Endoscopic and Minimally Invasive Bariatrics: Medical Management of Obesity

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Judith Korner, MD, PhD
Professor, Department of Medicine
Division of Endocrinology
Director, Weight Control Center
Columbia University Medical Center
Cornerstone of Weight Loss Treatment

• Behavior Therapy, Diet, Exercise
Long-Term Weight Loss with Non-Pharmacologic Treatment

VLCD: ≤800 kcal/day  BMOD: behavior + 1200kcal/day  Combined: VLCD + behavior

Neurohormonal Changes Associated with Weight Loss

# A Guide to Selecting Treatment: National Institutes of Health (NIH) Guidelines*

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<th>Treatment</th>
<th>25–26.9</th>
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<td>Weight-loss</td>
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*Yes alone indicates that the treatment is indicated regardless of the presence or absence of comorbidities. The solid arrow signifies the point at which therapy is initiated.

*** The FDA has approved use of LAGB for patients with BMI ≥ 30 who also have at least one condition linked to obesity, such as heart disease or diabetes.

History of Drugs for Weight Loss

- 1947: Methamphetamine
  Phendimetrazine (Bontril)
- 1957: Phentermine (Adipex, Suprenza)
- 1982: Diethylpropion (Tenuate)
  Phenolpropanolamine (Dexedrin, Acutrim)
- 1973: Fenfluramine
- 1996: Dexfenfluramine (Redux)
- 1997: Meridia (sibutramine)
- 1999: Orlistat (Xenical/Alli)
- 2012: Lorcaserin (Belviq)
- 2012: Topiramate + Phentermine (Qsymia)
- 2014: Bupropion + Naltrexone (Contrave)
- 2014: Liraglutide (Saxenda)
Drugs That May Promote Weight Gain

• Psychiatric/neuro
  – Antipsychotics
  – Antidepressants
  – Lithium
  – Antiepileptics

• Steroid hormones
  – Hormonal contraceptives
  – Corticosteroids
  – Progestational steroids

• Diabetes treatments
  – Insulin
  – Sulfonylureas
  – Thiazolidinedione

• Antihistamines

• β-adrenergic blockers

Noradrenergic Agents

- Schedule IV drugs have a low potential for abuse

- **Phentermine** (Adipex-P, Fastin): 18.75-37.5 mg/day

- **Phentermine resin** (Ionamin): 15-30 mg/day

- **Diethylpropion** (Tenuate, Tenuate Dospan):
  25 mg 3x/day or sustained release 75 mg/day

- **Phenylpropanolamine** (Dexatrim, Acutrim): withdrawn from market due to association with hemorrhagic stroke

Yanovski NEJM 346:591 2002
Noradrenergic Agents (cont’d)

- Approved by the FDA for short-term use:
  - ~ 3 months
- Studies show between 2-10 kg weight loss over placebo
- Side effects: insomnia, dry mouth, constipation, euphoria, palpitations, hypertension
Orlistat: Mechanism of Action

30% of fat not absorbed
Weight Change Over 104 Weeks

**Weight Loss (%)**

**Diet**
- Hypocaloric
- Eucaloric

**Week**
- 0
- 15
- 30
- 45
- 60
- 75
- 90
- 104

**Placebo**

**Orlistat**

- -4.5%
- -8.1%*

*P < 0.05 (vs placebo).
Orlistat: Safety

- GI events (flatulence, anal leakage) are related to increased fecal fat excretion and are a predictable consequence of the mode of action of orlistat
  - Events may help/hinder compliance as patients test their limits

- Reductions in fat-soluble vitamins levels and absorption of some medications have been demonstrated

- Vitamin supplementation is recommended

- Post-marketing reports of liver injury but no cause-effect relationship with orlistat has been established

Xenical [package insert]. Nutley, NJ: Roche Laboratories Inc; 2007 and FDA
Lorcaserin (Belviq)- Mechanism of Action


5-HT 1B: pulmonary HTN; 5-HT 2B: pulmonary HTN and cardiac valvulopathy
MC4R Deficiency

9 yo boy
MC4R -/-

16 yo brother
MC4R +/+ 

Phenotype: hyperphagia, obesity, increased bone mineral density, incr linear growth, severe hyperinsulinemia

Lorcaserin: Serotonin receptor 5-HT2c Agonist (no valvulopathy)

Lorcaserin (Belviq): Adverse Effects/warnings/precautions

- Most common adverse effects: headache (17%), dizziness, fatigue, nausea, dry mouth, constipation, hypoglycemia (in pts with DM)

- Serotonin syndrome or Neuroleptic malignant syndrome: esp in conjunction with SSRIs, TCAs, triptans, MAOIs, antipsychotics, bupropion, dextromethorphan, St. John’s Wort

- Bradycardia: 5-10 bpm decr in HR

- Lab changes: incr PRL or decr WBC count

- Should not take with drugs associated with valvular heart disease (ie. cabergoline)
Phentermine-Topiramate (Qsymia)

- Phentermine
  - Increase in NE -> incr metabolism -> incr locomotor activity
  - Increase in DA -> decr appetite

- Topiramate
  - Decr appetite via unknown mechanism (GABA)

Effect of Phentermine/Topiramate ER (Qsymia) on Weight Loss in Obese Adults Over 2 Years

Decrease Progression to T2D
Adverse events:

Most common: paraesthesia, dizziness, dysgueusia, insomnia, constipation, dry mouth

Other: increase HR, depression, anxiety, irritability, impairment of concentration, **difficulty with memory and word finding**, acute angle closure glaucoma, nephrolithiasis, hyperchloremic non-anion gap metabolic acidosis, hypokalemia

CLEFT PALATE
Topiramate

Randomized double-blind placebo-controlled trial in obese adults

Figure 2. Mean weight loss was significantly greater with topiramate than placebo.

Zonisamide

- Zonisamide, an antiepileptic with dopaminergic, serotonergic activity and Na & Ca channel blocker
- 16 week RCT with 16 week single blind extension
- Dose 400 – 600mg/day
- 60 subjects randomized, 51 completed
- Most common side effect: fatigue

**Unintended Consequence: Weight Loss**
Several drugs may, as a side effect, cause weight loss. Preliminary results of a study found Zonisamide, an anti-epileptic drug, caused more weight loss than a placebo.

Placebo
1.8% weight loss

Zonisamide
9.4 % weight loss in 32 weeks

Gadde KM, JAMA 2003 289:1820-1825

Graph, NY Times, 4/15/03
Naltrexone + Bupropion (Contrave)

Unclear mechanism of action:

- Bupropion stimulates POMC neurons; activates mesolimbic reward centers
- Naltrexone prevents inhibition of POMC neurons by beta-endorphin
Naltrexone + Bupropion (Contrave)

Greenway et al, Lancet 376:595-605, 2010
Naltrexone/Bupropion

Side Effects:
- Nausea, headache, constipation, dizziness, vomiting, and dry mouth were also more frequent in the naltrexone plus bupropion groups vs. placebo
- Transient increase of ~1 mm Hg in mean systolic and diastolic blood pressure and 2 bpm HR
- Combination treatment was not associated with increased depression or suicides vs. placebo BUT possible activation of mania, depression, suicide

Contraindications:
- Pregnancy, uncontrolled HTN, seizure disorders, anorexia or bulimia, use of other bupropion-containing products, MAOIs, CHRONIC OPIOID USE, ABRUPT DISCONTINUATION OF ALCOHOL
- May trigger an angle-closure attack

Other drug interactions:
- Antidepressants, antipsychotics, beta-blockers, Type 1D antiarrhythmics, ticlopidine, clopidogrel

GLP-1 Modulates Numerous Functions in Humans

GLP-1: Secreted upon the ingestion of food

Stomach:
- Helps regulate gastric emptying

Liver:
- ↓ Glucagon reduces hepatic glucose output
- ↓ Postprandial glucagon secretion

Beta cells:
- Enhances glucose-dependent insulin secretion

Alpha cells:
- Enhances glucose-dependent insulin secretion

Promotes satiety and reduces appetite

Effects of Liraglutide (GLP1R agonist) on Body Weight in Nondiabetic Obese Adults

Data are mean (95% CI) for the ITT population


10.3 kg weight loss

Data are mean (95% CI) for the ITT population
Liraglutide

Side Effects:

- Nausea, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase
- At year 1, nausea and/or vomiting was associated with greater weight loss with liraglutide 3.0 mg, but even those who did not experience these events lost more weight than those on placebo or orlistat

Warnings and Precautions:

- Acute pancreatitis, cholelithiasis, hypoglycemia, increase heart rate, renal impairment, hypersensitivity
- Thyroid C-cell tumors in rodents: contraindicated in patients with personal or family history of medullary thyroid carcinoma or MEN 2

Diabetes Prevention Program – Modest Weight-Loss Reduces the Incidence of New-Onset Diabetes in an At-Risk Population

Cumulative Incidence of Diabetes (%)

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<tr>
<th>Weight loss</th>
<th>Decrease in risk*</th>
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<tr>
<td>0.1 kg</td>
<td>31%</td>
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<tr>
<td>2.1 kg</td>
<td>31%</td>
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<tr>
<td>5.6 kg</td>
<td>58%</td>
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*Decrease in risk of developing diabetes, compared to placebo group.

Not covered by Medicare/Medicaid and many commercial insurance

Older generics (phentermine)

Off-label use: i.e. metformin; topiramate +/- phentermine

Discount programs/ Co-Pay

Free lifestyle programs