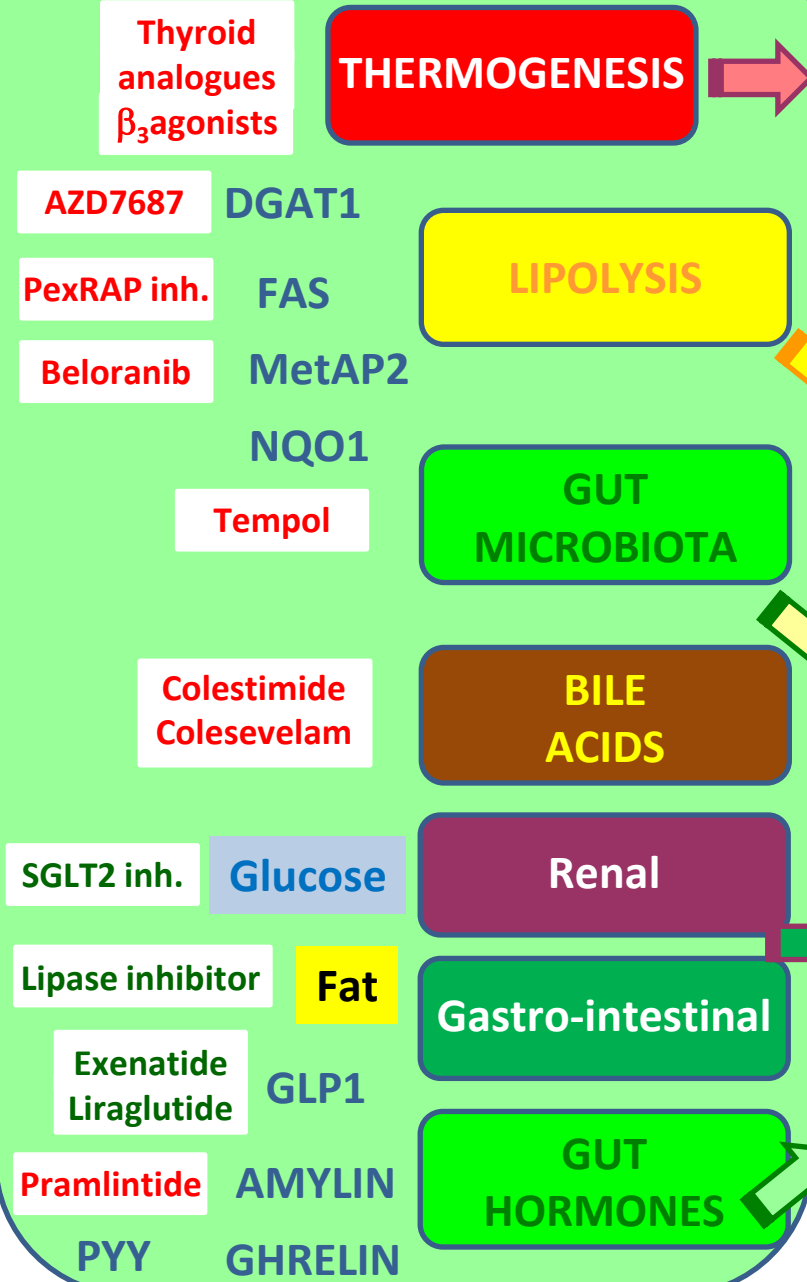
George A. Bray, MD  
For the authors

# Figure Components of Lifestyle Program that Predict Weight Loss



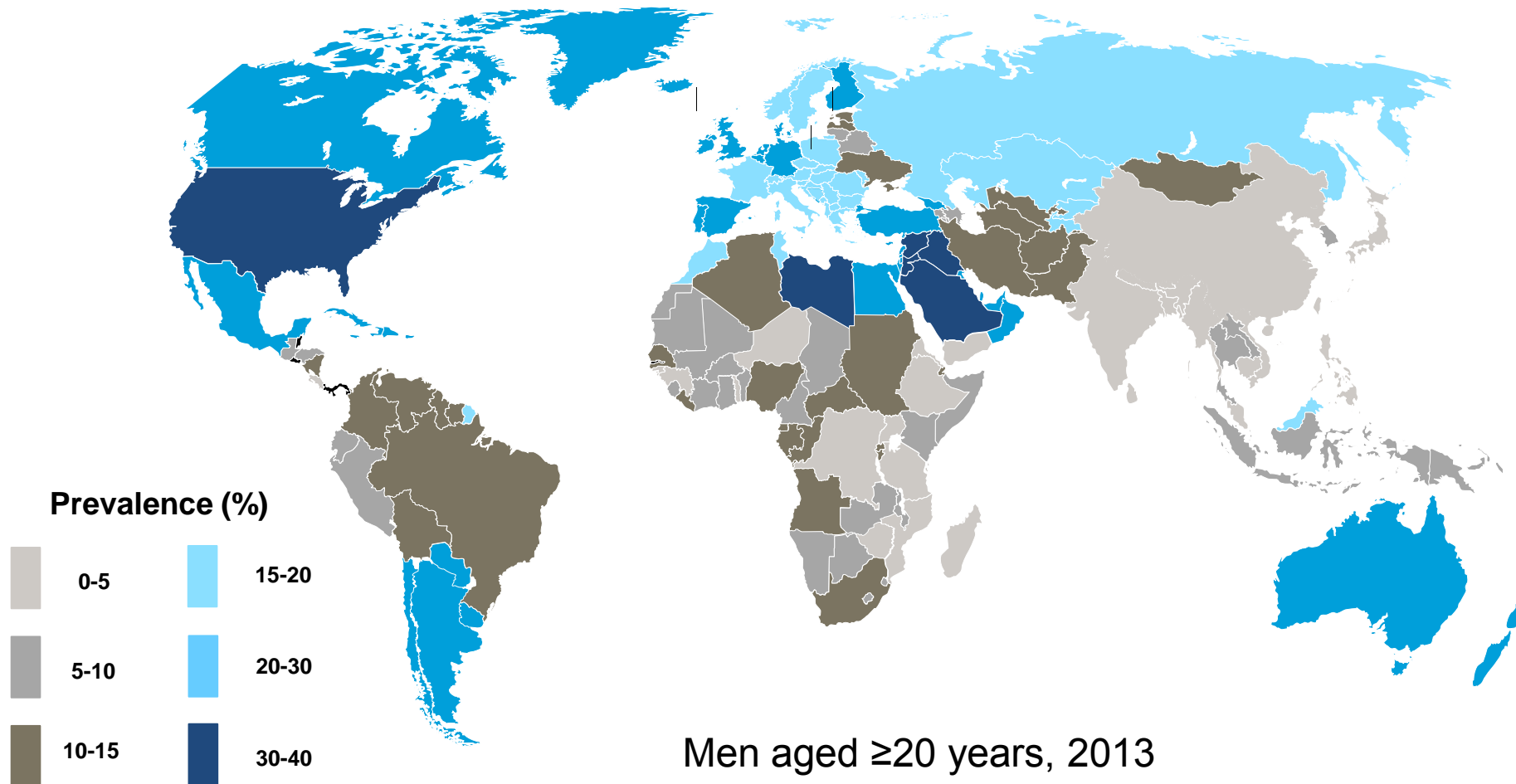
# PERIPHERAL SYSTEMS

# CENTRAL NERVOUS SYSTEM



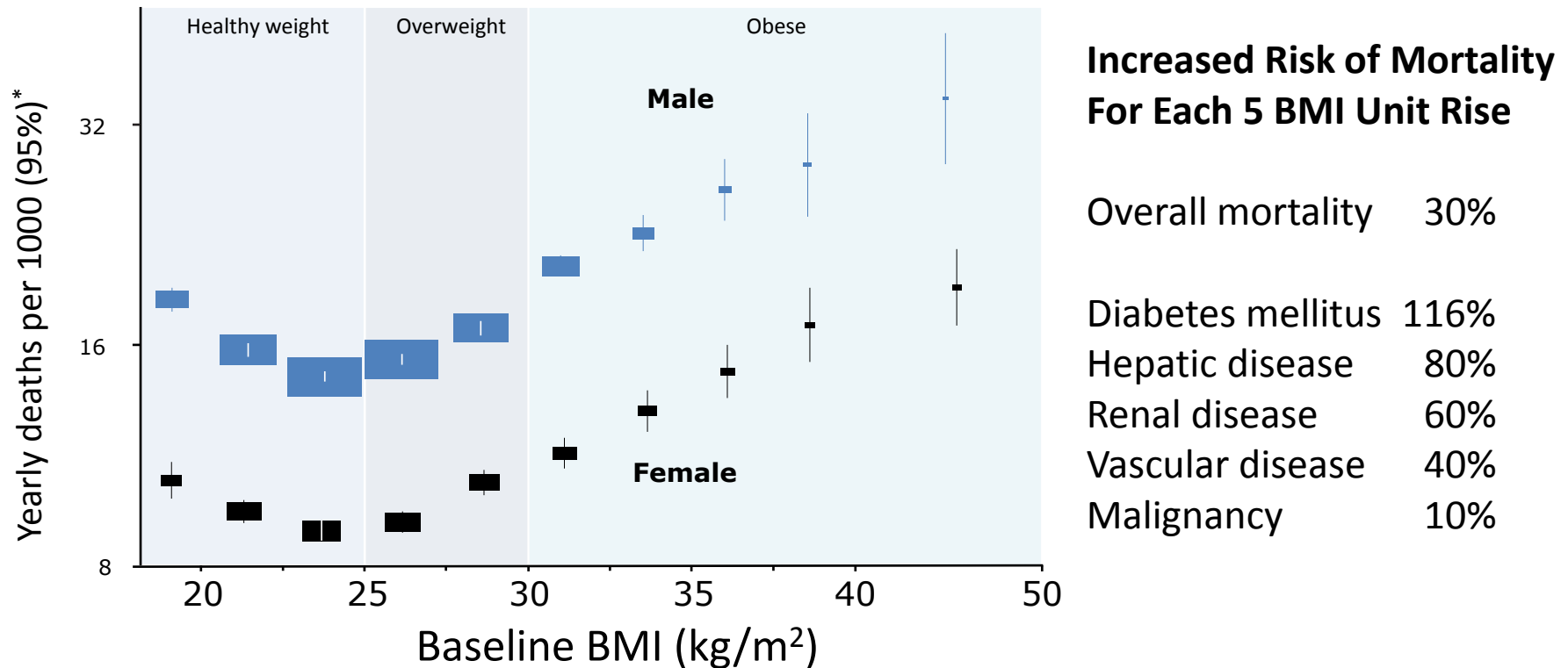


# The global obesity pandemic



Between 1980 and 2013, the proportion of men who were overweight or obese increased by 28.8%

# Obesity is associated with increased risk of mortality



\*Area of square is inversely proportional to the variance of the log risk.

Data based on 57 prospective studies encompassing ~900,000 adults, 35–89 years of age. BMI = body mass index.

Prospective Studies Collaboration. *Lancet*. 2009;373:1083-1096.

**Table 1: Medications Affecting Weight Gain and Alternative Approaches**

<b>Drug Class</b>	<b>Weight Gain</b>	<b>Weight Neutral</b>	<b>Weight Loss</b>
Anti-Diabetics	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 and others)
Anti-depressants/ Mood stabilizers	Monoamine Oxidase Inhibitors (Many) Tricyclics (some, ie doxepin) Serotonin Reuptake Inhibitors (SSRI) (Some, i.e. paroxetine ) mirtazapine Lithium	Citalopram, Fuvoxamine, Vortionzetine, Duloxetine, Venlafaxine, Nefazodone Sertraline (<1 year) psychotherapy	Venlafaxine Bupropion Fluoxetine (short term)
Anti-psychotics	Clozapine Risperidone Olanzapine Quetiapine Haloperidol Perphenazine Quetiapine	Ziprasidone Aripiprizole psychotherapy	
Anticonvulsants	Carbamazepine Gabapentin Valproate	Lamotrigine?	Topiramate Zonisamide
Anti-histamines	Cycloheptadine Diphenhydramine Doxepin	Steroid inhalers Decongestants	
Adrenergic blockers	Propranolol Doxazosin	Angiotensin converting enzyme inhibitors (ACEI)	

		Angiotensin receptor blockers (ARBs) Calcium channel blockers	
Adrenal steroids	Corticosteroids	Non-steroidal anti-inflammatory drugs	
Oral contraceptives			

tid = three times a day; bid = twice a day; ER = extended release; SR = sustained release; MAOI = monoamine oxidase inhibitor; SNRI = Serotonin-norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor; a = Phentermine only approved in the US for "a few weeks" usually consider  $\leq 12$  weeks; b = randomized controlled trials lasting more than 52 weeks; c = Data from Munro (Munro JF Br Med J. 1968 Feb 10;1(5588):352-4) after 9 months of treatment; d = Assuming average patient in the Orlistat and placebo groups weighed 100 kg at baseline. (Phentermine has many trade names in the US; Orlistat = Xenical worldwide; Lorcaserin = Belviq in US; Phentermine/topiramate = Qsymia in the US; Naltrexone SR/Bupropion = Contrave in the US and Mysimba in Europe; Liraglutide for obesity = Saxenda worldwide; liraglutide for diabetes Victoza )

**Table 2. Medications for weight management: Mechanism of action, availability and dosing. Information is from US Product Label, except where noted.**

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

Medication and recommended dose	Mechanism of action	Available for Chronic Use unless otherwise stated		Mean percent weight loss with drug/ with placebo		Advantages	Disadvantages
		US	EU	Placebo	Drug		
Phentermine 15 mg – 30 mg Oral	Sympathomimetic	For short term use	No	Not stated in label	Not stated in label	Inexpensive	Side effect profile No long-term data <sup>b</sup>
Orlistat 120 mg tid, before meals Oral	Pancreatic lipase inhibitor	Yes	Yes	-2.6% <sup>d</sup>	-6.1% <sup>d</sup>	Not absorbed Long-term data <sup>b</sup>	Modest weight loss Side-effect profile
Lorcaserin 10 mg bid Oral	5-HT <sub>2C</sub> serotonin agonist with little affinity for other serotonergic receptors	Yes	No	-2.5%	-5.8%	Mild Side effects Long-term data <sup>b</sup>	Expensive Modest weight loss
Phentermine/Topiramate ER 7.5 mg/46 mg; 15mg/92 mg indicated as rescue Oral (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 <sup>b</sup>	Expensive Teratogen
Naltrexone	Opioid receptor	Yes	Yes	-1.3%	-5.4%	Greater weight loss	Moderately expensive

SR/ Bupropion SR 32 mg/ 360 mg Oral (requires titration)	antagonist Dopamine & noradrenaline reuptake inhibitor					Reduces food addiction Long-term data <sup>b</sup>	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 <sup>b</sup>	Expensive Injectable

**Table 3: Surgical Procedures for Treatment of Obesity**

<b>Procedure</b>	<b>Weight loss after 3 years Δ BMI (kg /m<sup>2</sup>) (95% CI)</b>	<b>Effects on type 2 diabetes remission (%) (95% CI) at years –</b>	<b>Mortality % (95% CI) &lt;30 day &gt;30day</b>	<b>Re-operation rate % (95% CI)</b>	<b>Complications % (95% CI)</b>
Adjustable gastric banding (AGB)	-11.43 (-18.14 to -4.72)	67.58 (49.51-82.83)	0.07 (0.02-0.12) 0.21 (0.08-0.37)	7.01 (3.99-11.24)	7.80 (3.90-13.00)
Sleeve Gastrectomy (SG)	-16.78 (-20.57 to -12.99)	85.53 (72.69-94.07)	0.29 (0.11-0.63) 0.34 (0.14-0.60)	2.96 (1.70-4.71)	8.90 (5.60-13.00)
Roux-en-Y gastric bypass (RGB)	-21.88 (-27.96 to -15.79)	92.83 (85.29-97.21)	0.38 (0.22-0.59) 0.39 (0.01-0.86)	5.34 (4.48-6.48)	12.00 (7.30-17.00)

Data in table are from Chang (2014). Note that for this analysis, surgical procedures were grouped: AGB includes laparoscopic gastric banding and Swedish band; SG includes sleeve gastrectomy and vertical banded gastroplasty; RGB includes laparoscopic and open procedures as well as biliopancreatic diversion with or without duodenal switch.



**Supplemental Table Common side effects and contraindications and warnings for medications used to treat patients who are overweight or obese.**

Information is from US Product Label, except where noted.<sup>89-95</sup>

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

Medication	Common Side Effects	Contraindications and Warnings
Phentermine 15 -30 mg	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Elevated Blood Pressure and Pulse</li> <li>• Insomnia</li> <li>• Dry mouth</li> <li>• Constipation</li> <li>• Anxiety</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindicated with history of cardiovascular disease</li> <li>• Use with caution in patients with even mild hypertension</li> <li>• Contraindicated with MAOIs, hyperthyroidism, glaucoma, history of drug abuse</li> <li>• Primary pulmonary hypertension (rare)</li> <li>• Hypoglycemia with diabetes</li> <li>• Only indicated for short-term use – “a few weeks”</li> </ul>
Orlistat 120 mg tid,	<ul style="list-style-type: none"> <li>• Steatorrhea</li> <li>• Oily spotting</li> <li>• Flatulence with discharge</li> <li>• Fecal urgency</li> <li>• Oily evacuation</li> <li>• Increased defecation</li> <li>• Fecal incontinence</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindicated in pregnancy</li> <li>• Warning: ↑cyclosporine exposure</li> <li>• Liver failure (rare)</li> <li>• Requires co-administration of multiple vitamin</li> <li>• Increased risk of gall bladder disease</li> </ul>
Lorcaserin 10 mg bid	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Dizziness</li> <li>• Nausea</li> <li>• Dry mouth</li> <li>• Fatigue</li> <li>• Constipation</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindicated in pregnancy</li> <li>• Use with caution with SSRI, SNRI, MAOIs, St John’s wort, Triptans, Bupropion, Dextromethorphan</li> <li>• Contraindicated in pregnancy</li> </ul>

Phentermine/ Topiramate ER 7.5 mg/46 mg	<ul style="list-style-type: none"> <li>• Insomnia</li> <li>• Dry mouth</li> <li>• Constipation</li> <li>• Paresthesias</li> <li>• Dizziness</li> <li>• Dysgeusia</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindicated in pregnancy</li> <li>• Fetal toxicity; monthly pregnancy test suggested</li> <li>• Contraindicated with hyperthyroidism, glaucoma</li> <li>• Do not use with MAOIs or sympathomimetic amines</li> <li>• Acute myopia (rare)</li> </ul>
Naltrexone SR/ Bupropion SR 32 mg/ 360 mg	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Constipation</li> <li>• Headache</li> <li>• Vomiting</li> <li>• Dizziness</li> </ul>	<ul style="list-style-type: none"> <li>• Boxed warning: suicide risk in depression</li> <li>• Contraindicated in pregnancy</li> <li>• Contraindicated in seizure disorders, uncontrolled hypertension, glaucoma</li> <li>• Do not use with opioids, MAOIs</li> <li>• Hepatotoxicity (rare)</li> </ul>
Liraglutide 3.0 mg	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Vomiting</li> <li>• Diarrhea</li> <li>• Constipation</li> <li>• Headache</li> <li>• Dyspepsia</li> <li>• Fatigue</li> <li>• Dizziness</li> <li>• Abdominal pain</li> </ul>	<ul style="list-style-type: none"> <li>• Boxed warning: thyroid C cell tumors in rodents</li> <li>• Contraindicated with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia.</li> <li>• Pancreatitis</li> <li>• Hypoglycemia in diabetes</li> <li>• Increased risk of gall bladder disease</li> </ul>

tid = three times a day; bid = twice a day; ER = extended release; SR = sustained release; MAOI = monoamine oxidase inhibitor; SNRI = Serotonin-norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor

**Table 1: Medications Affecting Weight Gain and Alternative Approaches**

<b>Drug Class</b>	<b>Weight Gain</b>	<b>Weight Neutral</b>	<b>Weight Loss</b>
Anti-Diabetics	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 and others)
Anti-depressants/ <u>Mood stabilizers</u>	<u>Monoamine Oxidase Inhibitors (Many)</u> <u>Tricyclics (some, ie doxepin)</u> <u>Serotonin Reuptake Inhibitors (SSRI) (Some, i.e. paroxetine )</u> <u>mirtazapine</u> <u>Lithium Tricyclics</u> <u>Monoamineoxidase inhibitors (Many)</u> <u>Serotonin reuptake Inhibitors (SSRI) (Many)</u>	<u>Citalopram, Fuvoxamine, Vortionzetine, Duloxetine, Venlafaxine, Nefazodone</u> <u>Sertraline (&lt;1 year)</u> <u>psychotherapy</u>	Venlafaxine Bupropion Fluoxetine (short term)
<u>Anti-psychotics</u>	<u>Clozapine</u> <u>Risperidone</u> <u>Olanzapine</u> <u>Quetiapine</u> <u>Haloperidol</u> <u>Perphenazine</u> <u>Quetiapine</u>	<u>Ziprasidone</u> <u>Aripiprizole</u> <u>psychotherapy</u>	
<u>Anticonvulsants</u>	<u>Carbamazepine</u> <u>Gabapentin</u> <u>Valproate</u>	<u>Lamotrigine?</u>	<u>Topiramate</u> <u>Zonisamide</u>

Anti-histamines	Cycloheptadine Diphenhydramine Doxepin	Steroid inhalers Decongestants	
Adrenergic blockers	Propranolol Doxazosin	Angiotensin converting enzyme inhibitors (ACEI) Angiotensin receptor blockers (ARBs) Calcium channel blockers	
Adrenal steroids	Corticosteroids	Non-steroidal anti-inflammatory drugs	
Oral contraceptives			

tid = three times a day; bid = twice a day; ER = extended release; SR = sustained release; MAOI = monoamine oxidase inhibitor; SNRI = Serotonin-norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor; a = Phentermine only approved in the US for "a few weeks" usually consider  $\leq 12$  weeks; b = randomized controlled trials lasting more than 52 weeks; c = Data from Munro (Munro JF Br Med J. 1968 Feb 10;1(5588):352-4) after 9 months of treatment; d = Assuming average patient in the Orlistat and placebo groups weighed 100 kg at baseline. (Phentermine has many trade names in the US; Orlistat = Xenical worldwide; Lorcaserin = Belviq in US; Phentermine/topiramate = Qsymia in the US; Naltrexone SR/Bupropion = Contrave in the US and Mysimba in Europe; Liraglutide for obesity = Saxenda worldwide; liraglutide for diabetes Victoza )

**Table 2. Medications for weight management: Mechanism of action, availability and dosing. Information is from US Product Label, except where noted.**

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

Medication and recommended dose	Mechanism of action	Available for Chronic Use unless otherwise stated		Mean percent weight loss with drug/ with placebo		Advantages	Disadvantages
		US	EU	Placebo	Drug		
Phentermine 15 mg – 30 mg Oral	Sympathomimetic	Yes <sup>a</sup> <u>For short term use</u>	No	-4.5% <sup>e</sup> <u>Not stated in label</u>	-12% <sup>e</sup> <u>Not stated in label</u>	Inexpensive <b>Greater weight loss</b>	Side effect profile No long-term data <sup>b</sup>
Orlistat 120 mg tid, before meals Oral	Pancreatic lipase inhibitor	Yes	Yes	-2.6% <sup>d</sup>	-6.1% <sup>d</sup>	Not absorbed Long-term data <sup>b</sup>	Modest weight loss Side-effect profile
Lorcaserin 10 mg bid Oral	5-HT <sub>2C</sub> serotonin agonist with little affinity for other serotonergic receptors	Yes	No	-2.5%	-5.8%	Mild Side effects Long-term data <sup>b</sup>	Expensive Modest weight loss
Phentermine/Topiramate ER 7.5 mg/46 mg; 15mg/92 mg indicated as rescue Oral (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 <sup>b</sup>	Expensive Teratogen
Naltrexone	Opioid receptor	Yes	Yes	-1.3%	-5.4%	Greater weight loss	Moderately expensive

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SR/ Bupropion SR 32 mg/ 360 mg Oral (requires titration)	antagonist Dopamine & noradrenaline reuptake inhibitor					Reduces food addiction Long-term data <sup>b</sup>	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 <sup>b</sup>	Expensive Injectable

**Table 3: Surgical Procedures for Treatment of Obesity**

<b>Procedure</b>	<b>Weight loss after 3 years Δ BMI (kg /m<sup>2</sup>) (95% CI)</b>	<b>Effects on type 2 diabetes remission (%) (95% CI) at years –</b>	<b>Mortality % (95% CI) &lt;30 day &gt;30day</b>	<b>Re-operation rate %(95% CI)</b>	<b>Complications % (95% CI)</b>
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