The Skinny On Obesity Meds

Stacy M. Chronister, D.O.
Clinical Assistant Professor
Department of Internal Medicine
Oklahoma State University

Disclosures

- No financial disclosures
- Generic and branded names may be interchanged during the lecture
- Off-label use of medications will be discussed

Objectives

- Define Obesity
- Understand which patient is a candidate for weight loss medications
- Understand the new management approach to overweight and obesity
- Learn the MOA, risks, side effects, and potential efficacy of weight loss medications
- Recognition of common weight gaining medications

LONDON | Thu Jul 29, 2010

(Reuters) - British Public Health Minister has urged doctors to call overweight patients 'fat' rather than 'obese.'

"Doctors and health workers are too worried about using the term 'fat'", said the health minister, *"but doing so will motivate people to take personal responsibility for their lifestyles."*

"Calling them 'obese' does not provide sufficient motivation. Just call them fat: Plain-speaking doctors will jolt people into losing weight."

DIAGNOSIS	ANTHROPO-METRIC COMPONENT	CLINICAL COMPONENT	Prevention/ Treatment
Normal	BMI < 25		Primary
Overweight Stage 0	BMI 25-29.9	No obesity-related complications	Secondary
Obesity Stage 0	BMI ≥ 30	No obesity-related complications	
Obesity Stage 1	BMI ≥ 25	Presence of 1 or more mild-to-moderate obesity-related complications	Tertiary
Obesity Stage 2	BMI ≥ 25	Presence of 1 or more severe obesity-related complications	

AMA, June 2013

"…..the view of obesity as a behavioral decision is debunked by biomedical evidence……..obesity is a primary disease, and the full force of our medical knowledge should be brought to bear on its prevention and treatment……"

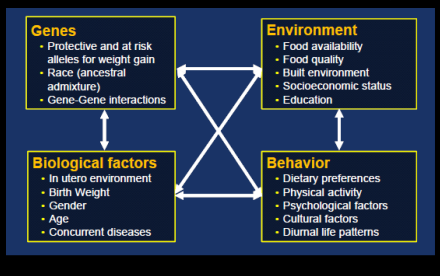
AMA: Essential Criteria of A Disease

1. Characteristic signs or symptoms
2. Impairment in the normal functioning of some aspect of the body
3. Results in harm or morbidity

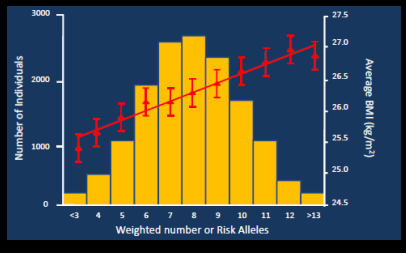
Obesity Definition

Obesity is a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences.

Determinants of Obesity



BMI increases as the number of alleles increases



Old Treatment Paradigm
Treat Weight *LAST*

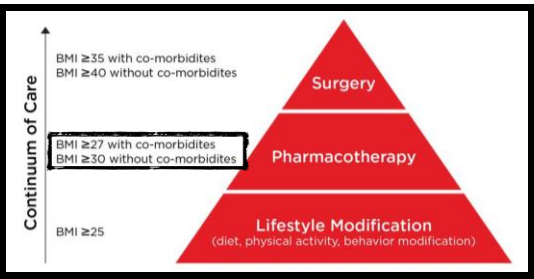
	Dys-lipidemia	HTN	IGT
Monitor	Lipid panels Lipoproteins subsets	Blood Pressure Ambulatory Blood Pressure	Blood sugar Glycosylated hemoglobin distribution
Diet	↓ Total fat ↓ Chol. ↑ Fiber	↓ Sodium ↑ K ↔	↓ Sugar Distribute CHO, PRO, Fat
Meds	Statins Fibrates Resins Niacin	Central acting Renal effective Peripherally acting diuretics THiazide diuretics	Insulin Sulfonylureas Glidizones Absorption agents

	Overweight/Obesity
Monitor	Weight and BMI
Diet	Any diet patient will adhere to
Exercise	150 minutes of moderate-intensity aerobic activity/wk and muscle-strengthening activities on ≥ 2 days/wk
Meds	Orlistat, phentermine, phentermine/topiramate, lorcaserin

CHANGING THE TREATMENT PARADIGM

New Treatment Paradigm
Treat Weight *FIRST*

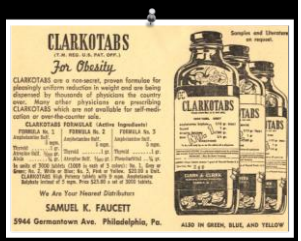
	Overweight/Obesity		
Monitor	Weight and BMI		
Diet	Any diet patient will adhere to		
Exercise	150 minutes of moderate-intensity aerobic activity/wk and muscle-strengthening activities on > 2 days/wk		
Meds	Orlistat, phentermine, phentermine/topiramate, lorcaserin		
	Dys-lipidemia	**HTN**	**IGT**
Monitor	Lipid panels Lipoproteins subsets	Blood Pressure Ambulatory Blood Pressure	Blood sugar Glycosylated hemoglobin distribution
Diet	↓ Sat + trans fat ↑ Omega-3s ↑ MUFA ↓ Simple CHOs ↓ ETOH	DASH Diet ↓ Sodium ↓ ETOH	Glycemic index diet ↑ Fiber Diabetic diet
Meds	Statins Fibrates	ACE Inhibitors ARBs Thiazide diuretics	Metformin Exenatide Liraglutide



Treatment Pyramid

Use of Anti-Obesity Medications

- BMI: ≥30 or ≥27+comorbidity
- Combine with behavioral modification, physical activity, and nutrition for optimal results
- Continue medications only in responders
- Use combinations if mono therapy does not give desired results
- Long-term continuation if indicated


CLARKOTABS

For Obesity.

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CLARKOTABS FORMULAE (Active Ingredients)

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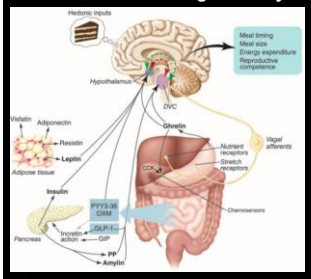
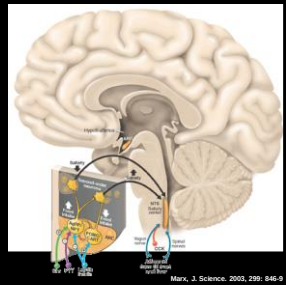
Interacting Pathways of Energy Regulation





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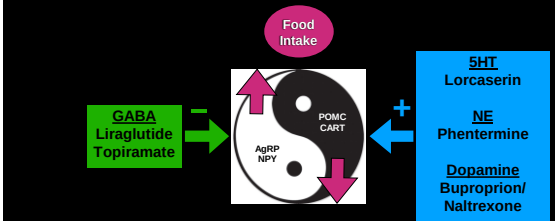
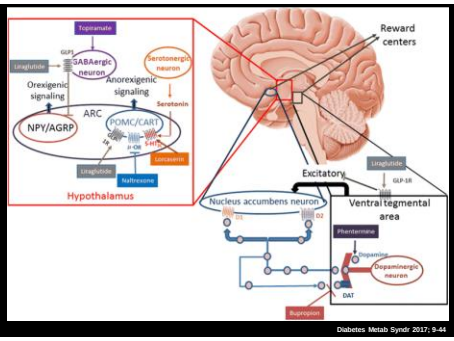
Central Mechanisms of Action



POMC=ProOpioMelanoCortin
CART=Cocaine and Amphetamine Regulated Transcript
NPY=Neuropeptide Y
AgRP=Agouti-Related Peptide



Diabetes Metab Syndr 2017; 9-44

Current Anti-Obesity Medications

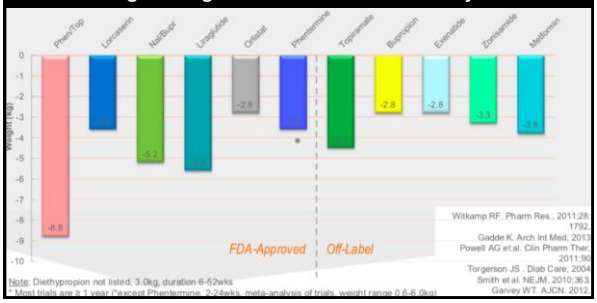
FDA approved

- Phentermine
- Diethylproprion
- Phendimetrazine
- Orlistat
- Lorcaserin
- Phentermine/Topiramate
- Naltrexone/Bupropion
- Liraglutide

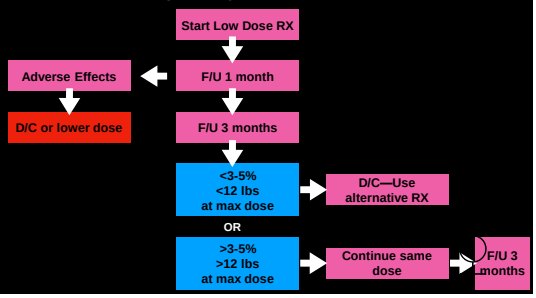
Off Label Use

- Metformin
- Exenatide (and other GLP-1s)
- Canagliflozin (and other SGLT-2is)
- Pramlintide
- Topiramate
- Zonisamide
- Bupropion

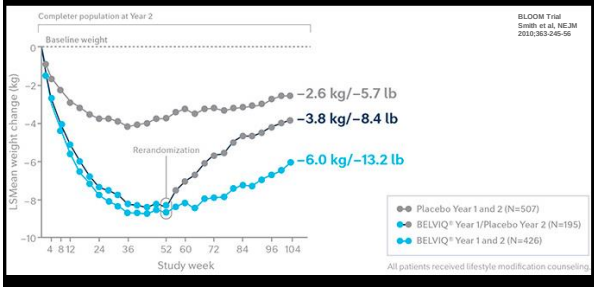
Average Weight Loss with Anti-Obesity Meds



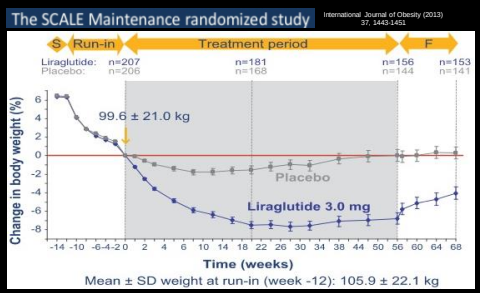
Med Continuation: *High Responders lose >5% in 3 months*



Medications are needed for long durations



Medications are needed for maintenance



Anti-Obesity Medications

+	Potential Targets	**Mechanism of Action:**
CI	Contraindications* *Not a complete list	**Dosing:**
AE	Common Adverse Effects	**Advice/Precautions:**

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 of Action:
- Pancreatic lipase inhibitor—Blocks ~30% of fat intake

Dosing:
- Start 120mg daily
- Range: 120mg/d—120mg TID
- Alli is an 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

Phentermine

+ Increased hunger
Low metabolic rate

CI Active CV disease
Poorly controlled HTN
Cardiac arrhythmias
Hyperthyroidism
Glaucoma

AE Dry mouth
Constipation
Insomnia
Palpitations, HA, Irritability

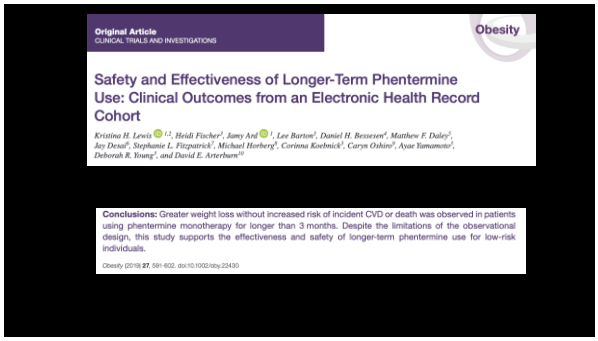
Mechanism of Action:
- Inhibits Na-dependent NE transporter to reduce NE uptake
- Inhibits serotonin and dopamine reuptake

Dosing:
- 15-30mg capsule, 37.5mg tablet QD-BID
- 8mg TID
- 1/2 of 37.5mg tablet

Advice/Precautions:
- *Schedule IV controlled substance*
- Monitor BP, awareness of caffeine intake
- ***NO*** evidence of addiction, withdrawal
- ***NO*** established relationship related to cardiac valvulopathy or pulmonary hypertension

Why you shouldn't be afraid of phentermine

- Phentermine is the most widely used anti-obesity drug in the U.S.
- Warnings of adverse CV and psychiatric effects are included in FDA labeling. However, the few clinical reports of such adverse effects are anecdotal.
- When phentermine was approved (1959) the expectations were that it would prove to be addictive. Due to the structural similarities between phentermine and amphetamine and on evidence in rats that phentermine stimulated spontaneous activity. No evidence suggesting the drug had human addiction potential appeared in clinical trials conducted prior to approval.
- After 60 years, there is no evidence in peer-reviewed medical literature to support the hypothesis that phentermine has significant human addiction potential.
- One retrospective study investigated symptoms occurring when patients treated with long-term phentermine ceased taking it. The study found that patients on long-term phentermine who ceased phentermine abruptly by their choice did not have an amphetamine-like withdrawal symptom complex. Significantly, **there was no evidence of phentermine cravings**.



Topiramate (Topamax ®)

+

Migraines, seizures, binge eating, excessive cravings (carbs), on mood stabilizers (sub/alt), on phentermine

CI

Severe depression
Pregnancy
Kidney Stones

AE

WARNING: Acute angle glaucoma, SI, pregnancy

Parasthesias, somnolence, kidney stones, cognitive impairment, taste aversion

Mechanism of Action: *Unclear*
- AMPA, Glutamate receptor
- Carbonic anhydrase
- GABA-A (isozymes II, IV)
- Voltage-dependent sodium channels

Dosing:
- Start 25mg daily
- Range: 25-200mg/day

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

Try zonisamide if cognitive impairment or dyspepsia is intolerable

Phentermine/Topiramate CR (Qysmia®)

+

Non-child bearing pt
Excessive hunger
Mild SE with phentermine

CI

Active CV Disease
Uncontrolled HTN
Hyperthyroidism
Glaucoma
Kidney Stones
During or within one day of MAOI

AE

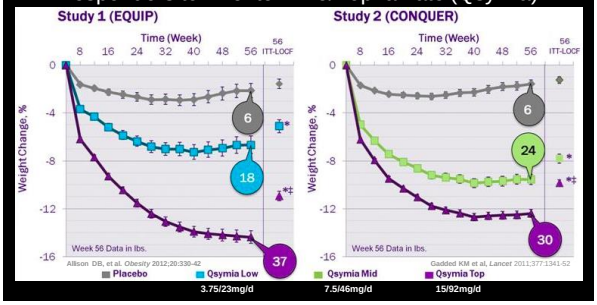
Dry mouth, restlessness, insomnia, palpitations, HA, constipation
Parasthesias, dysgeusia, somnolence, cognitive impairment

Mechanism of Action:
- Sympathomimetic (NE) release in hypothalamus decreases hunger
- AMPA, GABA receptor—decreases cravings

Dosing:
- Start 3.75/23mg x14d then 7.5/46mg
- Range 3.75/23mg—15/92mg/day

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
- 1/4 cup lemon/lime juice for paresthesias

Responders to Phentermine/Topiramate (Qsymia)



Lorcaserin (Belviq ®)

+

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

CI

Pregnancy

AE

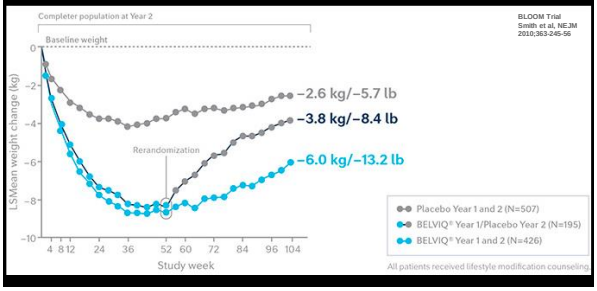
Headache, nausea dizziness, dry mouth, fatigue, nasopharyngitis
priapism

Mechanism of Action:
- Selective serotonin 5HT2c receptor agonist
- Increases satiety via alpha-MSH and POMC neuron activation

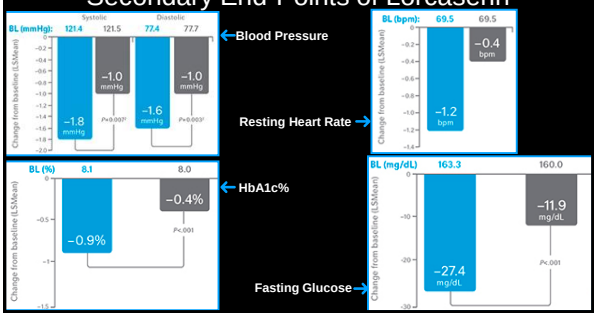
Dosing:
- 10mg BID or 20mg XR daily
- Can use QD daily in evening as combination

Advice/Precautions:
- Schedule IV controlled substance
- Watch co-administration with SSRIs, bupropion or concern about serotonin syndrome
- Caution with congestive heart failure
- No concern about combo with phentermine

Weight Loss Over 2 Years



Secondary End-Points of Lorcaserin



Naltrexone/Bupropion (Contrave ®)

+ Excessive hunger and cravings
Patients who smoke
On bupropion already

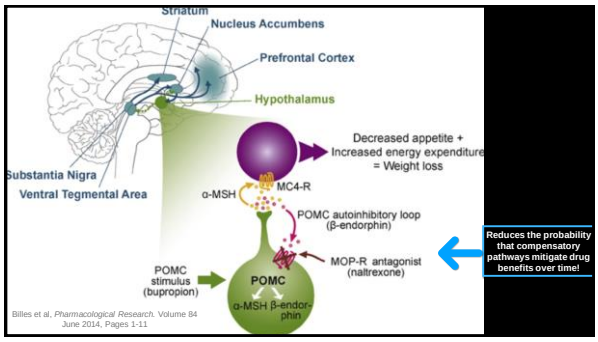
CI Seizures, uncontrolled HTN
Bulimia
Chronic Opioid Use
Upcoming surgery

AE WARNING: Neuropsychiatric rxns, SI, behavior changes nausea, headache, insomnia, dizziness, dry mouth

Mechanism of Action:
- Reuptake inhibitor DA and NE activity increases POMC activity
- Naltrexone blocks B-endorphin, POMC auto inhibitor

	Morning dose	Evening dose
Starting: Week 1	1	
Week 2	1	1
Week 3	2	1
Week 4-onward	2	2

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



Liraglutide (Saxenda ®)

+ Diabetes or Prediabetes
(Not indicated for diabetes tx)
Pts with insurance coverage

CI Medullary thyroid CA (including FHx)
MEN type II
Hx of pancreatitis

AE Nausea, HA, Angioedema
Gastroparesis
Cannot be combined with DPP4i

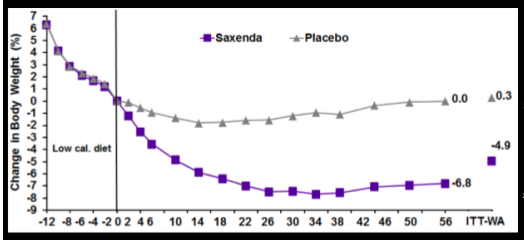
Mechanism of Action:
- GLP-1 receptor agonist
- Increase satiety, decreases gastric emptying
- 97% homologous to human GLP-1
- Central acting by inhibition of NPY/AgRP

Dosing: Daily SC injections

WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5
0.6 mg	1.2 mg	1.8 mg	2.4 mg	3.0 mg

Advice/Precautions:
- Nausea may improve with time
- No data to support reports on increased risk of pancreatic ductal neoplasia and pancreatic cancer

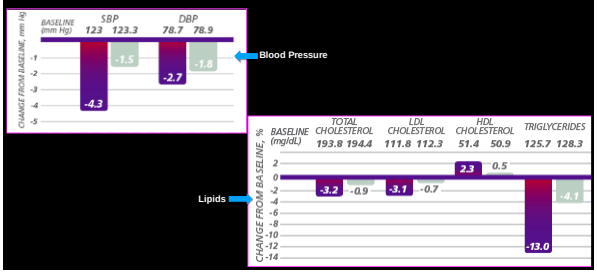
Average Weight Loss With Liraglutide 3mg



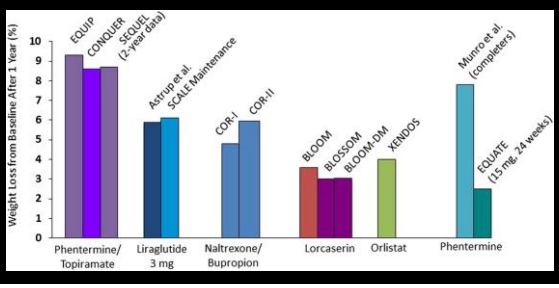
Astrup A, et al. Int J Obes (Lond) 2012; 36: 843–854.

Wadden TA, et al. the SCALE study. Int J Obes (Lond) 2013; 37: 1443–1451.

Improvements in Secondary End-Points with Liraglutide 3mg



Comparison of Anti-Obesity Medications



Before Adding A Med…

Determine if a med is the cause!

Weight Gain Promoting Medications	Alternate Agents
Diabetes Treatments: Insulin Sulfonylureas Thiazolidinediones	Amylin analog—pramlintide GLP-1 agonists metformin SGLT-2 inhibitors DPP4 inhibitors
Glucocorticoids Prednisone, Methyl-prednisolone, etc	Immunosuppressive agents DMARDs
Contraceptives Depo-provera	Non-hormonal contraception OCPs
Beta-Blockers Propranolol, Metoprolol, Atenolol	Other anti-hypertensives such as ACEi Third generation BBs have less weight gain (carvediolol, nebivolol)
Anti-Histamines Diphenhydramine, Hydroxyzine, Cetirizine, Fexofenadine	Loratadine

Weight Gain Promoting Medications	Alternate Agents
Atypical Antipsychotics: clozapine, olanzapine, quetiapine, risperidone, aripiprazole	ziprasidone
Anti-Depressants: Tricyclics: nortriptyline, amitriptyline SSRIs: paroxetine, citalopram, escitalopram Others: trazodone, mirtazipine, venlafaxine	bupropion sertraline CBT memantine or ketamine L-methylfolate (Deplin ®)
Anti-Epileptics gabapentin, valproic acid	topiramate zonisamide lamotrigine
Mood Stabilizers lithium	topiramate zonisamide lamotrigine cariprazine (Vraylar ®)

Want to know more?

Sign up for a roundtable event

Questions?

stacy.chronister@okstate.edu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