Anti-Obesity Drugs in the Pipeline and the Role of Bariatric Surgery for Diabetes

Rx

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Conflicts of Interest and Disclosures

• DSMB Longitudinal Assessment of Bariatric Surgery
• DSMB: Enteromedics
Failed Weight Loss Medications

• Fen/Phen
• PPA, Ephedra
• Leptin (Mittendorfer, Diabetes. 2011 May;60(5):1474-7)
• Ciliary Neurotrophic Factor, Ecopipam
• CB-1 antagonists
• Sibutramine (N Engl J Med. 2010 Sep 2;363(10):905-17)
Current Issues for Anti-Obesity Drug Use

- Currently available medications are not that effective
- Issues of off label use
- Need long term therapy
- Not paid for by insurance
- Issue of “anti-medication bias”
- Potential market is enormous
Orlistat in Overweight and Obese Patients with Type 2 Diabetes

**Figure 4**—HbA1c over 1 year of double-blind treatment with placebo (○) or 120 mg orlistat (●). P = 0.002, least-squares mean difference from placebo in the change from baseline over 52 weeks.

**Figure 3**—Fasting serum glucose levels over time with placebo (○) or 120 mg orlistat (●). P = 0.02, least-squares mean difference from placebo in the change from baseline over 52 weeks.

Kelley Diabetes Care 25:1033-41, 2002
## 4 Years of Treatment With Orlistat

Drug well tolerated with no long-term adverse events

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Orlistat*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss at 1 y, kg</td>
<td>7.5</td>
<td>11.4</td>
</tr>
<tr>
<td>Weight loss at 4 y, kg</td>
<td>4.1</td>
<td>6.9**</td>
</tr>
<tr>
<td>&gt;10% weight loss at 4 y</td>
<td>16%</td>
<td>26%**</td>
</tr>
<tr>
<td>&gt;5% weight loss at 4 y</td>
<td>37%</td>
<td>53%**</td>
</tr>
<tr>
<td>4-year incidence of T2DM</td>
<td>9.0%</td>
<td>6.2%‡</td>
</tr>
</tbody>
</table>

‡Represents a 37% reduction in the incidence of T2DM beyond the impact of diet and lifestyle intervention ($P = 0.0032$)

*120 mg TID.  
**$P < 0.001$ vs placebo.

*Sjostrom L et al. Diabetes Care 2004;27:155*
Weight loss drugs in the pipeline

- Naltrexone SR/Bupropion SR
- Topiramate/Phentermine
- Lorcaserin
- Liraglutide/Exenatide
- Pramlintide/Metreleptin
- Tesofensine
Bupropion SR Enhances Weight Loss

Weight Loss With Naltrexone SR/Bupropion SR Combination Therapy as an Adjunct to Behavior Modification: The COR-BMOD Trial

Wadden TA; Obesity (2011) 19 1, 110–120
## Side Effects of Bupropion plus Naltrexone in the Treatment of Obesity

**Greenway FL, Obesity (2008) 17 1, 30–39**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>P+P (N = 53) n (%)</th>
<th>P+NAL (N = 58) n (%)</th>
<th>BUP+P (N = 55) n (%)</th>
<th>BUP+NAL (N = 51) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with &gt; 1 TEAE</td>
<td>19 (35.8%)</td>
<td>32 (55.2%)</td>
<td>30 (54.5%)</td>
<td>29 (56.9%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1.9%)</td>
<td>20 (34.5%)</td>
<td>5 (9.1%)</td>
<td>16 (31.4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (13.2%)</td>
<td>2 (3.4%)</td>
<td>10 (18.2%)</td>
<td>8 (15.7%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (3.8%)</td>
<td>6 (10.3%)</td>
<td>5 (9.1%)</td>
<td>7 (13.7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (7.5%)</td>
<td>5 (8.6%)</td>
<td>5 (9.1%)</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>Vomiting NOS</td>
<td>1 (1.9%)</td>
<td>8 (13.8%)</td>
<td>3 (5.5%)</td>
<td>3 (5.9%)</td>
</tr>
<tr>
<td>Diarrhea NOS</td>
<td>0 (0.0%)</td>
<td>2 (3.4%)</td>
<td>4 (7.3%)</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0 (0.0%)</td>
<td>1 (1.7%)</td>
<td>3 (5.5%)</td>
<td>7 (13.7%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (5.7%)</td>
<td>0 (0.0%)</td>
<td>2 (3.6%)</td>
<td>2 (3.9%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (3.8%)</td>
<td>2 (3.4%)</td>
<td>3 (5.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Gastroenteritis NOS</td>
<td>1 (1.9%)</td>
<td>2 (3.4%)</td>
<td>3 (5.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0 (0.0%)</td>
<td>1 (1.7%)</td>
<td>3 (5.5%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>3 (5.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>3 (5.7%)</td>
<td>2 (3.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Abdominal pain (upper)</td>
<td>0 (0.0%)</td>
<td>1 (1.7%)</td>
<td>0 (0.0%)</td>
<td>3 (5.9%)</td>
</tr>
<tr>
<td>Subjects who discontinued due to adverse event*</td>
<td>5 (9.4%)</td>
<td>14 (24.1%)</td>
<td>9 (16.4%)</td>
<td>9 (17.6%)</td>
</tr>
</tbody>
</table>

*Incidence >5% in at least 1 treatment group with onset during weeks 1–16.

\[N, number of randomized subjects; \( n \), number of subjects with event; TEAE, treatment-emergent adverse event.\]

*Discontinuation from 1 or both study drugs during weeks 1–16 due to adverse events starting during weeks 1–16.
Topiramate (Topimax)

- Developed and FDA approved as an anti-seizure medication
- “Side effect” of weight loss noted
- A number of weight loss trials begun with thousands of patients planned for 2 years duration.
- Studies halted due to side effects: cognitive problems, memory loss, paresthesias.
Topiramate Mean Long-Term Weight Loss: All Observations

Van der Merwe T et al. 12th European Congress on Obesity; 2003. Abstract P4-114/367.
Qnexa (Vivus)

- Combination of phentermine and topiramate
  - Full dose 15 mg phentermine, 92 mg topiramate
- EQIP randomized placebo controlled trial
  1,267 morbidly obese patients followed for 1 year
  - 10.4% placebo subtracted weight loss, 14.7% total weight loss among completers
- CONQUER Trial: 2,487 obese patients with co-morbidities
  - Full dose 13.2% weight loss, improved CVD risk markers
Phentermine Topiramate Combination Therapy of Obesity

Gadde KM; Lancet. 2011 Apr 16;377(9774):1341-52
## Side Effects of Phetermine Topiramate Combination

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=993)</th>
<th>Phetermine 7.5 mg plus topiramate 46.0 mg (n=498)</th>
<th>p value</th>
<th>Phetermine 15.0 mg plus topiramate 92.0 mg (n=994)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>0</td>
<td>5 (1%)</td>
<td>0.0041</td>
<td>15 (2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (&lt;1%)</td>
<td>6 (1%)</td>
<td>0.0196</td>
<td>9 (&lt;1%)</td>
<td>0.0647</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>0.2865</td>
<td>6 (&lt;1%)</td>
<td>0.6058</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>0</td>
<td>2 (&lt;1%)</td>
<td>0.1114</td>
<td>8 (&lt;1%)</td>
<td>0.0077</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>1.0000</td>
<td>7 (&lt;1%)</td>
<td>0.0698</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>1.0000</td>
<td>5 (&lt;1%)</td>
<td>0.2180</td>
</tr>
<tr>
<td>Lethargy</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>5 (&lt;1%)</td>
<td>0.0622</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td>0.7259</td>
<td>16 (2%)</td>
<td>0.0512</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
<td>0.0453</td>
<td>14 (1%)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>1.0000</td>
<td>9 (&lt;1%)</td>
<td>0.1448</td>
</tr>
<tr>
<td>Irritability</td>
<td>1 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
<td>0.0453</td>
<td>9 (&lt;1%)</td>
<td>0.0212</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
<td>0.4075</td>
<td>5 (&lt;1%)</td>
<td>0.7260</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>1.0000</td>
<td>6 (&lt;1%)</td>
<td>0.2881</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
<td>2 (&lt;1%)</td>
<td>0.1114</td>
<td>7 (&lt;1%)</td>
<td>0.0155</td>
</tr>
<tr>
<td><strong>Other disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (&lt;1%)</td>
<td>0</td>
<td>0.3077</td>
<td>9 (&lt;1%)</td>
<td>0.2653</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>6 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
<td>0.7394</td>
<td>8 (&lt;1%)</td>
<td>0.7898</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td>1.0000</td>
<td>3 (&lt;1%)</td>
<td>0.5068</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>1.0000</td>
<td>11 (1%)</td>
<td>0.0220</td>
</tr>
</tbody>
</table>

Gadde KM; Lancet. 2011 Apr 16;377(9774):1341-52
Qnexa: Side Effects

• Side effects
  – Dry mouth: 21%
  – Tingling: 20%
  – Insomnia: 10%
  – Nausea: 7%

• Neurocognitive effects resulted in discontinuation in 2.6%, 18% stopped medication for some AE

• No evidence of increased levels of depression or suicidal ideation.
Lorcaserin (APD356) is a potent, selective 5-HT2C agonist with ~15-fold and 100-fold selectivity vs. 5-HT2A and 5-HT2B receptors, respectively.
Relative Efficacy of Newer Drugs for the Treatment of Obesity

<table>
<thead>
<tr>
<th></th>
<th>Duration (years)</th>
<th>Sample size</th>
<th>Dropouts</th>
<th>Weight loss with drug</th>
<th>Weight loss with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orlistat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-analysis of 13 randomised controlled trials</td>
<td>1-4</td>
<td>6196</td>
<td>~30%</td>
<td>-2.9% *</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Lorcaserin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLOOM</td>
<td>1</td>
<td>3182</td>
<td>50%</td>
<td>-5.8%</td>
<td>-2.2</td>
</tr>
<tr>
<td>BLOSSOM</td>
<td>1</td>
<td>3206</td>
<td>45%</td>
<td>-5.8%</td>
<td>-2.8</td>
</tr>
<tr>
<td><strong>Naltrexone plus bupropion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB-301</td>
<td>1</td>
<td>1164</td>
<td>50%</td>
<td>-6.1</td>
<td>-1.3</td>
</tr>
<tr>
<td>NB-302</td>
<td>1</td>
<td>793</td>
<td>42%</td>
<td>-9.3</td>
<td>-5.1</td>
</tr>
<tr>
<td>NB-303</td>
<td>1</td>
<td>1496</td>
<td>46%</td>
<td>-6.5</td>
<td>-1.9</td>
</tr>
<tr>
<td>NB-304</td>
<td>1</td>
<td>505</td>
<td>45%</td>
<td>-5.0</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

Gadde KM; Lancet. 2011 Apr 16;377(9774):1341-52
FDA Criteria for a New Anti-Obesity Drug

www.fda.gov/cder/guidance/index.htm

- Dose ranging study with at least 3 doses
- Pivotal trial with at least 1500 subjects completing 1 year of observation, and 200-500 completing 2 years of follow up.
- 6 week run it with behavior modification
- Need to measure relevant endpoints such as lipids, glucose and insulin.
- 5% placebo subtracted weight loss.

www.fda.gov/cder/guidance/7544dft.pdf
Summary of Medications

• A large number of new medications in the pipeline
• Qnexa looks the best for weight loss
• Lorcaserin may be fenfluramine in sheep’s clothing
• Liraglutide/exenatide may have the best acceptance
• None have been approved by the FDA
Gastric Bypass

5 Parts
- Gastric restriction
- Gastric exclusion
- Duodenal exclusion
- Jejunal exposure
- Vagal disruption
Types of Bariatric Surgery

- Vertical banded gastroplasty (VBG)
- Adjustable gastric banding (LAGB)
- Roux-en-Y gastric bypass (RYGB)
- Billiopancreatic diversion (BPD)
- BPD with duodenal switch (BPD-DS)

## Health Benefits of Bariatric Surgery

<table>
<thead>
<tr>
<th></th>
<th>LAGB</th>
<th>RYGB</th>
<th>BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of T2DM</td>
<td>48%</td>
<td>84%</td>
<td>98%</td>
</tr>
<tr>
<td>Resolution of hypertension</td>
<td>43%</td>
<td>68%</td>
<td>83%</td>
</tr>
<tr>
<td>Improvement of hyperlipidemia</td>
<td>59%</td>
<td>97%</td>
<td>99%</td>
</tr>
<tr>
<td>% Excess weight loss</td>
<td>47%</td>
<td>62%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Abbreviations: LAGB, laparoscopic adjustable gastric banding; RYGB, Roux-en-Y gastric bypass; BPD, biliopancreatic diversion; T2DM, type 2 diabetes mellitus.

Rubino F; Annu Rev Med. 2010;61:393-411
Adjustable Gastric Banding and Conventional Therapy for Type 2 Diabetes

Dixon JB, JAMA, 2008; 299: 316-23

- Previous studies had shown that diabetes frequently resolves following bariatric surgery.
- This group had done a previous randomized trial in Metabolic Syndrome.
- This was a randomized trial of lap banding versus conventional therapy in 60 subjects with diabetes for <2 years and a BMI between 30-40 kg/m²
- This is an outstanding group with outstanding results, so results may not be universally applicable.
Effects of Bariatric Surgery on Weight and Diabetes Status

73% remission of diabetes in the surgery Group versus 13% in the control group

Adams TD, NEJM 2007; 357:753-61
How does Bariatric Surgery help Type 2 Diabetes?

Bose M; Obes Surg 2009 Feb;19(2):217-29
Glucose, insulin, proinsulin, C-peptide, glucagon and amylin concentrations during a 3-h oral glucose tolerance test (50 g glucose) before () and 1 (○), 6 (●) and 12 months (×) after gastric bypass in obese women with Type 2 diabetes. Data are the mean SEM.

Bose M; J Diabetes 2010 Mar;2(1):47-55
Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) concentrations during a 3-h oral glucose tolerance test (50 g glucose) before () and 1 ( ), 6 ( ) and 12 months ( ) after gastric bypass in obese women with Type 2 diabetes. Data are the mean SEM

Bose M; J Diabetes 2010 Mar;2(1):47-55
# Risks of Bariatric Surgery: the LABS Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (N=4610)</th>
<th>Laparoscopic Adjustable Gastric Banding (N=1198)</th>
<th>Laparoscopic Roux-en-Y Gastric Bypass (N=2975)</th>
<th>Open Roux-en-Y Gastric Bypass (N=437)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>15 (0.3)</td>
<td>0</td>
<td>6 (0.2)</td>
<td>9 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep-vein thrombosis or venous thromboembolism</td>
<td>20 (0.4)</td>
<td>3 (0.3)</td>
<td>12 (0.4)</td>
<td>5 (1.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Tracheal reintubation</td>
<td>20 (0.4)</td>
<td>2 (0.2)</td>
<td>12 (0.4)</td>
<td>6 (1.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>51 (1.1)</td>
<td>1 (0.1)</td>
<td>45 (1.5)</td>
<td>5 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>11 (0.2)</td>
<td>0</td>
<td>6 (0.2)</td>
<td>5 (1.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Placement of percutaneous drain</td>
<td>16 (0.3)</td>
<td>0</td>
<td>13 (0.4)</td>
<td>3 (0.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Abdominal operation</td>
<td>118 (2.6)</td>
<td>9 (0.8)</td>
<td>94 (3.2)</td>
<td>15 (3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Failure to be discharged by day 30</td>
<td>17 (0.4)</td>
<td>0</td>
<td>13 (0.4)</td>
<td>4 (0.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Composite end point‡</td>
<td>189 (4.1)</td>
<td>12 (1.0)</td>
<td>143 (4.8)</td>
<td>34 (7.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* The total excludes 166 procedures, including 117 sleeve gastrectomies, 47 biliopancreatic diversions with or without a duodenal switch, 1 vertical banded gastroplasty, and 1 open adjustable gastric banding.

† P values are for the comparison between treatment groups. Values were calculated with the use of the chi-square test.

‡ This end point is a composite of death; deep-vein thrombosis or venous thromboembolism; reintervention with the use of a percutaneous, endoscopic, or operative technique; or failure to be discharged from the hospital within 30 days after surgery.
Sleeve Gastrectomy

• Consensus conference convened by ASMBS this spring
• Self report of 106 surgeons on 14,776 sleeve gastrectomy operations
• Mortality=0.2%
• Average EWL=60% at 1 year, 62% at 3 years and 49% at >4yrs
• Staple line leak was the most common complication occurring in 1.5-2%
• Concluded that this is a reasonable primary operation

a Duodenal-jejunal bypass (DJB)
b DJB with SG
c Sleeve gastrectomy (SG)
d Ileal interposition (IT)
Natural Orifice, or Endoluminal Procedures

BaroSense (Menlo Park, California).
endoluminal bariatric sleeve has been developed by GI Dynamics (GI Dynamics, Newton, Massachusetts).
Bariatric Surgical Guidelines

• American Association of Clinical Endocrinologists/the Obesity Society/American Society for Metabolic and Bariatric Surgery 2008
  • Evidence based A-D recommendations
  • 164 recommendations
  • 777 references
  • 83 pages long
Bariatric Surgery Resources

American Society for Bariatric Surgery
www.asbs.org

International Bariatric Surgery Registry (IBSR)
www.surgery.uiowa.edu/ibsr

International Federation for the Surgery of Obesity
www.obesity-online.com/ifso

Betsy Lehman Center for Patient Safety and Medical Error Reduction: Expert Panel on Weight Loss Surgery
www.mass.gov/dph/betsylehman/index.htm
Exenatide for Weight Reduction
Open-Label Extension – Combined

Baseline Weight
- Placebo BID: 98 kg
- 5 µg Exenatide BID: 100 kg
- 10 µg Exenatide BID: 100 kg

Placebo-Controlled
Open-Label Extension

Time (wk)
- Placebo BID
- 5 µg Exenatide BID
- 10 µg Exenatide BID

Mean ∆ Weight (kg)
- 82-wk completers; N = 393; Mean (SE); Weight was a secondary endpoint
Data on file, Amylin Pharmaceuticals, Inc.
Liraglutide (Victoza)

- Novo Nordisk once daily GLP-1 analog.
- Seeking approval for use in diabetes
- Approved for marketing in Europe in July 2009
- FDA has expressed some concern over risk for inducing thyroid tumors.
- Company is conducting studies to support a weight loss indication.

Astrup A, Lancet. 2009 Nov 7;374(9701):1606-16
Liraglutide: The LEAD-3 Mono trial

Garber A, Lancet. 2009 Feb 7;373(9662):473-81
Percent of Patients Taking Liraglutide who Experienced Nausea

Astrup A, Lancet. 2009 Nov 7;374(9701):1606-16
Tesofensine in the Treatment of Obesity

• Inhibits the pre-synaptic uptake of NE, serotonin and dopamine
• Was developed for use in Alzheimer’s and Parkinson’s disease
• Found to produce a dose related weight loss in these populations
• Recent trial in obese individuals

Tesofensine in the Treatment of Obesity

Bupropion plus Naltrexone in the Treatment of Obesity

Randomization included: BUP (300 mg) + NAL (50 mg), BUP (300 mg) + placebo (P), NAL (50 mg) + P or P+P for up to 24 weeks

Greenway FL, Obesity (2008) 17 1, 30–39
Pramlintide and Metreleptin for Weight Loss

Ravussin E; Obesity (Silver Spring). 2009 Sep;17(9):1736-43
Treatment with Fenfluramine and Phentermine

Weintraub, Clin Pharmacol Ther, 1992
Figure 2. Annual volume of antiobesity medications reported in the United States, 1991-2002, IMS HEALTH National Disease and Therapeutic Index. Data for 2002 are an estimate (E) based on January to March 2002 figures. HCl indicates hydrochloride.
Weight Loss in the SOS Study

Sjostrom L NEJM 2007: 357-741-752