Weight, Weight, Don't Tell Me…
Weight Management for the Internist

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Question

Who currently thinks of obesity as a chronic disease?
Objectives

1) Identify patients with overweight and obesity
2) Identify obesity as a chronic disease
3) Understand mechanisms involved in hunger and obesity
4) Be able to screen for and treat complications
5) Identify weight-promoting meds
6) Feel comfortable appropriately treating patients with overweight and obesity
Definition

Overweight: BMI 25 - 29.9 kg/m²
Class 1 obesity: 30 - 34.9
Class 2 obesity: 35 - 39.9
Class 3 obesity: >40
Your Patients (and CMS) Care

- **Pro Tip:** Your patients know they have overweight/obesity and it effects their health. ASK if they want to discuss treatment.

- **USPSTF**
  - Screen and offer referral for multidisciplinary treatment for BMI >30

- **Center for Medicare and Medicaid Services**
  - BMI screening and follow-up → clinical quality measure, Physician Quality Reporting System

- **2013 meta-analysis:** Patients are nearly 4 times more likely to attempt weight loss when their physician provides weight loss advice.

Rose, et al. 2013
Weight Stigma

- Social rejection and devaluation to those who don’t comply with social norms for BMI and shape
- Women - stigmatized across employment, education, relationships, media, healthcare
- Stigma → overeating, decreased exercise, decreased self-regulation, increased cortisol
- Physicians: implicit and explicit bias → “lazy”, “weak-willed”, “bad”, “waste of time”
- Identify your own biases and mitigate

Tomiyama, et al. 2018
2013 American Medical Association: “recognize obesity as a disease state with multiple pathophysiological aspects requiring a range of interventions to advance obesity treatment and prevention.”
Pathogenesis

Genetics
Environment
Energy Balance Dysregulation
Energy Balance Dysregulation

- Hypothalamic arcuate nucleus
  - Short- and long-term energy balance
- Central and peripheral signals
  - Adipose, stomach, pancreas
  - Reduced food or increased activity—> negative energy balance —> compensatory adaptation
Energy Balance Dysregulation: Ghrelin

- 1 example of MANY regulatory hormones
- Produced in oxyntic glands of **gastric fundus**
- Stimulates GH release, appetite, and fat accumulation
- Activates hypothalamus indirectly via vagus nerve
- Hunger and starvation —> ↑ levels
- **Weight loss** —> ↑ Ghrelin —> ↑ Appetite

Muller, et al. 2015
High heritability of BMI (40-70%)

Twelve rare forms of monogenic obesity
- Leptin deficiency, melanocortin-4 receptor (MC4-R) mutation
- MC4-R heterozygous mutations most common cause of monogenic obesity
Mean correlations for body mass index (BMI):
- 0.74 for monozygotic ("identical") twins
- 0.32 for dizygotic ("fraternal") twins
- 0.25 for siblings
- 0.06 for adoptive relatives

Body Mass in Twins

Monozygotic Twins (Intrapair Correlation = 0.66)

Dizygotic Twins (Intrapair Correlation = 0.26)

Borjeson, 1976
The Biggest Loser?
Metabolism

- Average Resting Metabolic Rate:
  - Pre-contest - 2,607 kcal/day
  - Contest End - 2,000
  - 6 Yr Post-Contest - 1,900!
  - 27% decrease!

1) What class obesity or overweight?
2) Discuss treatment options appropriate to severity
3) Eval for complications/contributing diagnoses (OSA, binge eating disorder, depression/anxiety)
4) Review meds → transition to weight negative options
5) Lifestyle medicine
6) Weight loss medications
7) Surgery
Obstructive Sleep Apnea

- **Untreated**: increased visceral fat, decreased exercise, increased appetite (especially for refined carbs)

- **Screening**:
  - STOP-BANG → highest Sn for mild and severe
  - STOP → highest Sn for moderate

Amra, et al. 2018
Binge Eating Disorder

- Recurrent episodes of binge eating, episodes characterised by both of the following:
  - Eating, in a discrete period of time (e.g. within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.
  - A sense of lack of control

- Episodes are associated with three or more of the following:
  - eating much more rapidly than normal
  - eating until feeling uncomfortably full
  - eating large amounts of food when not feeling physically hungry
  - eating alone because of feeling embarrassed by how much one is eating
  - feeling disgusted with oneself, depressed or very guilty afterward

- Marked distress regarding binge eating is present
- On average, at least once a week for three months
- not associated with the recurrent use of inappropriate compensatory behaviours (purging, excessive exercising)
Be patient and compassionate
Diabetes Prevention Program (DPP), LOOK-AHEAD, POUNDS-Lost, CALERIE

○ Intensive lifestyle intervention (ILI) vs. placebo, ILI vs. DM2 support, Macronutrient differences, Calorie restriction

○ ILI= 16-41 interventions in 12 months (tough to replicate in primary care!)

○ Weight loss at 12 months: 7-12%

○ Weight loss at 2 years: 4-11% (11% from Calorie restriction)

○ * Mean BMI’s: 34, 36, 33, 25 (CALERIE)

You have to go __ (insert diet here)!

- No particular diet is best
- Most important - Limit sugary beverages and processed foods

Shai et al, 2008
ACC/AHA/TOS Guideline

- Typically 1200-1500 kcal/d (women)
- 1500-1800 kcal/d (men)
- Calorie restrict by 500 kcal/d, 750 kcal/d, or 30%

Physical Activity
New findings of improved: sleep, executive function, depression, anxiety, QOL

Reduced risk of breast and colon cancer

Only 30% get ANY moderate-to-vigorous activity

Sedentary patient?
  ○ Light intensity (light walk) improves mortality, CVD risk, incidence of DM2

Some moderate intensity PA?
  ○ Little bit more is beneficial!

NO TIME THRESHOLD!! ANY AMOUNT COUNTS!

Lastly, individual interventions (You) work
Medical Therapy

- KEY: Adjunctive to lifestyle intervention
- Aid adherence to lifestyle, offset metabolic adaptation
  - BMI $\geq 30$ or
  - BMI $\geq 27$ + comorbidities (HTN, DM2, DLD, OSA)
# Adding Insult to Injury

<table>
<thead>
<tr>
<th>Drug Class/Type</th>
<th>Common Name</th>
<th>Proprietary or Brand Name</th>
<th>Alternative Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes Therapies</strong> (may cause up to 8 kg weight gain in an intensive 5-month treatment course)</td>
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<tr>
<td>Insulin</td>
<td>insulin lispro</td>
<td>Humalog*</td>
<td>metformin (Glucophage*, Glucophage* XR, Fortamet*, Glumetza*, Riomet*, generics)</td>
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<td></td>
<td>insulin aspart</td>
<td>Novolog*</td>
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<td>insulin glulisine</td>
<td>Apidra*</td>
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<td>Thiazolidinediones (TZDs)</td>
<td>pioglitazone</td>
<td>Actos*</td>
<td>Linagliptin (Tradjenta*)</td>
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<td>saxagliptin (Onglyza*)</td>
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<td>sitagliptin (Januvia*)</td>
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<td>exenatide (Byetta*)</td>
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<td>Liraglutide (Victoza*)</td>
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<td>acarbose (Prandase*, Precose*)</td>
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<td>miglitol (Glyset*)</td>
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<td>Sulfonylureas (SUs)</td>
<td>glipizide</td>
<td>Glucotrol*</td>
<td>*These combination products tend to have fewer side-effects and less weight gain:</td>
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<tr>
<td></td>
<td>glyburide</td>
<td>Glucotrol* XL</td>
<td>metformin/pioglitazone (Actoplus Met*)</td>
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<td></td>
<td>glimepiride</td>
<td>Diabeta*</td>
<td>glyipizide/metformin (Metaglip*)</td>
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<td>chlorpropamide</td>
<td>Micronase*</td>
<td>glyburide/metformin (Glucovance*)</td>
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<td>tolbutamide</td>
<td>Glynase*</td>
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<td>Amaryl*</td>
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<td>Diabinese*</td>
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<td></td>
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<td>generics</td>
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<tr>
<td>Psychiatric/Neurologic Therapies</td>
<td>amitriptyline</td>
<td>Elavil*</td>
<td>Bupropion (Aplenzin*, Wellbutrin**, Wellbutrin SR**, Wellbutrin XL**, Zyban**) *Black Box warning for increased risk of seizure.</td>
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<tr>
<td></td>
<td>doxepin</td>
<td>Adapin*</td>
<td>nefazodone (generics) *Black Box warning for liver failure and suicidal thoughts.</td>
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<tr>
<td></td>
<td>imipramine</td>
<td>Dilenor*</td>
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<td></td>
<td>nortriptyline</td>
<td>Sinequan*</td>
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<td>trimipramine</td>
<td>Tofranil*</td>
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<td></td>
<td>mirtazapine</td>
<td>Tofranil* PM</td>
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<tr>
<td>* Selective Serotonin Reuptake Inhibitors (SSRIs)</td>
<td>sertraline</td>
<td>Zoloft*</td>
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<tr>
<td>Initial weight-loss followed by gain within 6 months in a minority of patients</td>
<td>paroxetine</td>
<td>Paxil*, Paxil* CR, Pexeva*</td>
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<td></td>
<td>fluvoxamine</td>
<td>Luvox*, Luvox* CR</td>
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<td>** Lithium</td>
<td>Eskalith*, Eskalith CR*, Lithobid*</td>
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<td>Gains in 11% to 65% of treated patients; up to 10 kg or more in 6 to 10 years</td>
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<td>Antipsychotics (most likely to cause weight gain)</td>
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<td>haloperidol</td>
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<td>loxapine</td>
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<td>fluphenazine</td>
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<td>risperidone</td>
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<td>quetiapine</td>
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<td>generics</td>
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<td>Oxilapine*, generics</td>
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<td>Clozaril*, FazaClo*</td>
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<tr>
<td>Thorazine*</td>
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<td>generics</td>
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<td>Risperdal*, Risperdal*</td>
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<td>M-TAB*</td>
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<td>Zyprexa*</td>
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<td>Seroquel*, Seroquel* XR</td>
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<tr>
<td>Ziprasidone (Geodon*)</td>
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</tbody>
</table>
**Antiseizure/anticonvulsants**

| Variable gains of up to 15 to 20 kg | valproic acid (sodium valproate, divalproex sodium) | Depakote* Depakene* Depakote* ER Depakote* Sprinkle Stavzor* | topiramate (Topamax*) zonisamide (Zonegran*) lamotrigine (Lamictal®) *Black Box warning for serious rash. |
| Gains of up to 15 kg during 3 months of treatment | carbamazepine | Carbatrol* Epitol* Equetro* Tegretol* Tegretol* XR Horizant* Neurontin* |

**Steroid Hormones**

**Oral Corticosteroids** (used to treat systemic anti-inflammatory diseases) Polymyalgia rheumatica: 2 to 13 kg

| Gains in >50% patients receiving 1 year daily prednisone | prednisone cortisone | Prednisone Intensol* Sterapred* Sterapred* DS |

**Inhaled Corticosteroids** (used to treat asthma)

| budesonide ciclesonide fluticasone | Pulmicort* Alvesco* Flovent* |

**Hormone Therapy/Contraception**

| estrogen progestagens |

* denotes branded medications.
## Obesity Action Coalition

### Miscellaneous Agents

| Antihistamines (Taken for sleep in patients affected by obesity, Benadryl® can mask sleep apnea; also used as allergy medication) | diphenhydramine | Aler-Dryl® | Benadryl® | Diphenhist® | Nytol® | PediaCare Children’s Allergy® | Siladryl® | Silphen® | Sominex® | Unisom® | generics | decongestants and inhalers |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Beta-Adrenergic Blockers (used to lower blood pressure) | propranolol | Inderal® | Inderal® LA | InnoPran® | InnoPran® XL | Pronol® | Lopressor® | Toprol® | Toprol XL® | Tenormin® | **ACE Inhibitors:** | ramipril (Altace®+) | benazepril (Lotensin®+) | enalapril (Vasotec®+) | lisinopril (Prinivil®, Zestril®+) |
| metoprolol | | | | | | | | | | | **Angiotensin II Receptor Blockers:** | losartan (Cozaar®+) | candesartan (Atacand®+) | | | |
| atenolol | | | | | | | | | | | **Ca++ Channel Blockers** | | | | | |
Pharmacotherapy: FDA-approved

Phentermine
Lorcaserin (Belviq)
Phentermine/Topiramate (Qsymia)
Bupropion/Naltrexone (Contrave)
Liraglutide (Saxenda)
Diethylpropion
Phendimetrazine
Orlistat
<table>
<thead>
<tr>
<th></th>
<th>Phentermine</th>
<th>Orlistat</th>
<th>Phentermine/Topiramate ER (Qsymia)</th>
<th>Lorcaserin (Belviq)</th>
<th>Naltrexone SR/Bupropion SR (Contrave)</th>
<th>Liraglutide 3.0mg (Saxenda)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated wt loss</strong></td>
<td>5.1% @ 28wk</td>
<td>3.1% at 1yr 120mg TID</td>
<td>6.6% at 1yr 7.5/46mg daily 8.7% at 2yr (high dose)</td>
<td>3.6% at 1yr 10mg BID 3.1% at 2yr</td>
<td>4.8% at 56wk 16/160mg BID</td>
<td>5.6% at 56wk 3mg daily</td>
</tr>
<tr>
<td><strong>Long-term?</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<tr>
<td><strong>Schedule IV Controlled Substance</strong></td>
<td>Yes</td>
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<td>Yes</td>
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</tbody>
</table>
Who does not prescribe phentermine due to concerns about safety/addiction potential?
Abuse, dependence, withdrawal symptoms do not occur in long-term use

Sys/Dias BP changes
- SBP/DBP $-6.9/-5.0$ mm Hg at 26 weeks
- $-7.3/-5.4$ at 52 weeks

Hendricks, et al. 2011
Hendricks, et al. 2014
Pharmacotherapy

- **Orlistat (Xenical)**
  - Pancreatic/gastric lipase inhibitor
  - **Dose**: 120mg TID before meals
  - **Side Effects**: Oily spotting, flatus, incontinence
  - **CI**: Pregnancy, cholestasis, chronic malabsorption syndromes
Lorcaserin (Belviq)
- Selective 5HT2c agonist- promotes satiety
- Reminder: Fenfluramine potent 5HT-2b (on heart valves)
- **Dose**: 10mg PO BID
- Mean wt loss 5.8% vs. 2.2% (placebo)
- **SE**: Headache, dizziness, fatigue, dry mouth
- **CI**: Pregnancy, MAO Inhibitors
- Valvulopathy? (no increased risk in CAMELLA-TIMI 61)
Liraglutide (Saxenda)
- GLP-1 agonist - delayed gastric emptying and increased satiety
- **Dose**: 3.0mg SC daily - Start 0.6mg, go slow!
- **SE**: N/V, constipation, hypoglycemia
- **CI**: Pregnancy, personal/family history of medullary thyroid Ca or MEN2
Phentermine/Topiramate

- Norepi-releasing agent (Phentermine)
- GABA-modulator: decreased appetite (Topiramate)

**Starting dose**: 3.75mg/23mg x 2 weeks

**Max dose**: 15mg/92mg

**SE**: Insomnia, dry mouth, paresthesias, dizziness, dysgeusia, congenital cleft lip/palate

**CI**: Pregnancy, hyperthyroid, glaucoma, MAOI’s

Monthly pregnancy tests recommended
Naltrexone/Bupropion

- Norepinephrine, Mu opioid receptor antagonism,
- **Starting dose**: 8mg/90mg daily x 1 week
- **Maintenance dose**: 32mg/360mg
- **SE**: Nausea, constipation, headache, vomiting, insomnia, dry mouth, diarrhea
- **CI**: Uncontrolled HTN, epilepsy, anorexia or bulimia, drug/alcohol withdrawal, MAOIs, long-term opioid use, pregnancy
Medications, cont

**DM2**
- Metformin
- Exenatide
- Sodium-glucose transporter 2 inhibitors
- Glucagon-like peptide-1 receptor agonists
- Pramlintide

**Seizures/Migraines**
- Topiramate
- Zonisamide

**Depression**
- Bupropion

**Binge-Eating Disorder**
- Lisdexamfetamine (Vyvanse)
SGLT-2 Inhibitors:
- Empagliflozin, Dapagliflozin, Canagliflozin, Ertugliflozin
- Lose up to 300kcal/day → metabolic adaptation (remember?) → 2-3% wt loss

GLP1-RA’s
- Liraglutide (Victoza), Semaglutide (Ozempic), Dulaglutide (Trulicity)
- Liraglutide vs. Semaglutide
  - **Lira**: 34% lost 10% of TBW
  - **Sema**: 19-65% lost 10%
- **High dose (0.4mg/d of Semaglutide)**: mean 13.8% TBWL at 52 weeks! 7.8% for Liraglutide 3.0mg/d
Metabolic Bariatric Surgery

Criteria:
- BMI >40 or
- >35 + comorbidities
- Failed 6+ months organized weight management (arbitrary timeline)
Surgeons treat diabetes, too! (better?)

- 2018 JAMA
  - Israeli study 33,540 patients
  - LABG, RYGB, LSG vs. Usual Care
  - Mortality
    - 1.3% surg group
    - 2.3% non-surgical
  - DM2 Remission: LSG 32%, RYGB 19.3, LABG 14.7
2019 Denmark study
- DM2 and RYGB
- 1111 patients
- 1st yr: ¾ achieved remission
- 5 yr relapse rate 27%
Obesity is a chronic disease with strong genetic predisposition (just like HTN, DM2, etc..). Treat it as such
- Identify and rectify own weight bias
- Screen for complications
- Avoid weight-promoting medications
- Refer for multi-disciplinary support
- Use medications when indicated
- Refer for metabolic/bariatric surgery


References


