Module 9
Effects of Other Medications on Weight and Potential Future Obesity Treatments

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Introduction............................................................................................................................................4

Think Ahead: Off-Label Use.............................................................................................................5

Avoiding Medications That Cause Weight Gain...........................................................................6

Case: Mr. Perez and Weight Gain Medications.............................................................................7

Diabetes Medications & Weight........................................................................................................7

Obesity Guidelines for Diabetes Medications..................................................................................8

Weight-Gaining or Neutral Diabetes Medications.........................................................................9

Weight Losing DM Medications: Metformin..................................................................................10

Weight-Losing DM Medications: GLP-1 Analogs...........................................................................11

Weight-Losing DM Medications: SGLT2 Inhibitors.........................................................................12

Quiz: Underlying Biology of Diabetes Medications.........................................................................13

Poll: Change Mr. Perez's Medication?.............................................................................................13

Discussing Options..........................................................................................................................13

Discussing Options..........................................................................................................................14

Case: Ms. Parker and Weight-Gain Medications............................................................................15

Psychoactive Meds & Weight............................................................................................................15

Antidepressants & Weight................................................................................................................16

Mood Stabilizers & Weight...............................................................................................................17

Antipsychotics & Weight..................................................................................................................18

Ms. Parker's Concerns.....................................................................................................................19

Poll: Switching Medications...........................................................................................................19

Discussing Options..........................................................................................................................20

Other Meds Associated With Weight Gain.....................................................................................20

Antihypertensives & Weight............................................................................................................21

Contraception & Weight..................................................................................................................21

Quiz: Meds To Avoid Weight Gain................................................................................................22

Weight-Loss Supplements and Over-the-Counter Medications......................................................23

Case: Ms. Perez and Meds with Weight Loss Side Effects.................................................................25
Quiz: Antidiabetes Meds and Weight Loss

Metformin and Weight Management in Non-Diabetics

GLP-1 Analogs and SGLT2 Effects on Non-Diabetics

Quiz: Weight-Loss Medications and Non-Diabetics

More Medications With Weight Loss Side Effect

Poll: Off-Label Use

Case: Mr. Akins and Potential Weight-Loss Treatments

Medications In Development

Manipulating Gut Microflora

Microflora and Comorbidities of Obesity

Case: Ms. Collins and Eating Disorders with Weight Gain

Ms. Collins: Eating Patterns & Plan

Binge Eating Disorder

Treating Binge-Eating Disorder

Other Eating Disorders

Ms. Collins Binge Eating

Lisdexamfetamine Overview/Indications

Other Lisdexamfetamine Effects

Poll: Would you prescribe?

Clinical Protocol Steps in This Module

Module Summary

Resources available through this module

References used in this module
Module 2

EFFECTS OF OTHER MEDICATIONS ON WEIGHT AND POTENTIAL FUTURE OBESITY TREATMENTS

Goal:
To prepare providers to evaluate patient medications for contributions to excess weight, select appropriate weight-neutral or weight-negative medications as replacements, treat conditions that may contribute to weight gain, and be aware of future potential directions for weight-loss treatment.

After completing this module participants will be able to:
• Evaluate medications commonly prescribed in primary care for whether they produce weight gain.
• Discuss with patients weight gain effects vs. therapeutic effects of common medications.
• Identify weight-neutral or weight-negative medications that could replace patients’ current weight-gaining medications.
• Recognize medications, currently prescribed for various conditions not directly related to obesity, that have weight-loss as a side effect.
• Be prepared to discuss with patients and follow the development of other potential future weight-loss treatments.
• Make informed choices about pharmacological treatment of eating disorders that contribute to weight gain.

Professional Practice Gaps
Evidence-based guidelines recommend use of weight-losing and weight-neutral medications and the avoidance of medications that contribute to weight gain in the management of various medical conditions in patients who are overweight or obese. For example, in the treatment of type 2 diabetes mellitus (Apovian et al., 2015). Clinicians should discuss possible weight effects of medications with patients.

Some medications used for other conditions may hold promise as potential weight-loss medications in the future. Many new medications have been approved by the FDA recently for use in weight-loss treatment.

Guidelines authors reported that weight-gaining medications are often prescribed even when weight-neutral or weight-losing medications are available (Apovian et al., 2015).

In our needs analysis survey of primary care providers (N=25), 88% said they needed further training regarding the use of pharmacotherapy in weight management, while 32% of providers were not confident with the use of pharmacotherapy in weight management (Tanner, 2011).
INTRODUCTION

Evaluating Medications for Weight-Gaining Properties

This module discusses a number of medications and treatments that support weight loss but are not approved by the FDA for that purpose, as well as some medications that actually cause weight gain.

- Many medications prescribed for conditions, such as diabetes mellitus and psychiatric diagnoses, can contribute to weight gain, which is important to recognize in patients with weight problems. Oftentimes, a weight-neutral or weight-losing medication can be substituted. (Mr. Perez and Ms. Parker case).
- Certain medications used to treat medical conditions other than obesity have a side effect of weight loss. Typically, the amount of weight lost is small. Some of these medications are being studied as potential weight-loss drugs for people who do not have the condition for which the medication is currently FDA approved. (Ms. Perez case).
- Many weight-loss medications and devices are in development or testing. We describe some of the more likely candidates. (Mr. Adkins case)
- There are some medications that are approved by the FDA for weight-related causes, but not for weight loss. We review when this is an appropriate alternative treatment method. (Ms. Collins case)

An important message in this module, in terms of current treatment of patients with weight problems, is avoiding medications that cause weight gain. The other sections of this module will help give you an idea of what weight-loss treatments you may see in the future. Some of your patients may get these treatments in other countries where they may be approved for weight-loss already.

Meet the Patients:
We will follow the story of the following patients to illustrate the effect of these medications on them:

MR. PEREZ
He has type 2 diabetes and obesity, and is in for a routine check-up
How can his diabetes medications be changed to reduce weight gain?

MS. PEREZ
Ms. Perez would like a metformin prescription to lose weight even though she does not have diabetes
Is this an FDA-approved use of metformin?
MS. COLLINS
Ms. Collins is not happy with the rate of her weight loss
Is medication a good adjunctive treatment for her at this time?

MS. PARKER
She has concerns about recent weight gain while being treated for depression
Might current antidepressants be contributing to her excess weight?

MR. AKINS
Mr. Akins would like to try a new weight-loss method he heard about
Is the new treatment available in the U.S.?

THINK AHEAD: OFF-LABEL USE
Think Ahead: Which of the following medications can produce weight loss, but is NOT FDA-approved for weight loss treatment in non-diabetics?

Choose one
1. Bupropion/Naltrexone
   - Feedback: Incorrect. This topic is discussed on Weight Losing DM Medications: Metformin.
2. Liraglutide
   - Feedback: Incorrect. This topic is discussed on Weight Losing DM Medications: Metformin.
3. Metformin
   - Feedback: Correct. This topic is discussed on Weight Losing DM Medications: Metformin.
4. Nortriptyline
AVOIDING MEDICATIONS THAT CAUSE WEIGHT GAIN

Medical Evaluation Protocol Step: Evaluate medications for weight-gain effects.

The Biology of Medication-Induced Weight Gain

Some medications used for treating various conditions predispose patients to gain weight (orexigenic). The biological mechanisms involved include the following:

- Decreased postprandial thermogenesis
- Increase appetite through CNS effects on satiety
- Increased fat deposition
- Increased blood sugar and insulin resistance
- Worsened dyslipidemia
- Fluid retention
- Lowered activity from sedative effects
- Decreased exercise tolerance due to fatigue

(Sharma et al., 2001; ADA et al., 2004; Ucok & Gaebel, 2008; Dal'Ava, 2012)

Classes of Medications That May Cause Weight Gain

Entire classes of medications may cause weight gain or just some medications within the group. The amount of weight gained varies, but can be a significant contributor to excess weight. Classes of medications that include at least some medications that cause weight gain include the following:

- Diabetes medications
- Psychotropic medications:
  - Antipsychotics
  - Mood stabilizers
  - Antidepressants
- Contraceptives
  - Antihypertensives
  - Antiepileptics
  - Antiretroviral
  - Corticosteroids
  - Sedating antihistamines

(Domecq et al., 2015)
CASE: MR. PEREZ AND WEIGHT GAIN MEDICATIONS

This case will illustrate how certain medications taken for diabetes can contribute to excess weight and how replacing them with other medications, if possible, can help reduce weight.

Meet Your Patient

Patient Name: Emiliano Perez Age: 56 y/o
Height: 6’1” Weight: 330 lbs BMI: 43.5 kg/m² Waist: 54”
BP: 120/80 Pulse: 85 Respiration: 18/min

Chief Complaint: Routine check-up

History of Present Illness: Mr. Perez has gained 7 pounds since being prescribed insulin plus a sulfonylurea (glipizide) for type 2 diabetes, 3 months ago by another doctor.

Medical History: Type 2 diabetes, GERD, dyslipidemia, high blood pressure, and gout.

Medications: Esomeprazole & cisapride (GERD), allopurinol (GOUT), enalapril (High blood pressure), and a sulfonylurea (glipizide) for type 2 diabetes.

Weight History: Weight has increased by 7 pounds in the few months since starting his diabetes medication. Diet: Follows the diet recommended for his diabetes with the exception of drinking about 8 beers a week.

Physical Activity Level: Low - very sedentary, no activity of at least moderate intensity.

Weight-Related Diagnosss: E66.01 Morbid Obesity; E65 Localized Adiposity (Central)

CASE OBJECTIVES

The learner will be able to:
- Describe the weight-gain effects of medications commonly prescribed in primary care.
- Discuss with patients weight-gain effects vs. therapeutic effects of common medications.
- Identify weight-neutral or weight-negative medications that could replace patients’ current weight-gaining medications.

DIABETES MEDICATIONS & WEIGHT

Mr. Perez

Mr. Perez is currently on a sulfonylurea (glipizide) for his type 2 diabetes.

Could his medication be affecting his weight?
Effect of Diabetes Medications on Weight
Weight loss is often more difficult for individuals with diabetes than for those without. Patients with type 2 diabetes often lose less weight than non-diabetics (Franz et al., 2007; Hollander, 2007). Because type 2 diabetes is so common among obese individuals, consider prescribing a medication that either promotes weight loss or is weight-neutral. Even with such changes in medication, remember lifestyle changes for diet and exercise are still needed to lose weight (Hollander, 2007). Keep in mind the individual patient's need for blood glucose control.

Weight-Losing Medications:
- GLP-1 agonists (Exenatide, liraglutide)
- Biguanide (Metformin)
- SGLT2 inhibitors (Canagliflozin, dapagliflozin, empagliflozin)
- Synthetic amylin analog (Pramlintide)

(Mayo Clinic, 2011)

Weight-Neutral Medications:
- Dipeptidyl peptidase-4 (DPP-4) inhibitors (Saxagliptin, sitagliptin, linagliptin)
- Alpha-glucosidase inhibitors (Acarbose, miglitol)

(Mayo Clinic, 2011)

Weight-Gaining Medications:
-Meglitinides (Repaglinide, nateglinide)
- Sulfonylureas (Glipizide, glimepiride, glyburide)
- Insulin

(Mayo Clinic, 2011)

PRACTICE TIP
The 2013 diabetes treatment algorithm by the American Association of Clinical Endocrinologists (AACE) proposed that weight-neutral or weight-reducing medications be selected earlier in the treatment decision process (Garber et al., 2013).

OBESITY GUIDELINES FOR DIABETES MEDICATIONS
Pharmacological Obesity Treatment Guidelines for Type 2 Diabetes
Treatment Protocol Step: Weigh risks vs. benefits of changing medications that promote weight gain and prescribe new medications as indicated.

GUIDELINES FOR PHARMACOLOGICAL MANAGEMENT OF OBESITY
The Endocrine Society's clinical guidelines for Pharmacological Management of Obesity made recommendations regarding medications used to treat type 2 diabetes and their effects on weight:
- For patients with type 2 diabetes who are overweight or obese, use of first and second-line medications that are weight-losing and weight-neutral for diabetes management.
• Discuss with patients needing glucose-lowering medications the possible weight effects and the use of antihyperglycemic medications that promote weight loss or are at least weight-neutral

(Strong Recommendations|Moderate Quality Evidence)

The guidelines for Pharmacological Management of Obesity also suggest the following for treating diabetes:

• For patients with type 2 diabetes mellitus who are overweight or obese, use antidiabetic medications that additionally promote weight loss (such as GLP-1 analogs or SGLT-2 inhibitors) in addition to the first-line agent for type 2 diabetes mellitus, metformin (Apovian et al., 2015).

• Add metformin, pramlintide, or GLP-1 agonists to offset insulin-associated weight gain in obese patients needing insulin therapy.

(Suggested Recommendations|Moderate Quality Evidence)

The guidelines further elaborate suggestions for patients requiring insulin, as described later in this section.

(Apovian et al., 2015)

WEIGHT-GAINING OR NEUTRAL DIABETES MEDICATIONS

Weight-Gaining Diabetes Medications

Insulin

Insulin is a highly effective agent at controlling serum glucose, but strongly associated with weight gain (Apovian et al., 2015). The Endocrine Society's clinical guidelines for Pharmacological Management of Obesity have recommended the following for patients with type 2 diabetes mellitus:

• In patients who are overweight or obese, in addition to metformin, use medications that promote weight loss, such as GLP-1 analogs or SGLT-2 inhibitors.

• In patients who are obese, the addition of at least one of the following weight-losing hypoglycemic agents, metformin, pramlintide, or GLP-1 agonists, to offset insulin-associated weight gain in obese patients needing insulin therapy. "The first-line insulin for this type of patient should be basal insulin. This is preferable to using either insulin alone or insulin with sulfonylurea. We also suggest that the insulin therapy strategy be considered a preferential trial of basal insulin prior to premixed insulins or combination insulin therapy."

(Suggested Recommendation|Moderate Quality Evidence)

(Apovian et al., 2015)

Sulfonylureas

Glipizide, glimepiride, and glyburide stimulate the pancreas to produce and secrete insulin. Sulfonylureas contribute to modest weight gain, and may cause hypoglycemia as a side effect. However, they are available as generic and are inexpensive.

(Mayo Clinic, 2011)
Glitozones
Pioglitazone and rosiglitazone are peroxisome proliferator-activated receptor gamma (PPAR) agonists that improve insulin sensitivity in skeletal muscle and hepatocytes.

Glitozones also lead to weight gain (via PPAR receptors on adipocytes-stimulating lipogenesis). They also increase adiponectin levels, though, and may worsen congestive heart failure and hepatotoxicity. There is a potentially significant increased coronary artery disease risk (rosiglitazone) and bladder cancer risk (pioglitazone).

(Richter et al., 2007; Nissen & Wolski, 2007)

Weight-Neutral Diabetes Medications
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
Sitagliptin and saxagliptin are weight-neutral (Apovian et al., 2015). They prolong the action of incretins (GLP1 and GIP) and are approved as monotherapy or add-on therapy for type 2 diabetes. They have an easy dosing regimen. The FDA has warned that this class of drugs may cause severe and debilitating joint pain (FDA, 2015).

WEIGHT LOSING DM MEDICATIONS: METFORMIN
Metformin (Biguanide)
Action: Reduces blood glucose

- **Effect on Weight:** Modest weight loss
  - Research: Given to obese women with non-insulin dependent diabetes mellitus for 24 weeks, metformin produced 8 kg more weight loss than placebo. Metformin produced relatively more reduction in appetite and calorie intake
    (Lee & Morley, 1998)
- **Other Advantages:**
  - Not associated with hypoglycemia
  - Improves disorders of fat pathophysiology ("adiposopathy") associated with obesity, such as: insulin resistance, polycystic ovarian syndrome, fatty liver, and cardiovascular disease
    - Associated with a 39% relative risk reduction in myocardial infarction and 36% relative risk reduction in all-cause mortality (Takeda Pharma., 2010)
  - Inexpensive
  - **Peripheral Mechanism:** Reduces hepatic glucose production and improves insulin sensitivity
  - **Side Effects:**
    - Common side effects: Nausea, vomiting, upset stomach, diarrhea, weakness, or metallic taste in mouth
    - Rare side effects: Lactic acidosis (symptoms: dizziness, severe drowsiness, muscle pain, or chills)

(Nasri & Rafieian-Kopaei, 2014)

- **Special Precautions/Contraindications:**
Renal impairment, with elevated serum creatinine levels (≥ 1.5 mg/dL in men and ≥ 1.4 mg/dL in women), or abnormal creatinine clearance

Discontinue use prior to procedures using contrast dye

May increase risk of vitamin B12 deficiency

(King, 1999)

Available as: A generic drug and as extended release tablet.

(Inzucchi et al., 2014; Malin & Kashyap, 2014; King, 1999)

WEIGHT-LOSING DM MEDICATIONS: GLP-1 ANALOGS

GLP-1 Analogs

Action: Reduces blood sugar.

Effect on Weight: Weight loss, decreased food intake

CNS Mechanism: Act directly on receptors in the hypothalamus (POMC neurons) and area postrema

Peripheral Mechanisms:
  - Simulate glucoregulatory actions of glucagon-like peptide-1 (GLP-1)
  - Enhance glucose dependent insulin release
  - Suppress inappropriate glucagon release
  - Delays gastric emptying

(Apovian et al., 2015)

Peripheral Mechanisms:

Indications: Treatment of diabetes. Require subcutaneous injections. They are an add-on therapy with metformin.

Side Effects:
  - Common side effects: Nausea, vomiting, diarrhea, dyspepsia, headache, hypoglycemia
  - Rare side effects: Hemorrhagic pancreatitis (symptoms: acute back pain or vomiting)

(Parker, 2014)

Special Precautions/Contraindications: History of pancreatitis, gastroparesis, severe renal impairment, creatinine 1.4 female/1.5 male

AVAILABLE AS:

Liraglutide: To improve glycemic control at a dose of 1.8 mg/day (FDA, 2013) as an adjunct to weight-loss diet and exercise for adults with type 2 diabetes mellitus (Drugs.com, 2000-2015). It is injected once daily and achieves goal A1C levels in the majority of patients.

Effect on Weight: Typically results in a modest weight loss of around 3 to 5% (Inoue et al., 2011). It also induces feelings of satiety.

Note: Also approved by the FDA for use in the treatment of obesity, even in patients who do not have diabetes, in another formulation (FDA, 2014).
• **Exenatide**: Injected twice daily 30 to 60 min prior to meals. Starting dose is 5 mcg for one month then increased to 10 mcg (Drugs.com, 2000-2015).
  - **Effect on Weight**: In a study with 330 metformin-treated diabetic patients for 30 weeks: Exenatide @ 10 mcg had a weight loss of 2.8 kg over placebo, exenatide 5 mcg had a weight loss of 1.6 kg over placebo. (DeFronzo et al., 2005)
• **Albiglutide**: A once weekly medication in this class approved by the FDA in April 2014 (Drugs.com, 2000-2015).

WEIGHT-LOSING DM MEDICATIONS: SGLT2 INHIBITORS

**Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitor**

**Action**: Lowers serum glucose

- **Effect on Weight**: Modest weight loss: It has an average of about 3-5% reduction initial body weight after 6 months. Clinical trials in patients with type 2 diabetes mellitus, up to 90 weeks long, have shown weight loss up to 4.7 kg (Barnett, 2013). Also decreases waist circumference. Weight loss is highest when blood glucose is highest. Weight loss stabilizes after a couple of weeks (Haas, et al, 2015).

**AVAILABLE AS:**

- Canagliflozin (Invokana®)
- Dapagliflozin (Farxiga™)
- Empagliflozin (Jardiance®)

(Valentine, 2012)

- **Peripheral Mechanism**: Blocks glucose reabsorption in the proximal convoluted tubule of the kidney (Barnett, 2013). Increases glucose excretion in urine.
- **Side Effects**: Include genital yeast infections, especially in women, urinary tract infections, dehydration resulting in dizziness and fainting, renal function decline.
- **Special Precautions/Contraindications**: Should not be used in patients with type 1 diabetes, in patients with increased ketones in their blood or urine, or patients with severe renal impairment, end-stage renal disease.

**CAUTION TIP**

The FDA has issued a warning that the use of SGLT2 inhibitors may lead to ketoacidosis. Patients being prescribed SGLT2 inhibitors should be closely monitored for symptoms of ketoacidosis, including difficulty breathing, nausea, and vomiting (FDA, 2015).

**Pramlintide**

Pramlintide (Symlin®) a synthetic amylin analogue for insulin-dependent diabetics is also weight-negative. One study found that, in non-diabetic patients, pramlintide significantly reduced calorie consumption at a buffet meal (Jones, 2007; Virji, 2007).

Amylin inhibits gastric emptying and inhibits glucagon. It reduces meal size and food intake. It has been shown to lower glucose and body weight in non-diabetics but has not been approved for these purposes (Kim et al., 2011).
**QUIZ: UNDERLYING BIOLOGY OF DIABETES MEDICATIONS**

Liraglutide is an agonist of the antihyperglycemic, anorectic gut hormone GLP-1. Based on this information, you can predict that a patient with type 2 diabetes mellitus taking liraglutide would most likely experience:

**Choose one**

1. Increase in A1C
   - Feedback: Incorrect! This medication does not cause an increase in A1C (Inoue et al., 2011).

2. Weight gain
   - Feedback: Incorrect. This medication usually results in weight loss (Inoue et al., 2011).

3. Increased feeling of fullness
   - Feedback: Correct! This medication tends to cause an increased feeling of satiety (Inoue et al., 2011).

4. All of the above.
   - Feedback: Incorrect. This medication is not linked to increases in A1C and weight gain (Inoue et al., 2011).

**POLL: CHANGE MR. PEREZ'S MEDICATION?**

Would you change Mr. Perez's diabetes medication to one that is more weight neutral or reducing?

1. Yes
   - 69% (67 votes)

2. No
   - 3% (3 votes)

3. I need more information
   - 26% (25 votes)

4. Unsure
   - 2% (2 votes)

Total votes: 97

**DISCUSSING OPTIONS**

**Change In Medication**

Guidelines for the pharmacological management of obesity recommend discussing with patients any weight effects of medications and the pros and cons of switching to another medication (Apovian et al., 2015).

**Provider:** The medication you are on, the sulfonylurea glipizide, does often cause weight gain. I'd like to try switching to metformin, which is not as likely to increase weight, and it tends to produce similarly good blood glucose control. In fact, it may even decrease your weight, which is very important for improving your diabetes.
Mr. Perez: That sounds good!

Surgical Considerations
Provider: Looking at your case, you also meet the qualifications for weight-loss surgery. Would that be something you’d be interested in getting a recommendation for?

Mr. Perez: No, I don't think I need to go to that extreme. The medications should help, right?

Provider: The medications may help with your weight, but other changes are necessary in order to reach and maintain a healthy weight. Would you like to talk about them now?

Mr. Perez: Sure. I really want to get my weight down.

The provider continues the dialogue to provide brief interventions intended to change Mr. Perez's diet and physical activity level to support weight loss. It is important for patients to understand that, even with medications that promote weight loss, the effect will be small. Patients will still need to adopt a comprehensive approach to weight loss.

DISCUSSING OPTIONS

Change In Medication
Guidelines for the pharmacological management of obesity recommend discussing with patients any weight effects of medications and the pros and cons of switching to another medication (Apovian et al., 2015).

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Mr. Perez: Sure. I really want to get my weight down.

The provider continues the dialogue to provide brief interventions intended to change Mr. Perez's diet and physical activity level to support weight loss. It is important for patients to understand that, even with medications that promote weight loss, the effect will be small. Patients will still need to adopt a comprehensive approach to weight loss.
CASE: MS. PARKER AND WEIGHT-GAIN MEDICATIONS

Antidiabetic medications are not the only class of medications that produce weight gain. This case will illustrate how certain antidepressants can contribute to excess weight. It will also illustrate how replacing them with other antidepressants can help reduce weight. In addition, we will look at other classes of medications that produce weight gain.

Meet Your Patient

Patient Name: Ruth Ann Parker  Age: 59 y/o  
Height: 5’2”  Weight: 165 lbs  BMI: 30.2 kg/m²  Waist: 36.5”  
BP: 123/89  Pulse: 80  Respiration: 19/min  
Chief Complaint: Concerned about current weight gain.

History of Present Illness: Has been gaining weight since starting a SSRI antidepressant. Has attempted weight-loss diet and exercise, but has difficulty controlling her appetite.

Medical History: Has been in relatively good health, however, she has a family history of depression. Diagnosed and prescribed an SSRI antidepressant 1 year ago.

Medications: SSRI antidepressant (Paroxetine).

Weight History: Slow weight gain since starting medication. Changes in diet have been unsuccessful for losing weight.

Physical Activity Level: Walks 5x per week, 30 min/day

Weight Related Diagnoses: E66.9 Obesity, unspecified; E65 Localized Adiposity (Central)

CASE OBJECTIVES

The learner will be able to:

- Describe the weight gain effects of medications commonly prescribed in primary care.
- Discuss with patients weight-gain effects vs. therapeutic effects of common medications.
- Identify weight-neutral or weight-negative medications that could replace patients’ current weight-gaining medications.

PSYCHOACTIVE MEDS & WEIGHT

Treatment Protocol Step: Weigh risks vs. benefits of changing medications that promote weight gain and prescribe new medications as indicated.

Ms. Parker

Ms. Parker is currently on the antidepressant paroxetine and thinks it might be causing weight gain. Could an antidepressant affect her weight?
A number of mental health medications have the potential to affect weight. The following medications will be highlighted and detailed throughout Ms. Parker's case.

- Antipsychotics
- Mood Stabilizers
- Antidepressants

ANTIDEPRESSANTS & WEIGHT

Some antidepressants cause weight gain or make it difficult to lose weight and a few antidepressants may be associated with weight loss. The weight effect profile for each antidepressant should be reviewed before prescribing.

Antidepressants with Weight Gain

**SSRI ANTIDEPRESSANTS**

SSRIs are not likely to cause weight gain short term if used less than 6 months. They are more likely to increase weight if used >1yr. Paroxetine is responsible for the most significant weight gain.

The SSRIs vary in weight-gain effect. For example, mean gain for these common SSRIs is:

- Sertraline: Weight neutral
- Citalopram: 1.5 kg weight gain
- Paroxetine: 14 kg weight gain

(Adams et al., 2008; Deshmukh & Franco, 2003)

**TRICYCLIC ANTIDEPRESSANTS**

Tricyclic antidepressants (TCAs) are very effective antidepressants that are strongly weight-positive, with the exception of nortriptyline which appears to be weight-neutral (Adams et al., 2008; Deshmukh & Franco, 2003).

**MONOAMINE OXIDASE INHIBITORS**

Monoamine Oxidase Inhibitors (MAOIs) that bind irreversibly to receptors (eg., phenelzine, isocarboxazid, tranylcypromine) typically cause weight gain, especially phenelzine (Deshmukh & Franco, 2003).

Antidepressants without Weight Gain

**BUPROPION (WELLBUTRIN®)**

Bupropion, an aminoketone antidepressant, may facilitate weight loss (Gadde et al., 2001). It is approved by the FDA in combination with naltrexone for weight management in obesity (FDA, 2014). It is also used for smoking cessation (Zyban®).
FLUOXETINE (PROZAC®)

Fluoxetine, a SSRI antidepressant, has been shown to promote weight loss for up to 6 months. However, following 6 months, it has not been shown to continue to facilitate weight-loss (Domecq et al., 2015; Yanovski & Yanovski, 2014).

NEFAZODONE

The antidepressant, nefazodone is also less likely to cause weight gain in long-term therapy (Deshmukh & Franco, 2003). It has multiple mechanisms of action, especially acting as 5-HT2A receptor antagonist and to a lesser extent, as a serotonin-norepinephrine reuptake inhibitor (SNDRI). Rare hepatotoxicity is a concern.

MOOD STABILIZERS & WEIGHT

Mood Stabilizers and Weight Gain

Some mood stabilizing drugs used to treat mania carry the risk of weight gain. A primary cause of medication-induced weight gain is increased appetite and cravings (Ruetsch et al., 2005). This can result from an interference in central nervous system functions that regulate energy balance.

Example Mood Stabilizer Medication Weight Effects

**HIGH TO MODERATE WEIGHT GAIN**

- **Lithium**: Weight gain (4.5-12 kg) occurs in 25% of patients over long-term treatment. Proposed mechanisms for weight gain include increased appetite, fluid retention, and subclinical hypothyroidism.
- **Valproic acid**: Weight gain (3-10 kg) occurs in 20-25% of patients over the course of 3-12 months. Valproic acid may also cause polycystic ovarian syndrome in women, which typically includes weight gain.
- **Carbamazapine**: Produces moderate weight gain in some patients.

(Carlat Psychiatry Report, 2008; Fink, 2008)

**LOW WEIGHT GAIN TO NEUTRAL**

- **Gabapentin**: Causes a mean weight gain of 0.9-3 kg in some patients after 12 weeks of treatment.
- **Lamotrigine**: No weight gain is produced.

(Carlat Psychiatry Report, 2008; Fink, 2008; Ruetsch et al., 2005)

**Recommended Alternative Medications**

Adding a medication that produces weight loss can help reduce medication-triggered increases in weight. For example, topiramate and metformin have been shown, in some instances, to reduce appetite and limit medication-related weight gain (Domecq et al., 2015; Fink, 2008).

Switching to a different medication to treat the condition may also achieve the same results with little or no risk of gaining weight (Fink, 2008).
ANTIPSYCHOTICS & WEIGHT
Antipsychotics often contribute to weight gain, including both first and second generation antipsychotics (Ucok & Gaebel, 2008).

The Evidence
- The weight gain from second-generation antipsychotics can be particularly dramatic; it is often rapid, producing up to 5 kg in the first 10 weeks of therapy (Allison & Casey, 2001).
- Weight gain from second-generation antipsychotics does not plateau, even after a year on a particular therapy (ADA et al., 2004). The weight gained is typically in the form of increased body fat.

Note that 80% of patients receiving atypical antipsychotics (AAP) increase their baseline weight by 7% (ADA et al., 2004).

Impaired glucose tolerance, type 2 diabetes mellitus, and obesity are more common in patients with psychiatric illness.

GUIDELINES FOR BETTER WEIGHT OUTCOMES
The Endocrine Society's clinical guidelines for Pharmacological Management of Obesity (Apovian et al., 2015) recommend the use of weight-neutral rather than weight-gaining antipsychotics when they are indicated. They also recommend making patients aware of the potential for weight gain with each medication prescribed and including patients in the decision-making.

For patients who need an antipsychotic that promotes weight gain, monitoring of BMI quarterly and weight management interventions have been recommended (Ucok & Gaebel, 2008). Interventions with a unit increase or more in BMI might also include considering a change in medication.

Example Weight Gaining Anti-Psychotic Medications
There is considerable variation in weight-gain effects of antipsychotics (ADA et al., 2004).

- A year at a typical dose of olanzapine can produce over 10 kg weight gain and lead to type 2 diabetes (Nemeroff, 1997).
- Other weight gaining antipsychotics include: aripiprazole, risperidone, haloperidol, clozapine, chlorpromazine, and quetiapine (Domecq et al., 2015; Monnelly et al., 2015; Ucok & Gaebel, 2008).

Recommended Alternative Medications
Weight neutral antipsychotics include: Ziprasidone) and Molindone (Monnelly et al., 2015; Ucok & Gaebel, 2008)

Sometimes trying a different form of the same medication, from one that is absorbed in the stomach to one that dissolves in the mouth, can reduce weight gain. For example, for olanzapine, changing to the oral disintegrating form, might reduce weight gain.

Although it is off-label, metformin or topiramate are sometimes added to offset the weight gain associated with atypical antipsychotics.
PRACTICE TIP

Compare the additional metabolic risk of weight gain and the potential for metabolic syndrome to the benefits of symptom improvement, before prescribing these medications.

MS. PARKER'S CONCERNS

The provider discusses with Ms. Parker her chief complaint, that she believes her antidepressant (the SSRI paroxetine) is causing weight gain.

**Provider:** I see from your records that you were prescribed the antidepressant, paroxetine, over a year ago and now have some concerns about the possible side effect of weight gain.

**Ms. Parker:** Yes. Even though I like that it has helped my depression, I think it's the reason I gained 15 pounds.

**Provider:** What makes you think it comes from the medication?

**Ms. Parker:** When I went on it, my appetite picked up a little and I craved more carbohydrates, especially in the past couple of months.

**Provider:** That antidepressant is an SSRI, which is typically not bad in terms of causing weight gain, but paroxetine does sometimes cause weight gain, especially after you have been on it a while.

PRACTICE TIP

With failed weight-loss attempts, re-evaluation for potential contributory factors, such as unusual stress or a new dietary habit, is important. Remember to consider that medical conditions and medications that cause weight gain and untreated psychological conditions may also contribute to the problem (Pistelli et al., 2009; Luppino et al., 2010; Sicat, 2014; Shlisky et al., 2012; WIN, 2013).

POLL: SWITCHING MEDICATIONS

What anti-depressant would you choose for Ms. Parker at this point?

1. Continue with paroxetine  
   - 4% (4 votes)
2. Switch to another SSRI  
   - 37% (37 votes)
3. Switch to a tricyclic antidepressant (TCA)  
   - 0% (0 votes)
4. Switch to bupropion  
   - 45% (45 votes)
5. Switch to nefazodone  
   - 0% (0 votes)
6. Switch to no antidepressant  
   - 4% (4 votes)
7. Not sure  
   - 10% (10 votes)

Total votes: 100
DISCUSSING OPTIONS

The provider discusses with Ms. Parker, her options for antidepressants as well as their weight effects.

**Provider:** Your antidepressant, paroxetine, could be contributing to your weight gain. We could switch to another antidepressant called fluoxetine (Prozac®), which is in the same class of antidepressants, the SSRIs, but usually causes less weight gain. Hopefully, it would have similar effects on your depression. It even helps a little with weight loss in some people. If that does not work, there are some other antidepressants we could try.

**Ms. Parker:** I would like to try that.

**Provider:** Okay, we will be monitoring your weight and depression and can adjust your prescription as needed.

OTHER MEDS ASSOCIATED WITH WEIGHT GAIN

"Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline" (Apovian et al., 2015) suggests other potential substitutions for medications that cause weight gain. The conditions described include the following:

**Anti-hypertensives and Contraceptives**

Certain medications in these categories contribute to weight gain and are discussed in detail on the following pages.

Other medications associated with weight gain include the following:

**Antiepileptics**

Many antiepileptic drugs, e.g., gabapentin and valproic acid, have potential for weight gain. Guidelines recommend making patients aware of this potential and including patients in the decision-making (Apovian et al., 2015).

**Antiretroviral Therapy**

Antiretroviral therapy typically lead to weight gain and fat mass redistribution (Apovian et al., 2015). Guidelines recommend monitoring patients and considering the cardiovascular risk of the weight gain.

**Steroids**

For patients with chronic inflammatory disease, consider the potential for weight gain with corticosteroids (Apovian et al., 2015). To avoid weight gain, nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs can be used when possible over corticosteroids.

**GERD and Ulcer Remedies**

Proton-Pump Inhibitors (PPIs) have been associated with a small weight gain. In one study, a mean gain in body weight of 2.2 kg was seen, compared to controls, in GERD patients over a period of 2 years (Yoshikawa, et al., 2009). This effect may be mediated through an effect on gut microbiota, as
evidenced by a trend toward less weight loss and higher abundance of obesity-associated gut flora obesity post bypass surgery in patients also taking PPIs (Ward et al, 2014).

**Allergy Remedies**
Guidelines suggest the use of antihistamines with less central nervous system activity (less sedation) to limit weight gain (Apovian et al., 2015).

**ANTIHYPERTENSIVES & WEIGHT**

**Beta Blockers Cause Weight Gain**
Beta-blockers increase body fat, resulting in weight gain of 1 to 3 kg in 6 months to a year. The mechanism appears to be through a decreased in basal metabolic rate, post-prandial thermogenesis, and exercise tolerance (Sharma et al., 2001; Wiysonge et al., 2007). Studies also show that beta blockers have relatively low or lack of cerebrovascular or renal disease benefit (Rosendorff et al., 2007). This was found in patients who do not have symptomatic coronary artery disease, history of myocardial infarction, or heart failure or who are elderly.

**Recommended Alternative Medications**
Anti-hypertensives that do not cause weight gain include the following:

- Angiotensin-converting enzyme inhibitor (ACE inhibitors) (e.g., Captopril, enalapril, etc.)
- Angiotensin II Receptor Blockers (ARBs) (e.g., Valsartan, losartan, etc.)
- Beta-3 agonists are being studied for anti-obesity indication
- Hydrochlorothiazide could be an alternative (though it can cause hyperuricemia and hyperglycemia) a consideration if the patient has metabolic syndrome, which is common. Furthermore, it guards against dehydration.
- Losartan or lisinopril

Note: ARBs and ACE inhibitors also reduce the development of diabetes and may protect from obesity-related nephropathy.

(Abuissa et al., 2005; White et al., 2011; Kumar et al., 2010)

**GUIDELINES FOR THE PHARMACOLOGICAL MANAGEMENT OF OBESITY**
The Endocrine Society's clinical practice guideline on the Pharmacological Management of Obesity (Apovian et al., 2015) recommends the following regarding drugs used to treat hypertension that potentially cause weight gain and their alternatives:

- "We recommend angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers rather than beta-adrenergic blockers as first-line therapy for hypertension in patients with type 2 diabetes mellitus who are obese. (Strong Recommendation|High Quality Evidence)"

**CONTRACEPTION & WEIGHT**

**Pharmacological Obesity Treatment Guidelines**
Due to weight gain with injectable contraceptives, the Endocrine Society's clinical practice guideline on the Pharmacological Management of Obesity (Apovian et al., 2015) suggests the following:
Prescribe oral contraceptives over injectable medications for female patients seeking contraception who have a BMI >30 or a BMI > 27 with comorbidities. They noted that the quality of the evidence is low, however, and also recommended discussing the choice with women and considering risks vs. benefits.

Methods Producing Weight Gain
Depo Shot: Weight gain from the depo shot (mean 6.2 kg) was 3.9 kg more than from oral contraceptives and 3.4 kg more than non-users in a long-term (5-year) trial of medroxyprogesterone acetate (Depo-Provera®) in adolescents (Beksinska et al., 2010).

IUD: In trials over twelve months, IUDs had the following weight and body mass effects:
- Levonorgestrel IUD: 2.9 kg gain (2.5% gain fat mass; 1.4% loss of lean mass)
- Copper IUD: 1.4 kg gain (1.3% loss fat mass; gain of 1% lean mass)
(Beksinska et al., 2010; Dal'Ava et al., 2012; Gallo et al., 2014)

Methods That Are Weight-Neutral
Oral contraceptives and contraceptive patches: While estrogen does cause weight gain, current oral contraceptives have much less estrogen than the ones that initially were shown to cause weight gain. Compared to a “dummy method”, current oral and patch contraceptives:
- Did NOT lead to additional weight gain over dummy method
- Did NOT lead to perception of additional weight gain
- Did NOT lead to significant discontinuation due to weight gain
(Beksinska et al., 2010; Dal'Ava et al., 2012; Gallo et al., 2014)

Guidelines
Guidelines recommend oral contraceptives over injectable medications for women seeking contraception and who have BMI ≥30 or ≥ 27 with comorbidities (Apovian et al., 2015). Risks and benefits should be considered as well.

PRACTICE TIP
When prescribing contraception, also consider the androgenic effects of progesterone, including dyslipidemia: 2nd generation, such as levonorgestrel, is most androgenic. 3rd generation, such as norgestimate, is non-androgenic.
(Beksinska et al., 2010; Dal'Ava et al., 2012; Gallo et al., 2014)

QUIZ: MEDS TO AVOID WEIGHT GAIN
Question 1 of 1
In patients who are obese and have type 2 diabetes, as well as hypertension, which medication is to be avoided?

Choose one
1. Angiotensin-Converting Enzyme (ACE) Inhibitors
   - Feedback: Incorrect. The Endocrine Society's clinical practice guideline on the Pharmacological Management of Obesity (Apovian, 2015) recommends the following
regarding drugs used to treat hypertension that potentially cause weight gain and their alternatives:

"We recommend angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers rather than beta-adrenergic blockers as first-line therapy for hypertension in patients with type 2 diabetes mellitus who are obese. (Strong Recommendation|High Quality Evidence)"

2. Beta-blockers
   - Feedback: Correct. The Endocrine Society's clinical practice guideline on the Pharmacological Management of Obesity (Apovian, 2015) recommends the following regarding drugs used to treat hypertension that potentially cause weight gain and their alternatives:

"We recommend angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers rather than beta-adrenergic blockers as first-line therapy for hypertension in patients with type 2 diabetes mellitus who are obese. (Strong Recommendation|High Quality Evidence)"

3. Angiotensin Receptor Blockers (ARBs)
   - Feedback: Incorrect. The Endocrine Society's clinical practice guideline on the Pharmacological Management of Obesity (Apovian, 2015) recommends the following regarding drugs used to treat hypertension that potentially cause weight gain and their alternatives:

"We recommend angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers rather than beta-adrenergic blockers as first-line therapy for hypertension in patients with type 2 diabetes mellitus who are obese. (Strong Recommendation|High Quality Evidence)"

4. Calcium Channel Blockers
   - Feedback: Incorrect. The Endocrine Society's clinical practice guideline on the Pharmacological Management of Obesity (Apovian, 2015) recommends the following regarding drugs used to treat hypertension that potentially cause weight gain and their alternatives:

"We recommend angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers rather than beta-adrenergic blockers as first-line therapy for hypertension in patients with type 2 diabetes mellitus who are obese. (Strong Recommendation|High Quality Evidence)"

WEIGHT-LOSS SUPPLEMENTS AND OVER-THE-COUNTER MEDICATIONS

Overview
Many patients use over-the-counter drugs or dietary supplements to support weight-loss. As many as 8.7% of the population used a weight-loss supplement in the last year (Blanck et al., 2007). Common motivations include trying to find something that will make weight-loss easier or make weight-loss efforts more
It is important for both patient and provider to know the ingredients associated with such products, safety/interactions, and effectiveness.

**Weight-Loss Supplements**
Although weight-loss supplements are regulated by the FDA, they are not approved by them as weight-loss medications. That is because, like other dietary supplements, they are not considered drugs. The manufacturers are responsible for making sure that the product is safe.

Not only do some ingredients in weight-loss supplement and products lack evidence for any effectiveness, but some have been associated with potential risks to the user. A wide variety of ingredients are found in weight-loss supplements. Only some of them have evidence to support possible effects on body weight. Evidence is typically only available for specific individual ingredients. The body of evidence supporting efficacy and safety is small; the effect is also typically small. Many products are combinations of ingredients, each having a mild effect on weight or folklore about such an effect. **Recommend that patients use caution because efficacy and safety are typically not well documented. Also, efficacy and safety may not be the same for a combination of ingredients as they are for each one individually.**

Be sure to ask patients about supplement use and consider whether there are known drug interactions. Keep in mind that many patients do not tell their health care providers about taking these supplements. Less than a third of patients who use supplements for weight-loss tell their providers about taking them (Blanck et al., 2007). You may have to ask patients explicitly to learn about dietary supplements for weight loss they may take.

**Examples of Weight-Loss Supplements**
- Garcinia Cambogia Extract
- Caffeine
- Rasberry Ketones
- Green Coffee Bean Extract
- Glucomannan
- Green Tea Extract
- Conjugated Linoleic Acid (CLA)
- Forskolin
- Bitter Orange

**Over-the-Counter Orlistat**
Orlistat is a weight-loss medication that is available in both prescription and over-the-counter preparations. In either formulation, like all weight-loss medications, it should be used in conjunction with lifestyle changes including exercise, diet, and behavioral support. The over-the-counter product dosage is 60 mg (alli®), which is about half of the prescription dose (Medscape, 2018). Some of the potential risks of Orlistat include:

- Adverse gastrointestinal function (diarrhea, flatulence)
- Drug interactions with:
  - Vitamins: Fat-soluble vitamins and beta carotene absorption may be reduced [medscapereference]
  - Cyclosporine, levothyroxine, amiodarone PO, antiepileptic drugs, antiretroviral drugs, and warfarin [medscapereference]

Check this product’s drug information page for more details.
CASE: MS. PEREZ AND MEDS WITH WEIGHT LOSS SIDE EFFECTS
This section talks about another group of medications: those that have weight loss as a side effect but are not approved for that purpose. This brief case describes a patient who is interested in this type of medication.

MS. PEREZ
Ms. Perez has learned that her father's diabetes medication has helped him lose weight and she wants a prescription for herself, even though she does not have diabetes.

CASE OBJECTIVES
The learner will be able to:

- Describe medications currently prescribed for various conditions that may have potential as weight-loss medications.

Medications used to treat various medical conditions that have weight loss as a side effect include:

- Naloxone (opioid antagonist)
- Bupropion (anti-depressant/smoking cessation)
- Several classes of anti-diabetes drugs (which were discussed earlier in this module)
  - Metformin
  - GLP-1 analogs*
  - SGLT2 inhibitors

But none of the above medications, *with the exception of the GLP-1 analog, liraglutide, have been approved by the FDA for weight loss. These medications may have the potential to be developed in the future for weight loss in patients who do not have the conditions for which they are currently approved.

GUIDELINES FOR OBESITY TREATMENT USING OFF-LABEL MEDICATIONS
Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline made the following recommendations with respect to the use of drugs, already approved for other indications, to treat chronic obesity:

- "3.1 We suggest against the off-label use of medications approved for other disease states for the sole purpose of producing weight loss. A trial of such therapy can be attempted in the context of research and by healthcare providers with expertise in weight management dealing with a well-informed patient. (Ungraded Best Practice Recommendation)"

(Apovian et al., 2015)
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QUIZ: ANTIDIABETES MEDS AND WEIGHT LOSS

Potential Medications
A number of medications being used to treat type 2 diabetes show potential as weight-loss medications, even in obese patients not having this diagnosis. In many instances, weight loss is greater in patients with pre-diabetes than patients with normal blood glucose (Napolitano et al., 2014; Seifarth et al., 2013). These medications include:

1. Metformin
2. GLP-1 analogs
3. Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Patient Experience
Ms. Perez: You recently prescribed my father metformin for his diabetes. He’s lost a lot of weight on the medication so I was wondering if I could get a prescription for metformin, too.
Provider: Why do you feel that you need a prescription for metformin? According to your records, you don’t have a diagnosis of diabetes.
Ms. Perez: I want to use it to lose weight, too.

Question: What would you say in response to Ms. Perez’s request?
Suggested Answer: I am sorry, but Metformin is not a drug that should be prescribed solely for weight loss.

METFORMIN AND WEIGHT MANAGEMENT IN NON-DIABETICS
In addition to reducing hepatic glucose production and improving insulin sensitivity, which is important for treating diabetes, metformin also induces modest weight loss.

Research on Metformin in Weight Management
Although metformin is only approved for treatment of type 2 diabetes mellitus, it has been studied as a weight-loss drug in adults and children, potential reducer of obesity-related comorbidities, and support of weight-loss maintenance.

RESEARCH IN OBESE/OVERWEIGHT ADULT NON-DIABETICS:
A few studies have looked at metformin and weight loss in adult non-diabetics.

- One trial found weight loss was significantly greater (p<0.0001) for metformin-treated adults (average weight change: -5.8 kg ±7) compared to no treatment controls (average weight change: +0.8 kg ±3.5) (Seifarth et al., 2013). Age, baseline BMI, and gender were not related to amount of weight lost.
  Weight loss was significantly greater in patients having more insulin resistance.

Note, however that based on a review of the evidence, The Canadian ask Force on Preventive Health Care’s Recommendations for prevention of weight gain and use of behavioural and pharmacological interventions to manage overweight and obesity in adults in primary care recommended the providers...
NOT routinely use metformin as a pharmacologic intervention for weight loss – Weak recommendation; moderate-quality evidence (Brauer P et al., 2015).

In obese non-diabetic children multiple clinical studies have shown that adding metformin to lifestyle changes results in significantly more mean reduction in weight than controls, but not enough to be clinically significant (McDonagh et al., 2013). The difference was greatest at 6 months, but was not significant at one year.

Benefits for Patients with Specific Conditions
Metformin also appears to:

- Help prevent type 2 diabetes mellitus
- Improve disorders of fat pathophysiology ("adiposopathy"), such as:
  - Insulin resistance
  - Polycystic ovarian syndrome
  - Cardiovascular disease (especially in comparison to sulfonylurea)
- Fatty liver
- Decrease weight gain from antipsychotics
- Improve HIV protease inhibitor-associated abnormalities, such as HIV lipodystrophy
- Decrease cancer rates and improve treatment response for certain forms of cancer (colon, ovary, lung, breast, prostate)

(Inzucchi et al., 2014; Malin & Kashyap, 2014)

GLP-1 ANALOGS AND SGLT2 EFFECTS ON NON-DIABETICS

GLP-1 Analogs and Obesity
THE GLP-1 ANALOGS were developed for treatment of type 2 diabetes mellitus. They are only effective if blood sugar is elevated (Parker, 2013), and also produce modest weight loss.

Effect on weight: The GLP-1 Analogs produce modest weight loss in diabetes and without diabetes. In fact, one GLP-1 analog, liraglutide, has been approved for use as an obesity treatment (FDA, 2014).

EVIDENCE
Effectiveness of liraglutide (3 mg) on weight loss was demonstrated in 3 multicenter studies in controlled trials with patients not having diabetes mellitus (FDA, 2014). Both groups were counseled to follow a calorie reduction diet and increase physical activity.

- Mean weight loss in the 1-year trials was 4.5% more than placebo (FDA, 2014).
- More patients on liraglutide lost at least 5% of their body weight than placebo (62% vs. 34%) (FDA, 2014).
- Cardiovascular and metabolic risk factors were improved more than placebo, including systolic and diastolic blood pressure, heart rate, and serum lipids (FDA, 2014).
- A subsequent study in non-diabetics found a slightly greater reduction in glycated hemoglobin, fasting glucose, and fasting insulin levels with liraglutide vs. placebo (Pi-Sunyer et al., 2015).
- Mean weight loss after 2 years on liraglutide was 7.8 kg in one study (Astrup et al., 2012).
• GLP-1 analogues also have shown promise as treatment for hypothalamic obesity in adults (Zoicas et al., 2013)

**Effect in Diabetes:** Liraglutide is also FDA-approved in a different product (Victoza®) to improve glycemic control in adults with type 2 diabetes mellitus (FDA, 2013). This product is an adjunct to the diet and exercise recommended for diabetes. Liraglutide is used at a different dose for diabetes from the one used in non-diabetics for weight loss.

**SGLT2 and Obesity**

**SODIUM-GLUCOSE CO-TRANSPORTER (SGLT2) INHIBITORS,** are a class of drugs used in the treatment of type 2 diabetes mellitus.

**Effect on weight:** Modest weight loss is seen with this medication in individuals with type 2 diabetes mellitus (Barnett, 2013). A decrease in abdominal circumference has also been reported. Weight loss is not seen with this medication in individuals not having diabetes, however. The reason is probably related to the drug's glucuretic effect (eliminating excess blood glucose via urine), which increases with higher blood sugar.

**EVIDENCE**

• SGLT2 inhibitors failed to demonstrate a difference between treatment and control groups in terms of weight loss or other changes in body mass in non-diabetics. However, in this study, taking SGLT2 was associated with an improvement in leptin/adiponectin ratio, which is related to insulin resistance. This suggests that SGLT2 inhibitors may hold promise in mitigating at least some metabolic effects of obesity (Napolitano et al., 2014).

**QUIZ: WEIGHT-LOSS MEDICATIONS AND NON-DIABETICS**

Which of the following medications shows the least promise as a weight loss drug for non-diabetics?

**Choose one**

1. Metformin
   • Feedback: Incorrect! This medication is linked to weight loss (Mayo Clinic, 2011).

2. A GLP-1 Analog
   • Feedback: Incorrect. These medications usually result in weight loss (Mayo Clinic, 2011).

3. A Sulfonylurea
   • Feedback: Correct! This medication is linked to weight gain (Mayo Clinic, 2011).

4. An SGLT2 Inhibitor
   • Feedback: Incorrect. This medication is linked to weight loss (Mayo Clinic, 2011).

**MORE MEDICATIONS WITH WEIGHT LOSS SIDE EFFECT**

**Stimulants**

As was discussed in the module on Biology and Pharmacotherapy, the sympathomimetic amine stimulants, such as Phentermine and Phendimetrazine are approved as anti-obesity medications (Bays et al., 2018). However, other medications having a stimulant effect that are being prescribed for
other reasons, may have a weight loss effect. For example, Adderall, which is approved for treatment of ADHD and narcolepsy, may produce weight loss, but is not approved for that purpose.

**Bupropion**

Bupropion is an antidepressant approved for treatment of both major depressive disorder and seasonal affective disorder (Drugs.com, 2000-2015). Bupropion is also used in formulation to help with smoking cessation.

**Effect on weight:** Bupropion tends to be weight-neutral or produce weight loss. In contrast, other antidepressants tend to produce weight gain or are weight-neutral. Bupropion is approved as a weight-loss medication in combination with naltrexone (FDA, 2014).

**EVIDENCE**

- In overweight to obese patients on a mildly restricted calorie diet, those patients on bupropion gradually increased to 200 mg bid lost significantly more weight (4.9% weight loss) than control patients not given bupropion (1.3% weight loss) (Gadde et al., 2001). Around 2/3 of patients on bupropion lost over 5% of their baseline weight compared to only 18% of control patients.

- **CNS Mechanism for Weight Loss:** Bupropion works centrally as an appetite suppressant (Gadde et al., 2001). Bupropion weakly inhibits reuptake of dopamine and norepinephrine, which activates POMC neurons in the hypothalamus (first order anorexigenic pathway) (Apovian et al., 2015).

**Naloxone**

Naloxone is an opioid antagonist (Drugs.com, 2000-2015). It is FDA-approved for use to reverse the effects of opioids.

**Effect on weight:** Naloxone is being investigated for treatment of overeating and obesity that is caused by the opioidergic system, which is responsible for binge eating disorder, a major cause of obesity (Lightlake Therapeutics, 2012). Some people, possibly from a genetic predisposition, become addicted to foods that release endorphins. Intranasal naloxone is being developed to treat this problem. There may also be some positive effect on depression and time spent thinking about binging.

**EVIDENCE**

- BMI decreased especially from week 12 to 24 (p=0.015) and in severe obesity in efficacy trials (Lightlake Therapeutics, 2012). Because naloxone is fairly short-acting, around 2 hours after intranasal application, the manufacturers propose it will not extinguish positive behaviors like exercise.

**PRACTICE TIP**

These medications are not approved purely for treatment of obesity. It is thus essential to know their current status (in process/approved or not approved) and communicate that status with your patients.
POLL: OFF-LABEL USE

Have you prescribed medications off-label for the treatment of obesity?

1. Yes, and will continue
   • 18% (16 votes)
2. Yes, but may not continue
   • 14% (12 votes)
3. No, and am not considering it
   • 45% (39 votes)
4. No, but am considering it
   • 23% (20 votes)

Total votes: 87

CASE: MR. AKINS AND POTENTIAL WEIGHT-LOSS TREATMENTS

This section talks about another group of weight-loss medications and treatments: those that are in development. In this brief case, the patient is interested in a weight-loss device that does not currently have FDA approval.

MR. AKINS

Mr. Akins heard about a new treatment for obesity that suctions food back out after you eat it. He would like to try this.

What do you know about this treatment? Is this currently available in the United States?

CASE OBJECTIVES

The learner will be able to:

- Describe other potential future weight-loss treatments.

Research Directions

Directions currently being explored in research that may lead to the development of new weight loss drugs or devices include the following:

- Blocking gut hormones responsible for producing hunger
- Stimulating gut hormones that reduce appetite or produce feelings of satiety
- Shrinking blood vessels that supply fat cells to prevent their growth
- Reducing cytokine production by abdominal adipose tissue
Impact Obesity v1

- Targeting genes that affect body weight
- Manipulating the gut microflora to control weight
- Combining drugs that affect appetite and addiction
- Electrical stimulation of the prefrontal cortex to improve control of eating (Gluck, et al, 2015) (WIN, 2013)

Obesity Treatment Devices with FDA approval (FDA, 2018):
- Electrical stimulation system
- Insertion of objects to fill up the stomach and produce a sensation of fullness. Several gastric balloon systems do have FDA approval.
- The FDA also has approved a device that uses suction to partially remove stomach contents after food has been consumed.

Research Examples
- Drugs that have combined actions are being explored in order to offset unwanted side effects from a single drug’s action. For example, in one drug being developed, a combination of glucagon and GLP-1 reduced appetite and led to weight loss. GLP-1 was added to protect against the hyperglycemic effect of glucagon (Cegla J et al., 2014).
- Animal research is looking at the impact of drug-activated genes on obesity and some research has successfully modulated metabolic activity affecting weight (Chrysovergis et al., 2014). Further testing on the relevance to human biological change is warranted.

MEDICATIONS IN DEVELOPMENT

A number of weight-loss drugs are currently under review or in testing for potential FDA approval. They target different biological mechanisms affecting weight and have shown varying efficacy.

Lipase Inhibitor
Cetilistat is under review in Japan to be used for weight loss (Sheridan, 2014). It has already been approved for Japanese patients who are obese and have both dyslipidemia and type 2 diabetes (Hainer, 2014). In trials for weight loss, the medication was seen to provide an overall weight reduction of 2.8% in patients versus a 1.1% reduction in those taking the placebo (Sheridan, 2014).

Peptide-Based Melanocortin-4 Receptor Agonist
RM-493 as an individualized treatment has not recorded 1-year efficacy for weight loss yet but is currently in Phase 2 of testing (Sheridan, 2014). Testing in mice as a combination therapy with RM-493 and the weight loss/diabetes medication, liraglutide, has shown initial promise. The subjects had enhanced control of both glycemic and cholesterol metabolism, as well as an improvement in overall body mass (Clemmensen et al., 2015).

Methionine Aminopeptidase 2 Inhibitor
Fexaramine is a medication in development that is absorbed in the gut, as opposed to the bloodstream like many weight-loss medications. It is meant to create signals in the body that mirror those experienced when consuming a large meal (Salk Institute, 2015). Fex has undergone testing in
mice, to determine the effect the medication may have on obesity, and has been met with success. Initial testing showed that Fex helps to limit the production of hepatic glucose, as well as encourage the browning of white adipose tissue (Fang et al., 2014).

**FXR Agonist**

Fucoxanthin, a carotenoid derived from plants, induces activity of an uncoupling protein (UCP1) found in abdominal adipose tissue. UCP1 induction produces fatty acid oxidation and heat in white adipose tissue (WAT), which may contribute to weight loss. Fucoxanthin also improves insulin resistance and decreases blood glucose by regulating WAT cell cytokine secretion. Fucoxanthin may be developed in the future as a nutritional additive for weight-loss treatment (Gammone & D’Orazio, 2015).

**MANIPULATING GUT MICROFLORA**

**The Microbiome**

Bacteria regularly live in the gut and are often referred to as the microbiome. They are important for metabolizing nutrients, synthesizing vitamin K, fermenting sugars, digesting cellulose, promoting angiogenesis, and supporting the function of nerves in the gut (Bays et al., 2017). There are over 1000 species, primarily anaerobic.

The intestine has two major phyla:

- Bacteroidetes - gram negative - These appear to assist with epithelial cell maturation and function.
- Firmicutes - gram positive. These may be more efficient at extracting calories from otherwise indigestible carbohydrates.

**Relationship of Gut Microflora to Obesity**

The microflora of obese individuals differs from that of lean individuals in its composition (Hullar & Lampe, 2013). On average the gut microflora in obesity has less diversity. Furthermore, obesity is associated with more firmicutes and bacteroidetes (Bays et al., 2017). Thus, the microorganisms found in the intestines of people who are obese appear to be more efficient at extracting energy from foods that are less digestible (Hansen et al., 2015).

Prebiotics promote growth of certain bacteria and can be ingested to promote the growth of gut flora. Some have the potential to produce weight loss (Hansen, 2015). This is achieved by increasing satiety through the production of short chain fatty acids, and decreasing appetite, in mice (Cani et al, 2009).

Probiotics are live bacteria and can be ingested to change the composition of gut flora (Hansen, 2015). Most probiotics are gram-positive Lactobacillus and Bifidobacterium.

**EVIDENCE**

Although a number of studies have found a relationship between gut flora and obesity (Turnbaugh et al., 2009; Schwiertz et al., 2010), results identifying a problematic type of microflora have been
inconsistent. Research has since found differences in microflora metabolic pathways (Hullar & Lampe, 2013; Harstra et al., 2014). Meta-analysis revealed it is not which microbes, but the genetic makeup of those microbes that correlates with obesity (Pollard, 2015). Genetic differences in gut microflora affect their metabolism of sugar and fat.

**Modifying gut flora as a treatment for metabolic syndrome?** The makeup of gut flora can be modified to some extent by several means, most of which, thus far, have been more effective at producing metabolic changes than weight loss (Hansen et al., 2015):

- Prebiotics, which stimulate the growth or activity of specific gut microorganisms, have been used to alter gut flora and produce weight loss. They have been shown to affect the composition of the gut microflora in rodent and human studies and have reduced both energy intake and body weight (Hansen et al., 2015).
- Diet changes, such as limiting foods high in phosphatidylcholine or carnitine, have been effective in changing gut flora composition, impacting the metabolic profile in humans (Hansen et al., 2015).
- Fecal transplants, like probiotics, in humans, so far have shown the most promise in altering the metabolic profile rather than weight loss (Harstra et al., 2015; Hansen et al., 2015).
- Weight loss surgery (Roux-en-Y and Vertical Sleeve Gastrectomy) has been shown to shift the gut microbiome (Tremaroli V et al, 2015). The surgically altered microbiome reduced fat deposition in mice when it was transferred to them.

**MICROFLORA AND COMORBIDITIES OF OBESITY**

**Mechanisms for Comorbid Effects**

The metabolites of certain microflora affect host metabolic and intestinal health through the following pathways: increased mucosal permeability and inflammation and changes in immune function and bile acid homeostasis (Hansen et al., 2015). Reduced diversity of the gut flora is associated with obesity, low-grade inflammation, insulin resistance, and dyslipidemia. A causal role is not definitely established. Some animal research found that high triglyceride diet in animals let to microbiota change that led to metabolic toxemia, the onset of inflammation and insulin resistance (Everard et al, 2014).

Microbiota in the gut also promote an increase in body fat via alterations in:

- bile acid metabolism that affect glucose and lipid metabolism
- gut hormones by reducing thermogenesis and impairing satiety (Bays et al., 2017).

Prebiotics which promote the growth of certain gut bacteria, can reduce insulin resistance and hyperglycemia. This effect is mediated through changes in gut hormones, and reducing endotoxemia by improving the intestinal barrier and reducing inflammation (Hansen et al, 2015; Everard et al, 2014).
Probiotics, which are live bacteria that can be used to change gut flora, have been shown to improve the metabolic profile in murine models, as well as humans to some extent (Hansen et al., 2015). Only certain probiotics are effective. Most probiotics are gram-positive Lactobacillus and Bifidobacterium.

**Examples of Comorbidities Affected**
Causality is not absolutely established, but the gut microbiome composition and function is changed in obesity, cardiovascular disease and type 2 diabetes (Hansen et al., 2015). Basic science research suggests possible mechanisms:

- **Atherosclerosis**: Intestinal microbiota have also been implicated in obesity comorbidities, including atherosclerosis (Koeth et al., 2013; Tang et al., 2013). The composition of intestinal flora is modified by choline derived from eating red meat, egg yolks, dairy products, and other foods high in phosphatidylcholine or carnitine (Hansen et al., 2015). Choline is metabolized to trimethylamine-N-oxide (TMAO), which promotes atherosclerosis (Koeth et al., 2013; Tang et al., 2013). TMAO is produced by particular gut microorganisms and is suppressed by antibiotics, supporting the theory that gut flora are involved in the process.

- **Insulin resistance**: Transplanting fecal microbiota from lean donors into males with metabolic syndrome, improved insulin sensitivity and increased microbial diversity. Butyrate-producing bacterial strains were increased with this treatment and are decreased in type 2 diabetes (Harstra et al., 2015). Butyrate is involved, in producing satiety and in the integrity of the intestinal barrier. More research is underway on this and other aspects that might be manipulated to reduce type 2 diabetes.

**CASE: MS. COLLINS AND EATING DISORDERS WITH WEIGHT GAIN**

**Medical Evaluation Protocol Step:** Evaluate eating disorders contributing to weight gain (depression and anxiety, binge eating, night eating).

**Treatment Protocol Step:** Treat eating disorders contributing to weight gain (depression and anxiety, binge eating, night eating).

Binge eating and night eating disorders have been shown to benefit from counseling, especially cognitive-behavioral approach. Additionally, a number of pharmacological treatments have been shown to be effective for these disorders and will be presented in this case. A medication was approved by the FDA in 2015 for treating this disorder. The following case describes a patient who has been counseled in primary care to make lifestyle changes for weight loss. She has made changes in both her diet and physical activity level. During counseling, the provider discovers that she has binge eating disorder.

**Patient Name:** Rebecca Collins  **Age:** 45 y/o
Height: 5' 5"  Weight: 290 lbs  BMI: 48.3 kg/m²  Waist: 41"
BP: 126/80  Pulse: 90  Respiration: 18/min

Chief Complaint: Concerns about weight issues.

History of Present Illness: Dyslipidemia has been fairly well-controlled with atorvastatin for the past 4 years. Has not mentioned concerns about weight.

Medical History: Hypertension, controlled with medications. A family history of hypertension (mother) and high cholesterol (father). Previous lab results showed the following:

Lab Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>218 mg/dL *Borderline high (below 200 mg/dL ideal)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>30 mg/dL *Low (60 mg/dL and above ideal)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>158 mg/dL *Borderline high (below 100 mg/dL ideal)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>154 mg/dL *Borderline high (below 150 mg/dL ideal)</td>
</tr>
<tr>
<td>Total Cholesterol to HDL-D Ratio</td>
<td>7.3:1 *High</td>
</tr>
<tr>
<td>Fasting Serum Glucose</td>
<td>98 mg/dl (High normal)</td>
</tr>
</tbody>
</table>

Medications: Lovastatin 20mg 1x/daily for dyslipidemia; Enalapril 10mg 2x/daily for hypertension.

Weight History: Weight has varied within a 30 lb range during the past decade. Prior weight loss attempts have been unsuccessful long-term.

Physical Activity Level: Walking 20 mins/day, 6x/week

Weight Related Diagnoses: E66.01 Severe Obesity; E65 Localized Adiposity (Central)

CASE OBJECTIVES
The learner will be able to:

- Make informed choices about pharmacological treatment of eating disorders that contribute to weight gain.

MS. COLLINS: EATING PATTERNS & PLAN

Screening Protocol Step: Evaluate for problematic eating patterns.

After a discussion about food choices, the provider asks Ms. Collins about her eating patterns:

Provider: Sometimes it helps to look for patterns of eating. Tell me about when you normally eat meals or snacks.

Ms. Collins: I snack a lot during the day, because my job is very stressful.

Provider: Could you try some other response to stress, such as deep breathing or getting up and moving once an hour to clear your mind and so the stress doesn't build up in your body?
Ms. Collins: I'll have to think about that. I think the stress does build up, though. When I get home I binge on whatever I can find, sometimes two day's worth of food all at once. I can't seem to stop.

Provider: How often do you find yourself eating a lot all at once like that?

Ms. Collins: Embarrassed to say, but at least 2 or 3 times a week. Sometimes more. I also binge on weekends, too, when I can relax, so it's not just from stress.

BINGE EATING DISORDER
Prevalence of Binge-Eating Disorder

Binge eating disorder (BED) is common among people who are obese, affecting between 15% and 50% of obese patients (Myers & Wiman, 2014; WIN, 2013). Therefore, it is important to understand this disorder well enough to screen for it and make referrals for treatment as needed.

Characteristics of Binge Eating Disorder
Binge-eating disorder, or BED, is described in the DSM-5 as:

- Recurring episodes of eating significantly more food in a short period of time than most people would eat under similar circumstances
- Episodes marked by feelings of lack of control
- Someone with binge eating disorder may eat too quickly, even when not hungry
- The person may have feelings of guilt, embarrassment, or disgust and may hide binging behaviors
- Characterized by marked distress
- Occurs, on average, at least once a week over three months

Episodes of binge eating are not followed by fasting, excessive exercise, or purging, unlike bulimia nervosa.

(APA, 2013; Myers & Wiman, 2014)

People with BED report more health problems, sleep trouble, stress, and suicidal thoughts than people who do not have an eating disorder (WIN, 2013).

TREATING BINGE-EATING DISORDER
Treatment Protocol Step: Recommend changes in dietary patterns that will support weight-loss and help stop weight gain.

Provider: It looks like this pattern of binge eating is probably making a significant contribution to your excess weight. Counseling is often an effective way to treat binge eating. Would you like to hear more about that option?

Ms. Collins: I could use some support with this, but isn't there just some drug I could take?
Provider: The one medication approved to treat binge eating has a high potential for addiction and some health risks for the heart. Because you have some cardiovascular health risks, I'd like to avoid prescribing it until other options have been explored. Psychological treatment appears to be just as effective as the medication, so I'd recommend seeing a psychologist specializing in this area first.

Ms. Collins: Okay, if you think it will help.

TREATMENT FOR BED often involves a combination of common treatment methods and depends on the needs of the individual. To reduce or eliminate binge-eating behaviors, a patient may undergo psychotherapy, such as Cognitive Behavioral Therapy, nutritional therapy, or be prescribed medication (WIN, 2013). Counseling, particularly cognitive behavioral therapy (CBT) has been shown to be effective at improving binge eating (Berkman et al, 2015).

Counseling: CBT has been shown to help improve the different aspects of binge eating, that is:

- Increasing abstinence
- Decreasing the frequency of binge eating
- Reducing eating-related obsessions

(Berkman et al, 2015)

CBT helps patients to focus on their current problems and how to address and solve them by changing their thoughts to more productive ones. This involves learning how to identify distorted or detrimental thinking patterns, recognizing and changing inaccurate or damaging beliefs, relating to others in a positive manner, and ultimately changing behaviors. CBT is particularly effective in BED patients (Murphy et al., 2010).

Pharmacotherapy: Lisdexamfetamine (Vyvanse®) is a central nervous system stimulant that has been approved by the FDA to treat binge eating disorder (FDA, 2015; Shire US Inc., 2015). It has shown to reduce the number of binge eating days. It was previously used to treat ADHD, but studies have shown that it can also be used for BED. It is the first FDA-approved medication specifically for this disorder. However, along with lisdexamfetamine, second-generation antidepressant medications and topiramate have also been shown to be effective at addressing the major characteristics of binge eating (Berkman et al, 2015).

Antidepressants also may be effective for treating co-occurring anxiety or depression (NIMH, 2011).

OTHER EATING DISORDERS

Other types of eating disorders that are comorbid with obesity fairly frequently include bulimia nervosa and night eating syndrome. People with bulimia are often normal weight and a minority are obese. A familiarity with these conditions will facilitate recognizing them and making appropriate referral.

BULIMIA NERVOSA is characterized by recurrent inappropriate compensatory behaviors to prevent weight gain, such as self-induced vomiting. Bulimia nervosa primarily affects women (90%) between the ages of 16-22. Of bulimic patients, 80% are within a normal weight; however, bulimia nervosa does occur in the obese as well (Harrington et al., 2015; Sim et al., 2010).

NIGHT EATING DISORDER is a combination of an eating disorder, sleep disorder, & mood disorder. It is characterized by consuming 25-50% of daily calories, typically high in carbohydrates, after the
evening meal. Risks for night eating disorder include obesity (6-14%), patients seeking bariatric surgery (8-24%), and being female (3:2 ratio) (Vander Wal, 2012; 2014; Allison et al., 2006).

TREATMENT FOR OTHER EATING DISORDERS

**Bulimia Nervosa**
- Cognitive Behavioral Therapy (CBT).
- SSRI antidepressants or in combination (superior).
- Avoid bupropion due to risk of seizures.

(Harrington et al., 2015; Sim et al., 2010)

**Night Eating Syndrome**
- Highly responsive to sertraline (Zoloft).
- Encourage regular meal consumption earlier in daytime.
- Increase protein in patient's diet.

(Vander Wal, 2012; 2014; Allison et al., 2006)

**MS. COLLINS BINGE EATING**

Ms. Collins returns for a follow-up weight management appointment for chronic obesity.

**Provider:** How have you been doing since our last appointment?

**Ms. Collins:** I've been seeing the psychologist, which has been helping me. I've been diagnosed as having binge eating disorder, but I haven't been able to get it under control yet. I'll do well for a while, but then I binge when my stress levels rise.

**Provider:** It can be difficult to address binge eating, and you might have some setbacks where you lapse back into old eating patterns during certain periods.

**Ms. Collins:** I know, but I think the frequent lapses are really starting to affect my recovery. I saw that there's a medication called Vyvanse® that could help me, though. Do you think I could get a prescription for that?

**LISDEXAMFETAMINE OVERVIEW/INDICATIONS**

**Lisdexamfetamine**

**Action:** Lisdexamfetamine is a central nervous system stimulant that is FDA-approved to treat Binge Eating Disorder (BED) in adults (FDA, 2015; Shire US Inc., 2015); it is also used to treat ADHD. It may help to reduce the number of binge eating days.

- **CNS Mechanism:**
  Lisdexamfetamine is a prodrug of dextroamphetamine. Amphetamines block the reuptake of norepinephrine and dopamine into presynaptic neurons and increase the release of monoamines into the extraneuronal space.
  (Shire US Inc., 2015)

- **Dosage:**
  Recommended starting dose is 30 mg once daily, adjusted in increments of 20 mg at weekly intervals to reach the recommended target dose of 50 to 70 mg/day (Shire US Inc., 2015).

- **Advantages:**
  Reduced weekly binge eating days in patients with moderate to severe BED (Shire US Inc., 2015).
• **Disadvantages:**
  Lisdexamfetamine is a federally controlled substance because it is highly addictive. It is not approved for weight loss (Shire US Inc., 2015).

**EVIDENCE**
Two randomized, double-blind, parallel-group and placebo-controlled studies evaluated the efficacy of lisdexamfetamine. Adults aged 18-55 years with moderate to severe BED (Study 10: N=374, Study 11: N=350) were given 30, 50, and 70 mg/day doses or a placebo for 12-weeks.

- Participants on lisdexamfetamine had a statistically significant reduction from baseline in mean number of binge days per week.
- Those on lisdexamfetamine also showed greater improvement as compared to the placebo users across key secondary outcomes, including a larger reduction on an obsessive-compulsive scale modified for BED.

(Shire US Inc., 2015)

**OTHER LISDEXAMFETAMINE EFFECTS**

**Side Effects and Risks**
Common side effects include (Based on 30 mg/70 mg Total Daily Dose):

- Dry mouth (36%)
- Insomnia (20%)
- Decreased appetite (8%)
- Increased heart rate (7%)
- Restlessness (2%)
- Anxiety (5%)
- Weight loss (4%)
- Hyperhidrosis (4%)
- Abdominal pain (2%)
- Vomiting (2%)
- Gastroenteritis (2%)
- Diarrhea (4%)

***Information on this page is not a comprehensive list of side effects, contraindications, or precautions. This partial list was up to date as of February 2015. For the most up-to-date information, view the medication's latest package insert.***

**Contraindications**

- Monitor patients with pre-existing symptoms of psychosis or mania. May cause psychotic or manic symptoms in patients with no preexisting history (Shire, 2015).
- Contraindicated with allergies/known sensitivity to amphetamines or other stimulants (Shire, 2015).
- Contraindicated with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease (Drugs.com, 2015).
- The drug can pass into breast milk and may harm a nursing baby (Drugs.com, 2015).
**Special Precautions/Drug Interactions**

- Bupropion: Concurrent use increases the risk of seizures, especially at higher doses. (Shire, 2015)
- Monitor patients for peripheral vasculopathy, including Raynaud's phenomenon (Shire, 2015).
- Avoid if monoamine oxidase (MAO) inhibitors have been taken within the past 14 days (Shire, 2015; Drugs.com, 2015).
- Acidifying, including fruit juices or vitamin C, can decrease blood levels while alkalinizing agents can increase blood levels (Shire, 2015).

**POLL: WOULD YOU PRESCRIBE?**

Like 30% of obese patients, Ms. Collins has binge eating disorder. Based on the information you've seen, would you prescribe lisdexamfetamine for her?

1. Would prescribe  
   - 20% (19 votes)
2. Might prescribe  
   - 57% (54 votes)
3. Would not prescribe  
   - 23% (22 votes)

Total votes: 95

**CLINICAL PROTOCOL STEPS IN THIS MODULE**

The following Clinical Protocol Steps for patients with obesity were illustrated in this module:

**Medical Evaluation**

- Evaluate medications for weight gain effects.
- Evaluate psychological disorders contributing to weight gain (depression and anxiety, binge eating, and night eating).

**Lifestyle Screening and Assessment**

- Evaluate for problematic eating patterns.

**Treatment**

- Weigh risks vs. benefits of changing medications that promote weight gain and prescribe new medications as indicated.
- Treat psychological disorders contributing to weight gain (depression and anxiety, binge eating, and night eating).
MODULE SUMMARY

Medications Contributing To Weight Gain
Medications may contribute to weight gain through a variety of mechanisms, including effects on satiety, thermogenesis, adipocyte function, insulin resistance, dyslipidemia, fluid retention, sedation, and fatigue. Certain medications in the following classes may cause weight gain:

- Diabetes medications
- Contraceptives
- Psychotropic medications
- Anti-epileptics
- Beta blockers
- Steroids
- Anti-retroviral medications

Patients who are taking medications in the above categories, should be evaluated for whether their current medications are contributing to excess weight. If so, consider whether viable alternatives are available that would stabilize or even reduce their weight.

Medications with Weight Loss as a Side Effect
Some medications used to treat other conditions even produce weight loss as a side effect, and may be a good choice for people who have those conditions and obesity. They also are being explored as weight loss medications in many instances. However, they have not been approved by the FDA specifically for weight loss, except the GLP-1 analog, liraglutide. Examples include:

- Naloxone (opioid antagonist)
- Bupropion (anti-depressant/smoking cessation)
- Anti diabetes drugs: Metformin, GLP-1 analog, SGLT2 inhibitors

Potential Future Treatments
There are a number of treatments in the research phase promoting weight loss involving the following mechanisms:

- Blocking gut hormones responsible for producing hunger
- Stimulating gut hormones that reduce appetite or produce feelings of satiety
- Shrinking blood vessels that supply fat cells to prevent their growth
- Targeting genes that affect body weight
- Manipulating the gut microflora to control weight
- Combining drugs that affect appetite and addiction
- Manipulating gut microflora through diet or transplant
- Reducing stomach size through balloon devices to partially fill the gastric space
- (WIN, 2013)

There are also treatments that can lead to weight loss though they are not approved for that purpose. Be sure to clarify the difference for your patients.
RESOURCES AVAILABLE THROUGH THIS MODULE:

- **Effect of Diabetes Medications on Weight**
  The following resource is intended to give providers a quick tool for comparing various diabetes medications effect on weight. The information on this page is not intended to serve as a comprehensive list of all diabetic medications effects. This resource was up to date as of May, 2015. For the latest and most complete information, view the medication’s latest package insert.

- **Lisdexamfetamine dimesylate Medication Guide**
  A guide to the medication lisdexamfetamine dimesylate containing instructions on how to take the medication, information about potential side effects, and other important aspects of the drug.

- **Screening Form - Questionnaire on Eating and Weight Patterns**
  Form used to evaluate for binge eating disorder

REFERENCES USED IN THIS MODULE:

**Practice Gap References**


**Module Content References**


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