

Anti-obesity drugs

Guidance on appropriate prescribing and management

A report of the Nutrition Committee of the
Royal College of Physicians of London

April 2003

ROYAL COLLEGE OF PHYSICIANS OF LONDON
11 St Andrews Place, London NW1 4LE

Registered Charity No 210508

Copyright © 2003 Royal College of Physicians of London

ISBN 1 86016 181 2

Front cover illustration: Merriton Sharp

Typeset by Dan-Set Graphics, Telford, Shropshire

Printed in Great Britain by Sarum ColourView Group, Salisbury, Wiltshire

Contents

Members of the Nutrition Committee	v
Summary and recommendations	vii
1 Introduction	1
Background	1
Scope and purpose of guidance	1
Levels of evidence and grades of recommendation	2
2 Non-pharmacological management of overweight and obese patients	3
Dietary intervention	3
Lifestyle intervention	3
Physical activity	3
3 Assessment	5
Clinical assessment	5
Body weight related health risk	5
Motivation to lose weight	6
Weight loss targets	6
4 Anti-obesity drug therapy	8
Rationale	8
Selection of patients	8
Management pathways and therapeutic responsiveness	9
Essential elements of a drug treatment programme	9
Types of drugs	9
Drugs acting on the gastrointestinal system: pancreatic lipase inhibitors	9
Centrally acting drugs	10
Indications for using a particular type of drug	10
Sibutramine	11
Orlistat	11
Duration of treatment	12
Phentermine and diethylpropion	12
Contraindications	12
The elderly and children	13
Monitoring and longer-term follow-up	13
Audit and outcome measures	13

Cost effectiveness	13
Longer-term anti-obesity drug treatment	13
Drugs not suitable for the treatment of overweight and obesity	14
5 Good medical practice and ethical considerations	15
Prescribing practice	15
Documentation	15
General Medical Council	15
Appendix I Prescribing information for orlistat and sibutramine	17
References	20

Members of the Nutrition Committee

PG Kopelman MD FRCP (*Chair*) Professor of Clinical Medicine, Deputy Warden, Barts and The London, Queen Mary's School of Medicine and Dentistry, University of London

WR Burnham MD FRCP, Consultant Physician and Gastroenterologist, Barking, Havering and Redbridge Hospitals NHS Trust; Chairman, Nutritional Advisory Group, Oldchurch Hospital, Romford

M Elia MD FRCP, Professor of Clinical Nutrition and Metabolism and Honorary Consultant Physician, Institute of Human Nutrition, University of Southampton and Southampton General Hospital

N Finer FRCP MB, Clinical Director, Wellcome Trust Clinical Research Facility; Honorary Consultant in Obesity, Addenbrooke's Hospital, Cambridge

THJ Goodship MD FRCP, Reader in Nephrology, University of Newcastle upon Tyne; Honorary Consultant Nephrologist, The Newcastle upon Tyne Hospitals NHS Trust

JM Graham MFCM BM, Principal Medical Officer, Department of Health, London

GKT Holmes MD FRCP, Consultant Gastroenterologist, Derbyshire Royal Infirmary, Derby

BJM Jones MD FRCP MRCS LRCP, Consultant Physician, Department of Gastroenterology, Russells Hall Hospital, Dudley

MEJ Lean MD FRCP(Edin) FRCPS(Glas), Professor of Human Nutrition, Department of Human Nutrition, University of Glasgow, Glasgow Royal Infirmary

JE Lennard-Jones MD FRCP FRCS, Emeritus Professor of Gastroenterology, University of London; Emeritus Consultant Gastroenterologist, St Mark's Hospital, London

RT Przemioslo MD MRCP, Consultant Physician, Frenchay Hospital, Bristol

A Shenkin FRCP FRCP(Glas) FRCPath, Professor of Clinical Chemistry, University of Liverpool, Liverpool

DBA Silk MD FRCP, Professor of Clinical Nutrition, Consultant Physician, Department of Gastroenterology and Nutrition, Central Middlesex Hospital, London

AF Williams FRCP FRCPCH, Senior Lecturer and Consultant Paediatrician, Department of Child Health, St George's Hospital Medical School, London

MJ Wiseman FRCP MRCS LRCP, Physician and Independent Consultant in Nutrition, Institute of Human Nutrition, University of Southampton

Summary and recommendations

- 1 Overweight and obesity are serious medical problems that affect over 55% of the adult population. Both conditions require appropriate and effective management by suitably trained members of a multidisciplinary team.
- 2 A weight loss of between 5% and 10% of the initial body weight reduces the health risks associated with obesity. The aims of treatment for overweight and obesity should be modest weight loss maintained for the long term, with treatment methods and goals being decided for each individual after careful assessment of the degree of overweight and any associated comorbid conditions.
- 3 The first-line strategy for weight loss and its maintenance is a combination of supervised diet, exercise and behaviour modification. These approaches must be pursued throughout treatment even when adjunctive therapies are used.
- 4 Anti-obesity drugs may be used in adult patients at medical risk from obesity (BMI 30 or greater), or overweight patients with established comorbidities (BMI 27) if the drug licence permits, where dietary and lifestyle modifications have been unsuccessful in achieving a 10% weight reduction after at least three months of supervised care.
- 5 Not all obese patients respond to drug therapy. An anti-obesity drug should therefore be prescribed for no longer than 12 weeks in the first instance and weight loss should then be measured. The drug treatment should be stopped in those obese patients who have not achieved a 5% weight reduction after 12 weeks of drug treatment. If a 5% weight loss is attained then the drug may be continued beyond this initial period, provided body weight is continually monitored and weight is not regained. Rapid weight regain is common after short-term use of anti-obesity drugs (12 weeks or less).
- 6 The duration of treatment with an anti-obesity drug must never exceed the time period recommended by the product licence for the drug.
- 7 Prescribers of anti-obesity drugs must be aware of their possible adverse actions. When assessing the suitability of a patient for drug treatment, it is important to consider the risk/benefit ratio, remembering that while medical benefits from moderate weight loss are high, drug therapy is not without risk.
- 8 The prescription of an anti-obesity drug should only be made in appropriate clinical settings. All obese patients receiving drug therapy should be given regular review.
- 9 There should be written notification to the patient's GP when the prescription for an anti-obesity drug is provided by another physician. There is an ethical duty to point out the

advantage of this to the patient, who should also be told of the risk of conflicting treatment or misdiagnosis when the GP is not informed.

- 10 Complaints about doctors whose practice fails to observe the guidelines set out in this report should be directed to the General Medical Council.
- 11 Investment should be made in trials of sound methodological quality conducted in a relevant local setting with patients being followed for long enough to judge the long-term effectiveness of the drug intervention.
- 12 The use of anti-obesity drugs should be closely monitored through post-marketing surveillance and the UK Yellow Card Reporting Scheme.

I Introduction

Background

1.1 Obesity is defined as a body mass index (BMI) of 30 or more, where a person's BMI is defined as their weight in kg divided by the square of their height in metres. Overweight is defined as a BMI between 25 and 29.9.* Overweight and obesity are diseases in which an excess of body fat has accumulated such that health may be adversely affected. They can cause and exacerbate many health problems, both independently and in association with other diseases. Life insurance and epidemiological studies confirm that increasing degrees of overweight and obesity are important predictors of decreased longevity. Despite this evidence, some clinicians still consider obesity to be a self-inflicted condition of little medical significance that does not warrant medical intervention, including drug therapy.²

1.2 In 1980, 6% of men and 8% of women in the UK were obese. In 2000, the respective figures had increased to 21% and 21.4%. About 55% of the adult population is overweight or obese. During the 20 years from 1980, self-reported energy intake has changed little. However, changes in diet to a lower proportion of energy from carbohydrates and a higher proportion from fats have occurred, making it easier to eat an energy-dense diet. These dietary changes, coupled with a marked decline in physical activity, increase the risk of obesity.^{2,3}

Scope and purpose of guidance

1.3 The Royal College of Physicians of London published its first report on the appropriate use of anti-obesity drugs in 1997 after discussions with the Department of Health, the Medicines Control Agency (MCA) and the General Medical Council (GMC). After the publication of that report, new information became available about two of the drugs detailed in the report that resulted in the manufacturer withdrawing them from clinical practice. The second report, published in 1998, built on the general recommendations included in the previous report and included new information about appropriate prescribing.⁴ The working party that drew up the recommendations emphasised the continuing need for information about drug prescription to be reviewed: this is the objective for this third report. The guidance is intended to provide clarity about the rationale for appropriate prescribing of an anti-obesity drug in the light of advice from the GMC and guidance documents from the National Institute for Clinical Excellence (NICE). NICE has undertaken a detailed, evidence-based evaluation of the health benefits, costs and risks of specific drugs for the treatment of obesity, and the present guidance should be read in conjunction with the relevant NICE publications.^{5,6}

*BMI cut-off values are ethnic-dependent and appear to be lower in certain populations: a BMI of 27.5 or greater in an Asian patient is associated with comparable morbidities to those seen in a Caucasian patient with a BMI of 30.¹

Levels of evidence and grades of recommendations

1.4 The evidence provided for guidance shown in Tables 1 and 2 is drawn from previous systematic reviews listed in the references, and the revised grading system is from the Scottish Intercollegiate Guidelines Network (SIGN).⁷

Table 1 Levels of evidence from SIGN 50: a guideline developer's handbook⁷

1⁺⁺	High quality meta-analyses, systematic reviews of randomised control trials (RCTs), or RCTs with a very low risk of bias
1⁺	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1⁻	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2⁺⁺	High quality systematic reviews of case-control or cohort studies
2⁺	High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2⁻	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Table 2 Grades of recommendation

A	At least one meta-analysis, systematic review, or RCT rated as 1 ⁺⁺ , and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1 ⁺ , directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2 ⁺⁺ , directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1 ⁺⁺ , or 1 ⁺
C	A body of evidence including studies rated as 2 ⁺ , directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2 ⁺⁺
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2 ⁺

1.5 We have also included a grade to show best practice points as follows:

RBP	Recommended best practice based on the clinical experience of the SIGN guideline development group ⁷
------------	---

2 Non-pharmacological management of overweight and obese patients

2.1 The primary intervention for the management of overweight and obesity is a combination of dietary restriction and lifestyle change (RBP).^{4,8-17}

Dietary intervention

2.2 Understanding of the role played by energy intake in the aetiology of obesity is confounded by failure to report food intake accurately. Under-reporting is widely recognised as a feature of obesity, with comparisons of energy intake and expenditure showing a consistent shortfall in self-reported food intake of approximately 30% of energy requirements. An initial assessment of any patient with a weight problem must therefore include a dietary review and appropriate dietary advice.

2.3 Control of diet is the cornerstone of the management of overweight and obese patients and its importance must be emphasised. Long-term changes in food choices, eating behaviour and lifestyle are needed, rather than a temporary restriction of specific foods. The treatment should be nutritionally sound and aim to promote a healthier diet while moderating energy intake and increasing physical activity [1⁺⁺].^{8,10,11,13-15}

Lifestyle intervention

2.4 Behavioural interventions use strategies to facilitate change in an individual's lifestyle. Behavioural weight control programmes encourage patients to become more aware of their eating and physical activity, focusing on changing the lifestyle and environmental factors that are controlling behaviour. The key difference between behavioural methods and other forms of treatment for obesity is that they lay particular emphasis on personal responsibility for initiating and maintaining treatment rather than relying on external forces [1⁺].^{8-12,14,15,17}

Physical activity

2.5 The most variable component of energy expenditure is physical activity, representing 20–50% of total energy expenditure, so an analysis of physical activity of an individual should be a critical element of any therapeutic assessment. Cross-cultural studies of physical activity and BMI demonstrate a sevenfold increased risk of overweight (BMI >25) in those with a low physical activity ratio (total energy expenditure/resting metabolic rate (RMR)). Thus, the primary intervention for overweight and obesity should also emphasise the need for an increase in regular physical activity.^{8,9,14,15,17}

2.6 When physical activity is used in the treatment of obesity, weight losses are modest and average 2–3 kg. For any given weight loss, fat-free mass (FFM) is better preserved in exercising than non-exercising subjects. This is important because FFM is the best predictor of resting

metabolic rate which is the largest contributor to daily energy expenditure. Regular physical activity has other important physiological benefits that include reducing blood pressure, improving atherogenic lipid profiles and improving glucose tolerance [1⁺]. These are substantial benefits which should be emphasised to all patients; persuading an obese person to participate in regular physical activity is not easy [A]. It is unnecessary for the obese patient to exercise strenuously to derive benefit – improved fitness is achieved with less vigorous exercise such as walking increased distances and swimming [A]. Continuation of physical activity for at least two years from the start of the weight loss intervention is associated with enhanced maintenance of the lost weight [B].^{9,12,14–16}

3 Assessment

Clinical assessment

3.1 An outline of the requirements for a clinical assessment of an overweight or obese patient is given in Box 1 [RBP]. Height should be measured accurately using a stadiometer, and weight measured by accurate scales calibrated against known weights. Fat distribution is assessed by measurement of the waist circumference and should be used to refine an assessment of risk for patients with a BMI of 25 to 34.9.¹⁴ Waist circumference is taken as the mid-point between the lower rib margin and the iliac crest. The neck circumference should be measured – a circumference of 43 cm (17 inches) or more indicates a likelihood of obstructive sleep apnoea. The results of all these assessments should be properly documented.

Box 1 The clinical assessment of an overweight or obese patient

Take measurements of:

- height and weight: calculate BMI
- waist circumference
- neck circumference
- blood pressure and resting pulse rate

Check for:

- any evidence of cardiac valvular disease
- any evidence of pulmonary hypertension, cor pulmonale or congestive cardiac failure
- signs of dyslipidaemia
- signs of thyroid disease
- ophthalmic evidence for sustained hypertension or diabetic retinopathy in a diabetic patient
- any evidence of diabetes mellitus

3.2 Measurements of the resting pulse rate and blood pressure are important. Skin should be examined for any sign of acanthosis nigricans (pigmented, 'velvety', skin creases especially in the axillae and/or neck) which suggests insulin resistance. Moderate hirsutism and/or severe acne in women may indicate the polycystic ovary syndrome. Gastrointestinal reflux is a common cause of symptoms which may include persistent cough in an obese patient.

Body weight related health risk

3.3 An estimation of an obese patient's absolute risk status requires an assessment of associated disease conditions [RBP], for example:

- ▶ established coronary heart disease (CHD)
- ▶ other atherosclerotic diseases
- ▶ type 2 diabetes
- ▶ sleep apnoea
- ▶ gynaecological abnormalities
- ▶ osteoarthritis
- ▶ gallstones
- ▶ stress incontinence

It is important to document whether the patient has some or all of the characteristic features of the metabolic syndrome (insulin resistance syndrome), such as upper body obesity, hypertension, type 2 diabetes, CHD and dyslipidaemia.

3.4 Patients are classified as being at high absolute risk if they have three of the cardiovascular risk factors listed in Box 2. Such patients usually require specific management of the risk factors.

Box 2 Cardiovascular risk factors

- | | |
|---|--|
| • Cigarette smoking | • Low high-density lipoprotein (HDL) cholesterol (<1 mmol/l) |
| • Hypertension | • Impaired fasting blood glucose |
| • High-risk low-density lipoprotein (LDL) cholesterol (>4 mmol/l) | • Family history of premature CHD |

Motivation to lose weight

3.5 Not all patients are prepared to lose weight despite a referral or an opportunistic intervention by a medical practitioner. Furthermore, patients may see the prescription of an anti-obesity drug as an alternative to lifestyle change that absolves them of a need to undertake dietary restriction and increased physical activity. As a consequence, it is often useful to consider a patient's 'readiness to change' to confirm that a patient understands the need for weight loss, and is prepared to follow medical advice to achieve and maintain an agreed weight goal [RBP].^{9,11,12,14}

Weight loss targets

3.6 The success or failure of a treatment programme is usually judged by an arbitrarily chosen target weight loss. This may be based upon rates of weight loss or an absolute and/or relative weight loss. Assessment of success must take account of the age of the patient, the initial degree of overweight or obesity, the presence of indicators of associated risk or complications, and previous attempts at weight control.

3.7 Weight loss goals for overweight and obese patients should be tailored to the individual. A weight loss of 5% of the initial body weight will result in some improvement, while a loss of

10% is of major benefit, with clinically useful changes such as lowered blood pressure, reduction in plasma total cholesterol and triglycerides, an increase in HDL cholesterol and a significant improvement in diabetic control [1⁻]. The primary goal of treatment for patients treated with an anti-obesity drug should therefore be a 10% reduction from the initial weight, with consequential amelioration of many of the associated risk factors. Nevertheless, weight loss should be approached incrementally with new weight loss goals negotiated with the patient once the original target has been achieved [B].^{2,9,14}

3.8 After an initial period of relatively rapid weight reduction, an average continuing weight loss of anything up to 1 kg per week should be considered as acceptable [B/C].

3.9 The management of overweight and obesity should not replace the need to treat, where indicated, other diseases or risks (such as type 2 diabetes, dyslipidaemia), even though weight loss may reduce or obviate need for such treatment.^{9,14,17}

4 Anti-obesity drug therapy

Rationale

4.1 Obesity is not a single disorder but a heterogeneous group of conditions with multiple causes. Although genetic differences are undoubtedly important, the marked rise in the prevalence of obesity is best explained by behavioural and environmental changes that have resulted from technological advances. In such circumstances, it is appropriate to consider pharmacological treatment as an *adjunct* to the other treatment modalities.

4.2 Current drug treatment of obesity is directed at reducing energy/food intake either by an action on the gastrointestinal system or via an action through the central nervous system control of appetite and feeding. Before prescribing a drug, a clinician must firstly assess whether the patient understands the purpose of the drug treatment (in combination with lifestyle change to improve health status) and how it works, and secondly, assess the likely outcome of treatment. The clinician should ensure that there are no medical or psychiatric contraindications to drug therapy. This requires an appropriate documented clinical assessment of the patient (see Chapter 3).

4.3 It is important that doctors who prescribe such drugs are fully familiar with either the primary literature or an authoritative summary, such as this report.

Selection of patients

4.4 The accepted first-line strategy for weight reduction and weight maintenance is a combination of diet, exercise and behaviour modification, lasting at least three months [RBP] (see Chapter 2). Exceptionally, this period may be shortened if the clinician judges that drug treatment is justified at an earlier stage due to overriding medical circumstances.

4.5 Box 3 lists the criteria that should be applied to judge the suitability of a patient for drug treatment. The criteria for using an anti-obesity drug are similar to those applied to the treatment of other relapsing disorders. It is important to avoid offering anti-obesity drug therapy to patients who are seeking a 'quick fix' for their weight problem. The initiation of drug treatment will depend on the clinician's judgement about the risks to an individual from continuing obesity. It may be appropriate after at least three months of supervised diet, exercise and behavioural management, or at a subsequent review, if a patient's BMI is equal to or greater than 30 and weight loss is less than 10% of the presenting weight [C]. In certain clinical circumstances, it may also be appropriate to consider anti-obesity drug treatment for those patients with established comorbidities whose BMI is 27 or more if this is permitted by the drug's licence [C]. An anti-obesity drug should not be prescribed for a patient whose BMI is less than that specified in the product licence for the drug – the licence indication does not presently take account of the morbidity from obesity seen in certain populations at a lower BMI.^{4,9,13,18,19}

Box 3 Criteria for selecting obese patients suitable for anti-obesity drug therapy

- Drug treatment may be appropriate where diet and exercise have not achieved acceptable weight loss relative to associated medical risk.
- In such patients, drug treatment may be appropriate for
 - those whose BMI is ≥ 30
 - those with established comorbidities whose BMI is ≥ 27 , if the drug licence permits.
- Weight lowering drugs should be targeted at those at high risk from obesity, not at obesity alone.

The following groups should have priority for drug treatment:

- Patients with established comorbidities such as type 2 diabetes, hypertension, dyslipidaemia
- Patients who are physically restricted by their weight either because of breathlessness or arthritis
- Patients considered to be at high risk – for example, those with family histories of overweight or obese parents who died prematurely from CHD or developed type 2 diabetes with complications.

Management pathways and therapeutic responsiveness

4.6 Figure 1 (overleaf) shows a management pathway for the appropriate prescription of an anti-obesity drug.

4.7 The experience from the use of anti-obesity drugs during 12–24 month randomised controlled trials indicates that approximately 50% of the actively treated patients respond, as judged by a 5–10% reduction in body weight maintained over 12 months [2⁺⁺]. The weight loss occurs in the ‘responder’ group within 12 weeks. This indicates a suitable time period when a response to drug treatment can be identified and a decision taken on whether to continue the medication. If the drug is efficacious in helping a patient to lose and/or maintain weight loss, and there are no serious side effects, it may be continued. If not, it should be discontinued [B]. Once a weight loss target has been achieved, there should be an opportunity for re-negotiation of a new target, if indicated, and/or long-term monitoring with reinforcement. Continuing assessment of drug therapy for efficacy and safety is essential throughout treatment.^{4–6,9,13,18,19}

Essential elements of a drug treatment programme

4.8 Any centre that claims to provide specific expertise in weight management should include in its practice all the elements outlined in Box 4 (p. 11) [RBP].

Types of drugs

4.9 There are currently two categories of anti-obesity drugs – those that act on the gastrointestinal system (pancreatic lipase inhibitors), and those that act on the central nervous system to primarily suppress appetite.

Drugs acting on the gastrointestinal system: pancreatic lipase inhibitors

4.10 Orlistat inhibits pancreatic and gastric lipase thereby decreasing ingested triglyceride hydrolysis. It produces a dose-dependent reduction in dietary fat absorption thereby leading to weight loss in obese subjects.

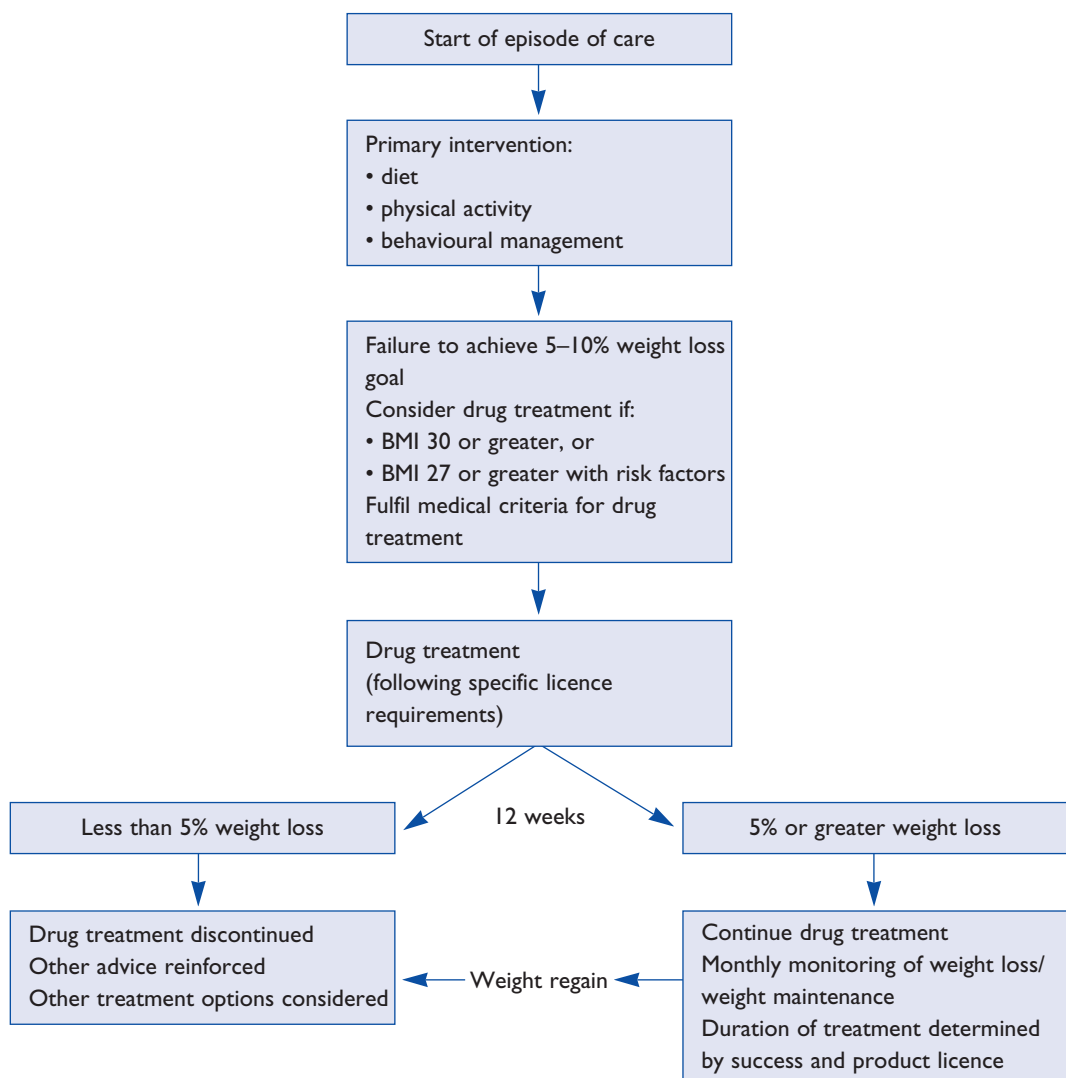


Fig 1 A management pathway for the appropriate prescription of an anti-obesity drug

Centrally acting drugs

4.11 Sibutramine promotes a sense of satiety through its central action as a serotonin and norepinephrine re-uptake inhibitor. In addition, it may mitigate against the fall in thermogenesis through stimulation of peripheral norepinephrine receptors.

4.12 Prescribing information for orlistat and sibutramine is given in Appendix 1.

Indications for using a particular type of drug

4.13 No good clinical studies have directly evaluated sibutramine against orlistat, or explored which particular patients will benefit more from one drug than the other. Clinicians need to make a judgement on the basis of clinical experience, although there are some pointers related to the particular pharmacological actions of the compound.^{5,6,18,19} They should always refer to the specific licence requirements for the particular drug.

Box 4 Essential elements of an appropriate setting for anti-obesity drug treatment

- Trained staff directly involved in the running of the weight loss programme. These staff (medical, nursing and other healthcare professionals) should have attended courses on the management of obesity and must be given the opportunity to continue their education.
- A printed programme for weight management that includes clear advice on diet, behavioural modification techniques, physical exercise and strategies for long-term lifestyle change. Such a programme may include a family and/or group approach.
- Suitable equipment, in particular accurate and regularly calibrated weighing scales and stadiometer.
- Specified weight loss goals for patients with energy deficits being achieved by moderating food intake and increasing physical expenditure.
- Documentation of individual patients' health risks. This will include BMI, waist circumference, blood pressure, blood lipids, cigarette smoking and comorbid conditions.
- A clearly defined follow-up procedure which involves collaboration between the different settings of care, and provides regular monitoring and documentation of progress, along with details of criteria for judging the success of weight loss. This will allow a weight loss programme to be properly supported, medical conditions to be monitored and problems or issues to be addressed at the earliest opportunity. It is also advisable to have a checklist of possible adverse drug effects, eg anxiety, disturbances of sleep, breathlessness, depression and diarrhoea.

Sibutramine

4.14 The following groups of patients may be suitable for sibutramine [D]:

- ▶ Those whose appetites and eating habits are uncontrollable
- ▶ Frequent snackers
- ▶ Nocturnal eaters
- ▶ Those who need immediate weight loss for medical reasons
- ▶ Patients with low HDL cholesterol values
- ▶ Those with no contraindications to the use of sibutramine (specifically cardiac abnormalities or an elevated blood pressure, ie >140/90 mmHg on repeated measurements).

4.15 Sibutramine should be discontinued if the resting pulse rate is increased to more than 10 beats per minute and the blood pressure exceeds 145/95 mmHg.

Orlistat

4.16 The following patients may be suitable for orlistat [D]:

- ▶ Those who have lost at least 2.5 kg in weight prior to consideration of drug treatment
- ▶ Patients requiring longer-term behavioural change

- ▶ Patients in whom a dietary assessment suggests high fat intake
- ▶ Patients with elevated LDL cholesterol values
- ▶ Patients with impaired glucose tolerance
- ▶ Patients who have repeatedly lost weight in the short-term and then rapidly regained it
- ▶ Those with an ability to adhere to a low fat diet for the longer term.

Duration of treatment

4.17 The duration of treatment should not exceed the period indicated by the product licence.^{5,6} The product licence for sibutramine advises that treatment should be continued beyond four weeks only if the patient has lost 2 kg or more.

4.18 The prescription for both sibutramine and orlistat may be continued beyond three months if a patient has lost at least 5% of their body weight from the start of drug treatment. The drug should be stopped thereafter if weight regain occurs despite continuation of the treatment.

Phentermine and diethylpropion

4.19 On 26 November 2002, the European Court of First Instance annulled previous European Commission decisions (2000) to withdraw the licences (Marketing Authorisations) for two anorectic agents. In accordance with this, the Medicines Control Agency has reinstated the relevant marketing authorisations for diethylpropion and phentermine, which can now be prescribed.²⁰

4.20 This decision related to a long-standing legal action and was not based upon either new safety or new efficacy information relating to these anorectic agents. Both drugs were evaluated and originally licensed by criteria less stringent than have been required since 1997 by both the EU Committee for Proprietary Medicinal Products and the US Food and Drugs Administration. Published evidence of the use of phentermine and diethylpropion indicates short-term induction of weight loss that is frequently followed by weight regain on cessation of the drug. There are no recent published randomised controlled trials of the drugs demonstrating efficacy beyond 26 weeks. Both drugs remain restricted to three months use in the terms of their product licences.

4.21 In the absence of new information about their longer-term efficacy and safety, phentermine and diethylpropion cannot be advocated as part of a structured management programme for overweight and obese patients.

Contraindications

4.22 Centrally acting drugs are not recommended for patients who are concurrently taking other selective serotonin re-uptake inhibitors. It is therefore crucial to confirm that such drugs have not already been prescribed. It is probably also unwise to co-prescribe with tricyclic antidepressants, monamine oxidase inhibitors and lithium, all of which may potentiate the central effects of serotonin with adverse results.

4.23 Combination therapy with anti-obesity drugs is contraindicated because of the absence of evidence for synergy between the two drugs, and lack of information about safety.

The elderly and children

4.24 There is limited information about the use of anti-obesity drugs in patients over the age of 75 years. For that age group, the accepted practice is to aim for weight maintenance rather than weight loss. Neither sibutramine nor orlistat is licensed for use in children.

Monitoring and longer-term follow-up

4.25 Patients prescribed anti-obesity drugs require the following [RBP]:

- ▶ Monitoring of weight (ideally monthly – not less than two monthly)
- ▶ Monitoring of pulse rate and blood pressure
- ▶ Monitoring of obesity-related risks and diseases (eg dyslipidaemia, type 2 diabetes)
- ▶ A record of their treatment plan which should be incorporated into local audit data recording systems
- ▶ As weight loss progresses, possible adjustments of medications taken by the patient for obesity-related or obesity-responsive diseases and risks. For example, the dose of an oral hypoglycaemic agent may need to be reduced as insulin sensitivity increases with weight loss.

4.26 Once the drug has been discontinued, patients should be monitored for at least a further six months in order to discourage weight regain. Weight loss during treatment with an anti-obesity drug is usually regained over time following cessation of treatment but typically at a slower rate than that experienced during weight loss.

Audit and outcome measures

4.27 Table 3 (overleaf) lists the measures that may be used to judge the success or otherwise of an anti-obesity drug [RBP]. Ultimately, the success of anti-obesity drugs must be judged by a reduction in outcome measures that include myocardial infarction, cerebrovascular accidents, physical disability and death.

Cost effectiveness

4.28 Calculations made for the National Institute for Clinical Effectiveness (NICE) on the cost effectiveness of current anti-obesity drugs suggest a figure of £15,000–30,000 (\$/Euro 22,500–45,000) per Quality Adjusted Life Year (QALY) gained.^{5,6}

Longer-term anti-obesity drug treatment (over two years)

4.29 At the present time, the benefits from longer-term drug therapy are merely expectations derived from epidemiological data and observed changes in surrogate end-points such as lipids, blood pressure and diabetic status. There are no hard data related to defined outcomes, including a reduction in early mortality, because of the absence of clinical trials that extend beyond two years. It is important to bear this in mind when considering long-term drug therapy for a patient.

Table 3 Process measures to judge the success of anti-obesity drug treatment

Measures	Immediate benefits	Longer-term benefits
Physical measures	Weight loss Reduction in waist circumference Improvement in comorbidities	Reduced breathlessness Decreased sleep apnoea Reduced angina Reduced blood pressure
Metabolic measures	Decreased fasting blood glucose and plasma insulin Improvement in fasting lipid profile Decreased HbA1c (if diabetic)	Reduction in doses of concomitant medications
Functional measures	Increased mobility Decreased symptoms Improved well being and mood Improved health-related quality of life	Reduced time away from work Increased involvement in social activities Decreased number of consultations with health professionals

Drugs not suitable for the management of overweight and obesity

4.30 There is no published evidence to suggest that bulk forming agents (eg methyl cellulose) have any beneficial long-term action for weight reduction:

- ▶ Diuretics, human chorionic gonadotrophin (HCG), amphetamine, dexamphetamine and thyroxine are **not** treatments for obesity and **should not** be used to achieve weight loss.
- ▶ Under no circumstance should thyroxine be prescribed for obesity in the absence of biochemically proven hypothyroidism.
- ▶ Metformin and acarbose may be useful in the management of the obese non-insulin-dependent diabetic patient: they have no proven efficacy for obesity alone and are not licensed for such use.

5 Good medical practice and ethical considerations

Prescribing practice

5.1 Due to the need to monitor carefully the effect of drugs used for the management of obesity, it is mandatory, in the opinion of the Royal College of Physicians, that equal care is taken in prescribing such drugs within and outside the NHS. The reasons for this are:

- ▶ to ensure patients are not exposed to drug therapies for excessive duration without benefit being clearly demonstrated
- ▶ to avert the possibility that patients may inappropriately seek continuous treatment by using different sources for prescriptions or, indeed, receive multiple prescriptions for the same drug thereby leading to overdose
- ▶ to ensure coordination of reporting of adverse reactions. The principal means for reporting adverse drug reactions in the UK is through the Yellow Card Reporting Scheme. It is of critical importance that healthcare professionals report suspected adverse reactions to any anti-obesity drug through this Scheme.

Documentation

5.2 In order to reinforce good prescribing practice in all settings, clear documentation is required at every stage:

- ▶ Prescribers should regularly document the issue of prescriptions to identify misuse, poor compliance or unduly protracted therapy.
- ▶ There should be clear documentation in the case notes detailing, with dates, previous treatment with an anti-obesity drug.
- ▶ There should be written notification to the patient's general practitioner (GP), if the prescription is initiated by another physician, which details the reasons for treatment, the dose and its intended duration, and alerts the doctor to possible untoward effects. The letter should also include details of the proposed follow-up, and subsequent correspondence should include further information about progress.

General Medical Council

5.3 Such documentation is in line with the recommendations of the General Medical Council's standards for good practice. The principles of good practice and care include advice that doctors must prescribe only the treatment, drugs or appliances that serve the patient's needs.²¹

5.4 There is an ethical duty to point out the advantages to a patient of their GP being informed, and the risk of conflicting treatment or misdiagnosis when the GP is uninformed. It must be emphasised that it is the responsibility of the doctor treating the obesity to make the GP or other doctor involved in the care of the patient fully cognisant of details of management.

5.5 Where patients do not wish their GP to be informed, or do not have a GP, the doctor must take responsibility for providing all necessary after-care for the patient and, if an anti-obesity drug is proposed, ensuring that the patient is not suffering from any medical condition or receiving any other medication which would make the prescription of such a drug unsuitable or dangerous.

5.6 Complaints about doctors whose practice fails to observe this guidance should be directed to the General Medical Council. Complaints may be made by anybody including, but not restricted to, the affected patient.

APPENDIX I Prescribing information for orlistat and sibutramine

The information below has been taken from British National Formulary (BNF) No 44 (September 2002) which should be consulted for further information. The BNF is published each March and September and the latest edition should be consulted for up-to-date advice. The following information is reproduced with permission from BNF No 44 © 2002 British Medical Association and the Royal Pharmaceutical Society of Great Britain.

ORLISTAT

Orlistat, a pancreatic lipase inhibitor, reduces the absorption of dietary fat. It is used in conjunction with a mildly hypocaloric diet in individuals with a body mass index (BMI) of 30 kg/m² or more *or* in individuals with a BMI of 28 kg/m² in the presence of other risk factors such as type 2 diabetes, hypertension, or hypercholesterolaemia.

Some of the weight loss in those taking orlistat probably results from individuals reducing their fat intake to avoid severe gastrointestinal effects including steatorrhoea. Vitamin supplementation (especially of vitamin D) may be considered if there is concern about deficiency of fat-soluble vitamins. Orlistat is not licensed for use longer than 2 years because there is insufficient experience beyond this period. However, on stopping orlistat, there may be a gradual reversal of weight loss.

Indications: adjunct in obesity.

Cautions: diabetes mellitus may impair absorption of fat-soluble vitamins.

If a multivitamin supplement is required, it should be taken at least 2 hours after orlistat dose or at bedtime.

Contraindications: chronic malabsorption syndrome; cholestasis; pregnancy and breast-feeding.

Side effects: liquid oily stools, faecal urgency, flatulence, less frequently abdominal and rectal pain (gastrointestinal effects minimised by reduced fat diet); headache, menstrual irregularities; anxiety, fatigue; rarely hepatitis.

Dose: 120 mg taken immediately before, during, or up to 1 hour after each main meal (up to max 360 mg daily); max period of treatment 2 years; CHILD not recommended.

Note: if a meal is missed or contains no fat, the dose of orlistat should be omitted.

NICE guidance for orlistat

The National Institute for Clinical Excellence has recommended that orlistat should be prescribed under the following conditions:

- ▶ only for individuals who have lost at least 2.5 kg body weight by dietary control and increased physical activity in the preceding month
- ▶ only for individuals aged between 18 and 75 years
- ▶ arrangements should exist for primary care staff (mostly practice nurses) supported by community dietitians to offer specific advice, support and counselling on diet, physical activity, and behavioural strategies to those receiving orlistat
- ▶ treatment should continue beyond 3 months only if weight loss is greater than 5% from start of treatment
- ▶ treatment should continue beyond 6 months only if weight loss is greater than 10% from start of treatment
- ▶ treatment should not usually continue beyond 1 year and never beyond 2 years.

SIBUTRAMINE HYDROCHLORIDE

Sibutramine inhibits the re-uptake of noradrenaline and serotonin. It is used in the adjunctive management of obesity in individuals with a body mass index (BMI) of 30 kg/m² or more (and no associated comorbidity) *or* in individuals with a BMI of 27 kg/m² or more in the presence of other risk factors such as type 2 diabetes or hypercholesterolaemia. Sibutramine is not licensed for use longer than 1 year. On stopping it, there may be a reversal of weight loss.

Indications: adjunct in obesity.

Cautions: monitor blood pressure and pulse rate (every 2 weeks for first 3 months *then* monthly for 3 months *then* at least every 3 months) – discontinue if blood pressure or pulse rate raised at two consecutive visits; sleep apnoea syndrome (increased risk of hypertension); epilepsy; hepatic impairment (avoid if severe); renal impairment (avoid if severe); monitor for pulmonary hypertension; family history of motor or vocal tics.

Duration of treatment: discontinue treatment if:

- ▶ weight loss after 3 months less than 5% of initial body weight
- ▶ weight loss stabilises at less than 5% of initial body weight
- ▶ individuals regain 3 kg or more after previous weight loss.

In individuals with comorbid conditions, treatment should be continued only if weight loss is associated with other clinical benefits.

Contraindications: history of major eating disorders; psychiatric illness, Tourette's syndrome; history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmias, and of cerebrovascular disease; uncontrolled hypertension; hyperthyroidism; prostatic hypertrophy; phaeochromocytoma; angle closure glaucoma; history of drug or alcohol abuse; pregnancy; breast-feeding.

Side effects: most commonly constipation, anorexia, dry mouth, insomnia; also nausea, tachycardia, palpitations, hypertension, vasodilation, light-headedness, paraesthesia, headache, anxiety, sweating, taste disturbance; rarely, blurred vision.

Dose: initially 10 mg daily in the morning, increased if weight loss less than 2 kg after 4 weeks to 15 mg daily; discontinue if weight loss less than 2 kg after 4 weeks at higher dose (see also Duration of treatment above); max period of treatment 1 year; CHILD, ADOLESCENT under 18 years, and ELDERLY over 65 years: not recommended.

NICE guidance for sibutramine

The National Institute for Clinical Excellence has recommended that sibutramine should be prescribed in accordance with the summary of product characteristics and under the following conditions:

- ▶ it should be prescribed only for individuals who have seriously attempted to lose weight by diet, exercise, and other behavioural modification
- ▶ arrangements should exist for appropriate healthcare professionals to offer specific advice, support and counselling on diet, physical activities and behavioural strategies to those receiving sibutramine.

References

- 1 Choo V. WHO reassesses appropriate body mass index for Asian population. *Lancet* 2002;**360**:235.
- 2 Kopelman PG. Obesity as a medical problem. *Nature* 2000;**404**:635–43.
- 3 Joint Health Survey (on behalf of the Department of Health). Health Survey for England, 2001 – available from www.doh.gov.uk/stats/tables/trendtab06.xls
- 4 Royal College of Physicians of London. *Clinical management of overweight and obese patients with particular reference to the use of drugs*. London: RCP, 1998.
- 5 National Institute for Clinical Excellence (NICE). *Guidance on the use of orlistat for the treatment of obesity in adults* (March 2001). www.nice.org.uk
- 6 National Institute for Clinical Excellence (NICE). *Guidance on the use of sibutramine for the treatment of obesity in adults* (October 2001). www.nice.org.uk
- 7 Scottish Intercollegiate Guidelines Network (SIGN). *SIGN 50: a guideline developers' handbook*. Edinburgh: SIGN, April 2002.
- 8 US Department of Health and Health Sciences (Public Health Sciences). *Physical activity and health: a report of the Surgeon General (Executive Summary)*. Pittsburgh: Superintendent of Documents, 1996.
- 9 National Institutes of Health (NIH), National Heart, Lung and Blood Institute (NHLBI). *Clinical guidelines on the identification, evaluation and treatment of overweight and obesity: the evidence report*. Washington: US Government Press, 1998.
- 10 Executive summary of the clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults. *Arch Intern Med* 1998;**158**:1855–67.
- 11 National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity and health risk. *Arch Intern Med* 2000;**160**:898–904.
- 12 National Task Force on the Prevention and Treatment of Obesity. Medical care for obese patients: advice for health care professionals. *Am Fam Physician* 2002;**65**:81–8.
- 13 National Task Force on the Prevention and Treatment of Obesity. Long-term pharmacotherapy in the management of obesity. *JAMA* 1996;**276**:1907–15.
- 14 Scottish Intercollegiate Guidelines Network (SIGN). *Integrating prevention with weight management*. Edinburgh: SIGN, 1996.
- 15 Harvey EL, Glenny AM, Kirk SF, Summerbell CD. A systematic review of interventions to improve health professionals' management of obesity. *Int J Obes* 1999;**23**:1213–22.
- 16 Douketis JD, Feightner JW, Attia J, Feldman WF. Periodic health examination, 1999 update: 1. Detection, prevention and treatment of obesity. Canadian Task Force on Preventive Health Care. *CMAJ* 1999;**160**:513–25.
- 17 NHS Centre for Reviews and Dissemination. University of York. Prevention and treatment of obesity. *Eff Health Care* 1997;**3**:1–12.
- 18 Haddock CK, Poston WSC, Dill PL, Foreyt JP, Ericsson M. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomised clinical trials. *Int J Obes* 2002;**26**:262–73.

- 19 Committee on Nutrition, Massachusetts Medical Society. *Obesity treatment using drug therapy*, White Paper. Waltham MA: The Massachusetts Medical Society, 1998.
- 20 Medicines Control Agency statement on European legal action relating to anorectic agents.
www.mca.gov.uk/whatsnew/whatsnew_2002.htm#2002
- 21 General Medical Council. *Good Medical Practice*. London: GMC, 2001.