

Update on Weight Loss Pharmacotherapy

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Learning Objectives

- List the medications that are currently available for the treatment of obesity, describe their mechanisms of action, and list their side effects.
- List the medications that are used for other health problems that contribute to weight gain and describe an approach to minimizing this problem.
- List the medications that are in the pipeline that likely will become available over the coming several years.

Currently Available Options

- Effectiveness
- Accept weight where it is
 - Diet/Exercise, 4-8% weight loss
 - Drugs, 5-8% weight loss
 - Surgery 20-30% weight loss
- Low
↓
High

Currently Available Options

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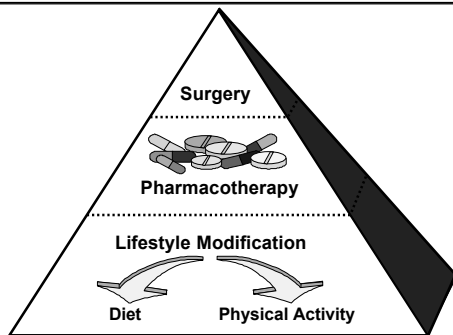
Risk
Low
↓
High

A Guide to Selecting Treatment

Treatment	BMI category				
	25-26.9	27-29.9	30-34.9	35-39.9	≥40
Diet, physical activity, and behavior therapy	With co-morbidity +	+	+	+	+
Pharmacotherapy		With co-morbidity +	+	+	+
Surgery				With co-morbidity +	+

The Practical Guide. 2000

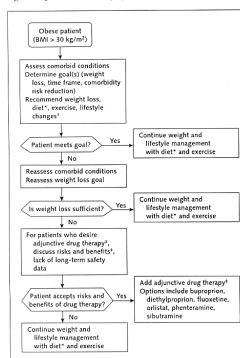
Obesity Treatment Pyramid



Drug Treatment of Obesity

- Current medications 5-8% wt loss
- Treatment probably needs to be lifelong.
- Drugs probably not paid for by insurance.
- Issues of FDA approval, long term safety, and efficacy.
- Choice of mechanisms, OTC versus prescription, combinations?

Figure. Algorithm for managing obesity.



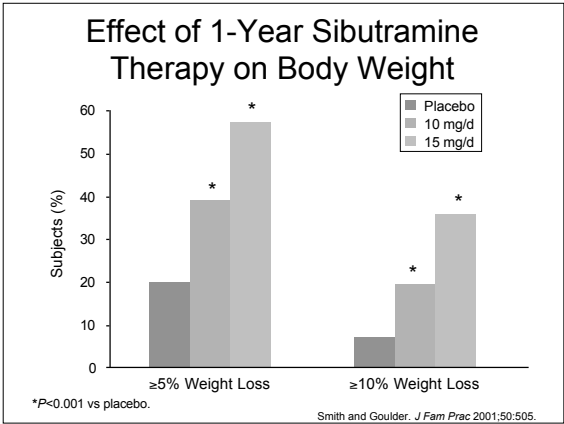
Clinical Practice Guideline
From the American College
Of Physicians
Ann Intern Med
142:525-531, 2005

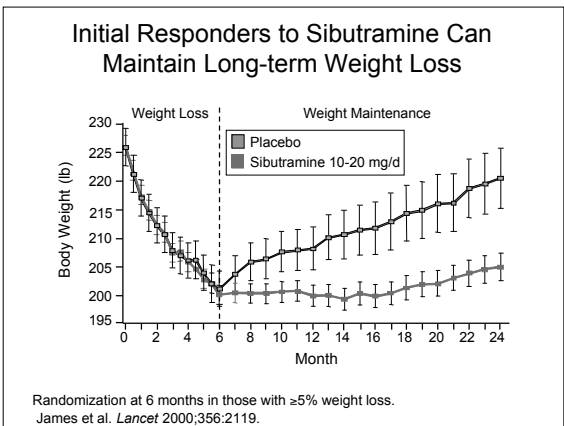
"For patients who choose to use
Adjunctive drug therapy, options
include sibutramine, orlistat, phentermine
Diethylpropion, fluoxetine, and bupropion.
The agent of choice will depend on the
Side effects profile of each drug and the
Patient's tolerance of those side effects."

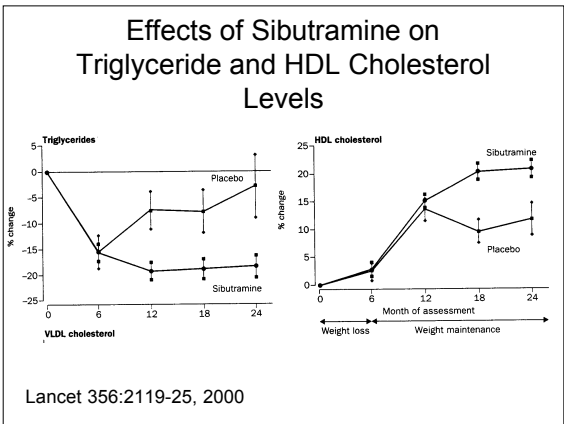
BMI = body mass index. *References 13-15. U.S. Preventive Services Task Force recommendations (11, 12). †Assess side effects and efficacy; no data are available past 12 months except for orlistat.

Sibutramine

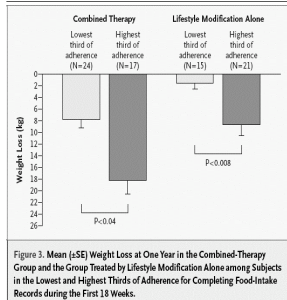
- Meridia (Abbott) 10-15mg/d, \$90.00/mo
- combination NE/serotonin re-uptake inhibitor
- Inhibits appetite (increases satiety)
- 50-60% lose 5% of body weight or more
- 30% of subjects lose 10%







Adherence correlates with weight loss when combining diet and medications



Wadden, NEJM 353:2111-2120, 2005

Adverse Effects of Sibutramine Therapy

Adverse Effect	Subjects (%)	
	Placebo	Sibutramine
Dry mouth	4.2	17.2
Constipation	6.0	11.5
Insomnia	4.5	10.7
Dizziness	3.4	7.0
Hypertension	0.9	2.1
Tachycardia	0.6	2.6
Palpitation	0.8	2.0

Meridia Package Insert, 1997.

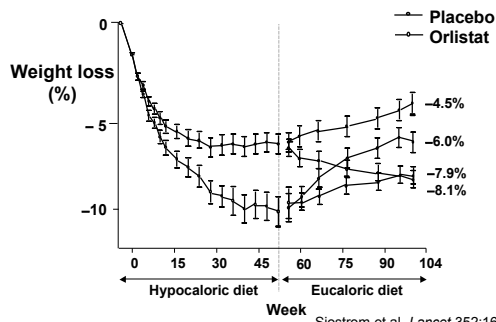
Orlistat

- Xenical (Roche)
- Pancreatic Lipase inhibitor
- Inhibits fat absorption by 30%
- 120 mg tid, \$100.00/mo
- GI side effects: oily stools, urgency
- MVI to prevent fat soluble vitamin deficiency

Orlistat

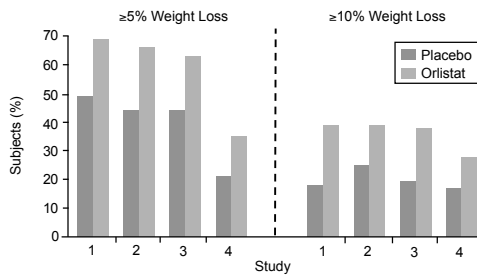
- Thousands of patients studied up to 4 years of exposure.
- Approved for long term use
- 5-8% weight loss on average
- May be useful in those with poorly controlled hypertension or psych problems
- Recently FDA panel supported OTC application

Effect of Orlistat on Body Weight



Sjostrom et al. *Lancet* 352:167, 1998

Clinical Trials Evaluating Effect of 1-Year Orlistat Therapy on Body Weight



$P < 0.05$ orlistat vs placebo.

1. Sjostrom et al. *Lancet* 1998;352:167.
2. Davidson et al. *JAMA* 1999;281:235.
3. Rossner et al. *Obes Res* 2000;8:49.
4. Finer et al. *Int J Obes Relat Metab Disord* 2000;24:306.

Effects of Orlistat on Glucose and HbA1c in Overweight and Obese Patients with Type 2 Diabetes

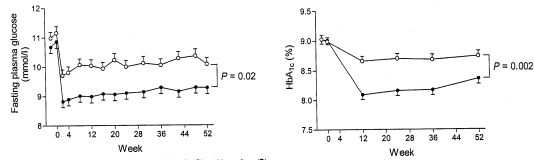


Figure 4—HbA_{1c} over 1 year of double-blind treatment with placebo (○) or 120 mg orlistat (●). P = 0.002. Inset squares mean difference from placebo in the change from baseline over 52 weeks. Figure 3—Fasting serum glucose levels over time with placebo (○) or 120 mg orlistat (●). P = 0.002. Inset squares mean difference from placebo in the change from baseline over 52 weeks.

Kelley Diabetes Care 25:1033-41, 2002

4 Years of Treatment With Orlistat Reduces the Risk of Developing Diabetes

	Placebo	Orlistat*
Weight loss at 1 y, kg	7.5	11.4
Weight loss at 4 y, kg	4.1	6.9**
>10% weight loss at 4 y	16%	26%**
>5% weight loss at 4 y	37%	53%**
4-year incidence of T2DM	9.0%	6.2%‡

*Represents a 37% reduction in the incidence of T2DM beyond the impact of diet and lifestyle intervention (P = 0.0032)

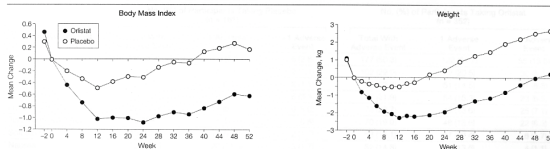
*120 mg TID.

**P < 0.001 vs placebo.

Sjostrom L et al. Diabetes Care 2004;27:155

Effects of Orlistat on BMI and Weight in Obese Adolescents

Figure 2. Change in Mean Body Mass Index and Weight



P < .001 for body mass index (orlistat vs placebo). P < .001 for weight change (orlistat vs placebo). Body Mass Index is calculated as weight in kilograms divided by the square of height in meters. Coefficient of variation is about 14% for each data point for body mass index and about 16% for weight.

JAMA 293:2873-2883, 2005

Gastrointestinal Side Effects of Orlistat Therapy

	Year 1		Year 2	
	Placebo	Orlistat	Placebo	Orlistat
Fatty/oily stool	5	31	1	8
Increased defecation	7	20	2	2
Liquid stools	10	13	5	8
Fecal urgency	3	10	2	3
Flatulence	3	7	2	3
Flatus with discharge	0	7	0	1
Fecal incontinence	0	7	0	2
Oily evacuation	1	6	0	5
Low plasma vitamin conc.:				
Vitamin A	0.6	0.3	0.8	0
Vitamin D	0.6	5.1	0.8	3.1
Vitamin E	0.9	4.6	0	1.6

Values are percentage of subjects. Sjostrom et al. *Lancet* 1998;352:167.

OTC Orlistat (Alli)

- On the market since spring 2007, 100 million in sales so far
- 60 mg dose, about 60 cents/tablet
- Data suggests less weight loss in “overweight” category
- Drug interactions with coumadin (vit K) and cyclosporin (reduced drug levels)

Phentermine

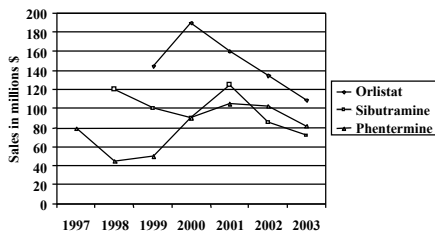
Zhaoping L et al. *Ann Int Med*, 2005

- Increases NE content in the brain
- Chemically related to amphetamine, not addictive
- 15-37.5 mg/d, \$40.00/month
- FDA approved for only 3 months use
- 5-8% weight loss
- Side effects: hypertension, headache, nervousness

Phentermine

- Most widely prescribed anti-obesity drug
- No evidence of serious side effects when used as a single drug
- Is it ethical to prescribe long term?
 - Legally?
 - Beneficence
 - Non-Maleficence
 - Autonomy

Sales of Rx Obesity Medications (US)



Average length of therapy per patient per year is 90-93 days

Other Medications: That may Increase Weight

- Anti-diabetic medications
 - Sulfonylureas
 - Insulin
 - TZDs
- Mood Stabilizers, antipsychotics
- Birth Control Pills: Depo Provera
- Glucocorticoids: Prednisone

What to do About These Medications

- Monitor weight and encourage lifestyle changes
- Choose a different medication that does not cause weight gain
- Choose a lower dose
- Weigh risks and benefits of this medication

Bupropion (Wellbutrin)

- Antidepressant
- Not FDA approved for weight loss
- However, there is some evidence of this drug inducing a slow gradual weight loss
- I don't prescribe for weight loss, but suggest that the individual speak with their psychiatrist about this.

Topiramate (Topimax)

- Developed and FDA approved as an anti-seizure medication
- "Side effect" of weight loss noted
- A number of weight loss trials begun with thousands of patients planned for 2 years duration.
- Studies halted due to side effects: cognitive problems, memory loss, paresthesias.

Summary of Medications

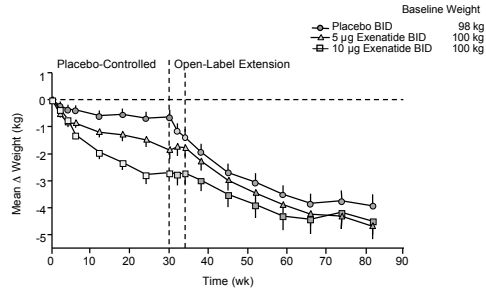
- Xenical and Sibutramine are options but are not ideal because of limited weight loss, cost and lack of insurance coverage.
- Phentermine is less expensive but is not FDA approved for long term use.
- Make sure that other medications are not contributing to weight gain.

Pharmacotherapy: New Drugs

Obesity Rx Treatment

- Only 4% of obese people get a prescription medication to treat this condition.
- 66% of hypertensive people get Rx medication
- If 66% of obese patients were treated this would equal 43 million people
- In 2001 the antihypertensive market in the US was \$8.3 billion
- New Drugs: Phentermine/topiramate, Bupropion/naltrexone, lorcaserin, Tesofensine and liraglutide.

Exenatide for Weight Reduction Open-Label Extension – Combined



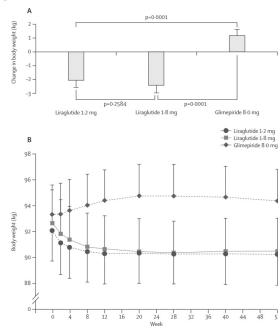
82-wk completers: N = 393; Mean (SE); Weight was a secondary endpoint
Data on file, Amylin Pharmaceuticals, Inc.

Liraglutide (Victoza)

- Novo Nordisk once daily GLP-1 analog.
- Seeking approval for use in diabetes
- Approved for marketing in Europe in July 2009
- FDA has expressed some concern over risk for inducing thyroid tumors.
- Company is conducting studies to support a weight loss indication.

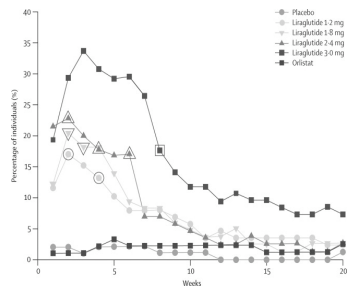
Astrup A, Lancet. 2009 Nov 7;374(9701):1606-16

Liraglutide: The LEAD-3 Mono trial



Garber A, Lancet. 2009 Feb 7;373(9662):473-81

Percent of Patients Taking Liraglutide who Experienced Nausea



Astrup A, Lancet. 2009 Nov 7;374(9701):1606-16

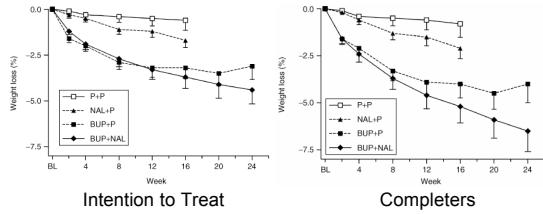
Qnexa (Vivus)

- Combination of phentermine and topiramate
 - Full dose 15 mg phentermine, 92 mg topiramate
- EQUIP randomized placebo controlled trial 1,267 morbidly obese patients followed for 1 year
- 10.4% placebo subtracted weight loss, 14.7% total weight loss among completers
- CONQUER Trial: 2,487 obese patients with co-morbidities
- Full dose 13.2% weight loss, improved CVD risk markers

Qnexa

- Side effects
 - Dry mouth: 21%
 - Tingling: 20%
 - Insomnia: 10%
 - Nausea: 7%
- Neurocognitive effects resulted in discontinuation in 2.6%, 18% stopped medication for some AE
- No evidence of increased levels of depression or suicidal ideation.

Bupropion plus Naltrexone (Contrave, Orexigen) in the Treatment of Obesity



Randomization included: BUP (300 mg) + NAL (50 mg), BUP (300 mg) + placebo (P), NAL (50 mg) + P or P+P for up to 24 weeks

Greenway FL, Obesity (2008) 17 1, 30–39

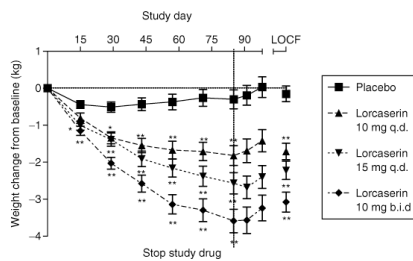
Side Effects of Bupropion plus Naltrexone in the Treatment of Obesity

	P+P (N = 53) n (%)	P+NAL (N = 58) n (%)	BUP+P (N = 55) n (%)	BUP+NAL (N = 51) n (%)
Subjects with > 1 TEAE	19 (35.8%)	32 (55.2%)	30 (54.5%)	29 (56.9%)
Nausea	1 (1.9%)	20 (34.5%)	5 (9.1%)	16 (31.4%)
Headache	7 (13.2%)	2 (3.4%)	10 (18.2%)	8 (15.7%)
Doziness	2 (3.8%)	6 (10.3%)	5 (9.1%)	7 (13.7%)
Fatigue	4 (7.5%)	5 (8.6%)	5 (9.1%)	5 (9.8%)
Vomiting NOS	1 (1.9%)	8 (13.8%)	3 (5.5%)	3 (5.9%)
Diarrhea NOS	0 (0.0%)	2 (3.4%)	4 (7.3%)	3 (5.9%)
Insomnia	0 (0.0%)	1 (1.7%)	3 (5.5%)	1 (1.9%)
Back pain	3 (5.7%)	0 (0.0%)	2 (3.6%)	2 (3.9%)
Nasopharyngitis	2 (3.8%)	2 (3.4%)	3 (5.5%)	0 (0.0%)
Gastroenteritis NOS	1 (1.9%)	2 (3.4%)	3 (5.5%)	0 (0.0%)
Dry mouth	0 (0.0%)	1 (1.7%)	3 (5.5%)	1 (2.0%)
Irritability	0 (0.0%)	0 (0.0%)	3 (5.5%)	0 (0.0%)
Paresthesia	3 (5.7%)	2 (3.4%)	0 (0.0%)	0 (0.0%)
Abdominal pain (upper)	0 (0.0%)	1 (1.7%)	0 (0.0%)	3 (5.9%)
Subjects who discontinued due to adverse event*	5 (9.4%)	14 (24.1%)	9 (16.4%)	9 (17.6%)

Incidence >5% in at least 1 treatment group with onset during weeks 1–16.
 N, number of randomized subjects; n, number of subjects with event; TEAE, treatment-emergent adverse event.
 *Discontinuation from 1 to both study drugs during weeks 1–16 due to adverse events starting during weeks 1–16.

Greenway FL, Obesity (2008) 17 1, 30–39

Lorcaserin in the Treatment of Obesity



Lorcaserin (APD356) is a potent, selective 5-HT_{2C} agonist with ~15-fold and 100-fold selectivity vs. 5-HT_{2A} and 5-HT_{2B} receptors, respectively

Smith S, Obesity (Silver Spring). 2009 Mar;17(3):494-503

Summary of Medications

- A large number of new medications in the pipeline
- Qnexa looks the best for weight loss
- Lorcaserin may be fenfluramine in sheep's clothing
- Liraglutide may have the best acceptance
- A fair amount of side effects but they don't look severe
