Obesity Pharmacotherapy: Options and Applications in Clinical Practice

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Obesity Pharmacotherapy

- Few providers prescribe pharmacotherapy.
- Few patients use pharmacotherapy.
- Pharmacotherapy can be extremely effective but also misused, overused, or underused.
- Patients respond differently to each medication.
- Combining therapeutic options significantly improves weight loss and other outcomes.
- Pharmacotherapy can be effective for weight maintenance, not just weight loss.
Few Eligible Patients Use Obesity Pharmacotherapy

FDA-approved Pharmacotherapy Options for the Treatment of Obesity

• Phentermine and other noradrenergic agents
• Orlistat
• Phentermine/topiramate ER
• Lorcaserin
• Naltrexone SR/bupropion SR
• Liraglutide 3.0mg

ER = extended release; SR = sustained release.
Phentermine

• Sympathomimetic amine, NE release
• Blunts appetite
• Approved in 1959 for short-term use, schedule IV
• Dosing: 8 to 37.5 mg qAM; use lowest effective dose
• Contraindications: pregnancy, nursing, MAOIs, glaucoma, drug abuse history, hyperthyroidism
• Relative contraindications: uncontrolled hypertension, tachycardia, history of CAD, CHF, stroke, arrhythmia
• Warnings: primary pulmonary hypertension, valvular heart disease, tolerance, risk of abuse, concomitant use with alcohol

CAD = coronary artery disease; CHF = congestive heart failure; HTN = hypertension; MAOIs = monoamine oxidase inhibitors; NE = norepinephrine.
Orlistat

• Lipase inhibitor, decreases fat absorption
• Approved 1999; long-term use
• Not scheduled
• 120 mg TID with meals (Rx) or 60 mg TID (OTC)
• Use MVI with fat-soluble vitamins at bedtime
• Contraindications: pregnancy, chronic malabsorption syndrome, cholestasis
• Possible gastrointestinal adverse events

MVI = multi-vitamin; OTC = over-the-counter.
Lorcaserin

- Selective 5-HT2C receptor agonist
- Increases satiety
- Approved in 2012 for long-term use; schedule IV
- Single dose: 10 mg BID
- Contraindications: pregnancy
- Warnings: co-administration with serotonergic or antidopaminergic agents, valvular heart disease, psychiatric disorders (euphoria, suicidal thoughts, depression), priapism
- Discontinue if less than 5% weight loss after 12 weeks of use

Lorcaserin: Outcomes by Responder Status

LOR = lorcaserin; PBO = placebo.
Phentermine/Topiramate ER

- Phentermine: sympathomimetic amine; blunts appetite
- Topiramate: increases GABA activity, carbonic anhydrase inhibitor, and other actions; prolongs satiety
- Approved in 2012 for long-term use; schedule IV
- “Recommended” dose: 7.5/46 mg; max: 15/92 mg
- Discontinue if less than 3% weight loss after 12 weeks
- Contraindications: pregnancy, glaucoma, MAOIs, hyperthyroidism

GABA = gamma-aminobutyric acid.
Naltrexone SR/Bupropion SR

- Naltrexone: opioid receptor antagonist; blocks autoinhibition of POMC neurons and amplifies the effect of bupropion
- Bupropion: dopamine/noradrenaline reuptake inhibitor
- Not a controlled substance
- Standard dose: 32/360 mg (2 BID)
- Consider discontinuation if <5% weight loss after 16 weeks
- Black box warning for suicidal thoughts in adolescents
- Contraindications: pregnancy, uncontrolled hypertension, seizure disorders, chronic opioid use, MAOIs

POMC = pro-opiomelanocortin.
Contrave (naltrexone SR/bupropion SR) prescribing information.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/200063s000lbl.pdf;.
Liraglutide 3.0 mg

• Glucagon-like peptide 1 (GLP-1) receptor agonist
• Multiple actions; effect on weight is primarily via POMC neurons
• Liraglutide 1.8 mg FDA-approved in 2010 for T2DM
• Liraglutide 3.0 mg FDA-approved for primary indication of obesity in December 2014
• Not a controlled substance
• Dosing: weekly escalation by 0.6 mg SC
• Discontinue if <4% weight loss at 16 weeks
• REMs: medullary thyroid carcinoma, acute pancreatitis

T2DM = type 2 diabetes mellitus; REMs = Risk Evaluation and Mitigation Strategies; SC = subcutaneous.
Weight Loss in Patients Completing 1 Year of Treatment

Phentermine/Topiramate CR: Long-term Outcomes - 2 Years

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Liraglutide 3.0 mg: Long-term Outcomes - 3 Years

Orlistat: 
Long-term Outcomes - 4 Years

• Cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat
  • risk reduction: 37.3% ($P = 0.0032$)
• Mean weight was significantly greater with orlistat (5.8 vs. 3.0 kg with placebo; $P < 0.001$)

Lorcaserin: Long-term Benefits Require Long-term Use

• Among pts in the lorcaserin group who had weight loss of >5% or more at year 1, the loss was maintained in a greater proportion of pts who continued to receive lorcaserin in year 2 than in those who reassigned to placebo (67.9% vs 50.3%, \(P<.001\)).

• Mean body weight among pts who received lorcaserin in both years was lower than that among pts who received placebo in both years and lower than that among pts who received lorcaserin in year 1 and placebo in year 2.

Liraglutide 3.0 mg for Weight Maintenance

## Improvements in Risk Factors and Comorbidities

<table>
<thead>
<tr>
<th></th>
<th>Orlistat</th>
<th>Lorcaserin</th>
<th>Phentermine/topiramate ER</th>
<th>Naltrexone/bupropion SR</th>
<th>Liraglutide 3.0 mg</th>
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<tbody>
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</tbody>
</table>

BP = blood pressure; HDL = high-density lipoprotein; HR = heart rate; LDL = low-density lipoprotein; TG = triglycerides; WC = waist circumference.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common AE</th>
<th>Contraindication</th>
<th>Safety Consideration</th>
<th>Tolerability</th>
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</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Insomnia</td>
<td>CVD, CHF, arrhythmias</td>
<td>Primary pulmonary hypertension</td>
<td>Discontinuation (CNS): Phentermine – 17% Placebo – 3%</td>
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<td></td>
<td>Dry mouth</td>
<td>Uncontrolled hypertension</td>
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<td>Agitation</td>
<td>MAOI use</td>
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<td>Constipation</td>
<td>Hyperthyroidism</td>
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<td>Glaucoma</td>
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<td>Pregnancy</td>
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<tr>
<td>Orlistat</td>
<td>GI complaints</td>
<td>Chronic malabsorption</td>
<td>May increase cyclosporine exposure; Liver failure</td>
<td>Discontinuation: Orlistat – 8.8% Placebo – 5%</td>
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<tr>
<td></td>
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<td>Gallbladder disease</td>
<td>Multivitamin administration</td>
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<tr>
<td>Phentermine/topiramate ER</td>
<td>Dry mouth</td>
<td>Glaucoma</td>
<td>Teratogenicity</td>
<td>Discontinuation: Top dose – 17% Low doses – 12% Placebo – 8%</td>
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<tr>
<td></td>
<td>Paresthesias</td>
<td>Hyperthyroidism</td>
<td>Metabolic acidosis</td>
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<td>Headache</td>
<td>MAOI use</td>
<td>Glaucoma</td>
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<td></td>
<td>Insomnia</td>
<td>Use with caution with serotonergic drugs</td>
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<td>Pregnancy</td>
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<tr>
<td>Lorcaserin</td>
<td>Headache</td>
<td>MAOI use</td>
<td>Serotonin syndrome</td>
<td>Discontinuation: Lorcaserin – 8.6% Placebo – 6.7%</td>
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<tr>
<td></td>
<td>Dizziness</td>
<td>Use with caution with serotonergic drugs</td>
<td>Valvular heart disease</td>
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<td>Fatigue</td>
<td>Pregnancy</td>
<td>Depression</td>
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<td>Dry mouth</td>
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<td>Priapism</td>
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<tr>
<td>Naltrexone/bupropion SR</td>
<td>Nausea</td>
<td>Seizure disorder</td>
<td>Suicide in adolescents</td>
<td>Discontinuation: Naltrexone/bupropion – 24% Placebo – 12%</td>
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<tr>
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<td>GI complaints</td>
<td>Uncontrolled hypertension</td>
<td>Elevated blood pressure, pulse</td>
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<tr>
<td></td>
<td>Headache</td>
<td>Chronic opioid use</td>
<td>Glaucoma</td>
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<tr>
<td></td>
<td>Insomnia</td>
<td>MAOI use</td>
<td>Hepatotoxicity</td>
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<td>Pregnancy</td>
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<tr>
<td>Liraglutide 3.0</td>
<td>Nausea</td>
<td>Personal/family history of medullary thyroid carcinoma</td>
<td>Thyroid c-cell tumors (rodents)</td>
<td>Discontinuation: Liraglutide – 9.8% Placebo – 4.3%</td>
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<tr>
<td></td>
<td>GI complaints</td>
<td>or MEN2</td>
<td>Acute pancreatitis</td>
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<td></td>
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<td>History of pancreatitis</td>
<td>Gallbladder disease</td>
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<td>Hypoglycemia</td>
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<td>Tachycardia</td>
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<td>Renal impairment</td>
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<td>Suicidal behavior</td>
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What’s the “Best” Medication?!

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SUCRA = surface under the cumulative ranking curve.
Choosing Between Options

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Choosing Between Options

Drug factors

- Contraindications
- Dual benefits
- Studied populations

Patient factors

- Patient preferences
- Adverse events
- Prior experiences
- Access

Physician factors

- Provider knowledge/comfort
# Contraindications and Cautions

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Avoid/Caution</th>
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</thead>
<tbody>
<tr>
<td>Elevated seizure risk</td>
<td>Naltrexone/bupropion</td>
</tr>
<tr>
<td>History of recurrent kidney stones</td>
<td>Phentermine/topiramate, orlistat</td>
</tr>
<tr>
<td>History of glaucoma</td>
<td>Phentermine/topiramate</td>
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<tr>
<td>Uncontrolled hypertension</td>
<td>Naltrexone/bupropion, phentermine</td>
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<td>Coronary artery disease</td>
<td>Phentermine</td>
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<tr>
<td>Moderate-to-severe renal impairment</td>
<td>Do not exceed half-dose: phentermine/topiramate, naltrexone/bupropion Caution: liraglutide, lorcaserin</td>
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<tr>
<td>Moderate-to-severe hepatic impairment</td>
<td>Do not exceed half-dose: phentermine/topiramate, naltrexone/bupropion Caution: liraglutide, lorcaserin</td>
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<tr>
<td>SSRI use</td>
<td>Caution: lorcaserin</td>
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</tbody>
</table>

SSRI = selective serotonin reuptake inhibitor.
## Dual Benefits

<table>
<thead>
<tr>
<th>If Patient has Obesity and...</th>
<th>Consider (But not Explicitly Approved)...</th>
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</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Naltrexone/bupropion</td>
</tr>
<tr>
<td>Depression</td>
<td>Naltrexone/bupropion</td>
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<tr>
<td>Migraines</td>
<td>Phentermine/topiramate ER</td>
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<tr>
<td>Diabetes</td>
<td>Liraglutide 3.0 mg</td>
</tr>
<tr>
<td>Chronic constipation</td>
<td>Orlistat</td>
</tr>
<tr>
<td>Elevated LDL</td>
<td>Orlistat</td>
</tr>
</tbody>
</table>
Patients with Extreme Obesity (BMI >45)

BMI = Body Mass Index; PHEN/TPM = phentermine/topiramate.

Choosing Between Options

Drug Factors
- Contraindications
- Dual benefits
- Studied populations

Patient Factors
- Patient preferences
- Adverse events
- Prior experiences
- Access

Physician Factors
- Provider knowledge/comfort
Combination Therapy

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Emerging Therapeutic Options: Setmelanotide

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Emerging Therapeutic Options: Setmelanotide

- Setmelanotide - a melanocortin-4 receptor agonist
- Investigator-initiated, open-label study
- Two patients with proopiomelanocortin deficiency treated with setmelanotide
- Patients had a sustainable reduction in hunger and substantial weight loss
  - 51.0 kg after 42 weeks in Patient 1
  - 20.5 kg after 12 weeks in Patient 2
New and Emerging Medical Devices for the Treatment of Obesity

• Novel oral capsulated device
  - Taken before meals
  - Particles released and expand in stomach by absorbing water
  - Designed to enhance satiety and delay gastric emptying

Final Thoughts on Pharmacotherapy

• Treatment of obesity with pharmacotherapy as an adjunct to lifestyle modification is a valuable option for obesity treatment.

• Several options are available and FDA approved.

• Understand potential benefits and risks of agents when planning treatment.

• Different patients respond to different medications.

• If one option doesn’t work well, consider others.