Pharmacotherapy for weight loss

Christian F Rueda-Clausen, Raj S Padwal

A severely obese 28 year old woman (body mass index (BMI) 37.9) with type 2 diabetes, controlled hypertension, and sleep apnoea is seeking your advice about weight loss. She has lost 6 kg over the past year by reducing portion sizes, but her weight has recently plateaued. She does not want to consider bariatric surgery and asks instead about drug treatments.

What are antiobesity drugs? Current treatment for obesity consists primarily of health behaviour modification (diet, exercise, and behavioural therapy) for all patients and bariatric surgery for a minority of selected severely obese people. Because health behaviour modification is unsuccessful in many patients, and the availability of bariatric surgery is limited, additional adjunctive, effective, and safe obesity treatments are needed.

To date, antiobesity drugs have not adequately filled this therapeutic void. The serotonergic agents fenfluramine and dexfenfluramine were withdrawn in 1997 because of associations with cardiac valvulopathy and pulmonary hypertension. After the withdrawals of rimonabant (Acomplia) in 2009 for depression and suicidal ideation, and sibutramine (Meridia, Reductil) in 2010 because of increased cardiovascular risk, orlistat became the only agent available for long term weight management.

In 2012, two new oral agents—phentermine and extended release (ER) topiramate (Qsymia) and lorcaserin (Belviq)—were approved by the US Food and Drug Administration as adjuvants to health behaviour modification in patients with a BMI of greater than 30 or greater than 27 if they also had an obesity related comorbidity, such as hypertension, dyslipidaemia, or type 2 diabetes. As discussed elsewhere, the European Medicines Agency did not approve either agent, citing toxicity concerns and a lack of morbidity and mortality data. Here, we provide a clinically focused summary to guide GPs in the use of these drugs.

What are the currently available pharmacological options for obesity? Orlistat This inhibitor of gastric and pancreatic lipase prevents intestinal fat metabolism and absorption. Prescription orlistat (Xenical) has been available since 1999 and over the counter orlistat (Alli) since 2007.

Phentermine-ER topiramate Phentermine is an amphetamine analogue that enhances satiety by increasing hypothalamic noradrenaline (norepinephrine) levels. Phentermine monotherapy for obesity was approved in 1959 for short term use only; it is currently the most commonly prescribed antiobesity drug in the US. Topiramate, which is approved for epilepsy and migraine prophylaxis, putatively reduces weight by decreasing food intake, decreasing lipogenesis, increasing thermogenesis, improving insulin sensitivity, and increasing secretion of adiponectin.

Lorcaserin This is a selective agonist of serotonin (5-hydroxytryptamine or 5-HT) 2c receptors that stimulates pro-opiomelanocortin (POMC) producing neurones in the hypothalamus, resulting in generation of α-melanocortin stimulating hormone, which acts on melanocortin receptors to decrease food intake and enhance satiety.

How well do they work? Orlistat In a meta-analysis of 16 randomised controlled trials (RCTs; 10 631 patients), orlistat (120 mg three times a day) reduced weight by 2.9 kg (95% confidence interval 2.5 to 3.2) more than placebo after one year. Compared with placebo, 21% (19% to 24%) more patients in the orlistat group achieved at least 5% weight loss (number needed to treat (NNT) 5) and 12% (8% to 16%) more achieved at least 10% weight loss (NNT 8). Orlistat improved systolic blood pressure (−1.5 mm Hg, −0.9 to −2.2) and low density lipoprotein-cholesterol (−0.26 mmol/L, −0.22 to −0.30 mmol/L) more than placebo. Orlistat also improved glycosylated haemoglobin (HbA1c) in patients with diabetes to a greater extent than placebo (−0.39%, −0.18% to −0.59%) and, in one trial, reduced the four year incidence of type 2 diabetes from 9.0% to 6.2% (hazard ratio 0.63, 0.46 to 0.86).

Overall, orlistat leads to small amounts of weight loss and modest improvements in cardiovascular risk profiles. Long term adherence to treatment is poor (<2% at two years). Current evidence is limited by high study attrition rates (averaging 30%), and the lack of data on cardiovascular morbidity and mortality makes it difficult to draw definitive conclusions about the overall benefits of this agent.

Phentermine-ER topiramate Two large, 56 week, phase III RCTs (EQUIP11 and CONQUER12) compared phentermine-ER topiramate with placebo (table 1). All patients received advice on health behaviour modification. Those receiving phentermine-ER topiramate (15 and 92 mg/d, respectively) lost 8.8-10.8 kg more weight than those receiving placebo (P<0.05) and were significantly (P<0.05) more likely to lose at least 5% (NNT 2) and 10% (NNT 3) of initial body weight. Other cardiovascular risk factors were improved, including systolic blood pressure (−3.8 mm Hg, −2.8 to −4.7), total cholesterol (−0.15 mmol/L, −0.2 to 0.15), and HbA1c (−0.2%, −0.16% to −0.24%). In a 52 week blinded extension of the CONQUER study, annualised rates of progression to overt diabetes in 475 people with prediabetes,
Table 1 | Effect of phentermine-extended release topiramate on anthropometric indices†‡

<table>
<thead>
<tr>
<th>Study†</th>
<th>Intervention</th>
<th>Weight (% of baseline)</th>
<th>Weight (kg)</th>
<th>5% weight loss (n %)</th>
<th>10% weight loss (n %)</th>
<th>Waist circumference (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQUIP15</td>
<td>Active (498)</td>
<td>−1.09</td>
<td>−12.6</td>
<td>332 (67)</td>
<td>235 (47)</td>
<td>−10.9</td>
</tr>
<tr>
<td>Placebo (498)</td>
<td>−1.6</td>
<td>−1.8</td>
<td>86 (17)</td>
<td>37 (7)</td>
<td>−3.1</td>
<td></td>
</tr>
<tr>
<td>CONQUER77</td>
<td>Active (981)</td>
<td>−2.4</td>
<td>−10.2</td>
<td>687 (70)</td>
<td>467 (48)</td>
<td>−9.2</td>
</tr>
<tr>
<td>Placebo (979)</td>
<td>−1.2</td>
<td>−1.4</td>
<td>204 (21)</td>
<td>72 (7)</td>
<td>−2.4</td>
<td></td>
</tr>
</tbody>
</table>

*Patients receiving active treatment were randomised to phentermine and extended release topiramate. Results are presented for the 15 and 92 mg/d, respectively, dose only.
†EQUIP: Design: double blind placebo controlled randomised trial. Duration: 56 weeks. Inclusion criteria: body mass index (BMI) 35, with or without controlled hypertension or dyslipidaemia. Participants: 43 (standard deviation 12) years old, 82% female, 80%, white, weight 116 (21) kg, BMI 42 (6). CONQUER: Design: double blind placebo controlled randomised trial. Duration: 56 weeks. Inclusion criteria: BMI 27-45 (or diabetes regardless of BMI) plus metabolic syndrome. Participants: 51 (10 years old, 70% female, 86% white, weight 103 (18) kg, BMI 37 (5).
‡P value <0.05 (active metformin, a sulfonylurea, or both; BMI 27-45. Participants: 53 (8) years old, 54% female, 60% white, weight 104 (18) kg, BMI 36 (4).

Table 2 | Effect of lorcaserin on anthropometric indices*†

<table>
<thead>
<tr>
<th>Study†</th>
<th>Intervention</th>
<th>Weight (% of baseline)</th>
<th>Weight (kg)</th>
<th>5% weight loss (n %)</th>
<th>10% weight loss (n %)</th>
<th>Waist circumference (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQUIP15</td>
<td>Active (1538)</td>
<td>−5.8*</td>
<td>−5.8*</td>
<td>738 (48)*</td>
<td>356 (23)*</td>
<td>−6.8*</td>
</tr>
<tr>
<td>Placebo (1499)</td>
<td>−2.2</td>
<td>−2.2</td>
<td>300 (20)</td>
<td>120 (8)</td>
<td>−3.9</td>
<td></td>
</tr>
<tr>
<td>EQUIP15</td>
<td>Active (1561)</td>
<td>−5.8*</td>
<td>−5.8*</td>
<td>737 (47)*</td>
<td>353 (23)*</td>
<td>−6.3*</td>
</tr>
<tr>
<td>Placebo (1541)</td>
<td>−2.8</td>
<td>−2.9</td>
<td>385 (25)</td>
<td>150 (10)</td>
<td>−4.1</td>
<td></td>
</tr>
<tr>
<td>BLOSSOM66</td>
<td>Active (253)</td>
<td>−4.5*</td>
<td>−4.7*</td>
<td>94 (38)</td>
<td>41 (16)*</td>
<td>−5.5*</td>
</tr>
<tr>
<td>Placebo (248)</td>
<td>−1.5</td>
<td>−1.6</td>
<td>40 (16)</td>
<td>11 (4)</td>
<td>−3.3</td>
<td></td>
</tr>
</tbody>
</table>

*Patients receiving active treatment were randomised to lorcaserin. Results are presented for the 10 mg twice daily dose only.
†BLOSSOM: Duration: 52 weeks. Inclusion criteria: type 2 diabetes with glycated haemoglobin of 7-10% on orlistat, “hard” endpoint data are needed to verify these benefits are clinically important.

What are the safety issues and precautions?

Orlistat

Orlistat is minimally absorbed and faecally excreted, so doses do not need to be reduced in patients with liver or kidney impairment. Gastrointestinal adverse effects (including steatorrhoea and abdominal distension) occur in about 25% of patients (number needed to harm (NNH) 4) and faecal incontinence in 2-8% (NNH 16) .

Orlistat should be avoided in patients with chronic malabsorption or cholestasis and in pregnancy. Isolated cases of liver failure and calcium oxalate nephrolithiasis have been reported. Orlistat may decrease the absorption of fat soluble vitamins (A, D, E, and K) and drugs (including ciclosporin, amiodarone, anticonvulsants, and levothyroixine). These drugs should be taken two to four hours after the ingestion of orlistat.

Phentermine-ER topiramate

Common adverse effects of phentermine-ER topiramate include paraesthesias (21% of patients, NNH 5), nausea (7%, 33) dizziness (10%, 14), dysgeusia (10%, 11), constipation (17%, 11), and dry mouth (21%, 5). Neuropsychiatric related adverse events were also more common, including depression (7%, 33), anxiety (4%, 50), irritability (3%, 50), insomnia (10%, 20), and disturbances in attention (4%, 33).

Although phentermine-ER topiramate (15 and 92 mg/d, respectively) increases heart rate by about 2 beats/min, the FDA judged that the potential increase in cardiovascular risk was balanced by improvements in blood pressure and other cardiovascular risk factors.

The drug is contraindicated in pregnancy because topiramate has been associated with teratogenicity, mainly in the form of orofacial clefts.

Because this agent is renally excreted, reduce the dose in patients with a creatinine clearance less than 50 ml/min (maximum of phentermine 7.5 mg and ER topiramate 46 mg daily). Avoid in patients with nephrolithiasis or renal tubular acidosis or use lower doses and monitor renal function closely because topiramate can also promote acidemia by inhibiting renal carbonic anhydrase.

Because the drug is not recommended in severe liver disease owing to the lack of safety data in this population, use lower doses (maximum of phentermine 7.5 mg and ER topiramate 46 mg daily) in moderate hepatic failure (Child-Pugh class B) and avoid the drug in severe liver disease (Child-Pugh class C).

Other contraindications to phentermine-ER topiramate include severe vascular disease, moderate-severe hypertension, hyperthyroidism (owing to the risk of increased heart rate), and glaucoma (owing to the risk of angle-closure glaucoma). Severe anxiety or agitation (phentermine may aggravate symptoms); history of drug misuse (because of the risk of dependence, although this risk seems more theoretical than real); and current or recent use of monoamine oxidase inhibitors, which can enhance amphetamine related increases in blood pressure, are also contraindications.

Lorcaserin

Lorcaserin is metabolised in the liver to multiple inactive metabolites that are renally excreted. It is not
### Table 3 | Details of the use of antiobesity drugs and contraindications

<table>
<thead>
<tr>
<th>Orlistat</th>
<th>Phentermine-extended release topiramate</th>
<th>Lorcaserin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipated weight loss (kg)</td>
<td>2-3</td>
<td>9-11</td>
</tr>
<tr>
<td>Daily dose frequency</td>
<td>With each meal</td>
<td>Once</td>
</tr>
<tr>
<td>Recommended dose</td>
<td>120 mg three times a day</td>
<td>15-92 mg each morning</td>
</tr>
<tr>
<td>Dose escalation and dose tapering on discontinuation</td>
<td>Not needed</td>
<td>Needed</td>
</tr>
<tr>
<td>Available formulations</td>
<td>60 mg</td>
<td>3.75 mg-23 mg</td>
</tr>
<tr>
<td></td>
<td>120 mg</td>
<td>7.5 mg-46 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.25 mg-69 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mg-92 mg</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>No adjustment needed</td>
<td>Increased risk of calcium oxalate nephrolithiasis</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>No adjustment needed</td>
<td>If moderate impairment (Child-Pugh class B), use lower dose (maximum 7.5 mg-46 mg daily; do not use in severe impairment (Child-Pugh class C)</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>No risk identified</td>
<td>Increase risk of hypoglycaemia in patients taking antidiabetic agents</td>
</tr>
<tr>
<td>Patients with psychiatric illness</td>
<td>No risk identified</td>
<td>Potential risk of agitation, sleep disturbances, anxiety and theoretical (but low likelihood) risk of recreational abuse. See contraindications (below)</td>
</tr>
<tr>
<td>Other contraindications</td>
<td>Chronic malabsorption or cholestatics, pregnancy</td>
<td>Pregnancy, glaucoma, hyperthyroidism, severe vascular disease, moderate-severe hypertension, severe anxiety or agitation, history of drug misuse, current or recent monoamine oxidase inhibitor use</td>
</tr>
</tbody>
</table>

**Recommended:**
- In patients with a creatinine clearance less than 30 mL/min. Periodically monitor liver enzymes or avoid use in patients with severe hepatic impairment.
- Do not co-prescribe with other agents that may increase the risk of serotonin syndrome.

**Common adverse effects of lorcaserin include headache (18% of patients, NNH 14), upper respiratory tract infection (15%, 13), dizziness (8%, 25), nausea (8%, 33), constipation (7%, 33), and dry mouth (5%, 33).**

- Hypoglycaemia is slightly more common in patients taking oral hypoglycaemic drugs (8.3% for lorcaserin v. 6.3% for placebo; P=0.4).
- Priapism is a rare adverse effect.

- Lorcaserin treatment has not been associated with depression or suicidal ideation, and the potential for recreational misuse is low. Although studies in rats raised concerns of mammary and brain tumours, these findings have not been replicated in other animal models, and risk has been judged to be low in humans. Clinical trials to date do not indicate an increased risk of cardiac valvulopathy; however, studies are underpowered and further postmarketing surveillance is needed.

**How are these agents taken and monitored (table 3)?**

**Orlistat**
- The dose is 60-120 mg three times daily, taken with meals.
- Doses can be skipped if the meal is small or has a low fat content.

**Phentermine-ER topiramate**
- The recommended initial dose of 3.75 mg and 23 mg, respectively, as a single daily dose in the morning to avoid insomnia, is prescribed for two weeks and then doubled to 7.5 and 46 mg once daily for 12 weeks. If 3% weight loss has not been achieved, either discontinue the drug or increase the dose to 11.25 mg and 69 mg daily for two weeks and then to 15 mg and 92 mg daily. If 5% weight loss is not achieved after 12 weeks, the drug should be tapered over one to two weeks, to avoid withdrawal, and then discontinued.

**Lorcaserin**
- The recommended oral dose is 10 mg twice daily. Discontinue after 12 weeks if at least 5% weight reduction has not been achieved.

**How cost effective are these new agents?**
- One month of orlistat therapy costs $120 (£71.5; €88) to $140. The two newer agents cost $240 a month. Cost
effectiveness analyses are available only for orlistat; a National Institute for Health and Care Excellence health technology assessment reported a cost per quality adjusted life year of £19,000 in the United Kingdom.¹

Case outcome
You discuss average weight loss that studies show with these drugs, possible side effects, and the costs for each agent. You also mention that the drugs have not been proved to lower risk of heart disease or stroke. In this patient, because no absolute contraindications exist, any one of the three agents can be used. You suggest, if her weight has not dropped by at least 5% (and preferably 10%) after 12-24 weeks the drug should be stopped and another one tried. Because the patient is of childbearing age, the need for contraception and monthly pregnancy testing should be discussed if phentermine-ER topiramate is prescribed.

Contributors: Both authors wrote the first draft of the paper and revised subsequent versions of the manuscript. RSP is guarantor.


Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required: Patient dead, anonymised, or hypothetical.


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ANSWERS TO ENDGAMES, p 40
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PICTURE QUIZ
Asymmetric hearing loss and tinnitus

1 The figure shows a well delineated lesion of the right internal auditory canal extending into the cerebellopontine angle. The lesion is hypointense on T2 weighted imaging (A), isointense on non-contrast T1 weighted imaging (B), and it enhances strongly on T1 weighted imaging after administration of intravenous contrast (C).

2 The diagnosis is a right vestibular schwannoma. Vestibular schwannomas or acoustic neuromas are benign tumours arising from the sheath that surrounds the vestibulocochlear (eighth cranial) nerve.

3 Vestibular schwannomas usually present with unilateral or asymmetric sensorineural hearing loss, tinnitus, and dizziness or imbalance. Patients in whom these symptoms are asymmetric or unilateral should be referred to an otolaryngologist.

4 The available options are radiological surveillance with clinical observation, radiotherapy, or microsurgical excision. Treatment is individualised and depends mainly on tumour size and comorbilities.

ANATOMY QUIZ
Radiograph of the left foot of a 7 month old infant

A: Talus bone
B: Calcaneus (heel bone)
C: Cuboid bone
D: First metatarsal
E: Proximal phalanx of the second toe

STATISTICAL QUESTION
What are the four phases of clinical research trials?
The above trial is best described as a phase III trial (answer c)

39