MEDICAL MANAGEMENT OF PATIENTS
WITH OBESITY

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MEDICINE
Disclosure Statement:

I W. Jeffrey McDaniel MD, DO NOT have a financial interest/ arrangement of affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation
Goals:

1. Recognize that obesity is a multifactorial disease of epic proportion

2. We have to take a comprehensive chronic disease state model of treatment if we are going to find better results for our patients

3. Recognize medications that promote obesity and recommend alternatives

4. Become more familiar with anti-obesity medications, their indications contraindications

5. Improve outcomes!!!!
Obesity Prevalence in United States Adults 2015:
Centers for Disease Control and Prevention:

Accessed September 2017
• No state has <20% prevalence
• 3 states and the District of Columbia prevalence 20-25%
• 22 states have a prevalence of obesity between 25-30%
• 20 states have a prevalence between 30-<35%
• 5 states (Alabama, Arkansas, Louisiana, Mississippi, and West Virginia) have a prevalence of 35% or greater
• The South has the highest prevalence of obesity (32.0%), followed by the Midwest (31.4%), the Northeast (26.9%), and the West (26.0%)
Obesity Crisis versus Opioid Crisis

**OBESITY EPIDEMIC**
- *1.4 TRILLION DOLLARS/YEAR! (750X THE COST OF OPIOID EPIDEMIC)*

**OPIOID EPIDEMIC**
- 55 BILLION DOLLARS/YEAR IN HEALTH AND SOCIAL COSTS RELATED TO PRESCRIPTION OPIOID ABUSE

Milken Report; https://www.samhsa.gov/atod/opioids
Obesity Trends in % those with BMI>30 age 20-74 (Our Future???)

Prevalence of Obesity Among U.S. Adults Aged 20-74

Derived from NHANES data (http://www.cdc.gov/nchs/data/hestat/obesity_adult_09_10/obesity_adult_09_10.html#table1)

NHANES data: http://www.cdc.gov/nchs/data/hestat/obesity_adult_09_10/obesity_adult_09_10.html#table1
Few People with Obesity are Treated in the U.S.

~80 million adults with obesity

<1% receive a prescription (Rx) for Anti Obesity Medication in a given month

~195,000 people per year receive bariatric surgery

Treatment
Medical Management and Coordination

- Nutrition
- Physical Activity
- Behavior Therapy
- Pharmacotherapy
- Bariatric Surgery
• Treat adipocyte and adipose tissue dysfunction, which treats sick fat disease (SFD or adiposopathy)

• Treat excessive body fat, which treats fat mass disease (FMD)

• Treating diseases due to increased body fat and its adverse metabolic and biomechanical consequences may improve patient health, quality of life, body weight, and body composition
Conditions that may promote fat mass gain:

**Genetic Syndromes**
- Isolated (i.e., Prader Willi)
- Familial (melanocortin 4 receptor deficiency)

**Medical Conditions**
- Hypothalamic damage
- Immobility
- Insulinoma
- Some cases of untreated hypothyroidism
- Hypercortisolism (Cushing’s disease)
- Sleep disorders

**Psychological and Behavioral Conditions**
- Mental stress
- Depression
- Anxiety
- Post-traumatic stress syndrome
- Binge-eating disorder
- Night-eating syndrome
- Eating disorders not otherwise specified

Reference/s: [73, 111, 112]
Concomitant Medications
Identify and Manage Concomitant Pharmacotherapy That Might Alter Body Weight

**Cardiovascular Medications**

May increase body weight:
- Some beta-blockers
  - Propranolol
  - Atenolol
  - Metoprolol
- Older and/or less lipophilic dihydropyridine ("dipine") calcium channel blockers may increase body weight gain due to edema, compared to non-dihydropyridines and lipophilic dihydropyridines, and the increased edema may exacerbate obesity-related edema (and sleep apnea related peripheral edema), and also confound body weight as a measure of body fat
  - Nifedipine
  - Amlodipine
  - Felodipine

**Diabetes Mellitus Medications**

May increase body weight:
- Most insulins
- Sulfonylureas
- Thiazolidinediones
- Meglitinides

May decrease body weight:
- Metformin
- Glucagon-like peptide-1 agonists
- Sodium glucose co-transporter 2 inhibitors
- Alpha glucosidase inhibitors

Reference/s: [12, 27, 113, 114, 310]
Metformin

May help improve adiposopathic disorders:
- Insulin resistance
- Polycystic ovarian syndrome
- Fatty liver
- Cardiovascular disease (especially when compared to sulfonylurea)

May help treat complications of other concurrent drug treatments:
- Antipsychotic-related weight gain
- Human immunodeficiency virus (HIV) protease inhibitor-associated abnormalities (i.e., HIV lipodystrophy)

May help reduce the overall cancer rate and help improve the treatment of multiple cancers:
- Colon
- Ovary
- Lung
- Breast
- Prostate

May enhance effects of gastrointestinal hormones applicable to weight loss (e.g., glucagon-like peptide-1, Peptide YY)
### Identify and Manage Concomitant Pharmacotherapy That Might Alter Body Weight

#### Hormones

May increase body weight:
- Glucocorticoids
- Estrogens

Variable effects on body weight:
- Progestins
  - Injectable or implantable progestins may have greatest risk for weight gain
  - May be dependent upon the individual
- Testosterone
  - May reduce percent body fat and increase lean body mass, especially if used to replace testosterone deficiency in men

#### Anti-seizure Medications

May increase body weight:
- Carbamazepine
- Gabapentin
- Valproate

May decrease body weight:
- Lamotrigine
- Topiramate
- Zonisamide
Identify and Manage Concomitant Pharmacotherapy That Might Alter Body Weight

May increase body weight:
- Some tricyclic antidepressants (tertiary amines)
  - Amitriptyline
  - Doxepin
  - Imipramine
- Some selective serotonin reuptake inhibitors (e.g. paroxetine)
- Some irreversible monoamine oxidase inhibitors
  - Isocarboxazid
  - Phenelzine
- Mirtazapine

May decrease body weight:
- Bupropion

Variable effects on body weight:
- Some tricyclic antidepressants (secondary amines)
  - Desipramine
  - Nortriptyline
  - Protriptyline
- Some selective serotonin reuptake inhibitors
  - Citalopram
  - Escitalopram
  - Fluoxetine
  - Sertraline
- Some serotonin and norepinephrine re-uptake inhibitors
  - Desvenlafaxine
  - Duloxetine
  - Venlafaxine
- Some irreversible monoamine oxidase inhibitors (i.e., tranylcypromine)
**Mood Stabilizers**

May increase body weight:
- Gabapentin
- Lithium
- Valproate
- Vigabatrin

Variable/neutral effects on body weight:
- Carbamazepine (sometimes reported to increase body weight)
- Lamotrigine (sometimes reported to decrease body weight)
- Oxcarbazepine

**Migraine Medications**

May increase body weight:
- Amitriptyline
- Gabapentin
- Paroxetine
- Valproic acid
- Some beta-blockers

May decrease body weight:
- Topiramate
## Identify and Manage Concomitant Pharmacotherapy That Might Alter Body Weight

### Antipsychotics

<table>
<thead>
<tr>
<th>May substantially increase body weight:</th>
<th>May somewhat increase body weight:</th>
<th>Variable/neutral effects on body weight:</th>
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<tbody>
<tr>
<td>• Clozapine</td>
<td>• Asenapine</td>
<td>• Amisulpride</td>
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<td>• Olanzapine</td>
<td>• Chlorpromazine</td>
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<td>• Lithium</td>
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### Hypnotics

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<th>May increase body weight:</th>
<th>May have limited effects on body weight:</th>
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<td>• Diphenhydramine</td>
<td>• Benzodiazepines</td>
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<td>• Melatonergic hypnotics</td>
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<td>• Trazodone</td>
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Identify and Manage Concomitant Pharmacotherapy That Might Alter Body Weight

**Human Immunodeficiency Virus (HIV) Medications**

May increase body weight:
- Some highly active antiretroviral therapies (HAART) protease inhibitors without HIV lipodystrophy

May decrease body weight:
- Some highly active antiretroviral therapies (HAART) protease inhibitors with HIV lipodystrophy

**Chemotherapies**

May increase body weight:
- Tamoxifen
- Cyclophosphamide
- Methotrexate
- 5-fluorouracil
- Aromatase inhibitors
- Corticosteroids

Reference/s: [113, 123, 124]
Eating Disorders and Obesity: Binge-eating Disorder

**Diagnosis:**
- Frequent episodes of consuming large amounts of food more than once per week for at least three months
  - No self-induced vomiting (purging)
  - No extra exercising
  - Feelings of lack of self control, shame, and guilt
- Occurs in 2-3 percent of U.S. adults
- Often considered the most common eating disorder
- May occur in up to 50 percent of patients with severe obesity
- Eating Attitudes Test may assist with diagnosis

**Treatment:**
- Often requires treatment by a qualified clinician
- Cognitive behavior therapy
- Lisdexamfetamine dimesylate is the only pharmacotherapy with an FDA indication to treat binge-eating disorder
- Although not FDA indicated for this use, clinical trials suggest other pharmacotherapies may be efficacious
  - Some selective serotonin reuptake inhibitors
  - Topiramate

Reference/s: [213-218]
Lisdexamfetamine dimesylate is a central nervous system stimulant indicated for the treatment of:
  - Moderate to severe binge-eating disorder (BED)
  - Attention Deficit Hyperactivity Disorder (ADHD)

Limitations:
  - Not indicated for weight loss; safety and effectiveness for the treatment of obesity have not been established

Drug Enforcement Agency Schedule II drug

Dosing for BED: Once in the morning with or without food. Avoid afternoon doses. Capsule may be opened and mixed with yogurt, water, or orange juice (see drug interactions).
  - Starting dose = 30 mg every morning for one week
  - Titration dose = 50 mg every morning for one week
  - Top dose = 70 mg every morning
  - Recommended dose = 50-70 mg every morning
  - Severe renal impairment: Maximum dose is 50 mg per day
  - End-stage renal disease: Maximum dose is 30 mg per day
Potential Drug Interactions

- Agents that alter urinary pH can alter blood levels of amphetamine
  - Acidifying agents decrease amphetamine blood levels (e.g., ascorbic acid)
  - Alkalinizing agents increase amphetamine blood levels (e.g., sodium bicarbonate)
- Concurrent administration with monoamine oxidase (MAO) inhibition may contribute to hypertensive crisis

Pharmacokinetics

- Lisdexamfetamine is rapidly absorbed from the gastrointestinal tract, converted to dextroamphetamine and L-lysine primarily in the blood due to the hydrolytic activity of red blood cells
- Lisdexamfetamine is not metabolized by cytochrome P450 enzymes
- Approximately 96 percent of oral dose radioactivity is recovered in the urine (42 percent related to amphetamine, 25 percent to hippuric acid, and 2 percent to intact lisdexamfetamine)
- Plasma elimination half-life is less than one hour
Lisdexamfetamine Dimesylate: Potential Adverse Experiences

**Most Common Adverse Reactions:**

- Anorexia
- Anxiety
- Decreased appetite
- Decreased weight
- Diarrhea
- Dizziness
- Dry mouth
- Irritability
- Insomnia
- Nausea
- Upper abdominal pain
- Vomiting
- Increased heart rate
- Constipation
- Feeling jittery
Lisdexamfetamine Dimesylate: Contra-indications

- Central nervous system stimulants (amphetamines and methylphenidate-containing products), including lisdexamfetamine dimesylate, have high potential for abuse and dependence

- Risk of abuse should be assessed prior to prescribing

- Patients should be monitored for signs of abuse and dependence while on therapy

- Known hypersensitivity (e.g., anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticarial) to amphetamine products or other ingredients in lisdexamfetamine dimesylate

- Use with monoamine oxidase (MAO) inhibitor or within 14 days of the last MAO inhibitor dose

Reference/s: [219]
Lisdexamfetamine Dimesylate: Warnings

- **Serious cardiovascular reactions**
  - Due to reports of sudden death in children and adolescents with serious heart problems, as well as sudden death, stroke, and myocardial infarction in adults, avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious health arrhythmia, or coronary artery disease.

- **Blood pressure or heart rate increases**
  - Blood pressure and pulse should be monitored. Benefits and risks should be considered before use in patients for whom blood pressure increases may be problematic.

- **Psychiatric adverse reactions**
  - May cause psychotic or manic symptoms in patients with no prior history or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use.

- **Suppression of growth**
  - Height and weight should be monitored in pediatric patients during treatment.

- **Peripheral vasculopathy, including Raynaud’s phenomenon**
  - Stimulants are associated with peripheral vasculopathy, including Raynaud’s phenomenon. Careful observations for digital changes is necessary during treatment with stimulants.
Anti-obesity Medications
Anti-obesity Medications

Adjunct to nutritional, physical activity, and behavioral therapies.

Objectives:

- Treat disease
  - Adiposopathy or sick fat disease (SFD)
  - Fat mass disease (FMD)
- Facilitate management of eating behavior
- Slow progression of weight gain/regain
- Improve the health, quality of life, and body weight of the patient with overweight or obesity

5-10 percent weight loss may improve both metabolic and fat mass disease.

Reference/s: [239]
FDA-approved Anti-obesity Medication Indications:

- Patients with obesity (e.g., BMI ≥ 30kg/m²)*
- Patients who are overweight (e.g., BMI ≥ 27kg/m²) with presence of increased adiposity complications (e.g., type 2 diabetes mellitus, hypertension, dyslipidemia)*

If no clinical improvement after 12-16 weeks with one anti-obesity medication, consider alternative anti-obesity medication or increasing anti-obesity medication dose (if applicable).

*While body mass index (BMI) is the only measure listed in the prescribing information for anti-obesity medications, BMI has limitations. Especially in muscular individuals or those with sarcopenia, overweight and obesity are more accurately assessed by other measures.
Update to FDA Pregnancy and Lactation Labeling

• In December 2014, the FDA issued its “Pregnancy and Lactation Labeling Final Rule” (PLLR), which went into effect on June 30, 2015.

• The PLLR removed letter pregnancy categories - A, B, C, D, and X.

• Due to the fact that the prescribing information materials for most anti-obesity medications have yet to be updated to reflect the new rules, the Obesity Algorithm continues to include pregnancy and lactation categories.

• In general, anti-obesity drugs should not be administered to, nor taken by women who are pregnant or trying to become pregnant.
Current Anti-Obesity Medications

FDA Approved
- Phentermine
- Diethylpropion
- Phendimetrazine
- Orlistat
- Lorcaserin
- Phentermine/Topiramate
- Naltrexone/Bupropion
- Liraglutide

Off Label Use
- Metformin for diabetes
- Exenatide
- Canagliflozin (Dapa-Empa-)
- Pramlintide for seizures
- Topiramate
- Zonisamide for migraines
- Bupropion for depression
- Naltrexone for addiction
Pharmacotherapy

Examples of Anti-obesity Medications Approved in 1999 or Before

• Phentermine
• Diethylpropion
• Phendimetrazine
• Benzphetamine
• Orlistat

Examples of Anti-obesity Medications Approved in 2012 and Beyond

• Lorcaserin
• Phentermine HCL/topiramate extended release
• Naltrexone HCL/bupropion HCL extended release
• Liraglutide

Reference/s: [243]
Sympathomimetic Amines

- Examples: Phentermine, diethylpropion, phendimetrazine, benzphetamine
- Increases satiety
- Drug Enforcement Agency (DEA) Schedule weight-management agents
  - DEA IV for phentermine and diethylpropion
  - DEA III for phendimetrazine and benzphetamine
- Potential adverse experiences include:
  - Palpitation
  - Tachycardia
  - Increased blood pressure
  - Overstimulation
  - Tremor
  - Dizziness
  - Insomnia
  - Dysphoria
  - Headache
  - Dryness of mouth
  - Dysgeusia
  - Diarrhea
  - Constipation
  - Pregnancy category X

Reference/s: [27, 244-247]
Gastrointestinal Lipase Inhibitors

- Example: Orlistat
- Impairs gastrointestinal energy absorption
- Potential adverse experiences include:
  - Oily discharge from the rectum
  - Flatus with discharge
  - Increased defecation
  - Fecal incontinence
  - May increase risk of cholelithiasis
  - May increase risk of urinary oxalate
  - Rare post-marketing reports of severe liver injury
  - May decrease fast-soluble vitamin absorption (e.g., vitamins A, D, E, K, and beta carotene)
  - Pregnancy category X

Reference/s: [244, 248, 249]
Indications and Use

- Serotonin (5-hydroxytryptamine) 2c receptor agonist anti-obesity medication
- Drug Enforcement Agency Schedule IV drug
- Dose = 10 milligrams (mg) twice per day for immediate release formulation; 20 mg once per day for extended release formulation

Potential Drug Interactions

- The safety of lorcaserin co-administration with other serotonergic or anti-dopaminergic agents is not yet established, which includes selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, triptans, bupropion, dextromethorphan, St. John’s Wort: use with extreme caution due to the risk of serotonin syndrome or neuroleptic malignant syndrome. Similarly, other listed potential drug interaction include tricyclic antidepressants, lithium, tramadol, and dopamine antagonists.

Pharmacokinetics

- Lorcaserin is metabolized in the liver with metabolites excreted in the urine
Lorcaserin

Most Common Adverse Reactions*
- Headache
- Dizziness
- Fatigue
- Nausea
- Constipation
- Cough
- Dry Mouth
*May increase prolactin levels

Contra-indications
- Pregnancy (Category X)

Warnings and Precautions
- The safety of coadministration with other serotonergic or antidopaminergic agents has not been established. If Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS) – like Reactions occur, lorcaserin should be immediately discontinued and the patient provided supportive treatment.
- If signs or symptoms of valvular heart disease develop, then consider lorcaserin discontinuation and evaluate the patient for possible valvulopathy.
- May cause disturbances in attention or memory; use with caution in patients working with hazardous machinery when starting lorcaserin treatment.
- Due to potential euphoria and dissociation, do not exceed recommended dose of lorcaserin 10 mg twice daily, or 20 mg extended-release formulation once a day.
- Discontinue lorcaserin if depression or suicidal thoughts develop.
- Among patients treated with diabetes mellitus medications, weight loss may cause hypoglycemia.
- Patients experiencing priapism should seek emergency treatment if an erection lasts >4 hours, and lorcaserin should be used with caution in patients predisposed to priapism.
Completion of Risk Evaluation and Mitigation Strategy (REMS) program to inform prescribers and female patients about the increased risk of congenital malformations (especially orofacial clefts) in infants exposed to phentermine HCL/topiramate extended release during the first trimester of pregnancy*

Indications and Use

- Drug Enforcement Agency Schedule IV drug
- Phentermine is a shorter-acting sympathomimetic amine approved as monotherapy as a weight-management drug
- Topiramate is a longer-acting neurostabilizer approved as monotherapy for seizure disorders and migraine headache prevention
- Doses = Once daily in the morning with or without food
  - Starting dose = 3.75 mg/23 mg (phentermine/topiramate extended release)
  - After 14-day intervals, and as clinically indicated, escalate doses to:
    - Recommended dose = 7.5 mg/46 mg
    - Titration dose = 11.25 mg/69 mg
    - Top dose = 15 mg/92 mg

*Completion of the FDA-mandated REMS program is optional and not required prior to prescribing phentermine HCL/topiramate extended release. Implementation of a REMS program by clinicians and pharmacies is intended to provide appropriate safety information to females of reproductive potential.
Potential Drug Interactions

• May alter the exposure to oral contraceptives, causing irregular menstrual bleeding but not an increased risk of pregnancy
  – Oral contraceptives should not be discontinued if spotting occurs
• May potentiate central nervous system depressants such as alcohol
  – Patients should avoid concomitant alcohol
• May potentiate hypokalemia of non-potassium-sparing diuretics

Pharmacokinetics

• Phentermine is metabolized by the liver, with most excreted by the kidney
• Topiramate is excreted mainly by the kidney
Most Common Adverse Reactions

- In clinical trials, adverse reactions occurring more than or equal to 5 percent of the time include:
  - Paresthesia
  - Dizziness
  - Dysgeusia (taste distortion/perversion)
  - Insomnia
  - Constipation
  - Dry mouth

Laboratory Abnormalities May Include

- Metabolic acidosis
- Elevated creatinine
- Lowering of glucose levels
Contra-indications

- Contra-indicated:
  - Glaucoma
  - Hyperthyroidism
  - During or within 14 days of taking monoamine oxidase inhibitors
  - Women of reproductive potential should have a negative pregnancy test before treatment and monthly thereafter and should use effective contraception while on phentermine HCL/topiramate extended release
  - Pregnancy or nursing (Pregnancy category X)

- Should be discontinued in patients with:
  - Unacceptable increases in adrenergic responses, such as increase in heart rate, especially in those with cardiac and/or cerebrovascular disease
  - Suicidal behavior and ideation
  - Acute myopia and secondary angle-closure glaucoma
  - Unacceptable mood and sleep disorders
  - Cognitive impairment
  - Pregnancy or nursing
**Indications and Use**

- Naltrexone is an opioid antagonist
- Bupropion is an aminoketone antidepressant with relatively weak inhibition of neuronal reuptake of norepinephrine and dopamine
- Drug Enforcement Agency Schedule: Not a scheduled drug
- Tablets = 8 mg/90 mg (naltrexone HCL/bupropion HCL extended release)
- Dosing:
  - Week 1 = 1 tablet in AM, no tablets in PM
  - Week 2 = 1 tablet in AM, 1 tablet in PM
  - Week 3 = 2 tablets in AM, 1 tablet in PM
  - Week 4 and beyond = 2 tablets in AM, 2 tablets in PM
Potential Drug Interactions

- Monoamine oxidase inhibitors: Increased risk of hypertensive reactions
- Drugs Metabolized by CYP2D6: Bupropion inhibits CYP2D6 and can increase concentrations of:
  - Antidepressants (e.g., selective serotonin reuptake inhibitors and many tricyclics)
  - Antipsychotics (e.g., haloperidol, risperidone, and thioridazine)
  - Beta-blockers (e.g., metoprolol)
  - Type 1C antiarrhythmics (e.g., propafenone and flecainide)
- CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel) can increase bupropion exposure. Do not exceed one tablet twice daily when taken with CYP2B6 inhibitors.
- CYP2B6 inducers (e.g., ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital, and phenytoin) may reduce efficacy by reducing bupropion exposure. Avoid concomitant use.
- Should be dosed with caution with drugs that lower seizure threshold
- CNS toxicity can occur when used concomitantly with dopaminergic drugs (e.g., levodopa and amantadine)
- Drug laboratory test interactions:
  - Can cause false positive urine test results for amphetamines
Pharmacokinetics

- Both parent and the 6-beta-naltrexol metabolite are active
- Naltrexone and 6-beta-naltrexol are not metabolized by cytochrome P450 enzymes
- Naltrexone and its metabolites are excreted primarily by the kidney
- Bupropion is extensively metabolized
- CYP2B6 is the principal isozyme involved in the formation of hydroxybupropion, whereas cytochrome P450 isozymes are not involved in the formation of the other active metabolites
- Bupropion and its metabolites inhibit CYP2D6
- Following oral administration of 200 mg of 14C-bupropion in humans, 87 percent and 10 percent of the radioactive dose were recovered in the urine and feces, respectively
Most common adverse reactions

- Nausea
- Constipation
- Headache
- Vomiting
- Dizziness
- Insomnia
- Dry mouth
- Diarrhea

Contra-indications

- Uncontrolled hypertension
- Seizure disorders, anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs
- Use of other products containing bupropion
- Chronic opioid use
- During or within 14 days of taking monoamine oxidase inhibitors
- Known allergy to any of its ingredients
- Contra-indicated during pregnancy or nursing mothers (pregnancy category X)
Naltrexone HCL/Bupropion HCL Extended Release

Warnings

- Monitor for depression or suicidal thoughts and discontinue if these symptoms develop
- Risk of seizure may be minimized by adhering to the recommended dosing schedule and avoiding co-administration with high-fat meals
- Monitor blood pressure and heart rate in all patients, especially those with cardiac or cerebrovascular disease
- Hepatotoxicity: Cases of hepatitis and clinically significant liver dysfunction observed with naltrexone exposure
- Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants
- Weight loss may cause hypoglycemia in patients treated with anti-diabetes mellitus medications. Glucose levels should be monitored.
Indications and Use

- Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist
- Drug Enforcement Agency Schedule: Not a scheduled drug
- Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg
- Inject subcutaneously in the abdomen, thigh, or upper arm; the injection site and timing can be changed without dose adjustment
- Recommended dose of liraglutide for treatment of obesity is 3 mg daily, any time of day, without regard to the timing of meals
- Dosing:
  - Week 1 = 0.6 mg per day
  - Week 2 = 1.2 mg per day
  - Week 3 = 1.8 mg per day
  - Week 4 = 2.4 mg per day
  - Week 5 and onward = 3.0 mg per day

*Liraglutide for obesity was approved by the Food and Drug Administration (FDA) with a Risk Evaluation and Mitigation Strategy (REMS) program. While optional and not required prior to prescribing Liraglutide for obesity, the manufacturer provides a communication plan, implemented towards healthcare providers likely to prescribe Liraglutide for obesity. The goal is to inform healthcare providers about the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with Liraglutide for obesity.

*Evaluate the change in body weight after 16 weeks and discontinue Liraglutide for obesity if the patient has not lost at least 4% of baseline body weight since it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.
Potential Drug Interactions

- Liraglutide delays gastric emptying. This may impact absorption of concomitantly administered oral medications.
- Liraglutide has low potential for pharmacokinetic drug-to-drug interactions related to cytochrome P450 and plasma-protein binding

Pharmacokinetics

- Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration.
- Liraglutide exposures are similar among three subcutaneous injection sites (upper arm, abdomen, and thigh); absolute bioavailability of liraglutide following subcutaneous administration is approximately 55 percent.
- Liraglutide is endogenously metabolized similar to large proteins without a specific organ as a major route of elimination.
- Following a [3H]-liraglutide dose, intact liraglutide is not detected in urine or feces, with only a minor part excreted as liraglutide-related metabolites in urine or feces (6 percent and 5 percent, respectively).
Most common adverse reactions

- Nausea
- Hypoglycemia
- Diarrhea
- Constipation
- Vomiting
- Headache
- Decreased appetite
- Dyspepsia
- Fatigue
- Dizziness
- Abdominal pain
- Increased lipase

Contra-indications

- Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2
- Hypersensitivity to liraglutide or any product components
- Pregnancy
Liraglutide

Warnings

- Counsel patients regarding the risk of medullary thyroid carcinoma (thyroid C-cell tumors) and the symptoms of thyroid tumors
- Discontinue promptly if pancreatitis is suspected; do not restart if pancreatitis is confirmed
- If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated
- Serious hypoglycemia can occur when liraglutide is used with an insulin secretagogue (i.e., a sulfonylurea)
  - Consider lowering the dose of anti-diabetes drugs to reduce the risk of hypoglycemia
- Monitor heart rate at regular intervals to evaluate for possible heart rate increase
- Renal impairment has been reported post-marketing, usually in association with nausea, vomiting, diarrhea, or dehydration, which may sometimes require hemodialysis
  - Use caution when initiating or escalating doses of liraglutide in patients with renal impairment
- Post-marketing reports exist regarding serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema)
  - If these occur, then liraglutide and other suspect medications should be discontinued, and the patient instructed to promptly seek medical advice
- Monitor for depression or suicidal thoughts and discontinue liraglutide if symptoms develop
Average Weight Loss with Anti-Obesity Agents

- Liraglutide
- Phen/Top
- Zonisamide
- Exenatide
- Buproprion
- Topiramate
- phenterm
- Lorcaserin
- Nal/Bup
- Metformin

Column1 Off Label FDA appr
Question: 1

- HC 78 y.o. WM with T2DM, CAD p PTCA w DES x2, Class 1 obesity presents for Medicare Annual Wellness Exam
- c/o Fatigue, Dyspnea on exertion x 6 weeks, no chest pain, weight gain of 12 lbs.
- Medications: ASA 81 mg daily, Atorvastatin 80 mg daily, Metoprolol XL 25 mg daily, NTG 0.4 mg prn
- Vitals: T 98.5, P 61, BP 118/71, Weight 209 BMI 32.7
- Hemoglobin A1c 6.1
- Cardiology scheduled a stress test in less than 7 days

- For Management of his Obesity you recommend
- A) Phentermine 37.5 mg capsule by mouth every morning
- B) Phentermine/Topiramate start at lowest dose and work up
- C) Metformin 500 mg by mouth twice a day and Stop Metoprolol
- D) Proceed with stress test and instruct patient to go to ER by 911 for cp not relieved by nitroglycerin and schedule follow up visit for management of obesity
SV 43 year old BM with T2DM, HTN, A fib rate controlled, Major Depressive Disorder presents for Therapeutic lifestyle change. He is disabled and wants to get his life back.

Medications: Amlodipine 5mg daily, apixaban 5 mg twice a day, carvediolol 25 mg twice a day, Furosemide 40 mg daily, insulin degludec 30 units at bedtime, metformin 1000 mg twice a day and Sotalol 80 mg twice a day.

Vitals: T 93.1 P 91 BP 153/98 Weight 357 lb BMI 48.42 Hemoglobin A1c 7.5

Failed Belviq, Mom did well with WLS and he is interested. Patient Health Questionaire =23 c/w severe depression, no suicidal ideation

For Management you recommend
A) Go to nearest psychiatric hospital
B) Stop Carvediolol
C) Add Liraglutide
D) Start Bupropion for depression and obesity, come for teaching class a new way of eating, discuss liraglutide, reducing insulin with endocrinology, and refer to bariatric surgery.
results

- PHQ 9 23-14 in 4 weeks, increased Bupropion to 300 mg
- Got in with bariatric surgery
- FU PHQ9 on 3/15/18 6
- Weight loss 13 lbs
- Fat mass – 9 lbs
- Feels he’s on the right track now that he’s eating better
Question: 3

- 8/31/15 DP 40 year old WM presents for physical exam last seen 2011. since then 39 lb weight gain. c/o unintentional weight loss, excess thirst and urination and thinks he has an enlarged prostate.
- Vitals : T 97.7 BP 141/91 P 86 Weight 295 lb BMI 39.73
- Exam: notable for Tinea pedis moderately severe bilateral feet and Tinea cruris ,prostate normal
- Urinalysis glucosuria >1000, ketones negative. FSBS 240 fasting, EKG normal
- Labs Hemoglobin A1C 11.3, C peptide 2.4 (0.8-3.85),
- Dx Newly diagnosed T2DM, Class 2 obesity with significant co-morbidity, Elevated BP, Tinea pedis, unintentional weight loss.
- What do you recommend?
  - A) Diabetic Teaching
  - B) asa 81 mg, metformin 1000 qd, then bid , atorvastatin 40 mg , Lisinopril 2.5 mg
  - C) Insulin therapy
  - D) Referral to endocrinology
  - E) Well Formulated Ketogenic Diet
  - F) All of the above
What did he do? What were the results?

- He agreed to do the ketogenic diet and take the metformin and atorvastatin.
- He did not do to Diabetic teaching, take aspirin, Lisinopril, insulin or see endocrinology.
- Lab: 10/9/15 Fructosamine =226
- 2/23/16 Hemoglobin A1C =5.5
- 5/23/2016 A1c 5.7
- 11/2/17 A1C=5.6
The End