



MASSACHUSETTS
GENERAL HOSPITAL
WEIGHT CENTER

Anti-Obesity Medication Update

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AMERICAN BOARD
of OBESITY MEDICINE
CERTIFIED DIPLOMATE



HARVARD
MEDICAL SCHOOL



MASSACHUSETTS
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Disclosures

- Novo Nordisk Speakers Bureau (past)
- Bariatrix/SetPoint Health Advisory Board
- Procter and Gamble (husband employer)



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Objectives

- Appreciate utility of medications as a tool for optimal obesity treatment
- Understand the options and mechanism of action for anti-obesity medications
- Identify patients who would benefit from anti-obesity medication use (indications and contraindications)
- Guide patients on treatment expectations and outcomes with medication use

Obesity is a disease

- Disease
 - an impairment of the normal state of the living animal that interrupts or modifies the performance of the vital functions
- Obesity
 - a disease in which excess body fat has accumulated to a level that may have an adverse effect on health.



© World Obesity Federation

Multi-factorial Chronic Disease

Medical

- Genetic (over 100 sites now)
- Sleep apnea, inflammation, insulin resistance, vitamin D deficiency, diabetes

Mental/Behavioral

- Food addiction, eating disorders, compulsive eating, ADHD, prior trauma

Mechanical/functional

- Arthritis, fibromyalgia, poor exercise tolerance



Obesity Phenotypes

- Behavioral
 - Depressed emotional eating
 - Binge eating/all or nothing thinking
 - ADHD
 - Addictive eating
 - Too busy chaotic eating
 - Anxious/PTSD comfort eating

- Medical
 - Diabetes
 - Insulin resistance
 - Testosterone deficient
 - Insomnia/OSA
 - Medication side effects

- Societal
 - Low income
 - Lack of knowledge
 - Cultural habits and norms

What works for treating obesity?

- Metabolic surgery
- Medications combined with lifestyle changes
- Structure
- Environmental stimulus control
- Accountability/follow up appointments

Anti-obesity Medications

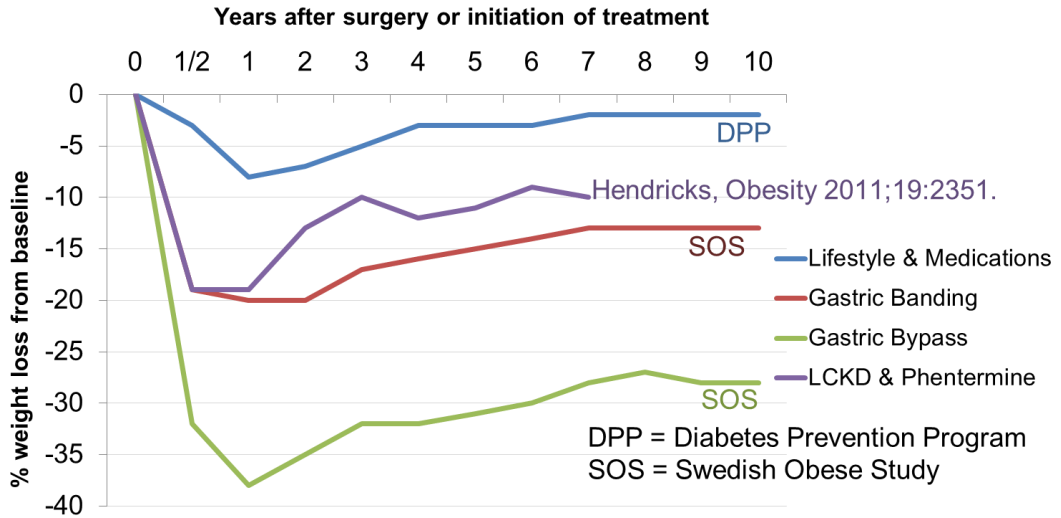
Adjunct to nutritional, physical activity, and behavioral therapies
for patients with BMI \geq 30 or BMI \geq 27 with co-morbidities

Objectives:

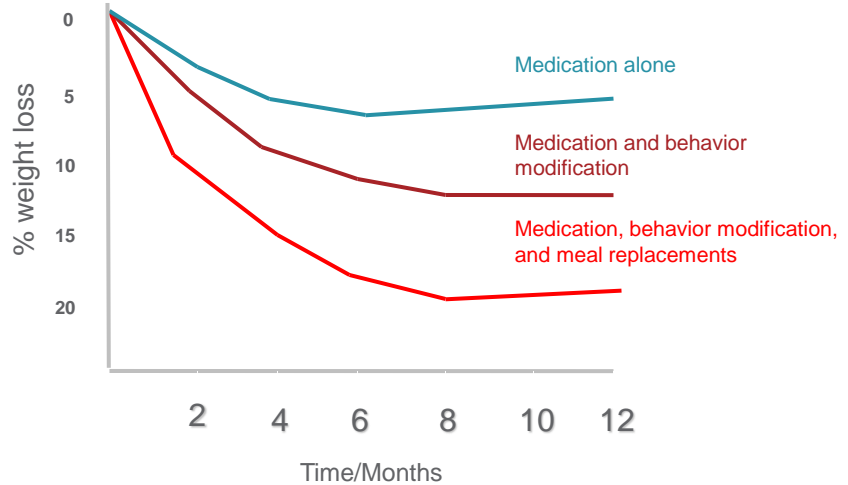
- Treat disease
 - Adiposopathy or sick fat disease (SFD)
 - Fat mass disease (FMD)
- Facilitate management of eating behavior
- Slow progression of weight gain/regain
- Improve the health, quality of life, and body weight of the patient with overweight or obesity

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

Why Use Medication with Obesity Treatment = Better results



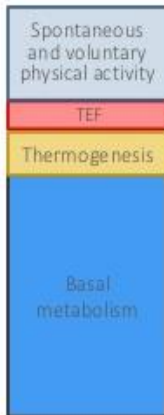
Medications are combined with lifestyle and structure



Wadden, Arch Int Med. 2001;161:218

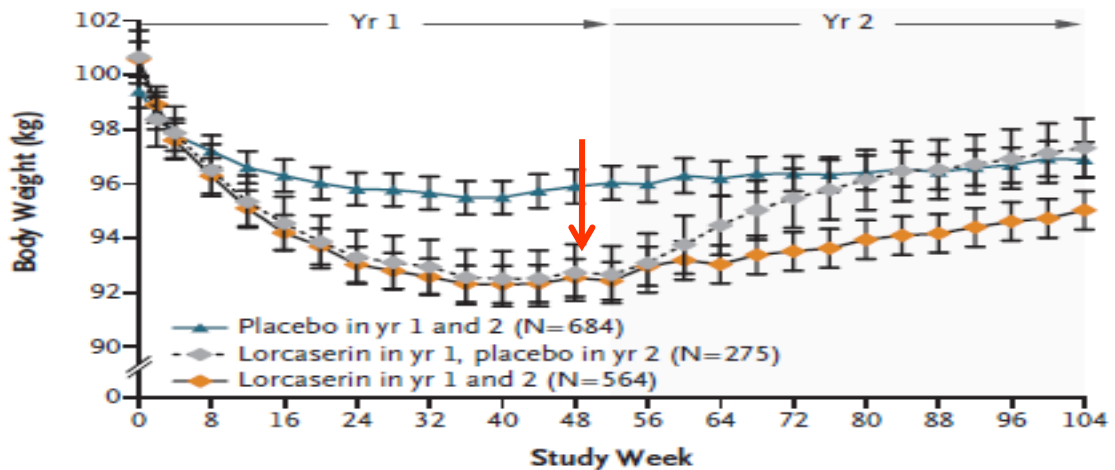


Components of Total Energy Expenditure



- Basal metabolic rate \sim energy needed to sustain the metabolic activities of cells and tissues, and to maintain blood circulation, respiration, GI, and renal function.
- Thermogenesis \sim energy expended to maintain body temperature.
- Thermic effect of food (TEF) \sim energy expenditure associated with the digestion and assimilation of food, \sim 10% TEE
- Physical Activity \sim energy expended for physical activity

Medications are used for long term and maintenance

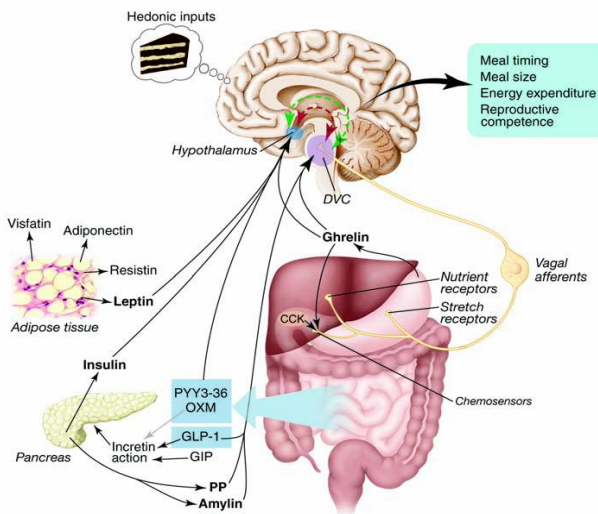


Smith et al. *NEJM* 2010;363:245-56

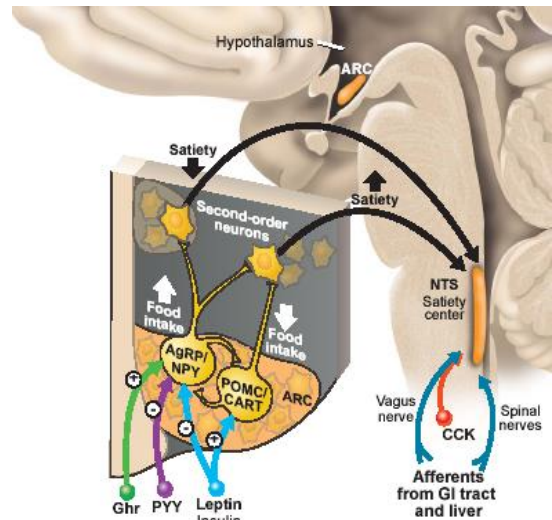
Why medication in obesity treatment?

- Better results
- Better maintenance
- Better when combined with other interventions
 - meal replacements, behavior change, structure, accountability

Interacting Pathways of Energy Regulation

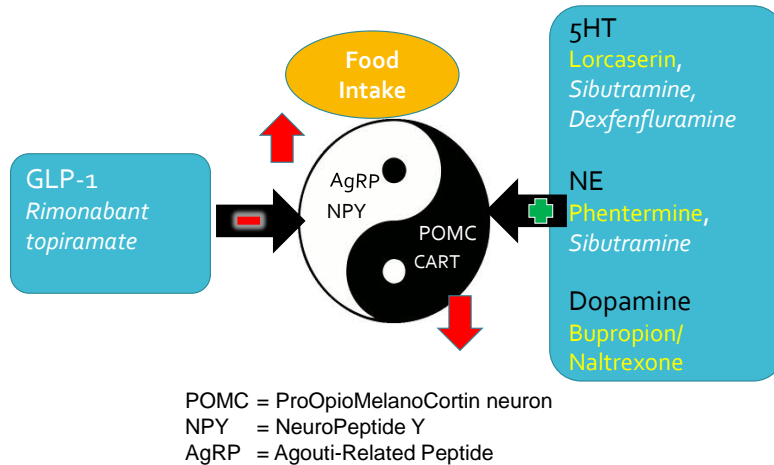


Badman MK, Flier JS. *Science* 2005;307: 1909-1914



Marx J. *Science*. 2003; 299. 846-9

Central Mechanisms of Action of Anti-obesity Meds



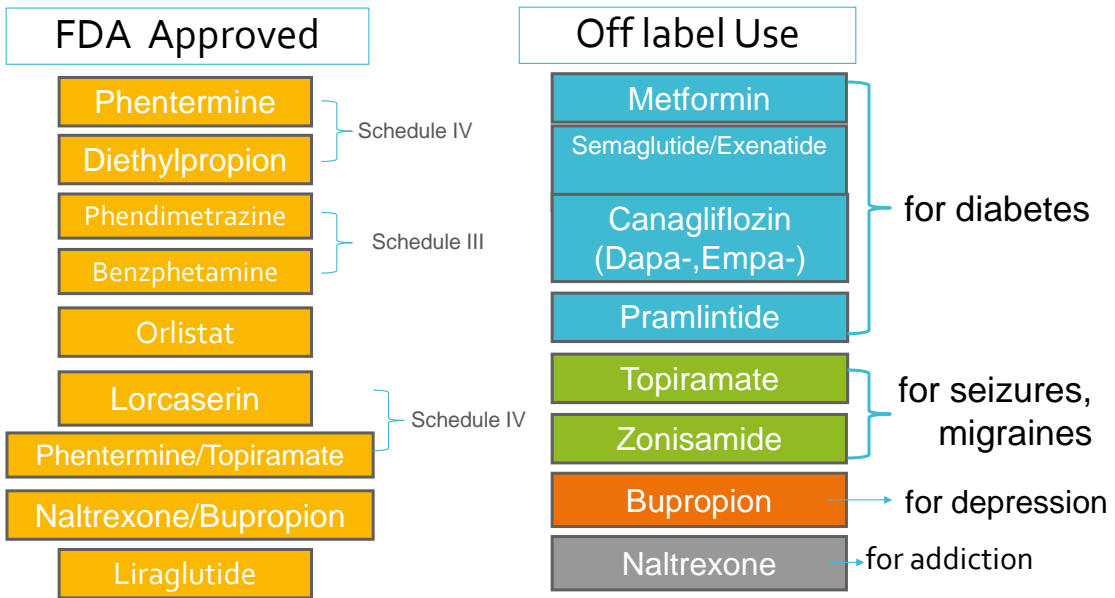
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Minimize Weight Promoting Medications

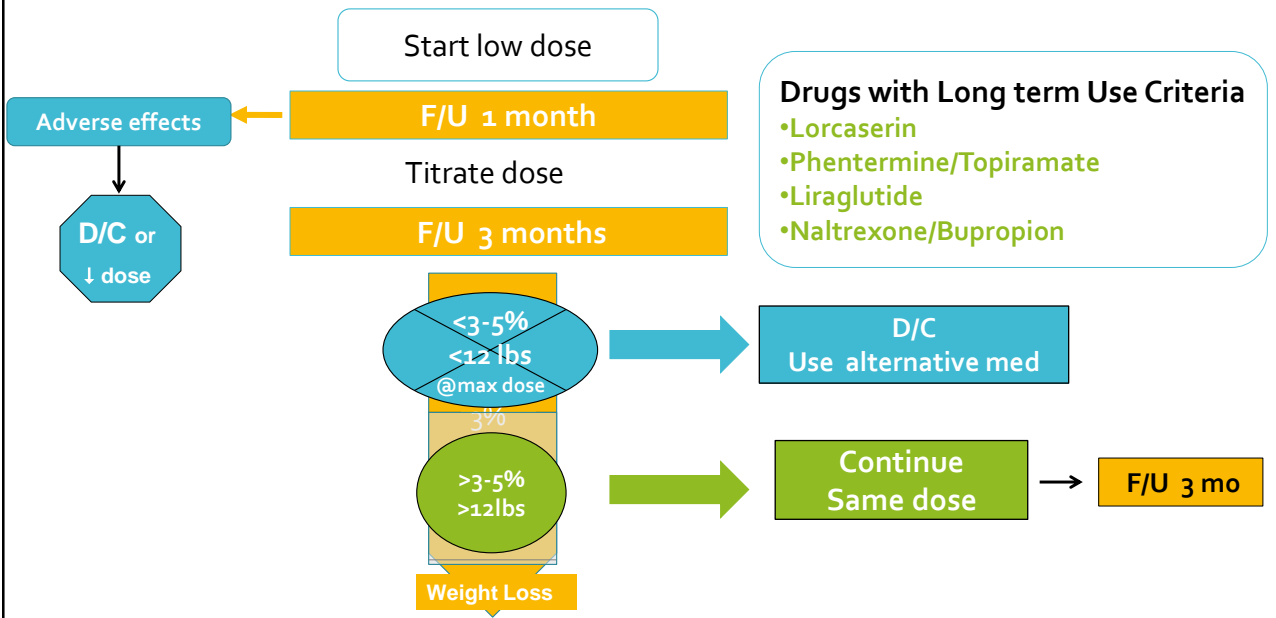
- Beta blockers
- Sulfonylureas
- Insulin-try to get to lowest dose with adequate control
- Atypical antipsychotics (even new ones)
- Tricyclics
- Depakote
- Depo-provera (consider IUD)
- Pioglitazone
- Gabapentin
- Lithium
- mirtazapine
- SSRI's (sertraline seems most neutral, paroxetine worst)



Current Anti-Obesity Medications



High Responders lose >5% in 3-months



Use of Anti-Obesity Medications

1. BMI indications: **BMI \geq 30 or BMI \geq 27 + Comorbidity**
2. Combine with behavioral modification, physical activity and nutrition for optimal results
3. Continue medications only in responders
4. Use combinations if monotherapy does not give desired results
5. Long term use

Weight loss expectations

Weight loss %	% patients on liraglutide 3mg (Saxenda®)	% patients on semaglutide 0.4mg daily (Phase II)	% patients on phentermine/topiramate 15/92mg (Qsymia®)	% patients on lorcaserin (Belviq®) 10mg BID	% patients on bupropion/naltrexone (Contrave®)
> 5%	63%	80%	67%	47%	42%
> 10%	33%	65%	47%	22%	21%
> 15%			32%		10%
> 20%	6%	40%			

O'Neil PM, Birkenfield AL, McGowan B, et al. A randomized, phase II, placebo- and active-controlled dose-ranging study of semaglutide for treatment of obesity in subjects without diabetes. Presented at the 100th Annual Meeting of The Endocrine Society, Chicago, Illinois; March 18, 2018. Abstract OR12-5.

Question 1

A 55yo F with class II obesity (BMI 35kg/m²) who responded well to a past commercial weight loss program is frustrated as she stopped losing weight.

PMH: HTN, depression, glaucoma and seizures as a child

Meds: lisinopril 20mg/d, escitalopram 20mg/d and timolol ophthalmic 0.25% solution /day

She is interested in medication. What is the next best step?

- a. Start her on phentermine 15mg daily
- b. Start her on phentermine-topiramate CR (Qsymia) 3.25/23mg daily
- c. Start her on lorcaserin XR 20mg daily
- d. Start her on naltrexone-bupropion 9/80mg daily

Question 1

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- c. **Start her on lorcaserin XR 20mg daily**
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Sympathomimetics

- Drug class: phenethylamines – includes amphetamine, methamphetamine, phentermine, diethylpropion, epinephrine, dopamine, and many others.
- Phentermine is not an “amphetamine”
- All are approved only for “short term use” (reapproved in 1970)
 - Largely due to concerns over addiction potential
 - Despite the fact that addiction had occurred *only* with amphetamine.

Phentermine

+

Increased hunger
 Low Metabolic Rate

CI

Active cardiovascular disease
 Poorly controlled HTN
 Cardiac Arrhythmias
 Hyperthyroidism
 Glaucoma

AE

Dry mouth, Constipation, Insomnia
 Palpitations, HA, Irritability

Mechanism/Action:

- Inhibits Na²⁺-dependent NE transporter, reduces NE uptake
- Inhibits serotonin and dopamine reuptake

Dosing:

- 15-30mg capsule, 37.5mg tablet
- 8mg TID
- ½ of 37.5mg tablet used as well
- Daily or BID

Advice/Precautions:

- [Schedule IV controlled substance](#)
- Monitor blood pressure, awareness of caffeine intake
- **No** evidence of addiction, withdrawal
- **No** established relationship related to cardiac valvulopathy or pulmonary hypertension

Diethylpropion

+

Increased hunger
Low Metabolic Rate

CI

Active cardiovascular disease
Uncontrolled HTN
Cardiac Arrhythmias
Hyperthyroidism
Glaucoma

AE

Dry mouth, Constipation, Insomnia
Palpitations, HA, Irritability

Mechanism/Action:

- Inhibits Na²⁺-dependent NE transporter, reduces NE uptake
- Weaker sympathomimetic effect v. phentermine

Dosing:

- Start 25mg tablets TID (or 75mg SR tablet QD)
- Can be added in afternoon

Advice/Precautions:

- **Schedule IV controlled substance**
- Monitor blood pressure, awareness of caffeine
- **No** evidence of addiction, withdrawal
- **No** established relationship related to cardiac valvulopathy or pulmonary hypertension

Orlistat

+

Hypercholesterolemia
Low risk medication

CI

Cholestasis
Chronic Malabsorption syndrome

AE

Flatulence, Diarrhea,
Bloating, cramping, Abd pain
Increase urinary oxalate
Fat soluble vitamin deficiency

Mechanism/Action:

- Pancreatic lipase inhibitor – blocks ~30% of fat intake

Dosing:

- Start 120mg daily
- Range: 120mg/d -120mg TID
- **Alli is OTC, available in 60mg*

Advice/Precautions:

- Advise daily multivitamin
- Monitor fat-soluble vitamins (A,D,E,K)
- Decrease levels of cyclosporin if co-administered
- No causal relationship with liver failure

Orlistat and the risk of acute liver injury: self controlled case series study in UK
Clinical Practice Research Datalink *BMJ* 2013;346:f1936

Topiramate (Topamax®)

*off label

+

Migraines, Seizures, Binge Eating
Excess cravings (carbohydrate)
Anxiety, mood stabilization
Soda addiction

CI

Severe depression
Pregnancy
Kidney stones

AE

WARNING: acute angle
glaucoma, suicidal ideation,
pregnancy

Paresthesias, Somnolence,
kidney stones, **Cognitive
Impairment**, taste aversion

Mechanism/Action: *Unclear*

- AMPA/kainate subtype ,glutamate receptor
- Carbonic anhydrase
- GABA-A (isozymes II,IV)
- Voltage-dependent sodium channels

Dosing:

- Start 25mg daily
- Range: 25-200mg/d

Advice/Precautions:

- Take at night if trouble with drowsiness
- Interaction with OCPs
- Use **BIRTH CONTROL** d/t increased risk of cleft lip and palate
- Hyperchloremic NAGMA

Phentermine / Topiramate CR (Qsymia®)

+

Non child bearing patient
Excessive hunger
Improved results vs
phentermine alone

CI

Active cardiovascular disease
Uncontrolled HTN
Hyperthyroidism
Glaucoma
Kidney stones
During or within 1 day MAOI

AE

Dry mouth, Restlessness, Insomnia,
Palpitations, HA, Constipation
Paresthesias, **dysgeusia**,
Somnolence, Cognitive impairment

Mechanism/Action:

- Sympathomemetic (NE) release in hypothalamus decreases hunger
- AMPA, GABA receptor - decrease cravings

Dosing:

- Start 3.75/23mg x 14d then 7.5/46mg
- Range: 3.75/23mg – 15/92mg/d

Advice/Precautions:

- **Schedule IV controlled substance**
- Counsel on use of BIRTH CONTROL due to increased risk of cleft lip and palate
- **Pregnancy test prior to start then MONTHLY**
- Increase hydration
- ¼ cup lemon/lime juice for parasthesias

Low cost alternative to Qsymia©

Know your
state laws!!!

- Replicate 15mg phentermine and 92mg topiramate with generics
- Doses of phentermine
 - 8mg tablets Lomaira© (more expensive, more flexible dosing) \$45 for 90 tabs
 - 15mg and 30mg capsules \$30 for 30 caps
 - 37.5mg tablets (can use ½ tab and save \$) \$30 for 30 tabs lasting 60 days
- Cheapest option is ½ of 37.5mg tab daily (as low as \$4/mo)
- Topiramate start at 25mg once a day for 2 weeks then increase to 25mg BID and then to 50mg BID as tolerated. Can consider XR version if patient has coverage
- Phentermine longer than 3 months is off label but sanctioned by medical experts

Lorcaserin (Belviq®)

+

Unable to tolerate phentermine
 Older patient on multiple meds
 Diabetes
 Night eating

Mechanism/Action:

- Selective serotonin(5HT) 2c receptor agonist
- Increases satiety via alpha-MSH and POMC neuron activation

CI

Pregnancy

Dosing:

- 10mg BID or 20mg XR daily
- Can use QD in evening as combination

AE

Headache, Nausea,
 Dizziness, Dry mouth, Fatigue,
 Nasopharyngitis
 Priapism

Advice/Precaution:

- [Schedule IV controlled substance](#)
- Watch co-administration with SSRIs, bupropion for concern about serotonin syndrome
- Caution with congestive heart failure

Naltrexone/Bupropion (Contrave[®])

+

Excessive hunger and cravings
Patients who smoke
On bupropion already

Mechanism/Action:

- Reuptake inhibitor DA and NE activity increases POMC
- Naltrexone blocks B-endorphin, POMC autoinhibitor

CI

Seizures, Uncontrolled HTN
Bulimia
Chronic Opioid Use

Dosing

	Morning	Evening
Week 1	1 pill	1 pill
Week 2	2 pills	2 pills
Week 3	3 pills	3 pills
Week 4 and maintenance	4 pills	4 pills

AE

WARNING: neuropsychiatric rxns, suicidal thoughts & behavior
Nausea, Headache, Insomnia, Dizziness, Dry mouth

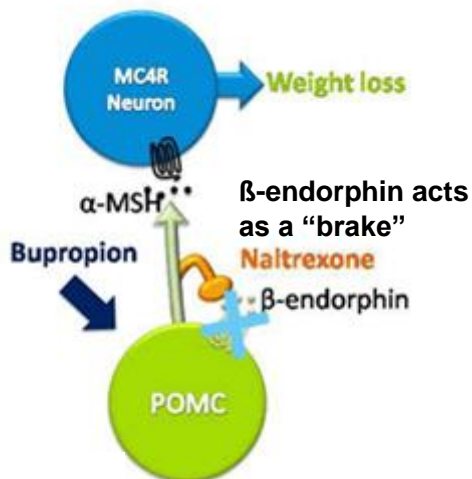
Advice/Precaution:

- Avoid opioid use, ask about surgery!
- Results of LIGHT trial (2016) do not show reduction in CV events
- Avoid high fat diet (increases bioavailability)



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Contrave[™] ↓ food intake via dual action at POMC



- Accelerate POMC neuron firing which reduces eating and increases energy expenditure
- Reduce the probability that compensatory pathways mitigate drug benefits over time
 - Beta endorphin
 - AgRP



GLP-1 agonists

- Liraglutide
 - Once a day 1.8mg Victoza
 - Once a day 3mg Saxenda
- Semaglutide for diabetes
 - 0.25 weekly for 4 weeks
 - 0.5 weekly for 4 weeks
 - 1.0 mg weekly
- Semaglutide for obesity in Phase 3 trials
 - 2.4mg weekly
- Decrease appetite and decrease gastric emptying for increase in satiety
- Metabolic medication
- Caution in renal insufficiency
- Increase risk of gallstones
- Thyroid cancer black box warning in mice

Liraglutide (Saxenda®)

+

Diabetes or prediabetes
 Cardiovascular disease
 Patients with insurance coverage

CI

Medulary Thyroid Ca (incl FHx)
 MEN type II
 History of pancreatitis

AE

Nausea, HA, Angioedema
 Renal impairment
 Hypoglycemia

Mechanism/Action:

- GLP-1 receptor agonist
- Increase satiety, decreases gastric emptying
- 97% homologous to human GLP-1

Dosing:

- Start 0.6mg SC QD, titrate each week to 3.0mg QD

Advice/Precautions:

- Nausea may improve with time
- Data does **not** support *an increased risk of pancreatic ductal neoplasia and pancreatic cancer*

Semaglutide (Ozempic®)

*off label

+

Diabetes or prediabetes
Patients with insurance coverage

Mechanism/Action:

- GLP-1 receptor agonist once weekly
- Increase satiety, decreases gastric emptying

CI

Medulary Thyroid Ca (incl FHx)
MEN type II
History of pancreatitis

Dosing for diabetes:

- Start 0.25mg SQ for 4 weeks, then 0.5mg SQ for 4 weeks, then 1.0mg
- Weight loss study was 0.4mg daily

AE

Nausea, HA, GERD
Renal impairment
Hypoglycemia

Advice/Precautions:

- Nausea may improve with time
- *Discuss smaller meal portions*

Canagliflozin (other Gliflozins)

*off label

+

Diabetes

Mechanism/Action:

- Inhibitor of the Na²⁺glucose co-transporter 2 (SGLT-2) in the proximal kidneys: prevents reabsorption of filtered glucose in kidney – causing glucosuria

CI

Severe Renal Impairment

Dosing:

- Start 100mg daily for canagliflozin
- Range: 100-300mg/d

AE

Amputation?
Candidiasis, UTI,
Hyperlipidemia
Ketoacidosis

Advice:

- Monitor renal function: Hyperkalemia
- Increased risk for bone turnover
- Normoglycemic ketoacidosis with ketogenic lifestyle

Insulin resistance

- Genetic
- Dietary
- PCOS
- Can drive eating behavior
- Treated with metformin, diet, exercise, sleep



Acanthosis nigricans



Metformin

*off label

+

Diabetes, Pre-diabetes
 PCOS, Insulin resistance
 Atypical antipsychotic medication-
 induced weight gain
 History of cancer

Mechanism/Action:

- Activates AMPK; decreases hepatic glucose production, increases muscle glucose uptake

CI

Renal failure

Dosing:

- Start 500mg XR QD (Range: 500mg – 2000mg)

AE

Nausea, Vomiting,
 Diarrhea, abdominal pain

Advice/Precautions:

- Monitor for Vitamin B12 deficiency/add B12 supp
- Watch with topiramate
- Reports *Lactic Acidosis* in the presence of renal insufficiency

Question 2

47yo M with BMI 33kg/m² and type 2 diabetes (A1c 7.5%) lost 6 lbs in 3 weeks on metformin XR. However, he developed diarrhea and was changed to glyburide 10mg/d by his PCP. After two months, he presents to your office, and has gained 14 lbs.

After discontinuing his glyburide, which of the following medications would be the most appropriate to add to this patients' regimen to promote weight loss?

- a. Insulin
- b. Sitagliptin
- c. Pioglitazone
- d. Liraglutide

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- b. Sitagliptin
- c. Pioglitazone
- d. **Liraglutide**

Anti-Obesity Medication Summary 2018

Drug	Side Effects	Mechanisms	Website/Coupon Support Program
Phentermine 37.5mg 8mg dose Lomaira®	Anxiety, agitation, palpitations, dry mouth	Decreased appetite and food intake	www.lomaira.com Coupon – Yes Support - No
Phentermine/Topiramate (Qsymia®) 7.5mg/46mg 15mg/92mg	Numbness and tingling, word finding issues, makes carbonated beverages taste bad	Decreased appetite and food intake, taste changes	www.qsymia.com Coupon – Yes Support – Yes Mayo diet and online program
Lorcaserin (Belviq®) 20mg XR daily 10mg twice a day	Fatigue, dry mouth, headache	Decreased appetite and food intake, increased feeling of fullness	www.belviq.com Coupon – Yes Support – Yes Online program
Naltrexone/bupropion (Contrave®) 8mg naltrexone/90mg bupropion 2 tablets BID	Nausea, anxiety, increase in blood pressure, do not use with opioids	Decreased appetite and reward	www.contrave.com Coupon – Yes Support – No online Rx program
Saxenda® 3mg once daily injection	Nausea, diarrhea, constipation, do not use if history of medullary thyroid cancer or pancreatitis	Reduced food intake, increase feeling of fullness, improved blood sugar metabolism	www.saxenda.com Coupon – Yes Support – Yes RD online/telephone coaching Obesity educators

Educate Your Patient – Manage Expectations!

Let your patient know in advance:

- Weight loss is **often** slower than patients expect
- Plateaus are common
- Maintaining weight loss is difficult without an intervention plan
- Medications may be necessary long term or intermittent indefinitely
- Obesity is a chronic disease and the disease of obesity is incurable but manageable
- Long-term favorable patient health outcomes is the primary goal of therapy
- 5-10% weight loss produces health benefits



In Summary

- Consider medication use early in treatment
- Utilize medications long term like other chronic diseases, assess ongoing needs.
- If medications stopped, add back early if weight regain (includes patients after surgery)
- Choose medications that fit patient best

Useful Resources



- www.Lookaheadtrial.org for handouts and free materials using meal replacements
- www.obesitymedicine.org Obesity Algorithm E-Book
- www.dietdoctor.com (low carb lifestyle)
- www.saxendapro.com (handouts for accountability)



Questions?

Thank You!
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