The place of drug treatment in obesity

Julian Barth

ARTICLE POINTS

1 The NSF for Diabetes: Delivery Strategy

2 It is essential that a full history of all previous attempts to lose weight is explored including diets, attendance at slimming clubs, exercise and reason for failure of previous attempts.

3 The key to pharmacotherapy is in the timing; the maximal weight loss is in the first few months of a therapeutic programme.

4 Maintenance of the weight that has been lost should be considered as important as actual loss; orlistat and sibutramine are effective for both primary weight loss and in maintaining loss achieved by earlier dieting.

5 The use of drugs to achieve weight loss should be carefully monitored and the risk-benefit ratio assessed in each individual.

KEY WORDS

- **Obesity**
- **Weight loss**
- **Pharmacotherapy**
- **Realistic goals**
- **Exercise and diet**

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Introduction

The traditional approach to weight management was: firstly, to recognise obesity; secondly, to identify the ideal body weight; and then to offer a prescription for an 800 kcal/day diet. Following a period of time it was customary to castigate the person as a failure and await the development of the co-morbidities. This is clearly a recipe for disaster. The NSF for Diabetes: Delivery Strategy (2002) has defined obesity as the most significant modifiable risk factor for type 2 diabetes, therefore action to reduce overweight and obesity will need to be central to local prevention strategies (Section 1.3).

It is argued that most of the management of obesity should lie within the realms of public health and management of the environment by food, public transport and leisure activity policies. However, this is in the power of government and there is still the need for healthcare professionals to help the 20% of the UK population who are currently obese (BMI>30). In an average practice of 2000 people, it is likely that 400 of them are obese. So what is the best approach and which modality should be used?

Why should the obese lose weight?

Most people who present to their GP for help with weight loss have unrealistic expectations and are hoping for a 'magic potion' which will give them the figure of their dreams. However, they should be educated about the benefits of a 10% loss in body weight. This will not be sufficient to remodel their physique, but if maintained for 10 years will be balanced by a 20–25% fall in total mortality, 30–40% fall in diabetes-related deaths and 40–50% fall in cancer-related deaths. Moreover, there are improvements in easily measurable surrogate markers of cardiovascular disease, such as reductions in lipid levels, HbA_{1c} and blood pressure.

Before starting drug treatment

Most patients will be aware that they are overweight and will either need to be persuaded of the benefits of weight loss or will need to be encouraged to try again. Many will already have already tried dieting and may be convinced of their inability to achieve any success with this method. Primarily, it is important to establish the reason why individuals wish to lose weight and determine what attempts have been made and (possibly more importantly) the reasons for their failure.

The ultimate aim of all obesity treatments for the physician is long-term weight loss. The average patient, on the other hand, can only visualise a short-term future. They may already be convinced that the only way forward can be through treatment with drugs. Whilst it is likely that treatment with anti-obesity medications may produce some weight loss when used in isolation, all the clinical trial data supports the notion that long-term results can only be achieved when pharmacotherapy is used in combination with other modalities.

It is essential therefore that a full history of all previous attempts to lose weight is explored including diets, attendance at slimming clubs, formal exercise and general physical activity. People should also be asked for the reasons that may have been responsible for failure of previous attempts. There are few tools at

the physicians' disposal and it is important that no modality is excluded, particularly if it has not been rewarded by weight loss in the past.

Indications for drug therapy

The justification for treating obese individuals with drugs is that they are at increased risk of early morbidity and death. Although the definitive evidence for a reduction in mortality with therapeutic weight loss has not yet been gathered, there is abundant evidence that improvement occurs in all the surrogate markers for vascular disease such as hypertension, hyperlipidaemia and glucose intolerance. These factors are reduced whether weight loss is achieved by diet alone, pharmacotherapy or surgery. Many people will have other conditions that will be improved by weight loss, including not only all of the vascular disorders but also arthritis, infertility and sleep apnoea.

Timing of drug therapy

The key to pharmacotherapy is in the timing. The majority of studies demonstrate that the critical period for maximal weight loss is in the first few months of a therapeutic programme. Good motivation is essential since the maximal benefit requires additional lifestyle changes.

However, it is difficult to assess motivation. People may appear to be motivated but may lack the ability to translate this into compliance with lifestyle changes. Our clinical experience and that of most trials is that only 30% of patients achieve 5% weight loss at the NICE prescribed 3 month period (www.nice.org.uk).

Drugs and obesity

The number of drug treatments available for obesity has undergone considerable change over the past decade. Firstly, new drugs have been developed and NICE have approved both orlistat (NICE, 2000) and sibutramine (NICE, 2001) for treatment of obese (BMI>30) and overweight people with co-morbidities. Secondly, a large number of agents are in development, and are waiting to fill the enormous market created by the withdrawal of dexfenfluramine in 1997 due to its cardiac and pulmonary toxicity.

Orlistat

Orlistat is a potent inhibitor of pancreatic and intestinal lipases. There is no appreciable systemic absorption and it results in the inhibition of the absorption of approximately 30% of dietary triglycerides (Zhi et al, 1994).

Most of the adverse reactions are gastrointestinal as might be predicted from the mode of action. These range from oily spotting and flatus with discharge to faecal urgency, increased defecation and faecal incontinence (Sjostrom et al, 2002). Most people who take orlistat only report a single episode of such an event. Indeed, fewer than 4% of orlistat-treated patients withdraw from clinical trial due to gastrointestinal side-effects (Sjostrom et al, 1998). The incidence of such events is related to the fat content of the diet; most people soon learn to avoid high-fat meals whilst on treatment. This may also improve efficacy by encouraging people to remain on a low-fat diet.

The evidence base for orlistat shows that the majority of people treated for 12 months lose in excess of 10% of their body weight whilst actively taking an hypocaloric diet (Sjostrom et al, 1998). Maintenance of this weight loss requires continued maintenance of the dietary measures, as relaxation leads to a slow regain. However, the latest research was a 4 year programme that demonstrated that despite this slow regain, the mean weight loss is still 7% after 4 years. Moreover, after this 4 year period, 9% of the placebo treated group had developed type 2 diabetes whereas the orlistat-treated group had an incidence of only 6.2% (Sjostrom et al, 2002).

Trials of orlistat have been performed in primary care in the US. A study by Hauptmann et al (2000) was characterised by a considerably reduced level of intervention compared with those in secondary care. Participants were treated

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by primary care physicians with no special nutritional training. The main intervention was a series of leaflets and videos designed to promote weight loss through behavioural change. Despite the reduced dietary intervention, mean weight loss at 12 months was 7.94 kg for participants treated with orlistat, compared with 4.14 kg for the placebo-treated group. Participants on active treatment were more likely to maintain weight loss over 2 years. Qualitatively similar improvements in lipid profile and blood pressure were seen when compared with other studies.

Sibutramine

Sibutramine is a centrally-acting serotonin and noradrenaline reuptake inhibitor, that was initially developed as an antidepressant. However, early clinical trials showed that weight loss occurred in many patients. Sibutramine is thought to work principally by increasing satiety; people taking it feel full sooner than they would otherwise, and therefore reduce their meal size (Hansen et al, 1999).

The main side-effects of sibutramine include a rise in blood pressure of 2–3mmHg and a rise in pulse rate of 4–6 beats per minute, probably related to activation of the sympathetic nervous system. Other side-effects include a dry mouth, nausea and constipation. Sibutramine cannot be taken with any psychoactive preparations to avoid precipitating the serotonin syndrome (Giese and Neborsky, 2001).

Sibutramine is effective at producing weight loss with doses varying from 5–30 mg daily. Weight loss is proportional to dose. People receiving 10 mg or 15 mg of sibutramine (as in clinical practice), achieve weight loss of 6.1% and 7.4%,

respectively, compared with a weight loss on placebo of 1.2% (Bray et al, 1999). A dose of 10 mg of sibutramine has also been shown to be effective as a tool to maintain weight loss produced by a very low calorie diet, whereas the placebo group rapidly regained weight (Apfelbaum et al, 1999).

Further studies in people with diabetes and hyperlipidaemia have also shown significant improvements in all metabolic variables (Finer et al, 2000; Dujovne et al, 2001).

The value of taking a holistic approach to weight loss was shown by Wadden et al. They treated obese participants with sibutramine, supplemented with either clinical advice on diet and exercise or group therapy. There was greater overall loss in the latter group (Wadden et al, 2001). Moreover, if treatment was initiated with a period of meal replacement by low calorie supplements, even greater long-term loss was achieved.

Fluoxetine

People with obesity are often depressed. This may be a primary condition or a consequence of their weight. The latter may be complicated by increased eating as a means of coping with their stress (Twenge et al, 2002). Mood improvement may occur with weight loss but depression is more likely to be an impediment to changing lifestyle.

Fluoxetine may be a suitable agent for treatment as it is an effective antidepressant. Moreover, its pharmacological action as a highly specific serotonin reuptake inhibitor means it has a negative effect on appetite. Unlike other antidepressants, fluoxetine results in significant short-term weight loss in people with diabetes (O'Kane et al, 1994) and people without diabetes (Goldstein et al, 1994). Whilst not recommended as a treatment for obesity it is a useful adjunct for people with depression. Fluoxetine is licensed for the treatment of binge eating.

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2 Factors predicting successful weight loss are: ongoing support; regular contact with a therapist; implementation or continuing regular physical activity; regular meal patterns; self-monitoring; and the development of a strategy to cope with relapses.

1 Obesity is a condition that carries considerable morbidity and mortality. The primary goal of treatment should be a weight loss of 10%, and it is important to set this realistic goal with patients.

2 Drug treatment with the newer agents may be appropriate if diet and lifestyle modification has not resulted in clinically beneficial weight loss.

Aims of drug treatment of obesity

The Royal College of Physicians Working Party on Obesity Management stressed the need for both weight loss and long-term maintenance of weight loss (RCP, 1998). Most people with obesity can lose (and often have lost) weight but have regained it following cessation of their diet. Maintenance of the weight that has been lost should be considered as important as actual loss. As outlined above, orlistat and sibutramine are effective for both primary weight loss and in maintaining loss achieved by earlier dieting.

The maintenance of lost weight is likely to be compromised by the NICE recommendations that treatment is limited to 1–2 years therapy. The recommendation to stop successful treatment is not given for other treatments. Hopefully, these recommendations will be relaxed as long-term safety data becomes available (NICE, 2000; NICE, 2001).

Prognostic factors

Factors predicting successful weight loss are: ongoing support; regular contact with a therapist; implementation or continuing regular physical activity; regular meal patterns; self-monitoring; and (probably most importantly) the development of a strategy to cope with relapses. Converse factors are likely to predict failure. These include negligible professional and social support, dysfunctional family life, emotional trauma, and the abandonment of healthy lifestyle changes.

Drugs that promote weight gain

It is important to bear in mind the risks of accidentally promoting weight gain as a side-effect of drug treatment for another condition. The following classes of medication have been reported to cause weight gain:

- Steroids.
- β-blockers.
- Antidiabetic agents.
- Antihistamines.
- Antipsychotic agents (Umbricht and Kane, 1996).
- Antidepressants.
- Anticonvulsants.
- Antimigraine agents.
- Breast cancer treatments (Demark-Wahnefried et al, 1993).

The gain for each of these drugs ranges from 1–10 kg.

Considerable controversy exists regarding hormone replacement therapy (HRT) and weight gain. A recent randomised controlled trial demonstrated that all women gain weight during the menopausal transition but women who received HRT gained less weight than those in the placebo group (Espeland et al, 1997).

In my experience, the majority of obese people have a medical co-morbidity which may be a direct result of their weight or may be an attenuating factor. These diseases are wide-ranging but most important are: diabetes; hyperlipidaemia; hypertension; cardiovascular diseases; respiratory diseases; musculoskeletal diseases; and psychiatric disorders. These conditions are all managed in part with the medicines listed above.

Conclusion

Obesity is a condition that carries considerable morbidity and mortality. The primary goal of treatment should be a weight loss of 10%, and it is important to set this realistic goal with patients. Drug treatment with the newer agents may be appropriate if diet and lifestyle modification has not resulted in clinically beneficial weight loss. The use of such agents should be carefully monitored and the risk-benefit ratio assessed in each individual. It is important that anti-obesity drugs are only given for clinical obesity and should only be used within the context of a therapeutic framework that at a minimum includes dietetic support and strong support for increased physical activity. ■

Evidence-based guidelines for the management of obesity

National Institute of Health Clinical Guidelines: http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.htm
Scottish Intercollegiate Guidelines Network: http://www.sign.ac.uk/pdf/qrg8.pdf

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DIABETES AND PRIMARY CARE JOURNAL – AWARD-WINNING JOURNALISM

Janet James (third from the right) and the other award winners.

An article published in *Diabetes and Primary Care* has won the First Annual Roche Award For International Obesity Journalism. The trophy along with 7500 euros was given to Janet James, Diabetes Development Nurse at Royal Bournemouth Hospital, at an awards ceremony held at the 12th European Congress on Obesity in Helsinki (May 30, 2003). Her article *Childhood obesity: a big problem for small people* (volume 4, no 3, 2002) was picked from over 140 entries from 20 different countries; all entries were judged by an independent panel of leading journalists and international obesity experts.

One of the judging panel members and Chairman of the International Obesity Task Force, Professor Philip James, said that Janet's article, highlighting the prevalence of childhood obesity, was 'topical, interesting, thoroughly researched and left a lasting impression on the reader. Journalism of this calibre increases public awareness of the health risks associated with excess weight, and may contribute to stemming the escalating obesity epidemic', he said.

Professor James also launched the 2nd Roche International Award for Obesity Journalism at the Awards Ceremony in Helsinki. The Award is open to journalists from print, broadcast and electronic media and all entries must be published or broadcast between May 29, 2003 and March 1, 2004. The closing date for submissions is March 1, 2004. A prize of 7500 euros will be presented to the winners in the medical and two consumer journalism categories. The winner and runner-up in each category will also receive sponsorship to attend a major global obesity congress. For more information about the Awards, including application details, visit www.managingyourweight.com/formedia/formedia_ja.cfm or email obesityjournalism@shirehealthinternational.com