

Approval for publication Signed \_\_\_\_\_  
Date \_\_\_\_\_ Number of amended pages returned \_\_\_\_\_

# Pharmacotherapy of Obesity Currently Marketed and Upcoming Agents

Harold Bays<sup>1</sup> and Carlos Dujovne<sup>2</sup>

- 1 Louisville Metabolic and Atherosclerosis Research Center, Louisville, Kentucky, USA
- 2 Radiant Research at Kansas Foundation for Clinical Pharmacology, Kansas City, Kansas, USA

## Contents

Abstract	.....
1. Current Approaches to Obesity	.....
2. Antiobesity Drugs in Development	.....
2.1 Antiobesity Drugs that Predominantly Decrease Appetite or Increase Satiety	.....
2.2 Antiobesity Drugs that Predominantly Increase Metabolic Rate or Thermogenesis	.....
2.3 Antiobesity Drugs that May Decrease Appetite/Increase Satiety and Increase Metabolic Rate/Thermogenesis	.....
2.4 Antiobesity Drugs that Predominantly Affect the Gastrointestinal System	.....
2.5 Other Antiobesity Drugs	.....
3. Current Guidelines for Drug Treatment of Obesity	.....
4. Rationale and Prospects for Combination and Aggressive Use of Antiobesity Drugs	.....
4.1 Antiobesity Drugs and Coronary Artery Disease	.....
5. Conclusion	.....

## Abstract

In many industrialized nations, obesity is now considered an epidemic, resulting in accelerated morbidity and mortality. Obesity is associated with an increased risk of coronary artery disease as well as the metabolic syndrome comprised of abdominal obesity, increased fasting blood glucose, dyslipidemia and hypertension, which are all recognized cardiovascular risk factors. Diet, exercise, and lifestyle changes constitute important recommendations for treatment. Unfortunately, although effective in some individuals, these recommendations have proven to be ineffective in adequately addressing the broad, enlarging scope of this public health problem.

Drug treatment is often indicated but is somewhat limited by the minimal number of well tolerated drugs that have proven to have long-term efficacy in maintaining bodyweight loss. For example, phentermine may result in modest bodyweight loss through suppression of appetite, but potential cardiovascular adverse effects exist and the efficacy is mainly short-term. Sibutramine, an inhibitor of serotonin and norepinephrine (noradrenaline) reuptake, may increase satiety and result in modest bodyweight loss. However, cardiovascular adverse effects may occur in susceptible patients. Nonetheless, sibutramine is one of the few drugs that has been approved by the US Food and Drug Administration (FDA) for bodyweight loss. Orlistat, a lipase inhibitor, is also approved by the FDA for bodyweight loss but may have bothersome gastrointestinal adverse effects, especially among patients who do not adhere to the recommended low-fat diet. Ongoing studies continue to evaluate other obesity drug treatments that may result in bodyweight reduction through a number of different mechanisms.

It is anticipated that the development of effective and well tolerated antiobesity drugs will elevate the pharmacologic treatment of obesity to the status of other cardiovascular risk factors and metabolic disorders. This may be especially important given that dyslipidemia, hypertension and type 2 diabetes mellitus are often secondary to, or exacerbated by, obesity.

Obesity in the US and other industrialized nations is now considered an epidemic.<sup>[1]</sup> Estimates of the prevalence of obesity vary. Earlier estimates suggested that over 20% of adults in Europe and the US were obese,<sup>[2]</sup> More recent reports suggest that approximately 50 to over 60% of adults in the US are overweight or obese.<sup>[3-8]</sup>

According to the International Obesity Task Force,<sup>[7]</sup> obesity is defined as a body mass index (BMI) [bodyweight in kilograms divided by height in meters squared]  $\geq 30$  kg/m<sup>2</sup>.<sup>[6,9]</sup> Patients meeting this criterion for obesity have a significantly increased risk of numerous morbidities.<sup>[10]</sup> For example, obesity substantially increases the risk of mortality<sup>[11]</sup> as well as cardiovascular risk factors such as dyslipidemia, hypertension, and type 2 diabetes mellitus. Obesity may also increase the risk of other disorders, including gallbladder disease, sleep apnea, orthopedic disorders, and various forms of cancer.<sup>[12,13]</sup>

Obesity is associated with an increased risk of coronary heart disease (CHD) and congestive cardiomyopathy.<sup>[13,14]</sup> In fact, obesity is an important listed criterion in defining metabolic syndrome. The third report of the National Cholesterol Education Program Expert Panel (Adult Treatment Panel III)<sup>[15]</sup> has recognized the importance of the metabolic syndrome as a cardiovascular risk factor, defined it as abdominal obesity, atherogenic dyslipidemia, hypertension and elevated fasting glucose (table I), and made specific treatment recommendations for patients with this metabolic abnormality which reportedly afflicts approximately 22% of adults in the US.<sup>[16]</sup>

Clinicians recognize the prevalence of obesity in their clinical practice and the common comorbidities listed above. Treating obesity is often frustrating because of the limited success of diet and lifestyle interventions and the limited number of effective and well tolerated pharmacologic therapies available. For example, it is not uncommon for clinicians to encounter patients with obesity with a history of bodyweight gain that the patients perceive is not related to caloric intake; these patients often believe that their obese state must be 'hormonally' related or a result of some as yet undiagnosed medical condition. It is true that a minority of

patients with obesity may have an underlying medical condition or may be receiving a concurrent drug treatment that contributes to their obese state.<sup>[17]</sup> These potential secondary causes (such as hypercortisolism and hypothyroidism) should be evaluated and treated as necessary. But it is a basic law of thermodynamics that the scientific and medical explanation of obesity is solely the result of caloric intake that exceeds calories expended. This explanation is often not welcomed by patients, because the subsequent initial treatment is appropriate diet, routine physical exercise, and behavior recommendations, which may represent significant and poorly accepted lifestyle changes on the part of the patient with obesity.

## 1. Current Approaches to Obesity

In order to assist healthcare providers in the management of the obesity epidemic, public health initiatives and diet and exercise guidelines have been recommended by national organizations.<sup>[18]</sup> However, despite these recommendations, the prevalence of obesity, particularly among the young, has increased.<sup>[7,8]</sup> This might reasonably suggest that public health guidelines have not been in the past, and may not be in the future, sufficient in stemming the epidemic of obesity. Therefore, as with other epidemics, it is likely that drug treatments for obesity will grow as an important therapeutic option for this widespread disorder, and drug research will continue to focus on the development of effective and well tolerated drug treatments for patients with obesity.

Current drug treatments include those that decrease appetite or increase satiety, thermogenic agents, and digestive inhibitors<sup>[17,19]</sup> and are outlined in table II.

The mechanism of action of most current drugs that decrease appetite or increase satiety is through an increase in the availability of anorexigenic central nervous system (CNS) neurotransmitters such as norepinephrine (noradrenaline), serotonin (5-hydroxytryptamine, 5-HT), dopamine, or a combination of these.<sup>[20]</sup>

Amphetamines are sympathetic amines that are rarely used drugs for the treatment of obesity. Amphetamine drugs such as dextroamphetamine (dexamphetamine) suppress appetite, and increase metabolic rate. As a result of their stimulant effect, they may cause dangerous cardiovascular adverse effects such as tachycardia and hypertension. They also have high abuse potential and are therefore considered a US Drug Enforcement Administration (DEA) Schedule II drug, with sale and manufacturer restrictions. Although dextroamphetamine does have an indication for treatment of narcolepsy and attention deficit hyperactivity disorder, it does not have a specific indication for the treatment of obesity.

Benzphetamine and phendimetrazine are both US DEA

**Table I.** The National Cholesterol Education Program (Adult Treatment Panel III)<sup>[15]</sup> definition of the metabolic syndrome

**Three or more of the following must be present:**

Waist circumference >102cm (40 inches) in men and >88cm (35 inches) in women
Plasma triglyceride level $\geq 1.69$ mmol/L (150 mg/dl)
Plasma high-density lipoprotein cholesterol level <1.04 mmol/L (40 mg/dl) in men and <1.29 mmol/L (50 mg/dl) in women
Blood pressure $\geq 130 / \geq 85$ mm Hg
Fasting blood glucose level $\geq 6.1$ mmol/L (110 mg/dl)

**Table II.** Currently used antiobesity drugs**Drugs that primarily decrease appetite or increase satiety**

Sibutramine  
 Benzphetamine  
 Phendimetrazine  
 Mazindol  
 Diethylpropion (amfepramone)

**Drugs that increase RMR and thermogenesis and decrease appetite**

Dextroamphetamine (dexamphetamine)<sup>a</sup>  
 Phentermine  
 Caffeine<sup>b</sup>  
 Ephedrine<sup>b</sup>

**Drugs acting in the gastrointestinal tract**

Orlistat

- a Dextroamphetamine is not approved by the US Food and Drug Administration for the treatment of obesity.  
 b Caffeine and ephedrine are commonly used in over-the-counter combination preparations and not as individual treatments for obesity.

**RMR** = resting metabolic rate.

Schedule III anorectic sympathomimetic amines with a pharmacologic activity similar to the amphetamines and are approved for short-term treatment of obesity.

Non-amphetamine DEA Schedule IV anorexiant include mazindol, which is an isoindole compound, and diethylpropion (amfepramone), which is a sympathomimetic amine. All of these approved drugs primarily decrease appetite, but because they may have effects somewhat similar to amphetamines, they may have some potential to increase metabolic rate. These drugs have less stimulant activity than amphetamines, have low abuse potential, and have an indication for short-term treatment of obesity (for only a few weeks). It is presumed that 'a few weeks' is around 12 weeks.<sup>[20]</sup> Among their potential adverse effects are cardiovascular effects that include cardiac dysrhythmias, tachycardia, and edema.

Given these potential adverse effects and the fact that for the vast majority of patients obesity requires lifelong treatment, the health benefits of using these anorexiant for only a few weeks in the treatment of a lifelong condition is questionable. Thus, these drugs are not widely prescribed for the treatment of obesity in the US.

Another DEA Schedule IV appetite suppressant is the noradrenergic sympathomimetic agent phentermine, which is also a non-amphetamine anorexiant that is indicated for short-term treatment of obesity (a few weeks). If effective, phentermine usually results in only modest bodyweight reduction and usually for only a few weeks. Phentermine is contraindicated in patients with cardiovascular conditions such as advanced arteriosclerosis,

symptomatic cardiovascular disease, and moderate to severe hypertension.

Another over-the-counter noradrenergic agent phenylpropanolamine was withdrawn from the US market in 2000 because of unacceptable risks of stroke especially in adult women.<sup>[21]</sup>

Fluoxetine is a highly selective serotonin reuptake inhibitor (SSRI) that may decrease appetite in some patients. However, definitive and significant bodyweight loss has been reported inconsistently in clinical trials. Trials of other drugs such as bupropion and sertraline have yet to demonstrate definitive, long-term efficacy in the treatment of obesity, even among patients with coexistent depression. As a result, fluoxetine, bupropion and sertraline have not received FDA approval for the treatment of obesity.

Sibutramine inhibits serotonin and norepinephrine reuptake and has been approved by the FDA for the treatment of obesity. Its effectiveness in the treatment of obesity is thought to be primarily through increasing satiety, although there may be some stimulation of thermogenesis in animals by activating  $\beta$ -adrenoceptors in brown adipose tissue. Controlled studies have demonstrated that bodyweight loss occurs for the first 6 months of treatment with sibutramine and is maintained for up to 1.5 years afterwards.<sup>[5,6,22]</sup> However, bodyweight gain frequently recurs after discontinuation of this drug. In the Sibutramine Trial of Obesity Reduction and Maintenance, participants who lost more than 5% of their bodyweight after 6 months of therapy were randomized to receive sibutramine or placebo for a further 18 months.<sup>[20,23]</sup> Some bodyweight regain was seen in both groups during the second year of follow-up; however, the bodyweight loss in the sibutramine-administered group was significantly greater than the placebo group for the full 2 years of the trial.

Studies of sibutramine treatment have also demonstrated improvement in important cardiovascular risk factors, such as blood lipid levels,<sup>[24]</sup> and improved blood glucose metabolism as measured by blood hemoglobin A<sub>1c</sub> levels.<sup>[25]</sup>

Potential cardiovascular adverse effects of sibutramine include mild increases in blood pressure and heart rate. Other adverse effects include dry mouth, insomnia, and constipation. Of most concern is that some patients may experience substantial increases in blood pressure with sibutramine, and thus close monitoring is required. Sibutramine is contraindicated in patients with uncontrolled hypertension, CHD, cardiac dysrhythmias, congestive heart failure, or stroke.

Ephedrine and caffeine are commonly used in combination over-the-counter bodyweight loss preparations. They may also have appetite suppressant and thermogenic properties. However, these effects are short lived (weeks), and adverse effects may

include tremor, insomnia, and more severe cardiovascular adverse effects such as cardiac dysrhythmias.

Orlistat is a gastrointestinal lipase inhibitor that impairs the absorption of dietary fat. Significant and sustained bodyweight reduction for at least 2 years has been noted in clinical trials.<sup>[5]</sup> CHD risk factors have been shown to improve as well. This drug initially was evaluated as a hypolipidemic agent, since lipid blood levels improve with orlistat treatment, and this benefit may exceed what would be expected based upon bodyweight loss alone.<sup>[26-28]</sup> Orlistat treatment may also favorably affect glucose metabolism by improving glucose tolerance and delaying development of type 2 diabetes mellitus in patients with obesity,<sup>[29]</sup> and it improves blood glucose levels in patients with type 2 diabetes mellitus.<sup>[30]</sup> High blood pressure may be improved as well.<sup>[31]</sup>

Orlistat treatment may result in gastrointestinal adverse effects such as flatus, oily stools, fecal urgency and fecal incontinence. In addition, abdominal pain may occur, particularly among patients who do not comply with the recommended low-fat diet. Malabsorption of fat-soluble vitamins (A, D, E, and K) has rarely, if ever, occurred, but a daily multivitamin in the evening is recommended concurrently with orlistat treatment as a preventative measure.

The above describes the limited number of drugs available for the safe and effective treatment of obesity for many patients. Thus, new antiobesity drugs in development will pursue new mechanisms of action as well as continue to explore mechanisms of action of established antiobesity drugs (table III).

## 2. Antiobesity Drugs in Development

### 2.1 Antiobesity Drugs that Predominantly Decrease Appetite or Increase Satiety

A reduction in caloric intake will continue to be a mainstay of treatment of patients with obesity who have been unresponsive to diet, exercise, and behavior modification.<sup>[32]</sup>

One antiobesity drug in phase III clinical trials is the cannabinoid (CB) receptor antagonist rimonabant, which may decrease caloric consumption by decreasing appetite. Rimonabant blocks the CB<sub>1</sub> receptor, which is found throughout the CNS, and is a member of the G protein-coupled receptor family. The endogenous CB system may be involved with a number of CNS functions, including appetite.<sup>[33]</sup> Blocking or antagonizing these functions may result in bodyweight reduction.<sup>[34]</sup>

Another antiobesity drug in phase III of development is ciliary neurotrophic factor (CNTF),<sup>[35]</sup> which is a nerve growth factor (cytokine) that is not found in appreciable levels in the blood

**Table III.** Antiobesity drugs in various stages of development

#### Drugs that primarily decrease appetite or increase satiety

Ciliary neurotrophic factor  
Cannabinoid (CB<sub>1</sub>) receptor antagonist (rimonabant)  
P57  
Dopamine antagonist (risperidone)  
Selective 5-HT<sub>2C</sub> receptor agonists  
Topiramate  
Dopamine and norepinephrine (noradrenaline) reuptake inhibitors  
Melanocortin-4 receptor (MC4R) agonists  
Neuropeptide Y antagonists

#### Drugs that primarily increase RMR or thermogenesis

Adipocyte complement – related protein of 30kD (Acrp30)  
β-adrenergic receptor stimulators (β-agonists)  
Thyroid receptor agonists

#### Drugs that increase RMR and thermogenesis and decrease appetite 'Second-generation' leptin<sup>a</sup>

#### Gastrointestinal-acting drugs

Cholecystokinin-A promoter (CCK-A promoter)  
Glucagon-like peptide-1 (GLP-1)  
Lipase inhibitor  
Phytosteranol  
Ghrelin antagonists

#### Other

Growth hormone fragment  
Insulin sensitizers (protein tyrosine phosphatase drugs, peroxisome proliferation activator gamma receptor antagonists, short-acting bromocriptine, carboxypeptidase inhibitors, somatostatin agonists)  
Other hormone-acting drugs

<sup>a</sup> Newer generation leptin or leptin-like drugs might increase thermogenesis.

**5-HT** = serotonin (5-hydroxytryptamine); **RMR** = resting metabolic rate.

but is released locally in the hypothalamus at the cellular level. It was originally studied as a potential treatment for amyotrophic lateral sclerosis (ALS). It did not demonstrate efficacy in patients with ALS, however bodyweight reduction was observed. Phase II studies with CNTF, a hormone with some leptin-like neuroendocrine effects, have shown some promise in bodyweight reduction.

P57 is an extract from a cactus that reportedly has been eaten by African tribesmen in order to decrease hunger during long hunting trips. Clinical trials are planned to determine its safety and effectiveness in the treatment of obesity.

Dopamine receptor antagonists may also reduce appetite and thus caloric intake. For example, risperidone was shown to result in bodyweight reduction in a very small trial involving treatment of patients with Prader-Willi syndrome.<sup>[36]</sup> Ecopipam, a dopamine (D<sub>1</sub>) receptor antagonist, was originally developed as a

treatment for schizophrenia. It has recently been withdrawn from clinical trials with regard to treatment of obesity.

Selective 5-HT<sub>2C</sub> receptor agonists are being evaluated as antiobesity drugs because they are thought to induce satiety. The selectivity of these newer potential agents may have an advantage over older antiobesity drugs which acted on the serotonergic system. For example, dexfenfluramine, withdrawn from the market because of associated heart valve abnormalities, indirectly resulted in the indiscriminate activity of 5-HT receptors, including those in peripheral tissue. Specifically, it has been suggested that activation of 5-HT<sub>2B</sub> receptors accounted for the fenfluramine-associated valvular heart disease.<sup>[37,38]</sup> In contrast, the distribution of 5-HT<sub>2C</sub> receptors i.e., expressed in high density in the brain (notably in the hypothalamus) but absent or present in low density in peripheral tissues, indicates that selective 5-HT<sub>2C</sub> receptor agonists may not have adverse effects related to peripheral 5-HT receptor activation.

At least one trial has suggested that topiramate, originally intended for use as an antiepileptic drug, may be beneficial in treating binge-eating disorder.<sup>[39]</sup> Other dopamine and norepinephrine reuptake inhibitors are also in development. However, the current clinical obesity trial program with topiramate has been discontinued. Finally, other potential antiobesity drugs in development included melancortin-4-receptor (MC4R) agonists and neuropeptide Y antagonists.

## 2.2 Antiobesity Drugs that Predominantly Increase Metabolic Rate or Thermogenesis

Other antiobesity drugs in development may increase resting metabolic rate or thermogenesis. This is important because for most people approximately two-thirds of the body's energy expenditure is a result of maintaining essential body functions and body temperature. The resting metabolic rate is, in turn, dependent upon lean body mass (such as muscle mass) and decreases with age. Therefore, in the event that exercise is not sufficient in achieving sufficient energy expenditure, drugs that increase energy expenditure might hold promise for bodyweight reduction.

Adipocyte complement-related protein of 30kD (Acrp30) has been shown to result in bodyweight loss in mice by increasing fatty acid oxidation in muscle.<sup>[40]</sup>  $\beta_3$ -Adrenoceptors, located mainly in adipose tissue, are thought to be involved in lipolysis and thermogenesis. Selective  $\beta$ -adrenoceptor agonists may therefore theoretically increase metabolic rate and decrease body fat. Thyroid hormone preparations have been evaluated in the treatment of obesity since approximately 1900. Because of the adverse effects of possible hyperthyroidism and potential acceleration of osteoporosis, thyroid hormone is contraindicated as a

treatment for obesity.<sup>[19]</sup> However, thyroid hormone does increase thermogenesis,<sup>[41]</sup> and antiobesity drugs in development include agents that target certain actions at the thyroid hormone receptor level but do not result in the undesirable adverse effects of current thyroid hormone preparations.

## 2.3 Antiobesity Drugs that May Decrease Appetite/Increase Satiety and Increase Metabolic Rate/Thermogenesis

Yet other potential drug treatments, such as leptin (probably the most studied obesity-related hormone) may both reduce appetite/increase satiety and increase energy expenditure. Because leptin is produced by fat cells and regulates food intake and energy expenditure, it was hoped that administration of recombinant leptin would result in bodyweight loss. However, its physiological effects are complex, and although some clinical trials have suggested benefit,<sup>[42]</sup> other studies of bodyweight reduction with peripheral leptin have been disappointing.<sup>[21]</sup> Phase II trials with 'second-generation' leptin are currently ongoing in the hopes of demonstrating superior efficacy compared with native leptin. For example, some studies suggest that, in contrast to rodents, no relationship has been found between blood leptin levels and energy expenditure in humans.<sup>[43]</sup> Future studies of 'second generation' leptin may help further illuminate the role of leptin in human energy expenditure.

## 2.4 Antiobesity Drugs that Predominantly Affect the Gastrointestinal System

Yet other potential antiobesity drugs may act directly on the gastrointestinal system (GI). For example, cholecystokinin-A (CCK-A) promoter is a gut hormone produced in the upper small intestine as well as a neuropeptide in nerve terminals in the CNS and peripheral nervous system.<sup>[44]</sup> It activates gastric fibers and causes satiety,<sup>[6]</sup> and thus CCK-A agonists may conceivably prove to be a useful treatment for obesity.

Glucagon-like peptide-1 (GLP-1) is a gut hormone that inhibits glucagon secretion and stimulates glucose-induced insulin secretion. It may therefore reduce blood glucose levels in patients with diabetes mellitus and may inhibit gastric emptying,<sup>[45,46]</sup> but does not result in lipolysis.<sup>[47]</sup> GLP-1 is also one of a number of hormones that signals satiety,<sup>[21]</sup> and thus bodyweight loss may also occur through this additional mechanism. Other GI-acting antiobesity drugs include lipase inhibitors, which are thought to work similarly to the current lipase inhibitor, orlistat, phytostanols which impair cholesterol absorption among other properties, and ghrelin antagonists. Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor secreted by the

stomach, and may account for the observed increased appetite after dieting. Inhibition of this hormone may be a potential target in the treatment of obesity, and the weight regain so often associated with bodyweight loss during obesity treatment.

### 2.5 Other Antiobesity Drugs

Other drugs in development, such as growth hormone fragments, may have potential favorable effects upon obesity. Growth hormone, given to patients with growth hormone deficiency, results in an increase in lean body mass and a reduction in fat mass. The use of growth hormone in patients with Prader Willi syndrome has been shown to result in sustained fat utilization and increased physical strength.<sup>[48]</sup> The use of growth hormone fragment in patients with obesity without absolute growth hormone deficiency may also hold promise in improving body composition.

Drugs that increase insulin sensitivity or otherwise affect insulin metabolism may be effective in treating obesity and include protein tyrosine phosphate drugs, peroxisome proliferation activator gamma receptor antagonists, short-acting bromocriptine, carboxypeptidase inhibitors, and somatostatin agonists. Hyperinsulinemia is often associated with early stages of obesity and may worsen insulin resistance in skeletal muscle while adipose tissue remains insulin sensitive. This often results in the 'obesity metabolic cycle' where hyperinsulinemia is followed by worsening insulin resistance, followed by even greater hyperinsulinemia. Not only might this worsen the predisposition to further obesity, but may also eventually result in glucose intolerance and frank type 2 diabetes mellitus. Thus correction of this cycle might reasonably be expected to improve both these two adverse consequences of the obesity metabolic cycle.

Other hormonally acting drugs include novel corticosteroid drugs such as fluasterone, which is a synthetic analog of the adrenal steroid hormone, dehydroepiandrosterone. It has also been shown in animals that human corticorelin may increase thermogenesis and fat oxidation, and decrease food intake, and may present a novel strategy to increase energy expenditure.<sup>[49]</sup> Finally, obesity drugs in development may target 11 beta-hydroxysteroid dehydrogenase type 1 which affects corticoid metabolism, and may increase visceral obesity and increase the risk of metabolic syndrome.

### 3. Current Guidelines for Drug Treatment of Obesity

One approach to obesity treatment is to address obesity therapy in a manner similar to treatment of other metabolic diseases, such as dyslipidemia, hypertension, and type 2 diabetes mellitus. Education and behavior modification can be an effective first

step, particularly with regard to appropriate diet and exercise recommendations. If these nonpharmacologic, lifestyle interventions fail, then the clinician may consider drug treatment based upon recommended guidelines.<sup>[7,50,51]</sup> According to these guidelines, physicians might consider using drug treatment in patients with comorbidities and a BMI  $\geq 27$  kg/m<sup>2</sup> or in those with BMI  $\geq 30$  kg/m<sup>2</sup> with or without comorbidities.

The rationale for initiation of drug treatment according to these guidelines is the well-documented morbidity and mortality risk of obesity and concurrent metabolic abnormalities that so often accompany obesity. Realistically, the only FDA-approved antiobesity drugs with well-controlled, long-term, safety and efficacy trials are sibutramine and orlistat. Trials of these drugs have lasted for up to 2 years and demonstrated significant and sustained bodyweight loss. Concomitant benefit of drug treatment has also been observed in comorbidities such as improved glucose metabolism and improved blood lipid levels.

The choice between these two current drug treatment options is dependent upon anticipated potential benefits and risks as they relate to the age and health status of the patient as well as the known mechanisms of action and potential adverse effects of the drugs. For example, patients with underlying cardiovascular disorders, such as poorly controlled hypertension or significant CHD, would not be candidates for treatment with sibutramine, as these conditions may worsen as a result of a possible increase in pulse rate and blood pressure. Patients with concomitant gastroenteropathies such as cholestasis, significant irritable bowel syndrome, and chronic malabsorption syndromes (such as active inflammatory bowel disease) would not be good candidates for treatment with orlistat.

Therefore, the choice of which drug is best in the individual patient should be based upon the individual clinical presentation of the patient. For example, a patient with obesity who has consistently failed low-fat, low-caloric diets and has no history of significant atherosclerotic cardiovascular disease, uncontrolled hypertension, or dysrhythmia/tachycardia may be a candidate for sibutramine therapy. Alternatively, a patient with obesity with a history of chronic constipation who is willing to adhere to a low-fat diet might respond well to orlistat.

### 4. Rationale and Prospects for Combination and Aggressive Use of Antiobesity Drugs

Perhaps one of the more intriguing aspects of antiobesity drugs in development will be their potential use in combination drug treatment. Again, in many ways, the treatment of the metabolic condition of obesity is not unlike many other metabolic disorders. For example, dyslipidemia, hypertension, and type 2

diabetes mellitus are often managed by a multifactorial approach including education, dietary counseling, behavior modification, and, if needed, drug treatment. If this is not sufficient, then combination drug treatment is often employed. This approach to these other metabolic conditions is well accepted.

A small study in 34 women who were treated with sibutramine for 1 year and then randomized to placebo or orlistat did not demonstrate any additional significant bodyweight loss.<sup>[52]</sup> However, confirmatory large, long-term clinical trials of the combined use of sibutramine and orlistat have yet to be performed. Therefore, insufficient data are available to determine the long-term safety and efficacy of this combination. However, as with treatments of other metabolic diseases, it is conceivable that the use of this combination might allow for equal or perhaps greater efficacy and possibly the use of lower dosages, and thus a possible reduced risk of adverse effects.

It may be reasonable to conclude that the treatment of obesity should be as aggressive as the recommended guidelines for the treatment of dyslipidemia, hypertension, and type 2 diabetes mellitus, given the marked increase in morbidity with obesity and that obesity-related morbidities (such as dyslipidemia, hypertension, and type 2 diabetes mellitus) might substantially improve with treatment of obesity alone. In fact, it might be worth considering aggressive treatment of obesity as a first-line treatment for patients with obesity-related metabolic abnormalities rather than multiple combination drug treatments for the comorbidities that result from the obese state. Hence, if such an approach becomes as accepted for obesity as it is for the metabolic conditions that may be the result of obesity, then early intervention with combination drug treatments may soon be subject to more studies.

#### 4.1 Antiobesity Drugs and Coronary Artery Disease

With specific regard to atherosclerosis, it should be noted that, despite antiobesity drug treatments being associated with an improvement in CHD risk factors (such as dyslipidemia, hypertension, and type 2 diabetes mellitus), no outcome trial has yet demonstrated a reduction in CHD events with antiobesity drugs. Although the benefits of reduction in CAD risk factors with antiobesity drugs may seem intuitive, it should be remembered that until definitive trials were completed,<sup>[53,54]</sup> it was not definitively known that 'tight' blood glucose control reduced chronic complications in patients with type 1 or type 2 diabetes mellitus, although this may have been predicted by the most obvious manifestation of diabetes mellitus, which was high blood glucose levels. Similarly, even though epidemiologic studies had demonstrated a clear association between elevated blood cholesterol levels and an increased risk for CHD, it was not until outcomes

trials were completed<sup>[55,56]</sup> that it became universally accepted that drug treatment of hyperlipidemia reduced CHD morbidity and overall mortality.

It is likely that until such definitive outcome trials are performed with antiobesity drugs, there may be doubts among some clinicians as to the benefits of long-term, aggressive use of antiobesity drugs specifically for the purpose of reducing actual CHD events. Certainly, there may remain doubts as to the advisability of using antiobesity drugs as initial therapy to treat dyslipidemia, hypertension, or type 2 diabetes mellitus as opposed to, or in preference to, established lipid-altering drugs or antihypertensive drugs that have proven benefit on CHD outcomes in long-term trials. Therefore, even though antiobesity drugs may have proven benefits with regard to CHD risk factors such as dyslipidemia, hypertension, and type 2 diabetes mellitus, the definitive benefit of antiobesity drugs in reducing CHD events (and overall mortality) will remain unknown until CHD outcome trials are completed.

## 5. Conclusion

Obesity results from an imbalance between caloric consumption and energy expenditure. Obesity may result in significant morbidity alone, and may cause or exacerbate important comorbidities such as cardiovascular risk factors. The treatment approach to patients with obesity includes dietary counseling, education, routine physical exercise, behavior modification, and, if needed, drug treatment. Sibutramine and orlistat are currently available for the treatment of obesity and antiobesity drugs in development include agents that decrease appetite, increase satiety, and increase energy expenditure. Other potential antiobesity drugs are recombinant gut hormones that may result in bodyweight loss through their physiological actions locally at the gut or in the CNS. Insulin sensitizing drugs are being developed to address the 'obesity metabolic cycle.' Other hormones may work to favorably alter body composition.

It is to be expected that once more antiobesity drugs become available, agents with different mechanisms of action may be used in combination, as is currently accepted for the treatment of other metabolic conditions such as dyslipidemia, hypertension, and type 2 diabetes mellitus.

## Acknowledgements

The authors would like to acknowledge Amy Goodwin, RN for her assistance in research for this article.

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this manuscript. However, both authors do participate, and

receive research grants from companies involved in metabolic and obesity clinical trials.

## References

- World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation on Obesity; 1997 Jun 3-5; Geneva. Geneva: World Health Organization, 1998:
- Mokdad AH, Serdula MK, Dietz WH, et al. The spread of the obesity epidemic in the United States. *JAMA* 1999; 282: 1519-22
- Must A, Spadano J, Coakley EH, et al. The disease burden associated with overweight and obesity. *JAMA* 1999; 282: 1523-9
- Patel MR, McGuire DK. Pounds of prevention: obesity therapy. *Am Heart J* 2001; 142: 388-90
- Klein S. Medical management of obesity. *Surg Clin North Am* 2001 Oct 1; 81 (5): 1025-38
- Berke EM, Morden NE. Medical management of obesity. *Am Family Physician* 2000 Jul; 62 (2): 419-26
- Prevalence of overweight and obesity among adults: United States. International Obesity TaskForce [online]. Available from URL: <http://www.who.int/> [Accessed 2002 May 20]
- National Center for Chronic Disease Prevention and Health Promotion <http://www.cdc.gov/nccdphp/dnpa/obesity> [Accessed 2002 May 13]
- Lyznicki M, Young DC, Riggs JA, et al. Obesity: assessment and management in primary care. *Am Family Physician* 2001 Jun 1; 63 (11): 2185-96
- Kral JG. Morbidity of severe obesity. *Surg Clin North Am* 2001 Oct; 81 (5): 1039-61
- Allison DB, Fontaine KR, Manson JE, et al. Annual deaths attributable to obesity in the United States. *JAMA* 1999; 282: 1530-8
- Gumbiner B. The treatment of obesity in type 2 diabetes mellitus. *Prim Care* 1999 Dec; 26 (4): 869-83
- Poston WC, Foreyt JP. Successful management of the obese patient. *Am Fam Physician* 2000 Jun 15; 61 (12): 3615-22
- Massie BM. Obesity and heart failure - risk factor or mechanism? *N Engl J Med* 2002; 347 (5): 358-9
- National Heart, Blood, and Lung Institute. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [online]. Available from URL: <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm> [Accessed 2002 May 20]
- Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults. *JAMA* 2002; 287: 356-9
- Dickerson LM, Carek PJ. Drug therapy for obesity. *Am Fam Physician* 2000 Apr 1; 61 (7): 2131-8
- Stone NJ, Kushner R. Effects of dietary modification and treatment of obesity. *Med Clin North Am* 2000 Jan; 84 (1): 95-122
- Hensrud DD. Pharmacotherapy for obesity. *Med Clin North Am* 2000 Mar; 84 (2): 463-76
- Yanovski SZ, Yanovski JA. Obesity. *N Engl J Med* 2002; 346: 8: 591-602
- Lustig RH. The neuroendocrinology of obesity. *Endocrinol Metab Clin North Am* 2001 Sep; 30 (3): 765-85
- Wirth A, Krause J. Long-term weight loss with sibutramine. *JAMA* 2001; 286: 1331-9
- James WP, Astrup A, Finer N, et al. Effect of sibutramine on weight maintenance after weight loss: a randomized trial. *Lancet* 2000; 356: 2119-25
- Dujovne CA, Zavoral JH, Rowe E, et al. Effects of sibutramine on body weight and serum lipids. *Am Heart J* 2001 Sep; 142 (3): 489-97
- Lean MEJ. Sibutramine: a review of clinical efficacy. *Int J Obes Relat Metab Disord* 1997; 21 Suppl. 1: S30-6; discussion 37-9
- Davidson M, Hauptman J, DiGirolamo M, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat. *JAMA* 1999; 281: 235-42
- Sjostrom L, Rissanen A, Andersen T, et al. Randomized placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet* 1998; 352: 167-72
- Mittendorfer B, Ostlund R, Patterson BW, et al. Orlistat inhibits daily cholesterol absorption. *Obes Res* 2001; 9 (10): 599-604
- Heymsfield SB, Segal KR, Hauptman J, et al. Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med* 2000 May 8; 160 (9): 1321-6
- Lindgarde F. The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: The Swedish Multimorbidity Study. *J Intern Med* 2000 Sep 1; 248 (3): 245-54
- Rossner S, Sjostrom L, Noack R, et al. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity: European Orlistat Obesity Study Group. *Obes Res* 2000 Jan 1; 8 (1): 49-61
- Wadden TA, Foster GD. Behavioral treatment of obesity. *Med Clin North Am* 2000 Mar; 84 (2): 441-61
- Sharpe P, Smith G. Cannabis: time for scientific evaluation of this ancient remedy? *Anesth Analg* 2000 Feb; 90 (2): 237-40
- Sanofi-Synthelabo [online]. Available from URL: <http://en.sanofi-synthelabo.com/> [Accessed 2002 May 20]
- Regeneron Pharmaceuticals [online]. Available from URL: <http://www.regeneron.com> [Accessed 2002 May 20]
- Durst R, Rubin-Jabotinsky K, Raskin S, et al. Risperidone in Prader-Willi syndrome [letter]. *J Am Acad Child Adolesc Psychiatry* 2000 May; 39 (5): 545-6
- Rothman RB, Baumann MH, Savage JE, et al. Evidence for possible involvement of 5-HT (2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* 2000 Dec 5; 102 (23): 2836-41
- Fitzgerald LW, Burn TC, Brown BS, et al. Possible role of valvular serotonin 5-HT (2B) receptors in the cardiopathy associated with fenfluramine. *Mol Pharmacol* 2000 Jan 01; 57 (1): 75-81
- Shapira NA. Treatment of binge-eating disorder with topiramate: a clinical case series. *J Clin Psychiatry* 2000 May 1; 61 (5): 368-72
- Fruebis J. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci U S A* 2001 Feb 13; 98 (4): 2005-10
- Lebon V, Dufour S, Petersen KF, et al. Effect of triiodothyronine on mitochondrial energy coupling in human skeletal muscle. *J Clin Invest* 2001 Sep; 108: 733-7
- Heymsfield SB, Greenberg AS, Fujioka D, et al. Recombinant leptin for weight loss in obese and lean adults. *JAMA* 1999; 282: 1568-75
- Pi-Sunyer FX, Laferrere B, Aronne LJ, et al. Obesity: a modern day epidemic. *J Clin Endocrinol Metab* 1999 Jan 1; 84 (1): 3-12
- Ahren B, Holst JJ, Efendic S. Antidiabetogenic action of cholecystokinin-8 in type 2 diabetes. *J Clin Endocrinol Metab* 2000 Mar; 85 (3): 1043-8
- Verdich C, Flint A, Gutzwiller JP, et al. A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans. *J Clin Endocrinol Metab* 2001 Sep; 86 (9): 4382-9
- Zander M, Madsbad S, Madsen JL, et al. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet* 2002 Mar 9; 359 (9309): 824-30

47. Bertin E, Arner P, Bolinder J, et al. Action of glucagon and glucagon-like peptide-1-(7-36) amide on lipolysis in human subcutaneous adipose tissue and skeletal muscle in vivo. *J Clin Endocrinol Metab* 2001 Mar; 86 (3): 1229-34
48. Myers SE, Carrel AL, Whitman BY, et al. Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength, and agility and growth in Prader-Willi syndrome. *J Pediatr* 2000 Jul; 137 (1): 43-9
49. Smith SR, Jonge DL, Pellymouner M, et al. Peripheral administration of human corticotropin-releasing hormone: a novel method to increase energy expenditure and fat oxidation in man. *J Clin Endocrinol Metab* 2001 May; 86 (5): 1991-8
50. The North American Association for the Study of Obesity [online]. Available from URL: <http://www.naaso.org> [Accessed 2002 June 5]
51. National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults [online]. Available from URL: <http://www.nhlbi.nih.gov/guidelines/obesity> [Accessed 2002 May 20]
52. Wadden TA. Effects of sibutramine plus orlistat in obese women following 1 year of treatment by sibutramine alone, a placebo-controlled trial. *Obes Res* 2000 Sep 1; 8 (6): 431-7
53. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329: 977-86
54. Turner R, Cull C, Holman R. United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1996; 124 (1 Pt 2): 136-45
55. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol* 1986; 8: 1245-55
56. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994 Nov 19; 344 (8934): 1383-9

---

Correspondence and offprints: Dr *Carlos Dujovne*, Radiant Research at Kansas Foundation for Clinical Pharmacology, 12200 W 106th, Suite 330, Kansas City, KS 66215, USA.  
E-mail: [carlosdujovne@radiantresearch.com](mailto:carlosdujovne@radiantresearch.com)