Realistic Expectations:
Drugs in the Treatment of Obesity

Lora Cotton, D.O.
January 20, 2013
Overview

- Approach
- FDA approved agents will be covered
- FDA approval guidelines
- Candidates
- Expectations
- Mechanisms, Classes and Agents
- Off Label Use of FDA approved agents
- Drugs to Avoid in Obesity Treatment
- Take Home Points
Approach

- Intention - understand basics of current agents
- Population statistics – cultural disease
- Individualize treatment for each patient
- Long term improvement in overall health is the goal
- Support life long healthy lifestyle
- Safety concerns
- Early versus late adopters
- A “Magic Bullet” is not available
FDA Approval for Weight Loss Agents
Draft guidance 2007

• Phase 3 duration and size
  • One year - placebo controlled
  • 3,000 patient minimum randomized to treatment
  • 1,500 patient minimum randomized to placebo

• Efficacy criteria:
  • Mean weight loss 5% greater in active-product vs. placebo-treated, and statistically significant, OR
  • Proportion who lose ≥ 5% of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant
Who is a Candidate?

- BMI > 30
- BMI > 27 with comorbidities
  - pre-DM, HTN, Dyslipidemia, OSA
- Actively dieting and exercising
- No contraindications – unstable illness, CAD, Liver disease, etc.
- Compliance considerations
Reasonable Expectations

- 5 - 10% decrease in weight over a year
- Combined with diet and exercise – a must
- Weight loss slows and then ceases when maximal therapeutic effect is reached
- Decreased body weight = decreased energy expenditure
- Weight will likely go up when drug is stopped
Reasonable Expectations

- 5 – 10% decrease in weight does improve lipids, hypertension, insulin sensitivity
- No agent yet claims decrease in cardiac events
- Editorial statement:
  - Lower BMI decreases surgical risk
  - Decreases upper airway obstruction
  - Improved function from weight loss increases quality of life and likelihood of continued lifestyle improvement
Potential Strategies for Anti-Obesity Drug Action

- Reduce food intake
- Blocking nutrient absorption
- Increasing thermogenesis
- Modulating fat metabolism/storage
- Modulating the central regulation of body weight
Classes

- Lipase Inhibitors
- Serotonin Agonists
- Sympathomimetics
- Antidepressants
- Antiepileptics
- Diabetes Drugs
- Hormones
Lipase Inhibitor
Orlistat (Xenical, Alli)

- Increased fecal fat excretion
- Up to 30% ingested fat not absorbed
- Mean weight loss: 3 kg more than placebo over 12 months
- Significant ↓ HgbA1c and LDL
- Dosing: 120 mg TID (Xenical), 60 mg TID (Alli)
- Side Effects: cramps, flatulence, steatorrhea, fecal incontinence, AKA “treatment effects”
- Multivitamin supplementation recommended
- Contraindications: Pregnancy, malabsorption, ↓ gallbladder function
Sympathomimetics

- Amphetamine, Phentermine, Diethylpropion
  - ↑ NE release or inhibit NE reuptake
  - Appetite suppressant
  - Mean weight loss: 4 – 8 kg
  - Only approved for “short term” use (12 weeks)
  - Side Effects: ↑ SBP/DBP, ↑ HR, difficulty urinating, palpitations, restlessness, insomnia, tolerance, abuse
  - Controlled/scheduled drugs
  - Contraindications: CAD, Hypertension, MAOI’s, drug abuse history
Serotonin Agonists

- Locaserin (Belviq) - NEW!
  - Selective 5HT 2C agonist
  - Appetite suppressant
  - Significantly ↓ SBP/DBP, HR, total cholesterol and LDL, CRP, fasting FSBS
  - Mean weight loss 5.8 kg (2.9 kg in placebo) over 12 months – approved for long term use
  - Dosing: 10 mg QD-BID
  - Discontinue if less than 5% weight decrease in 12 weeks
Locaserin – cont.

- Fenfluramine (remember Fen-Phen) was also a selective serotonin 2C receptor agonist
- Locaserin is much more selective – no increase in valvopathy was noted in safety study
- Warnings: serotonin syndrome, neuroleptic malignant syndrome, valvular heart disease, cognitive impairment, euphoria, depression, suicidal thoughts, disassociation, priapism
- Expected schedule IV classification by DEA
- Side Effects: headache, nausea, dizziness, URI
- Contraindications: Pregnancy category X – pregnancy test and contraception
Combination Medication

- Qsymia (NEW!) is Phentermine + Topiramate
  - Mean weight loss: 8-10% body weight (1 % in placebo) over one year
  - Dosing: 3.75/23 mg x 14 days, then 7.5/46 mg
  - Duration: Indefinite?
  - DEA schedule IV
  - Should taper off QOD x 1 week when D/C
  - Contraindications: Pregnancy, MAOI, Hyperthyroid
Qsymia - prescribing

- Take once daily in morning. Avoid evening dose to prevent insomnia.
- Recommended dose: Qsymia 3.75 mg/23 mg (phentermine 3.75 mg/topiramate 23 mg extended-release) daily for 14 days; then increase to 7.5 mg/46 mg daily.
- Discontinue or escalate dose (as described) if 3% weight loss is not achieved after 12 weeks on 7.5 mg/46 mg dose.
- Discontinue Qsymia if 5% weight loss is not achieved after 12 weeks on maximum daily dose of 15 mg/92 mg.
- Discontinue 15 mg/92 mg dose gradually (as described) to prevent possible seizure.
- Do not exceed 7.5 mg/46 mg dose for patients with moderate or severe renal impairment or patients with moderate hepatic impairment.
Qsymia
Warnings and Precautions

- Fetal Toxicity (X) – pregnancy test and contraception
- Increase in Heart Rate
- Suicidal Behavior and Ideation
- Acute Myopia and Secondary Angle Closure Glaucoma
- Mood and Sleep Disorders
- Cognitive Impairment
- Metabolic Acidosis: Measure electrolytes before/during treatment
- Elevated Creatinine: Measure creatinine before/during treatment
- Use of Antidiabetic Medications: Weight loss may cause hypoglycemia.
Off Label Agents

- FDA approved, but not for weight loss
- Weight loss was noted in clinical trials
- Use for approved indication
- Weight loss could be seen as a potentially beneficial side effect
Antidepressants
Not FDA Weight Loss agents

- Bupropion (Wellbutrin) – as single agent
  - 300 mg QD / 400 mg QD
  - Mean weight loss: (2.2% more at 300 mg; 5.1% more at 400 mg)
  - May prevent weight gain during smoking cessation
- Fluoxetine (Prozac)
  - 60 mg QD
  - Mean weight loss: 4.8 kg (placebo: 2.2) in 6 months; 50% regained at 12 months
Antiepileptics
Not FDA Weight Loss agent

• Topiramate (Topamax) – as single agent
  • Increases satiety
  • Mean weight loss: 5.23 kg (2.17 kg in placebo) over 6 months
  • Sides: somnolence, difficulty concentrating, paresthesia, metabolic acidosis

• Zonisamide (Zonegran)
  • Binds Na, Ca channels, binds GABA
  • mean weight loss: 9.6% (1.6% in placebo) over 32 weeks
  • Sides: drowsiness, irritability, N/V, HA, metabolic acidosis
Diabetes Medications
Not FDA Weight Loss agent

• Metformin
  • Diabetes Prevention Program – lost 2.5% body weight after 2.5 years
  • Maintained thru 10 year observation

• Exenatide (Byetta, Bydureon) – GLP -1 Agonist
  • Mean weight loss: 4.5 kg without diet/exercise changes after 18 months
  • Weight loss not related to severity of nausea
Drugs that Cause Weight Gain

- Paroxetine (Paxil)
- Valproic acid (Depakote)
- Lithium
- Mirtazapine (Remeron)
- Olanzapine (Zyprexa)
- Chlorpromazine (Thorazine)
- Amitriptyline (Elavil)
- Atenolol (Tenormin)
- Corticosteroids
- Insulin
- Sulfonylureas
- Antihistamines
- Oral contraceptive pills
UpToDate Recommendations

- First line: Orlistat
  - Approved for up to 4 years duration, but can reasonably continue longer
- First line in diabetics: Metformin
  - Add orlistat if additional weight loss needed
- 2nd line: consider sympathomimetics
  - Abuse potential
- Qsymia/Belviq - ??
- Antidepressants
  - High doses lacking long term data
Take Home Points

• Consider your patient as an individual
  • Appropriate candidate? Compliance?
• Know the drug you are prescribing – read the package insert
  • Warnings, precautions, interactions and pregnancy
• Educate about reasonable expectations
• Emphasize long term healthy lifestyle habits
• Appropriate follow up
...suddenly that treadmill doesn’t look so bad
References

- UpToDate
- Drugs.com
- Health.com
- FDA.gov
- Qsymia package insert
- Belviq package insert
- Special thanks to Michael Sayler, D.O. who let me use his slide set as a starting point