REVIEW ARTICLE

Drugs 1999 Jun; 57 (6): 883-904
0012-6667/99/0006-0883/$22.00/0

© Adis International Limited. All rights reserved.

Current Concepts in the Pharmacological Management of Obesity

Peter J. Carek and *Lori M. Dickerson*

Medical University of South Carolina, Charleston, South Carolina, USA

Contents

Abstract

The pharmacological management of obesity has gained increasing attention as new weight loss treatments are approved and a significant proportion of the public strives to lose weight. Obesity is associated with a high mortality rate, multiple chronic medical conditions, and carries an enormous financial burden. Obesity is a multifactorial condition, most often due to an imbalance in energy intake and expenditure.

Despite the greater focus on management of obesity, weight loss remains a difficult goal to achieve. Obesity is a chronic medical condition that may require long term treatment, therefore the risks and benefits of all pharmacological agents

must be carefully considered. Noradrenergic appetite suppressants (ie. phenylpropanolamine, phentermine) result in weight loss but stimulatory effects limit their use. The serotonergic agents (fenfluramine , dexfenfluramine) were effective weight loss drugs, but were voluntarily withdrawn from the US market last year because of cardiovascular and pulmonary complications. The combination noradrenergic/serotonergic agent sibutramine is indicated for the management of obesity, particularly in the presence of other cardiovascular risk factors. Modest weight loss is achieved with sibutramine, although weight gain is significant after discontinuation. In addition, long term safety data are not yet available. The thermogenic combination of ephedrine plus caffeine is minimally effective, and adverse effects are usually transient. Other thermogenic agents, such as β_3-agonists, are still under investigation.

Agents may alter digestion through lipase inhibition (orlistat) or fat substitution (olestra). Orlistat decreases systemic absorption of dietary fat, decreasing body weight and cholesterol. Olestra is a fat substitute that has been incorporated into snack foods. Olestra substitution for dietary fat has not been studied as a weight loss strategy, although olestra has no caloric value and may be beneficial. The use of orlistat and olestra may be limited by gastrointestinal adverse effects. Finally, the manipulation of leptin and neuropeptide Y are under investigation for the treatment of obesity.

Pharmacological agents should be used as an aid to a structured diet and exercise regimen in the treatment of obesity. Weight loss agents may result in initial weight loss, but sustained weight loss is not always achieved even with continuation of treatment. The effect of weight loss obtained while using pharmacotherapeutic agents on morbidity and mortality has not been established. Therefore, diet and exercise should be the focus of any weight loss programme. There is a continued need for safe and effective pharmacotherapeutic agents for the treatment of obesity.

Obesity is among the most common and serious health problems in the US. Approximately one-quarter to one-third of American adults are overweight, translating to over 60 million people.[1,2] Given these statistics, the Western cultural obsession with slimness and the detrimental societal and psychological effects of obesity, it is not surprising that 50% of all women and 25% of all men are trying to lose weight and are spending $US30 billion annually on weight loss treatments.[3,4]

Excess weight is directly associated with a higher mortality rate.[5] Furthermore, being overweight and obese is associated with additional risk factors for excess mortality, specifically hypertension, hyperlipidaemia and diabetes mellitus and also other chronic diseases (table I). One-third of all hypertension in the Western world is associated with obesity.[6] Obese patients have a 50% greater likelihood of having a serum cholesterol level of at least 250 mg/dl (6.47 mmol/L; multiply by 0.02586 to convert to mmol/L) and have a higher prevalence of coronary heart disease.[6,7] Type 2 diabetes mellitus is 5 times more prevalent in moderately obese people and 10 times more prevalent in severely obese people.[8] Men who are overweight are more likely to die of colorectal and prostatic cancers than nonobese patients; obese women have a higher risk of dying of endometrial, gallbladder, cervical, ovarian and breast cancers.[9] Obese patients also are at greater risk for gallbladder disease, pulmonary disease, gout, carcinoma and arthritis.[6]

Not surprisingly, these health risks are associated with a tremendous financial burden. Colditz[10] estimated total direct and indirect costs attributable to obesity in 1986 to be more than

© Adis International Limited. All rights reserved.

Table I. Diseases associated with obesity (adapted from Pi-Sunyer,[6] with permission)

Type 2 diabetes mellitus
Insulin resistance
Hypertension
Dyslipidaemia
Coronary artery disease
Cancer: endometrial, cervical, ovarian, breast, prostate, gallbladder, colon
Menstrual irregularities, hirsutism, infertility
Gallbladder disease
Restrictive lung disease, sleep apnoea
Gout
Osteoarthritis
Thromboembolic disease

$US39 billion or greater than 5% of the total costs of all illnesses. More than $US22 billion of this amount was related to the cardiovascular complications of obesity.

1. Aetiology of Obesity

Obesity should be considered a multifactorial condition. Genetic, cultural, socioeconomic, behavioral and situational factors all play a role in eating and weight control. Most obesity is primary, that is, no obvious cause exists other than an imbalance in energy intake and expenditure. Genetic alterations, endocrine diseases (including Cushing's syndrome, hypothyroidism and hypogonadism), drugs or neurological disorders rarely cause obesity. Many of these conditions often involve obesity as a sign, but only a small fraction of cases of obesity are actually caused by these factors and their associated pathophysiology.

Recently, several genetic mutations have been implicated in the development of obesity. A mutation in the gene coding for the β_3-adrenergic receptor is associated with an increased capacity to gain weight in morbidly obese patients.[11] In theory, low β_3-adrenergic activity could promote obesity by slowing lipolysis and causing retention of lipids in fat cells.[12] The clinical importance of this mutation requires further study.

2. Treatment of Obesity

Unfortunately, the treatment of obesity is difficult. The clinician must understand that, like diabetes or hypertension, obesity is a chronic medical condition that is rarely cured; most often the goal is palliation. Similar to many chronic diseases, the most efficient and beneficial treatment for obesity that will satisfy the desires of most patients for rapid resolution and provide long term results is not available. As a caloric deficit of 3500 kcal is necessary to lose 1 lb of adipose tissue, and most experts recommend losing no more than 1 to 2 lbs (approximately 0.5 to 1.0kg) per week, weight loss by most methods is typically slow or recidivism is very high.[13] Modest reductions in weight and weight maintenance should be stressed in any weight loss programme.

Of the many options for controlling obesity, behavioral therapy including dietary changes is preferred.[13,14] In earlier studies, behavioral therapy was shown to be more favourable and cost efficient than pharmacological treatment for maintenance of weight loss.[15] Although pharmacotherapy produced a more rapid initial weight loss, behavioral therapy better maintained weight loss. Dietary modifications may range from education with only slight changes in caloric intake to the other extreme of very low calorie diets (VLCD) in the range of 400 to 800 kcal/day. Physical activity and exercise is a key to successful weight loss. A weight loss programme must incorporate physical activity to increase caloric expenditure while controlling intake to obtain the necessary caloric deficit.

Though behavioral modification incorporating dietary restrictions and appropriate exercise is the preferred treatment for obesity, the pharmacologic treatment of obesity is an area of continued research and development (table II). The pharmacotherapy of obesity has been reviewed by several authors.[16-23] Subsequent to these publications, the pharmacological treatment of obesity has be altered dramatically with the voluntary withdrawal of fenfluramine and dexfenfluramine from the US market.

© Adis International Limited. All rights reserved.

Table II. Pharmacological agents for the treatment of obesity (adapted from Cerulli et al.,[16] with permission)

Appetite suppressants
Centrally acting adrenergic agents
benzphetamine, diethylpropion, mazindol, phendimetrazine, phentermine, phenylpropanolamine
Serotonergic agents
dexfenfluramine, fenfluramine, fluoxetine
Adrenergic/serotonergic agents
sibutramine
Thermogenic agents
Adrenergic agents
ephedrine-caffeine
β_3-Agonists
BRL 26830A, BRL 35135, RO 40-2148, RO 16-8714, CL 316243, ZD 7114
Digestion inhibitors
Lipase inhibitors
orlistat
Carbohydrate-based fat substitutes
various
Protein-based fat substitutes
various
Fat-based fat substitutes
olestra
Hormonal manipulation
Leptin analogues
Neuropeptide Y antagonists

3. Appetite Suppressants

Various pharmacological agents, referred to as anorectic drugs, are used as adjuncts to behavioral therapy in weight reduction programmes. The 2 classes of anorectic drugs currently available are the noradrenergic agents [i.e. diethylpropion, mazindol, phendimetrazine, benzphetamine, phenylpropanolamine (PPA) and phentermine] and the serotonergic agents (i.e. fenfluramine, dexfenfluramine and fluoxetine). Noradrenergic drugs affect the appetite centre while the serotonergic drugs affect the satiety centre.

3.1 Noradrenergic Agents

Adrenergic agonists have many of the pharmacological properties of noradrenaline (norepinephrine) and enhance catecholamine neurotransmission leading to increased sympathetic activity and reduced appetite. The first noradrenergic agent introduced was amphetamine. Amphetamines, including agents such as methamphetamine and phendimetrazine, have a significant abuse potential. The addictive potential of amphetamine is likely related to its effect on dopamine and its anorectic effect caused by the influence on noradrenergic neurotransmission.[20] Chemical manipulation of the side chains and ring structure of amphetamine have led to the development of additional β-phenethylamines with a reduced risk of CNS stimulation and abuse.[13]

With the exception of mazindol, the noradrenergic agents are chemically related to amphetamine, the prototype agent of this class. All noradrenergic agents act by activating central β- and/or dopaminergic receptors in the hypothalamus.[13,23] Amphetamine was formerly used to promote weight loss; however, because of its high abuse potential, its chemical structure was manipulated to find more suitable alternatives.[24] The resulting compounds retained the anorectic properties of amphetamine but displayed greatly reduced stimulant effects and abuse liability.[13] Currently, in the US, the use of Drug Enforcement Agency (DEA) Controlled Substances Schedule II drugs such as amphetamine, dexamphetamine or phendimetrazine in the treatment of obesity is prohibited.

Adrenergic anorectic agents currently available for use in a weight loss regimen include benzphetamine, phendimetrazine, diethylpropion, mazindol, PPA and phentermine. Benzphetamine, phendimetrazine, diethylpropion and mazindol have been reviewed extensively and are rarely used as an adjunct in weight loss (table III). With the exception of PPA and phentermine, these agents are rarely used by patients or in clinical practice.

As the noradrenergic agents share a similar mechanism of action, they similarly share adverse effects including as nervousness, irritability, headache, sweating, dry mouth, nausea and constipation.[24] Diethylpropion, phentermine and mazindol may interfere with sleep to a greater extent than other agents. All noradrenergic agents may poten-

© Adis International Limited. All rights reserved.

tially interact with monoamine oxidase inhibitors (MAOI), and concomitant administration should be avoided.[23]

Because of their chemical and pharmacological similarity to amphetamine, concerns about abuse and dependence are present. However, if the drugs are given according to the manufacturers' dosage recommendations, physical dependence, psychological dependence and abuse of the noradrenergic agents is very rare.[24,25]

3.1.1 Phenylpropanolamine

PPA, a sympathomimetic drug and a synthetic derivative of ephedrine, is available as an over-the-counter appetite suppressant and decongestant. In earlier studies, participants who took PPA consistently lost more weight than those who received placebo without any increase in untoward effects.[26-28]

In recent studies with large patient populations, PPA has been shown to be an effective adjunct in weight loss treatment. 106 healthy, overweight (115 to 130% ideal bodyweight) women participated in a 14-week, double-blind, placebo-controlled study.[29] On average, the participants who were given PPA 20 mg/day, lost significantly more weight (6.1 ± 0.6kg or 8.0 ± 0.8%) than did individuals in the placebo group (4.3 ± 0.7kg; 5.5 ± 0.8%; $p < 0.05$). 13 participants taking the active medication and 15 participants taking placebo withdrew early from the study. Dry mouth was the most common adverse effect in participants receiving PPA. In a similar study, Greenway[30] noted a significant difference in weight loss in individuals receiving PPA 75 mg/day versus those individuals receiving placebo over a 14-week period (5.96 ± 1.01 *vs* 2.35 ± 1.16 lbs, $p < 0.05$).

101 otherwise healthy, overweight individuals (115 to 145% of ideal bodyweight) participated in a 2-phase study comparing PPA with placebo as an adjunct to caloric restriction.[31] During the initial double-blind phase which lasted 8 weeks, participants given sustained-release PPA 75 mg/day lost significantly more weight than the placebo-treated group (2.59 ± 0.35 *vs* 1.07 ± 0.4kg, $p < 0.01$). The dropout rate for the PPA group was 29.4%, whereas the dropout rate for the placebo-treated group was 44%. In the 36 participants who continued in the extended double-blind study, the difference persisted, where the PPA group had a cumulative weight loss of 5.1 ± 1.48kg and the placebo group had a 0.30 ± 0.9kg weight loss. No significant difference between the groups was observed in blood pressure, pulse rate or any subjective adverse effects.

The most common adverse effects of PPA include nervousness, sleeplessness, dizziness, palpitations and headaches. Additionally and noted in the study by Greenway,[30] PPA 75mg daily was not associated with a clinically significant rise in blood pressure. When PPA is used in the treatment of obesity, the manufacturers recommend physician supervision if patients are being treated for high blood pressure, depression or anxiety disorder or have heart disease, diabetes or thyroid disease.

3.1.2 Phentermine

Phentermine is similar to amphetamine and modulates noradrenergic neurotransmission to decrease appetite; however, it has little or no effect on dopaminergic neurotransmission, which decreases the potential for abuse.[20] In an earlier study,[32] weight loss with intermittent phentermine was as effective as treatment with continuous phentermine (30mg) and more effective than that with placebo (13.0 *vs* 12.2 *vs* 4.8kg, respectively). This study involved women who were greater than 120% of ideal bodyweight. Subsequently, Camp-

Table III. Review of selected noradrenergic agents (adapted from Bray,[13] with permission)

Drug	No. of studies	Dosage (mg/day)	Duration (weeks)	Patients (n)		Mean weight loss (kg)	
				drug	placebo	drug	placebo
Deithylpropion	8	50-75	6-25	9-41	4-33	3.1-11.7	0.9-6.1
Mazindol	22	2-4	6-64	11-114	10-114	1.4-15.7	+0.7-11.6
Benzphetamine	1	97	8	50	50	4.0	1.7
Phendimetrazine	1	105	12	36	35	3.4	0.5

© Adis International Limited. All rights reserved.

bell et al.[33] and Tuominen et al.[34] have demonstrated a mean weight loss of 5.3 and 3.6kg over a 5-month and 12-week period of treatment with phentermine, respectively.

The use of phentermine as a single agent is usually limited by intolerance to its stimulatory activity. Previously, phentermine was used in combination with fenfluramine. Lethargy and drowsiness, adverse effects of fenfluramine, were felt to counteract the effects of phentermine. In a study by Weintraub et al.,[35] weight loss in individuals receiving the combination (8.4 ± 1.1kg) was significantly greater than in those receiving placebo (4.4 ± 0.9kg) and equivalent to that of those receiving fenfluramine (7.5 ± 1.2kg) or phentermine (10.2 ± 1.2kg) alone. Adverse effects were less frequent with the combination regimen than with other active treatments. In other studies, the combination has been demonstrated to be more effective in achieving weight loss than either agent alone.[21]

Phentermine, in dosages ranging from 30 to 37.5 mg/day, is indicated in the management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. The most common adverse effects of phentermine include headache, insomnia, nervousness and irritability. Palpitations, tachycardia and elevations in blood pressure may also occur. The use of MAOI is contraindicated during or within 14 days of the use phentermine, as hypertensive crisis may results. Other CNS active substances should be used with caution. Phentermine should not be used in individuals with hyperthyroidism, glaucoma, agitated states, advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension or a history of drug abuse.

3.2 Serotonergic Agents

Serotonergic agents can affect food intake in two ways: by reducing snacking, which suggests the individual is less hungry or has reduced food-seeking behaviour; or by decreasing the amount consumed at a particular meal or eating episode.[16] In addition, serotonergic drugs have been reported to increase basal metabolic rate by 100 cal/day, which may play a minor role in weight reduction.[36] Fenfluramine and dexfenfluramine were voluntarily withdrawn from the market in the US last year.

3.2.1 Fenfluramine

Fenfluramine is the racemic mixture of *d*- and *l*-fenfluramine (the dextroisomer seems to be the active form). It is a β-phenethylamine with a similar chemical formula to amphetamine, although it has a different mechanism of action and adverse effect profile. The mechanism of action of fenfluramine is to partially inhibit the reuptake of serotonin and to release serotonin into the synaptic cleft, thus acting on the hypothalamus to decrease food intake.

The combination of fenfluramine and phentermine has been shown to act synergistically and result in weight loss in obese patients. A complicated and extensively reviewed study series examined the effect of an extended-release preparation of fenfluramine combined with phentermine versus placebo as an adjunct to behaviour modification, a caloric-restricted diet and an exercise programme.[37-41] The study was conducted in several phases, with a maximum follow-up period of 210 weeks.

In phase I of the study (weeks 0 to 34), 121 individuals were randomised to receive either 60mg extended-release fenfluramine plus 15mg phentermine or placebo added to behaviour modification, caloric restriction and exercise.[37] The participants weighed 154 ± 1.2% of ideal bodyweight. By week 34, participants receiving active medication (n = 58) had lost an average of 14.2 ± 0.9kg (15.9 ± 0.9% of initial weight) or about 0.5kg per week versus a loss of 4.6 ± 0.8kg (4.9 ± 0.9% of initial weight) in placebo-treated participants (n = 54). Only 9 participants left the study during this initial phase.

Phase II of the study was open-labelled, where participants received either continuous fenfluramine and phentermine or intermittent therapy (weeks 34 to 104).[38] At the beginning of this phase, the 54 patients in the placebo group of the first phase were switched to active continuous drug treatment.

© Adis International Limited. All rights reserved.

Those receiving fenfluramine plus phentermine during weeks 0 to 34 either continued to receive medication (fenfluramine 60 mg/day plus phentermine 15 mg/day) or began targeted intermittent therapy (fenfluramine 60 mg/day plus phentermine 15 mg/day during the targeted periods of October to January and April to June). Participants who did not lose 10% of initial weight received an augmented dose of fenfluramine 60mg and phentermine 30mg. The placebo-to-active groups lost an additional 9.1 ± 0.8kg in the period from week 34 to week 60. At week 60, these participants were assigned to either continuous medication, intermittent therapy or augmented therapy. A small number of patients (n = 12) who did not lose weight in the initial active treatment group received augmented therapy.

83 (68%) of the original participants completed up to week 104. At the end of this phase of the study, overall weight loss was 10.8 ± 0.7kg (11.6 ± 0.8% of initial weight); participants who continued to receive fenfluramine plus phentermine lost 11.6 ± 0.8kg, participants receiving intermittent therapy lost 11.6 ± 1.3kg, and participants receiving augmented therapy lost 6.5 ± 1.5kg. 29 individuals dropped out of the study during this phase.

77 of the original participants entered an open-label, dosage adjustment study (phase III, weeks 104 to 156) designed to achieve weight loss to a goal of 120% of the ideal bodyweight.[39] 59 individuals, who were divided into 4 dosage groups, completed week 156. Completers of this study segment gained an average of 2.7 ± 0.5kg between weeks 104 and 156, but remained 9.4 ± 0.8kg (10.5%) below baseline. Interestingly, upward dosage adjustment (n = 36) resulted in further weight loss in 11 and no weight gain in 6 participants. 59 individuals completed this phase of the trial.

52 patients entered a second double-blind, randomised, placebo-controlled study (weeks 156 to 190) similar to phase I in which active medication was compared with placebo.[40] Although participants in both the active medication and placebo groups gained weight, participants receiving fenfluramine plus phentermine (n = 27) gained significantly less (4.4 ± 0.5kg or 5.3 ± 0.5% of initial weight) than participants receiving placebo (n = 24) [6.9 ± 0.8kg or 8.5 ± 1.1% of initial weight]. At week 190, both groups were still below their initial weight (active medication group, 5.0 ± 1.4kg; placebo group, 2.1 ± 1.2kg). Only 1 participant did not complete this phase of the trial. During phase IV, participants receiving fenfluramine plus phentermine had 26 moderate or severe complaints versus 8 participants receiving placebo.

In the last phase of the study (weeks 190 to 210), patients who completed the study up to week 190 (n = 51) were monitored after cessation of medication.[41] Caloric restriction, behaviour modification sessions, exercise reinforcement and physician visits continued. Three patients withdrew before the end of this phase. At week 210, participants' weight averaged 1.4 ± 1.0kg below their weights at week 1 of the trial. On average, participants gained 2.7 ± 0.5kg (3.2%) in the period from weeks 190 to 210.

The findings from this phase indicate that participants had difficulty maintaining weight loss with anorexiant medication. Despite clinically significant initial weight loss and long periods of time with sustained weight loss, permanent resetting of weight control mechanisms could not be shown for these participants and long term (<5 years) weight loss was not demonstrated in these trials.

The significance of the findings of this study are limited by several issues. First, a large number of patients dropped out before completing the entire trial period. Second, patients with comorbid conditions commonly associated with obesity were excluded, making the data and conclusions difficult to extrapolate to the general obese population seen in clinical practice. Finally, dietary restrictions and exercise regimens were not monitored in an objective manner. The contributions of these modalities to the overall weight loss effect could not be determined.

Common adverse effects associated with fenfluramine use include dry mouth, nausea, diarrhoea, constipation, altered dreams and nightmares, lethargy, asthenia, somnolence and dizziness. Depression has been reported during treatment or on with-

© Adis International Limited. All rights reserved.

drawal of therapy. Fenfluramine should not be administered during or within 14 days of MAOI therapy, as hypertensive crisis may result. Concomitant use with other serotonergic agents should be carefully evaluated and monitored, as the risk of developing serotonin syndrome may be increased. This syndrome is characterised by a constellation of symptoms, including confusion, fever, shivering, sweating and diarrhoea.

In a case-series report, valvular heart disease was identified in 24 women (mean age, 44 ± 8 years) who were given the phentermine-fenfluramine combination for a mean of 11 ± 6.9 months.[42] These individuals initially presented with cardiovascular symptoms or a heart murmur. Echocardiogram in all patients demonstrated unusual valvular morphology and regurgitation. Eight women also had newly documented pulmonary hypertension. Cardiac surgery was necessary in 5 patients. The valve features were identical to those seen in carcinoid or ergotamine-induced valve disease. Graham and Green[43] reported an additional 28 cases of valvular disease in women who had taken fenfluramine and phentermine (median daily dosages of 60 and 30mg, respectively).

Following this initial report, the US Food and Drug Administration (FDA) received 144 individual, provider-initiated reports involving both fenfluramine and dexfenfluramine, with or without phentermine, in association with valvulopathy.[44,45] Of the 132 spontaneous reports with complete information, 113 (86%) met the case definition (documented aortic regurgitation of mild or greater severity and/or mitral regurgitation of moderate or greater severity after exposure to these drugs). Of these 113 cases, 2 (2%) used fenfluramine alone; 16 (14%) used dexfenfluramine alone; 89 (79%) used a combination of fenfluramine and phentermine; and 6 (5%) used a combination of all 3 drugs. The median duration of drug use was 9 months. Based upon this and data from 4 other prevalence surveys, the FDA requested the voluntary withdrawal of fenfluramine and dexfenfluramine from the US market; on September 15 1997, the manufacturers and the FDA announced the withdrawal of the drugs. The clinical significance of these case reports has yet to be determined.

3.2.2 Dexfenfluramine

Dexfenfluramine, which is available in 65 countries but has recently been voluntarily withdrawn from the US market, is the active form of fenfluramine.[24] Similar to fenfluramine, dexfenfluramine is a highly selective serotonin agonist that acts by both enhancing serotonin release into nerve synapses and inhibiting its reuptake. Unlike the racemate, dexfenfluramine has minimal or no sympathetic activity or effects on the dopaminergic system. Dexfenfluramine, which has been reviewed extensively,[46,47] was indicated for the management of obesity in patients with a body mass index (BMI) greater than 30 kg/m^2, or 27 kg/m^2 with risk factors (i.e. hypertension, diabetes mellitus, hyperlipidaemia).

The International Dexfenfluramine Study was a 1-year, multicentre, randomised, placebo-controlled, double-blind trial.[48] Patients received either dexfenfluramine 15mg twice daily (n = 404) or placebo (n = 418). By the end of the study, 189 (45%) of the patients had withdrawn from the placebo group and 150 (37%) from the dexfenfluramine group. More patients in the placebo group withdrew because they were dissatisfied with the weight loss (84 *vs* 49, p = 0.019). Of those individuals completing the trial, the weight loss in the dexfenfluramine group was significantly greater than the weight loss in the placebo group (9.82 ± 0.5 *vs* 7.15 ± 0.49kg). The maximum weight loss was achieved at 6 months. The following adverse effects were reported significantly more commonly in the dexfenfluramine group than in the placebo group: tiredness (28.4 *vs* 19.8%, p < 0.01), diarrhoea (15.3 *vs* 9.3%, p < 0.01), polyuria (6.9 *vs* 3.1%, p < 0.05), drowsiness (5.2 *vs* 2.3%, p < 0.05) and dry mouth (12.1 *vs* 4.3%, p < 0.001).

Wiley and colleagues[49] studied 34 obese patients with type 2 diabetes mellitus who were randomised to receive dexfenfluramine 15mg twice daily or placebo in addition to their usual therapy of metformin alone or combined with a sulphonylurea. After 12 weeks, patients in the treatment

© Adis International Limited. All rights reserved.

group lost a significant amount of weight (dexfenfluramine 98.7 ± 5.0 to 94.9 ± 5.2kg *vs* placebo 87.7 ± 4.8 to 87.1 ± 4.6kg). Only 1 patient discontinued the study. Adverse effects of dexfenfluramine therapy included dryness of the mouth in 2 patients and gastrointestinal (GI) disturbance in 8 patients.

Manning and colleagues[50] compared 4 weight loss strategies over a 1-year period in 159 overweight patients with type 1 and type 2 diabetes. The intervention groups consisted of dietary counselling with follow-up clinic visits, behavioral therapy, dexfenfluramine 15mg twice daily for the first 3 months, or combined home and clinic visits. An additional 58 patients were monitored as controls. After 3 months, the weight loss was greatest in the dexfenfluramine group (mean weight losses 1.6, 1.2, 3.4 and 1.7kg, respectfully). However, after 1 year, the weight loss was similar between groups.

In addition to the adverse effects noted above and the risk of the development of valvular heart disease, the development of primary pulmonary hypertension (PPH) has been noted with the long term (>3 months) use of dexfenfluramine as reported in a case-control study.[51] PPH is a rare disease with an annual incidence estimated at 1 per 200 000 to 1 to 2 per million.[52] The International Primary Pulmonary Hypertension Study Group reported an increased odds ratio of 23.1 (95% CI 6.9 to 77.7) when anorectic drugs were used for a period of longer than 3 months. This was based on findings from a case-control study involving 95 patients with PPH and 335 age- and gender-matched controls from 35 centres in France, Belgium, the UK and The Netherlands.[49] In a follow-up editorial, Manson and Faich[53] calculated that 1260 excess lives are lost per million women per year as a consequence of an average excess weight of 13kg, compared with 28 cases per million person-years of PPH associated with appetite suppressant drugs. This figure is noted to be the magnitude of risk of death from penicillin-induced anaphylaxis or oral contraceptive–associated venous thromboemboli and myocardial infarction. Assuming a 50% mortality rate associated with PPH, they calculated a benefit/risk ratio of 20 : 1 associated with appetite suppressant drug therapy, translating to 280 lives saved compared with 14 deaths caused by the drugs per million person-years of treatment. A causal relation with appetite suppressant drugs is not established unequivocally by this study.

In a study reported[54] during a recent meeting of the American College of Cardiology meeting in Atlanta, 1072 patients were randomised in nearly equal numbers to 1 of 3 study groups (dexfenfluramine sustained-release, dexfenfluramine 15mg twice daily and placebo). When the drug was withdrawn from the market, 76% of the participants had taken the drug for 2 months or less and only 14% had used the formulations for more than 90 days. Using echocardiography, aortic valve problems were found in 5.8, 5.0 and 3.6% of patients, respectively. In addition, mitral valve leaking was identified in 1.8, 1.7 and 1.2% of patients, respectively. The differences were reported as not being significant, but may be related to the short period of administration.

As with fenfluramine, the use of dexfenfluramine is contraindicated during or within 14 days of MAOI therapy. In addition, the concomitant use of serotonergic agents should be carefully evaluated and monitored, as the risk of developing serotonin syndrome may be increased.

3.2.3 Fluoxetine

Fluoxetine is a highly selective serotonin reuptake inhibitor. Because of its serotonergic effects, fluoxetine has been postulated to be an anorectic agent, though evidence for this effect is not consistent. Fluoxetine may also increase energy expenditure by raising basal body temperature.[21] Though FDA-approved in the US for treatment of depression, bulimia and obsessive-compulsive disorder, fluoxetine is not approved for weight loss.

Though initial studies indicated that fluoxetine was an effective in the treatment of obesity,[55,56] fluoxetine, as an effective agent in the long term weight lose of obese patients, has not been demonstrated. In a randomised trail of 45 obese patients (BMI 37.6 kg/m^2), patients receiving fluoxetine

© Adis International Limited. All rights reserved.

lost significantly more weight than those receiving placebo (12.3 ± 3.0 *vs* 5.5 ± 1.4kg, p = 0.011) after 29 weeks.[57] By the end of the 52 week study, each group weighed significantly less than they did at baseline, although the difference between groups was no longer significant.

In a manufacturer-sponsored, 1-year, double-blind trial, obese, mostly Caucasian (83%) and female (80%) adult outpatients were randomised to receive either fluoxetine 60mg once daily or placebo.[58] Though significant weight loss occurred during the study in the treatment group, no significant difference in mean weight loss existed between the 2 groups at the conclusion of the trial.

The fluoxetine group reported adverse effects significantly more often. Adverse effects included asthenia, diarrhoea, sweating, insomnia, somnolence, bronchitis, nervousness, nausea and vomiting, tremor and thirst.[58] Patients receiving placebo reported significantly more 'allergic reactions.' Twice as many patients discontinued therapy because of adverse events in the fluoxetine group as the placebo group (17.8 *vs* 8.3%), but the overall percentage of patients completing the study was similar in both groups (43% of fluoxetine group compared with 47% of placebo group). Fluoxetine therapy resulted in significantly greater mean weight loss than placebo therapy for 28 consecutive weeks, but it was not successful in maintaining the loss beyond this period.

Insulin-treated, obese, type 2 diabetic patients receiving fluoxetine 60 mg/day lost significantly more weight than the placebo group (average of 9.3 ± 2.4kg compared with 1.9 ± 2.9kg in the placebo group).[59] The fluoxetine group also showed a significantly larger decrease in daily insulin dose throughout the active treatment phase. A positive correlation between the decrease in bodyweight and the decrease in insulin dose was noted in both groups. No significant differences in the incidence of any specific adverse effect were found between the 2 groups, but this lack of difference may reflect the small sample size. The most commonly reported adverse effects in the placebo group were 'injury' followed by headache, decreased libido, pain, surgery and tooth disorder.

3.3 Adrenergic/Serotonergic Agents

3.3.1 Sibutramine

Sibutramine, a β-phenethylamine with a potent reuptake inhibitor of noradrenaline and serotonin, recently received US FDA approval for use in the management of obesity.[19,20] Sibutramine and its metabolite have 2 mechanisms of action.[60] First, by inhibiting monoamine uptake, it suppresses appetite in a fashion similar to other selective serotonin reuptake inhibitors. Second, sibutramine stimulates thermogenesis indirectly by activating the β_3-system in brown adipose tissue.

Initially tested for its antidepressant activity, sibutramine was found to cause weight loss (1 to 2kg) in both healthy and depressed patients.[61] Weintraub et al.,[62] in a double-blind, placebo-controlled trial involving 60 individuals, found an average weight loss of 2.9 ± 2.3kg for participants receiving sibutramine 5 mg/day, 5.0 ± 2.7kg for those receiving sibutramine 20 mg/day and 1.4 ± 2.1kg for those receiving placebo during an 8 week trial. The difference in weight loss for the group receiving sibutramine 20 mg/day was significantly different ($p < 0.001$) than the group receiving placebo. The group receiving sibutramine 5 mg/day was not significantly different from the placebo group in terms of weight loss.

In a double-blind, placebo-controlled trial involving 173 healthy, obese patients for 24 weeks, Ryan et al.[63] and Bray et al.[64] found the average weight loss during a 24-week period was 3.7 ± 0.98kg for sibutramine 1 mg/day, 3.9 ± 0.96kg for sibutramine 5mg/day, 5.8kg for sibutramine 10 mg/day, 6.4 ± 0.96kg for sibutramine 15 mg/day, 7.2 ± 0.96kg for sibutramine 20 mg/day, 8.3 ± 0.94kg for sibutramine 30 mg/day and 0.8 ± 0.96kg in the placebo group. The effects of the 1 and 5 mg/day dosages of sibutramine were not significantly different from those of placebo. Participants in the sibutramine 30 mg/day group averaged a 9% weight loss from their initial weight and close to a 9% difference from the placebo group. The dropout

© Adis International Limited. All rights reserved.

rate in this study was 15%. Following discontinuation of therapy, weight gain was noted in all groups.

Following the initial study, 122 of the abovementioned patients participated in an open-label extension study.[65] Initially, participants received sibutramine 15mg daily, with 68% of participants being titrated to 30mg daily. 38 individuals completed 72 weeks and 18 individuals completed 96 weeks of the study. At 40 weeks, the mean weight loss was 6.0 ± 0.68kg. For the 18 individuals completing the entire trial of 96 weeks, the mean weight loss was only 2.6 ± 1.1kg. 13 participants were terminated from the trial for possible adverse effects of the medication. These adverse effects included elevated blood pressure, anxiety, paranoia, depression, mood swings and chest pain. One patient developed cholecystitis requiring cholecystectomy, a condition reported to occur with rapid weight loss associated with treatment. As a placebo group was not included in this trial, these reported adverse effects may or may not be related to the treatment.

In a long term study of sibutramine, 485 individuals were randomised to received placebo or sibutramine 10 or 15 mg/day.[66] After 12 months, the participants in the placebo group lost an average of 1.8kg while the participants in the sibutramine 10 and 15 mg/day groups lost an average of 4.8 and 6.1kg, respectively.

Sibutramine is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced caloric diet. It is recommended for obese patients with an initial BMI >30 kg/m^2, or >27 kg/m^2 in the presence of other risk factors (e.g. hypertension, diabetes, hyperlipidaemia). The recommended starting dosage of sibutramine is 10 mg/day administered once daily with or without food. If there is inadequate weight loss, the dosage may be titrated after 4 weeks to a total of 15mg once daily. The 5mg daily dose should be reserved for patients who do not tolerate the 10mg dose.

The most common adverse effects associated with the use of sibutramine were dry mouth, anorexia, constipation and insomnia.[64,67] A mild increase in blood pressure and heart rate have been noted in some, nonhypertensive study participants.[63]

4. Thermogenic Agents

4.1 Ephedrine Plus Caffeine

The ephedrine-caffeine combination seems useful for the treatment of obesity as it possesses both anorectic and thermogenic properties with only mild, transient adverse effects. Ephedrine increases the release of noradrenaline, which decreases food intake, and acts as a sympathomimetic agent to stimulate heart rate, blood pressure and enhance thermogenesis. Caffeine, a methylxanthine, increases calcium permeability in sarcoplasmic reticulum, inhibits phosphodiesterase (which promotes the accumulations of cyclic AMP, and competitively blocks adenosine receptors. By these mechanisms, caffeine and ephedrine act as a synergistic combination. As with other similar β-agonists, ephedrine and caffeine have both acute (cardiac arrhythmias, increased energy expenditure, increased lipolysis, hyperglycaemia and hyperinsulinaemia) and chronic (weight loss, body fat loss, muscle hypertrophy and improved insulin sensitivity) effects.[68] Currently, this combination is marketed as a stimulant and is readily available over the counter. In addition, caffeine is used in combination with 'herbal products' to promote weight loss. These combination products may have adverse effects similar to those mentioned above.

The mechanism behind the weight-reducing effects of ephedrine-caffeine are not well understood.[65] Because of its similarity to noradrenaline, ephedrine is considered to suppress food intake via adrenergic pathways in the hypothalamus and related structures. This effect my be potentiated by caffeine. As noted by Astrup et al.,[68] the present ephedrine-caffeine combination was chosen because of its superior ability, compared with its components given in other proportions, to stimulate energy expenditure as measured by indirect calorimetry in humans.

© Adis International Limited. All rights reserved.

Ephedrine (20mg) with caffeine (200mg or 2 to 3 cups of coffee) given 3 times daily was found to be more effective than placebo, caffeine, or ephedrine given separately as adjuvant in the treatment of obesity in 180 patients treated for 24 weeks.[69] The mean weight loss in the treatment group was 16.6kg. Adverse effects were transient and comparable to placebo after 8 weeks of treatment.

The adverse effects of the ephedrine-caffeine combination include tremor, insomnia and dizziness. These specific adverse effects are usually transient. After long term administration, muscle fatigue and stress may occur.

4.2 β_3-Agonists

The β_3-adrenoceptor functions in a variety of metabolic activities including lipolysis, thermogenesis and the metabolic and motility functions of the GI tract. Catecholamine-stimulated lipolysis in white and brown adipose tissue and thermogenesis in brown adipose tissue are both mediated by β_3-receptors. In animal models, the principal action of the β_3-receptor seems to be enhanced thermogenesis in brown adipose tissue, the tissue responsible for oxidising lipids to produce heat and eliminate excess fat.[70,71] The specific physiology of the human β_3-receptor is not known, and whether it is coupled to lipolysis and thermogenesis in humans in the same ways in the rat or mouse is questioned. In addition, humans have little brown adipose tissue.

Recently, several genetic mutations have been implicated in the development of obesity. A mutation in the gene coding for the β_3-adrenoceptor is associated with an increased capacity to gain weight in morbidly obese individuals.[11] Additionally, a similar mutation of the β_3-adrenoceptor is associated with abdominal obesity and resistance to insulin.[72]

BRL 26830A is a new β_3-adrenoceptor agonist, which increases metabolic rate and causes a reduction in weight by decreasing the body lipid content in obese rats.[73] This agent shows a high degree of selectivity for thermogenesis relative to β_1 cardiac or β_2 bronchial effects, and evidence suggests that both brown adipose tissue and skeletal muscle contribute to this activity.[74-76] Other effects of β_3-agonists on the energy balance in rats and mice have been noted (table IV). Other agents currently in the early stages of development for use in obesity include BRL 35135, RO 40-2148, RO 16-8714, BTA 243 (CL 316243), and ZD 7114.[16]

In a double-blind, placebo-controlled study, individuals given BRL 26930A 400mg daily for 18 weeks lost significantly more weight (15.4 ± 6.6 *vs* 10.0 ± 5.9kg) than those individuals given placebo.[74] Urinary excretion of nitrogen was similar in both groups, whereas measurements of skinfold thickness indicated a 4.1kg difference in the amount of fat lost, suggesting that weight loss with BRL 26830A was mainly from adipose and not lean tissue. Short term administration of BRL 26830A to a group of 6 individuals who had taken the drug for 18 weeks showed that the expenditure of energy increased 11.6% during the second hour after administration, which suggests that BRL 26830A may enhance weight loss thermogenically.[77] The common adverse effects with BRL 26830A are shaking hands and tremulousness. No patient withdrew because of the severity of adverse effects.

5. Digestion Inhibitors

A different strategy for the treatment of obesity is using agents that interfere with the breakdown and digestion of dietary fat, ultimately inhibiting fat absorption from the GI tract. Therefore, fat substitutes may enhance weight loss without causing systemic adverse effects. A reduction in fat is

Table IV. Effects of β_3-adrenoceptor agonists on the energy balance in rats and mice (adapted from Arch & Wilson,[71] with permission)

Animal body type	Effect
Obese	Weight loss without reduced food intake. All weight loss is lipid: protein unchanged or increased. Thermogenesis, which increases during repeat dosing
Lean	Duration of thermogenesis reduced, especially on repeat dosing. Food intake increases if thermogenic stimulus is prolonged

© Adis International Limited. All rights reserved.

recommended in most weight loss diets; however, patient compliance with these diets is poor.[78] Therefore, digestion inhibitors may have a role in creating the negative energy balance necessary for subsequent weight loss.

5.1 Lipase Inhibitors

Gastric and pancreatic lipase aid in the digestion of dietary triglycerides by forming free fatty acids from dietary triglycerides, which are then absorbed at the brush border of the small intestine. Inhibition of these enzymes by lipase inhibitors leads to inhibition of the digestion of dietary triglycerides, decreased cholesterol absorption and decreased absorption of lipid-soluble vitamins (A, D, E, K).[16,79]

5.1.1 Orlistat

Orlistat is a lipase inhibitor that is a chemically synthesised hydrogenated derivative of lipstatin, a natural product of *Streptomyces toxytricini*.[79,80] It received US FDA approval in May 1997, but has not yet been marketed.[81] It is a potent and irreversible inhibitor of gastric, pancreatic and pancreatic carboxylester lipase, inhibiting the digestion of dietary triglycerides, decreasing the absorption of cholesterol and lipid-soluble vitamins.[16,79] As a result, orlistat decreases the systemic absorption of dietary fat, decreases bodyweight, decreases plasma cholesterol and can cause steatorrhoea.

Drent and van der Veen[79] studied the effects of diet plus orlistat in 52 obese men and women. After demonstrating compliance with the prescribed regimen, 44 patients were randomised to 12 weeks of orlistat 50mg 3 times daily or placebo; all patients continued prescribed dietary therapy. An additional 5 patients dropped out of the study because of noncompliance (n = 3), dissatisfaction with weight loss (n = 1) and faecal incontinence (n = 1). Initial weight loss in the placebo run-in period was 2.63 ± 1.08kg. After randomisation, weight loss was 4.3 ± 3.4kg in the orlistat group and 2.1 ± 2.8kg in the placebo group (p = 0.025, 95% CI 0.2 to 4.2kg). No effect was seen on blood pressure, serum total cholesterol or triglycerides although all patients had normal lipid profiles at enrolment. Vitamin E levels dropped in the orlistat group, but remained within the normal range. Vitamin A levels did not change during the study. GI adverse effects observed in the orlistat group were generally mild, and included abdominal pain, liquid stool, nausea, vomiting and flatulence.

In a second study, the efficacy and tolerability of various doses of orlistat in combination with a low fat diet were evaluated in 237 obese men and women.[82] 49 patients withdrew because of noncompliance during the diet therapy run-in period. Therefore, 188 patients were randomised after the run-in period, during which the mean weight loss was 2.4 to 2.6kg. Subsequently, patients were randomised to orlistat 10, 60 or 120mg 3 times daily or placebo for 12 weeks. Mean weight loss in the placebo group was 2.98 ± 0.38kg (± SEM), 3.61 ± 0.38kg in the 30mg orlistat group, 3.69 ± 0.39kg in the 180mg orlistat group and 4.74 ± 0.38kg in the 360mg orlistat group (versus placebo, p = 0.001). A decrease in low density lipoprotein cholesterol (LDL-C) and total cholesterol was noted in the orlistat 180 and 360mg group when compared with placebo (p = 0.01), but no difference was noted in high density lipoprotein-cholesterol (HDL-C) or triglycerides. Vitamin E levels dropped in the orlistat 180 and 360mg groups, but did not cross the normal limits. Vitamin A levels changed minimally. Adverse effects in the orlistat group again were mainly GI in nature, and 3 patients withdrew for this reason.

The tolerability and efficacy of orlistat have been evaluated in a year long, multicentre study; however, the results are currently published from only 1 site.[83] 46 obese men and women were randomised to orlistat 120mg 3 times daily or placebo plus a low fat diet, which were continued throughout the study. Mean reduction in bodyweight reached a maximum at 6 months, when the placebo group lost 5.5 ± 4.5kg and the orlistat group lost 8.6 ± 5.4kg. This represented a 5.7% reduction in weight in the placebo group and an 8.4% reduction in weight in the orlistat group. After the 6-month peak weight loss, individuals in the placebo group started to regain their weight, while the treatment

© Adis International Limited. All rights reserved.

group maintained their weight loss. At 1 year, weight loss in the placebo group was approximately 2.6% less than the initial value, whereas weight loss in the orlistat group was maintained at 8.4%. Metabolic parameters improved in the orlistat group, where total and LDL-C dropped 1.6 and 4.2% respectively. A significant drop in α-tocopherol and β-carotene levels was noted in the orlistat group, in which 6 participants required fat-soluble vitamin supplementation. Vitamin D levels did fall, but remained in the normal range. The dropout rate was 48% in the placebo group and 39% in the orlistat group, despite the increase in GI adverse effects in the orlistat group.

To further investigate GI adverse effects, Zhi and colleagues[84] examined the dose-response relationship of orlistat on faecal fat excretion in normal and obese volunteers in a retrospective, population-based analysis. They reviewed 11 phase I clinical trials, involving 171 men and women, in which orlistat 30 to 1200 mg/day or placebo was administered for 9 to 10 days. The investigators calculated the mean faecal fat excretion percentage, relative to ingested fat, and correlated that with the orlistat dosage. The results suggested that the dose-response curve levelled off at 400mg daily, during which 32% of fat was excreted in the faeces. Practically, dosages above 400mg daily will not result in a further increase in fat excretion or increase the inhibition of dietary fat absorption.

Orlistat has not yet been released to the US market because of some concern over reports of breast neoplasm in users.[82] The incidence of breast and other forms of cancer in orlistat versus non-orlistat users in currently unknown. Nine cases of breast neoplasm were found in patients taking orlistat 120mg 3 times daily, 1 case was found in the 60mg 3 times daily group and 1 case was found in the placebo group. Five of the 9 cases were detected within 6 months of initiating the study.[85] As orlistat has minimal systemic absorption, these findings are poorly understood. However, the question of orlistat use and risk of breast neoplasm will be investigated in the Xendos Xenical Swedish study, currently in the randomisation phase.[86]

Several single-dose studies have been undertaken to investigate the effects of orlistat on the pharmacokinetics of other agents. Orlistat did not affect the pharmacokinetics of captopril or atenolol, but did increase the half-life of furosemide (frusemide) and prolong the time to peak plasma concentration of nifedipine.[87] The pharmacokinetic profile of nifedipine extended-release tablets (Procardia XL®) was not altered by coadministration of orlistat.[88] When orlistat was combined with warfarin, there were no changes in prothrombin time or vitamin K status in the patient population.[89] Similarly, orlistat did not alter digoxin or phenytoin pharmacokinetics.[90,91] Orlistat did not alter the glucose-lowering effects of glibenclamide (glyburide),[92] nor did it influence the ovulation-suppressing action of oral contraceptives.[93]

A major concern regarding the use of orlistat is the subsequent effects on fat-soluble vitamin levels. The effect of orlistat on the pharmacokinetics of β-carotene, vitamin A and vitamin E has been studied in healthy volunteers receiving orlistat 120mg 3 times daily. After a single dose of 25000IU of vitamin A and 400IU of vitamin E, orlistat did not alter vitamin A levels but did decrease the absorption of vitamin E.[94] After a single dose of β-carotene 30, 60 or 120mg, orlistat decreased β-carotene absorption by one-third.[95]

5.2 Fat Substitutes

In an effort to maintain the taste preference for foods, while decreasing the fat content of the American diet, manufacturers have welcomed the development of fat substitutes. Fat substitutes mimic some of the roles of fat in food processing, and allow for a reduction in the intake of high fat foods without changing food selection while maintaining palatability. Fat substitutes are either carbohydrate-based, protein-based or fat-based (table V).[96] Currently, most are carbohydrate-based, although the new fat-based olestra has drawn significant market attention. Fat substitutes are all FDA approved or are deemed generally recognised as safe (GRAS) substances.[96] GRAS substances are derived from common food components, whereas food additives

© Adis International Limited. All rights reserved.

Table V. Fat substitutes: how to identify, their use in foods, and regulatory status (adapted from Warshaw et al.,[96] with permission)

Category of fat substitute	Examples of trade names	Examples of how identified on food label	Types of foods used in	Examples of role in foods and calorie content	Regulatory status
Carbohydrate-based					
Polymers	Maltrin, Lycadex Paselli Excell, Stellar, N-Oil, Sta-Slim, Oatrim	Maltodestrin, corn syrup solid, hydrolysed corn starch, modified food starch, polydextrose	Frozen desserts, cheese, baked goods, sauces, dressings, sour cream, yoghurt, baked bread, meats and poultry	Gelling, thickening, stabilising, increasing shelf-life, antistaling, adds creaminess and texture, decreases calories 1 kcal/g when hydrated in a product	GRAS approval
Hydrocolloids: gums, gels, and fibres	Slendid, Viscarin, Sactarin, Gelcarin, Fibrex, Avicel, Novagel, Rohodigel, Uniguar, Pycol, Jaquar	Pectin, carrageenan, sugar beet fibre or powder, cellulose gel, locus bean gum, xanthan gum, guar gum	Yogurt, sour cream, salad dressings, bakery products, frozen desserts, cheese spreads, sauces	Binds water, texturiser, thickener, stabiliser, provides mouth-feel of fat, decreases calories 0-0.5 kcal/g	GRAS approval
Polyols (sugar alcohols)/bulking ingredients	Lycasin, Hystar, Neosor, Litesse, Sta-Lite	Hydrogenated starch hydrolysate (HSH), hydrogenated glucose syrup, sorbitol, maltitol syrup, polydextrose	Baked goods, confections, chewing gum, frozen dairy desserts, gelatins, puddings, sauces, salad dressings, meat-based products	Adds bulk, aids in retaining moisture, texturiser, lowers freezing point, inhibits crystallisation, decreases calories compared with gat 1-4 kcal/g	GRAS approval; polydextrose approved as food additive
Protein-based					
	Simplesse, K-Blazer, Lita, Dairy-lo, Ven-lo	Microparticulated egg white and milk protein, whey protein concentrate	Cheese, butter, mayonnaise, salad dressings, sour cream, bakery products, spreads	Provides mouth-feel of fat, cannot be used in fried foods, 1.3 kcal/g, ingredients being developed may have higher calories	GRAS approved
Fat-based					
	Caprenin, Olean, Salatrim, emulsifiers (ie. Polyglycerolesters)	Caprenin, olestra; others being developed not yet determined as to listing	Salatrim - chocolate and confections, cookies and crackers. Olestra - savory snack foods (i.e. Chips) and crackers	Acts very similar to 'fat', provides creamy texture. Caprenin and Salatrimhave 5 kcal/g because of decreased absorption, olestra has 0 kcal/g because it is not absorbed	GRAS or food additive approval

GRAS = 'generally regarded as safe'.

© Adis International Limited. All rights reserved.

are substances not previously found in the food supply.

The fat-based fat substitutes are undergoing critical review with respect to efficacy, tolerability and ability to interact with other commonly used drugs. Therefore, this article will consider fat-based fat substitutes in some detail. A full review of fat substitutes has recently been published.[96]

The goal of fat-based substitutes is to decrease caloric value from fat while maintaining the creaminess and richness derived from added fat. The fat-based substitutes caprenin and salatrim, contain 5 kcal/g, in comparison to the caloric value of natural fat of 9 kcal/g.[96]

5.2.1 Olestra

Olestra, a sucrose polyester and the most recent fat-based substitute, contains 0 kcal/g. This fat substitute was approved in the US by the FDA in January 1996 as a food additive.[97] With 6 to 8 fatty acid side chains, olestra is too large to be hydrolysed by digestive enzymes and is not absorbed. The FDA has approved it to be used in prepackaged snacks (potato, corn and tortilla chips and crackers). A 28g serving of potato chips fried in fat contains 10g of fat and 150 calories, while a similar serving of olestra potato chips contains no fat and 70 calories. Expanded use of this fat substitute will require US FDA approval of a new food additive.

Also contained in olestra are the fat-soluble vitamins A, D, E and K in order to compensate for their decreased absorption. All olestra-containing products must carry the following information label: 'This product contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E and K have been added'. In addition, the FDA has mandated post-marketing surveillance of olestra to ensure that there is a reasonable certainty of no harm.[96]

The effect of olestra on lipid metabolism has been evaluated in healthy individuals and in patients with metabolic diseases such as hypercholesterolaemia and diabetes mellitus. Olestra may reduce cholesterol by substituting dietary fat and reducing the intake of saturated fatty acids. Simple weight reduction and reduction in total caloric intake through olestra-containing products may lead to improvement in cholesterol profiles. In addition, olestra may inhibit the absorption of co-ingested fat through solubilisation of fat into olestra, and increase the excretion of bile acids and faecal sterols into the GI tract.[98] In general, total and LDL-C are maximally reduced by 20%, whereas HDL-C and triglycerides are usually not affected. Interestingly, HDL-C was increased 11% in a 1-month study of olestra 30 g/day.[98-101] Therefore, olestra is not sufficient as a sole cholesterol-reducing agent, but may be a beneficial adjunct to traditional non-pharmacological and pharmacological therapy for hyperlipidaemia.

The tolerability and safety of olestra has been extensively studied, whereas the effects on weight loss from long term substitution of dietary fat with olestra have not been evaluated. Short term studies (<4 weeks) reported no change in weight when olestra was substituted for dietary fat in a conventional diet.[100,101] A 4-week study found significant weight loss (3.7kg) when a hypocaloric diet substituted dietary fat for olestra (30 g/day).[99] Therefore, olestra may be effective in enhancing weight loss when used in a calorie-restricted diet. In addition, the effects of olestra on food intake have not been evaluated, which would be have importance as fat intake is usually associated with increased satiety. After olestra consumption, some investigators have reported increased hunger, while some have reported a decrease in hunger.[101,102]

The major concern regarding the regular consumption of olestra-containing products is the GI adverse effect profile. Cheskin and colleagues[103] compared the GI effects of ad libitum consumption of potato chips made with olestra and triglycerides in 1123 healthy individuals. There was no significant difference in presence or frequency of GI symptoms at 40 hours to 10 days after ingestion between the olestra and triglyceride groups, although fewer olestra chips were consumed during the study (60 *vs* 77g, $p < 0.01$). Gastric emptying and GI transit were not altered in healthy participants ingesting a 45g fat meal, in which 30g was

© Adis International Limited. All rights reserved.

substituted with olestra.[104] In 89 patients with inflammatory bowel disease, chips or cookies containing olestra or triglycerides were administered daily for 4 weeks.[105] Patients were classified as in remission, worsened or relapsed according to the investigator's global assessment. There was no difference in the olestra and triglyceride group with respect to relapse rate or percent experiencing worsening of symptoms. Despite these results, numerous other clinical trial participants have reported significant GI adverse effects such as bloating, flatulence, diarrhoea, loose stools and anal leakage.[97-100,106]

The potential effects on the fat-soluble vitamins (A, D, E and K) and carotenoids is an additional concern relating to the increasing use of olestra. The absorption of fat-soluble vitamins from the digestive tract can only be affected by the presence of olestra if both foods are eaten at the same time. Regardless of time of administration, olestra appears to have no significant effect on the absorption of vitamin K.[100,107-109] In human studies, olestra has led to decreases in 25-hydroxyergocalciferol, but has not changed overall vitamin D status.[107-110] This lack of change in overall activity is explained by the significant contribution of cutaneous calciferol synthesis to overall vitamin D activity, rather than nutritional intake of vitamin D.[111]

When olestra was consumed in large quantities, plasma vitamin A and E levels decreased significantly.[99-101,112,113] Based on this information, the US FDA has required that all olestra-containing foods also be supplemented with vitamins A, D, E and K and labelled as such.[97] The absorption of carotenoids, a class of fat-soluble compounds with possible antioxidant properties, has been significantly reduced by administration with olestra;[114] however, carotenoids are not supplements in olestra-containing foods. The manufacturer will be required to continue to monitor the long term consequences of olestra consumption on nutritional status.

The systemic bioavailability of orally administered medications could potentially be altered by coadministration with olestra, particularly if those medications are lipophilic in nature.[115] When studied, olestra did not alter the systemic absorption of a single dose of propranolol, diazepam, norethindrone or ethinylestradiol.[115] In a 28-day study, olestra did not alter the systemic concentration of oral contraceptives (ethinylestradiol 30μg and norgestrel 300μg), nor did it minimise the efficacy as indicated by ovulation.[116] Because of the possible effect of olestra on vitamin K absorption, it should be used with caution in patients taking warfarin, although this has not been adequately studied to date.

6. Hormonal Manipulation

The GI tract and CNS contain several peptides and hormones which regulate feeding behaviour. For example, cholecystokinin, serotonin and insulin act to decrease food intake and decrease appetite.[16] On the other hand, neuropeptide Y (NPY) increases food intake and decreases energy expenditure.[117] Leptin may limit food intake and increase energy expenditure.[118] Therefore, agonists and antagonists of these hormones and peptides are actively under investigation for the treatment of obesity.

6.1 Leptin and Neuropeptide Y

Derived from the Greek 'leptos' meaning thin, leptin is a 167 amino acid peptide that has attracted significant scientific attention as a potential cure for obesity.[119] This 'fat-melting hormone' was first reported in 1994, when Zhang and colleagues[118] cloned and sequenced the murine and human ob gene and identified the gene product, leptin, from adipose tissue. The ob gene encodes leptin, which may be secreted by adipocytes, and is thought to travel a signalling pathway to the brain to regulate satiety and weight loss.[120,121] Also related is NPY, which stimulates food intake. It is thought that leptin reduces concentrations of NPY, leading to a decrease in food intake.[120] Therefore, it is thought that adipocytes detect an excess of adipose tissue, secrete leptin (and further NPY), to act centrally at the hypothalamus and regulate bodyweight and

© Adis International Limited. All rights reserved.

energy expenditure.[120] In addition to the metabolic effects of leptin, it may have a role in reproduction and neuroendocrine signalling (fig. 1).

In mice, obesity is related to mutations in the ob gene, leading to a reduction in circulating leptin.[119] Subsequent leptin administration leads to weight loss in this species; however, in humans, this relationship is not as clear. In humans, leptin resistance has been postulated as a cause of obesity.[119,121] Considine and colleagues[122] measured leptin levels in 136 nonobese and 139 obese individuals using a radioimmunoassay in an effort to correlate with bodyweight and changes in bodyweight. The mean serum leptin level in the obese group was 31.3 ± 24.1 μg/L, whereas values of 7.5 ± 9.3 μg/L were observed in the normal-weight individuals. Serum leptin levels decreased with weight loss in 7 obese participants, but increased again during maintenance of the weight loss. The authors concluded that obese individuals were relatively insensitive to endogenous leptin production. Caro and colleagues[123] have suggested that leptin resistance is caused by a decreased capacity to transport leptin into the brain.

In the United Kingdom Prospective Diabetes Study (UKPDS), elevated serum leptin levels were found to be related to hyperinsulinaemia and impaired insulin sensitivity in more than 1000 patients with type 2 diabetes.[124] Insulin may chronically stimulate leptin production, through a tropic effect on adipocytes.[125] *In vitro*, troglitazone has led to a 40% reduction in the insulin-related increase in leptin levels.[125] In a 3-month trial, obese patients were given troglitazone 400mg daily and serum leptin levels were measured. Troglitazone led to a significant reduction in fasting and post-meal insulin levels but did not change leptin levels.[125]

Currently, clinical trials are underway to investigate the effects of leptin analogues and NPY antagonists on bodyweight and metabolic control in humans. In addition to the effects of leptin on food intake, weight control and energy expenditure, efforts must focus on the relationship of leptin to other neuroendocrine and reproductive activities.

7. Conclusions

Pharmacotherapeutic agents, if recommended and prescribed, should be an aid to a structured diet and exercise regimen in the treatment of obesity. Expected weight loss with an antiobesity agent varies greatly depending on the effort devoted to a diet and exercise regimen and the initial weight of

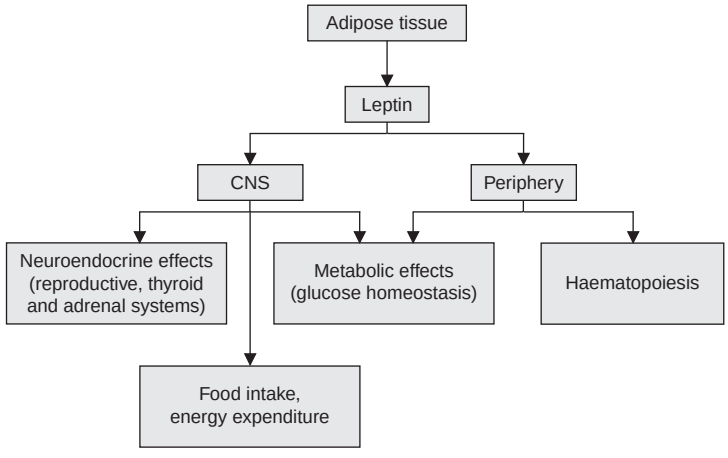

Fig. 1. The activity of leptin in central and peripheral pathways (adapted from Auwerx & Staels,[119] with permission).

© Adis International Limited. All rights reserved.

Table VI. Review of commonly available medications for the management of obesity

Agent	Reference	Duration	Mean weight loss (kg)[a]	Adverse effects
Phenylpropanolamine	29	14 weeks	6.1	Dry mouth, nervousness, sleeplessness, dizziness, palpitations, headaches
	30	14 weeks	5.96	
	31	8 weeks	2.59	
Phentermine	32	36 weeks	13.0	Headache, insomnia, nervousness, irritability, palpitations, tachycardia, increased blood pressure
	33	6 months	5.3	
	34	12 weeks	3.6	
Sibutramine	62	8 weeks	5.0	Dry mouth, anorexia, constipation, insomnia, mild increase in blood pressure
	63,64	8 weeks	5.0	
	65	96 weeks	2.6	
Ephedrine plus caffeine	69	24 weeks	16.6	Tremor, insomnia, dizziness (after long term administration, muscle fatigue and stress may occur)

a Mean weight loss in group given maximum dose of medication.

the patient; these factors are difficult to control in clinical trial settings. The clinical significance of any weight loss programme must ultimately be evaluated according to the ability to maintain long term weight control once weight reduction has been achieved. To date, most studies demonstrate effectiveness of currently available antiobesity agents during the early phases of an overall weight reduction programme (table VI).

This effectiveness has yet to be maintained during long term use and the dropout rate found in these studies are often high. While the short term safety of these agents has been demonstrated, the long term tolerability of many antiobesity regimens has not been adequately evaluated. In addition, the effect of weight loss obtained through the use of pharmacotherpeutic agents on overall morbidity and mortality has not been established. However, like hypertension, hyperlipidaemia and diabetes, obesity is often considered a chronic medical problem that requires long term, continuous, multifaceted management.

Weight gain after discontinuation of antiobesity agents is common. Antiobesity agents appear to be more effective with short term or initial weight loss rather than achieving and maintaining desirable weight on a long term or permanent basis. As with the other common chronic medical conditions, the need exists to develop a safe and effective pharmacotherapeutic agent for the treatment of obesity which aids a programme in diet and exercise and promotes long term weight reduction.

References

1. Gray DS. Diagnosis and prevalence of obesity. Med Clin North Am 1989; 73: 1-13
2. Kuczmarski RJ, Flegal KM, Campbell SM, et al. Increasing prevalence of overweight among US adults: the National Health and Nutrition Examination Surveys, 1960 to 1991. JAMA 1994; 272: 205-11
3. Levy SL, Heaton AW. Weight control practices of U.S. adults trying to lose weight. Ann Intern Med 1993; 119: 661-6
4. Serdula MK, Collins ME, Williamson DF, et al. Weight control practices of US adolescents and adults. Ann Intern Med 1993; 119: 667-71
5. Bray GA. Obesity: definition, diagnosis, and disadvantages. Med J Aust 1985; 142 Suppl.: S2-8
6. Pi-Sunyer FX. Medical hazards of obesity. Ann Intern Med 1993; 119: 655-60
7. Van Itallie TB. Health implications of overweight and obesity in the United States. Ann Intern Med 1985; 103: 983-8
8. United States National Commission on Diabetes. Report of the National Commission on Diabetes to the Congress of the United States. Bethesda (MD): U.S. Department of Health, Education and Welfare; 1975. Publication no.: 76-1021; Vol. 1
9. Garfinkel L. Overweight and cancer. Ann Intern Med 1985; 103: 1034-6
10. Colditz GA. Economic costs of obesity. Am J Clin Nutr 1992; 55: 503S-7S
11. Clement K, Vaisse C, Manning B, et al. Genetic variation in the β_3-adrenergic receptor and an increased capacity to gain weight in patients with morbic obesity. N Engl J Med 1995; 333: 352-4
12. Arner P. The β_3-adrenergic receptor - a cause and cure for obesity. N Engl J Med 1995; 333: 382-3
13. Bray GA. Use and abuse of appetite-suppressant drugs in the treatment of obesity. Ann Intern Med 1993; 119: 707-13
14. NIH consensus statement covers treatment of obesity. Am Fam Phys 1991; 44: 305-6
15. Stunkard AJ, Craighead LW, O'Brien R. Controlled trial of behaviour therapy, pharmacotherapy, and their combination in the treatment of obesity. Lancet 1980; I: 1045-7
16. Cerulli J, Lomaestro BM, Malone M. Update on the pharmacotherapy of obesity. Ann Pharmacother 1998; 32: 88-102
17. Rosenbaum M, Leibel RL, Hirsch J. Obesity. N Engl J Med 1997; 337: 396-407

© Adis International Limited. All rights reserved.

18. Weiser M, Frishman WH, Michaelson D, et al. The pharmacologic approach to the treatment of obesity. J Clin Pharmacol 1997; 37: 453-73
19. Ryan DH. Medicating the obese patient. Endocrinol Metab Clin North Am 1996; 25: 989-1004
20. Bray GA. Evaluation of drugs for treating obesity. Obes Res 1995; 3 Suppl. 4: 425S-34S
21. Goldstein DJ, Potvin JH. Long term weight loss: the effect of pharmacologic agents. Am J Clin Nutr 1994; 60: 647-57
22. Bray GA. Drug treatment of obesity. Am J Clin Nutr 1992; 55: 538S-44S
23. Björntorp P. Regional patterns of fat distribution. Ann Intern Med 1985; 103: 994-5
24. Jung RT, Chong P. The management of obesity. Clin Endocrinol 1991; 35: 11-20
25. Silverstone T. Appetite suppressants: a review. Drugs 1992; 43: 820-36
26. Hoebel BG, Krauss IK, Cooper J, et al. Body weight decreased in humans by phenypropanolamine taken before meals. Obes Bar Med 1975; 4: 200-6
27. Altschuler S, Frazer DL. Double-blind clinical evaluation of the anorectic activity of phenylpropanolamine hydrochloride drops and placebo drops in the treatment of exogenous obesity. Curr Ther Res 1986; 40: 211-7
28. Griboff SI, Berman R, Silverman HI. A double-blind clinical evaluation of a phenylpropanolamine-caffeine-vitamin combination and a placebo in the treatment of exogenous obesity. Curr Ther Res 1975; 17: 535-43
29. Weintraub M, Ginsberg G, Stein EC, et al. Phenylpropanolamine OROS (Acutrim) vs. placebo in combination with caloric restriction and physician-managed behaviour modification. Clin Pharmacol Ther 1986: 39: 501-9
30. Greenway F. A double-blind clinical evaluation of the anorectic activity of phenylpropanolamine versus placebo. Clin Ther 1989; 11: 584-9
31. Schteingart DE. Effectiveness of pheylpropanolamine in the management of moderate obesity. Int J Obesity 1992; 16: 487-93
32. Munro JF, MacCuish AC, Wilson EM, et al. Comparison of continuous and intermittent anorectic therapy in obesity. BMJ 1968; 1: 352-4
33. Campbell C, Bhalla IP, Steel IM, et al. A controlled trial of phentermine in obese diabetic patients. Practitioner 1977; 218: 851-5
34. Tuominen S, Hietula M, Kuusankoski M. Double-blind trial comparing fenfluramine, phentermine and dietary advice on treatment of obesity. Int J Obes 1990; 14 Suppl. 2: 138
35. Weintraub M, Hasday JD, Mushlin AI, et al. A double-blind clinical trial in weight control: use of fenfluramine and phentermine alone and in combination. Arch Intern Med 1984; 144: 1143-8
36. Scalfi L, D'Arrigo E, Carredente V, et al. The acute effect of dexfluramine on resting metabolic rate and post prandial thermogenesis in obes subjects: a double-blind placebo-controlled study. Int J Obes Relat Metab Disord 1993; 17: 91-6
37. Weintraub M, Sundaresan PR, Madan M, et al. Long term weight control study I (weeks 0 to 34): the enhancement of behaviour modification, caloric restriction, and exercise by fenfluramine puse phentermine versus placebo. Clin Pharmacol Ther 1992; 51: 586-94
38. Weintraub M, Sundaresan PR, Schuster B, et al. Long term weight control study (weeks 34 to 104): an open-label study of continuous felfluramine plus phentermine versus targeted intermittent medications as adjuncts to behaviour modification, caloric restriction, and exercise. Clin Pharmacol Ther 1992; 51: 595-601
39. Weintraub M, Sundaresan PR, Schuster B, et al. Long term weight control study III (weeks 104 to 156): an open label study of dose adjustment of fenfluramine and phentermine. Clin Pharmacol Ther 1992; 51: 602-7
40. Weintraub M, Sundaresan PR, Schuster B, et al. Long term weight control study IV (weeks 156-190): the second double blind phase. Clin Pharmacol Ther 1992; 51: 608-14
41. Weintraub M, Sundaresan PR, Schuster B, et al. Long term weight control study V (weeks 190-210): follow up of particpants after cessation of medication. Clin Pharmacol Ther 1992; 51: 615-8
42. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997; 337: 581-8
43. Graham DJ, Green L. Further cases of valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997; 337: 635
44. Centers for Disease Control and Prevention. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services interim public health recommendation, November 1997. MMWR 1997; 46 (45): 1061-6
45. Graham DJ, Green L. Further cases of valvular heart disease associated with dexfenfluramine. N Engl J Med 1997; 337: 636
46. Davis R, Faulds D. Dexfenfluramine: an updated review of its therapeutic use in the management of obesity. Drugs 1996; 52: 696-724
47. McTavish D, Heel RC. Dexfenfluramine: a review of its pharmacological properties and therapeutic potential in obesity. Drugs 1992; 43: 713-33
48. Guy-Grand B, Apfelbaum M, Crepaldi G, et al. International trial of long term dexfenfluramine in obesity. Lancet 1989; II: 1142-4
49. Wiley KA, Molyneaux LM, Overland JE, et al. The effects of dexfenfluramine on blood glucose control in patients with type 2 diabetes. Diabet Med 1992; 9: 341-3
50. Manning RM, Jung RT, Leese GP, et al. The comparison of four weight reduction strategies aimed at overweight diabetic patients. Diabet Med 1995; 12: 409-15
51. Abenhaim L, Moride Y, Brenot F, et al. Appetite suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 1996; 335: 609-16
52. The International Primary Pulmonary Hypertension Study (IPPHS). Chest 1994; 105 Suppl.: 37S-41S
53. Manson JE, Faich GA. Pharmacotherapy for obesity - do the benefits outweigh the risks? N Engl J Med 1996; 335: 659-60
54. Weissman NJ. Prevalence of valvular abnormalities in patients exposed to dexfenfluramine - result of a randomized placebo-controlled trial. Presented at the 47th Annual American College of Cardiology meeting; 1998 Mar 29-Apr 1; Atlanta
55. Levine LR, Enas GG, Thompson WL, et al. Use of fluoxetine, a selective serotonin-uptake inhibitor, in the treatment of obesity: a dose-response study. Int J Obesity 1989; 13: 635-45
56. Piji H, Koppeschaar HPF, Willekens FLA, et al. Effect of serotonin re-uptake inhibition by fluoxetine on body weight and spontaneous food choice in obesity. Int J Obesity 1991; 15: 237-42
57. Darga LL, Carroll-Michals L, Botsford SJ, et al. Fluoxetine's effect on weight loss in obese subjects. Am J Clin Nutr 1991; 54: 321-5

© Adis International Limited. All rights reserved.

58. Goldstein DJ, Rampey AH, Enas GG, et al. Fluozetine: a randomized clinical trial in the treatment of obesity. Int J Obesity 1994; 18: 129-35
59. Gray DS, Fujioka K, Devine W, et al. Fluoxetine treatment of the obese diabetic. Int J Obesity 1992; 16: 193-8
60. Weiser M, Frishman WH, Michaelson MD, et al. The pharmacologic approach to the treatment of obesity. J Clin Pharmacol 1997; 37: 453-73
61. Kelly F, Jones SP, Lee IK. Sibutramine: weight loss in depressed patients [abstract]. Int J Obes 1995; 19 Suppl. 2: 145
62. Weintraub M, Rubio A, Golika A, et al. Sibutramine in weight control: a dose-ranging, efficacy study. Clin Pharmacol Ther 1991; 50: 300-7
63. Ryan DH, Kaiser P, Bray GA. Sibutramine: a novel new agent for obesity treatment. Obes Res 1995; 3 Suppl. 4: 553S-9S
64. Bray GA, Ryan DH, Dordon D, et al. A double-blind, randomized placebo-controlled trial of sibutramine. Obes Res 1996; 4: 263-70
65. Ryan DH, Bray GA, Wilson JK, et al. Treatment for 2½ years with sibutramine [abstract]. Obes Res 1996; 4 Suppl. 1: 31S
66. Jones SP, Smith IG, Kelly F, et al. Long-term weight loss with sibutramine. Int J Obes 1995; 19 Suppl. 2: 41
67. Lean MEJ. Sibutramine - a review of clinical efficacy. Int J Obes 1997; 21: S30-6
68. Astrup A, Toubro S, Christensen NJ, et al. Pharmacology of thermogenic drugs. Am J Clin Nutr 1992; 55 Suppl.: 246S-8S
69. Quaade F, Breum L, Toubro S, et al. The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in the treatment of human obesity: a double-blind trial [abstract]. Int J Obes 1990; 14: 50
70. Berkowitz DE, Nardone NA, Smiley RM, et al. Distribution of β_3-adrenoreceptor mRNA in human tissues. Eur J Pharmacol 1995; 289: 223-8
71. Arch JRS, Wilson S. Prospects of β3-adreneceptor agonists in the treatment of obesity and diabetes. Int J Obes 1996; 20: 191-9
72. Widen E, Lehto M, Kanninen T, et al. Association of a polymorphism in the β_3-adrenergic receptor gene with features of the insulin resistance syndrome in Finns. N Engl J Med 1995; 333: 348-51
73. Arch JRS, Ainsworth AT. Thermogenic and antiobesity activity of a novel β-adrenoceptor agonist (BRL 26830A) in mice and rats. Am J Clin Nutr 1983; 38: 549-58
74. Arch JRS, Ainsworth AT, Cawthorne MA, et al. Atypical β-adrenoceptor on brown adipocytes as target for anti-obesity drugs. Nature 1984; 309: 163-5
75. Arch JRS, Ainsworth AT, Ellis RDM, et al. Treatment of obesity with thermogenic β-adrenoceptor agonists: studies on BRL 26830A in rodents. Int J Obes 1985; 9: 231
76. Thurlby PL, Ellis RDM. Differences between the effects of noradrenaline and the β-adrenoceptor agonist BRL 26830A in brown adipose tissue and hind limb of the anaesthetized rat. Can J Physiol Pharmacol 1986; 64: 1111-4
77. Connacher AA, Jung RT, Mitchell PEG. Weight loss in obese subjects on a restricted diet given BRL 26830A, a new atypical β-adrenoceptor agonist. BMJ 1988; 296: 1217-20
78. Aronne, LJ. Obesity. Med Clin North Am 1998; 82 (1): 161-81
79. Drent ML, van der Veen EA. Lipase inhibition: a novel concept in the treatment of obesity. Int J Obes 1993; 17: 241-4
80. Guerciolini R. Mode of action of orlistat. Int J Obes 1997; 21 Suppl. 3: S12-23
81. F-D-C Rep 1997; May 19: 3-5
82. Drent ML, Larsson I, William-Olsson T, et al. Orlistat (RO 18-0647), a lipase inhibitor, in the treatment of human obesity: a multiple dose study. Int J Obes 1995; 19: 221-6
83. James WPT, Avenell A, Broom J, et al. A one-year trial to assess the value of orlistat in the management of obesity. Int J Obes 1997; 21 Suppl. 3: S24-30
84. Zhi J, Melia AT, Guerciolini R, et al. Retrospective population-based analysis of the dose-response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. Clin Pharmacol Ther 1994; 56: 82-5
85. F-D-C Rep 1998; March 16: 3
86. F-D-C Rep 1998; March 23: 9
87. Weber C, Tam YK, Schmidtke-Schrezenmeier G, et al. Effect of the lipase inhibitor orlistat on the pharmacokinetics of four different antihypertensive agents in healthy volunteers. Eur J Clin Pharmacol 1996; 51: 87-90
88. Melia AT, Mulligan TE, Zhi J. Lack of effect of orlistat on the bioavailability of a single-dose of nifedipine extended-release tablets (Procardia XL) in healthy volunteers. J Clin Pharmacol 1996; 36: 352-5
89. Zhi J, Melia AT, Guerciolini R, et al. The effect of orlistat on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. J Clin Pharmacol 1996; 36: 659-66
90. Melia AT, Zhi J, Koss-Twardy SG, et al. The influence of reduced dietary fat absorption induced by orlistat on the pharmacokinetics of digoxin in healthy volunteers. J Clin Pharmacol 1995; 35: 840-3
91. Melia AT, Mulligan TE, Zhi J. The effect of orlistat on the pharmacokinetics of phenytoin in healthy volunteers. J Clin Pharmacol 1996; 36: 654-8
92. Zhi J, Melia AT, Koss-Twardy SG, et al. The influence of orlistat on the pharmacokinetics and pharmacodynamics of glyburide in healthy volunteers. J Clin Pharmacol 1995; 35: 521-5
93. Hartman D, Guzelhan C, Zuiderwijk PBM, et al. Lack of interaction between orlistat and oral contraceptives. Eur J Clin Pharmacol 1996; 50: 421-4
94. Melia AT, Koss-Twardy SG, Zhi J. The effect of orlistat, an inhibitor of dietary fat absorption, on the absorption of vitamins A and E in healthy volunteers. J Clin Pharmacol 1996; 36: 647-53
95. Zhi J, Melia AT, Koss-Twardy SG, et al. The effect of orlistat, an inhibitor of dietary fat absorption, on the pharmacokinetics of beta-carotene in healthy volunteers. J Clin Pharmacol 1996; 36: 152-9
96. Warshaw H, Franz M, Powers MA, et al. Fat replacers: their use in foods and role in diabetes medical nutrition therapy. Diabetes Care 1996; 11: 1294-300
97. Blackburn H. Olestra and the FDA. N Engl J Med 1996; 334: 984-6
98. Grundy SM, Anastasia JV, Kesaniemi YA, et al. Influence of sucrose polyester on plasma lipoproteins, and cholesterol metabolism in obese patients with and without diabetes mellitus. Am J Clin Nutr 1986; 44: 620-9
99. Glueck CJ, Jandacek R, Hogg E, et al. Sucrose polyester: substitution for dietary fats in hypocaloric diets in the treatment of familial hypercholesterolemia. Am J Clin Nutr 1983; 37: 347-54
100. Mellies MJ, Vitalie C, Jandacek RJ, et al. The substitution of sucrose polyester for dietary fat in obese, hypercholesterolemic outpatients. Am J Clin Nutr 1985; 41: 1-12
101. Glueck CH, Hastings MM, Allen C, et al. Sucrose polyester and covert caloric dilution. Am J Clin Nutr 1982; 35: 1352-9
102. Cotton JR, Westrate JA, Blundell JE. Replacement of dietary fat with sucrose polyester: effects on energy intake and appe-

© Adis International Limited. All rights reserved.

tite control in non-obese males. Am J Clin Nutr 1996; 63: 891-6
103. Cheskin LJ, Miday R, Zorich N, et al. Gastrointestinal symptoms following consumption of olestra or regular triglyceride potato chips: a controlled comparison. JAMA 1998; 279 (2): 150-2
104. Aggarwal AM, Camilleri M, Phillips SF, et al. Olestra, a nondigestible, nonabsorbable fat. Effects on gastrointestinal and colonic transit. Dig Dis Sci 1993; 38: 1009-14
105. Zorich NL, Jones MB, Kesler JM, et al. A randomized, double-blind study of the effect of olestra on disease activity in patients with quiescent inflammatory bowel disease. Olestra in IBD study group. Am J Med 1997; 103 (5): 389-99
106. Freston JW, Ahnen DJ, Czinn SJ, et al. Review and analysis of the effects of olestra, a dietary fat substitute, on gastrointestinal function and symptoms. Regul Toxicol Pharmacol 1997; 26 (2): 210-8
107. Jones DY, Koonsvitsky BP, Ebert ML, et al. Vitamin K status of free-living subjects consuming olestra. Am J Clin Nutr 1991; 53: 943-6
108. Schlagheck TG, Riccardi KA, Zorich NL, et al. Olestra dose response on fat-soluble and water-soluble nutrients in humans. J Nutrition 1997; 127 Suppl. 8: 1646S-65S
109. Koonsvitsky BP, Berry DA, Jones B, et al. Olestra affects serum concentrations of alpha-tocopherol and carotenoids but not vitamin D or vitamin K status in free-living subjects. J Nutrition 1997; 127 Suppl. 8: 1636S-45S
110. Schlagheck TG, Kesler JM, Jones MB, et al. Olestra's effect on vitamins D and E in humans can be offset by increasing dietary levels of these vitamins. J Nutrition 1997; 127 Suppl. 8: 1666S-85S
111. Jones DY, Miller KW, Koonsvistky BP, et al. Serum 25-hydroxyvitamin D concentrations of free-living subjects consuming olestra. Am J Clin Nutr 1991; 53: 1281-7
112. Fallat RW, Glueck CJ, Lutmer R, et al. Short term study of sucrose polyester a nonabsorbable fat-like material as a dietary agent for lowering plasma cholesterol. Am J Clin Nutr 1976; 29: 1204-15
113. Glueck CJ, Mattson FH, Jandacek RJ. The lowering of plasma cholesterol by sucrose polyester in subjects consuming diets with 800, 300, or less than 50mg of cholesterol per day. Am J Clin Nutr 1979; 32: 1636-44
114. Westrate JA, van het Hof KH. Sucrose polyester and plasma carotenoid concentrations in healthy subjects. Am J Clin Nutr 1995; 62: 591-7
115. Roberts RJ, Leff RD. Influence of absorbable and nonabsorbable lipids and lipid like substances on drug bioavailability. Clin Pharmacol Ther 1989; 45: 299-304
116. Miller KW, Williams DS, Carter SB, et al. The effect of olestra on systemic levels of oral contraceptives. Clin Pharmacol Ther 1990; 48: 34-40
117. Leibowitz SF. Brain peptides and obesity: pharmacologic treatment. Obes Res 1995; 3 Suppl. 4: 573S-89S
118. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372: 425-32
119. Auwerx J, Staels B. Leptin. Lancet 1998; 351: 737-42
120. Bray GA. Leptin and leptinomania. Lancet 1996; 348: 140-1
121. Caro JF, Sinha MK, Kolaczynski JW, et al. Leptin: the tale of an obesity gene. Diabetes 1996; 45: 1455-62
122. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996; 334: 292-5
123. Caro JF, Kolaczynski JW, Nyce MR, et al. Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. Lancet 1996; 348: 159-61
124. Widjaja A, Stratton IM, Horn R, et al. UKPDS 20: plasma leptin, obesity, and plasma insulin in type 2 diabetic subjects. J Clin Endocrinol Metab 1997; 82: 654-7
125. Nolan JJ, Olefsky JM, Nyce MR, et al. Effect of troglitazone on leptin production. Studies *in vitro* and in human subjects. Diabetes 1996; 45: 1276-8

Correspondence and reprints: Dr *Peter J. Carek*, Department of Family Medicine, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425, USA.
E-mail: carekpj@smtpgw2.musc.edu

© Adis International Limited. All rights reserved.