Past, Present and Future of Pharmacotherapy for Obesity

Dan Bessesen, MD
Chief of Endocrinology; Denver Health Medical Center
Professor of Medicine, University of Colorado School of Medicine
Daniel.Bessesen@ucdenver.edu

Disclosure

Affiliation: Advisory Board/Panel

Company: Data Safety Monitoring Board for Enteromedics Inc.

Relationship: Active

Learning Objectives

• List the currently available FDA approved weight loss medication and the unique benefits of each

• Describe an approach to helping a patient with co-morbid health problems select a weight loss agent in a manner that reduces risk and maximizes potential benefits

• List the barriers to prescribing weight loss medications and describe an approach to addressing them
A Case

► A 45 year old woman comes to see you for help losing weight. She says she is eating very little and yet cannot lose weight. She tried Weight Watchers 3 years ago and lost 10 lbs but has regained that weight.
► Her current weight is 201 lbs and she is 5’5” tall giving her a BMI=33.5 kg/m²
► She has a history of diabetes treated with metformin 1 g BID with an A1C=7.8,

A Case

► She has hypertension well controlled on 12.5 mg/d HCTZ, she has no history of heart disease.
► She has depression treated with bupropion, and headaches.

A Case

► How do you approach discussing weight with her?
► Do you discuss weight loss medications with her?
► Are weight loss medications safe? Effective? Worth the money?
► Which weight loss medication might be best for her?
► How do you follow her if you do prescribe?
General issues

► Eligible patients: BMI >30 kg/m² or 27-30 kg/m² with a weight related co-morbidity.
► Previous lifestyle treatment, peak lifetime non-pregnant weight.
► Weight loss is 5-10% more than lifestyle alone.
► If a medication works, will need to be taken chronically (intermittently?).
► Typically not paid for by insurance so cost is an important factor for many patients.

A Guide to Selecting Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BMI category</th>
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<tbody>
<tr>
<td>Diet, physical activity, and behavior therapy</td>
<td>25-26.9</td>
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<tr>
<td>Pharmacotherapy</td>
<td>27-29.9</td>
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<td>Surgery</td>
<td>30-34.9</td>
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<td>35-39.9</td>
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<td>≥40</td>
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<tr>
<td>Diet, physical activity, and behavior therapy</td>
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<tr>
<td>With co-morbidity</td>
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<tr>
<td>Pharmacotherapy</td>
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<td>With co-morbidity</td>
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Jensen, Circulation 2013

Treatment Options: Effectiveness

Dietary self monitoring
- Cut out sodas
- Popular diet books
- Intensive Lifestyle Programs
- DPP like Groups
- Meal Replacements
- Balloons
- GI approaches
- Gastric Bypass
- GBPS with Medications
- Or BPD

Weight Watchers
- 0%
- 5%
- 10%
- 20%
- 30%
- Pharmacotherapy
- Combination
- Lifestyle and Meds
- Sleeve Gastrectomy
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Phentermine

- Increases NE content in the brain
- Dose: 15-37.5 mg/d, New 8 mg dose (Lomaira)
- Cost: $15-25.00/month
- Most widely prescribed wt. loss medication (74% of current market, (Obesity, 2016 24: 1955)
- FDA approved for only 3 months use
- 3-6% weight loss
- Side effects: tachycardia, hypertension, headache, nervousness, sleeplessness

CVD Safety: Legacy of Sibutramine

- SCOUT trial: Increased CVD in Sibutramine treated patients.
- High risk patients, continued medication even if they did not lose weight
- 2012 Case/control study >6000 pts in UK and Germany showed significantly lower ASCVD risk in sibutramine users
- 2015 case/control study >23,000 pts in UK increased risk in those with CVD (DM, DM+1RF) but not in those without.

Hayes Int J Obesity 2015, 1–6doi:10.1038/ijo.2015.86
Phentermine: Long term Prescribing?
Endocrine Society Guidelines

- Has no evidence of serious cardiovascular disease, serious psychiatric disease or a history of substance abuse
- Has been informed about weight loss medications that are FDA approved for long-term use and told that these have been documented to be safe and effective whereas phentermine has not
- Does not demonstrate a clinically significant increase in pulse or BP when taking phentermine
- Demonstrates a significant weight loss while using the medication.

J Clin Endocrinol Metab. 2015 Feb;100(2):342-62

Orlistat (Xenical)

- Pancreatic Lipase inhibitor
- Inhibits fat absorption by 30%
- 120 mg three times per day
- Cost: $100.00/mo
- GI side effects: oily stools, urgency
- MVI to prevent fat soluble vitamin deficiency

Orlistat

- Thousands of patients studied up to 4 years of exposure.
- Tested in adolescents
- Evidence of diabetes prevention
- Safest weight loss medication, approved for long term use, OTC form
- 3-6% weight loss on average
- Drug interactions: Coumadin, cyclosporin
Lorcasarin (Belviq)

- Serotonin 2C receptor agonist
- Previous serotonin agonists fenfluramine and dexfenfluramine caused cardiac valve disease, removed from market
- 2C receptor only in the brain not in heart
- Studies in 1-2,000 people for up to 2 years do not show evidence if valvulopathy with lorcasarin.

Lorcasarin (Belviq)

- Weight loss: 4-6% no better than phentermine or orlistat
- Least side effects: minimal headache, dizziness and nausea
- Cost: $220/mo
- No tachycardia, safe for pts with CVD risk
- Unclear if physicians will prescribe off label with phentermine (no data on safety or efficacy so I would not do this)
Phentermine/Topiramate ER

- Combination gives greater efficacy with fewer side effects
- Doses 7.5/46 mg and 15/92 mg phentermin/topiramate
- Cost: $150.00/month
- Side effects: dry mouth, paraesthesias, insomnia, dizziness, anxiety, irritability and disturbance in attention
Phentermine/Topiramate ER

- Risk of birth defects: women need – pregnancy test on starting and monthly while using.
- Reduces blood pressure, glucose, insulin, triglycerides and raises HDL
- Some physicians prescribe off label using generic phentermine and topiramate.
- Most effective medication available 10-12% weight loss.

Phentermine/Topiramate ER: SEQUEL Trial

Phen/Top: Effects on Blood Pressure

CONQUER Trial
Naltrexone SR/Bupropion SR

- Combination of Naltrexone SR 8 mg and Bupropion SR 90 mg titrated to 2 BID.
- Bupropion stimulates hypothalamic pro-opiomelanocortin (POMC) neurons reduces food intake.
- Naltrexone blocks opioid receptor-mediated POMC auto-inhibition, augmenting POMC firing in a synergistic manner. Alters reward pathways.
- Intermediate in effectiveness and side effects

Naltrexone SR/Bupropion SR

- Worrisome side effects: increased blood pressure and pulse, lowers seizure threshold, suicidal ideation (black box).
- Common side effects: Nausea, constipation, diarrhea, headache, dry mouth
- Cost $200/month
- Stop if clinically significant increase in BP or pulse
- Stop if <5% weight loss at 3 months
Naltrexone SR/Bupropion SR: Diabetes Trial

Variability in Response to naltrexone ER/bupropion ER

Liraglutide 3 mg

- GLP-1 agonist
- Main side effect is nausea, increases pulse initially
- Variability in response with responders losing more weight
- Reduction of metabolic syndrome, reduced progression to diabetes
- AWP >$1,000/mo. Most expensive of available agents
- Intermediate in efficacy and side effects
Liraglutide 3 mg in Obesity

Side Effects with Liraglutide

Table 1. Adverse events with an incidence of 5% or more in any treatment group, by system-organ class and preferred term

Liraglutide: CVD outcomes

Comparison of Wt Loss Drugs

Behavior + Meds better than either alone
Pharmacotherapy plus Meal Replacements

Look AHEAD More Wt. Loss is Better

► Primary analysis did not show a CVD benefit
► Study was powered for an event rate of 3.125%/year and at the 3 year mark the event rate was 0.7%/year (Clin Trials. 2012 Feb;9(1):113–24)
► Individuals who lost >10% of their bodyweight in the 1st yr of the study had a 21% lower risk of the 1o outcome (p=0.034) and a 24% reduced risk of the 2o outcome (p=0.003)

Lancet Diabetes Endocrinol 2016; 4: 913–21

Low Utilization of Weight Loss Medications

Barriers to Prescribing

- Safety issues: perception is that these medications are dangerous
- Efficacy concerns: 5-10% is not enough for many patients
- Lack of payment: 1/3rd of payers to not cover, 1/3rd have limited coverage, 1/3rd have coverage but may be sold as an add on (Miller).
- Provider issues: Long, complex discussion with patients, lack of training

Physician Attitudes Towards Prescribing

- “Promoting and prescribing drugs to treat obesity does a disservice to our patients, society, and ourselves. Such prescriptions may help patients lose a few pounds in the short run, but these drugs violate nearly every principle of careful, conservative prescribing, and they may well put patients at risk”
- 31% say they do not prescribe this class of medications.
- Experimental studies have found that physicians see patients with obesity as being less compliant, having less self-discipline and being more annoying.


Medications in the pipeline

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Mfg</th>
<th>Trials</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velopeptin</td>
<td>NPY5R antagonist</td>
<td>Shionogi</td>
<td>Phase 2</td>
<td>Discontinued</td>
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<tr>
<td>Obineptide</td>
<td>dual NPY2/Y4 R agonist</td>
<td>7TM Pharma</td>
<td>Phase 2</td>
<td>No info since 2010</td>
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<tr>
<td>Tesofensine</td>
<td>DA, NE, 5 re-uptake inhib</td>
<td>Saniona</td>
<td>Phase 2</td>
<td>In development</td>
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<tr>
<td>Bupropion + zonisamide</td>
<td>DA re-uptake inhib, GABA</td>
<td>Orexigen</td>
<td>Phase 2</td>
<td>No info since 2009</td>
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<tr>
<td>Beloranib</td>
<td>MetAP2 inhib</td>
<td>Zafgen</td>
<td>Phase 3</td>
<td>Halted</td>
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<tr>
<td>Celstat</td>
<td>Lipase inhib</td>
<td>Norgine BV</td>
<td>Phase 3</td>
<td>Approved in Japan</td>
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<tr>
<td>Setmelanotide</td>
<td>MC4R agonist</td>
<td>Rhythm Pharm</td>
<td>Phase 2</td>
<td>Genetic obesity</td>
</tr>
</tbody>
</table>
Novel Combinations

► Canagliflozin 300 mg and Phentermine 15 mg 26 wk phase 2 trial, n=335, 6.9% placebo subtracted weight loss, reduced blood pressure (Hollander P; Diabetes Care. 2017 Mar 13)
► Dapagliflozin plus exenatide 28 wk trial, n=695, 3.4 kg weight loss (Lancet Diab Endo. 2016 Dec;4(12):1004-1016)
► Pramlintide with phentermine 24 wk trial, n=244, 11.3% weight loss (Obesity 2010 Sep;18(9):1739-46)

Unimolecular Polypharmacy

► Dual agonists: glucagon/GLP-1
► Triple agonists: Glucagon/GLP-1/GIP
► Combinations with T3 or E2

Conclusions

► We have a number of safe and effective weight loss agents
► They are not prescribed very often
► The market is challenging currently
► We need a ‘statin’
► In the mean time, the goal is to have an honest, productive conversation with patients about the risks and benefits of these agents