Pharmacotherapy for weight loss in adults with type 2 diabetes: a systematic review of randomised controlled trials

CLAUDIA COELHO,1 RACHEL AGIUS,2 JAMES CRANE,1 BARBARA MCGOWAN1,3

Abstract
Background: Clinically significant weight loss improves glycaemic control and cardiovascular disease risk in patients with type 2 diabetes (T2DM).
Aim: To identify and assess the efficacy of medical treatments for weight loss in adults with T2DM.
Methods: A systematic review was conducted of peer-reviewed literature between July 2004 and July 2020 via PubMed, Embase, Web of Science, medRxiv and Cochrane Central Register of Controlled Trials. Randomised controlled trials (RCTs) in English investigating medical treatments for weight loss in patients with T2DM were included. RCTs of pharmacotherapy withdrawn from the market were excluded. No minimum length of follow-up time was established. Outcomes of interest were changes from baseline in body weight (%), changes from baseline in HbA1c (%), mmol/mol) and proportion of patients who achieved ≥5% weight loss. Quality assessment was evaluated using the Jadad score.
Results: Fifteen RCTs were included with a total of 4,207 participants with T2DM. Interventions included medications approved for obesity management (orlistat, liraglutide, naltrexone-bupropion and phentermine-topiramate) and other agents investigated for the primary purpose of weight loss (topiramate, metreleptin, dapagliflozin and exenatide) compared with placebo. The duration of the intervention varied from 12 to 56 weeks. Placebo-adjusted body weight loss ranged from 2.2% to 7.3%. Furthermore, 30.5–77.0% of participants achieved ≥5% weight loss. Placebo-adjusted change in glycated haemoglobin was 0.3–1.5% (3.3–16.4 mmol/mol). Conclusion: Current evidence demonstrates that pharmacotherapy for weight loss, except for leptin, is associated with weight loss and glycaemic improvement in patients with T2DM.

Key words: obesity, pharmacotherapy, type 2 diabetes, weight loss, systematic review

Background
Obesity is known to be one of the major drivers for the onset of type 2 diabetes (T2DM). In tandem with the worldwide surge in the prevalence of obesity, a parallel rise in the prevalence of T2DM has also been observed over the past decade, making it one of the most common metabolic conditions worldwide.1,2 Although lifestyle modification remains the mainstay of all obesity treatment strategies, obesity pharmacotherapy can be a safe and effective adjunct to lifestyle modification.3–5 To date, only seven drugs have been available for obesity treatment and three (sibutramine, rimonabant and lorcaserin) have been subsequently withdrawn for safety concerns. With the exception of orlistat available since 1998, remaining therapies have only recently become available within the last decade.6 This systematic review aims to summarise the efficacy of available pharmacotherapies in the setting of randomised clinical research trials, as well as those pharmacotherapies licensed for other indications subjected to randomised trial investigation for weight loss.

The aim of this study is to review systematically the evidence available and assess changes from baseline in body weight (%) for pharmacotherapy treatments for weight loss in patients with T2DM in comparison with placebo.

Methods
The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The methodology of the analysis and inclusion criteria were pre-specified in advance and documented in a protocol (see Appendix 1 available online www.bjd-abcd.com).

Eligibility criteria
The review included randomised controlled trials (RCTs) investigating pharmacotherapy for weight loss from peer-reviewed literature published in English since July 2004. The last systematic review on this topic conducted a search until June 2004. Participants were adult patients with T2DM. The intervention was defined as medical treatments with the primary objective of weight loss compared with placebo. This included pharmacotherapy approved for obesity treatment per se and other agents investigated for weight loss. Weight loss strategies such as behavioural therapy could be used in conjunction with the intervention. No minimum
length of follow-up time was established. Obesity pharmacotherapy used for shorter periods may offer an opportunity to bridge patients to other long-term treatments, or to achieve a targeted short-term weight loss goal (eg, in the run-up to orthopaedic surgery). Furthermore, the short-term duration response allows understanding on long-term pharmacotherapy maintenance. In clinical practice, if the patient is a non-responder (ie, does not lose at least 5% of body weight at 12 weeks maximum dose), treatment should be discontinued.

Pharmacotherapy withdrawn from the market due to safety concerns and non-regulated supplements were excluded from this review. Primary outcomes were defined as changes in body weight (%) from baseline. Secondary outcomes were defined as changes from baseline in glycated haemoglobin (HbA1c) (%), mmol/mol) and proportion of patients achieving ≥5% weight loss.

Information sources and search strategy
Electronic searches were performed of PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials and medRxiv, supplemented with searches of reference lists and selected journals. The databases were searched from July 2004 to July 2020. The final search strategy for PubMed was performed as follows: (((Weight Loss/drug therapy)[Mesh]) OR (Obesity/ drug therapy)[Mesh]) OR (Anti-Obesity Agents)[Mesh]) OR (Overweight/drg therapy)[Mesh]) OR (Appetite Depressants)[Mesh]) AND (Diabetes Mellitus, Type 2)[Mesh]. Filters: English, from 2004 to 2020.

Study selection and data collection process
Titles and abstracts were reviewed for relevance by one author. If information in the abstracts was insufficient, two review authors retrieved and assessed potentially relevant full texts for inclusion. In cases of uncertainty, the other review author was consulted and consensus attained; if required, a third author was consulted. For all included studies, one review author extracted the data using a standardised template and a second author verified the extracted data for accuracy. Mean values of change from baseline in weight and HbA1c during follow-up were extracted at the end of the intervention. All data reported as absolute values during follow-up were converted to change from baseline in unit percent by dividing by the baseline weight.

Assessment of risk of bias
The risk of bias was assessed by the Jadad score including appropriateness of randomisation, adequate blinding and detailed report of withdrawals. The Jadad score was used for descriptive purposes and not for study selection.

Results
Study selection
The PRISMA flow diagram is shown in Figure 1.

Study characteristics
Fifteen RCTs met our inclusion criteria with a total of 4,207 participants. The studies reported on eight different agents investigated for weight loss, four agents approved by the Food and Drug Administration and/or European Medicines Agent (EMA) for obesity treatment (orlistat, liraglutide, naltrexone-bupropion and phentermine-topiramate) and four others investigated for the primary purpose of weight loss (topiramate, metreleptin, dapagliflozin and exenatide). Orlistat, liraglutide and naltrexone-bupropion are approved by the EMA and are available in the UK; however, only orlistat is readily accessible in the National Health Service (NHS). More recently, the National Institute for Health and Care Excellence (NICE) has approved the use of liraglutide 3 mg (Saxenda®) in the English and Welsh NHS for patients with a body mass index >35 kg/m², pre-diabetes, increased cardiovascular risk and referred to a Tier 3 structured weight loss programme. Four trials were multinational, nine studies were multicentric based in one country and two studies were single-centre. The year of publication ranged from 2004 to 2020. In terms of T2DM background medication, three studies included patients treated solely with diet, in four studies participants were only taking metformin and in seven studies participants were on multiple glucose-lowering agents. Thirteen studies excluded patients on insulin, whilst one study specifically enrolled patients on basal insulin. All studies were randomised, double-blinded, placebo-controlled and parallel assignment. Participants were randomised to weight loss medication versus placebo. In all studies, with one exception, participants were placed on adjunctive lifestyle interventions, which included calorie restriction and increased physical activity recommendations. Fourteen studies reported on change in HbA1c, and 10 studies informed on the proportion of patients achieving ≥5% body weight loss. Outcome measures were assessed at the end of the intervention, which varied from 12 to 56 weeks.

<p>| Table 1 Quality assessment of eligible randomised controlled trials using the Jadad score to assess methodological quality of controlled clinical trials (including appropriateness of randomisation, adequate blinding and reports of withdrawals) |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Adequate sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Dropout addressed</th>
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</table>
One study reported on weight 12 weeks after treatment discontinuation. Quality assessment evaluated by the Jadad score is shown in Table 1 and study characteristics are shown in Table 2. Outcomes in body weight loss (%), changes from baseline in HbA1c (mmol/mol) and proportion of patients who achieved ≥5% weight loss are presented in Figures 2, 3 and 4, respectively.

**Pharmacotherapy approved for weight loss**

**Orlistat**

Five RCTs investigated orlistat, comprising a total of 976 patients. Sample size varied from 60 to 254 participants and study duration ranged from 12 to 52 weeks. The majority of patients were on metformin and sulfonylurea, a smaller subset of participants were taking insulin (n=14). All studies demonstrated significant body weight loss from baseline with orlistat, ranging from 3.3% at 12 weeks to 10.1% at 52 weeks. Furthermore, reduction in HbA1c of 0.5% (5.5 mmol/mol) at 24 weeks to 1.7% (18.6 mmol/mol) at 12 weeks was noted with orlistat versus 0.2% (2.2 mmol/mol) to 0.6% (6.6 mmol/mol) with placebo. At the end of the trial, in comparison to placebo, all studies found a significant body weight and HbA1c reduction, except for one trial in which no differences were found in glycaemic control. Two trials reported on the proportion of patients who achieved more than 5% body weight loss, 35.1–45.9% of patients assigned to orlistat versus 7.3–10.9% of those taking placebo. The discontinuation rate of the study drug was stated in three trials and varied from 6.4% to 13.5% for patients in the orlistat arm and from 4.0% to 13.8% in the placebo group.
### Table 2  
Study characteristics of eligible RCTs included in this systematic review (between 2004 and 2020) investigating pharmacotherapy for weight loss in adult patients with T2DM

<table>
<thead>
<tr>
<th>Author, year, ref</th>
<th>Settings</th>
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<th>Duration</th>
<th>Study population - baseline</th>
<th>Intervention</th>
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<tr>
<td>Guy-Grand, 200411</td>
<td>253 sites in France</td>
<td>n=193</td>
<td>24 weeks</td>
<td>NR for patients with T2DM</td>
<td>Orlistat or placebo 120 mg three times daily, oral tablet</td>
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</tbody>
</table>
| Berne, 20058 | 16 sites in Sweden | n=220 | 52 weeks | Orlistat (n=111) - Female sex: 50 (45); Age: 58.9 years (9.1); Race: White 111 (100); Body weight: 95.3 kg (12.6); BMI: 32.6 kg/m² (3.1); HbA1C: 7.6% (0.8); Diabetes duration: NR  
OADs: Metformin 35 (32), SUs 76 (68) | Orlistat or placebo 120 mg three times daily, oral tablet |
| Shi, 200512 | 12 sites in China | n=249 | 24 weeks | Orlistat (n=124) - Female sex: 64 (52); Age: 49 years (range 26-64); Race: Asian 124 (100); Body weight: 76.8 kg (2.1); BMI: 29.8 kg/m² (6.5); HbA1C: 7.3% (0.7); Diabetes duration: NR  
OADs: Exclusion criteria | Orlistat or placebo 120 mg three times daily, oral tablet |
| Kuo, 20069 | 1 site in Taiwan | n=60 | 12 weeks | Orlistat (n=30) - Female sex: 30 (100); Age: NR; Race: Asian 30 (100); Body weight: NR; BMI: NR; HbA1C: NR; Diabetes duration: 9.1 years (0.5)  
OADs: Metformin 30 (100), SUs 30 (100) | Orlistat or placebo 120 mg three times daily, oral tablet |
| Derosa, 201210 | 2 sites in Italy | n=254 | 52 weeks | Orlistat (n=126) - Female sex: 64 (50.8); Age: 53 years (6); Race: White (100); Body weight: 94.5 kg (9.6); BMI: 33.1 kg/m² (2.9); HbA1C: 8.4% (1.4); Diabetes duration: 6 years (4)  
OADs: Metformin 75 (63), SUs 22 (18.5), TZD 53 (44.5), α-glucosidase inhibitors 28 (23.5), DPP-4i 13 (10.9), GLP-1 agonists 9 (7.6), Glinides 19 (16), Insulin 14 (11.1) | Orlistat or placebo 120 mg three times daily, oral tablet |
| Davies, 201513 | 126 sites in 9 countries SCALE Diabetes | n=846 | 56 weeks | Liraglutide 3.0 mg (n=423), Liraglutide 1.8 mg (n=211) - Female sex: 203 (48), 103 (49); Age: 55 years (10.8), 54.9 (10.7); Race: White 353 (83.5), 177 (83.9); Body weight: 105.7 kg (21.9), 105.8 (21); BMI: 37.1 kg/m² (6.5), 37.0 (6.9); HbA1C: 7.9% (0.8), 8 (0.8); Diabetes duration: 7.5 years (5.7), 7.4 years (5.2)  
OADs: None 46 (11.2), 29 (14.2); Metformin 355 (84), 172 (82); SUs 107 (25), 51 (24); TZD 36 (1), 18 (9) | Liraglutide 3.0 mg, liraglutide 1.8 mg or placebo administered once daily by subcutaneous injection |
| Garvey, 202014 | 53 sites in 7 countries SCALE Insulin | n=396 | 56 weeks | Liraglutide 3.0 mg (n=198) - Female sex: 108 (56); Age: 55.9 years (11.3); Race: White 174 (87.9); Body weight: 100.6 kg (20.8); BMI: 35.9 kg/m² (6.5); HbA1C: 7.9% (1.1); Diabetes duration: 11.4 years (6.8)  
OADs: Metformin 175 (88.4); SUs 68 (34); SGLT-2i 44 (22.2); TZD 4 (2); Long acting insulin 180 (90.9); Intermediate-insulin 18 (9.1) | Liraglutide 3.0 mg or placebo administered once daily by subcutaneous injection |
| Hollander, 201315 | 53 sites in USA | n=505 | 56 weeks | NB, mITT (n=265) - Female sex: 147 (54.3); Age: 53.9 years (9.2); Race: White 207 (78.1); Body weight: 106.3 kg (19.1); BMI: 36.7 kg/m² (4.8); HbA1C: 8% (0.8); Diabetes duration: NR  
OADs: Metformin 212 (79.6), SUs 130 (49.1), TZD 82 (31.3) | Naltrexone Sustained-Release 32 mg combined with Bupropion Sustained-Released 360 mg, or placebo, oral tablet |
| Gadde, 201116 | 93 sites in USA CONQUER | n=388 | 56 weeks | PT 7.5/46 mg (n=67), PT 15/92 mg (n=164) - Female sex: 44 (66), 102 (62); Age: 52.5 years (9.3), 52.1 (10.1); Race: White 63 (94), 136 (83); Body weight: 97.2 kg (16.1), 103.2 (20.1); BMI: 35.3 kg/m² (4.3), 37.1 (5.2); HbA1C: 6.8% (1.2), 6.8 (1.1); Diabetes duration: 5.1 (4.3) years, 4.6 (3.6)  
OADs: Metformin 40 (60), 95 (58) | Phentermine 15 mg combined with topiramate 92 mg, phentermine 7.5 mg combined with topiramate 46 mg, or placebo, oral tablet |

Continued...
decreased by 1.1% (12 mmol/mol) in the liraglutide group and in participants taking placebo. In terms of metabolic control, mg lost 5.8% of their baseline body weight compared with 1.5% SCALE Insulin, the patients who were assigned to liraglutide 3.0 respectively. The 12-week follow-up evidenced weight regain. In mmol/mol) in the liraglutide 3.0 mg, 1.8 mg and placebo arms, re SCALE Diabetes had a 12-week observational follow-up period weeks, which included a 4-week titration phase. Additionally, patients medicated with insulin, whereas the SCALE Insulin trial arm versus 16.2% and 15.2% of participants in the liraglutide and discontinued the study drug compared with 33.9% in the placebo SCALE Diabetes, 23.4% participants in the liraglutide 3.0 mg arm the patients achieved ≥ 5% weight loss on liraglutide 3.0 mg. In 0.6% (6.6 mmol/mol) in the placebo-treated group. Furthermore, 21 participants on liraglutide (versus three participants on placebo) were able to discontinue insulin. In both trials, more than half of the patients achieved ≥ 5% weight loss on liraglutide 3.0 mg. In SCALE Diabetes, 23.4% participants in the liraglutide 3.0 mg arm discontinued the study drug compared with 33.9% in the placebo arm versus 16.2% and 15.2% of participants in the liraglutide and placebo arms, respectively, in SCALE Insulin.

Naltrexone-bupropion
In a 56-week trial of naltrexone-bupropion, 505 participants were randomised to naltrexone-bupropion or placebo in a 2:1 ratio. The investigational medicinal product was taken as a single tablet containing 8 mg naltrexone sustained release (SR) combined with 90 mg bupropion SR, or placebo. The dose was titrated over 4 weeks to a maintenance dose of 32 mg naltrexone SR and 360 mg bupropion SR, taken as 4 tablets daily. Patients assigned to naltrex-

<table>
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<tr>
<th>Author, year, ref</th>
<th>Settings</th>
<th>Sample size</th>
<th>Duration</th>
<th>Study population - baseline</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apovian, 2010&lt;sup&gt;17&lt;/sup&gt;</td>
<td>11 sites in USA</td>
<td>n= 194</td>
<td>24 weeks</td>
<td>Exenatide (n=96) - Female sex: 60 (63); Age: 54.5 years (10); Race: NR; Body weight: 94.9 kg (16.5); BMI: 33.6 kg/m² (3.7); HbA₁c: 7.7% (0.9); Diabetes duration: 5.7 years (5.5)</td>
<td>Exenatide twice daily injection 5 μg or placebo</td>
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<td>Bolinder, 2012&lt;sup&gt;18&lt;/sup&gt;</td>
<td>40 sites in 5 countries</td>
<td>n= 182</td>
<td>24 weeks</td>
<td>Dasagliflozin (n=89) - Female sex: 49 (55.1); Age: 60.6 (8.2); Race: White 89 (100); Body weight: 92.1 kg (14.1); BMI: 32.1 kg/m² (3.9); HbA₁c: 7.2% (0.4); Diabetes duration: 6 years (4.5)</td>
<td>Dasagliflozin 10 mg or placebo once daily, oral tablet</td>
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<tr>
<td>Moon, 2011&lt;sup&gt;19&lt;/sup&gt;</td>
<td>1 site in 1 country</td>
<td>n=71</td>
<td>16 weeks</td>
<td>Metreleptin (n=50) - Female sex: 21 (42); Age: 53.3 years (11.4); Race: NR; Body weight: NR; BMI: 32.7 kg/m² (0.5); HbA₁c: 8.01% (0.9); Diabetes duration: NR</td>
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<td>Rosenstok, 2007&lt;sup&gt;22&lt;/sup&gt;</td>
<td>22 sites in USA</td>
<td>n=113</td>
<td>16 weeks</td>
<td>Topiramate, mITT (n=54) - Female sex: 42 (78); Age: 51.8 (11.5); White: 38 (70); Body weight: 106 kg (17.2); BMI: 38.1 kg/m² (5.3); HbA₁c: 7.6% (0.9); Diabetes duration: NR</td>
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<td>Toplak, 2007&lt;sup&gt;21&lt;/sup&gt;</td>
<td>68 sites in Canada, Europe and Africa</td>
<td>n=307</td>
<td>24 weeks (planned for 52 weeks)</td>
<td>Topiramate 96 mg (n=102), 192 mg (n=105) (mITT)- Female sex: NR; Age: NR; Race: NR; Body weight: NR; BMI: NR; kg/m²: 7.1%, 7.1; Diabetes duration: NR</td>
<td>Topiramate 96 mg, topiramate 192 mg or placebo once daily, oral tablet</td>
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<tr>
<td>Stenlöf, 2007&lt;sup&gt;20&lt;/sup&gt;</td>
<td>20 sites in Sweden</td>
<td>n=229</td>
<td>40 weeks (planned for 52 weeks)</td>
<td>Topiramate 96 mg (n=74), 192 mg (n=77) - Female sex: NR; Age: NR; Race: NR; Body weight: NR; BMI: NR; kg/m²: 6.9%, 6.8%; Diabetes duration: NR</td>
<td>Topiramate 96 mg, topiramate 192 mg or placebo once daily, oral tablet</td>
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</table>

Results for continuous variables presented as mean (SD) and for categorical variables as n (%), unless stated otherwise.
BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 agonists, glucagon-like peptide-1; MITT, modified intent-to-treat; NB, naltrexone-buproprion; NR, not reported; OADs, oral antidiabetics; PT, phentermine-topiramate; RCTs, randomised controlled trials; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SUs, sulfonylureas; TZD, thiazolidinediones; T2DM, type 2 diabetes.

Liraglutide
Two RCTs evaluated the efficacy of liraglutide 3.0 mg on weight loss in patients with T2DM, with a total of 1,242 participants. The SCALE Diabetes trial with liraglutide 3.0 mg and 1.8 mg excluded patients medicated with insulin, whereas the SCALE Insulin trial recruited exclusively patients taking insulin. Both trials lasted 56 weeks, which included a 4-week titration phase. Additionally, SCALE Diabetes had a 12-week observational follow-up period after drug discontinuation. In SCALE Diabetes, the weight reduction was 6.0%, 4.7% and 2.0% with an associated HbA₁c reduction of 1.3% (14.2 mmol/mol), 1.1% (12 mmol/mol) and 0.3% (3.3 mmol/mol) in the liraglutide 3.0 mg, 1.8 mg and placebo arms, respectively. The 12-week follow-up evidenced weight regain. In SCALE Insulin, the patients who were assigned to liraglutide 3.0 mg lost 5.8% of their baseline body weight compared with 1.5% in participants taking placebo. In terms of metabolic control, HbA₁c decreased by 1.1% (12 mmol/mol) in the liraglutide group and 0.6% (6.6 mmol/mol) in the placebo-treated group. Furthermore, 21 participants on liraglutide (versus three participants on placebo) were able to discontinue insulin. In both trials, more than half of the patients achieved ≥ 5% weight loss on liraglutide 3.0 mg. In SCALE Diabetes, 23.4% participants in the liraglutide 3.0 mg arm discontinued the study drug compared with 33.9% in the placebo arm versus 16.2% and 15.2% of participants in the liraglutide and placebo arms, respectively, in SCALE Insulin.
Figure 2. Effect of weight loss pharmacotherapy versus placebo on body weight reduction (%) from baseline to follow-up. In all studies, participants were on adjunctive lifestyle interventions. The RCTs were grouped by weight loss agent. Weight loss was assessed at the end of the intervention, ranging from 12 to 56 weeks.

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<th>Liraglutide</th>
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<td>-1.8</td>
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<td>-1.4</td>
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<td>-5</td>
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Key: NS = Non-sig (vs placebo), * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001

RCTs, randomised controlled trials

Figure 3. Effect of weight loss pharmacotherapy versus placebo on HbA1c (mmol/mol) from baseline to follow-up. In all studies, participants were on adjunctive lifestyle interventions. The RCTs were grouped by weight loss agent. Weight loss was assessed at the end of the intervention, ranging from 12 to 56 weeks.

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<th>Orlistat</th>
<th>Exenatide</th>
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Key: NS = Non-sig (vs placebo), * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001

RCTs, randomised controlled trials
one-bupropion had a 5.0% reduction in their baseline body weight compared with 1.8% in patients on placebo. Moreover, HbA1c dropped by 0.6% (6.6 mmol/mol) in patients taking naltrexone-bupropion versus 0.1% (1.1 mmol/mol) in patients allocated to placebo. More thandouble the patients assigned to naltrexone-bupropion lost at least 5% of their initial body weight compared with those on placebo (44.5% versus 18.9%). Over the trial period, 160 (47.8%) participants in the naltrexone-bupropion group discontinued the study drug compared with 70 (41.2%) participants in the placebo group. Efficacy analyses were performed using the modified intent-to-treat and last observation carried forward.

**Phentermine-topiramate**

In CONQUER, a 56-week trial, 2,487 patients with two or more weight-related complications were randomised to either phentermine-topiramate at two different doses or placebo.16 The 388 participants who had T2DM were included in the review. Patients randomised to phentermine 15 mg plus topiramate 92 mg (PT 15/92 mg) or phentermine 7.5 mg plus topiramate 46 mg (PT 7.5/46 mg) lost 8.8% and 6.8% of their baseline body weight, respectively, compared with 1.9% in patients in the placebo group. Patients assigned to both doses of phentermine-topiramate showed HbA1c improvements of 0.4% (4.4 mmol/mol) compared with 0.1% (1.1 mmol/mol) in the placebo group. The proportion of patients who achieved ≥5% of weight loss was not reported. There was a 24.4% and 22.4% drug discontinuation rate for PT 15/92 mg and PT 7.5/46 mg, respectively, in comparison to 28.0% for placebo.

**Non-approved pharmacotherapy for weight loss**

**Exenatide**

Exenatide is an injectable incretin mimetic used for T2DM treatment. One RCT studied the effect of a lifestyle modification programme plus exenatide 5 μg twice daily injection on weight loss in 194 patients with T2DM medicated with metformin or sulfonylurea.17 At 24 weeks, participants on exenatide had a 6.5% body weight reduction compared with 4.1% in patients on placebo. The HbA1c change was 1.2% (13.1 mmol/mol) for participants taking exenatide versus 0.7% (7.7 mmol/mol) for placebo. Half of the participants taking exenatide achieved ≥5% weight loss compared with one-third of patients assigned to placebo. The discontinuation rate was 26.8% in the exenatide group and 26.2% in the placebo group.

**Dapagliflozin**

Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT-2) inhibitor approved for T2DM treatment. In a 24-week trial of dapagliflozin with 182 participants the authors aimed to confirm weight loss and determine if body weight reduction was due to fat or fluid components.18 Participants who were treated with dapagliflozin 10 mg lost 3.2% of their initial body weight and had an HbA1c reduction of 0.4% (4.4 mmol/mol) compared with a 1.0% weight loss and 0.1% (1.1 mmol/mol) HbA1c reduction in the placebo group. With dapagliflozin, 30.5% of individuals achieved ≥5% weight loss versus 4.3% with placebo. Additionally, body composition measurements demonstrated that the weight loss associated
Topiramate
Three RCTs investigated topiramate for weight loss, including a total of 649 participants. The formulations were 192 mg, 175 mg and 96 mg/day. In two trials there was a 6-week single-blind placebo run-in. In all trials there was a 7–8-week titration period. Patients were recently diagnosed with T2DM and drug-naive, or solely on metformin. Two trials were interrupted early due to the sponsor's decision to pursue other formulations to improve tolerability and simplify dosage. In a brought forward and intent-to-treat analysis performed at 24 weeks with 307 patients medicated with metformin for T2DM, topiramate showed significant body weight reduction (6.5% for topiramate 192 mg, 4.5% for topiramate 96 mg) and HbA1c improvement (0.6% for topiramate 192 mg, 0.4% for topiramate 96 mg) compared with the control group (1.7% body weight reduction, 0.1% HbA1c improvement). Moreover, in a brought forward and intent-to-treat analysis completed at 40 weeks with 229 patients naïve to glucose-lowering drug treatment, topiramate significantly reduced body weight (9.1% for topiramate 192 mg, 6.6% for topiramate 96 mg) and HbA1c (0.7% for topiramate 192 mg, 0.6% for topiramate 96 mg) compared with the control group (2.5% weight loss, 0.2% HbA1c reduction). An RCT with topiramate 175 mg/day for 16 weeks in 113 participants on metformin showed 5.8% baseline body weight loss in the topiramate arm compared with 2.3% in the placebo group and a placebo-adjusted HbA1c improvement of 0.5% (5.5 mmol/mol). In all studies, the proportion of patients assigned to topiramate who achieved ≥5% body weight loss ranged from 42% with topiramate 96 mg to 77.0% in individuals taking topiramate 192 mg.

Discussion
Weight loss effects
With the exception of leptin therapy, all pharmacotherapy agents investigated in this systematic review demonstrated significantly greater weight loss compared with placebo in patients with T2DM. The intensity of the lifestyle interventions in the clinical trials varied, so placebo-subtracted weight loss was used to compare weight loss attributable to pharmacological agents alone, which ranged from 2.2% to 7.3%. For agents authorised for obesity treatment only, the weight loss was greatest for orlistat at 2.8–7.3% (but with significant variability), 6.9% for phentermine-topiramate 15/92 mg, 4.0–4.3% for liraglutide 3.0 mg and 3.2% for naltrexone-bupropion 32/360 mg. Non-approved pharmacotherapy for weight loss achieved broadly similar weight reductions ranging from 2.2% to 6.6%, with the greatest weight loss observed with topiramate at 2.8–6.6%, 2.4% for exenatide and 2.2% for dapagliflozin. Of note, these endpoints were measured on different time scales, which may have impacted the weight loss magnitude which tends to plateau at 6 months. Furthermore, baseline weight and background medication for T2DM varied across studies. The variable weight loss observed with orlistat may be explained by the fact that the lowest weight loss (2.8%) was measured after 12 weeks of treatment, with maximum weight reduction unlikely to have been reached by that time point. Individuals assigned to topiramate 192 mg showed a notable placebo-subtracted weight loss of 6.6%, and 77% of participants achieved ≥5% weight loss. All participants had been recently diagnosed with T2DM and were drug naïve, which may partly explain these results. Topiramate at a lower dose (92 mg) is approved for weight loss in conjunction with phentermine 15 mg, as both drugs are used at lower doses with synergistic effect on weight loss, as shown by the significant body weight reduction of 6.9% in the CONQUER trial.

This systematic review compares with a meta-analysis in 2004 involving 2,231 patients, which assessed weight loss outcomes from 14 RCTs using either fluoxetine, orlistat or sibutramine in individuals with T2DM. The meta-analysis concluded that, whilst all pharmacotherapies achieved statistically significant weight loss over a short-term period, more studies with a longer follow-up period were required to fully understand the effect of these drugs on weight and other health outcomes. Individuals with T2DM may be somewhat more disadvantaged when it comes to successful weight management. It has been consistently shown that patients with T2DM lose less weight with any treatment modality than those who do not have T2DM. The COR-I and COR-II trials with naltrexone-bupropion in patients without T2DM revealed a greater weight loss compared with COR-Diabetes of 4.8% and 5.2% versus 3.2%, respectively. In the CONQUER trial with phentermine-topiramate, the subpopulation of patients with T2DM showed a weight reduction of 6.9% compared with the mean weight loss in all patients of 8.6%. In SCALE Obesity with liraglutide, patients without T2DM lost 5.4% of their body weight compared with 4% in SCALE Diabetes. The reasons for these observations have not yet been fully elucidated but it is thought that the pathophysiological processes of T2DM itself may make weight loss more difficult to achieve. The use of certain glucose-lowering agents such as insulin, sulfonylureas...
and thiazolidinediones has been associated with weight gain. Furthermore, fear of hypoglycaemia and use of polypharmacy in the management of co-morbidities associated with T2DM may render behavioural modification more challenging.3,28-30 SCALE Diabetes evaluated weight changes after drug discontinuation and showed weight gain, highlighting the need to maintain anti-obesity therapy long term.31 Several clinical trials with glucose-lowering agents have assessed weight loss as a secondary outcome. Clinical trial data suggest that SGLT-2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists produce a mean weight loss of approximately 2–3 kg in patients with T2DM. Despite their efficacy, there is considerable heterogeneity in their weight loss effect.31 The Semaglutide Treatment Effect in People with obesity (STEP trials 1–5) aims to investigate the effect of semaglutide 2.4 mg once weekly versus placebo on weight loss in adults with obesity. The STEP 2 trial specifically enrolled patients with T2DM. Results are expected to be published in 2021 and it is anticipated that semaglutide will be a new effective agent for weight loss.32

Glycaemic effects
For all but two of the studies (one with orlistat30 and the other with leptin39), significant glycaemic improvement was achieved with weight loss pharmacotherapy in comparison with placebo. The results of the systematic review showed a mean HbA1c corrected to placebo reduction of 0.3% (3.3 mmol/mol) to 1.5% (16.4 mmol/mol). The reduction in HbA1c yielded by glucose-lowering agents—namely, dapagliflozin and exenatide, 0.3% (3.3 mmol/mol) and 0.5% (5.5 mmol/mol), respectively—was aligned with the glycaemic improvements evidenced with pharmacotherapy approved for obesity: 0.5% (5.5 mmol/mol) for naltrexone-bupropion, 0.3% (3.3 mmol/mol) for phentermine-topiramate, 0.3–1.5% (3–16.4 mmol/mol) for orlistat and 0.5–1% (5.5–10.9 mmol/mol) for liraglutide 3.0 mg. The HbA1c was measured at different timelines in patients on various T2DM treatment regimens, which may have impacted HbA1c outcomes. Moreover, interpretation of HbA1c should be interpreted with care due to the concomitant reduction in the number and dose of glucose-lowering agents observed in patients taking anti-obesity agents, which may lead to underestimation of glycaemic improvement. For instance, the difference in HbA1c reduction with liraglutide 1.8 mg and liraglutide 3.0 mg in SCALE Diabetes was significant, albeit marginal at 0.2% (2.2 mmol/mol); however, patients assigned to liraglutide 3.0 mg demonstrated a greater decrease in use of glucose-lowering agents than those taking liraglutide 1.8 mg (13.1% vs 8.3%). With orlistat, HbA1c changes were beyond what would be expected with the magnitude of weight loss observed. The mechanism by which orlistat improves T2DM has been suggested to be partly weight-independent.33 Although weight reduction was more prominent with the higher dose of phentermine-topiramate, the change in HbA1c was the same for both doses (0.4%, 4.4 mmol/mol). Importantly, only liraglutide (at the 1.8 mg dose) and dapagliflozin have shown cardiovascular benefit in patients with T2DM.34,35 Cardiovascular outcome trials with naltrexone-bupropion were terminated prematurely twice due to early release of preliminary results and the sale of the drug rights to another pharmaceutical company.36

Limitations of the study
The searches conducted only included studies in English. There is a relative paucity of data and study heterogeneity was not assessed. The evidence is also limited by lack of ethnic diversity as the majority of participants were white or Asian, middle-aged with obesity class 1 and 2, which suggests that results may not be applicable to all patients with obesity. Furthermore, the maximum study duration was only 1 year and the study durations differed, which limits the scope for comparisons across weight loss medications.

Conclusions and implication of key findings
Significant weight loss and glycaemic improvement have been demonstrated in patients with T2DM treated with weight loss pharmacotherapy up to 1 year. However, in the absence of longer term clinical trials, real-world data will be required to assess the long-term effects on sustainability of weight loss, improvement in HbA1c and cardiovascular outcomes. Further studies with larger groups of patients from black and minority ethnic backgrounds would be informative. When choosing pharmacotherapy for weight loss in patients with T2DM, several factors should be taken into account including co-morbidities, concomitant medications, expected weight loss, side effect tolerability and cost. Knowledge of weight-related and glycaemic effects of weight loss agents enable individualised regimens to be designed which may assist in obesity and diabetes management.

The approach for weight loss management should be a complications-centric model focused on preventing and ameliorating weight-related complications and not merely weight reduction.

Conflict of interest BM reports grants and personal fees from Novonordisk and personal fees from MSD, Jansen, Lilly, BI, Napp and Novonordisk outside the submitted work.

Funding None.

References


Appendix 1. Protocol

PHARMACOTHERAPY FOR WEIGHT LOSS IN ADULTS WITH TYPE 2 DIABETES – A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS
Not registered in Prospero
Claudia Coelho1, Rachel Agius2, James Crane1, Barbara McGowan1,3
1 Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom
2 Diabetes and Endocrine Centre, Mater Dei Hospital, Msida, Malta
3 King’s College London - Diabetes and Nutritional Sciences, London, United Kingdom

Review question
For adults with type 2 diabetes, which medical treatments are available for weight loss, and does it result in significant weight loss when compared with placebo?

Searches
The search comprises keywords for the following concepts: T2DM, weight loss and pharmacotherapy. The databases will be searched from July 2004 to July 2020. English language filters will be applied.
MEDLINE via PubMed (NLM/NCBI)
Web of Science
EMBASE
Cochrane Central Register of Controlled Trials (CENTRAL)
medRxiv
Supplemented with hand searches of reference lists and selected journals

Types of study to be included
Randomised controlled trials
Inclusion criteria: Medical treatments with the primary objective of weight loss, compared to placebo. Pharmacotherapy approved for obesity treatment per se and other agents investigated for weight loss. Weight loss strategies such as behavioural therapy could be used in conjunction with the intervention. No minimum length of follow-up time was established.
Exclusion criteria: Pharmacotherapy withdrawn from market due to safety concerns and non-regulated supplements.

Condition or domain being studied
Obesity

Participants/population
Adults with type 2 diabetes

Intervention(s), exposure(s)
Use of pharmacotherapy for the primary purpose of weight loss

Comparator(s)/control
Placebo

Main outcome(s)
a) Primary – Efficacy of Weight loss
Change from baseline in body weight (kg, %)

Additional outcome(s)
a) Secondary - Glycaemic control improvement
Change from baseline in HbA1c (% , mmol/mol)
b) Secondary – Efficacy of weight loss
Proportion of patients who achieved > 5% weight loss

Data extraction (selection and coding)
Titles and abstracts are reviewed for relevance by one author. If information in the abstracts is insufficient, 2 review authors will retrieve and assess potentially relevant full texts for inclusion. In cases of uncertainty, the other review author will be consulted, and consensus attained. For all included studies, one review author will extract the data using a standardized template (excel) and a second author verify the extracted data for accuracy. Mean values of change from baseline in weight and HbA1c during follow-up are extracted at the end of the intervention. All data reported as absolute values during follow-up will be converted to change from baseline in unit percent by dividing by the baseline weight. Authors of individual studies may be contacted for clarification.

Risk of bias (quality) assessment
Jadad score used at outcome and study level

Strategy for data synthesis
We will provide narrative synthesis of the findings from included studies. We will present the studies by drug name and summarize findings pertinent to weight loss and glycaemic control. We will not provide detailed summaries of their statistical findings but instead comment more broadly on study design characteristics and outcome measurements and how these may impact clinical use.

Analysis of subgroups or subsets
Not provided.

Contact details for further information
Author for correspondence – Prof Barbara McGowan Barb.h.mcgowan@gstt.nhs.uk

Type and method of review
Systematic review

Anticipated or actual start date
May 2020

Anticipated completion date
September 2020

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None specified.

Conflicts of interest
None specified.
None known

Language
English

Country
United Kingdom

Stage of review
Review completed September 2020

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