Current drugs for weight loss

Orlistat is the only weight loss drug currently licensed in the UK. Outside the UK, there are now four other agents approved for weight loss.

Dr Kate Millar and Dr Ruth Poole here review the evidence regarding the comparative efficacy and adverse effects of the five different drug treatments.

**Background**

According to WHO data, the global prevalence of obesity has doubled between 1980 and 2014. By 2014, 39% of the world’s adults (1.9 billion individuals) were overweight and 18% were obese (600 million individuals). As well as being a major risk factor for type 2 diabetes (T2DM), overweight and obesity contribute to morbidity and mortality from cardiovascular disease, osteoarthritis and some cancers such as endometrial, breast and colon. Excess weight now leads to more deaths than malnutrition worldwide. The reasons for this increase are complex. Easy access to energy rich foods and decreased activity have been recognised for many years but more recent evidence suggests that gut microbia, epigenetic mechanisms, increasing maternal age, greater fecundity among people with higher adiposity, and endocrine disrupting chemicals may all be having some effect.

Lifestyle modifications are generally ineffective for weight loss in the long term due to the body’s adaptations to lower energy expenditure in response to reduced caloric intake and the high levels of motivation needed to sustain significant changes. Even in clinical studies where patients are highly motivated, initial weight loss is followed by gradual weight regain. Equally, bariatric surgery is invasive and potentially dangerous. As more research has allowed a greater understanding of the pathways and signalling involved in regulating metabolism and appetite, this has fuelled interest into new potential therapeutic targets. The use of pharmacological agents for weight loss has historically been associated with significant side effect burden and safety concerns. Fenfluramine, a serotonin increasing anorectic, was withdrawn from the market in 1997 after being shown to cause potentially fatal pulmonary hypertension and cardiac valvulopathy. Rimonabant, a selective cannabinoid receptor blocker, was withdrawn in 2008 because of serious psychiatric side effects including risk of suicide. Sibutramine, a serotonin-norepinephrine reuptake inhibitor, was withdrawn in 2010 because of its association with increased cardiovascular events and strokes.

Orlistat is the only weight loss drug currently licensed in the UK. It works by inhibiting pancreatic lipases and thereby decreasing dietary fat absorption and increasing faecal fat excretion. Weight loss in the first year of treatment is around 5–10kg, and this has been shown to be maintained over four years with continued use. Orlistat reduces the risk of developing diabetes in obese patients with impaired glucose tolerance by around a third. In patients with diabetes, orlistat has been demonstrated to reduce HbA1c by 0.6% (7mmol/mol) over 52 weeks. It has also been shown to improve blood pressure and serum lipids beyond expected levels from weight reduction alone. Between 15–30% of patients experience gastrointestinal (GI) side effects associated with orlistat; generally these improve as patients learn to avoid high fat diets. Absorption rates of fat soluble vitamins A, D, E and K are lowered with orlistat; generally these improve as more fat soluble vitamins are added to the diet. Orlistat is generally mild with headache, back pain and naso-pharyngitis occurring with greater frequency than compared to the placebo group. Neuropsychiatric effects were not significantly increased in any of the trials. With regard to concerns of serotonin-associated valvulopathy, pooled analysis of the phase 3 trials showed that the rates of FDA defined valvulopathy were 2.3% and 2.2% for patients taking lorcaserin or placebo respectively.

**Lorcaserin (Belviq)**

Lorcaserin is a selective agonist of the serotonin 2C receptor which reduces food intake by increasing satiety. It was approved by the US Food and Drug Administration (FDA) in 2012 as an adjunct to lifestyle interventions for patients with BMI above 30kg/m² or above 27kg/m² with at least one medical comorbidity such as T2DM or obstructive sleep apnoea. It is not currently licensed in the UK.

A multicentre placebo-controlled trial of lorcaserin found that at one year 47.5% of patients in the lorcaserin group had lost 5% or more of their body weight compared to 20.3% in the placebo group (p<0.001). This corresponds to a 3–4kg difference in weight loss between the two groups. They also showed that in year two weight loss was more likely to be maintained if they continued on lorcaserin rather than switching to placebo.

A trial looking at the efficacy of lorcaserin for weight loss in patients with T2DM randomised patients to lorcaserin 10mg once a day, 10mg twice a day or placebo. Patients were being treated with metformin, a sulphonylurea or both. At one year, there was no difference in weight loss between the two active treatment groups, but both had lost three times more weight than the placebo group (6% vs 2%) and significantly more patients lost more than 5% of their body weight on lorcaserin (44.7% once-daily dose and 37.5% twice-daily dose) compared to placebo (16.1%). There was also a significant improvement in glycaemic control with HbA1c decreasing 0.9% to 1.0% (10–11mmol/mol) in the lorcaserin groups and 0.4% (4mmol/mol) in the placebo group.

Adverse effects of lorcaserin are generally mild with headache, back pain and naso-pharyngitis occurring with greater frequency than compared to the placebo group. Neuropsychiatric effects were not significantly increased in any of the trials. With regard to concerns of serotonin-associated valvulopathy, pooled analysis of the phase 3 trials showed that the rates of FDA defined valvulopathy were 2.3% and 2.2% for patients taking lorcaserin or placebo respectively.

**Liraglutide (Saxenda)**

Liraglutide is an analogue of the incretin hormone glucagon-like peptide 1 (GLP-1) and has dual therapeutic benefits in terms of glycaemic control and weight loss due to enhanced postprandial insulin secretion, delayed gastric emptying and decreased food intake. Liraglutide is established in Europe and America.
as a treatment option for patients with T2DM with BMI above 30kg/m² or above 27kg/m² with at least one weight-related comorbidity at doses of 0.6mg to 1.8mg daily, and is linked to a significant reduction in weight (2–3kg) when compared to placebo or glimepiride. In the UK, liraglutide can only be prescribed for patients with a BMI above 35kg/m² unless there are comorbidities, and the maximum dose is 1.2mg daily. High-dose liraglutide (3mg) has been licensed as a treatment for weight loss in people without diabetes in the US since September 2014 under the trade name Saxenda, but is not yet licensed for this indication in the UK.

There is evidence that liraglutide, at the doses licensed for patients with diabetes, is being used in the UK for obese patients without diabetes. Twenty-two obese individuals without diabetes attending a specialist obesity service were enrolled in a 12-month study to see if liraglutide 1.8mg could avoid bariatric surgery. Fourteen completed the study with a mean weight loss of 12.1kg. Two participants withdrew because of lack of efficacy, two because of GI side effects and the rest failed to complete the study as their primary care funding of the treatment was withdrawn.

Other studies of the efficacy of liraglutide for inducing weight loss in those without diabetes have used higher doses. In a 56-week double-blind trial, 63.2% of patients receiving 3mg liraglutide lost at least 5% of their body weight compared to 27.1% in the placebo group. Additionally, HbA1c, quality of life and cardio-metabolic risk factors all improved. A randomised controlled trial comparing the efficacy of liraglutide with that of orlistat showed that patients taking the two highest doses of liraglutide (2.4 and 3.0mg) lost significantly more weight than those taking orlistat (6.3, 7.2 and 4.1kg, respectively).

The SCALE diabetes trial looked at the efficacy and safety of the higher liraglutide 3.0mg dose in patients with T2DM and found that at 56 weeks weight loss was 6.0% (6.4kg) with 1.8mg dose and 2% (2.2kg) with placebo. HbA1c significantly improved compared to placebo with treatment difference of -0.93% (10mmol/mol) in the 3.0mg dose group. Mean systolic blood pressure was significantly decreased (treatment difference -2.6mmHg) in the liraglutide dose compared to placebo without a dose effect. Liraglutide 3.0mg also significantly improved levels of total cholesterol, VLDL, HDL and triglycerides compared with placebo. Liraglutide was associated with a mean heart rate increase of 2.0 beats per minute compared to a reduction of 1.4 beats per minute for placebo. Given the improvements in the other cardiovascular risk factors, the long-term clinical relevance of this is unclear.

The higher dosages of liraglutide are, however, associated with a higher incidence of GI side effects. The 3mg dose caused GI side effects in 77% of participants and was the most common cause for cessation of treatment. There were eight people in the liraglutide groups who withdrew (2.2%) because of nausea, and five (1.3%; in the 2.4mg and 3.0mg groups) because of vomiting. Nobody in the placebo or orlistat groups withdrew because of such events.

Naltrexone/bupropion (Contrave/Mysimba)

The combination of naltrexone and bupropion was approved by the FDA in September 2014 under the trade name Contrave and in some European countries in March 2016 as Mysimba. It is not currently licensed in the UK. Bupropion stimulates hypothalamic proopiomelanocortin (POMC) neurons while naltrexone blocks opioid-mediated POMC neurone auto-inhibition, inducing satiety. Given their established uses in addiction, it is also postulated that this combination may help modulate central nervous system reward pathways. Efficacy and safety of naltrexone/bupropion combination therapy were tested in the Contrave Obesity Research (COR) studies. COR-I compared two different doses of naltrexone (16 and 32mg) combined with bupropion against placebo in 1742 participants. COR-II compared naltrexone/bupropion 32/360mg against placebo in 1496 participants. Primary endpoints in each trial were percentage weight loss and proportion of subjects achieving more than 5% weight loss. All participants were either obese (BMI 30–45kg/m²) or overweight (27–45kg/m²) with dyslipidemia and/or hypertension. Both trials were conducted over 56 weeks.

In COR-I, 48% of participants assigned to naltrexone 32mg plus bupropion had a decrease in body weight of 5% or more compared with 16% of participants assigned to placebo. Mean reduction in body weight was 6.1% in the naltrexone 32mg plus bupropion group versus 1.3% in the placebo group. Similar results were seen in COR-II with a 6.1% weight reduction by week 56 in the naltrexone/bupropion group against 1.2% in the placebo group, and 50.5% achieved a 5% weight loss compared to 17.1% of participants on placebo.

Side effects were common, particularly nausea, headache and constipation. Drop-out rates were high with only 54% of participants in COR-II completing the study. In the active treatment arm, this was due to side effects while, in the placebo arm, the same proportion of patients withdrew due to insufficient weight loss. Pulse and blood pressure were not adversely affected.

The LIGHT study was conducted to establish the cardiovascular safety of Contrave. More than 8000 participants were randomised either to naltrexone/bupropion or to placebo. However, the trial was stopped early after public release of confidential interim data by the sponsor suggesting a 40% reduction in major cardiovascular events in the naltrexone/bupropion group. This was not confirmed after further analysis, but cardiovascular safety was not established and further evaluation is required.

Phentermine/topiramate (Qsymia)

Phentermine is a centrally-acting sympathomimetic and acts as an appetite suppressant. As a single agent it is the most frequently prescribed drug for weight loss in the US where it is approved only for short-term (up to 12 weeks) use because of its addictive potential. Topiramate is an anti-epileptic drug, also licensed for migraine prophylaxis which has been noted to
Current drugs for weight loss

Table 1. Comparison of currently available weight loss treatments

<table>
<thead>
<tr>
<th>Weight loss treatment</th>
<th>Current UK licence</th>
<th>Mode of action</th>
<th>Weight loss potential</th>
<th>Metabolic benefits</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat(^{6,27})</td>
<td>Yes</td>
<td>Inhibition of pancreatic lipase; decreased absorption of ingested fat</td>
<td>10.2% over 1 year</td>
<td>Reductions in total and LDL cholesterol</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Lorcaserin(^{10})</td>
<td>No</td>
<td>Selective serotonin agonist; increased satiety; reduced food intake</td>
<td>5.8% over 1 year</td>
<td>Reduction in HbA(_1c) in patients with diabetes</td>
<td>Headache, back pain and naso-pharyngitis</td>
</tr>
<tr>
<td>Liraglutide(^{16,18,26})</td>
<td>No</td>
<td>GLP-1 agonist; increased satiety; reduced food intake</td>
<td>8% over 56 weeks</td>
<td>Reduction in HbA(_1c) in patients with diabetes; reduction in blood pressure and improved lipid profile</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Naltrexone/bupropion(^{19})</td>
<td>No</td>
<td>POMC (proopiomelanocortin) modulation; increased satiety; reduced food intake</td>
<td>6.1% over 56 weeks</td>
<td>–</td>
<td>Nausea, headache and constipation</td>
</tr>
<tr>
<td>Phentermine/topiramate(^{22})</td>
<td>No</td>
<td>Centrally-acting sympathomimetic; reduced appetite; reduced food intake</td>
<td>9.8% over 56 weeks</td>
<td>HbA(_1c) in patients with diabetes; reduction in blood pressure</td>
<td>Gastrointestinal, neurological and psychiatric</td>
</tr>
</tbody>
</table>

have some weight loss effects. Qsymia was approved as a combination treatment in the US in 2012 but is not licensed in the UK.

The benefits of low-dose Qsymia were assessed in the CONQUER trial. A total of 2487 patients were randomised to phentermine/topiramate at either 7.5/46mg or 15/92mg daily or to placebo; 20% of participants had T2DM at study entry. At 56 weeks, participants taking Qsymia had lost 8–10kg while those on placebo had lost 1.4kg. Five percent weight loss was achieved by 62% and 70% of participants in the two active arms and in 21% of participants taking placebo. There was a mean decrease in systolic blood pressure of 2.3mmHg compared to placebo in the 7.5/46mg dose and 3.2mmHg in the 15/92mg group following one year of treatment. Among the 388 subjects with T2DM, reductions in HbA\(_1c\) from baseline were 0.1% (1mmol/mol) for placebo compared to 0.4% (4mmol/mol) with both doses of Qsymia.\(^{22}\)

The SEQUEL trial was an extension of the CONQUER trial with participants continuing on the same dose of Qsymia or placebo for a further 52 weeks. Weight loss during the first 56 weeks in the Qsymia group was maintained over a further 52 weeks. Blood pressure was not different between the groups although 13.1% and 15.6% of patients in the two active treatment groups had reductions in their antihypertensive medications while 11% of participants taking placebo had their antihypertensive medications increased.\(^{23}\)

The most common adverse effects were dry mouth, constipation and paraesthesia as well as a dose-related increase in incidence of depression, anxiety and attention difficulties. This is further underlined as a study examining its use in the real world environment of a multidisciplinary weight loss clinic noted an adverse event cessation rate of 40% with neurological side effects predominating.\(^{24}\)

**Discussion**

As the prevalence of obesity and related comorbidities continues to climb, pharmacological interventions for weight loss remain limited. Overall, the usefulness of weight loss medications are limited by side effects which result in high drop-out rates in medical trials as well as poor compliance in real world prescribing. In a population-based cohort, at one year after prescription of orlistat or sibutramine, less than 10% of patients were still on their medication and by two years only 2% continued on either medication.\(^{25}\) A further difficulty is that weight loss tends to slow and then plateau with continued treatment and the majority of patients regain weight when their weight loss drugs are stopped. However, it is of interest that trials have shown that a good initial response predicts long-term response and this underlines not only the importance of assessing responses within six months and discontinuing treatment in those with no measurable benefit, but also the potential value of further investigating the characteristics/phenotype associated with a good response. This may allow for more personalised treatments in the future.

Belviq, Saxenda, Contrave and Qsymia have all been shown to be effective for weight management with the potential for weight loss of between 5.8–9.8% of starting weight over the first year of treatment (see Table 1). However, none are more effective than orlistat. There is also at this stage a lack of long-term data (more than two years) available for the new medications discussed in contrast to the established long-term safety profile of orlistat.

These new weight loss drugs need to be considered with caution. Each has demonstrated significant benefits for weight reduction but none is without significant side effects. Weight loss alone may be beneficial for patient self-esteem and for reduction in weight-related joint disease and thrombo-embolic risk. An ideal drug would also reduce the metabolic complications of obesity including glycaemia, blood pressure and lipid profile and demonstrate...
significant reductions in cardiovascular endpoints. At this stage, some of the new weight loss treatments have demonstrated reductions in HbA1c, blood pressure and cholesterol (see Table 1), but until recently none have shown reduction in myocardial infarction (MI), stroke or mortality. This has changed with the recent publication of the LEADER trial. In all, 9340 patients with T2DM and high cardiovascular risk were randomised to 1.8mg of liraglutide or placebo. Over 3.8 years of follow up, the primary outcome of death from cardiovascular disease, non-fatal MI or non-fatal stroke was 15% in the liraglutide arm and 14.9% in the placebo arm. Cardiovascular mortality was lower in the liraglutide group than in the placebo group (4.7% vs 6.0%) as was total mortality (8.2% vs 9.6%). Differences in non-fatal MI and stroke did not reach statistical significance.26

Arguably the most exciting and promising line of new pharmacological treatments are those targeted at gut hormones, given that research has proven their role in regulating appetite, metabolism, gut motility, secretion and even acting as neurotransmitters. GLP-1 analogues have paved the way towards developing gut hormones as therapeutics but have limited efficacy and dose-dependent side effects. However, other gut hormone pathways are also yet to be exploited and new combinations of hormone analogues are currently being developed. This includes peptide YY and pancreatic polypeptide analogues which are currently in phase 1 trials and hold potential to deliver better appetite suppression with fewer dose-dependent side effects. Furthermore, the use of agents to increase energy expenditure alongside appetite suppression is also under development which would represent a big step forward given that the body normally counter regulates weight loss by reducing energy expenditure and thus limiting weight loss. The potential use of glucagon receptor agonists in combination with GLP-1 in this way could therefore lead to a much greater weight loss than either peptide could achieve alone. New combinations of gut hormone analogues could thus mimic physiological processes to provide safe weight loss at a comparable level to surgery and this represents an exciting area of investigation for pharmacological agents in the future.

Conclusion

In the UK, orlistat remains the only licensed weight reduction treatment although, for patients with T2DM, GLP-1 agonists such as liraglutide already used for treatment of hyperglycaemia also benefit patients in terms of weight loss. Whether the increased side effects with the higher dose as Saxenda will outweigh the additional weight loss benefits in clinical practice remains to be seen.

The possibility of alternative oral medications such as Belviq, Contrave or Qsymia in the UK will depend on future studies of long-term efficacy and any long-term harms found during real world prescribing in the US and Europe.

Kate Millar, MChB, MRCP, Speciality Registrar, Royal Hampshire County Hospital, Winchester, UK

Ruth Poole, DM, FRCP, Consultant, Poole Hospital NHS Foundation Trust, Poole, UK

Correspondence to: Dr Ruth Poole, Poole Hospital NHS Foundation Trust, Poole BH15 2JB, UK; email: Ruth.Poole@poole.nhs.uk

Declaration of interests

There are no conflicts of interest declared.

References