The Pharmacological Management of Obesity

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In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

Jennifer Trujillo

Advisory Panel: BD, Novo-Nordisk
ADA Standards of Care: Obesity Management
Pharmacotherapy

• When choosing glucose-lowering meds for overweight or obese patients with T2DM, consider effect on weight. B

• Whenever possible, minimize the meds for comorbid conditions that are associated with weight gain. E

• Weight loss meds may be effective adjuncts for selected patients with T2DM and BMI ≥27 kg/m². A

• Potential benefits must be weighed against the potential risks of the weight loss medications. A
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## Glucose Lowering Medications: Effects on Weight

<table>
<thead>
<tr>
<th>Weight loss</th>
<th>Weight neutral</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Metformin</td>
<td>• DPP-4 inhibitors</td>
<td>• Sulfonylureas</td>
</tr>
<tr>
<td>• GLP-1 receptor agonists</td>
<td></td>
<td>• Meglitinides</td>
</tr>
<tr>
<td>• SGLT-2 inhibitors</td>
<td></td>
<td>• Thiazolidinediones</td>
</tr>
<tr>
<td>• α-glucosidase inhibitors</td>
<td></td>
<td>• Insulin</td>
</tr>
</tbody>
</table>

## Glucose Lowering Medications: Risk of Hypoglycemia

<table>
<thead>
<tr>
<th>Low Risk of Hypoglycemia</th>
<th>Higher Risk of Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Metformin</td>
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</table>

Hypoglycemia is common during weight loss with some diabetes medications, so...

Defend against hypoglycemia by adjusting diabetes meds, not by adding food.

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Medications That Cause Weight Gain

- Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone)
- Antidepressants (e.g., tricyclic antidepressants, SSRIs, MAOIs)
- Glucocorticoids
- Contraceptives containing progestins
- Anticonvulsants (e.g., gabapentin)
- Antihistamines
- Anticholinergics
- Antiretrovirals

A recent survey of data from the NHANES (2013-2016; n=11,055) showed that 25% of adults had taken one or more prescription medications that promote weight gain.

Obesity Management for the Treatment of Type 2 Diabetes:
# Effects of Neurobehavioral Medications on Weight

<table>
<thead>
<tr>
<th>Weight Loss</th>
<th>Weight Neutral</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Haloperidol</td>
<td>TCAs</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Aripiprazole</td>
<td>MAOIs</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td></td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
<td>Lithium</td>
</tr>
<tr>
<td>Zonisamide</td>
<td></td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td>Clozapine</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td></td>
<td>Quetiapine</td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
<td>Risperidone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gabapentin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valproate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Divalproex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mirtazapine</td>
</tr>
</tbody>
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Candidates for Pharmacotherapy

- Type 2 diabetes and BMI $\geq 27$ kg/m$^2$
  - Unable to lose weight with lifestyle changes alone
  - Weight regain with lifestyle changes
  - Presence of weight-related complications

- Understand that medication is adjunctive to lifestyle intervention
- Have realistic expectations about weight loss goals and outcomes
- Able to adhere with medication use
- No medical or psychiatric contraindications
## FDA-Approved Medications for Treatment of Obesity

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>FDA Approval</th>
<th>Short-term or Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Adipex-P Lomaira</td>
<td>1959</td>
<td>Short-term</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Xenical (Rx)</td>
<td>1999</td>
<td>Chronic</td>
</tr>
<tr>
<td></td>
<td>Alli (OTC)</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Belviq</td>
<td>June 2012</td>
<td>Chronic</td>
</tr>
<tr>
<td>Phentermine/topiramate ER</td>
<td>Qsymia</td>
<td>July 2012</td>
<td>Chronic</td>
</tr>
<tr>
<td>Naltrexone/bupropion SR</td>
<td>Contrave</td>
<td>September 2014</td>
<td>Chronic</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Saxenda</td>
<td>December 2014</td>
<td>Chronic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Victoza 2010)</td>
<td></td>
</tr>
</tbody>
</table>

Obesity Management for the Treatment of Type 2 Diabetes: *Standards of Medical Care in Diabetes - 2020. Diabetes Care 2020;42(Suppl. 1):S89-97.*
Some Caveats about Pharmacotherapy

• No head-to-head studies; no clear first-line agent
• Response to therapy is variable
• Weight loss meds are adjunctive to lifestyle changes
• Treatment decisions based on patient-specific factors: concomitant medications and disease states, patient preferences, tolerance of AEs, and cost.
• Efficacy in “sustained” weight loss = over 1-2 years. Long-term data is not available.
• Dropout rates in studies were high; adherence and persistent are concerns.
• Obesity is a chronic disease. Weight loss meds are considered chronic meds. Once they are discontinued, the benefit is lost.
Phentermine

- Norepinephrine-releasing agent
- 8 - 37.5 mg by mouth once daily
- Only approved for short-term use
- Adverse effects
  - **Common**: dry mouth, insomnia, dizziness, irritability, increased BP
  - **Serious**: dyspnea, angina, syncope, severe hypertension
- Inexpensive
- Should not be used in CVD, uncontrolled hypertension, seizures, pregnancy, hyperthyroidism, glaucoma, anxiety disorders, with other sympathomimetics
- No long-term data

Adipex-P (phentermine) prescribing information.
Orlistat

- Pancreatic and gastric lipase inhibitor
- Blocks ingested fat absorption
- Reinforces low-fat diet; no effect on appetite
- Over-the-counter (Alli): 60mg by mouth three times daily
- Prescription (Xenical): 120m by mouth three times daily
- Generally safe; non-systemic
- Adverse effects:
  - Abdominal pain, steatorrhea, oily spotting, flatulence with discharge, fecal urgency, oily evaluation, increased defecation, and fecal incontinence
- Can decrease absorption of fat soluble vitamins (A, D, E, K) and medications (cyclosporine, thyroid hormone replacement, anticonvulsants)

Xenical (orlistat) prescribing information.
Lorcaserin

• Serotonin (5-HT) 2c receptor agonist
• Inhibits appetite stimulation and promotes satiety
• 10mg orally twice daily or XR 20mg orally once daily
• Generally well tolerated
• Adverse effects:
  – Common: headache, dizziness, fatigue
  – Serious: suicidal ideation, bradycardia, priapism
• Safety issues:
  – Risk of serotonin syndrome (use cautiously with other serotonergic drugs)
  – Risk of heart valve disorder is low (2.4% v 2.0% placebo; none symptomatic); thought to be associated with serotonin 2B receptor (fenfluramine)

Phentermine/topiramate ER (Qsymia)

• Sympathomimetic amine & neurostabilizer
• Appetite suppression, increased satiety and decreased food consumption
• Additive weight loss effects in low-dose combination
• 15/92mg by mouth daily (max dose; after titration)
• Adverse Effects
  – **Common**: paresthesia, dry mouth, constipation, headache, insomnia
  – **Serious**: depression, anxiety, irritability, ↑ HR
• Safety issues: CV-related issues (↑ resting HR), teratogenicity in pregnancy [REMS program], use caution in patients with mood disorders

Qsymia (phentermine/topiramate ER) prescribing information.
Naltrexone/bupropion SR (Contrave)

- Opioid receptor antagonist & dopamine/NE reuptake inhibitor
- Reduces food intake centrally and may affect food craving
- Synergistic weight loss effects
- 16/180 mg by mouth twice daily (after titration)
- Adverse Effects
  - **Common**: nausea, constipation, headache, vomiting, insomnia
  - **Serious**: depression, precipitation of mania
- Safety issues: Contraindicated with seizure disorders, anorexia or bulimia, use of other bupropion products, chronic opioid use, use with MAOI. Black-box warning: suicidal ideation.
Liraglutide (Saxenda)

- GLP-1 receptor agonist
- Reduces appetite centrally; decreases gastric emptying, ↑ satiety
- 3 mg SC daily (after titration)
- Adverse effects:
  - **Common**: nausea, vomiting, diarrhea, constipation, hypoglycemia in T2DM
  - ** Serious**: pancreatitis (no causal relationship established); gallbladder disease
- Safety issues: thyroid c-cell tumor risk [REMS program]
- Has indication for diabetes at 1.8 mg dose, so has secondary benefit on glycemia

Saxenda (liraglutide) prescribing information.
Newer Agents: What do they have in common?

• Indication
  – Adjunct to diet & exercise with:
    • BMI ≥ 30 kg/m² or
    • BMI ≥ 27 kg/m² plus at least 1 weight-related comorbidity
  – Approved for long-term (chronic) use

• All achieved FDA efficacy bench marks for approval
  – ≥5% weight loss than placebo
  – at least 35% of those on medications achieve 5% weight loss and twice as many as on placebo

• Contraindicated in pregnancy
  – Phentermine/topiramate ER requires negative pregnancy test prior to use and monthly thereafter
## Comparisons in Efficacy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase 3 Clinical Studies</th>
<th>Average % weight loss from baseline</th>
<th>% achieving ≥ 5% weight loss</th>
<th>% in treatment arm completing study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorcaserin (Belviq)</td>
<td>BLOOM, BLOSSOM, BLOOM-DM</td>
<td>5.8 – 7%</td>
<td>38 – 48%</td>
<td>55 – 79%</td>
</tr>
<tr>
<td>Phentermine/topiramate ER</td>
<td>EQUIP, CONQUER, SEQUEL</td>
<td>10.5 – 14.4%</td>
<td>45 – 70%</td>
<td>57 – 83%</td>
</tr>
<tr>
<td>(Qsymia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone/bupropion SR</td>
<td>COR-I, COR-BMOD, COR-II, COR-DIABETES</td>
<td>4 – 11.5%</td>
<td>36 – 57%</td>
<td>49 – 54%</td>
</tr>
<tr>
<td>(Contrave)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Liraglutide (Saxenda)</td>
<td>SCALE-Diabetes, SCALE Obesity and Prediabetes,</td>
<td>6 – 8%</td>
<td>51 – 63%</td>
<td>72 – 78%</td>
</tr>
<tr>
<td></td>
<td>SCALE – Maintenance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Common AE</th>
<th>Contraindication</th>
<th>Safety Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Insomnia, dry mouth, agitation, constipation</td>
<td>CVD, CHF, arrhythmias, uncontrolled hypertension, MAOI use, hyperthyroidism, glaucoma, pregnancy</td>
<td>Primary pulmonary hypertension</td>
</tr>
<tr>
<td>Orlistat</td>
<td>GI complaints</td>
<td>Chronic malabsorption Gallbladder disease</td>
<td>Malabsorption of fat soluble vitamins (A, D, E, K) and meds (cyclosporine, thyroid replacement, anticonvulsants); liver failure</td>
</tr>
<tr>
<td>Lorcaserin (Belviq)</td>
<td>Headache, dizziness, fatigue, dry mouth</td>
<td>MAOI use, caution with serotonergic drugs, pregnancy</td>
<td>Serotonin syndrome, depression, priapism</td>
</tr>
<tr>
<td>Phentermine/topiramate ER</td>
<td>Dry mouth, paresthesias, headache, insomnia</td>
<td>Glaucoma, hyperthyroidism, MAOI use, pregnancy</td>
<td>Teratogenicity, metabolic acidosis, glaucoma</td>
</tr>
<tr>
<td>(Qsymia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone/bupropion SR</td>
<td>Nausea, GI complaints, headache, insomnia</td>
<td>Seizure disorder, uncontrolled hypertension, chronic opioid use, MAOI use, pregnancy</td>
<td>Suicidal ideation, elevated blood pressure, pulse, glaucoma, hepatotoxicity</td>
</tr>
<tr>
<td>(Contrave)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide (Saxenda)</td>
<td>Nausea, GI complaints</td>
<td>Personal/family history of medullary thyroid carcinoma or MEN2, history of pancreatitis, pregnancy</td>
<td>Thyroid c-cell tumors (rodents), acute pancreatitis, gallbladder disease, hypoglycemia</td>
</tr>
</tbody>
</table>
Likelihood of Achieving $\geq 5\%$ Weight Loss with Fewest Adverse Effects

SUCRA = surface under the cumulative ranking curve.
## Practical Comparisons

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost*</th>
<th>Route</th>
<th>Dosing Frequency</th>
<th>Dose Titration (Initiation)</th>
<th>Dose Tapering (Discontinuation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorcaserin</td>
<td>360</td>
<td>Oral</td>
<td>BID or Daily</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Phentermine &amp; Topiramate ER</td>
<td>223</td>
<td>Oral</td>
<td>Daily</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Naltrexone &amp; Bupropion SR</td>
<td>334</td>
<td>Oral</td>
<td>BID</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>1497</td>
<td>SC</td>
<td>Daily</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*30-day AWP cost, rounded to nearest dollar ($)

Discontinuing Medication

- If patient’s response to weight loss medications is <5% weight loss after 3 months
- If there are any safety or tolerability issues at any time
- Then, alternative medication(s) or treatment approaches should be considered. A
Therapeutic Gaps

• Clinical gaps
  – Lack of acceptance that obesity is a chronic disease
  – Underutilization of obesity medications (<1%)
    - Lack of familiarity and comfort in prescribing
    - Perceptions about the safety and efficacy
    - Cost
  – Continued high utilization of meds that cause weight gain

• Research gaps:
  – Use of obesity meds in kids
  – Use of obesity meds post bariatric surgery
  – Long-term data
Patient Case Study: Maria

- Weight 226 pounds, BMI 36.5 kg/m2 and A1C 10.7%
- Evaluate insulin therapy, dose, past medications
  - Basal insulin dose is very high (0.8 units/kg/day)
  - Is a GLP-1 RA or SGLT2i an option?
  - Hypoglycemia?
- Evaluate other meds and other medical problems to determine best weight loss medication for her
Take Away Points

• Anti-obesity medications are adjunctive. They must be used in combination with calorie-reduced diet, physical activity, and lifestyle and behavior modifications.

• All anti-obesity agents are limited by low utilization, low adherence, modest efficacy, adverse effects, and weight regain after medication cessation.

• Treatment decisions should be made based on patient-specific factors and benefits and risks of each medication.