Weight Loss Medications in Prediabetes and Type 2 Diabetes: Who, When, How?

Objectives
• Review clinical guidelines for weight loss
• Discuss evidence based medicine approaches for weight loss in pre-diabetes and diabetes
• Select & recommend appropriate medication therapy for obesity based on available data

Meet Beth...
Beth is a 50 year old female with T2DM x 18 yrs presenting to clinic stating she is very motivated to lose weight. Pertinent PMH: T2DM, HTN, depression.
• Vitals
  – BP: 132/76mmHg
  – HR: 76bpm
  – BMI: 34kg/m²
  – Weight: 280lbs
• Labs
  – SCr: 0.82mg/dL
  – eGFR=60mL/min
  – A1C: 8.1%

Current medications
– Metformin 500 mg PO BID (max dose due to diarrhea)
– Insulin glargine 80 units subcutaneously nightly
– Insulin aspart 24 units subcutaneously TIDAC
– Sertraline (Zoloft®)100mg PO daily
– Lisinopril 10 mg PO daily

Past medications
– Liraglutide ( Victoza®) 0.6mg subcutaneously daily (sig nausea)
– Canagliflozin (Invokana®) 100mg PO daily (recurrent UTIs)
The issue at hand

Shear Numbers

- BMI cutoffs

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5 kg/m²</td>
</tr>
<tr>
<td>Normal Weight</td>
<td>18.5-24.9 kg/m²</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥25-29.9 kg/m²</td>
</tr>
<tr>
<td>Obesity</td>
<td>≥30 kg/m²</td>
</tr>
<tr>
<td>(Asian population: 23-24.8 kg/m²)</td>
<td></td>
</tr>
</tbody>
</table>

- Height, Weight, and BMI every visit
  - Overweight or obese → measure waist circumference at least annually
    - Men ≥40 inches
    - Women ≥35 inches
  - ↑ risk of CVD, T2DM, and all-cause mortality

Nonpharmacologic/LSM

- Non-pharmacologic interventions
  - Education regarding risks of being overweight/obese and the health benefits of even modest, sustained weight loss (3-5%)
  - Comprehensive lifestyle intervention program
    » Reduced caloric intake
      - Women: 1,200-1,500 kcal/day
      - Men: 1,500-1,800 kcal/day
      - Decrease by 500-750 kcal/day
    » Evidence-based diet
    » Behavioral strategies
    » Increased physical activity

Medication vs. Surgery

- BMI ≥30 kg/m² or ≥27 kg/m² with comorbidity
  - Consider addition medication therapy in addition to comprehensive lifestyle intervention
  - Weight loss ≥5%
  - Intensive lifestyle intervention in addition to comprehensive lifestyle intervention
  - Assessment of efficacy and safety monthly for 3 months, then every 3 months if on medication therapy

- BMI ≥40 kg/m² or ≥35 kg/m² with comorbidity
  - Offer referral to bariatric surgeon in addition to comprehensive lifestyle intervention
  - Assessment of efficacy and safety monthly for 3 months, then every 3 months if on medication therapy

Screening

- Screening
  - Height, Weight, and BMI every visit
  - Overweight or obese → measure waist circumference at least annually
    - Men ≥40 inches
    - Women ≥35 inches
  - ↑ risk of CVD, T2DM, and all-cause mortality

CDC Diabetes Statistics Accessed 3/24/16


The Lancet, 2004; 157-163.
**Question 1**

What is the best initial plan to assist Beth with weight loss?

A. Implement lifestyle modifications alone
B. Implement lifestyle modifications and begin pharmacotherapy
C. Implement lifestyle modifications and refer for bariatric surgery
D. Inform Beth she has trialed all medication options to assist in weight loss and you are unable to assist her further.

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**Orlistat**

- **Xenical® (Rx)**
  - **Indication**
    - BMI ≥30 kg/m² or ≥27 kg/m² with other comorbidities in addition to a reduced-calorie diet; reduction of weight regain after prior weight loss
  - **Dosing**
    - 120 mg PO TID

- **Alli® (OTC)**
  - **Indication**
    - Weight loss in addition to reduced-calorie and low-fat diet in overweight patients ≥18 years of age
  - **Dosing**
    - 60 mg PO TID

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**Orlistat (Xenical®, Alli®)**

**Orlistat**

- **Mechanism of action (MOA)**
  - Lipase inhibitor
  - Inhibits ~30% of dietary fat absorption

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**Orlistat**

- **Progression to T2DM**
  - XENDOS
    - 37.3% RRR vs. placebo in patients with NGT and IGT at baseline (log-rank P=0.0032)
    - 45% RRR vs. placebo in patients with IGT at baseline (log-rank P=0.0024)
  - Heymsfield, et al
    - 3% of orlistat group with IGT vs. 7.6% of placebo group (60.5% RRR)
    - 22.5% more patients with IGT at baseline had NGT vs. placebo at study end (P=0.04)

- **Weight Loss**
  - ~2.3 kg more experienced vs. placebo
  - Significantly more patients achieve a 5 and 10% weight reduction vs. placebo
Orlistat
- Glycemic control
  - Significantly greater A1c reduction (~0.5-1%) and FPG
  - Reductions seen above and beyond reduction associated with weight loss
- Other parameters
  - Reductions in BP, lipids (increase in HDL), WC and BMI

Orlistat
- Side effects
  - Common
    - GI disturbances, oily/fatty stools
  - Severe
    - Liver/renal dysfunction
- Drug interactions
  - Cyclosporine, levothyroxine, warfarin
- Educate patient to take multivitamin daily

Orlistat
- Take home points
  - Significant ↓ in weight (2-3 additional kg vs. placebo)
  - Significant ↓ in IGT and T2DM incidence
  - Beneficial effects on glycemic and other parameters affecting CV risk
  - No studies looking at CV outcomes
  - Minimal side effects outside of GI disturbances
  - Approved for long-term use
  - Supplement with daily multivitamin

Noradrenergic Agents
- Noradrenergic agents
  - Diethylpropion (Tenuate®, Tenuate Dospan®)
  - Phendimetrazine (Bontril PDM®)
  - Benzphetamine (Regimex®)
  - Phentermine (Apidex-P®, Suprenza®)
    - Discussed later

Noradrenergic agents
- Mechanism of action
  - Sympathomimetic amines, similar to amphetamines
  - Weight loss mechanism: stimulates hypothalamus
    - NE release → reduced appetite and food intake
  - NE = norepinephrine
  - MSH = melanocyte-stimulating hormone
  - POMC = proopiomelanocortin neuron
  - MRC = melanocortin
Noradrenergic agents

• Indication
  – All: short-term use (<12 weeks)
  – Diethylpropion and benzphetamine:
    • BMI ≥30 kg/m² in addition to caloric restriction in patients who have not responded to diet and physical activity interventions
    • Do not continue if weight loss <4lbs at 4 weeks
  – Phendimetrazine:
    • BMI ≥30 kg/m² or ≥27 kg/m² with other comorbidities in addition to comprehensive lifestyle interventions

Diethylpropion. Aventis Pharmaceuticals, Inc.; 2003
Phendimetrazine. Epic Pharma, LLC; 2011
Benzphetamine. Pfizer; 2009

• Dosing
  – IR: 25mg PO TID 1hr prior to meals and in midevening if desired
  – ER: 75mg PO daily in midmorning

• Phendimetrazine (Schedule III)
  – Dosing
    • 105mg PO QAM (30-60 minutes before meal)

• Benzphetamine (Schedule III)
  – Dosing
    • Start at 25-50mg PO QAM
    • May increase to TID based on patient response

• No studies evaluating effect on glycemic control, progression to T2DM
• Weight loss (obese patients, 6 months)
  – ~6kg vs. placebo
• Contraindications
• Side effects

Phentermine (Adipex-P®)

Phentermine. Teva; 2012.

• Sympathomimetic amine that is similar to amphetamines

Noradrenergic agents

• Take home points
  – Not approved for use >12 weeks
  – Side effect profile undesirable
  – Minimal data in patients with pre-DM and T2DM

Phentermine - MOA

Norepinephrine
Appetite
Phentermine - Dosing

- 15mg – 37.5mg daily given in 1-2 divided doses
- Max dose: 37.5mg/day
- Renal impairment: use with caution
- Hepatic impairment: not studied

Phentermine - Adverse Drug Reactions

- Dry mouth
- Hypertension
- Tachycardia
- Palpitations
- Restlessness
- Insomnia

- Dizziness
- Euphoria
- Impotence/changes in libido
- Constipation/diarrhea
- Unpleasant taste

Phentermine - Efficacy

- Limited data from randomized clinical trials
- Placebo controlled trial in 108 obese women:
  - Phentermine 30 mg continuous or intermittent
  - Continuous lost 12.2 kg
  - Intermittent lost 13 kg
  - Placebo lost 4.8 kg

Phentermine - Contraindications

- History of cardiovascular disease
  - Arrhythmias, CHF, CAD, Stroke, Uncontrolled HTN
- Hyperthyroidism
- Glaucoma
- Agitated states
- History of drug abuse
- Pregnancy/Breast-feeding

Phentermine - Long Term Use

- No evidence of serious cardiovascular disease
- No history of substance abuse or serious psychiatric disease
- No clinically significant increase in BP or pulse when taking phentermine
- Demonstrated significant weight loss on phentermine

Phentermine - Contraindications

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Take Home Points

- Scheduled C-IV
- Pregnancy Category X
- Take before breakfast OR 1 – 2 hours after breakfast
  - AVOID late evening administration
  - Tablets can be split in ½ and administered BiD
- Short term use ONLY (12 weeks)
- Most effective with low-calorie diet, exercise, and behavior modification counseling
- Monitor: Weight, waist circumference, and BP
Phentermine/Topiramate ER (Qsymia®)

Phentermine/Topiramate ER - MOA
- Phentermine: same as Adipex-P®
- Topiramate: exact mechanism unknown
  - Effects on appetite suppression and satiety enhancement may be induced by a combination of pharmacologic effects

Phentermine/Topiramate ER - Dosing
- Start: 3.75mg/23mg once daily for 14 days then increase to 7.5mg/46 mg
- Evaluate weight loss after 12 weeks:
  - Lost 3% of baseline body weight?
    - No = discontinue or increase dose
    - Yes = may increase to 11.25 mg/69 mg for 14 days then 15 mg/92 mg

Phentermine/Topiramate ER - Renal Impairment
- CrCL > 50: No adjustment needed
- CrCL 30 – 50: Do not exceed 7.5/46 mg Daily
- CrCL < 30: Do not exceed 7.5/46 mg Daily
- ESRD/dialysis: Avoid use

Phentermine/Topiramate ER - Hepatic Impairment
- Mild: No adjustment needed
- Moderate: Do not exceed 7.5/46 mg Daily
- Severe: Avoid use

Phentermine/Topiramate ER - Dosing
- After 12 weeks lost at least 5% of baseline weight?
  - No = discontinue
  - Yes = continue
- To discontinue – taper gradually every other day for at least one week
**Phentermine/Topiramate ER – Adverse Drug Reactions**

- Increased heart rate
- Paresthesia
- Headache
- Insomnia
- Constipation
- Dry mouth
- Dizziness
- Altered taste

**Phentermine/Topiramate ER - Efficacy**

- **EQUIP**
  - Controlled release phentermine/topiramate in severely obese adults: a randomized controlled trial (n=1267) BMI ≥ 35
- **CONQUER**
  - Effects of low-dose, controlled release, phentermine & topiramate on weight and associated co-morbidities in overweight and obese adults randomized, placebo-controlled trial (n=2487) BMI 27-45

**Phentermine/Topiramate ER - Efficacy**

- Reduced progression to T2DM by 76%
- Safety study for patients that had completed CONQUER (n=676)
- Reduced progression to T2DM by 76%

**Contraindications**

- Glaucoma
- Hyperthyroidism
- Pregnancy
- Hypersensitivity
- MAO inhibitors during or within 14 days of therapy

**Warnings/Precautions**

- Fetal toxicity (REMS)
- Increased heart rate
- Suicidal thoughts
- Mood/Sleep disorders
- Cognitive impairment
- Potential seizures with abrupt withdrawal
- Hypoglycemia

**Take Home Points**

- Scheduled C-IV
- Pregnancy Category X
- Take in the morning without regard to meals
- Most effective with low-calorie diet, exercise, and behavior modification counseling
- Monitor: weight, HR, BP, K+, HCO₃, SCr, glucose, suicidality
- Taper to discontinue
Lorcaserin (Belviq®)

Belviq®

5HT₂C

↓ Food Consumption

↑ Satiety

Exact Mechanism is Unknown

Lorcaserin - Mechanism of Action*

Lorcaserin - Dosing

• 10mg twice daily
  – No titration needed
• Max dose: 10mg twice daily
• Evaluate response by week 12
  – If patient has NOT lost > 5% of baseline body weight → DISCONTINUE

Lorcaserin - Adverse Drug Reactions

• Headache
• Hypoglycemia
• Back pain
• Nausea
• Dizziness
• Fatigue
• Dry mouth

Contraindications:
Pregnancy

Lorcaserin - Warnings/Precautions

• Serotonin Syndrome – do not use with medications like Paxil®, Prozac®, Zoloft®, Celexa®, Lexapro®, Cymbalta®, Effexor® & Pristiq®
• Cognitive impairment
• Monitor for depression & suicidal thoughts
• Priapism
• Valvular Heart Disease
• Hypoglycemia

Renal Impairment

Hepatic Impairment

- No adjustment needed
- Use with caution
- Not recommended
- Not recommended
- Use with caution

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Renal Impairment

Hepatic Impairment

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8/12/2016

**Lorcaserin - Efficacy**

- **BLOOM**
  - Behavioral Modification and Lorcaserin for Overweight and Obesity Management (n=3182)
- **BLOSSOM**
  - Behavioral Modification and Lorcaserin Second Study of Obesity Management (n=4008)

**Take Home Points**

- Scheduled C-IV
- Pregnancy Category X
- Take without regard to meals
- Monitor: weight, waist circumference, CBC, glucose, signs of depression or suicidality
- Option for patients with CV disease

**Naltrexone/bupropion (Contrave®)**

**Lorcaserin - Efficacy**

- **BLOOM-DM**
  - Randomized, double-blind, placebo-controlled, multicenter (n=604)
  - Almost 3 years
  - T2DM on metformin and/or sulfonylurea
  - Able to participate in moderate intensity exercise program

**Take Home Points**

- Scheduled C-IV
- Pregnancy Category X
- Take without regard to meals
- Monitor: weight, waist circumference, CBC, glucose, signs of depression or suicidality
- Option for patients with CV disease

**Naltrexone/bupropion (Contrave®)**

**Lorcaserin - Efficacy**

- **BLOOM-DM**
  - Mean age 52
  - Women 54% (African American 20% & Hispanic 14%)
  - Exercise 30 minutes/day
  - Reduce calorie intake by 600 kcal below estimated daily requirements
  - HbA1C and fasting glucose decreased*
Naltrexone/bupropion - MOA

Opioid antagonist

Naltrexone

↓

Food Intake

Bupropion

DA/NE Reuptake Inhibitor

Exact mechanism is not fully understood!

Naltrexone/bupropion – Adverse Drug Reactions

• Nausea
• Constipation
• Headache
• Vomiting
• Dizziness
• Insomnia
• Dry mouth

• Withdrew in first 12 weeks:
  – 46% in Contrave® group
  – 45% in placebo group
• Due to adverse reactions:
  – 24% Contrave® & 12% placebo

Naltrexone/bupropion - Dosing

• Available: 8 mg naltrexone/90 mg bupropion
• Max Dose: 32 mg/360 mg (4 tablets) daily

• If patient has NOT lost > 5% of baseline body weight
  by 12 weeks: DISCONTINUE!

Naltrexone/bupropion - Contraindications

• Pregnancy
• Concomitant use of other bupropion products
• Chronic opioid pain medications
• Uncontrolled high blood pressure
• Seizures
• Bulimia or anorexia nervosa
• Use of MAO inhibitors within the last 14 days

Naltrexone/bupropion - Adverse Drug Reactions

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• Use of MAO inhibitors within the last 14 days

Naltrexone/bupropion - Warnings/Precautions

• Seizures
• Opioid withdrawal or vulnerability to overdose
• Increase in BP and HR
• Allergic reactions

• Hepatotoxicity
• Activation of mania
• Angle-closure glaucoma
• Hypoglycemia

BLACK BOX WARNING
Suicidal thoughts/behaviors
Neuropsychiatric reactions
Naltrexone/bupropion - Efficacy

• Contrave Obesity Research (COR)
• COR-I, COR-II and COR-BMOD (n=4031)
  – 56 week trials
  – Obese (BMI > 30) or overweight (BMI > 27) with HTN or dyslipidemia

Lancet 2010;376:595-605  
Obesity 2013;21:935-43  
Obesity 2011;19:110-20

Naltrexone/bupropion - COR-Diabetes

• Randomized, double-blind, placebo-controlled, multicenter (n=505)
• 56 weeks
• T2DM on metformin, sulfonylurea and/or thiazolidinedione (TZD)
• Contrave was increased over first 4 weeks


Take Home Points

• NOT a Controlled Substance
• Pregnancy Category X
• Do NOT take with high fat meals!
  – Take without regard to meals
• Do not cut, chew, or crush tablets
• Monitor: weight, BP, HR, glucose, renal/liver function, signs of depression, anxiety, and suicide
• Taper to discontinue
• Waiting for cardiovascular safety data

Naltrexone/bupropion – Efficacy

• COR-Diabetes
  – Mean age 54
  – Women 54% (Caucasian 80%)
  – Walk at least 30 minutes/day most days of the week
  – 500 kcal deficit/day
  – A1C*, fasting glucose, waist circumference, TG and HDL*

FDA Approved Diabetes Agents

• SGLT2 inhibitors (Diabetes)
  – Roughly 2.2-3.7kg weight loss
  – Via caloric reduction of ~ 300 calories
  – Increase in fatty acid oxidation
FDA Approved Diabetes Agents

- GLP1 agonists
  - All FDA Approved for Diabetes
  - Saxenda® (Liraglutide) 3mg daily
    - FDA approved for only weight loss NOT DM
    - Weekly titration up to 3mg daily
    - After 16 weeks of therapy, if not > 4% baseline weight \( \Rightarrow \) Stop
    - Between group comparison
      - ~4%-7.5% reduction in change from baseline weight
      - ~3cm – 4cm change in Waist circumference
      - Reduction in LDL, TC, TG
      - Increase in HR, HDL

Question 2

- Which is a contraindication for Beth to receive lorcaserin for weight loss?
  
  A. BMI of 34kg/m²
  B. History of seizures
  C. Current use of sertraline (Zoloft®)
  D. Her age

Clinical Insight and Nutshells

- Number Needed to Treat (NNT)

Revisit Beth...

Beth is a 50 year old female with T2DM x 18 yrs presenting to clinic stating she is very motivated to lose weight. Pertinent PMH: T2DM, HTN, depression.

- Current medications
  - Metformin 500 mg PO bid (max dose due to diarrhea)
  - Insulin glargine 80 units subcutaneously QHS
  - Insulin aspart 24 units subcutaneously TIDAC
  - Lisinopril 10 mg PO daily
  - Liraglutide (Victoza®) 0.6mg subcutaneously daily (skg nausea)
  - Canagliflozin (Invokana®) 100mg PO daily (recurrent UTIs)

Question 3: Think-Pair-Share

- What is the best pharmacotherapy to assist Beth with her weight loss?
  
  Orlistat
  Diethylpropion
  Phentermine
  Phentermine/topiramate
  Naltrexone/bupropion
  Liraglutide

References

### References


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