acofp'16
ACOFP 53rd Annual Convention & Scientific Seminars

The Landscape of Obesity Pharmacotherapy: Current and Future Treatment Options

Adarsh Gupta, DO, FACOFP

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Please check where applicable and sign below. Provide additional pages as necessary.

Name of CME Activity: ACOFP 53rd Annual Convention and Scientific Seminars

Dates and Location of CME Activity: April 6-9, 2016, The San Juan Puerto Rico Convention Center
Your presentation: Friday, April 8, 2015 from 9:00am-10:00am: The Landscape of Obesity Pharmacotherapy: Current and Future Treatment Options

Name of Faculty/Moderator: Adarsh K Gupta, DO, MS, FACOFP

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Organization With Which Relationship Exists	Clinical Area Involved
1. Eisai	1. Belviq Drug
2. Takeda	2. Contrave Drug
3. Novo Nordisk	3. Saxenda Drug
4.	4.

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- Did you travel to participate in this training? **Yes: X** **No:**
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Signature:  **Date:** 1/15/16

Adarsh K Gupta, DO, MS, FACOFP

Please email this form to joank@acofp.org as soon as possible
Deadline: Friday, January 15, 2016

Pharmacologic approach to obesity management

THE LANDSCAPE OF OBESITY PHARMACOTHERAPY: CURRENT AND FUTURE TREATMENT OPTIONS

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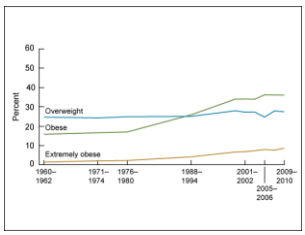
DIRECTOR, CENTER FOR INFORMATION MASTERY
ASSOCIATE PROFESSOR, FAMILY MEDICINE

OBJECTIVES

- Identify patients who are candidates for pharmacotherapy to promote weight loss
- Learn about short- and long-term anti-obesity agents
- Implement pharmacotherapy in consideration of medication and patient factors
- Implement strategies to discuss weight-loss medications with patients

LATEST OBESITY STATS

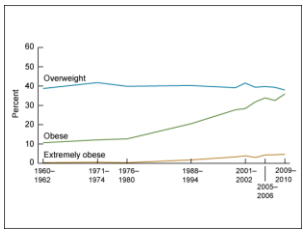
Women aged 20-74



Trends in overweight, obesity, and extreme obesity among women aged 20–74 years: United States, 1960–1962 through 2009–2010 (CDC.gov)

LATEST OBESITY STATS

Men aged 20-74



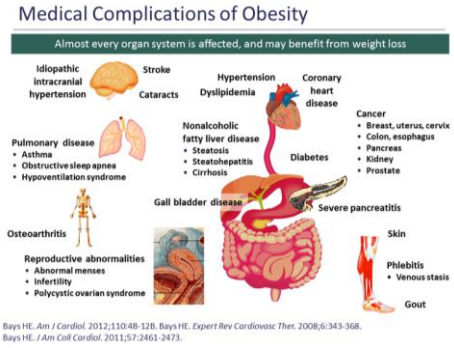
Trends in overweight, obesity, and extreme obesity among men aged 20–74 years: United States, 1960–1962 through 2009–2010 (CDC.gov)

LATEST OBESITY TRENDS

- Increasing Obese and Morbidly Obese population
- Obesity is more prevalent than smoking and is highly associated with chronic conditions and overall poor physical health similar to smoking and excessive alcohol use[1]

1. Sturm R. Does obesity contribute as much to morbidity as poverty or smoking? Public Health. 2001;115(3):229

TOXIC ENVIRONMENT

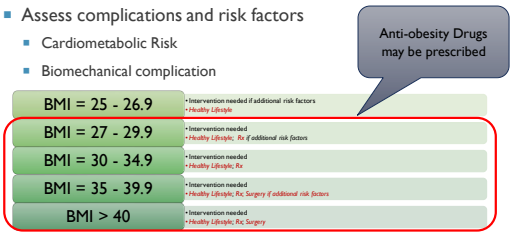


NEED TO ADDRESS OBESITY!

Weight Management Options

STEPS IN DETERMINING TREATMENT

- Determine BMI.
- Assess complications and risk factors
  - Cardiometabolic Risk
  - Biomechanical complication



STEPS IN DETERMINING TREATMENT

- Treatment Options
  1. Correcting underlying metabolic problems (if exists)
  2. Individualized healthy lifestyle program
  3. Adjunct Options
     1. Mild energy-deficit regimen
        - Diet, diet and exercise, behavioral therapy
     2. Aggressive energy-deficit regimen
        - VLCD w/extensive exercise program
     3. Obesity drugs
        - Optimize current medication
        - Anti-Obesity Medications
     4. Surgery

CORRECT OBESITY CAUSES

- Underlying medical conditions (if exists)
  - Hypothyroidism, Cushing's, PCOS, Insulin dependent Diabetes
- Optimize Medications
  - Psychotropic medications
  - Anti-depressants
  - Blood pressure medications
  - Diabetes medications
  - Steroids

HEALTHY LIFESTYLE PROGRAM

- Improved physical activity
  - Engage in physical activity each day : a total of 60 minutes for children, 30 minutes for adults
- Reduced calorie diet
  - Eat balanced diet
  - Avoid high calorie foods
  - Add variety in meals
- Stress management
- Improved sleep

ADJUNCT OPTIONS

- Meal Replacement Programs w/Exercise Program
  - Low calorie diet (LCD)
    - Reduced Calorie diet – 1200 – 1500 calories / day
    - Utilizing Meal Replacements
      - Calorie controlled
      - Packed with Essential Vitamin and Minerals
  - Very low calorie diet (VLCD)
    - Formula diet of 800 calories or less.
    - Must be under proper medical supervision.
    - Produce significant weight loss in moderately to severely obese patients

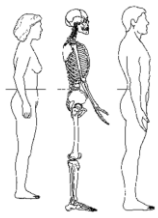
ADJUNCT OPTIONS

- Pharmacotherapy
  - Optimize current medication for weight neural or weight loss effect
  - Anti-obesity medications
    - BMI > 30 or >27 with co-morbidities
    - Problem here is that not every one with same height and weight have same amount of fat

ADJUNCT OPTIONS

- Pharmacotherapy

BMI	Health Risk	
	Waist less than or equal to: 40 in. (men) 35 in. (women)	Waist greater than: 40 in. (men) 35 in. (women)
18 or less	-	N/A
18-24	-	N/A
25-29	Increased	High
30-39	High	Very High
40 or greater	Extremely High	Extremely High



Measure at the Level of Iliac Crest

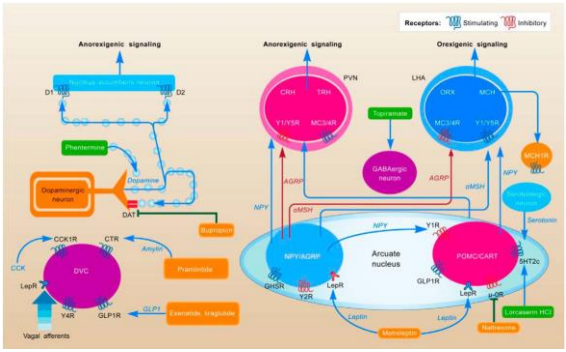
ADJUNCT OPTIONS

- Pharmacotherapy
  - Anti-obesity medications – additional considerations
    - Weight loss drugs should never be used without continued concomitant lifestyle modifications and as part of a comprehensive weight loss program.
    - Continual assessment of drug therapy for efficacy and safety is necessary.
    - If the drug is efficacious in helping the patient to lose and/or maintain weight loss and there are no serious adverse effects, it can be continued.
    - If not, it should be discontinued

ADJUNCT OPTIONS

- Pharmacotherapy
  - Anti-obesity medications – Contraindications
    - Pregnancy or lactation
    - Unstable cardiac disease
    - Uncontrolled hypertension (SBP >180, DBP > 110 mmHg)
    - Unstable severe systemic illness
    - Unstable psychiatric disorder or history of anorexia
    - Other drug therapy, if incompatible (eg MAO inhibitors, migraine drugs, adrenergic agents, arrhythmic potential)
    - Closed angle glaucoma (caution)
    - General anesthesia

SOURCE: NHLBI Obesity Education Initiative, Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults



Source: Clin Pharmacol Ther. 2014;95:53–66 (25).

SHORT-TERM PHARMACOTHERAPY

- These drugs were approved even before the concept of long-term approach of treating obesity came into being
- Currently 4 FDA-approved noradrenergic agents are indicated for short-term use (<12 weeks)
  - Phentermine, Diethylpropion, Phendimetrazine, Benzphetamine
- None of these drugs are required by the FDA to meet the current standard of at lease 5% weight loss

PHENTERMINE

- Originally approved for short-term use (in 1959)
  - There are no published studies of phentermine monotherapy beyond 9 months1
- In the trials that have been reported, phentermine appears to be effective during use, causing a reduction in hunger and appetite2
  - It is a sympathomimetic that acts as an appetite suppressant by inhibiting adrenaline reuptake

1. Goldstein DJ, Potvin JH. Long-term weight loss: the effect of pharmacologic agents. Am J Clin Nutr. 1994; 60:647-657
2. Glazer G. Long-term pharmacotherapy of obesity 2000. A review of efficacy and safety. Arch Intern Med. 2001;161

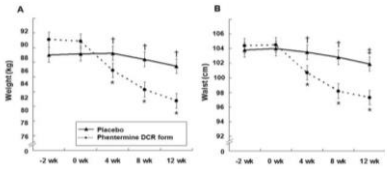
PHENTERMINE

- Results in modest weight loss (Level 2 evidence) [1]
  - Based on randomized, double-blind, placebo-controlled trial of 12 weeks of treatment with phentermine DCR 30 mg (n = 37) or placebo (n = 37), administered once daily in patients with obesity with controlled diabetes, hypertension or dyslipidemia.

1. Diabetes Obes Metab 2010 Oct;12(10):876

PHENTERMINE

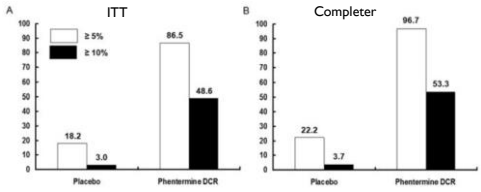
- Results in modest weight loss (Level 2 evidence) [1]
  - Mean weight loss of 8.1 kg vs. 1.7 kg (p , 0.001)
  - Mean waist circumference reduction of 7.2 cm vs. 2.1 cm (p < 0.001)



1. Diabetes Obes Metab 2010 Oct;12(10):876

PHENTERMINE

- Results in modest weight loss (Level 2 evidence) [1]
  - >5 % weight loss in 87% vs. 18% (p < 0.001)
  - >10 % weight loss in 49% vs. 3% (p < 0.001)



1. Diabetes Obes Metab 2010 Oct;12(10):876

OTHER SYMPATHOMIMETIC DRUGS

- Drugs that act like phentermine and are approved by FDA for short-term use include
  - **Benzphetamine** (approved for short-term use)
    - 25-50 mg PO QD – TID
    - Brand Name - Didrex
  - **Diethylpropion** (approved for short-term use)
    - 25 mg PO TID or 75 mg ER tab QD
  - **Phendimetrazine** (approved for short-term use)
    - 17.5 mg – 35 mg PO BID-TID. Max 70mg TID
    - 105 mg ER PO QAM
    - Bontrol SR, Bontril PDM

LONG-TERM PHARMACOLOGY

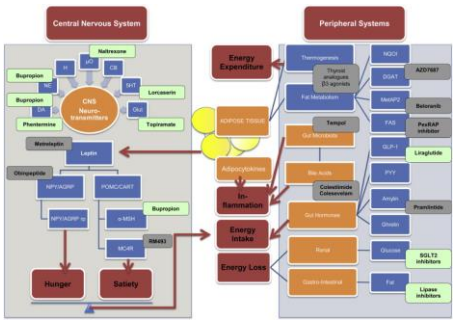
- These drugs are approved by FDA for chronic weight management
  - Orlistat (Xenical®), (Alli®)
  - Lorcaserin (Belviq®)
  - Phentermine/topiramate ER (Qsymia®)
  - Naltrexone/Bupropion SR) (Contrave®)
  - Liraglutide (Saxenda®)

MEDICATIONS APPROVED FOR CHRONIC WEIGHT MANAGEMENT

Medication	Mechanism of Action	Dosing	Response Evaluation
Orlistat	ORLISTAT		abel
Lorcaserin	LORCASERIN • Lorcaserin is a selective serotonin 2c (5HT-2c) receptor		loss at 12
Phentermine / Topiramate ER	PHENTERMINE / TOPIRAMATE ER • Phentermine-topiramate controlled-release compounds help to suppress appetite. • The combination medication uses lower doses of each		n to 59mg x 14 g (top oss at 12
Naltrexone SR/ Bupropion SR	NALTREXONE / BUPROPION SR • Bupropion component of this combination therapy is thought		loss at 12
Liraglutide 3.0mg	LIRAGLUTIDE 3.0mg • GLP-1R agonists, enhance insulin sensitivity, suppress appetite and delay gastric emptying. • Liraglutide works to stimulate the release of insulin from beta cells and suppresses glucagon secretion fromalpha cells when blood glucose levels are elevated		loss at 16

MEDICATIONS APPROVED FOR CHRONIC WEIGHT MANAGEMENT

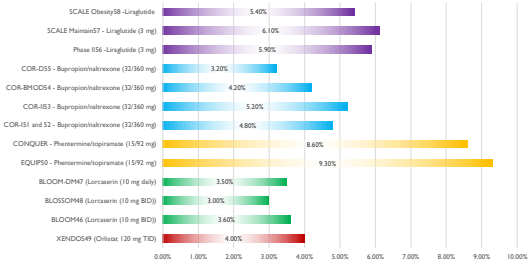
Medication	Safety	Contraindications	Side Effects
Orlistat	Warning: Increase cyclosporine exposure; rare liver failure; concomitant multivitamin advised	Chronic malabsorption; gall bladder disease	Steatorrhea (fatty stool discharge)
Lorcaserin	Warning: serotonin syndrome; valvular heart disease; congestive heart failure; cognitive impairment; depression; priapism	MAOIs. Use with caution with serotonergic drugs (SSRI, SNRI)	Headache, dizziness, fatigue
Phentermine / Topiramate ER	Warning: fetal toxicity; acute myopia; cognitive dysfunction; metabolic acidosis	Glaucoma; hyperthyroidism; MAOIs	Paresthesia, dysgeusia, dizziness, dry mouth
Naltrexone SR/ Bupropion SR	Boxed warning: suicidality Warning: BP, HR; Increased seizure risk; glaucoma; hepatotoxicity	Seizure disorder; uncontrolled HTN; chronic opioid use; MAOIs	Nausea, vomiting, headache, dizziness, insomnia
Liraglutide 3.0mg	Boxed warning: thyroid c-cell tumors in rodents Warning: acute pancreatitis, acute gall bladder disease, serious hypoglycemia if used with insulin secretagogue, heart rate increase; use caution in renal impairment; hypersensitivity reactions can occur; monitor for depression or suicidal thoughts	Patients with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia	Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain



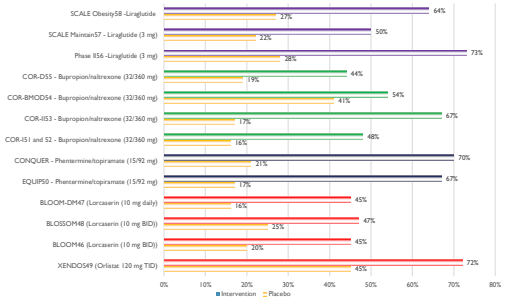
Targets for antiobesity drugs. Green boxes denote drugs approved (not all for obesity indications). Grey boxes denote drugs in phase I-III development.

Source: Andrea Pucci, Nicholas Finer, Canadian Journal of Cardiology, Volume 31, Issue 2, 2015, 142–152

MEAN WEIGHT LOSS ACHIEVED BY ANTI-OBESITY DRUGS IN ONE YEAR



PERCENTAGE OF PATIENT WITH >5% WEIGHT LOSS: INTERVENTION VS PLACEBO



EMERGING NOVEL ANTI-OBESITY AGENTS

- Pure CB1 receptor neutral antagonist
  - Unlike rimonabant, it has fewer side effects so far in studies

EMERGING NOVEL ANTI-OBESITY AGENTS

- Tesofensine
  - Monoamine Reuptake inhibitor
  - Incidentally found to induce weight loss during investigation as a therapy for Alzheimer disease and Parkinson disease
  - This agent prevents the reuptake of serotonin, noradrenaline and dopamine, and thereby suppresses appetite and increases thermogenesis
  - As with other agents that act on NE pathways, an increase in heart rate was observed in phase II clinical trials

Source: George, M., Rajaram, M., Shanmugam, E., 2014. New and emerging drug molecules against obesity. J. Cardiovasc. Pharmacol. Ther. 19 (1), 65a76.

EMERGING NOVEL ANTI-OBESITY AGENTS

- Velneperit
  - It has been well recognized over the last 2 decades that neuropeptide Y (NPY) stimulates food intake, reduces energy expenditure, and increases body weight by activating NPY receptors, Y1, and Y5 present in the hypothalamus.
  - Velneperit is a Y5 receptor antagonist that prevents the binding of NPY to the Y5 receptors and thus decreases hunger and controls energy balance.
  - The lack of significant benefit of velneperit over placebo in the low calorie diet study has raised several questions on the future prospects of the drug and the need for further drug development.

Source: George, M., Rajaram, M., Shanmugam, E., 2014. New and emerging drug molecules against obesity. J. Cardiovasc. Pharmacol. Ther. 19 (1), 65e76.

EMERGING NOVEL ANTI-OBESITY AGENTS

- Zonisamide-Bupropion
  - Zonisamide found to cause weight loss. Although the precise mechanism is yet to be elucidated, modulation of sodium channel, carbonic anhydrase inhibition, and enhancement of dopamine and serotonin transmission are said to play a role in inducing weight loss. Bupropion causes weight loss by increase in the levels of dopamine that decreases appetite
  - Combination of zonisamide with bupropion was observed to be superior to bupropion or zonisamide monotherapy in inducing weight loss in a pilot study.

Source: George, M., Rajaram, M., Shanmugam, E., 2014. New and emerging drug molecules against obesity. J. Cardiovasc. Pharmacol. Ther. 19 (1), 65e76.

EMERGING NOVEL ANTI-OBESITY AGENTS

- Cetilistat
  - It is a pancreatic lipase inhibitor that is undergoing phase III clinical trials.
  - Although cetilistat is similar to orlistat in its mechanism, it is claimed to have a superior safety profile that was demonstrated in a phase 2b clinical trial.

Source: Kopelman P, Groot G de H, Rissanen A, et al Obesity (Silver Spring). 2010;18(1):108-115

Thank You!!!

For more information, please contact
guptaad@rowan.edu