How Do We Treat Obesity?

Weight Loss Medications
<table>
<thead>
<tr>
<th>Anti-obesity Medication (Trade Name, Year of FDA Approval)</th>
<th>Mechanism of Action, Study Name, Study Duration, % TBWL Greater Than Placebo</th>
<th>Dose</th>
<th>Common Side Effects</th>
<th>Contraindications, Cautions, and Safety Concerns</th>
<th>Monitoring and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orlistat</strong> (Xenical™ (Alli™) – OTC, 1999)</td>
<td>Lipase Inhibitor XENDOS 1 yr: 4.0% 4 yr: 2.6%</td>
<td>120 mg PO TID (before meals) OTC: 60 mg PO TID (before meals)</td>
<td>- Steatorrhea - Fecal urgency - Incontinence - Flatulence - Oily spotting - Frequent bowel movements - Abdominal pain - Headache</td>
<td>✓ Contraindication: Pregnancy and breastfeeding ✓ Chronic malabsorption syndrome ✓ Cholestasis ✓ Oxalate nephrolithiasis - Rare severe liver injury - Cholelithiasis - Malabsorption of fat-soluble vitamins - Effects on other medications: Lipid-soluble vitamins, Warfarin (enhance) Antiepileptics (decrease) Levetiracetam (decrease) Cyclosporine (decrease)</td>
<td>Monitor for: - Cholelithiasis - Nephrolithiasis - Recommend standard multivitamin (to include vitamins A, D, E, and K) at bedtime or 2 hours after orlistat dose - Eating &gt;30% kcal from fat results in greater GI side effects - FDA-approved for children ≥ 12 years old - Monitor for levonorgestrel and orlistat 4 hours apart</td>
</tr>
<tr>
<td><strong>Lorcaserin</strong> (Belviq™, 2012)</td>
<td>Serotonin (5HT2c) receptor agonist BLOSSOM BLOOM 1 yr: 3.0%-3.6% 2 yr: 3.1%</td>
<td>10 mg PO BID</td>
<td>- Headache - Nausea - Dizziness - Fatigue - Xerostomia - Dry eye - Constipation - Diarrhea - Back pain - Nasopharyngitis - Hyperprolactinemia</td>
<td>✓ Contraindication: Pregnancy and breastfeeding ✓ Serotonin syndrome or neuroleptic malignant syndrome ✓ Safety data lacking in patients who have depression ✓ Concomitant use of SSRI, SNRI, MAOI, bupropion, St. John’s wort as may increase risk of developing serotonin syndrome ✓ Uncontrolled mood disorder ✓ Cognitive impairment ✓ Avoid in patients with severe liver injury or renal insufficiency ✓ Caution with patients with bradycardia, heart block, or heart failure ✓ Uncommon concern for potential cardiac valvulopathy ✓ Leukopenia</td>
<td>Monitor for: - Symptoms of cardiac valve disease - Bradycardia - Serotonin syndrome - Neuroleptic malignant syndrome - Depression - Severe mood alteration, euphoria, dissociative state - Confusion/somnolence - Priapism - Leukopenia - Euphoria at high doses could predispose to abuse - Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas</td>
</tr>
<tr>
<td><strong>Phentermine/Topiramate ER</strong> (Qsymia™, 2012)</td>
<td>NE-releasing agent (phentermine) GABA receptor modulation (topiramate) EQUIP CONQUER SEQUEL 1 yr: 8.6%-9.3% on high dose; 6.6% on treatment dose 2 yr: 8.7% on high dose; 7.5% on treatment dose</td>
<td>Starting dose: 3.75/23 mg PO QD for 2 weeks Recommended dose: 7.5/46 mg PO QD Escalation dose: 11.25/69 mg PO QD Maximum dose: 15/92 mg PO QD</td>
<td>- Headache - Parethesia - Insomnia - Decreased bicarbonate - Xerostomia - Constipation - Nausea - Prolactinemia</td>
<td>✓ Contraindication: Pregnancy and breastfeeding (topiramate teratogenicity) ✓ Hyperthyroidism ✓ Acute angle-closure glaucoma ✓ Concomitant MAOI use (within 14 days) ✓ Tachyarrhythmias ✓ Decreased cognition ✓ Seizure disorder ✓ Anxiety and panic attacks ✓ Nephrolithiasis ✓ Hyperchloremic metabolic acidosis ✓ Dose adjustment with hepatic and renal impairment ✓ Concern for abuse potential ✓ Combined use with alcohol or depressant drugs can worsen cognitive impairment</td>
<td>Monitor for: - Increased heart rate - Depressive symptomatology or worsening depression especially on maximum dose - Hypokalemia (especially with HCTZ or furosemide) - Acute myopia and/or ocular pain - Acute kidney stone formation - Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas - Potential for lactic acidosis (hyperchloremic non-anion gap) in combination with metformin - MSOD (allow ≥14 days between discontinuation) - 15 mg/92 mg dose should not be discontinued abruptly (increased risk of seizure); taper over at least 1 week - Health care professional should check HbA1C before initiating, followed by monthly self-testing at home - Monitor electrolytes and creatinine before and during treatment - Can cause menstrual spotting in women taking birth control pills due to altered metabolism of estrogen and progestins</td>
</tr>
<tr>
<td>Anti-obesity Medication (Trade Name)</td>
<td>Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo</td>
<td>Dose</td>
<td>Common Side Effects</td>
<td>Contraindications, Cautions, and Safety Concerns</td>
<td>Monitoring and Comments</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
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<td>---------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------</td>
</tr>
</tbody>
</table>
| Naltrexone ER/ Bupropion ER (Contrave*) | Opiate antagonist (naltrexone) Reuptake inhibitor of DA and NE (bupropion) COR-I COR-III COR-BMOD | Titrate dose:  
Week 1:  
1 tab (80/90 mg) PO QAM  
Week 2:  
1 tab (80/90 mg) PO BID  
Week 3:  
2 tabs (total 16/180 mg) PO QAM and 1 tab (8/90 mg) PO QHS  
Week 4:  
2 tabs (total 16/180 mg) PO QHS | • Nausea  
• Headache  
• Insomnia  
• Vomiting  
• Constipation  
• Diarrhea  
• Dizziness  
• Anxiety  
• Xerostomia | ✓ Contraindication  
• Pregnancy and breastfeeding  
• Uncontrolled hypertension  
• Seizure disorder  
• Anorexia nervosa  
• Bulimia nervosa  
• Severe depression  
• Drug or alcohol withdrawal  
• Concomitant MAOI (within 14 days)  
• Chronic opioid use  
• Cardiac arrhythmia  
• Dose adjustment for liver and kidney impairment  
• Narrow-angle glaucoma  
• Uncontrolled migraine disorder  
• Generalized anxiety disorder  
• Bipolar disorder  
• Safety data lacking in patients who have depression  
• Seizures (Bupropion lowers seizure threshold) | Monitor for:  
• Increased heart rate and blood pressure  
• Worsening depression and suicidal ideation  
• Worsening of migraines  
• Liver injury (naltrexone)  
• Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas  
• Seizures (Bupropion lowers seizure threshold)  
• MAOI (allow ≥14 days between discontinuation)  
• Dose adjustment for patients with renal and hepatic impairment  
• Avoid taking medication with a high-fat meal  
• Can cause false positive urine test for amphetamines  
• Bupropion inhibits CYP2D6 |
| Liraglutide 3 mg (Saxenda*) | GLP-1 analog SCALE Obesity & Prediabetes | Titrate dose weekly by 0.6 mg as tolerated by patient (side effects):  
0.6 mg SC QD  
1.2 mg SC QD  
1.8 mg SC QD  
2.4 mg SC QD  
3.0 mg SC QD | • Nausea  
• Vomiting  
• Diarrhea  
• Constipation  
• Headache  
• Dyspepsia  
• Increased heart rate | • Pregnancy and breastfeeding  
• Personal or family history of medullary thyroid cancer or MEN2  
• Pancreatitis  
• Acute gallbladder disease  
• Gastroparesis  
• Severe renal impairment can result from vomiting and dehydration  
• Use caution in patients with history of pancreatitis  
• Use caution in patients with cholelithiasis  
• Suicidal ideation and behavior  
• Injection site reactions | Monitor for:  
• Pancreatitis  
• Cholelithiasis and Cholecystitis  
• Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas  
• Increased heart rate  
• Dehydration from nausea/vomiting  
• Injection site reactions  
• Titrate dose based on tolerability (nausea and GI side effects) |

Abbreviations: BID = twice daily; DA = dopamine; FDA = US Food and Drug Administration; GI = gastrointestinal; HCTZ = hydrochlorothiazide; MAOI = monoamine oxidase inhibitor; MEN2 = multiple endocrine neoplasia type 2; NE = norepinephrine; OTC = over-the-counter medication; % TBWL = percent total body weight loss from baseline over that observed in the placebo group; PO = oral; QAM = every morning; QD = daily; QHS = every bedtime; SC = subcutaneous; SNI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TID = 3 times a day; T2DM = type 2 diabetes mellitus.

FDA indication for all medications: BMI ≥30 kg/m² or BMI ≥27 kg/m² with significant comorbidity.

After 3 to 4 months of treatment with antiobesity medication:
- For naltrexone ER/bupropion ER andlor contravers:
  - If the patient has not lost at least 5% of their baseline body weight at 12 weeks on the maintenance dose, the medication should be discontinued.
  - For phentermine/topiramate ER:
    - Continue medication if the patient has lost >5% body weight after 12 weeks on recommended dose (7.5 mg/42 mg); if the patient has not lost at least 3% of body weight after being on the recommended dose for 12 weeks then the medication should be discontinued, or the patient can be transitioned to maximum dose (15 mg/92 mg); if they do not lose at least 5% after 12 additional weeks on the maximum dose, the medication should be discontinued.

- For liraglutide 3 mg:
  - If the patient has not lost at least 4% of body weight 16 weeks after initiation, the medication should be discontinued.

References:
Phentermine

**Mechanism of Action**
- Sympathomimetic amine anorectic

**Indications**
- Short-term adjunct to diet and exercise in patients with
  - Treatment duration ≤12 weeks
  - BMI ≥30 kg/m²
  - BMI ≥27 kg/m² with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Hyperlipidemia
  - DEA Schedule IV Controlled Substance

**Dosing**
- 15, 30, or 37.5 mg once daily before breakfast or 1-2 hours after breakfast

See prescribing information for specific instructions

DEA = Drug Enforcement Agency; T2D = type 2 diabetes.
Phentermine: Summary of Warnings and Contraindications

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>Indicated for ≤12 weeks treatment duration</td>
</tr>
<tr>
<td>MAO inhibitor use</td>
<td>Coadministration with other weight loss drugs, including OTC products, and SSRIs not recommended</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Primary pulmonary hypertension</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Agitation</td>
<td>Drug tolerance and abuse/dependence risk</td>
</tr>
<tr>
<td>History of drug abuse</td>
<td>Impaired use of machinery/vehicles</td>
</tr>
<tr>
<td>Pregnant or nursing</td>
<td>Adverse drug reaction when used with alcohol</td>
</tr>
</tbody>
</table>

**Adverse Effects**

- Dry mouth
- Restlessness
- Insomnia
- Increase in pulse
- Increase in blood pressure

MAO = monoamine oxidase; OTC = over the counter; SSRI = serotonin reuptake inhibitor.

Phentermine: Clinical Efficacy

# Phentermine Adverse Events

<table>
<thead>
<tr>
<th>System</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Primary pulmonary hypertension and/or regurgitant valvular disease, palpitation, tachycardia, BP elevations, ischemic events</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Dryness of the mouth, unpleasant taste, diarrhea, constipation</td>
</tr>
<tr>
<td>Allergic</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Impotence, changes in libido</td>
</tr>
</tbody>
</table>
Orlistat

**Mechanism of Action**
- Reversible gastrointestinal lipase inhibitor

**Indications**
- Weight loss and weight maintenance in conjunction with a reduced calorie diet
  - BMI ≥30 kg/m²
  - BMI ≥27 kg/m² with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia

**Dosing**
- 120 mg thrice daily with each main meal containing fat, taken during or up to 1 hour after eating

See prescribing information for specific instructions

T2D = type 2 diabetes.
Orlistat: Summary of Warnings and Contraindications

Contraindications
- Pregnancy
- Chronic malabsorption syndrome
- Cholestasis

Warnings
- Decreased cyclosporine exposure
- Multivitamin supplement containing fat-soluble vitamins recommended to ensure adequate nutrition
- Hepatocellular necrosis, acute hepatic failure
- Increased urinary oxalate; monitor renal function
- Cholelithiasis
- Increased GI events with high-fat diets (fat >30% of total daily calories)

Adverse Effects
- Oily spotting
- Flatus with discharge
- Fecal urgency and incontinence
Orlistat: Clinical Efficacy

ITT Population, LOCF Analysis

<table>
<thead>
<tr>
<th>Time</th>
<th>Orlistat 120 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>52 weeks</td>
<td>-8.8 (P&lt;0.001)</td>
<td>-5.8</td>
</tr>
<tr>
<td>104 weeks</td>
<td>-7.6 (P&lt;0.001)</td>
<td>-4.5</td>
</tr>
</tbody>
</table>

ITT = intent to treat; LOCF = last observation carried forward; TID, three times daily.

Effect of Orlistat on Incidence of Diabetes in Obese Patients with Normal and Impaired Glucose Tolerance

XENDOS Study (N=3305)

IGT Patients
- Placebo + lifestyle
- Orlistat + lifestyle

All Patients
- Placebo + lifestyle
- Orlistat + lifestyle

Cumulative Incidence of T2D

Weeks

-45%
P = 0.0024

-37%
P = 0.0032

IGT = impaired glucose tolerance; XENDOS = Xenical in the prevention of Diabetes in Obese Subjects.
## Orlistat Adverse Events

<table>
<thead>
<tr>
<th>Event occurring in ≥5% of patients and occurring at least twice as often with orlistat as placebo, %</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Orlistat 120 mg TID (N=1913)</td>
<td>Placebo (N=1466)</td>
</tr>
<tr>
<td>Oily spotting</td>
<td>26.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Flatus with discharge</td>
<td>23.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Fecal urgency</td>
<td>22.1</td>
<td>6.7</td>
</tr>
<tr>
<td>Fatty/oily stool</td>
<td>20.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Oily evacuation</td>
<td>11.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Increased defecation</td>
<td>10.8</td>
<td>4.1</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>7.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

TID = three times daily.
Lorcaserin

Mechanism of Action
- Specific 5-HT2C (serotonin) receptor agonist

Indications
- Adjunct to diet and exercise in patients with
  - BMI ≥30 kg/m²
  - BMI ≥27 kg/m² with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia
    - Other

Dosing
- 10 mg twice daily
- Discontinue if 5% weight loss is not achieved within 12 weeks

Schedule IV Controlled Substance

See prescribing information for specific instructions

DEA = Drug Enforcement Agency; T2D = type 2 diabetes.
Lorcaserin: Summary of Warnings and Contraindications

Contraindications
- Pregnancy

Warnings
- Safety of coadministration with other serotonergic or antidopaminergic agents has not been established
- Valvular heart disease
- Cognitive impairment
- Psychiatric disorders: euphoria, dissociation, suicidal thoughts, depression
- Priapism
- Increased risk of hypoglycemia with antidiabetic medications
- Leukopenia
- Prolactin elevations

Adverse Effects
- Headache
- Dizziness
- Nausea

Effect of Lorcaserin on Body Weight in Obese Adults Over 1 Year

BLOSSOM Study
MITT Population, LOCF Analysis

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo (n=1601)</th>
<th>Lorcaserin 10 mg BID (n=1602)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BID = twice daily; BLOSSOM = Behavioral Modification and Lorcaserin Second Study for Obesity Management; LOCF = last observation carried forward; LS = least squares; MITT = modified intent to treat.

Effect of Lorcaserin on Body Weight in Obese Adults Over 2 Years

BLOOM Study
ITT Population; LOCF Analysis

BLOOM = Behavioral Modification and Lorcaserin for Overweight and Obesity Management; ITT = modified intent to treat; LOCF = last observation carried forward.

Effect of Lorcaserin on Progression to Type 2 Diabetes

Proportion of BLOOM and BLOSSOM Patients With Newly Diagnosed Diabetes After 52 Weeks of Treatment

BLOOM = Behavioral Modification and Lorcaserin for Overweight and Obesity Management; BLOSSOM = Behavioral Modification and Lorcaserin Second Study for Obesity Management.

Effect of Lorcaserin on Glycemia in Type 2 Diabetes

**BLOOM-DM Study**

<table>
<thead>
<tr>
<th>Baseline Mean A1C (%)</th>
<th>Change in A1C</th>
<th>Placebo (n=248)</th>
<th>Lorcaserin 10 mg BID (n=251)</th>
<th>Lorcaserin 10 mg QD (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0</td>
<td>-0.4</td>
<td>8.1</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>8.1</td>
<td>-0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.1</td>
<td>-1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Change in Diabetes Medications**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=248)</th>
<th>Lorcaserin 10 mg BID (n=251)</th>
<th>Lorcaserin 10 mg QD (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Increasing Use of Antidiabetic Agents (%)</td>
<td>88.3</td>
<td>82.9</td>
<td>76.6</td>
</tr>
</tbody>
</table>

*P<0.001 vs placebo. †P=0.087 vs placebo.

NNT = 4.4
To achieve a 1.0% reduction in A1C

*BLOOM-DM = Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus.*


**Effect of Lorcaserin on Cardiometabolic Risk Markers**

### BLOOM Study

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Lorcaserin 10 mg (5.8%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↓ -1.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↓ -1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓ -6.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, %</td>
<td>↓ -0.90</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↑ 2.87</td>
<td>0.049</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑ 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>↓ -1.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>↓ -21.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*P values represent comparisons to placebo.

Intent to treat, last observation carried forward analysis for total study population.

Effect of Lorcaserin on Hypertension

BLOSSOM Study

Blood Pressure

Systolic

Diastolic

Antihypertensive Use

Patients (%)

Decrease

Placebo

Lorcaserin 10 mg BID

BID = twice daily; BLOSSOM = Behavioral Modification and Lorcaserin Second Study for Obesity Management; LS = least squares.

Effect of Lorcaserin on Dyslipidemia

**BLOSSOM Study**

**Lipids**

- **Triglycerides**: -0.9, -4.3 (P=0.02)
- **HDL-C**: 1.3, 3.7 (P<0.001)
- **LDL-C**: 1.7, 0.3
- **ApoB**: 1.4, -2.9 (P<0.001)

**Lipid Medication Use**

- **Increase**: 5, 4
- **Decrease**: 1.4, 2.6

BID = twice daily; BLOSSOM = Behavioral Modification and Lorcaserin Second Study for Obesity Management; LS = least squares.

## Lorcaserin Adverse Events

<table>
<thead>
<tr>
<th>Event occurring in ≥5% of patients and more frequently than with placebo, %</th>
<th>Lorcaserin 10 mg BID (N=3195)</th>
<th>Placebo (N=3185)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Headache</strong></td>
<td>16.8</td>
<td>10.1</td>
</tr>
<tr>
<td><strong>Upper respiratory tract infection</strong></td>
<td>13.7</td>
<td>12.3</td>
</tr>
<tr>
<td><strong>Nasopharyngitis</strong></td>
<td>13.0</td>
<td>12.0</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>8.5</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>8.3</td>
<td>5.3</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>7.2</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Urinary tract infection</strong></td>
<td>6.5</td>
<td>5.4</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>6.5</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>Back pain</strong></td>
<td>6.3</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>5.8</td>
<td>3.9</td>
</tr>
<tr>
<td><strong>Dry mouth</strong></td>
<td>5.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>
Phentermine/Topiramate ER

Mechanism of Action

- Central noradrenergic effects
  - Phentermine: immediate-release sympathomimetic—affects appetite
  - Topiramate ER: delayed-release gabanergic—affects satiety

Indications

- Adjunct to diet and exercise in patients with
  - BMI ≥30 kg/m²
  - BMI ≥27 kg/m² with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia

Dosing

- Once daily in morning
  - Starting dose: phentermine 3.75/topiramate ER 23 mg for 14 days
  - Usual dose: 7.5/46 mg
  - Maximum dose: 15/92 mg

- If <3% weight loss after 12 weeks on usual dose, either discontinue medication or advance to maximum dose (transition dose phentermine 11.25 mg/topiramate ER 69 mg for 2 weeks)
- If <5% weight loss after 12 weeks on maximum dose, then discontinue the medication (to discontinue take every other day for one week)
- Schedule IV Controlled Substance

See prescribing information for specific instructions

T2D = type 2 diabetes.

Phentermine/Topiramate ER: Summary of Warnings and Contraindications

**Contraindications**
- Pregnancy
- Glaucoma
- Hyperthyroidism
- Treatment with monoamine oxidase inhibitors (MAOIs)

**Warnings**
- Fetal toxicity
- Increased heart rate
- Suicide and mood and sleep disorders
- Acute myopia and glaucoma
- Metabolic acidosis
- Creatinine elevations
- Hypoglycemia with concomitant antidiabetic therapy

**Adverse Effects**
- Dry mouth
- Tingling
- Constipation
- Altered taste sensation
- Upper respiratory infection
- Insomnia
Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 1 Year

EQUIP Study: ITT-LOCF Analysis

-10.9

Phen/TPM ER 15/92 (n=498)

-5.1

Phen/TPM ER 3.75/23 (n=234)

-1.6

Placebo (n=498)

*P<0.0001 vs placebo.

ITT = intent to treat; LOCF = last observation carried forward; Phen/TPM ER = phentermine/topiramate extended release.

Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years

**SEQUEL Study**
*(Completer Analysis)*

CONQUER Trial

SEQUEL Extension

Placebo n: 227
Phen/TPM 7.5/46 n: 153
Phen/TPM 15/92 n: 295

Weeks

0 12 20 28 36 44 52 60 68 76 84 92 100 108 LOCF

LS mean weight loss (%)

Data are shown with mean (95% CI).

Phen/TPM ER = phentermine/topiramate extended release.

Effects of Phentermine/Topiramate ER on Glucose, Insulin, and Progression to T2D

*All groups had lifestyle intervention.

NS = not significant; Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

Effects of Phentermine/Topiramate ER on Glucose, Insulin, and Progression to T2D

**SEQUEL Prediabetes/Metabolic Syndrome Cohort (N=475)**

### Glucose

- **Fasting**
  - Placebo*: -2.9 (†)
  - Phen/TPM ER 7.5/46 mg*: -10.1 (‡)
  - Phen/TPM ER 15/92 mg*: -18.6 (‡)

- **2-h OGTT**
  - Placebo*: -7
  - Phen/TPM ER 7.5/46 mg*: -18.6 (‡)
  - Phen/TPM ER 15/92 mg*: -181

### Insulin

- **Fasting**
  - Placebo*: -18
  - Phen/TPM ER 7.5/46 mg*: -37 (†)
  - Phen/TPM ER 15/92 mg*: -40 (‡)

- **2-h OGTT**
  - Placebo*: -275
  - Phen/TPM ER 7.5/46 mg*: -328 (§)
  - Phen/TPM ER 15/92 mg*: -350

*All groups had lifestyle intervention.

†P<0.05. ‡P<0.01. §P<0.001. ¶P<0.0001.

NS = not significant; Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

Effects of Phentermine/Topiramate ER in Patients at High Risk of Developing T2D

**SEQUEL Prediabetes/Metabolic Syndrome Cohort (N=475)**

- **Prediabetes (n=316)**
  - Placebo: 3.5
  - Phen/TPM ER 7.5/46 mg: 1.8 (49%, P=NS)
  - Phen/TPM ER 15/92 mg: 0.4 (89%, P=0.013)

- **Metabolic syndrome (n=451)**
  - Placebo: 6.4
  - Phen/TPM ER 7.5/46 mg: 1.5 (77%, P=0.009)
  - Phen/TPM ER 15/92 mg: 1.3 (80%, P<0.001)

*All groups had lifestyle intervention.

NS = not significant; Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

Effect of Phentermine/Topiramate ER on Incidence of Diabetes

**SEQUEL Prediabetes/Metabolic Syndrome Cohort (N=475)**

Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

Relationship Between Weight Loss and Prevention of Type 2 Diabetes

SEQUEL Prediabetes/Metabolic Syndrome Cohort (N=475)

ITT-LOCF Analysis

Annualized incidence rate of T2D

Magnitude of Weight Loss (%)

<5  ≥5 to <10  ≥10 to <15  ≥15

0  1  2  3  4  5  6  7  8

ITT, intent to treat; LOCF, last observation carried forward.
## Effect of Phentermine/Topiramate ER on Cardiometabolic Risk Markers

**CONQUER Study**

<table>
<thead>
<tr>
<th>Risk Factors (Mean % Weight Loss)</th>
<th>Phentermine/Topiramate ER 7.5/46 mg (8.4%)</th>
<th>Phentermine/Topiramate ER 15/92 mg (10.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↓  -4.7</td>
<td>↓  -5.6</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↓  -3.4</td>
<td>↓  -3.8</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓  -8.6</td>
<td>↓  -10.6</td>
</tr>
<tr>
<td>Total cholesterol, %</td>
<td>↓  -4.9</td>
<td>↓  -6.3</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↓  -3.7</td>
<td>↓  -6.9</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑  5.2</td>
<td>↑  6.8</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>↓  -2.49</td>
<td>↓  -2.49</td>
</tr>
<tr>
<td>Adiponectin, µg/mL</td>
<td>↑  1.40</td>
<td>↑  2.08</td>
</tr>
</tbody>
</table>

*P values represent comparisons to placebo.
Intent to treat, last observation carried forward analysis for total study population.

Effect of Phentermine/Topiramate ER on Hypertension

SEQEUL Study

Blood Pressure

<table>
<thead>
<tr>
<th>Group</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-3.2</td>
<td>-3.9</td>
</tr>
<tr>
<td>Phen/TPM ER 7.5/46 mg</td>
<td>-4.7</td>
<td>-3.7</td>
</tr>
<tr>
<td>Phen/TPM ER 15/92 mg</td>
<td>-4.3</td>
<td>-3.5</td>
</tr>
</tbody>
</table>

Antihypertensive Use

<table>
<thead>
<tr>
<th>Increase (%)</th>
<th>Placebo</th>
<th>Phen/TPM ER 7.5/46 mg</th>
<th>Phen/TPM ER 15/92 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>9.2</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>13.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increase Decrease

Patients (%)

BP = blood pressure; Phen/TPM ER = phentermine/topiramine extended release.
Effect of Phentermine/Topiramate ER on Dyslipidemia

**SEQUEL Study**

### Lipids

- **Triglycerides**
  - Placebo: -12.5, -13.7
  - Phen/TPM ER 7.5/46 mg: -10.7
  - Phen/TPM ER 15/92 mg: -9.7

- **HDL-C**
  - Placebo: 4.7
  - Phen/TPM ER 7.5/46 mg: 11.9

- **LDL-C**
  - Placebo: -5.6
  - Phen/TPM ER 7.5/46 mg: -9.0

- **Non-LDL-C**
  - Placebo: -5.6
  - Phen/TPM ER 7.5/46 mg: -9.3

### Lipid Medication Use

- **Increase**
  - Placebo: 20.3
  - Phen/TPM ER 7.5/46 mg: 11.1
  - Phen/TPM ER 15/92 mg: 10.5

- **Decrease**
  - Placebo: 3.1
  - Phen/TPM ER 7.5/46 mg: 5.9
  - Phen/TPM ER 15/92 mg: 5.8

*P<0.01 vs placebo.

Phen/TPM ER, phentermine/topiramate extended release.

### Selected Phentermine/Topiramate ER Adverse Events

<table>
<thead>
<tr>
<th>Event occurring in ≥5% of patients and more frequently than with placebo, %</th>
<th>Phentermine/Topiramate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.75 mg/23 mg (N=240)</td>
<td>7.5 mg/46 mg (N=498)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>4.2</td>
<td>13.7</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6.7</td>
<td>13.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>7.9</td>
<td>15.1</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15.8</td>
<td>12.2</td>
</tr>
<tr>
<td>Headache</td>
<td>10.4</td>
<td>7.0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12.5</td>
<td>10.6</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1.3</td>
<td>7.4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.9</td>
<td>7.2</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>7.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Back pain</td>
<td>5.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>6.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Influenza</td>
<td>7.5</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Mechanism of Action

- Naltrexone: opioid receptor antagonist
- Bupropion: norepinephrine-dopamine reuptake inhibitor

Indications

- Adjunct to diet and exercise in patients with
  - BMI ≥30 kg/m²
  - BMI ≥27 kg/m² with ≥1 weight-related comorbidity
  - Hypertension
  - T2D
  - Dyslipidemia
  - Other

Dosing

- Titrated to 2 tablets twice a day
  - Each tablet contains naltrexone 8 mg/bupropion 90 mg

See prescribing information for specific instructions

T2D = type 2 diabetes.
Naltrexone/Bupropion SR: Summary of Warnings and Contraindications

**Contraindications**
- Uncontrolled hypertension
- Seizures, anorexia, or discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs
- Chronic opioid use
- Use of other bupropion products or monoamine oxidase inhibitors
- Pregnancy

**Warnings**
- Suicidal behavior and ideation (black box warning)
- Seizure
- Increased blood pressure and heart rate
- Hepatotoxicity
- Angle-closure glaucoma

**Adverse Effects**
- GI: nausea, vomiting, constipation, diarrhea
- Headache, insomnia
- Dry mouth

Effect of Naltrexone/Bupropion SR on Body Weight

COR II Study MITT-LOCF Analysis
(N=1496)

28 weeks

-6.5

\( P<0.001 \)

56 weeks

-6.4

\( P<0.001 \)

\[ \text{Naltrexone/bupropion SR} \]

\[ \text{Placebo} \]

COR II = CONTRAVE Obesity Research II; LOCF = last observation carried forward; MITT = modified intent to treat; SR = sustained release.

Effect of Naltrexone/Bupropion SR on Cardiometabolic Risk Markers

<table>
<thead>
<tr>
<th>Risk Factors (Mean % Weight Loss)</th>
<th>Naltrexone/ Bupropion SR (6.4%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↑ 0.6</td>
<td>0.039</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↑ 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓ -9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↓ -6.2</td>
<td>0.008</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑ 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>↓ -28.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBG, mg/dL</td>
<td>↓ -2.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P value vs placebo.

BP, blood pressure; COR II, CONTRAVE Obesity Research II; FBG, fasting blood glucose; SR, sustained release.

Effect of Naltrexone/Bupropion SR on Glycemia in Type 2 Diabetes

**COR-Diabetes Study**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=159)</th>
<th>Naltrexone/ bupropion SR (n=265)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean A1C (%)</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>Change in A1C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in Weight</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Change in A1C**

- Placebo (n=159) 8.0
- Naltrexone/ bupropion SR (n=265) 8.0

**P**

-0.1

**ΔA1C (%)**

-0.5

-1

**Change in Weight**

- Placebo (n=159)
- Naltrexone/ bupropion SR (n=265)

-1.8

-5

**ΔWeight (%)**

-3

-5

**P**

<0.001

P<0.001

COR = CONTRAVE Obesity Research; LOCF = last observation carried forward; MITT = modified intent to treat; SR, sustained release.

### Naltrexone/Bupropion SR Adverse Events

<table>
<thead>
<tr>
<th>Event occurring in ≥5% of patients and more frequently than with placebo, %</th>
<th>Naltrexone/Bupropion SR 32 mg/360 mg (N=2545)</th>
<th>Placebo (N=1515)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>32.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>19.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Headache</td>
<td>17.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>8.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.1</td>
<td>5.2</td>
</tr>
</tbody>
</table>
Liraglutide (for Obesity)

**Mechanism of Action**
- GLP-1 receptor agonist

**Indications**
- Adjunct to diet and exercise in patients with
  - BMI $\geq 30$ kg/m$^2$
  - BMI $\geq 27$ kg/m$^2$ with $\geq 1$ weight-related comorbidity
  - Hypertension
  - T2D
  - Dyslipidemia
  - Other

**Dosing**
- Titrate to 3 mg once daily subcutaneous injection

See prescribing information for specific instructions.

T2D = type 2 diabetes.

Saxenda prescribing information. Plainsboro, NJ: NovoNordisk Inc.
Liraglutide (for Obesity): Summary of Warnings and Contraindications

**Contraindications**
- Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
- Pregnancy

**Adverse Effects**
- GI: nausea, diarrhea, constipation, vomiting, decreased appetite, dyspepsia, abdominal pain
- Headache, fatigue
- Dizziness
- Increased lipase

**Warnings**
- Thyroid tumors seen in rodent models
- Acute pancreatitis or gallbladder disease
- Hypoglycemia if used with sulfonylurea or glinide (in patients with T2D)
- Heart rate increase
- Renal impairment
- Suicidal behavior or ideation
- Do not use with insulin or to treat T2D

T2D = type 2 diabetes.

Saxenda prescribing information. Plainsboro, NJ: NovoNordisk Inc.
Effects of Liraglutide in Obese Patients

SCALE Obesity (N=3731)

Weight Change After 56 Weeks

Liraglutide (n=2437) Placebo (n=1225)

Weight Change (%)

-16 -14 -12 -10 -8 -6 -4 -2 0

P<0.001

Effects of Liraglutide on Body Weight Over 3 Years

All arms included lifestyle intervention: −500 kcal/day hypocaloric diet + 150 min/week increased physical activity.

Full analysis set, fasting visit data only. Line graphs are observed means (±SE). Points (square, triangle) are observed means with last observation carried forward (LOCF).

Effects of Liraglutide in Obese Patients with Prediabetes

**SCALE Obesity and Prediabetes**
*(N=2285)*

---

**Weight Change After 56 Weeks**

- Liraglutide 3 mg (n=1528)
- Placebo (n=757)

**Patients with Prediabetes After 56 Weeks**

- Liraglutide 3 mg (n=1528)
- Placebo (n=757)

<table>
<thead>
<tr>
<th>Change in Weight (kg)</th>
<th>Liraglutide 3 mg</th>
<th>Placebo</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10</td>
<td>-8.4</td>
<td>-2.8</td>
<td>-6</td>
</tr>
<tr>
<td>-8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001 vs placebo.

---

Effects of Liraglutide in Obese Patients with Prediabetes

SCALE Obesity and Prediabetes
(N=3731)

Cumulative Incidence of Type 2 Diabetes

Regression to Normoglycemia Among Patients with Prediabetes Treated With Liraglutide Over 3 Years

![Graph showing regression to normoglycemia](image)

- **Liraglutide 3.0 mg**
- **Placebo**

**Week**

- Proportion (%)
  - 0
  - 20
  - 40
  - 60
  - 80
  - 100

**Likelihood of normoglycemia >3X higher with liraglutide 3 mg**

- OR = 3.6 (95% CI, 3.0 to 4.4); \( P < 0.0001 \); NNT = ~3

All arms included lifestyle intervention: −500 kcal/day hypocaloric diet + 150 min./week increased physical activity.

Full analysis set. Statistical analysis is logistic regression.

CI = confidence interval; NNT = number needed to treat; OR = odds ratio.

Effect of Liraglutide 3 mg on Cardiometabolic Risk Markers

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Liraglutide 3 mg* (4.4%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↓ -2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↓ -0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓ -6.0</td>
<td>0.0003</td>
</tr>
<tr>
<td>Total cholesterol, %</td>
<td>↓ -2.0</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↓ -0.9</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑ 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL-C, %</td>
<td>↓ -6.0</td>
<td>0.0002</td>
</tr>
<tr>
<td>FFAs, %</td>
<td>↓ -5.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>↓ -3.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Placebo-adjusted values; P values represent comparisons to placebo (ANCOVA).

Full analysis set of 3-year data.

## Liraglutide (for Obesity) Adverse Events

<table>
<thead>
<tr>
<th>Event occurring in ≥5% of patients and more frequently than with placebo, %</th>
<th>Liraglutide 3 mg (N=3384)</th>
<th>Placebo (N=1941)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>39.3</td>
<td>13.8</td>
</tr>
<tr>
<td>Headache</td>
<td>13.6</td>
<td>12.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>19.4</td>
<td>8.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>5.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>5.1</td>
<td>2.7</td>
</tr>
</tbody>
</table>
Weight Loss Medications

Efficacy Considerations
## Comparison of Weight-Loss Medications Approved for Long-Term Use

### Placebo-Subtracted Changes from Baseline, Highest Approved Dose (Not Head-to-Head Trials)

<table>
<thead>
<tr>
<th>Study (no. weeks), no. ITT patients in treatment group</th>
<th>Orlistat&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Lorcaserin&lt;sup&gt;3-5&lt;/sup&gt;</th>
<th>Phentermine/topiramate&lt;sup&gt;6-8&lt;/sup&gt;</th>
<th>Naltrexone/bupropion&lt;sup&gt;9,10&lt;/sup&gt;</th>
<th>Liraglutide 3 mg&lt;sup&gt;11,12&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davidson et al (52), n=657</td>
<td>100.7</td>
<td>100.1</td>
<td>115.2</td>
<td>99.7</td>
<td>100.4</td>
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<tr>
<td>XENDOS (208), n=1640</td>
<td>110.4</td>
<td>100.4</td>
<td>103.0</td>
<td>100.3</td>
<td>106.2</td>
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<tr>
<td>BLOSSOM (52), n=1602</td>
<td>-3.0</td>
<td>-3.0</td>
<td>-9.3</td>
<td>-4.8</td>
<td>-6.0</td>
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<tr>
<td>BLOOM (52), n=1538</td>
<td>-2.8</td>
<td>-3.7</td>
<td>-8.6</td>
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<td>-5.4</td>
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<td>BLOOM-DM (52), n=256</td>
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<td>-8.7</td>
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<td>EQUIP (56), n=512</td>
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<td>CONQUER (56), n=995</td>
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<td>SEQUEL (108), n=295</td>
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<td>COR I (56), n=583</td>
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<tr>
<td>COR II (56), n=1001</td>
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<td>SCALE-Main (56), n=212</td>
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<tr>
<td>SCALE (56), n=2487</td>
<td>106.2</td>
<td></td>
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</tbody>
</table>

Baseline weight (kg)

-3.0 -2.8 -3.0 -3.7 -3.0 -9.3 -8.6 -8.7 -4.8 -5.2 -6.0 -5.4

ITT = intent to treat.

Heterogeneity of Treatment Effect for Weight Loss

Low-Carbohydrate Ketogenic Diet

Orlistat Plus Low-Fat Diet

Variability in Weight Loss with Lifestyle Therapy and Phentermine/Topiramate ER

Each vertical bar represents a single subject experience in subjects completing 56 weeks on study drug.
Weight Loss Medications

Combination Therapy
Effect of Lorcaserin Combined With Intensive Lifestyle Therapy on Body Weight in Obese Adults Over 1 Year

**BLOSSOM Study**

- Both the placebo and lorcaserin groups received intensive lifestyle intervention
  - Diet and exercise counseling at weeks 1, 2, 4, and monthly thereafter
  - Caloric intake 600 kcal below individual estimated energy requirements
  - 30 min moderate exercise per day

BID, twice daily; LS, least squares.
Both the placebo and lorcaserin groups received intensive lifestyle intervention

- Diet and exercise counseling at weeks 1, 2, 4, and monthly thereafter
- Caloric intake 600 kcal below individual estimated energy requirements
- 30 min moderate exercise per day
Combining Weight Loss Medications

- Combination therapy for obesity
  - Is logical
  - May target different pathways, potentially resulting in synergistic effects

- Combinations of FDA-approved weight-loss medications should only be used in a manner approved by the FDA or when sufficient safety and efficacy data are available to assure informed judgment regarding a favorable benefit-to-risk ratio

There are currently no long-term studies of weight loss drugs in non–FDA-approved combinations

Individualizing Therapy According to Comorbidities

Weight Loss Medications
# Preferred Weight-Loss Medications: Individualization of Therapy

<table>
<thead>
<tr>
<th>Clinical Characteristics or Coexisting Diseases</th>
<th>Orlistat</th>
<th>Lorcaserin</th>
<th>Phentermine/Topiramate ER</th>
<th>Naltrexone ER/Bupropion ER</th>
<th>Liraglutide 3 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Prevention (metabolic syndrome, prediabetes)</td>
<td>Insufficient data for T2DM prevention</td>
<td>Insufficient data for T2DM prevention</td>
<td></td>
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<tr>
<td>Type 2 Diabetes Mellitus</td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td>Monitor heart rate</td>
<td>Monitor BP and heart rate.</td>
<td>Monitor heart rate</td>
<td>Contraindicated in uncontrolled HTN</td>
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<tr>
<td>Cardiovascular Disease</td>
<td>CAD</td>
<td>Monitor heart rate</td>
<td>Monitor heart rate, BP</td>
<td>Monitor heart rate</td>
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<tr>
<td></td>
<td>Arrhythmia</td>
<td>Monitor for bradycardia</td>
<td>Monitor heart rate, rhythm</td>
<td>Monitor heart rate, rhythm</td>
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<tr>
<td></td>
<td>CHF</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
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<tr>
<td>Chronic Kidney Disease</td>
<td>Mild (50–79 mL/min)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Moderate (30–49 mL/min)</td>
<td></td>
<td></td>
<td>Do not exceed 7.5 mg/46 mg per day</td>
<td>Do not exceed 8 mg/90 mg bid</td>
</tr>
<tr>
<td></td>
<td>Severe (&lt;30 mL/min)</td>
<td>Watch for oxalate nephropathy</td>
<td>Urinary clearance of drug metabolites</td>
<td>Urinary clearance of drug</td>
<td>Avoid vomiting and volume depletion</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Mild-Moderate (Child-Pugh 5–9)</td>
<td>Watch for cholelithiasis</td>
<td>Hepatic metabolism of drug</td>
<td>Do not exceed 7.5 mg/46 mg per day</td>
<td>Do not exceed 8 mg/90 mg in AM</td>
</tr>
<tr>
<td></td>
<td>Severe (Child-Pugh &gt;9)</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
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<tr>
<td>Depression</td>
<td>Insufficient safety data</td>
<td>Avoid combinations of serotonergic drugs</td>
<td>Insufficient safety data</td>
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<tr>
<td>CLINICAL CHARACTERISTICS OR COEXISTING DISEASES</td>
<td>MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT</td>
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<tr>
<td></td>
<td>Orlistat</td>
<td>Lorcaserin</td>
<td>Phentermine/topiramate ER</td>
<td>Naltrexone ER/bupropion ER</td>
<td>Liraglutide 3 mg</td>
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<tr>
<td>Anxiety</td>
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<td>Psychoses</td>
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<td>Binge Eating Disorder</td>
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<td>Glaucoma</td>
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<td>Seizure Disorder</td>
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<tr>
<td>Pancreatitis</td>
<td>Monitor for symptoms</td>
<td></td>
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<tr>
<td>Opioid Use</td>
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<tr>
<td>Women of Reproductive Potential</td>
<td>Pregnancy</td>
<td></td>
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<tr>
<td>Breast-feeding</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
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<tr>
<td>Age ≥65 years *</td>
<td>Limited data available</td>
<td>Insufficient data</td>
<td>Limited data available</td>
<td>Insufficient data</td>
<td>Limited data available</td>
</tr>
<tr>
<td>Alcoholism/Addiction</td>
<td></td>
<td>Might have abuse potential due to euphoria at high doses</td>
<td>Insufficient data, Topiramate might exert therapeutic benefits</td>
<td>Avoid due to seizure risk and lower seizure threshold on bupropion</td>
<td></td>
</tr>
<tr>
<td>Post-Bariatric Surgery</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
<td>Limited data available</td>
<td>Insufficient data</td>
<td>Data available at 1.8 to 3.0 mg/day</td>
</tr>
</tbody>
</table>

* Use medications only with clear health-related goals in mind; assess patient for osteoporosis and sarcopenia.

**Abbreviations:** BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; HTN = hypertension; T2DM = Type 2 Diabetes Mellitus.
Weight Loss Medications

Summary
Summary

- Older obesity pharmacotherapies are limited by tolerability and dependence issues and are approved only for short-term use (≤12 weeks).

- Newer weight loss agents are typically better tolerated, have better safety profiles, and are approved for chronic weight management including weight maintenance.

- Pharmacotherapy for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone.