THE CHRONIC DISEASE OF OBESITY IN THE U.S.
Faculty

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- Novo Nordisk: Speaker and Advisory Bureau
- Takeda/Lundbeck: Speakers bureau
- Sanofi: Advisory board
LEARNING OBJECTIVES

1. Identify key recommendations and strategies from current clinical guidelines for the management of obesity.
2. Compare the safety, efficacy, and pharmacokinetic profiles of anti-obesity medications.
3. Identify best practices for selecting, initiating, and advancing appropriate pharmacological therapies for patient-specific management of obesity.
OVERVIEW

Obesity and its Consequences
PREVALENC E OF OVERWEIGHT AND OBESITY IN ADULTS

People who have overweight classification 35.2%

People with obesity – 36.5%
Etiology

- Heritable traits
- Chromosomal abnormalities

Genetic

- Medications causing weight gain

Obesogenic Medications

- Altered microbiome
- GI/CNS regulation of hunger + satiety hormones

Physiologic

- Altered microbiome
- GI/CNS regulation of hunger + satiety hormones

Environmental

- Endocrine disrupting chemicals
- Low macronutrient/high calorie foods

GI, gastrointestinal; CNS, central nervous system

GLP-1 = glucagon-like peptide 1
CCK = cholecystokinin
YY = peptide YY
FFA = free fatty acids
AA = amino acids

GABA = γ-aminobutyric acid, AgRP = agouti-related protein, NPY = neuropeptide, α-MSH = alpha-melanocyte-stimulating hormone, POMC = pro-opiomelanocortin, CART = cocaine and amphetamine-regulated transcript, MC4 = melanocortin 4 receptor

### Body Mass Index (BMI) in kg/m²

<table>
<thead>
<tr>
<th>Category</th>
<th>Overweight</th>
<th>Class 1 Obesity</th>
<th>Class 2 Obesity</th>
<th>Class 3 Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Range</td>
<td>25-29.9</td>
<td>30-34.9</td>
<td>35-39.9</td>
<td>≥40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥35 w/comorbidities</td>
</tr>
</tbody>
</table>

### Waist Circumference

<table>
<thead>
<tr>
<th>Category</th>
<th>Men Abdominal Obesity</th>
<th>Women Abdominal Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist Circumference</td>
<td>≥40 inches (&gt;102 cm)</td>
<td>≥35 inches (&gt;88 cm)</td>
</tr>
</tbody>
</table>

Waist circumference cut-points differ by ethnicity.

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Endocrine Society Pre-obesity: 26 kg/m²


OBESITY-RELATED COMPLICATIONS

- Diabetes risk, metabolic syndrome, and prediabetes
- Type 2 diabetes
- Dyslipidemia
- Hypertension
- Cardiovascular disease and cardiovascular disease mortality
- Urinary stress incontinence
- Nonalcoholic fatty liver disease
- Polycystic ovary syndrome
- Female infertility
- Male hypogonadism
- Obstructive sleep apnea
- Asthma
- Osteoarthritis
- Depression

The adverse health consequences of increased body fat (especially visceral fat) are not just ‘comorbidities’ or ‘associated risk factors’.

OBESITY-RELATED COMPLICATIONS
Obesity is a complex, multifactorial, chronic disease. Obesity is defined as a chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissues dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences.

Obesity is associated with a significant increase in mortality and many health risks.

The higher the BMI, the greater the risk of morbidity and mortality.

CLINICAL VIGNETTE: EVALUATION
MEET

PAMELA

- 42 years old
- Works part-time as a banker
- Lives with her husband and 2 daughters
- Has tried multiple times to lose weight
- Tried phentermine in past for weight loss but did not tolerate the side effects (“felt jittery”)
- Has not reached her weight goal
COMMUNICATION: USING THE 5AS

Ask
- Permission to discuss weight
- Explore readiness for change

Assess
- BMI, waist circumference, obesity stage
- Explore drivers + complications of excess weight

Advise
- Health risks of obesity + benefits of weight loss
- Long-term strategy + treatment options

Agree
- Expectations + targets
- Behavioral changes

Assist
- Identify barriers to optimal health
- Create follow-up plan

ASKING WITH PEOPLE FIRST LANGUAGE

- People First: Remove the Word “Obese” from Your Dictionary and Language
- Avoid labeling it = bias and discrimination

http://stopobesityalliance.org/wp-content/themes/stopobesityalliance/pdfs/STOP-Provider-Discussion-Tool.pdf
Suggestions From Stop Obesity Alliance

• Would it be okay if we discussed your weight?”
• “Our measurement indicate that you are carrying excess weight. This can be unhealthy for you and strain your body. If you’re interested we can talk about creating a plan of action together.”

http://stopobesityalliance.org/wp-content/themes/stopobesityalliance/pdfs/STOP-Provider-Discussion-Tool.pdf
**EVALUATION PARAMETERS**

**History: weight, activity, nutrition, family**

**Laboratory studies**
- Complete blood count (CBC), fasting lipid panel, fasting glucose, HbA1c, liver function tests, vitamin D, thyroid stimulating hormone (TSH)

**Assess + treat obesity-related comorbidities**
- Examples: sleep apnea, depression

**Physical exam**
- Measure weight + height to calculate BMI
- Waist circumference for patients w/ BMI >25kg/m²
- Blood pressure

PAST MEDICAL HISTORY + DIAGNOSTICS

Sleep Apnea: intermittent use of CPAP

GERD: treated with protonix

Osteoarthritis both knees: takes intermittent ibuprofen

Reproductive barrier: IUD

Mild depression and anxiety: treated successfully with citalopram

ETOH: drinks socially—1 glass of wine/week. No illicit drugs.

No history of seizures, hypertension, heart disease, or pancreatitis

BMI 29 kg/m²

CMP, CBC, TSH noncontributory

TC = 245

LDL = 134

TG = 173

HgbA1C = 5.8

PHQ9 = 4

BMI, body mass index; CMP, comprehensive metabolic panel; CBC, complete blood count; TSH, thyroid stimulating hormone; TC, total cholesterol; LDL, low-density lipoprotein; TG, triglycerides; HbA1c, glycated hemoglobin; PHQ9, Patient Health Questionnaire
I’ve tried to lose weight many, many times—at least 6 or 7. Sometimes I do lose weight, but I always gain it back again. I’m getting real frustrated.

I’ve been overweight since I was 17. I’m always thinking about food, especially sweets and snacks. I find it hard to curb my cravings—instead of eating only a few chips, I usually end up eating the whole bag.
EVALUATION SUMMARY

Prediabetes

Depression
GERD
Osteoarthritis

Weight gain
Regain
Cravings

Next steps?
GUIDELINE RECOMMENDATIONS

Best Practice Strategies
GUIDELINE RECOMMENDATIONS

**Similarities**

- Individualized eating plans
- Counseling patients to increase physical activity
- Behavioral interventions
- Medication may be appropriate for some patients
- Referral to an obesity specialist or surgery may be appropriate

**Differences**

Endocrine Society paradigm shift toward pharmacologic therapy over no therapy at all for patients:

- With a history of unsuccessful weight loss and maintenance
- Who meet label indications

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THERAPEUTIC GOALS

Weight loss of 5%-10% of body weight

Reduce obesity-associated complications within 6 months

Improve patient health and quality of life

Reduces CVD risk factors
Prevents/delays T2DM
Improves osteoarthritis

Reduces sleep apnea,
depression
Improves physical function

GUIDELINE-RECOMMENDED COMPREHENSIVE LIFESTYLE THERAPY*

**Meal Plan**
- Energy deficit ≥500 kcal/day
  - Low-carb
  - Low-fat
  - Volumetric
  - High protein
  - Vegetarian
  - Mediterranean
  - DASH

**Physical Activity**
- Individualized
  - ↑ >150 mins/week on 3-5 separate days
  - Track progress:
    - Daily activity logs
    - Pedometer logs
    - Training metrics

**Behavior**
- Self-monitoring
- Goal setting
- Education
- Problem-solving strategies
- Stimulus control
- Stress reduction
- Counseling

*Alone or with adjunctive therapies

TECHNOLOGY TO SUPPORT WEIGHT LOSS

Applications to log nutrition and physical activity

Body-weight scales w/ feedback

Wearable technology

Websites

Social media

NEXT STEPS

Explore readiness to change

Think:
Motivational Interviewing & Shared Decision Making

Continue lifestyle therapy

Agree on weight loss goal of 5-7% of Pamela’s current weight

Consensus to discuss medication options
WHICH THERAPY WOULD YOU RECOMMEND ADDING TO PAMELA’S LIFESTYLE PLAN?

A. Orlistat  
B. Phentermine/topiramate ER (Qsymia)  
C. Naltrexone/bupropion ER (Contrave)  
D. Phentermine  
E. Liraglutide (Saxenda)  
F. Lorcaserin (Belviq)
PHARMACOLOGIC THERAPY

Therapy Options, Factors to Consider When Selecting Therapy, and Efficacy/Safety Evidence
## FDA-Approved Short-Term Anti-obesity Therapies

<table>
<thead>
<tr>
<th>Generic Drug*</th>
<th>Dose</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>8mg-37.5mg</td>
<td>Anxiety disorder, CVD, hypertension, MAO inhibitors, glaucoma, hyperthyroidism, seizures, pregnancy/breastfeeding, drug abuse history</td>
<td>Insomnia, palpitations, tachycardia, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, gastrointestinal distress, anxiety, restlessness, increased blood pressure</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>25 mg or 75 mg, SR</td>
<td></td>
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<tr>
<td>Phendimetrazine</td>
<td>17.5-70 mg or 105 mg, SR</td>
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<tr>
<td>Benzphetamine</td>
<td>25-50 mg</td>
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</tbody>
</table>

*Mechanism of action = Sympathomimetic—noradrenergic causing appetite suppression

**References**


PHENTERMINE

- US Drug Enforcement Agency scheduled drug
  - Risk for addiction
- Not indicated for long term use
  - 13 weeks by label

Endocrine Society allows for possible long term use:
- No CVD
- No psychiatric/substance abuse history
- Has been informed about therapies that are approved for long-term use
- Document off-label use in patient’s medical record
- No clinical significant increase in pulse/BP when taking phentermine
- Demonstrates significant weight loss with phentermine
- Start at 7.5 or 15 mg/d—dose escalate if not achieving significant weight loss
- Monitor monthly during dose escalation

## FDA-APPROVED ANTI-OBESEITY THERAPIES

<table>
<thead>
<tr>
<th>Generic Drug</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat (oral)</td>
<td>Pancreatic lipase inhibitor—impairs gastrointestinal energy absorption, causing excretion of approximately 30% of ingested triglycerides in stool</td>
</tr>
<tr>
<td>Lorcaserin (oral)</td>
<td>Highly selective serotonergic 5-HT2C receptor agonist causing appetite suppression</td>
</tr>
<tr>
<td>Phentermine/ topiramate-ER (oral)</td>
<td>Noradrenergic + GABA-receptor activator, kainite/AMPA glutamate receptor inhibitor causing appetite suppression</td>
</tr>
<tr>
<td>Liraglutide (subcutaneous injection)</td>
<td>GLP-1 receptor agonist</td>
</tr>
<tr>
<td>Naltrexone/bupropion ER (oral)</td>
<td>Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor</td>
</tr>
</tbody>
</table>
# Long-term Efficacy for Anti-obesity Medications

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Length of Trial</th>
<th>Total Weight Loss</th>
<th>Mean Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>≥1 year</td>
<td>-5.3 kg</td>
<td>-6.1%</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>1 year</td>
<td>-5.8 kg</td>
<td>-5.8%</td>
</tr>
<tr>
<td>Phentermine/topiramate</td>
<td>≥1 year</td>
<td>-10.2 kg</td>
<td>-9.8%</td>
</tr>
<tr>
<td>Bupropion/naltrexone</td>
<td>≥1 year</td>
<td>-6.1 kg</td>
<td>-5.4%</td>
</tr>
<tr>
<td>Liraglutide*</td>
<td>≥1 year</td>
<td>-8.4 kg</td>
<td>-8.0%</td>
</tr>
</tbody>
</table>

GENERAL CONSIDERATIONS IN PHARMACOLOGIC INITIATION

Pharmacologic interventions may be helpful as adjuvant therapy with lifestyle interventions for patients with BMI ≥30 kg/m² or ≥27 kg/m² with comorbidities.

- Different patients respond to different medications
  - If one option does not work, consider others
- Discontinue medication in patients who do not respond with weight loss of at least 5% at 12 weeks
- Avoid in pregnancy
  - Pregnancy tests at baseline
  - Consider a disclosure signature

5 STEP STRATEGY FOR THERAPY SELECTION

1. Safety
2. Co-morbidities
3. Patient history
4. Cost + insurance
5. Side effects

© Obesity Action Coalition
<table>
<thead>
<tr>
<th>Dose Frequency</th>
<th>Efficacy</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
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</table>
| 60 mg OTC      | ▪ Mean weight loss ranged from 3.9% - 10.2% at year 1 in 17 RCTs (120mg TID)  
▪ ↓ BP, TC, LDL-C, fasting glucose at 1 year  
▪ Slows risk of progression to T2DM | Oily spotting, cramps, flatus with discharge, fecal urgency, fatty oily stool, increased defecation, fecal incontinence | Chronic malabsorption syndrome, pregnancy, breastfeeding, cholestasis, some medications (ex. warfarin, antiepileptic agents, levothyroxine, cyclosporine) |
| 120 mg TID within 1 h of fat-containing meal | | | |

**Practical Considerations**

- Consider fat-soluble multivitamin
- Limit fat intake to 30% of calories
- Counsel on risk of GI adverse events

Lexicomp  
# PHENTERMINE-TOPIRAMATE ER

<table>
<thead>
<tr>
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<th>Efficacy</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Initiate treatment at 3.75 mg/23 mg for 2 weeks</td>
<td>▪ 10% weight loss with treatment vs 2% placebo ▪ Improved cardiometabolic markers ▪ Reduced progression to T2DM</td>
<td>Pregnancy and breastfeeding, hyperthyroidism, glaucoma, use of monoamine oxidase inhibitors</td>
<td>Paresthesias, dizziness, taste alterations, insomnia, constipation, dry mouth, elevation in heart rate, memory or cognitive changes</td>
</tr>
<tr>
<td>▪ Increase to 7.5 mg/46 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Escalate to 11.25 mg/69 mg for 2 weeks then to max 15 mg/92 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Practical Considerations
- Titrate dose at initiation and discontinuation
- Drug Enforcement Agency Schedule IV drug
- Risk Evaluation and Mitigation Strategy
- Counsel about risk for mood disorders, suicidal thoughts
- Taper highest dose every other day for 1 week if discontinuation is necessary

Lexicomp
<table>
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<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly titration by 0.6mg over 5 weeks to target dose of 3.0mg</td>
<td>Mean weight loss 9% at 1 year</td>
<td>Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history, history of pancreatitis, pregnancy, breastfeeding</td>
<td>Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM, increased lipase, increased heart rate, pancreatitis</td>
</tr>
</tbody>
</table>

### Practical Considerations
- Injectable administration
- FDA approved for use in adults with BMI > 30kg/m² or BMI > 27 kg/m² with at least one complication.
- Risk Evaluation and Mitigation Strategy (medullary thyroid carcinoma, acute pancreatitis)

Lexicomp
<table>
<thead>
<tr>
<th>Dose Frequency</th>
<th>Efficacy</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| 10 mg twice daily ER 20mg daily | • Average weight loss 8%-10%  
• Improved cardiovascular risk factors  
• Improved HbA1c in patients with T2DM  
• Reduced risk of developing T2Dm in patients with prediabetes | Pregnancy, breastfeeding  
Caution with serotonergic agents (due to risk of serotonin syndrome)  
Avoid in patients w/severe hepatic or renal insufficiency, valvular heart disease | Headache, dizziness, fatigue, nausea, dry mouth, cough, and constipation  
Patients w/T2DM, back pain, cough, hypoglycemia |

**Practical Considerations**

- **Schedule IV Drug**
- ER is slowly absorbed and lasts throughout the day
- Independent effect on lowering HgbA1c

Lexicomp
**NALTREXONE NE-BUPROPION ER**

<table>
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<tr>
<th>Dose Frequency</th>
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<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate 8mg/90mg x 1 week, Weekly escalation to target dose of 32mg/360 mg (2 tablets BID)</td>
<td>Weight loss of 8.2% vs 1.4% (placebo), Improved cardiometabolic parameters, Fewer cravings, Lowered HbA1c in patients with T2DM</td>
<td>Uncontrolled hypertension, seizure disorder, anorexia or bulimia, drug or alcohol withdrawal, chronic opioid use, monamine oxidase inhibitors</td>
<td>Nausea, constipation, headache, dizziness, vomiting, insomnia, dry mouth, Transient increase in blood pressure</td>
</tr>
</tbody>
</table>

**Practical Considerations**
- Titrate dose on initiation
- Monitor blood pressure
- Monitor closely for depression

Lexicomp
MONITORING PROGRESS
At week 16 (includes titration period) Pamela has lost 2% of her baseline weight and her HbA1c remains 5.8%.

What would be your next management step?
If no clinical improvement after 12 weeks with one anti-obesity medication, consider:

- Increasing anti-obesity medication dose, if applicable
- Alternative anti-obesity medication

CONSIDERATIONS FOR SWITCHING PAMELA’S THERAPY

**LORCASERIN**?
- No history of CVD but borderline high LDL/TC
- Caution w/ SSRI
- Monitor for depression

**LIRAGLUTIDE**?
- HbA1c remains elevated
- No family history of thyroid or pancreatitis
MAINTAINING WEIGHT LOSS

Weight regain typically occurs when medication is stopped.  

Successful weight maintenance includes:

- Self-monitoring
- Weight loss of >2kg in 4 weeks
- Frequent/regular attendance at weight loss program
- Self-belief that weight can be controlled

Maintaining weight loss is made difficult by the reduction in energy expenditure that weight loss induces.

Adaptive responses to weigh loss promotes weight regain.

- Fall in energy expenditure
- Increase in appetite
- Dysfunctional hormonal system
OBESITY SPECIALIST REFERRAL--
CONSULTATION

Weight loss <5% at 3 months with approved medication

Safety or tolerability issues

Patient-centered concerns

BARIATRIC SURGERY

- BMI ≥40 kg/m² if surgical risk is acceptable
- BMI ≥35 kg/m² if >1 obesity-related disease
- BMI 30-34.9 kg/m² for T2DM and/or metabolic syndrome
- Inability to achieve + sustain healthy weight loss with prior weight loss efforts

PAMELA AT FOLLOW-UP WITH LIRAGLUTIDE

She has visited 10 times in 6 months for intensive behavioral therapy and monitoring.
AT FOLLOW-UP WITH LIRAGlutide (CONT.)

- Lost 8% baseline weight
- HbA1c = 5.4%
- Sleep apnea is minimal
- No longer requires ibuprofen for osteoarthritis
- Walking 10,000 steps/day, 5 days/week
- Hiking with friends on weekends
- Signed up for a charity 5K

Provider F/U
- Close follow-up
- Continue to prescribe medication with lifestyle
- Pregnancy prevention plan
- Close follow-up
Obesity is a chronic and often progressive condition.

Obesity management is not about simply reducing numbers on the scale.

Early intervention means addressing root causes and removing roadblocks.

Success is different for every individual.

A patient’s ‘best’ weight may never be an ‘ideal’ weight.

NO SHAME, NO BLAME

Adapted from http://www.obesitynetwork.ca/5As


