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Behavioral and pharmacologic therapies for obesity

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Abstract

This article reviews novel developments in the behavioral and pharmacologic treatment of obesity and explores the potential contribution of genomics research to weight control. A comprehensive program of lifestyle modification, comprised of diet, physical activity and behavior therapy, induces a mean loss of 7–10% of initial weight in individuals with obesity. Two trials demonstrated that weight loss of this magnitude, combined with increased physical activity, substantially reduced the risk of developing type 2 diabetes mellitus in individuals with impaired glucose tolerance. A third trial is now investigating whether a lifestyle intervention will reduce cardiovascular morbidity and mortality in overweight individuals who already have diabetes mellitus. Pharmacotherapy is recommended, in some patients, as an adjunct to lifestyle modification. Two medications—*orlistat* and *sibutramine*—are currently approved in the US for long-term weight loss. Both are efficacious when combined with lifestyle modification, although health concerns have been raised about the use of *sibutramine*. Several novel combination therapies, which target multiple hypothalamic pathways that regulate appetite and body weight, are currently under investigation. Genomic studies provide further evidence for the role of these pathways in the regulation of body weight. Identification of new genes controlling satiety and energy expenditure may yield valuable clues for the development of novel pharmacologic treatments.

Introduction

Individuals with obesity are encouraged to lose approximately 10% of their initial weight through consumption of a calorie-restricted diet and an increase in physical activity, according to expert committees of the WHO and the NIH.^{1,2} This lifestyle modification approach is considered the cornerstone of treatment for individuals with overweight or obesity (Table 1),^{1–3} If lifestyle modification alone is ineffective, pharmacotherapy should be considered for individuals with a BMI ≥ 30 kg/m² or in those with a BMI ≥ 27 kg/m² when comorbidities, such as hypertension or type 2 diabetes mellitus, are present.^{1,2} Bariatric surgery is reserved for individuals with a BMI ≥ 40 kg/m² (or for patients with a $\geq$ BMI 35 kg/m² and comorbidities) who are unsuccessful with lifestyle modification and pharmacotherapy.^{1,2}

This article reviews developments in lifestyle modification and pharmacotherapy for obesity and concludes with an examination of genes that contribute to obesity, which may yield new targets for pharmacologic intervention and ultimately gene therapy.

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Competing interests

T. A. Wadden declares an association with the following companies: Novo Nordisk, Orexigen Therapeutics, Vivus, Wyeth Pharmaceuticals. See the article online for full details of the relationships. The other authors declare no competing interests

Lifestyle modification

The benefits of lifestyle modification for the treatment of obesity have become evident from results of the Diabetes Prevention Program (DPP)⁴ and the Finnish Diabetes Prevention Study,⁵ which showed a 58% reduced risk of developing type 2 diabetes mellitus with lifestyle intervention compared with placebo. These two studies led to the initiation of the Look AHEAD (Action for Health in Diabetes) study,⁶ which is the first prospective, randomized trial to examine whether weight loss, combined with increased physical activity, will decrease cardiovascular morbidity and mortality, including fatal and nonfatal myocardial infarction and stroke. A total of 5,145 overweight individuals with type 2 diabetes mellitus were randomly assigned to an intensive lifestyle intervention (ILI), modeled on the DPP, or a diabetes support and education (DSE) group.⁷ After 1 year, participants in the ILI group lost 8.6% of their initial weight compared with 0.7% in patients in the DSE group ($P<0.001$).⁶ After 4 years, patients in the ILI group maintained a weight loss of 4.7% compared with 1.0% in individuals in the DSE group ($P<0.001$).⁸ Clinically significant improvements in fitness, levels of HbA_{1c} and HDL cholesterol, and systolic blood pressure were also maintained by patients in the ILI group, compared with those in the DSE group. Long-term follow-up, which is scheduled to conclude in 2014, will reveal whether these improvements are sufficient to reduce cardiovascular morbidity and mortality in the ILI group.

Options for lifestyle modification

In academic medical centers, lifestyle modification is typically provided weekly, according to a structured treatment protocol, for an initial period of 16–26 weeks.^{9,10} Instruction in nutrition, suitable physical activities and long-term weight management is provided to groups of 10–20 individuals in sessions of 60–90 min duration by registered dietitians, behavioral psychologists or other health-care professionals.^{9,10} Group treatment is more economical to provide and induces larger initial weight loss than individual care, even in participants who report a preference for individual treatment.¹¹ This phenomenon is potentially due to feelings of camaraderie and support provided by other group members, as well as competition between participants. Treatment may also be delivered via the internet and e-mail.¹² These latter approaches have the potential to reach the millions of individuals who would benefit from lifestyle modification. The most successful internet-based programs, however, typically induce a loss of only 4–5% of initial weight, about half of the amount achieved with meetings that occur face to face.^{12–15}

Diet—Consistent with US dietary guidelines,¹⁶ lifestyle modification programs typically encourage participants to consume a low-fat diet and to increase the intake of fruits, vegetables and whole grains.^{17,18} Nevertheless, lifestyle interventions can be combined with a variety of dietary approaches on the basis of individual preferences. Whereas low-carbohydrate, low glycemic index and Mediterranean diets have all been found to induce short-term weight loss,^{19–26} the optimal macronutrient composition of weight loss diets has not been established. Table 2 presents selected randomized trials that have examined weight loss with diets of varying macronutrient compositions. Despite the contest that has prevailed among advocates of these and other diets over the past decade, a randomized controlled trial²⁷ showed that macronutrient composition, in a specific diet did not affect short-term or long-term weight loss when the prescribed energy deficit was held constant, at 750 kcal per day.²⁷ This finding reaffirms that calorie intake—not macronutrient composition—determines weight loss. The amount or type of macronutrient, however, may affect the control of comorbid conditions, such as type 2 diabetes mellitus and cardiovascular complications.^{19,20,28} Dansinger and colleagues²⁶ suggested that the optimal diet for weight loss is the one to which individuals have the best adherence.

Physical activity—Physical activity is critical for improving cardiovascular disease risk factors in individuals with obesity, regardless of its effects on body weight.^{29,30} Several studies have shown that cardiorespiratory fitness attenuates the increased mortality risk associated with obesity.^{31–33}

Individuals with obesity should strive to engage in ≥ 150 min per week of moderate to vigorous activity, such as brisk walking.³⁰ Resistance training is particularly beneficial for maintaining fat-free mass during weight loss.^{34,35} Multiple short periods of activity per day have been shown to be as effective as a single long period of activity for the induction of weight loss.^{36,37} Similarly, increasing lifestyle activity, which includes all physical activity that is not scheduled exercise, is as effective as traditional, programmed exercise improving weight and cardiovascular health.^{38,39} Methods to increase lifestyle activity include taking the stairs instead of the elevator, walking to nearby places instead of driving, and doing yard work. Pedometers provide an inexpensive and convenient method of tracking increases in both lifestyle and programmed physical activity.⁴⁰

Cognitive behavioral therapy—Cognitive behavioral therapy for obesity incorporates skills of self-monitoring, stimulus control, and cognitive restructuring.^{9,10} Self-monitoring includes teaching patients to keep detailed records of the types and amounts of food and beverage consumed each day, which helps participants to calculate calories. In addition, this method helps participants become aware of any patterns to their intake, such as snacking in the evening.⁹ Stimulus control techniques help patients manage cues (or triggers) associated with eating, and include exercises such as limiting eating to one room in the house, eating at regular times of day, and refraining from eating while engaging in other activities, such as driving.⁹ Cognitive restructuring is based on the theory that a person's thoughts control their behavior (and their response to events). Cognitive-behavioral treatment teaches participants how to identify and challenge problem thinking patterns.⁹ For example, thoughts such as "I shouldn't have eaten that cookie, I've blown it, I'll never be able to do this," typically lead patients to give up on their diets. Patients are taught to practice developing more adaptive thoughts, such as "That wasn't the best choice for me but I'll get back on track right now and eat fewer calories at my next meal to compensate."

Long-term weight management—Patients treated by group lifestyle modification for 20–26 weeks lose an average of 7–10% of initial weight, but, in the absence of continuing care, regain about one-third of the lost weight in the year following treatment.^{9,10} Multiple factors seem to contribute to weight regain.¹⁰ First, upon leaving their highly supportive treatment groups, patients return to a toxic environment that explicitly encourages them to consume large quantities of foods—high in fat, sugar and calories.⁴¹ Second, metabolic adaptations to weight loss also probably contribute to weight regain.¹⁰ For example, after weight loss, energy expended during physical activity is reduced by $\geq 40\%$ as a result of an increased work efficiency of skeletal muscle.⁴²

Participation in weight-maintenance sessions, following acute weight loss, is the most reliable method of facilitating long-term weight control (with lifestyle modification).^{10,43} Individuals who attended group maintenance sessions every 2 weeks during the first year after weight reduction maintained 13.0 kg of a 13.2 kg weight loss, whereas study participants assigned to a control group had regained 5.1 kg by the end of the year.⁴⁴ Furthermore, Wing *et al.*⁴⁵ showed that monthly patient-provider contact, whether in person or via the internet, similarly improved the maintenance of a previous loss of 19.3 kg. This study revealed the importance of patients weighing themselves daily during weight maintenance and responding quickly to small increases in weight.¹⁷ High levels of physical activity (≥ 200 min duration or energy expenditure of 2,500 kcal per week) are also critical

for successful weight-loss maintenance.^{35,46,47} A high volume of activity may be needed to compensate for the increased work efficiency of skeletal muscle following weight loss.⁴²

Pharmacologic treatment of obesity

Weight-loss medications are recommended as an adjunct to lifestyle modification in patients unable to lose sufficient weight (that is, ~10% of their initial weight) with diet and exercise alone.^{2,3} At present, only two medications—orlistat and sibutramine—are approved by the FDA for long-term weight loss (Table 3). Despite their distinctly different mechanisms of action and adverse effect profiles, both medications, when combined with lifestyle modification, induced losses of approximately 10% of initial weight in trials of 1-year or 2-years duration.^{48–51} These losses were associated with marked improvements in several metabolic outcomes and risk factors of cardiovascular disease.⁵²

Orlistat

Orlistat, a pancreatic lipase inhibitor, prevents the hydrolysis and absorption of approximately 30% of dietary fat contained in a meal.^{52,53} This drug is prescribed as 120 mg, taken three times per day with meals. A meta-analysis,⁵⁴ which included 16 studies of approximately 10,000 participants who were treated with orlistat or placebo for at least 1 year, reported a mean placebo-subtracted weight loss of 2.9 kg.

The drug's mechanism of action often results in several gastrointestinal adverse effects, including abdominal pain, bloating, flatulence, oily stools and diarrhea. Some of these adverse effects can be reduced or avoided by limiting the fat intake per meal to 15 g. Thus, patients are negatively reinforced to consume a low-fat diet.

Several serious cases of adverse hepatic effects (for example, cholestatic hepatitis and subacute liver failure) have been reported over the past 10 years, prompting the FDA to issue an update on the safety of orlistat in September 2009.^{55,56} The FDA's review of orlistat revealed that jaundice, abdominal pain and weakness were the most frequent liver-related adverse events, whereas severe liver injury was rare.⁵⁶ At the present time, the FDA has not advised against the continued prescription of the medication. Moreover, orlistat can now be purchased over-the-counter in a low-strength dose (60 mg). Of note, no substantial serious adverse effects were reported after 4 years of treatment with orlistat in a diabetes prevention trial.⁵⁷

Sibutramine

Sibutramine, a selective serotonin and norepinephrine reuptake inhibitor, acts centrally to reduce food intake.^{52,53} The medication is prescribed at a dose of 10 mg or 15 mg once daily (typically in the morning). In a meta-analysis⁵⁴ that included seven studies on 2,838 participants treated with sibutramine for at least 1 year, the mean placebo-subtracted weight loss was 4.2 kg. The largest weight losses were obtained when the medication was combined with a comprehensive program of lifestyle modification.^{58,59} Common adverse effects include increased blood pressure and pulse rate, constipation, dry mouth and insomnia. Thus, health professionals must monitor blood pressure and heart rate regularly to determine that they remain at acceptable levels in patients receiving sibutramine.

Concerns about the safety of sibutramine arose following preliminary analysis of the ongoing Sibutramine Cardiovascular OUTcomes (SCOUT) trial,⁶⁰ which is assessing the safety of sibutramine in individuals with pre-existing cardiovascular diseases or diabetes mellitus. A higher rate of cardiovascular disease events was observed in the sibutramine group compared to placebo (11.4% versus 10.0%), although the increased risk was limited to participants with a prior history of cardiovascular disease-related complications. These

results underscore that sibutramine is contraindicated in individuals with pre-existing cardiovascular diseases (that is, coronary artery disease, stroke or transient ischemic attack), cardiac arrhythmias, congestive heart failure, peripheral arterial disease and uncontrolled hypertension.⁶¹ Sibutramine currently remains available in the US but was withdrawn from the European market in January 2010.⁶²

Phentermine

Phentermine, a sympathomimetic amine that promotes catecholamine release, has been available in the US since 1959. A meta-analysis,⁶³ which included six randomized trials, lasting 2–24 weeks, reported a mean placebo-subtracted weight loss of 3.6 kg. A 36-week study, however, published in 1968, revealed a mean placebo-subtracted loss of 7.5 kg.⁶⁴ Common adverse effects included insomnia, anxiety and other central nervous system effects. Additional studies revealed treatment-related events that included tachycardia, elevated blood pressure, palpitations and gastrointestinal effects.⁶⁵ Phentermine is only recommended for short-term use; its administration for a period >12 weeks is considered off-label in the US, whereas it is no longer a licensed drug in Europe.⁶⁵

Phentermine has also been prescribed in combination with other medications, most notably fenfluramine. The latter drug, however, was removed from the market in 1997 because of its association with cardiac valvulopathy.⁶⁶ Phentermine was not implicated in this disorder and remains the most widely prescribed weight-loss medication in the US today, principally because of its efficacy and low cost. Other medications that have been used off-label to achieve modest weight loss include fluoxetine, topiramate, diethylpropion, bupropion and zonisamide (Table 3).^{65,67}

Novel therapies in development

Given the complexity of the neural pathways that regulate appetite and body weight, investigators are searching for combination therapies that target multiple pathways to enhance weight loss (Table 3). Combination therapies typically comprise agents that have been found to induce weight loss in other conditions, but may be more tolerable because they are administered in lower doses than typically prescribed as individual components.⁶⁸

Many of the new combination therapies are designed to target multiple receptor subtypes in the arcuate nucleus (ARC) of the hypothalamus, an area of the brain critical for the control of energy homeostasis (Figure 1). Information about the body's current nutrient status and energy stores is conveyed to this region of the brain by peripheral hormones, such as leptin, ghrelin and insulin. Leptin binds to two opposing populations of neurons in the ARC.^{69–71} These neurons include the orexigenic, appetite-inducing neuropeptide Y (NPY) and agouti-related protein (AgRP) neurons and the anorexigenic, appetite-suppressing pro-opiomelanocortin (POMC) neurons. Both NPY/AgRP and POMC neurons project from the ARC to the paraventricular nucleus (PVN) of the hypothalamus (as well as other brain regions), which contains a dense neuronal population that expresses the melanocortin receptor 4 (MC4R). When leptin binds to its receptor on POMC neurons, it promotes the release of melanotropin α (also known as α -melanocyte stimulating hormone [α -MSH]) and cocaine and amphetamine-regulated transcript protein (CART), which both bind to MC4R. Leptin inhibits activation of NPY and AgRP neurons, thus, decreasing inhibitory input to POMC neurons while simultaneously reducing the release of orexigenic signals which act at downstream targets. These two phenomena (inhibition of NPY/AgRP neurons and disinhibition of POMC/CART neurons) lead to a subsequent increase in the release of CART and other anorectic neuropeptides in the PVN. Activation of MC4R in the PVN by α -MSH relays a satiety signal, resulting in a reduction in food intake. AgRP is an inverse

agonist at the MC4R, leading to increased food intake. In short, both leptin and insulin activate POMC neurons and inhibit NPY neurons.

Naltrexone and bupropion—The opioid receptor antagonist naltrexone has been combined with bupropion, a dopamine and norepinephrine reuptake inhibitor. Bupropion seems to increase firing of POMC neurons, whereas naltrexone blocks the β -endorphin-mediated autoinhibition of these neurons, thereby amplifying the effect of bupropion.^{72,73} In a 24-week, randomized, controlled trial of 419 patients with obesity, Greenway *et al.*⁷² found that all three doses of naltrexone (16 mg, 32 mg and 48 mg), combined with bupropion (400 mg per day), produced statistically significant placebo-subtracted weight losses of 4.6%, 4.7% and 3.5%, respectively. A subsequent 56-week, randomized, controlled trial of 793 study participants with obesity compared a sustained-release naltrexone–bupropion formulation (32 mg plus 360 mg, respectively) versus placebo, combined with intensive lifestyle modification.⁷³ A per-protocol analysis revealed that the patients treated with medication lost 9.3% of their initial weight, compared with 5.1% in participants who received placebo ($P<0.001$); A sensitivity analysis, however, revealed smaller losses of 7.8% and 4.9%, respectively ($P<0.001$). Common adverse effects included nausea, headache, insomnia and constipation. A new drug application was submitted to the FDA in March 2010.

Bupropion and zonisamide—Bupropion has also been combined with the antiepileptic agent zonisamide. The latter medication was found incidentally to induce weight loss in epilepsy trials.⁷⁴ A subsequent randomized, controlled trial of individuals with obesity demonstrated superior weight loss with zonisamide compared with placebo, when both were combined with a hypocaloric diet.⁷⁵ Zonisamide's precise mechanism of action for inducing weight loss is unknown, but it is thought to enhance serotonergic and dopaminergic activity.⁷⁵ In a 24-week phase IIb trial (designed to assess drug efficacy), the combination of bupropion and zonisamide induced an 8.6% weight loss, compared to 1.1% for placebo.⁷⁶ The most common adverse events were headache, nausea, insomnia, anxiety and dry mouth. Phase III studies are currently in progress.

Phentermine and topiramate—A combination of phentermine and controlled-release topiramate, another antiepileptic agent, has been found to induce weight loss (by unknown mechanisms).⁷⁶ In a 24-week, randomized, controlled trial of 200 individuals with obesity, Gadde *et al.*⁷⁷ found that the combination of phentermine and topiramate induced a weight loss of 11.4 kg, compared with losses of 6.6 kg with topiramate alone, 5.3 kg with phentermine alone and 2.2 kg with placebo. In a phase III trial, 756 patients with obesity were assigned to placebo or phentermine and controlled-release topiramate (7.5 mg phentermine plus 46 mg topiramate or 15 mg phentermine plus 92 mg topiramate) or single agent doses that comprised these combinations.⁷⁸ Medication was prescribed in combination with lifestyle modification. After 6 months, patients in the placebo group had lost 1.7% of their initial weight, compared with 8.5% and 9.2% in the combination groups that received the low and high combination doses, respectively. Typical adverse events included headache, paresthesias (skin tingling or numbness), dizziness, dry mouth, upper respiratory infections, nasopharyngitis and constipation.⁷⁹ In earlier studies,^{79,80} monotherapy with high doses of topiramate was associated with adverse neuropsychiatric events that included changes in cognition. A new drug application for the combination of phentermine and controlled-release topiramate was filed with the FDA in December 2009. On 15 July 2010, an FDA advisory panel voted against its approval by a vote of 10 to six. The final decision on this drug will be made by the FDA by the end of October 2010.

Pramlintide and metreleptin—The combination of pramlintide, an analog of islet amyloid polypeptide used in the treatment of diabetes mellitus, and recombinant human leptin was found to reduce food intake and weight in leptin-resistant, diet-induced obese rats.^{81,82} In a proof-of-concept study,⁸³ 177 patients with obesity were treated with either 360 µg pramlintide, or 5 mg metreleptin, twice daily, or a combination of the two, for 24 weeks. All participants were initially treated with a calorie-restricted diet and pramlintide for the first 4 weeks. Weight losses at week 20 were 7.2 kg, 7.2 kg, and 9.9 kg, respectively. A placebo group was not included in this study. Common adverse effects included pain at the injection sites and nausea. In February 2010, plans to undertake phase III studies of pramlintide and metreleptin were announced.

Lorcaserin—In contrast to the medications described above, lorcaserin is a monotherapeutic agent that selectively targets the 5-hydroxytryptamine receptor 2C (HTR2C), to modulate appetite.⁶⁸ Unlike the nonselective HTR agonist fenfluramine, lorcaserin is not thought to stimulate the HTR2B receptor, an effect that was associated with cardiac valvular disease.⁶⁸ Lorcaserin was found to produce dose-dependent weight loss in preclinical and clinical studies.^{84–86} A 2-year, randomized trial⁸⁷ included 3,182 patients with obesity who were assigned to either lorcaserin (10 mg twice daily) or placebo, combined with lifestyle modification. Mean placebo-subtracted weight loss at 1 year was 3.6 kg in the lorcaserin group ($P<0.001$). Compared with patients who received placebo, study participants treated with medication regained less weight during the second year ($P<0.001$). Echocardiograms performed at baseline and after 6, 12, 18 and 24 months did not reveal a drug-related effect on the development of valvulopathy. A new drug application for lorcaserin was filed with the FDA in December 2009.

Novel targets for pharmacotherapy

The development of obesity is highly influenced by genetics, with heritability estimates ranging between 20% and 80%.^{88–92} Most genes that contribute to this condition are still unknown, but rare monogenic defects that cause early-onset, severe obesity have shed new light on specific genes or genomic regions integral to the regulation of body weight.⁹³ Further identification of the pathways affected by these genes may elucidate novel targets for pharmacologic therapy. Development of receptor ligands (antagonists or agonists), or inhibitors of intracellular signaling mechanisms associated with these pathways, are of great interest to pharmaceutical companies targeting obesity. Ever more sophisticated gene therapy techniques are being developed, in which inert virus vectors that encode particular genes (e.g., leptin or POMC) are able to restore deficiencies associated with depletion (or mutation) of that gene.^{94,95} A benefit of these techniques is the high degree of location specificity, as function can be restored in very specific areas of the central nervous system.⁹⁶

Genetics and the leptin–melanocortin system

Defects in the hypothalamic leptin–melanocortin circuits have been implicated in many of the known monogenic forms of obesity. In humans, defects in leptin or the leptin receptor are well-characterized, but are exceedingly rare.⁹⁷ Other rare autosomal recessive mutations that result in hyperphagia and severe early-onset obesity have been described in the *POMC* and prohormone convertase 1 (*PC1*) genes. Collectively, these autosomal recessive mutations account for only 32 reported cases of obesity worldwide.⁹⁷

Mutations in the melanocortin system, however, are more common and may underlie more cases of adult obesity. These mutations are inherited in an autosomal dominant fashion, with severe obesity resulting from the inheritance of only one affected allele.⁹⁷ Mutations in *MC4R* are estimated to account for obesity in 1.8% of adults⁹⁸ and up to 6.0% of cases of

severe obesity in children.⁹⁹ The prevalence of defects in this pathway has spurred the search for *MC4R* agonists.

Subtle variants in the genes implicated in monogenic obesity may also contribute to more common forms of obesity, which typically result from interactions among numerous genes and the environment. In a large number of genome-wide association studies, which were performed in individuals with obesity and those with obesity-related phenotypes, the *MC4R* gene has been the most strongly replicated candidate gene.¹⁰⁰ Other successfully replicated associations were found for genes that encode adipokines and adipokine receptors (for example, leptin and its receptor, adiponectin, resistin, TNF and interleukin 6).⁹³ Genetic variants in some of these genes have been associated with distinct eating patterns, such as extreme snacking behavior or consumption of excessive portion size.¹⁰¹

Other genes implicated in obesity

Genome-wide association studies represent a powerful new technology that has led to the identification of new candidate genes in several disorders, including obesity. With this approach, the entire genome is screened to identify new, unanticipated genetic variants associated with disease.¹⁰⁰ At present, common variants in three genes have been associated with an increased risk of obesity: the fat mass and obesity associated (*FTO*), *MC4R*, and proprotein convertase subtilisin/kexin type 1 (*PCSK1*) genes. In association with these genes, 17 obesity loci have been identified (Table 4).

The *FTO* gene was the first locus identified to harbor common variants that predispose humans unequivocally to obesity and excess fat mass.¹⁰² Multiple studies have found that *FTO* variants are associated with increased appetite.^{103–106} Although the site of action of the *FTO* protein on energy balance remains unclear, *FTO* is highly expressed in the brain.^{102,107} Evidence from rodent studies suggests that *FTO* may modulate levels of Stat3, a transcription factor critical for leptin receptor signaling.¹⁰⁸ Another genome-wide association study of 17,000 individuals found common variants in the *MC4R* to be positively associated with BMI.¹⁰⁹ Both *FTO* and *MC4R* were validated as genes controlling BMI in two subsequent studies that utilized genome-wide association in very large cohorts.^{110,111} The *PCSK1* gene was identified in a genome-wide association study that included 1,380 Europeans with severe obesity.¹¹² All three genes are highly expressed in the central nervous system, particularly in the hypothalamus.¹¹³ Although each allele explains only a small proportion of the variance in adult BMI, individuals who carry a high number of risk alleles have a markedly increased BMI.¹¹³

Identification of new genes that control energy intake and expenditure may yield valuable clues about novel therapeutic targets, for which pharmacologic agents can be designed to correct absent or mutated gene products.¹¹⁴ Although gene therapy may be a potential treatment for obesity in the future, marked limitations in gene delivery systems, safety and the reliable control of gene expression currently precludes its use in humans.^{114,115}

Conclusions

Lifestyle modification to treat obesity is effective in inducing and maintaining losses of approximately 7–10% of initial weight, which can prevent or ameliorate obesity-related health complications, including type 2 diabetes mellitus and hypertension. Lifestyle modification incorporates both cognitive and behavioral techniques, including self-monitoring, stimulus control, and cognitive restructuring. Pharmacotherapy is recommended, in some patients, as an adjunct to lifestyle modification to improve the induction and maintenance of weight loss. Several new combination therapies are currently under development. Advances in genomic technology have lead to the identification of

many candidate genes for obesity, which may yield valuable clues for novel pharmacologic targets. Advances in pharmacologic treatment of obesity must be accompanied by thorough cost-effectiveness analyses and determination of which individuals with obesity will benefit the most from treatment. For example, the induction and maintenance of a 7% to 10% weight loss may prove to have the greatest health benefits – and cost savings – in persons at risk of type 2 diabetes mellitus. Improvements in patients' quality of life, which result from prevention of diabetes, must be included in the cost-benefit analysis. Ultimately, studies are needed to determine the cost of providing lifestyle modification and pharmacotherapy for individuals with obesity compared with the costs of treating type 2 diabetes mellitus and its associated complications.

Review Criteria

A literature search was performed using PubMed and MEDLINE for original articles published from 1970 onwards focusing on “lifestyle modification,” “behavioral weight management,” “cognitive behavioral therapy,” “pharmacotherapy for obesity,” and “sibutramine,” “orlistat,” “phentermine.” The senior author (T.A. Wadden) drew on his substantial knowledge of the literature for each of these sections. For the sections on the neural regulation of energy homeostasis and gene therapy we searched PubMed and Medline for original articles on “neural regulation” and “obesity” “gene therapy” and “obesity,” and “ob gene,” “pomc gene,” “FTO gene.” Again, several papers were identified by drawing on authors' own knowledge of the literature (M.L. Vetter and L.F. Faulconbridge). All articles identified were English-language, full-text papers, performed only in adults (except animal studies). Previous reviews from peer-reviewed journals were used in synthesizing data. We also searched the reference lists of identified articles for further papers.

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Figure 1.

Neuronal control of energy intake. Two different types of neurons in the arcuate nucleus of the hypothalamus contribute to the control of energy homeostasis. One type of neuron produces neuropeptide Y and agouti-related peptide, which stimulate food intake, whereas the other produces pro-opiomelanocortin and cocaine and amphetamine-regulated transcript protein, which inhibit food intake. Permission obtained from Macmillan Publishers Ltd © Barsh, G. S & Schwartz, M. W. *Nat. Rev Genet.* **3**, 589–600 (2002). Abbreviations: Ghsr, growth hormone secretagogue receptor; Lepr, leptin receptor; Mc3r/Mc4r, melanocortin 3/4 receptor; Y₁r, neuropeptide Y₁ receptor.

Table 1

A guide to selecting treatment

Treatment	BMI Category (kg/m ²)				
	25.0–26.9	27.0–29.9	30.0–34.9	35.0–39.9	≥ 40.0
Diet, physical activity, and behavior therapy	With comorbidities	With comorbidities	+	+	+
Pharmacotherapy	N/A	With comorbidities	+	+	+
Surgery	N/A	N/A	With comorbidities		

The + represents the use of indicated treatment regardless of comorbidities. Table reprinted with permission from the National Heart, Lung, and Blood Institute (NHLBI) as a part of the National Institutes of Health and the US Department of Health and Human Services in cooperation with the North American Association for the Study of Obesity (NAAASO).

Randomized trials comparing diets with varying macronutrient composition on weight loss and cardiometabolic risk factors.

Table 2

Study	N	Dietary Intervention	Weight Change	Months	Comment/Other Results
Sacks <i>et al.</i> ²⁷	811 (64% F) 79.5% completed	Low-fat, high-protein High-fat, average-protein High-fat, high-protein (lowest carbohydrate) Low-fat, average-protein (highest carbohydrate)	-3.8 kg -3.2 kg -3.4 kg -3.0 kg	24	LDL cholesterol decreased significantly more in lowest fat than in highest fat groups. HDL cholesterol increased more with lowest carbohydrate than with the highest carbohydrate diet. All diets decreased triglyceride levels similarly. All diets, except the highest carbohydrate, decreased fasting insulin (greater decrease in the high protein vs. average protein diets).
Shai <i>et al.</i> ²³	322 (14% F) 84.6% completed	Low-fat Mediterranean Low-carbohydrate	-2.9 kg ^a -4.4 kg ^b -4.7 kg ^b	24	No significant change in LDL cholesterol in any group. HDL cholesterol increased in all groups, significantly more in the low-carbohydrate than low-fat groups. Triglyceride levels decreased more in the low-carbohydrate than in the low-fat group. In participants with diabetes mellitus, only the Mediterranean diet group had a decrease in fasting glucose. Insulin, leptin, and blood pressure decreased, whereas adiponectin levels increased in all groups.
Gardner <i>et al.</i> ¹¹⁷	311 (100% F) 80% completed	Atkins (low-carbohydrate) Zone (even distribution) LEARN (calorie-restricted) Ornish (low-fat)	-4.7 kg ^a -1.6 kg ^b -2.2 kg ^{ab} -2.6 kg ^{ab}	12	Increase in HDL cholesterol larger in Atkins than Ornish group. Triglyceride levels decreased more in Atkins than Zone group. No differences in insulin or blood glucose between groups. Systolic blood pressure decreased more in Atkins than in all other groups. Diastolic blood pressure decreased more in Atkins group than in Ornish group.
Dansinger <i>et al.</i> ²⁶	160 (51% F) 58% completed	Atkins Zone Weight Watchers Ornish	-2.1 kg ^a -3.2 kg ^a -3.0 kg ^a -3.3 kg ^a	12	All participants had hypertension, dyslipidemia, and/or fasting hyperglycemia. Weight loss was associated with level of adherence. Each diet decreased LDL: HDL ratio. No significant effects on blood pressure or blood glucose at 12 months.
Stern <i>et al.</i> ¹¹⁸	132 (17% F) 62% completed	Low-carbohydrate Conventional (calorie-restricted)	-5.1 kg ^a -3.1 kg ^a	12	83% participants had diabetes or metabolic syndrome. HDL cholesterol levels decreased more in conventional diet group. In participants with diabetes mellitus, HbA1c levels decreased significantly more in low-carbohydrate group.
Foster <i>et al.</i> ¹¹⁹	63 (68% F) 59% completed	Low-carbohydrate (high-protein, high-fat) Conventional (high-carbohydrate, low-fat)	-4.4% ^a -2.5% ^a	12	HDL cholesterol increased more in the low-carbohydrate group. At 12 months, triglycerides were lower only in low-carbohydrate group. Diastolic blood pressure decreased in both groups. Area under the insulin curve decreased in both groups.
Yancy <i>et al.</i> ¹²⁰	120 (76% F) 65.8% completed	Low-fat diet Low-carbohydrate, ketogenic diet with nutritional supplements	-6.7% ^b -12.9% ^a	6	All participants were hyperlipidemic. Triglycerides decreased more and HDL cholesterol increased more in low-carbohydrate group.
Brinkworth <i>et al.</i> ¹²¹	66 (61% F) 57.6% completed	Low-protein (high-carbohydrate, low-fat) High-protein (low-carbohydrate, low-fat)	-2.2 kg -3.7 kg	16	All participants had type 2 diabetes mellitus. Systolic and diastolic blood pressure higher in low protein group during follow up. Levels of Blood glucose, insulin, HOMA, and HbA1c were reduced in both groups at week 12 but not at month 16.

Study	N	Dietary Intervention	Weight Change	Months	Comment/Other Results
Iqbal <i>et al.</i> ¹²²	144 (10% F) 47.2% completed	Low-carbohydrate Low-fat	-1.5 kg ^a -0.2 kg ^a	24	All participants had diabetes. No differences within or between groups for lipids or glycemic indexes.
Samaha <i>et al.</i> ¹⁹	132 (17% F) 59.8% completed	Low-carbohydrate Low-fat	-5.8 kg ^a -1.9 kg ^b	6	39% of participants had diabetes mellitus and 43% had metabolic syndrome. Triglycerides decreased and insulin sensitivity improved more in low-carbohydrate group.
Klemsdal <i>et al.</i> ¹²³	202 (58% F) 81% completed 58% female	Low-glycemic load Low-fat	-4.0 kg ^a -4.3 kg ^a	12	62% participants with metabolic syndrome. Waist circumference decreased more in low-fat diet group. Diastolic blood pressure decreased more in the low glycemic load group.
Das <i>et al.</i> ¹²⁴	34 (% F unknown) 85% completed	Low-glycemic load High-glycemic load	-7.8% ^a -8.0% ^a	12	Triglycerides, total, HDL, and LDL cholesterol decreased in both groups.
Estruch <i>et al.</i> ¹²⁵	772 (56% F) 99.6% completed	Mediterranean with olive oil Mediterranean with nuts Low-fat	-0.19 kg ^a -0.26 kg ^a -0.24 kg ^a	3	Systolic and diastolic blood pressure, total: HDL cholesterol, and plasma glucose all decreased more in the Mediterranean groups. Total cholesterol and triglycerides decreased only in the Mediterranean with nuts group. For non-diabetic participants, fasting insulin and HOMA scores were lower in both Mediterranean groups. CRP concentration decreased only in the Mediterranean with olive oil group.
Brehm <i>et al.</i> ¹²⁶	124 (63% F) 77% completed	High-monounsaturated fatty acid High-carbohydrate	-4.0 kg ^a -3.8 kg ^a	12	All participants had type 2 diabetes mellitus. Similar improvements in diastolic blood pressure, HDL cholesterol, HbA1c, fasting glucose, and fasting insulin in both groups.

* Different letters indicate statistically significant differences in weight loss between groups. Abbreviations: CRP, C-Reactive protein; F, female; HOMA, homeostatic model assessment.

Table 3

Commonly used anti-obesity medications and new combination therapies currently in phase III clinical trials

Drug	Mechanism	Adverse effects	Effects on weight	FDA status
Medications for long-term weight loss (data from meta-analysis)				
Sibutramine *	Norepinephrine and serotonin reuptake inhibitor (appetite suppressant)	Headache, insomnia, constipation, dry mouth, increased blood pressure, increased pulse	4.2 kg placebo-subtracted weight loss at 1 year	Currently approved for long-term weight loss in the US; undergoing safety review
Orlistat *	Pancreatic lipase inhibitor	Abdominal pain, bloating, flatulence, oily stools, diarrhea, decreased absorption of fat soluble vitamins	2.9 kg placebo-subtracted weight loss at 1 year	Currently approved for long-term weight loss
Medications for short-term weight loss or selected medications used off-label to promote weight loss (data from meta-analysis)				
Phentermine *	Sympathomimetic amine (appetite suppressant)	Increased blood pressure and pulse, headache, insomnia, constipation	3.6 kg placebo-subtracted weight loss in studies ranging from 2 to 24 weeks	Currently approved for short-term weight loss (12 weeks)
Diethylpropion *	Sympathomimetic amine (appetite suppressant that is similar in chemical structure to bupropion)	Dizziness, headache, insomnia, restlessness, mild increases in blood pressure, palpitations, mild tachycardia, mild gastrointestinal symptoms, rash	3.0 kg placebo-subtracted weight loss in studies ranging from 6 to 52 weeks	Used off-label
Zonisamide *	Antiepileptic agent	Increased nervousness, sweating, tremors, fatigue, hypersomnia, insomnia, gastrointestinal side effects	5.0% placebo-subtracted weight loss	Used off-label
Selected novel antiobesity drugs in development (data from single phase IIb and phase III trials)				
Phentermine plus topiramate [‡]	Sympathomimetic amine and antiepileptic agent (appetite suppressant)	Headache, paresthesias, dry mouth, upper respiratory infections, nasopharyngitis, constipation	7.5% placebo-subtracted weight loss	New drug application filed with FDA
Naltrexone plus bupropion	Opioid receptor antagonist and dopamine and norepinephrine reuptake inhibitor (appetite suppressant)	Nausea, headache, insomnia, constipation	4.2% placebo-subtracted weight loss	New drug application filed with FDA
Bupropion plus zonisamide	Atypical antidepressant and an antiepileptic agent	Headache, nausea, insomnia, anxiety, dry mouth	7.5% placebo-subtracted weight loss	Currently in phase III trials
Lorcaserin	Selective HTR2C receptor agonist	Headache, nausea, dizziness (no known effect on heart valves)	2.9 kg placebo-subtracted weight loss	New drug application filed with FDA

* Data from Li *et al.*⁶⁷[‡]Data from Haddock *et al.*⁶³ Abbreviation: HTR2C, 5-hydroxytryptamine receptor 2C.

Table 4

Overview and properties of 17 loci associated with variation in BMI

Genes and chromosomal location	Hypothesized molecular or cellular function	Additional phenotypes associated with loci
<i>NEGR1</i> (1p31)	Neuronal outgrowth	None
<i>SEC16B</i> , <i>RASAL2</i> (1q25)	Unknown	None
<i>TMEM18</i> (2p25; closest gene)	Neuronal development	Associated with T2DM
<i>ETV5</i> (3q27; locus with three genes)	Unknown	None
Gene desert; <i>GNPDA2</i> is one of three genes nearby (4p13)	Unknown	Associated with T2DM
<i>PRL</i> (6p22.2-p21.3)	Unknown	None
Locus containing <i>NCR3</i> , <i>AIF1</i> , and <i>BAT2</i> (6p21)	Unknown	Associated with weight, not BMI
<i>PTER</i> (10p12)	Unknown	None
<i>BDNF</i> (11p14; locus with four genes, strongest association near <i>BDNF</i>)	<i>BDNF</i> expression is regulated by nutritional state and MC4R signaling	Associated with T2DM
<i>MTCH2</i> (11p11.2; locus with 14 genes)	Cellular apoptosis	None
<i>FAIM2</i> (12q13; locus also contains <i>BCDIN3D</i>)	Adipocyte apoptosis	None
<i>SH2B1</i> (16p11.2; locus with 19–25 genes)	Neuronal role in energy homeostasis	<i>Sh2b1</i> -null mice are obese and diabetic
<i>MAF</i> (16q22-q23)	Transcription factor involved in adipogenesis and insulin-glucagon regulation	None
<i>FTO</i> (16q22.2)	Neuronal function associated with control of appetite	Associated with T2DM
<i>NPC1</i> (18q11.2)	Intracellular lipid transport	<i>Npc</i> -null mice show late-onset weight loss and poor food intake NPC1 interferes with function of raft-associated insulin signaling Haploinsufficiency in humans is associated with morbid obesity
<i>MC4R</i> (18q22)	Hypothalamic signaling	<i>MC4R</i> -deficient mice show hyperphagia and obesity
<i>KCTD15</i> (19q13.11)	Unknown	None

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