Update in Obesity Pharmacotherapy

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Objectives

• What do the guidelines say?
• What is the rationale for using weight loss medications?
• What options do we have and how effective are they?
• Are newer treatments better?
• How long should we treat with medications?
• What’s new in the pipeline?

New Obesity Guidelines


2013 ACC/AHA/TOS Guideline for the Management of Overweight and Obesity in Adults: Box 12

- The Panel did not review comprehensive evidence for pharmacotherapy for weight loss.
- Based on expert opinion, the panelists recommend that for individuals with BMI ≥30 or BMI ≥27 with ≥1 obesity-associated comorbid condition who are motivated to lose weight, pharmacotherapy can be considered as an adjunct to comprehensive lifestyle intervention to help achieve targeted weight loss and health goals.
- Medications should be FDA-approved, and clinicians should be knowledgeable about the product label. The provider should weigh the potential risks of the medication being considered against the potential benefits of successful weight loss for the individual patient.
- The rationale for use of medications is to help patients adhere to a lower calorie diet more consistently in order to achieve sufficient weight loss and health improvements when combined with increased physical activity. Medications work to reinforce lifestyle change and should be prescribed as an adjunct to lifestyle interventions.

Jensen et al. Circulation 2013

New Obesity Guidelines

Key Recommendations

- Diet, exercise and behavior modification are fundamental to all forms of weight management
- Consider changing medications for other chronic diseases that may cause weight gain
- Consideration should be given to adding an FDA approved weight loss medication to a lifestyle program in appropriate patients
- Only continue a weight loss medications if patients lose 5% of baseline weight at 3 months. If so, continue indefinitely vs considering intermittent therapy.
Rationale for Pharmacotherapy

• Weight loss and weight-loss maintenance are very difficult for many patients
• Overweight/obesity is a chronic disease that requires long-term therapies
• Weight loss pharmacotherapy should be considered as an “adjunct” therapy
• The primary function of most medications are to assist with weight loss and maintenance of lost weight by impacting hunger/satiety, allowing patients to more easily follow a diet
• Not a “short-term” fix or “kick start”

Criteria for Using Approved Medications

Weight Loss Drugs Approved by FDA

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>Saxenda</td>
</tr>
<tr>
<td>Naltrexone+Bupropion</td>
<td>Contrave</td>
</tr>
<tr>
<td>Phentermine+Topiramate</td>
<td>Qsymia</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Belviq</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Xenical, Alli</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Adipex, Fastin, Ionamin</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Tenuate, Tenuate, Dospan</td>
</tr>
<tr>
<td>Phendimetrazine</td>
<td>Bontril</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Desoxyn</td>
</tr>
<tr>
<td>Benzphetamine</td>
<td>Didrex, Regimex</td>
</tr>
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</table>
Phentermine

- Mechanism: decreases appetite
  - Appetite suppressant
  - Noradrenergic - Sympathomimetic
- Dose: 15-37.5 mg daily (AM)
- Generic, least expensive option
- Most commonly prescribed
- Side Effects: Increased BP and HR, insomnia, agitation, dry mouth, headache, tremor, constipation
- Efficacy: More weight loss than placebo (~5%?)
- FDA approved for short-term use (3 months)
  - “The Phentermine Conundrum”

Weight Loss with Phentermine


Effects of Phentermine Therapy on Short-Term Weight Loss


*DCR – diffuse controlled release
Effects of Long-Term Phentermine Therapy

Hendricks et al. Obesity 2012;19:2351-2360

N = 300
phentermine 30 mg + ketogenic diet

Orlistat

- **Mechanism:**
  - GI lipases inhibitor, decreases fat absorption
- **Dose:** 60-120 mg with meals
- **FDA approved for long-term use**
- **Side effects:** GI "events", potential for malabsorption of fat soluble vitamins, liver toxicity?, nephrolithiasis
- **Efficacy:**
  - More weight loss than placebo (~4%)  
  - Diabetes prevention in high risk individuals  
  - Improvements in glycemic control in T2D  
  - Reductions in triglycerides

The XENDOS Study: Effect of Long-Term Treatment With Orlistat

Now for the “new” stuff…

**Phentermine + Topiramate SR**

- **Mechanism:**
  - Appetite suppressant
  - Phentermine: sympathomimetic
  - Topiramate: mechanism on weight loss is not known
  - Combination gives greater efficacy with fewer side effects
- FDA approved for long-term use
- Sold under the trade name Qsymia®

**Phentermine + Topiramate: CONQUER Trial**

![Graph showing weight loss over weeks for different treatment groups](image)
Phentermine + Topiramate:
CONQUER Trial


Phentermine + Topiramate:
SEQUEL Trial


SEQUEL Study: Incidence of Diabetes with Phentermine/Topiramate vs Placebo

Garvey et al. Diabetes Care 2014;37:912-921
Phentermine + Topiramate

**Type 2 Diabetes**

-0.04

-0.4

-0.2

7.1

1.9


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**Phentermine + Topiramate**

- **Dosing:**
  - 3.75/23mg daily x 2 weeks → 7.5/46mg daily
  - After 12 weeks can ↑ to 11.25/69mg and/or 15/92mg
  - Stop if <5% wt loss at 12 wks at 15 mg/92 mg dose
- **Cost:** ~$150.00/mo (coupons $75?)
- **Side Effects:**
  - ↑ BP and HR, insomnia, agitation, dry mouth, headache, tremor, suicidal thoughts, acute glaucoma, mood/sleep disorders, cognitive impairment, metabolic acidosis, ↑ creatinine
- **Pregnancy Category X**
  - topiramate has been shown to increase risk for oral clefts
  - Pregnancy test on starting and monthly on drug

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**Lorcaserin**

- **Mechanism:**
  - Appetite suppressant – increased satiety
  - Selective serotonin 2C receptor agonist, activates POMC neurons leading to a-MSH activation of MC4R
- **Previous serotonin agonists fenfluramine and dexfenfluramine caused cardiac valve disease**
  - 2C receptor only in the brain not in heart
  - Studies in 1-2,000 people for up to 2 years do not show evidence of valvulopathy with lorcasarin.
- **FDA approved for long-term use**
- **Sold under the trade name of Belviq®**
Weight Loss with Lorcaserin


[Graph showing weight loss over study weeks]

ITT Completers

5.8% 2.2%

ITT Completers

7.2% 2.9%

Weight Loss with Lorcaserin


[Graph showing weight loss over study weeks]

47.5%

20.3%

22.6%

7.7%

Weight Loss with Lorcaserin


[Graph showing percentage of patients achieving weight loss]

≥5% Weight Loss

Lorcaserin (N=1338) P=0.001

Placebo (N=1499)

28.3%

22.6%

≥10% Weight Loss

7.7%
Lorcaserin: BLOOM Diabetes Study

![Graph showing changes in HbA1C and Fasting Plasma Glucose over study weeks for Lorcaserin and Placebo.]

*P < .001; †P < .05; least square mean change ± standard error of the mean.

HbA1C = glycosylated hemoglobin.


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Lorcaserin

- Dose: 10 mg twice daily
- Cost: ~$200/mo (coupons $75?)
- Side effects: minimal, headache, dizziness and nausea (rare priapism, monitor for depression)
- Role:
  - Less effective than others but less side effects
  - In patients with Diabetes?
  - In those whole eat “past” satiety?

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Phentermine and Fenfluramine “Phen-Fen”

![Graph showing weight loss over weeks for Phen 15/Fen 60 mg/mid and Placebo.]

N=121 p<0.001

Naltrexone + Bupropion SR

- **Mechanism:**
  - Naltrexone: opioid antagonist
  - Bupropion: reuptake inhibitor of dopamine and norepinephrine
  - Suppresses appetite and reward
  - The exact mechanisms leading to weight loss are not fully understood
- FDA approved for long-term use
- Sold under the trade name *Contrave®*

**Weight Loss with Naltrexone+Bupropion**

![Graph showing weight loss with Naltrexone+Bupropion](image)

Effects of Naltrexone+Bupropion on Hunger and Cravings


How hungry have you felt?
How full have you felt?
How difficult has it been to Control your eating?
How difficult has it been to Resist any food cravings?
How often have you eaten In response to food cravings?
How often have you had food cravings for starchy foods?

Effects of Naltrexone+Bupropion on Glycemic Control in T2DM

Hollander et al. Diabetes Care 36:4022, 2013

Naltrexone + Bupropion SR

- Dosing:
  - each tablet: 8mg of naltrexone and 90 mg of bupropion
  - Titrate up to 32/360 mg per day
  - Morning
    - Week 1: 1 tablet
    - Week 2: 1 tablet
    - Week 3: 2 tablets
    - Week 4: 2 tablets
  - Evening
    - none
    - 1 tablet
    - 1 tablet
    - 2 tablets
    - 2 tablets
  - Stop if <5% wt loss at 12 wks
Naltrexone + Bupropion SR

• Cost: with coupons ~$75
• Side Effects:
  – ↑BP and HR, nausea, vomiting, constipation, headache
• Precautions:
  – Suicidal thoughts and behaviors, seizures, hepatotoxicity, glaucoma, drug interactions
  – Opioid use
• Role: depression, reward eating, binge eating?

Liraglutide

• Mechanism:
  – GLP1-agonist
  – Suppresses appetite
  – Slows gastric emptying
• FDA approved for long-term use
• Sold under the trade name Saxenda®

Weight Loss with Liraglutide 3 mg/d

Weight Loss with Liraglutide


Weight Maintenance and Additional Weight Loss with Liraglutide After Low-Calorie-Diet

Liraglutide

- Cost: ???
- Dosing: start with 0.6 mg sc daily, titrate weekly until reach 3.0 mg sc daily
- Side Effects:
  - nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase
- Role: ?

Variability in Response:

- [Graph showing weight change over time]

Review of Different Weight-Loss Maintenance Strategies

- [Graph showing weight change over months for different strategies]

Ravussin et al. Obesity 2009;17:1736-43

**STORM: Sibutramine Promotes Weight Loss Maintenance**

*Same diet, exercise for sibutramine, placebo; P < 0.001, sibutramine vs placebo for weight maintenance*


**Weight Loss Maintenance after VLCD with Phentermine**

VLCD – 800 kcal/d for 8 wks

Loper et al. Obesity Week 2013.

**Weight Loss with Continuous and Intermittent Phentermine**

N = 108

Continuous vs Intermittent Therapy?

![Graph showing body weight change over time for continuous and intermittent sibutramine treatment.]


Behavior + Medication

![Graph showing weight loss over weeks for different treatment combinations.]


Emerging Pharmacotherapy

- Bupropion SR + Zonisamide SR
- Lorcaserin + phentermine
- Other GLP-1 agonists
- SGLT2 Inhibitors
- Beloranib
Summary of Current Obesity Pharmacotherapy Options

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Long-Term</th>
<th>Efficacy</th>
<th>Side Effects</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Daily</td>
<td>No</td>
<td>~5%</td>
<td>+</td>
<td>$</td>
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<tr>
<td>Orlistat</td>
<td>Meals</td>
<td>Yes</td>
<td>4-5%</td>
<td>+++</td>
<td>$$$</td>
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<tr>
<td>Phen/Topiramate</td>
<td>Daily</td>
<td>Yes</td>
<td>8-10%</td>
<td>++</td>
<td>$$$</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>BID</td>
<td>Yes</td>
<td>4-5%</td>
<td>+</td>
<td>$$$</td>
</tr>
<tr>
<td>Nalt/Bupr</td>
<td>BID</td>
<td>Yes</td>
<td>5-7%</td>
<td>++</td>
<td>$</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Daily</td>
<td>Yes</td>
<td>5-7%</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>

How Do I Use These Meds?

- Use as an adjunct to lifestyle modification
- Use with the intention of using long-term
- Consider intermittent use? (Most will do this on their own)
- Usually start with phentermine for cost reasons
- Consider contraindications or other comorbid conditions
  - On SSRI – avoid lorcaserin
  - Active or recent CVD – consider lorcaserin
  - Depression or smoker – consider naltrexone/bupropion?
  - Prediabetes – consider liraglutide?
- Consider eating-related behaviors?
  - Eat out of hunger – phentermine or phentermine/topiramate?
  - Trouble with overeating – lorcaserin?
  - Trouble with cravings and emotional eating – naltrexone/bupropion?

Obesity Pharmacotherapy: Summary

- Supported by a wide range of societies and guidelines
- Current medications result in modest but clinically meaningful weight loss
- Most effective at long-term weight loss maintenance
  - Should optimally be used long-term
  - What about intermittent therapy?
- Should be used as an adjunct to lifestyle modification
- Typically not covered by insurers, so cost is a major barrier
- Issues remain: efficacy, FDA, long-term safety, others?
Thank You For Your Attention!

Bon Appétit!