New obesity medications: 5 years already?

January 31, 2018

Objectives

• 1. Review the history of weight loss medications.

• 2. Consider reasons for provider bias against using weight loss medications.

• 3. Discuss clinical insights gained from using weight loss medications.

• 4. Understand the role and efficacy of weight loss medications and how to discuss this with patients.
Low adoption of weight loss medications: A comparison of prescribing patterns of antiobesity and antidiabetes pharmacotherapies


Low adoption of weight loss medications: A comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT2s

Mean increases in prescriptions/month:
- 25,259 for SGLT2s
- 5,154 for new antiobesity medications
- 2,718 for phentermine

Low adoption of weight loss medications

- Cost/lack of insurance coverage
- High discontinuation rate: most common reasons are noncompliance, lost to follow-up, lack of efficacy, and adverse events
  - 33% for phentermine
  - 38% for phentermine + topiramate
  - 44% for lorcaserin
  - 46% for naltrexone + bupropion
  - (vs 9-14% for SGLT2s)
- Unrealistic effectiveness expectations
  - % weight loss
  - Cardiovascular outcomes
- Concern that patients will be “stuck” taking the medications despite lack of efficacy
- History of antiobesity medications being removed from market for safety concerns

History of weight loss medications

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Serious adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1893/1949</td>
<td>Thyroid hormone</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>1933/1935</td>
<td>Dinitrophenol</td>
<td>Cataracts, neuropathy</td>
</tr>
<tr>
<td>1937/1971</td>
<td>Amphetamine</td>
<td>Addiction, psychosis</td>
</tr>
<tr>
<td>1965/1972</td>
<td>Minoxidil</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>1973/1997</td>
<td>Fenfluramine + phentermine</td>
<td>Cardiac valvar insufficiency</td>
</tr>
<tr>
<td>1960/2000 (USA)*</td>
<td>Phenytoinamide</td>
<td>Haemorrhagic stroke</td>
</tr>
<tr>
<td>2006/2009</td>
<td>Rimonabant</td>
<td>Depression, suicidal ideation</td>
</tr>
<tr>
<td>1997/2010</td>
<td>Sibutramine</td>
<td>Cardiovascular disease</td>
</tr>
</tbody>
</table>

*Phenytoinamide is still available in some European countries. Modified and updated from reference 1.

Table: History of drug treatments for obesity, by date of approval/withdrawal

New perspective #1: (most) medications for weight loss have been around for a long time

Current weight loss medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine (Adipex)</td>
<td>5/1959</td>
</tr>
<tr>
<td>Orlistat (Alli, Xenical)</td>
<td>4/1999</td>
</tr>
<tr>
<td>Lorcaserin (Belviq)</td>
<td>6/2012</td>
</tr>
<tr>
<td>Phentermine plus topiramate (Qsymia)</td>
<td>7/2012</td>
</tr>
<tr>
<td>Topiramate</td>
<td>1996</td>
</tr>
<tr>
<td>Bupropion plus naltrexone (Contrave)</td>
<td>9/2014</td>
</tr>
<tr>
<td>Bupropion</td>
<td>1985/1989</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>1984</td>
</tr>
<tr>
<td>Liraglutide (Saxenda)</td>
<td>12/2014</td>
</tr>
<tr>
<td>Liraglutide (Victoza)</td>
<td>2010</td>
</tr>
</tbody>
</table>

New perspective #2: weight loss medications should be used in combination with efforts at lifestyle modification

Mean weight loss: combined therapy vs medical therapy or lifestyle modification

New perspective #3: obesity is a disease and pharmacotherapy is recommended

- 1995, Institute of Medicine
- 1997, World Health organization
- 1998, National Institutes of Health
- 2005, American College of Physicians
- 2012, American Association of Clinical Endocrinologists, American College of Endocrinologists
- 2013, American Medical Association
- 2013, American Heart Association, American College of Cardiology, Obesity Society
- 2015, Endocrine Society

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Look AHEAD

![Graph showing weight change over years with annotations: Average effect across visits: -5.27 (P<.001), 1.1% change, 8.6%, 4.7% change.]

New perspective #4: weight loss is an important target

- Look AHEAD
  - Post-hoc analysis: weight loss ≥10% in first year vs <2%
  - Adjusted hazard ratio primary outcome: 0.79 (0.64-0.98), p= 0.034
  - Adjusted hazard ratio secondary outcome: 0.76 (0.63-0.91), p= 0.003

- Swedish Obese Subjects (SOS) study (20 year data)
  - Adjusted hazard ratio for cardiovascular death: 0.47 (0.29-0.76), p= 0.002
  - First time fatal or nonfatal cardiovascular events: 0.67 (0.54-0.83), p= 0.001

New perspective #5: there is [some] evidence that weight loss medications reduce CV disease

• Leader trial

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From the University of Iowa, Iowa City; the George Washington University, Washington, DC; the University of Miami, Miami, FL; the Cleveland Clinic Foundation, Cleveland, OH; the University of California, Los Angeles; the Mayo Clinic, Rochester, MN; the Duke Clinical Research Institute, Durham, NC; the University of Colorado, Denver; the New York University School of Medicine, New York; the University of Southern California, Los Angeles; the University of North Carolina, Chapel Hill; the University of Minnesota, Minneapolis; the University of Pennsylvania, Philadelphia; and the University of Exeter Medical School, Exeter, UK. 

New perspective #6: CV disease is not the only meaningful outcome for weight loss

- 3-5% weight loss
  - ↓ Triglycerides
  - ↓ Glucose, HgbA1c
  - ↓ Risk developing diabetes mellitus

- >5% weight loss
  - ↓ BP
  - ↓ LDL
  - ↑ HDL
  - ↓ Need for medications to control BP, glucose, lipids

- Other benefits
  - ↑ Physical fitness and physical function
  - ↓ Kidney disease
  - ↓ Retinopathy
  - ↓ Sleep apnea
  - ↓ Incontinence
  - ↑ Quality of life
  - ↓ Depression
  - ↓ Joint pain
  - ↓ Anthypertensives, insulin, statins

New perspective #7: obesity is a chronic disease, so medications for weight loss should be used long term

Reduced at 2 years
- Total cholesterol
- LDL cholesterol
- LDL/HDL ratio
- [glucose]
- [insulin]

GI symptoms (3-5%)

New perspective #8: medications are effective at causing weight loss

• Unrealistic effectiveness expectations
  – 0.77% drop in hemoglobin A1c (7.86 to 7.09%) is 9.8%.
  – 9.8 mm Hg drop in systolic BP (146.2 to 136.4 mm Hg) is 6.7%.
  – mean weight loss after 1 year of phentermine/topiramate is 10.9%.

• Multivariable analysis of data from obese adult (BMI ≥30) participants in the 2001–2006 NHANES.
  – Identify strategies associated with losing 5% and 10% of body weight.
    • 63% reported trying to lose weight in the previous year.
    • Among those attempting weight loss, 40% lost 5% and 20% lost 10% weight.
  – Although least utilized strategy (3.5%), antiobesity pharmacotherapy was most associated with self-reported body weight loss of ≥10% in the prior year (OR 2.05).


New perspective #8: medications are effective at causing weight loss

• Lorcaserin (Belviq)- 2012
  – 7794 participants (3 trials; 52 weeks each)

• Phentermine/topiramate (Qsymia)- 2012
  – 4430 participants (3 trials; 56 weeks for 2, 2 years for 1)

• Bupropion/naltrexone (Contrave)- 2014
  – 4536 participants (4 trials; 56 weeks each)

• Liraglutide (Saxenda)- 2014
  – 4999 participants (3 trials; 56 weeks each)
Pharmacotherapy for Obesity

• FDA approved for:
  – BMI of 27 to 29.9 kg/m² with comorbidity
  – All patients with BMI ≥30 kg/m²

• Stop medications if the patient does not lose ≥5% of their weight.
Contrave: individual weight loss at week 56

- Four phase 3, randomized, placebo-controlled, 56 week clinical trials of naltrexone/bupropion 32/360 mg
- 80% identified correctly who lost ≥5% at week 56 that had lost ≥5% at week 16.


Contrave: look for the responders

- Weight loss ≥5% at Week 16 associated with mean weight loss ≈12% at Week 56
  - Average weight loss= 6.7%
- 85% had a Week 56 weight loss of ≥5%
  - 52.4% lost ≥5%
- 57% had a Week 56 weight loss of ≥10%
  - 28.3% lost ≥10%

Pharmacotherapy for Obesity

- FDA approved for:
  - BMI of 27 to 29.9 kg/m² with comorbidity
  - All patients with BMI ≥30 kg/m²
- Stop medications if the patient does not lose ≥5% of their weight.
- Advise patients: medications work in the brain to suppress appetite and help maintain calorie goal - they do not increase metabolism, burn fat, or give energy.


B: Bupropion
Lg: Liraglutide
Lc: Lorcaserin
N: Naltrexone
P: Phentermine
T: Topiramate
Lorcaserin reduces body weight by decreasing energy intake without influencing energy expenditure

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>10 mg twice-daily lorcaserin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>wk 1* - baseline</td>
<td>wk 8* - baseline</td>
<td>wk 1* - baseline</td>
<td>wk 8* - baseline</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>-2.2 ± 0.9*</td>
<td>-3.8 ± 0.4*</td>
<td>0.01</td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td>-1.2 ± 0.3*</td>
<td>-0.9 ± 0.3*</td>
<td>0.39</td>
</tr>
<tr>
<td>24h EE from respiratory chamber (kcal/d)</td>
<td>-57 ± 20*</td>
<td>-96 ± 20*</td>
<td>0.17</td>
</tr>
<tr>
<td>24h RO from respiratory chamber</td>
<td>-103 ± 25*</td>
<td>-162 ± 20*</td>
<td>0.06</td>
</tr>
<tr>
<td>SMR from respiratory chamber</td>
<td>0.03 ± 0.00*</td>
<td>0.01 ± 0.00*</td>
<td>0.10</td>
</tr>
<tr>
<td>SMR adjusted for body composition (kcal/d)</td>
<td>-50 ± 17*</td>
<td>-97 ± 17*</td>
<td>0.06</td>
</tr>
<tr>
<td>RMR, ventilated hood (kcal/d)</td>
<td>-70 ± 20*</td>
<td>-106 ± 33*</td>
<td>0.12</td>
</tr>
<tr>
<td>Average METs (amband accelerometer)</td>
<td>0.03 ± 0.05</td>
<td>0.14 ± 0.05*</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Pharmacotherapy for Obesity

- FDA approved for:
  - BMI of 27 to 29.9 kg/m² with comorbidity
  - All patients with BMI ≥30 kg/m²
- Stop medications if the patient does not lose ≥5% of their weight.
- Advise patients: medications work in the brain to suppress appetite and help maintain calorie goal- they do not increase metabolism, burn fat, or give energy.
- Counsel patients on risks, costs, and potential benefits of weight loss medications including likelihood of achieving meaningful weight loss.

Martin et al. JCEM, 2011;96:837:45.
Lorcaserin (Belviq)

- 3 phase 3 clinical trials (BLOOM, BLOSSOM, BLOOM-DM)
- Average weight loss= 5.8% (2.2% placebo)
- 44.1% lost ≥5% (20.5% placebo)
- 20.5% lost ≥10% (7.3% placebo)
- Cost: $250/month ($90-100 with coupon)

- Contraindications
  - concomitant use with other serotonergic and dopaminergic drugs
  - pregnancy (category X)

- Adverse effects
  - nausea
  - dizziness
  - headache
  - fatigue
  - mood effects

Phentermine/topiramate (Qsymia)

- 2 phase 3 clinical trials (EQUIP, CONQUER)
- Average weight loss= 5.1-10.9%
- 66.7-70.0% lost ≥5%
- 47.2-48% lost ≥10%
- Cost: $200/month ($140-150 with coupon)

- Contraindications
  - known vascular disease
  - uncontrolled hypertension
  - glaucoma
  - MAO-I
  - hyperthyroidism
  - pregnancy (category X)

- Adverse effects
  - constipation
  - altered taste
  - dry mouth
  - insomnia
  - paresthesias
  - fatigue
  - metabolic acidosis, nephrolithiasis
  - mood changes
Bupropion/naltrexone (Contrave)

- 4 phase 3 clinical trials (COR-I, COR-II, COR-BMOD, COR-Diabetes)
- Average weight loss= 6.7% (2.4% placebo)
- 52.4% lost ≥5% (23.6% placebo)
- 28.3% lost ≥10% (9.7% placebo)
- Cost: $240/month ($90 with coupon)

- Contraindications
  - seizure history/alcohol abuse
  - opiate therapy
  - uncontrolled hypertension
  - severe depression/suicidality
  - pregnancy (category X)
  - MAO-I

- Adverse Effects
  - nausea
  - headache
  - constipation
  - dizziness
  - vomiting
  - dry mouth
  - mood changes
  - blood pressure: ↑1.5 mm Hg then ↓1 mm Hg
  - pulse: ↑1.5-2.5 bpm

Liraglutide (Saxenda)

- 4 phase 3 clinical trials (SCALE-Diabetes, SCALE-Obesity and Prediabetes, SCALE-Maintenance)
- Average weight loss= 6.5% (1.6% placebo)
- 56% lost ≥5% (23.4% placebo)
- 28% lost ≥10% (7.9% placebo)
- Cost: $1200/month (variable with coupon)

- Contraindications/Warnings
  - personal or FH of MTC/MEN
  - pregnancy (category X)
  - pancreatitis

- Adverse Effects
  - Nausea/vomiting
  - Diarrhea, constipation
  - Headache
  - Dyspepsia, abdominal pain
  - Dizziness
  - Fatigue
Weight loss summary: new obesity medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Ave wt loss</th>
<th>5% wt loss</th>
<th>10% wt loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belviq</td>
<td>5.8%</td>
<td>44.1%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Qsymia</td>
<td>5.1-10.9%</td>
<td>66.7-70.0%</td>
<td>47.2-48%</td>
</tr>
<tr>
<td>Contrave</td>
<td>6.7%</td>
<td>52.4%</td>
<td>28.3%</td>
</tr>
<tr>
<td>Saxenda</td>
<td>6.5%</td>
<td>56%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Comparison of antiobesity medications

- SUCRAs for Weight Loss and Adverse Event Outcomes

Khera et al. JAMA, 2016;315(22):2424-34.
Novel combinations: canagliflozin and phentermine

- Randomized, double-blind, PBO-controlled, multicenter
- N= 335, overweight or obese, without diabetes
- Canagliflozin 300 mg and phentermine 15 mg daily


Limitations

- Cost
- Interactions/contraindications
- Lack of really long-term (>2 years) safety data
- Limited data on long-term CV or mortality benefit
- No guidance on which medication would be more effective or better tolerated
Pharmacotherapy: my approach

• Medication approved for long-term use preferred.
  – Lorcaserin (Belviq)
  – Phentermine/topiramate (Qsymia)
  – Bupropion/naltrexone (Contrave)*
  – Liraglutide (Saxenda)*
  – Orlistat (Xenical, Alli)*
• Look for contraindications based on PMH.
• Look for interactions on medication list.
• Patient preference (benefit vs risk vs potential SE).
• Assess progress/tolerability at 1-2 months and at 3 months: ≥5% weight loss?

*Non-scheduled medications

Summary

• Likelihood of losing 5% (~50-70%) or 10% (~30-50%)
• Meant for long-term use (only work when taken)
• Work in the brain to reduce appetite
• Stop after 3 months if no loss of ≥5%
• Risk factor and symptom benefit with all
• Cardiovascular benefit with liraglutide
• CV benefit with all if lose ≥10%?
### Drugs that affect weight

<table>
<thead>
<tr>
<th>Weight Gainers</th>
<th>Weight Losers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (1.8 kg)</td>
<td>Metformin (1.1 kg)</td>
</tr>
<tr>
<td>Mirtazapine (1.5 kg)</td>
<td>Acarbose (0.4 kg)</td>
</tr>
<tr>
<td>Olanzapine (2.4 kg)</td>
<td>Pramlintide (2.3 kg)</td>
</tr>
<tr>
<td>Quetiapine (1.1 kg)</td>
<td>Liraglutide (1.7 kg)</td>
</tr>
<tr>
<td>Risperidone (0.8 kg)</td>
<td>Exenatide (1.2 kg)</td>
</tr>
<tr>
<td>Gabapentin (2.2 kg)</td>
<td>Zonisamide (7.7 kg)</td>
</tr>
<tr>
<td>Pioglitazone (2.6 kg)</td>
<td>Topiramate (3.8 kg)</td>
</tr>
<tr>
<td>Glimepiride (2.1 kg)</td>
<td>Bupropion (1.3 kg)</td>
</tr>
<tr>
<td>Glyburide (2.6 kg)</td>
<td>Fluoxetine (1.3 kg)</td>
</tr>
<tr>
<td>Glipizide (2.2 kg)</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin (0.55 kg)</td>
<td></td>
</tr>
</tbody>
</table>

Domecq et al. JCEM, Feb 2015, 100(2):363-370.

### Drugs that affect weight

- **Type 2 diabetes mellitus**
  - **Preferred**
  - **Less preferred**
  - **Least preferred**
    - GLP-1 agonists
    - SGLT2 inhibitors
    - Metformin
    - DPP4 inhibitors
    - Pramlintide, α-glucosidase inhibitors

- **Antihypertensives**
  - Use ACE/ARBs or CCB before β-blockers (carvedilol or nebivolol less associated with weight gain)

- **Antidepressants**
<p>|</p>
<table>
<thead>
<tr>
<th>Weight loss</th>
<th>+/-</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Citalopram</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Escitalopram</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Venlafaxine</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td></td>
<td>Duloxetine</td>
<td>Nortriptyline</td>
</tr>
</tbody>
</table>
Drugs that affect weight

- Antipsychotics
  - Aripiprazole, Ziprasidone, Quetiapine, Risperidone, Clozapine, Olanzapine

- Antiepileptics

<table>
<thead>
<tr>
<th>Weight loss</th>
<th>+/-</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>Lamotrigine</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Levetiracetam</td>
<td>Pregabalin</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Phenytoin</td>
<td>Valproic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbamazepine</td>
</tr>
</tbody>
</table>

- Contraceptives
  - Use oral (or IUD) instead of injectable/implants

- HIV medications
  - Monitor weight

- Chronic inflammatory disorders
  - Use NSAIDs and disease modifying agents rather than glucocorticoids

- Use antihistamines with less central nervous system activity (less sedation)