Review of Weight Loss Medications in Obesity

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Pharmacy Grand Rounds
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Objectives

• Identify currently available pharmacologic agents used for weight loss

• Discuss primary literature for weight loss medications

• Compare the efficacy and safety profiles of medications currently used for weight loss
## BMI Categories

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5 – 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25 – 29.9</td>
</tr>
<tr>
<td>Class I obesity</td>
<td>30 – 34.9</td>
</tr>
<tr>
<td>Class II obesity</td>
<td>35 – 39.9</td>
</tr>
<tr>
<td>Class III obesity</td>
<td>≥ 40</td>
</tr>
</tbody>
</table>

Diagnosing Obesity

**Anthropometric Component**
- BMI
  - $\geq 25$ kg/m$^2$ OR
  - $> 23$ kg/m$^2$ in South Asian, Southeast Asian, and East Asian
- Waist circumference if BMI $< 35$ kg/m$^2$
  - Males: $\geq 94$ cm
  - Females: $\geq 80$ cm

**Clinical Component**
- Prediabetes
- Metabolic syndrome
- Type 2 diabetes
- Dyslipidemia
- Hypertension
- Cardiovascular disease
- Nonalcoholic fatty liver disease
- Polycystic ovary syndrome
- Female infertility
- Male hypogonadism
- Obstructive sleep apnea
- Asthma/reactive airway disease
- Osteoarthritis
- Urinary stress incontinence
- GERD
- Depression

Initiate Weight Loss Medication in Overweight/Obesity:

- BMI > 30 kg/m²
- BMI > 27 kg/m² + > 1 weight related comorbidity

When should medications be used?

- When weight-related complications can be improved by weight loss
- Failure to lose weight with lifestyle therapy alone
- Weight regain on lifestyle therapy
- Presence of weight-related complications

Patient Case: 44 year old female, BMI 29

<table>
<thead>
<tr>
<th>Past Medical History</th>
<th>Current Medications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic pain</td>
<td>• Acetaminophen</td>
</tr>
<tr>
<td>• Depression</td>
<td>• Atorvastatin</td>
</tr>
<tr>
<td>• Dyslipidemia</td>
<td>• Levothyroxine</td>
</tr>
<tr>
<td>• Hypothyroidism</td>
<td>• Multivitamin</td>
</tr>
<tr>
<td>• Osteoarthritis</td>
<td>• Oxycodone ER</td>
</tr>
<tr>
<td></td>
<td>• Sertraline</td>
</tr>
<tr>
<td></td>
<td>• Vitamin D</td>
</tr>
</tbody>
</table>
Why would this patient qualify for weight loss medication therapy?

A. BMI is > 27
B. BMI is > 27 and she has osteoarthritis
C. BMI is > 27, she has hypothyroidism, and she is > 30 years of age
D. She does not qualify for pharmacotherapy
Goals of Treatment

**Improve patient health & quality of life**

**NOT**

*a pre-specified decrease in body weight*

Duration of Therapy?

- Pharmacotherapy should be chronic treatment

- Short-term generally not recommended
  - Has not shown to produce longer-term health benefits

How to pick a medication:

- Consider differences in:
  - Efficacy
  - Side effects
  - Cautions & warnings
  - Presence of weight-related complications
  - Medical history

- **Individualize weight-loss pharmacotherapy**

## Medication Options

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Mechanism of Action</th>
<th>Regulatory Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Xenical</td>
<td>Lipase inhibitor</td>
<td>Prescription</td>
</tr>
<tr>
<td></td>
<td>Alli Alli</td>
<td></td>
<td>OTC</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Belviq</td>
<td>Serotonin 5-HT2c receptor agonist</td>
<td>Schedule IV</td>
</tr>
<tr>
<td></td>
<td>Belviq XR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentermine +</td>
<td>Qsymia</td>
<td>NE-releasing agent &amp;</td>
<td>Schedule IV</td>
</tr>
<tr>
<td>Topiramate ER</td>
<td></td>
<td>GABA receptor modulation</td>
<td></td>
</tr>
<tr>
<td>Naltrexone ER +</td>
<td>Contrave</td>
<td>Opiate antagonist &amp; Reuptake inhibitor</td>
<td>Prescription</td>
</tr>
<tr>
<td>Bupropion ER</td>
<td></td>
<td>of DA &amp; NE</td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Saxenda</td>
<td>GLP-1 analog</td>
<td>Prescription</td>
</tr>
</tbody>
</table>


- NE = norepinephrine
- DA = dopamine
- GLP-1 = glucagon-like peptide-1
Khera et al. Meta-analysis

- **Objective:**
  - Compare weight loss & adverse effects amongst medications used to treat obesity

- **Studies inclusion criteria:**
  - Randomized clinical trials
  - Evaluated any of the 5 FDA approved weight loss medications
    - Using most effective recommended doses
  - 1 year
  - Overweight or obese ± weight related comorbidities

- **Primary Endpoint:**
  - Proportion of patients achieving ≥ 5% weight loss from baseline
  - Rate of discontinuation of treatment due to adverse events

Khera et al. Meta-analysis

• Population:
  • 28 randomized clinical trials
  • 29,018 participants

<table>
<thead>
<tr>
<th>Median of average age</th>
<th>Female</th>
<th>Median of average weight</th>
<th>Median of average BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.9 years</td>
<td>74%</td>
<td>100.5 kg</td>
<td>36.1</td>
</tr>
<tr>
<td>Medication</td>
<td>Mean excess weight loss vs. placebo</td>
<td>Proportion with ≥ 5% weight loss</td>
<td>Proportion with ≥ 10% weight loss</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Orlistat</td>
<td>2.6 kg</td>
<td>44%</td>
<td>20%</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>3.2 kg</td>
<td>49%</td>
<td>25%</td>
</tr>
<tr>
<td>Phentermine + Topiramate ER</td>
<td>8.8 kg</td>
<td>75%</td>
<td>54%</td>
</tr>
<tr>
<td>Naltrexone ER + Bupropion ER</td>
<td>5 kg</td>
<td>55%</td>
<td>30%</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>5.2 kg</td>
<td>63%</td>
<td>34%</td>
</tr>
<tr>
<td>Placebo</td>
<td>23%</td>
<td>9%</td>
<td>5%</td>
</tr>
</tbody>
</table>

AE: adverse event

Khera et al. Meta-analysis

• Conclusion:
  • All agents achieved ≥ 5% weight loss by 1 year
    • Highest proportion:
      • Phentermine+ topiramate ER
      • Liraglutide
  • Highest discontinuation rate due to adverse effects:
    • Liraglutide
    • Naltrexone ER + bupropion ER

Orlistat – safety

Side Effect Frequency

Abdominal Pain
Flatulence
Fecal Urgency
Oily Spotting
Headache
Steatorrhea

Orlistat – avoid

- **Chronic malabsorption syndrome**
- **Cholestasis**
- **Oxalate nephrolithiasis**
- **Cholelithiasis**
- **History of transplant**

Orlistat – clinical pearls

• Recommend MVI with vitamins A, D, E, K
  • Administer at bedtime or 2 hours after orlistat

• ↑ GI side effects with high fat diet
  • >30% kcal from fat

• Rare severe liver injury
Lorcaserin – safety

Side Effect Frequency

Lorcaserin – clinical pearls

• Serotonin syndrome
  • Monitor for DDIs

• Neuroleptic malignant syndrome

• Abuse potential due to euphoria at high doses
• Monitor for depression & suicidal thoughts or behavior
• Potential for cardiac valvulopathy?
• Hypoglycemia
Phentermine + Topiramate ER – safety

Side Effect Frequency

- P/T 7.5/46 mg
- P/T 15/92 mg
- Placebo


P/T = phentermine + topiramate ER
Phentermine/Topiramate ER – avoid

- Hyperthyroidism
- Acute angle-closure glaucoma
- Concomitant MAOI use (within 14 days)
- Recent or unstable cardiovascular disease
Phentermine/Topiramate ER – clinical pearls

- Weight loss response & AE are dose related
- REMS Program
  - Negative pregnancy test before initiation & monthly
- Spotting may occur with oral contraceptive use
- Take in the morning to avoid insomnia
- Do not stop abruptly – \( \uparrow \) risk of seizures
- Cognitive dysfunction
- Abuse potential
- Hyperchloremic metabolic acidosis
- Nephrolithiasis
- Depression and/or suicidal ideation

Garvey WT. et al. Endocrine Practice. 2016;22(7):842-884

REMS = risk evaluation and mitigation strategy
Naltrexone ER + Bupropion ER – safety

Side Effect Frequency

- Nausea: 35.00%
- Constipation: 20.00%
- Headache: 15.00%
- Sleep disorder: 10.00%
- Vomiting: 5.00%

N/B ER = naltrexone ER + bupropion ER

Naltrexone ER/Bupropion ER – avoid

- Uncontrolled hypertension
- Seizure disorder
- Drug or alcohol withdrawal
- Concomitant MAOI → within 14 days
- Chronic opioid use
- Black Box Warning
  - Suicidality & antidepressant drugs
  - Neuropsychiatric reactions
- Bipolar disorder
- Anxiety
- Narrow-angle glaucoma
Naltrexone ER/Bupropion ER – clinical pearls

- Avoid taking with high-fat meal

- Can cause false positive urine test for amphetamine

- Patients should be opioid free before initiation
  - Short-acting opioids: 7 – 10 days
  - Buprenorphine or methadone: 14 days

- Post-marketing cardiovascular studies

Liraglutide – safety

Side Effect Frequency

- Nausea
- Diarrhea
- Constipation
- Vomiting
- Headache

Liraglutide – avoid

• Personal or family history of:
  • Medullary thyroid cancer **OR**
  • MEN2

• Pancreatitis

• Suicidal ideation & behavior

**Contraindications**

MEN2 = Multiple endocrine Neoplasia syndrome type 2

Liraglutide – clinical pearls

• Only available by subcutaneous injection
  • Administer in abdomen, thigh, or upper arm

• REMS Program:
  • Potential risk of medullary thyroid carcinoma
  • Potential risk of acute pancreatitis

• Severe renal impairment due to vomiting & dehydration

• Use with caution in patients with cholelithiasis

(REMS = risk evaluation and mitigation strategy)
### Medication Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing Details</th>
</tr>
</thead>
</table>
| **Orlistat** | - RX: 120 mg TID before meals  
- OTC: 60 mg TID before meals |
| **Lorcaserin** | - IR: 10 mg BID  
- ER: 20 mg daily |
| **Phentermine + Topiramate ER**+ | - Starting Dose: 3.75/23 mg daily x2 weeks  
- Recommended Dose: 7.5/46 mg daily  
- Escalation Dose (if necessary): 11.25/69 mg daily x2 weeks  
- Max Dose: 15/92 mg daily |
| **Naltrexone ER + Bupropion ER**+ | - Start at 8/90 mg QAM  
- ↑ by 8/90 mg weekly up to 16/180 mg BID (max dose) |
| **Liraglutide** | - Start at 0.6 mg daily  
- ↑ by 0.6 mg weekly up to 3 mg daily (as tolerated) |

* = dose adjust for renal impairment  
+ = dose adjust for hepatic impairment  
RX = prescription  
OTC = over the counter  
IR = immediate release  
ER = extended release  
Medication Preference By Disease State

**Use Any:**
- Anxiety
  - Avoid P/T max dose 15/92 mg
- Diabetes Mellitus Type 2
- CrCl > 50

**Avoid All:**
- Congestive heart failure
- Pregnancy
- Breast-feeding
- Severe hepatic impairment (Child-Pugh >9)

P/T = phentermine + topiramate ER

## Medication Preference By Disease State

<table>
<thead>
<tr>
<th>Disease</th>
<th>Preferred</th>
<th>Use with Caution</th>
<th>Avoid</th>
</tr>
</thead>
</table>
| **CAD or Arrhythmia** | • Orlistat  
• Lorcaserin | • P/T  
• N/B  
• Liraglutide |                              |
| **HTN**          | • Orlistat  
• Lorcaserin  
• P/T  
• Liraglutide | • N/B | • N/B in uncontrolled HTN        |
| **Depression**   | • Orlistat  
• P/T – avoid max dose 15/92 mg  
• Liraglutide | • Lorcaserin  
• N/B | • Lorcaserin + SSRI or SNRI      |
| **Glaucoma**     | • Orlistat  
• Lorcaserin  
• Liraglutide | | • P/T  
• N/B |
# Medication Preference By Disease State

<table>
<thead>
<tr>
<th>Disease</th>
<th>Preferred</th>
<th>Use with Caution</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CKD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl 30 – 49</td>
<td>Any</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max Doses:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• P/T 7.5/46 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• N/B 8/90 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &lt; 30</td>
<td>Orlistat</td>
<td>Liraglutide</td>
<td>Lorcaserin P/T N/B</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>Lorcaserin</td>
<td>N/B Liraglutide</td>
<td></td>
</tr>
<tr>
<td>Mild – Moderate Hepatic Impairment</td>
<td>All</td>
<td></td>
<td>Orlistat P/T</td>
</tr>
<tr>
<td></td>
<td>Max Doses:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• P/T 7.5/46 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• N/B 8/90 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P/T = phentermine + topiramate ER  
N/B = naltrexone ER + bupropion ER  
CKD = chronic kidney disease  
BID = twice daily*  

## Medication Preference By Disease State

<table>
<thead>
<tr>
<th>Disease</th>
<th>Preferred</th>
<th>Use with Caution</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioid Use</strong></td>
<td>• Orlistat</td>
<td></td>
<td>• N/B</td>
</tr>
<tr>
<td></td>
<td>• Lorcaserin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• P/T</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Liraglutide</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>• Any</td>
<td></td>
<td>• Liraglutide if history of pancreatitis</td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>• Orlistat</td>
<td></td>
<td>• N/B</td>
</tr>
<tr>
<td></td>
<td>• Lorcaserin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• P/T</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Liraglutide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P/T = phentermine + topiramate ER  
N/B = naltrexone ER + bupropion ER  
d/c = discontinue  

Patient Case: 44 year old female, BMI 29

Past Medical History
- Chronic pain
- Depression
- Dyslipidemia
- Hypothyroidism
- Osteoarthritis

Current Medications:
- Acetaminophen
- Atorvastatin
- Levothyroxine
- Multivitamin
- Oxycodone ER
- Sertraline
- Vitamin D
What weight loss medication would you recommend that would be most efficacious & safe?

A. Orlistat  
B. Lorcaserin  
C. Phentermine/topiramate ER  
D. Naltrexone ER/bupropion ER  
E. Liraglutide
When to Stop Medication Treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Stop Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine + Topiramate ER</td>
<td>- After <strong>12 weeks</strong> lost &lt; 3% of weight on 7.5/46 mg:</td>
</tr>
<tr>
<td></td>
<td>• Discontinue <strong>OR</strong></td>
</tr>
<tr>
<td></td>
<td>• ↑ to 15/92 mg</td>
</tr>
<tr>
<td></td>
<td>- After <strong>12 additional weeks</strong> lost &lt; 5% of weight on 15/92 mg:</td>
</tr>
<tr>
<td></td>
<td>• Discontinue</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>- Discontinue if:</td>
</tr>
<tr>
<td></td>
<td>• After <strong>16 weeks</strong> lost &lt; 4% of weight</td>
</tr>
<tr>
<td>Lorcanerin Naltrexone ER +</td>
<td>- Discontinue if:</td>
</tr>
<tr>
<td>Bupropion ER</td>
<td>• After <strong>12 weeks</strong> lost &lt; 5% of weight on maintenance dose</td>
</tr>
</tbody>
</table>

Patient is on phentermine/topiramate ER 7.5/46 mg daily. By week 12 of therapy she has lost 3.5% of her baseline body weight. How long should she continue therapy?

A. Discontinue at 12 weeks, only intended for short-term treatment
B. Discontinue at 12 weeks since she lost < 5% of her baseline body weight
C. Continue current dose since she lost > 3% of her baseline body weight
D. Increase dose and re-evaluate at 6 months
Key Points

• Initiate weight loss drug therapy:
  • BMI > 30 kg/m²
  • BMI > 27 kg/m² + ≥ 1 weight related comorbidity

• **Individualize** pharmacotherapy!

• Re-evaluate continuation of therapy at 3 – 4 months
Questions & Discussion
Review of Weight Loss Medications in Obesity

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