Medications for Obesity Management

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Advocate Weight Management
Decision Making
When to Start Drug Therapy?

- Diet
- Exercise
- Behavior modification

- Drug Therapy
  - Concerns!
    - Efficacy
    - Safety
    - Weight Regain
Important Considerations for Drug Therapy

- BMI.
- Comorbid Conditions.
  - DM, HTN, Dyslipidemia & Heart Disease.
- Adjuncts to diet and exercise.

BMI > 30 kg/m² (failed diet and exercise alone)
BMI 27 - 29.9 (with comorbidities)
Drug Therapy is **NOT** a Cure of Obesity.
What are the Goals?

- **Normal Body Weight?**
  - Unrealistic!

**Success Factors.**
- Weight Loss > 2kg in first month / 1 lb per week.
- Weight change >5% below baseline in 3-6 months
- Significant reduction in risk factors with effective weight loss of 5-10 %

- **10-15 % weight loss = Very Good Response.**
- **> 15% weight loss = Excellent**

Max Duration of Drug Therapy Published,
- 4 years with Orlistat.
- HTN
- DM
- CAD
- Hyperlipidemia
- Depresion
- Medications that Produces Weight Loss
- Smoking
- Obesity
How Obesity Drugs Work!

- Suppress Appetite
- Early Satiety
- Alter Fat Digestion
**Common Names**

- Xenical
  - 120 mg TID
    - with meal or >30 min postprandial
- Alli
  - 60 mg PO TID

**How it works?**

Inhibits Pancreatic Lipase

**Pharmacokinetiics**

- < 1% is absorbed.
- Orlistat doesn’t alter
  - Digoxin
  - Phenytoin
  - Warfain (Except Vit K def)
  - Glyburide
  - Oral Contraceptives
  - Alcohol
  - Furosemide
  - Captopril
  - Nifedipine
  - Atenolol
- Cyclosporine

**Side Effects (15-30%)**

- Intestinal Borborygmi.
- Cramps
- Flatus
- Fecal Incontinence
- Oily Spotting
- Vit A,D,E,K Deficiency
Cautions !

• Advised to take Vitamin supplements Daily.
• Monitor Dose of Coumadin as less Vit k is available.
• GI side effects can be avoided by reducing fat intake < 30 %
• Should not be used if history of calcium Oxalate Stones.

• LIVER INJURY ! Rare, FDA revised label in 2009
  • 13 reported, 12 occurred out of USA
  • 40 million worldwide users
  • Causal relationship not established
  • But watch for :
    • Itching, Jaundice, Pale color stools, anorexia.
Orlistat - Studies

- RCT of 800 primary patients, 17 centers, Orlistat vs usual care >2 years
- Avg wt loss 8 kg vs 4 kg placebo.
- 50 % of orlistat patients lost 5% of initial body weight at year 1 vs 30% placebo
- 34% of Orlistat maintained 5% of initial wt loss at year 2 vs 24% placebo.

Hauptman J. Arch Fam Med. 2009.
Orlistat - Studies

- Longest trial, 4 year DB trial, 3304 overweight patients.
- 1st year weight loss 11% in orlistat vs 6% in placebo.
- Remaining 3 year small regain in both groups.
- 4 year weight loss 6.9% below initial body weight in orlistat vs 4.1% in placebo.
- Overall 37% reduction in conversion of patients from impaired GT into DM.
- In summary initial weight loss is greater and weight gain is slowed by Orlistat as compared to lifestyle/placebo.

Diabetes Care. 2002;25(6):1033
Weight loss with orlistat

[Graph showing weight loss progression with orlistat compared to placebo plus lifestyle changes over time.]
Orlistat - studies

- Orlistat and “adolescent” population
- RCT 1 year multicenter trial involving 530 obese adolescents
  - Weight gain of 0.53 kg vs 3.14 kg with placebo.
  - 27% of Orlistat vs 15% of placebo had a categorical BMI reduction of 5% or higher
  - DEXA confirmed fat mass loss.

Chanoine JP. JAMA. 2005
Orlistat - Benefits / Practical Summary

- May be used long-term up to 4 years for weight loss or for weight maintenance in adult obese patients
- Pediatric indication: 12-16 y/o obese adolescents
- Less commonly used though can be effective when used properly
- Use with low-fat diet only, limited use with low carb diet.
- Vitamin Supplementation is critical and should be taken at least 2 hours pre or post medication use.
- Improves blood pressure & serum lipid values.
LORCASERIN - “Appetite reducer“

Common names
- Belviq
  - 10 mg PO BID
  - Taken with or without food
  - No titration needed

How it works?
Selective serotonin 2C agonist

Adverse effects
- Generally mild
  - Headache - 18%
  - URI - 14.8%
  - Nasopharyngitis - 13.4%
  - Dizziness - 8%
  - Nausea - 7.5%

- DM II - May increase symp
  - Hypoglycemia

Pharmacokinetics
- Nonselective serotonin agonists
  - Fenfluramine
  - Dexfenfluramine

- 2A and 2B receptor agonists
  - Enhanced weight loss
  - More side effects
  - SEROTONIN INDUCED VALVULAR DISEASE.
• Should not be used with Creatinine clearance <30 ml/min.
• Contraindicated in pregnancy.
• Should not be used with other serotonergics!
  • SSRI
  • SSNRI
  • Bupropion
  • TCA
  • MAO Inhibitors
• Caution with Dextromethorphan
Lorcaserin - studies

- Efficacy similar to Orlistat.
- RCT, 3182 patients (BMI 36) 2 year study.
- 5% body weight reduction at 1 year 47.5% in lorcaserin vs 20.3% in placebo.
- At year 2, 67.9% maintained their weight in lorcaserin vs 50.3% in placebo group.
Lorcaserin Benefits / Practical Summary

• Efficacy similar to Orlistat with fewer side effects.
• Long term safety data are limited
• Slight but significant decrease in blood pressures, heart rate, total and LDL cholesterol, c-reactive protein, fibrinogen, fasting blood glucose and insulin levels
• FDA approved indications:
  • Obese $\geq$ 30 kg/m²
  • Overweight $\geq$ 27 kg/m² with at least 1 obesity related comorbidity.
SYMPATHOMIMETICS “Satiety stimulators”
Exact Mechanism for weight loss “Unknown”

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>TRADE NAME</th>
<th>DOSE</th>
<th>DAILY DOSAGE</th>
<th>SERUM HALF-LIFE</th>
<th>DEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Adipex, Fastin, Lonomin</td>
<td>15 mg, 30 mg, 37.5 mg</td>
<td>15mg-37.5 mg QD</td>
<td>4-19 hours</td>
<td>IV</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Tenuate, Tepanil</td>
<td>25 mg, 75 mg</td>
<td>25 mg TID, 75 mg QD</td>
<td>4-13 hours</td>
<td>IV</td>
</tr>
<tr>
<td>Phendimetrazine</td>
<td>Bontril</td>
<td>35 mg</td>
<td>35 mg TID</td>
<td>5 hours</td>
<td>III</td>
</tr>
</tbody>
</table>
Sympathomimetics Not Recommended!

- Potential side effects
  - Tachycardia
  - Increased blood pressure
  - Insomnia
  - Dry mouth
  - Constipation
  - Nervousness

- Contraindicated with CAD, Hypertension, Hyperthyroidism.
- Potential for Abuse / Contraindicated with history of drug abuse.
- Limited duration of use
Phenylethylamines - Studies

- Meta-analysis of phenteramine and diethylpropion
  - 3.6 kg additional weight loss at 6 M for phenteramine
  - 3.0 kg additional weight loss at 6 M for diethylpropion.

- Sympathomimetic + longitudinal care
  ASBP guidelines. Observational cohort
  11,000 patients followed up to 5 years.
  - Weight loss 10.2% - 6 Months
  - Weight loss 10.65% - 1 year
  - Weight loss 4.63% - 5 years

Li Z. Ann Internal Med. 2005
Phenylethylamines - Studies

- Sympathomimetic + Topiramate + Lifestyle
  - RCT of 700 subjects at 2 years
    - Placebo - 1.8% weight loss (IBW)
    - Phen/Top (7.5/46 mg) - 9.3% weight loss (IBW)
    - Phen/Top (15/92) - 10.5% weight loss (IBW)
    - Improved Cv variables and decreased incidence of DM vs placebo.

- Observational Study of Phentermine on BP
  - 300 patients treated for 52 weeks
    - Phentermine group lost significantly more weight
    - No significant difference in SBP, DBP or HR in phentermine vs untreated.

Li Z Ann Internal Med. 2005
Phenylethylamines - Benefits / Practical Summary

• Strongest in Efficacy
• Long term safety not studied.
• Side effects limits the use.
• Short term adjunct to lifestyle changes.
• Same criteria:
  • Obese $\geq 30$ kg/m$^2$
  • Overweight $\geq 27$ kg/m$^2$ with at least 1 obesity related comorbidity.
Bupropion

- **Brand name**: Wellbutrin, Wellbutrin XL, Zyban
- **Dose**:
  - Begin 150 mg PO QD for 3 days
  - Then titrate to 150 mg BID
  - Or 300 mg XL form
- **Dopamine & Norepinephrine reuptake inhibitor**

- **Pros and Cons**:
  - Very good antidepressant
  - Central acting appetite suppressant
  - Only antidepressant with consistent weight loss
  - May help blunt weight regain in smoking cessation
  - Caution:
    - May lower seizure threshold
    - Do not use in bulimic patients.
Phentermine-Topiramate (XL)

- What Combination offers?
  - Improves efficacy, tolerability.

- Adverse Effects
  - Dry mouth
  - Constipation
  - Paresthesia
  - Dose related increased psychiatric and cognitive deficits
  - Tachycardia
  - Contraindicated in
    - Pregnancy (Monthly HCG)
    - Hyperthyroidism
    - Glaucoma
    - MAO Inhibitors
  - Caution with history of renal stones

- 2012 US FDA approved this combo for.
  - BMI ≥ 30 kg/m²
  - BMI ≥ 27 kg/m² + at least 1 weight related comorbid condition.

- Dosage - QD
  - Start with 3.75/23 mg for 14 days
  - 7.5/46 mg for 12 weeks
  - 11.25/69 mg for 14 days.
  - Max dose - 15/92 mg
Weight loss with phentermine

The graph illustrates the weight loss over time for different treatment groups:

- **Placebo**
- **Continuous phentermine**
- **Alternate phentermine and placebo**

The x-axis represents time in weeks, ranging from 0 to 36, while the y-axis measures weight loss in both pounds (lbs) and kilograms (kg). The graph shows a significant decrease in weight loss over time for all groups, with the placebo group experiencing the least weight loss compared to the other two groups.
Obesity with Comorbidities

Weight-centric approach

Diabetes
- Metformin
- Pramlintide “T-1 DM”
- Exenatide
- Liraglutide

Smoking
- Bupropion

Epilepsy
- Topiramte
- Zonisamide

Depression
- Bupropion
Metformin

• Dose targeted to tighter glycemic control.
• Significant more weight loss (1-2 kg) vs placebo
• Doesn't qualify as a “weight-loss drug”
  • doesn’t produce enough weight loss ( 5 %)
• Best choice in Diabetics with obesity when indicated
• Cheap and generic.
• No hypoglycemia
• Contraindicated if Creat >1.4 in females and >1.5 in males.
• Consider ER form to counterening GI side effects.
Other Diabetic Drugs - Pramlintide

- Symlin (SC)
  - DM 1 - 30-60mcg SC QAC
  - DM 2 - 60-120 mcg SC QAC
- Simulates human Amylin
- Slows gastric emptying
- Reduces post prandial glucose surge
- Improves Hgb A1c.
- Modest weight loss
- Weight loss -2.75 and -2.75 kg in patients with or without DM respectively
- Larger trial, 651 patients with Type 1 DM in additional to insulin therapy
  - Weight decreased 0.4 kg vs 0.8 kg increase in placebo.
Other Diabetic Drugs - GLP-1 Analogs

- **Byetta (Exenatide) / Bydureon (Exenatide ER)**
  - Start 5 mcg BID 30-60 min before meals for 1 Month
  - Then increased to 10 mcg BID

- **Victoza (Liraglutide)**
  - Start 0.6 mg SQ QD for 1 week
  - Then 1.2 mg SQ QD (Max 1.8mg QD)

- Approved for Rx of DM type 2

- **Mechanism of action:**
  - Enhance glucose dependant Insulin release
  - Suppress inappropriate glucagon release
  - Delay Gastric emptying
  - Reduces appetite by directly acting on receptors in hypothalamus
**Liraglutide**

- **Brand name**: Saxenda
- **Dose**:
  - Begin 0.6 mg SQ daily
  - Increase weekly intervals (1.2, 1.8, 2.4 mg) daily
  - Recommended dose 3 mg daily
- **Not Recommended with severe renal (<30 Cr/Cl) and severe Liver Impairment.**
- **Contraindicated in Pregnancy.**

**Side effects**:
- GI - Nausea, Vomiting, Constipation in Diabetics
- Increased lipase, heart rate
- Pancreatitis, Gall Bladder disease.
- Renal Impairment
- Suicidal Thoughts!
- Only GLP-1, Approved for weight loss.
- Increased Risk of Thyroid Medullary Cancer
- Not for Obese Adolescents
GLP-1 Agonists - Studies - Practical Points

- RCT 330 Metformin treated diabetics for 30 weeks:
  - Exenatide 10 mcg - weight down 2.8 kg over placebo
  - Exenatide 5 mcg - weight down 1.6 kg over placebo.

- Great medications for DM an weight loss
- Weight is side effects of this medication group.
- Other Side effects: nausea, vomiting, diarrhea, dyspepsia, headache, hypoglycemia.
- Contraindicated: H/O pancreatitis, gastroperesis, sever renal impairment.
- Works synergistically with carb controlled dieting.
- Red Flag! Acute back pain or vomiting - check for pancreatic enzymes.
Official Weight loss with various medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Length of trial</th>
<th>Total weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>13 weeks</td>
<td>-6.4 kg</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>18 weeks</td>
<td>-6.5 kg</td>
</tr>
<tr>
<td>Mazindol</td>
<td>11 weeks</td>
<td>-5.7 kg</td>
</tr>
<tr>
<td>Orlistat</td>
<td>≥1 year</td>
<td>-5.3 kg</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>24 weeks</td>
<td>-4.8 kg</td>
</tr>
<tr>
<td>Bupropion</td>
<td>24 weeks</td>
<td>-8.0 kg</td>
</tr>
<tr>
<td>Exenatide</td>
<td>24 weeks</td>
<td>-2.9 kg</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>24 weeks</td>
<td>-2.8 kg</td>
</tr>
<tr>
<td>Metformin</td>
<td>1 year</td>
<td>-2.8 kg</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>≥1 year</td>
<td>-6.4 kg</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>1 year</td>
<td>-5.8 kg</td>
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<td>Phen/Topiramate</td>
<td>≥1 year</td>
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<tr>
<td>Buprop/Naltrex</td>
<td>≥1 year</td>
<td>-8.7 kg</td>
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References: