Pharmacologic Treatments for Obesity

Hypertension Highlights 2013

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Part II: Obesity and Cardiometabolic Diseases
San Francisco, California
May 15, 2013
American Society of Hypertension, Inc. (ASH)

Suzanne Oparil, MD

Disclosure of Relationships

Over the past 12 months

Consultant/Advisory Board: Bayer, Daiichi Sankyo Inc., Medtronic, Novartis and Pfizer

Research Support: AstraZeneca AB, Duke, Medtronic, Merck and Co., NIH/NHLBI, Novartis and Takeda

Health Consequences of Obesity

- Type II diabetes
- Hypertension, stroke
- Dyslipidaemia
- Cardiovascular disease
- Degenerative joint disease
- Sleep Apnea
- Liver - NAFLD/NASH
- Gallstones
- Pancreatitis
- Cataracts
- Some types of cancer (colon, breast, uterus, cervix, pancreas, kidney, prostate)
- Gynecologic - abnormal menses, infertility, PCOS
- Phlebitis, venous stasis
Weight Loss and BP

• One of the most effective means to reduce BP—observational and clinical trials show positive direct relationship

• 4–5 kg weight loss significantly lowers BP (7/5 mm Hg) in obese and non-obese individuals. Visceral obesity most important. Body fat reduction more important than weight reduction. Maintain lean muscle mass, with target body fat of <16 % (men) and <22% (women) with normal WC and WHR.

• Additive to other nonpharmacologic and pharmacologic treatment

• More effective in BP reduction when combined with exercise

• Reduces BP before and without achieving IBW

• Reduces incidence of hypertension by about 18%

• Reduces adipokines which increase BP and inflammation

Masuo K et al. Hypertens Res. 2011;Aug 4 EPUB
Bischoff SC et al. Int J Obes. (Lond);2011;June 14 EPUB

Prog Cardiovas Disease. 1999;41:451-60.
J Obesity Res. 1998;6(2):51S-209S.

Weight Loss and BP

• Role of hyperinsulinemia, insulin resistance, ↑ IVF, ↑ SNS activity, ↑ SVR, Na⁺ retention, PRA, aldosterone, sleep apnea, adipokines, inflammation (hs-CRP)

• Direct dose-response relationship

• Meta-analysis 11 Clinical Trials
  – SBP: 1.6 mm Hg / kg weight loss
  – DBP: 1.1 mm Hg / kg weight loss

• Short-term and long-term effects persist, but only 13% maintain weight loss at 36 months

Prog Cardiovas Disease. 1999;41:451-60.
J Obesity Res. 1998;6(2):51S-209S.
Short-term Obesity Therapy Does Not Result in Long-term Weight Loss

Guide for Selecting Obesity Treatment

<table>
<thead>
<tr>
<th>BMI Category (kg/m²)</th>
<th>Treatment</th>
<th>25-26.9</th>
<th>27-29.9</th>
<th>30-34.9</th>
<th>35-39.9</th>
<th>&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diet, Exercise, Behavior Tx</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Pharmacotherapy</td>
<td></td>
<td>With co-morbidities</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td></td>
<td></td>
<td>With co-morbidities</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Long-term weight loss outcomes

- Diet/lifestyle: <5 kg after 2-4 years
- Pharmacologic therapy: 5-10 kg after 1-2 years
- Surgery: 25-75 kg after 2-4 years

Douketis et al., Int J Obes, 2005
History of Weight Loss Drugs

- 1880’s Thyroid extract (hyperthyroidism)
- 1930’s Dinitrophenol (cataracts, neuropathy)
- 1940’s Amphetamines (addiction, CNS/cardiac toxic)
- 1960’s Rainbow pills -digitalis/diuretics (sudden death)
- 1970’s Aminorex (pulmonary hypertension)
- 1990’s Redux (cardiac valvulopathy)
Centrally-Acting Anorexigens Approved Post-1938

♦ 1947 – Desoxyephedrine/methamphetamine
♦ 1956 – Phenmetrazine (Preludin)
♦ 1959 – Phendimetrazine (Bontril)
♦ 1959 – Phentermine (Fastin, Ionamin) – W/D CPMP 2000
♦ 1959 – Diethylpropion (Tenuate)
♦ 1960 – Benzphetamine (Didrex)
♦ 1973 – Mazindol (Sanorex)$^2$
♦ 1997 – Sibutramine (Meridia) _ W/D 2010
♦ 1999 – Orlistat
♦ 2007 – OTC orlistat
♦ 2012 – Lorcaserin (Belviq)
♦ 2012 – Phentermine+Topiramate ER (Qsymia)
Primary efficacy criteria (one of the following)

- 5% greater (statistically significant) weight loss than placebo at 1 year
- At least 35% patients achieving 5% weight loss on drug and approximately double the proportion in the placebo-treated group

Sample size

- 3000 randomized to active dose of drug and no fewer than 1500 on placebo for 1 year

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*FDA. Guidance for industry developing products for weight management, draft guidance, revision 1, Feb 2007*
# Antiobesity drugs approved for long-term use

## Orlistat (Xenical)

| **Mechanism:** Lipase inhibitor. Reduces absorption of fat by one-third. |
| **Dose:** 120 mg t.i.d with meals (or within 1 hr) plus MVT |
| **Adverse effects:** (9% dropout) flatulence, fatty stools, fecal urgency and incontinence, decreased absorption of vitamins, primarily D. |
| **Drug interactions:** Cyclosporine |
| **Contraindications:** Chronic malabsorption syndromes, cholestasis |

$3.56 per day
Orlistat - Efficacy

• Over 1-4 years, orlistat treatment achieves 2.9 kg weight loss relative to placebo at the dose of 120 mg tid \(^1\)
• A greater proportion of patients achieve 10% weight loss (26% vs 14%)
• Low-dose orlistat (60mg) achieved 1.1 kg weight loss relative to placebo after 16 wks \(^2\)

\(^1\)Rucker et al. BMJ Dec 2008
Orlistat - Risks

• Most common are gastrointestinal - fatty/oily stool, faecal urgency, oily spotting, each occurring at 15%-30% in most studies.
• Decreases absorption of fat-soluble vitamins

Orlistat – Severe liver injury warning

- 26 May 2010: FDA approved revised label that included warning about serious liver injury
- 13 cases – one in US in and 12 foreign cases
- Two died of liver failure, 3 required liver transplantation

*FDA. Drug Safety Communication, 26 May 2010.*
Emerging antiobesity drugs

- Drugs reporting phase III results
  - Bupropion + naltrexone (Contrave)
  - Lorcaserin (Belviq)
  - Phentermine + topiramate (Qsymia)
Bupropion + Naltrexone (Contrave)

• Bupropion, primarily a norepinephrine uptake inhibitor, is marketed for treatment of depression and as a smoking cessation aid.
• Bupropion showed modest weight loss efficacy in three obesity trials.¹
• Naltrexone, an opioid receptor antagonist, is marketed to treat alcoholism and opioid addiction.
• Animal studies suggest pharmacodynamic synergy.²

Bupropion + Naltrexone (Contrave) Weight Loss (%)

ITT-LOCF weight loss

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight Loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.3%</td>
</tr>
<tr>
<td>16 mg N</td>
<td>5.0%</td>
</tr>
<tr>
<td>32 mg N</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

* P <0.0001 for placebo comparisons

Bupropion + Naltrexone (Contrave)
FDA Advisory Committee Meeting

**Concern**

- Small ↑ BP noted in first 2 months on ABPM

**Action**

- FDA required CV outcome trial (LIGHT), ongoing
Lorcaserin (Belviq)

- Activation of 5-HT2_C receptor decreases food intake via POMC neurons
- Fenfluramine and dexfenfluramine were agonists of both 5-HT2_C and 5-HT2_B
- Selective 5-HT2_C agonist
- 100-fold greater selectivity over 5-HT2B receptor

Thomsen WJ et al, J Pharmacol Exp Ther 2008;325:577-87
Lorcaserin (Belviq)
MAIN RESULTS

• Two phase III trials – BLOOM (2 yrs) and BLOSSOM (1 yr)
• Weight change at 1 yr
  • -5.8% (lorcaserin 10 mg bid) vs -2.5% (placebo)
  • 5% weight loss – 47% vs 23%
• 10 mg qd was somewhat less efficacious (40% losing 5%)
• FDA defined valvulopathy
  • RR 1.07 (0.74, 1.55)

FDA briefing document, Advisory committee meeting for lorcaserin, 16 Sep 2010
Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management

Lorcaserin (Belviq)
Weight loss (kg) over 2 years

Lorcaserin (Belviq)
Weight loss (kg) with lorcaserin 10 mg bid at 1 year

ECHO Findings

FDA-Defined Valvulopathy

ECHO Findings

Mitral Valve Insufficiency Score
Yr 2 vs. Baseline

ECHO Findings

Aortic Valve Insufficiency Score
Yr 2 vs. Baseline

BLOOM-DM Study

Change in Glycemic Parameters by Study Week

Lorcaserin (Belviq)
Common Adverse Events

• Frequent AEs with higher incidence
  • Headache
  • Dizziness
  • Nausea
Lorcaserin (Belviq)  
FDA advisory committee meeting  

• Concerns  
  • Noninclusion of representative sample  
  • Marginal efficacy  
  • Neoplasms in rats (breast, brain, and other regions)  
  • Discussion about the upper CI of relative risk  
  • Psychiatric and cognitive AEs
Phentermine

- Primary mechanism: Norepinephrine release, possible uptake inhibition
- Available as H Cl (15 mg, 30 mg, 37.5 mg) or resin (15 mg, 30 mg)
- A pooled analysis of 6 RCTs of 8-24 wk duration, conducted between 1975-99, estimated that phentermine treatment achieves 3.6 kg weight loss relative to placebo

1 Haddock et al. Int J Obes 2002;26:262-273
Phentermine + topiramate (Qsymia)

- Phentermine available since 1959 for short-term treatment of obesity
- Topiramate has been well studied for obesity.
- Consistently demonstrated dose-dependent weight loss efficacy in numerous trials ranging from 6 months to more than a year in obese and overweight patients with and without type 2 diabetes and hypertension.
- Reduction of BP and improvement of glycaemic control
- Neuropsychiatric adverse events have hindered its further development for treatment of obesity.

PHENTERMINE + TOPIRAMATE PHASE III TRIALS
Qsymia™

  • 56 wk trial in 1,267 severely obese patients (BMI ≥ 35 kg/m²) with no comorbidities.

  • 56 wk trial in 2,487 obese patients (BMI ≥ 27 and ≤ 45 kg/m²) with:
    ✓ Hypertension (SBP 140-160 mmHg and/or DBP 90-100 mmHg or on meds)
    ✓ Triglycerides 200-400 mg/dL or on meds
    ✓ FBS >100 mg/dL and/or 2 hrPC glucose >140 mg/dL or DX diabetes.
    ✓ Waist circumference ≥102 cm for men; ≥88 cm for women

  • A 108-week trial rolling-over 676 patients from CONQUER.
CONQUER

Effects of Phentermine+Topiramate on Bodyweight

Effects of PHEN/TPM on Blood Pressure in High-risk Patients

Preventive CV Benefit of Phentermine/Topiramate ER
Effects of PHEN/TPM on Lipids in High-risk Patients

Preventive CV Benefit of Phentermine/Topiramate ER

Preventive CV Benefit of Phentermine/Topiramate ER

Preventive CV Benefit of Phentermine/Topiramate ER

Effects of PHEN/TPM on Glycemic Indices in High-risk Patients

<table>
<thead>
<tr>
<th>Baseline Mean</th>
<th>Number</th>
<th>Fasting glucose (mmol/L)</th>
<th>Glycated haemoglobin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.6</td>
<td>153</td>
<td>-0.31</td>
<td>6.8</td>
</tr>
<tr>
<td>7.5</td>
<td>65</td>
<td>-0.54</td>
<td>6.8</td>
</tr>
<tr>
<td>7.3</td>
<td>155</td>
<td>-0.66</td>
<td>6.8</td>
</tr>
</tbody>
</table>

*p=0.0288 vs placebo
†p=0.0043 vs placebo

Effects of PHEN/TPM on Glycemic Indices in High-risk Patients

## Most Common TEAEs

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo N = 1,561</th>
<th>Treatment group</th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PHEN/TPM 3.75/23 mg N = 240</td>
<td>PHEN/TPM 7.5/46 mg N = 498</td>
<td>PHEN/TPM 15/92 mg N = 1580</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2.8</td>
<td>6.7</td>
<td>13.5</td>
<td>19.1</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>6.1</td>
<td>7.9</td>
<td>15.1</td>
<td>16.1</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4.4</td>
<td>5.8</td>
<td>3.6</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.9</td>
<td>5.0</td>
<td>6.4</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Nervous system events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1.9</td>
<td>4.2</td>
<td>13.7</td>
<td>19.9</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9.3</td>
<td>10.4</td>
<td>7.0</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1.1</td>
<td>1.3</td>
<td>7.4</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.4</td>
<td>2.9</td>
<td>7.2</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>0.6</td>
<td>0.4</td>
<td>2.0</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Psychiatric events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.7</td>
<td>5.0</td>
<td>5.8</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>2.2</td>
<td>3.3</td>
<td>2.8</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.9</td>
<td>2.9</td>
<td>1.8</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>0.7</td>
<td>1.7</td>
<td>2.6</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.3</td>
<td>5.0</td>
<td>4.4</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td>3.5</td>
<td>6.3</td>
<td>4.0</td>
<td>5.4</td>
<td></td>
</tr>
</tbody>
</table>
# Comparison of Obesity Drugs in Development or Approved

<table>
<thead>
<tr>
<th>Drug</th>
<th>LS mean percentage weight change from baseline (1 year)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>Orlistat 120 mg t.i.d.</td>
<td>-4.1</td>
<td>-0.3</td>
</tr>
<tr>
<td><strong>Qnexa®</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OB 302</td>
<td>-10.9</td>
<td>-1.6</td>
</tr>
<tr>
<td>OB 303</td>
<td>-9.8</td>
<td>-1.2</td>
</tr>
<tr>
<td><strong>Lorcaserin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APD356-009</td>
<td>-5.9</td>
<td>-2.2</td>
</tr>
<tr>
<td>APD356-011</td>
<td>-5.8</td>
<td>-2.8</td>
</tr>
<tr>
<td><strong>Contrave®</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB-301</td>
<td>-6.1</td>
<td>-1.3</td>
</tr>
<tr>
<td>NB-302</td>
<td>-9.3</td>
<td>-5.1</td>
</tr>
<tr>
<td>NB-304 (with T2DM)</td>
<td>-5.0</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

*LS: Least square; T2DM: Type 2 diabetes mellitus; t.i.d.: Three-times daily. Data taken from [105].*
SUMMARY

• Currently available agents, in conjunction with reduced caloric intake and increased physical activity, result in significant weight loss over 1-2 year followup in obese and high-risk overweight patients.

• Weight loss is accompanied by significant reductions in CVD risk factors, including SBP, lipids and glycemic indices in high-risk overweight and obese patients.

• Dose-dependent adverse effects can limit use.

• No CVD outcome data are available.

• Long term efficacy and safety require further investigation.
ACKNOWLEDGEMENT

Kishore Gadde, MD
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Durham, North Carolina
American Society of Hypertension, Inc. (ASH)

Suzanne Oparil, MD

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THANK YOU!
Drugs approved for other conditions

- Bupropion
  - modest weight loss in 3 trials, no further development
- Atomoxetine
  - modest weight loss in 1 small trial, no further development
- Zonisamide
  - Single centre 16-wk study, ongoing NIDDK-funded study
- Topiramate
  - Several short- and long-term RCTs in obesity and diabetes
  - Significant weight loss, but neuropsychiatric adverse effects limit further development
- Metformin
  - About 2 kg weight loss at 1 year vs 0.8 kg for placebo in nondiabetic adults in 2 trials
PHEN/TPM – FDA advisory committee meeting

• Concerns
  • Lack of 2-yr safety data
  • Terratogenicity with TPM in patients treated for epilepsy
  • Psychiatric (depression, anxiety) and cognitive AEs
  • Decreased serum bicarbonate and potential implications
  • Increase in heart rate (0.6 bpm for mid-dose, 1.6 bpm for high-dose)

• Vote for approval
  • Yes = 6
  • No = 10

FDA Endocrine and Metabolic Drugs Advisory Committee, 15 July 2010
Sibutramine Cardiovascular Outcomes (SCOUT) trial

• Enrolled 10744 patients in 16 countries
• Men and women, aged 55 or older, BMI 27-45 (or BMI 25-27 with large waist), with preexisting CVD, T2DM or both
• After 6-week lead-in period in which all subjects receive sibutramine 10 mg/d, 9804 were randomized to sibutramine 10 mg or placebo.
• Mean duration of treatment – 3.4 years
• Primary outcome: First occurrence of primary outcome event (nonfatal MI, nonfatal stroke, resuscitation after cardiac arrest, cardiovascular death)
• Weight change during lead-in period: -2.6 kg
• Weight change after randomization: -1.7 kg sibutramine, +0.7 kg placebo at 1 year; after that, both groups had small increases (+0.5 kg).

Sibutramine Cardiovascular Outcomes (SCOUT) trial

- Risk of primary outcome
  - 11.4% sibutramine vs 10.0% placebo (HR 1.16 [1.03, 1.31]; P=0.02)
- Nonfatal MI
  - 4.1% vs 3.2% (HR 1.28 [1.04, 1.57]; P=0.02)
- Nonfatal stroke
  - 2.6% vs 1.9% (HR 1.36 [1.04, 1.77]; P=0.03)
- Rates of cardiovascular death and death from any cause were not increased
- Patients with T2DM without preexisting CVD had no increased risk