Past, Present and Future of Pharmacotherapy for Obesity

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Disclosure

Affilitaion: Advisory Board/Panel

Company: Data Safety Monitoring Board for Enteromedics Inc.

Relationship: Active

Learning Objectives

- List the currently available FDA approved weight loss medication and the unique benefits of each
- Describe an approach to helping a patient with co-morbid health problems select a weight loss agent in a manner that reduces risk and maximizes potential benefits
- List the barriers to prescribing weight loss medications and describe an approach to addressing them

A Case

- A 45 year old woman comes to see you for help losing weight. She says she is eating very little and yet cannot lose weight. She tried Weight Watchers 3 years ago and lost 10 lbs but has regained that weight.
- Her current weight is 201 lbs and she is 5'5" tall giving her a BMI=33.5 kg/m^2
- She has a history of diabetes treated with metformin 1 g BID with an A1C=7.8,

A Case

- She has hypertension well controlled on 12.5 mg/d HCTZ, she has no history of heart disease.
- She has depression treated with bupropion, and headaches.

A Case

- How do you approach discussing weight with her?
- Do you discuss weight loss medications with her?
- Are weight loss medications safe? Effective? Worth the money?
- Which weight loss medication might be best for her?
- How do you follow her if you do prescribe?

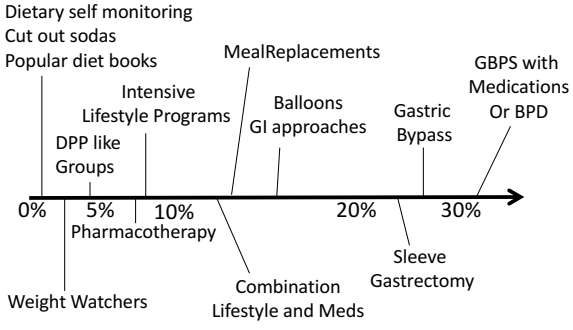
General issues

- Eligible patients: BMI >30 kg/m^2 or 27-30 kg/m^2 with a weight related co-morbidity.
- Previous lifestyle treatment, peak lifetime non-pregnant weight.
- Weight loss is 5-10% more than lifestyle alone.
- If a medication works, will need to be taken chronically (intermittently?).
- Typically not paid for by insurance so cost is an important factor for many patients.

A Guide to Selecting Treatment

	BMI category				
Treatment	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	+

Jensen, Circulation 2013

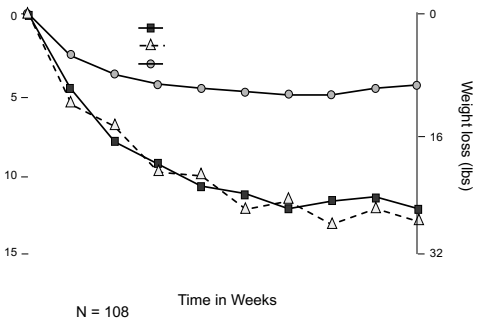


Treatment Options: Effectiveness

Phentermine

- Increases NE content in the brain
- Dose: 15-37.5 mg/d, New 8 mg dose (Lomaira)
- Cost: $15-25.00/month Cheapest
- Most widely prescribed wt. loss medication (74% of current market, (Obesity, 2016 24: 1955)
- FDA approved for only 3 months use
- 3-6% weight loss
- Side effects: tachycardia, hypertension, headache, nervousness, sleeplessness

Weight Loss with Continuous and Intermittent Phentermine



N = 108

Munro JF, et al. *Br Med J* 1968; 1:352-354.

CVD Safety: Legacy of Sibutramine

- SCOUT trial: Increased CVD in Sibutramine treated patients.
- High risk patients, continued medication even if they did not lose weight
- 2012 Case/control study >6000 pts in UK and Germany showed significantly lower ASCVD risk in sibutramine users
- 2015 case/control study >23,000 pts in UK increased risk in those with CVD (DM, DM+1RF) but not in those without.

N Engl J Med 2010;363:905-17; Tyczynski Drug Saf 2012. 35:629-44
Hayes Int J Obesity 2015, 1–6doi:10.1038/ijo.2015.86

Phentermine: Long term Prescribing?

Endocrine Society Guidelines

- Has no evidence of serious cardiovascular disease, serious psychiatric disease or a history of substance abuse
- Has been informed about weight loss medications that are FDA approved for long-term use and told that these have been documented to be safe and effective whereas phentermine has not
- Does not demonstrate a clinically significant increase in pulse or BP when taking phentermine
- Demonstrates a significant weight loss while using the medication.

J Clin Endocrinol Metab. 2015 Feb;100(2):342-62

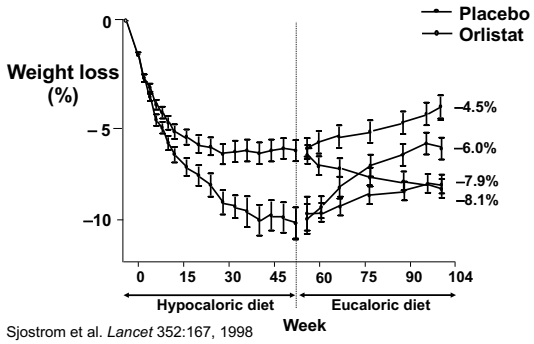
Orlistat (Xenical)

- Pancreatic Lipase inhibitor
- Inhibits fat absorption by 30%
- 120 mg three times per day
- Cost: $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.
- Tested in adolescents
- Evidence of diabetes prevention
- Safest weight loss medication, approved for long term use, OTC form
- 3-6% weight loss on average
- Drug interactions: Coumadin, cyclosporin

Effect of Orlistat on Body Weight



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

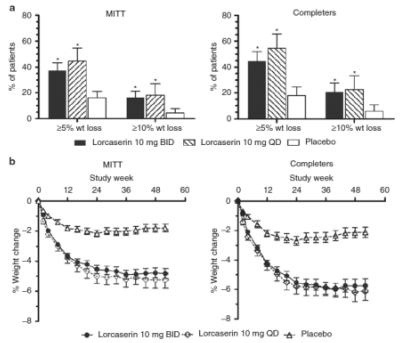
Lorcasarin (Belviq)

- Serotonin 2C receptor agonist
- Previous serotonin agonists fenfluramine and dexfenfluramine caused cardiac valve disease, removed from market
- 2C receptor only in the brain not in heart
- Studies in 1-2,000 people for up to 2 years do not show evidence if valvulopathy with lorcasarin.

Lorcasarin (Belviq)

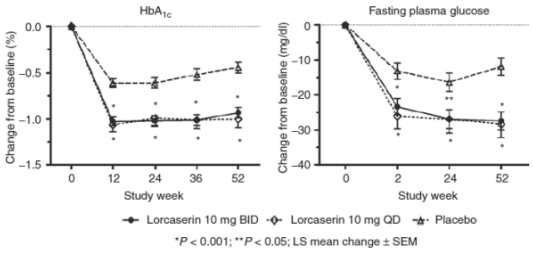
- Weight loss: 4-6% no better than phentermine or orlistat
- Least side effects: minimal headache, dizziness and nausea
- Cost: $220/mo
- No tachycardia, safe for pts with CVD risk
- Unclear if physicians will prescribe off label with phentermine (no data on safety or efficacy so I would not do this)

Lorcasarin:BLOOM Diabetes Study



Obesity (2012) 20, 1426–1436

Lorcasarin:BLOOM Diabetes Study



Obesity (2012) 20, 1426–1436

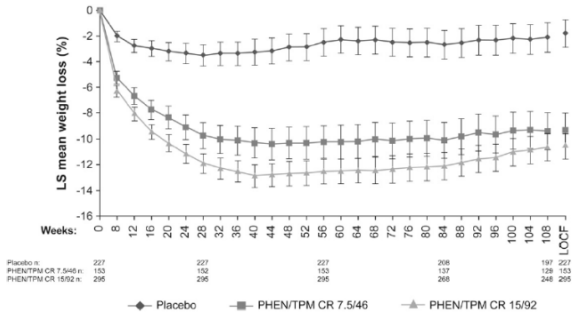
Phentermine/Topiramate ER

- Combination gives greater efficacy with fewer side effects
- Doses 7.5/46 mg and 15/92 mg phenterming/topiramate
- Cost: $150.00/month
- Side effects: dry mouth, paraesthesias, insomnia, dizziness, anxiety, irritability and disturbance in attention

Phentermine/Topiramate ER

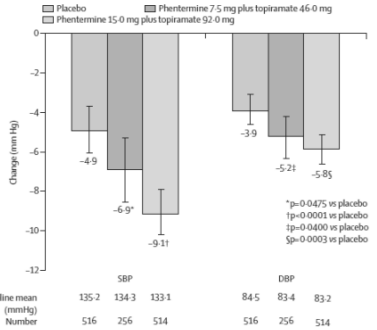
- Risk of birth defects: women need – pregnancy test on starting and monthly while using.
- Reduces blood pressure, glucose, insulin, triglycerides and raises HDL
- Some physicians prescribe off label using generic phentermine and topiramate.
- Most effective medication available 10-12% weight loss.

Phentermine/Topiramate ER: SEQUEL Trial



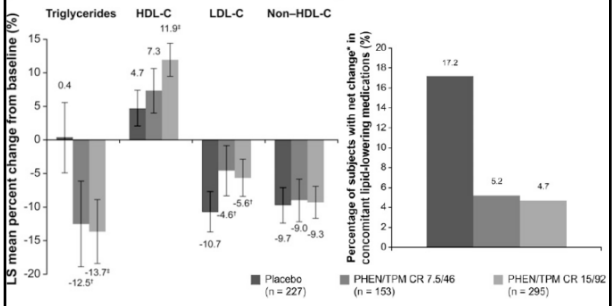
Am J Clin Nutr 2012;95:297–308

Phen/Top: Effects on Blood Pressure CONQUER Trial



Lancet. 2011 Apr 16;377(9774):1341-52

Phen/Top 2 year data on Lipids: SEQUEL Trial



Am J Clin Nutr 2012;95:297–308

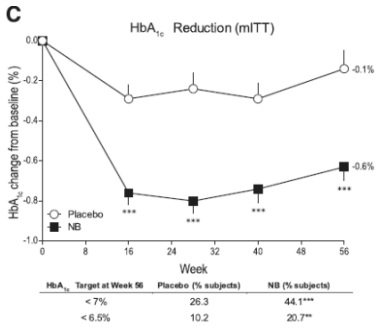
Naltrexone SR/Bupropion SR

- Combination of Naltrexone SR 8 mg and Bupropion SR 90 mg titrated to 2 BID.
- Bupropion stimulates hypothalamic pro-opiomelanocortin (POMC) neurons reduces food intake.
- Naltrexone blocks opioid receptor-mediated POMC auto-inhibition, augmenting POMC firing in a synergistic manner. Alters reward pathways.
- Intermediate in effectiveness and side effects

Naltrexone SR/Bupropion SR

- Worrisome side effects: increased blood pressure and pulse, lowers seizure threshold, suicidal ideation (black box).
- Common side effects: Nausea, constipation, diarrhea, headache, dry mouth
- Cost $200/month
- Stop if clinically significant increase in BP or pulse
- Stop if <5% weight loss at 3 months

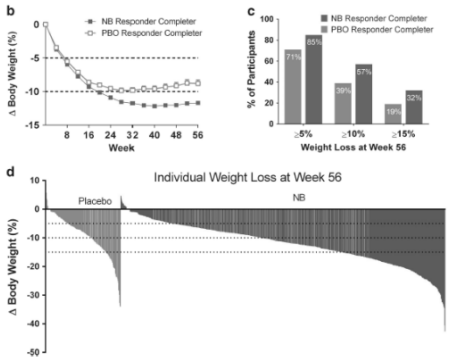
Naltrexone SR/Bupropion SR: Diabetes Trial



HbA1c Target at Week 56	Placebo (% subjects)	NB (% subjects)
< 7%	26.3	44.1***
< 6.5%	10.2	20.7**

Diabetes Care 36:4022–4029, 2013.

Variability in Response to naltrexone ER/bupropion ER

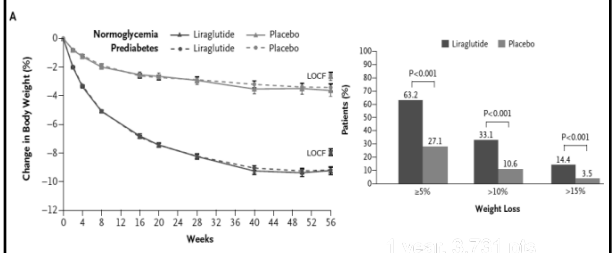


Int J Obes (Lond). 2016 Sep;40(9):1369-75

Liraglutide 3 mg

- GLP-1 agonist
- Main side effect is nausea, increases pulse initially
- Variability in response with responders losing more weight
- Reduction of metabolic syndrome, reduced progression to diabetes
- AWP >$1,000/mo. Most expensive of available agents
- Intermediate in efficacy and side effects

Liraglutide 3 mg in Obesity



1 year, 3,731 pts
2:1 randomization
Obese non-diabetic subjects

N Engl J Med 2015;373:11-22.

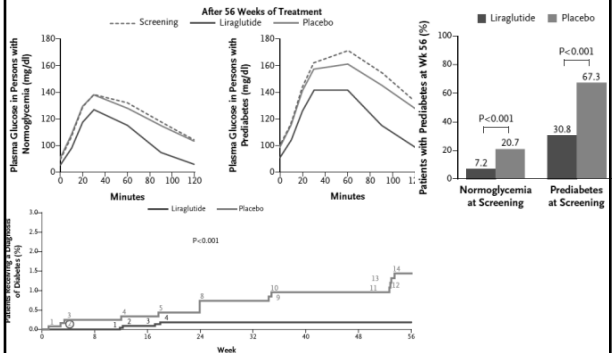
Side Effects with Liraglutide

Table 5. Adverse events with an incidence of 5% or more in any treatment group, by system organ class and preferred term

	Liraglutide 3.0 mg				*Placebo*			
	N	(%)	E	R	N	(%)	E	R
Gastrointestinal disorders	156	(73.6)	495	254.5	95	(45.2)	182	98.6
Nausea	101	(47.6)	181	93.1	36	(17.1)	55	29.8
Constipation	57	(26.9)	66	33.9	26	(12.4)	28	15.2
Diarrhea	38	(17.9)	53	27.3	26	(12.4)	34	18.4
Vomiting	35	(16.5)	44	22.6	5	(2.4)	6	3.3

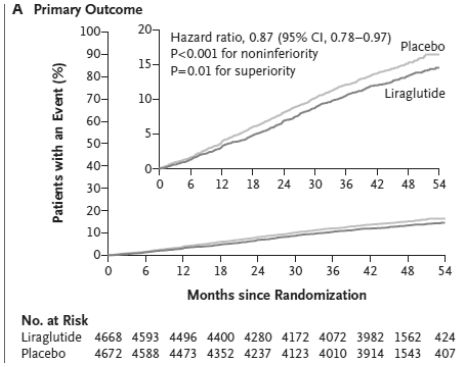
International Journal of Obesity (2013) 37, 1443–1451

Liraglutide 3 mg in Obesity



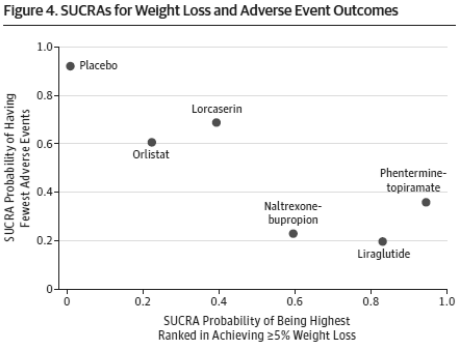
N Engl J Med 2015;373:11-22.

Liraglutide: CVD outcomes



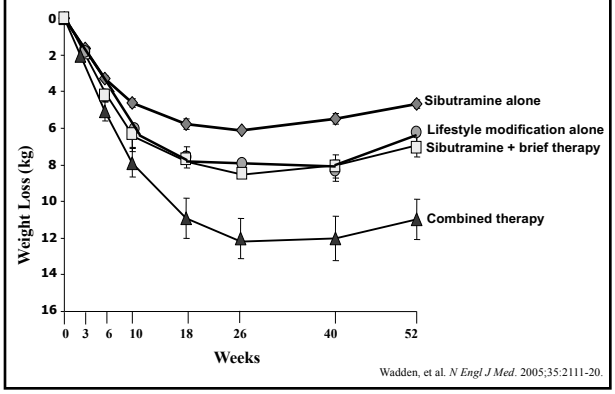
N Engl J Med 2016;375:311-22.

Comparison of Wt Loss Drugs



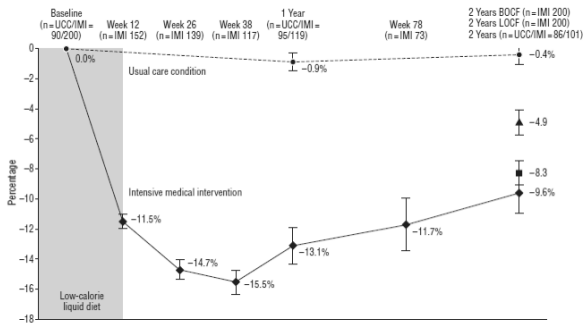
JAMA. 2016;315(22):2424-2434.

Behavior + Meds better than either alone



Wadden, et al. *N Engl J Med*. 2005;35:2111-20.

Pharmacotherapy plus Meal Replacements



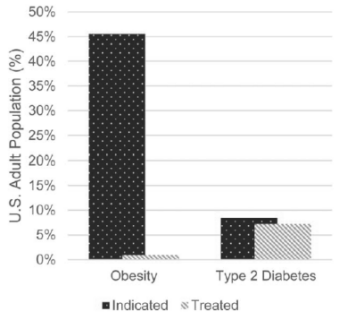
Arch Intern Med. 2010;170(2):146-154

Look AHEAD More Wt. Loss is Better

- Primary analysis did not show a CVD benefit
- Study was powered for an event rate of 3.125%/year and at the 3 year mark the event rate was 0.7%/year (Clin Trials. 2012 Feb;9(1):113-24)
- Individuals who lost >10% of their bodyweight in the 1st yr of the study had a 21% lower risk of the 1º outcome (p=0·034) and a 24% reduced risk of the 2º outcome (p=0·003)

Lancet Diabetes Endocrinol 2016; 4: 913–21

Low Utilization of Weight Loss Medications



Obesity (2016) 24, 1955–1961

Barriers to Prescribing

- Safety issues: perception is that these medications are dangerous
- Efficacy concerns: 5-10% is not enough for many patients
- Lack of payment: 1/3rd of payers to not cover, 1/3rd have limited coverage, 1/3rd have coverage but may be sold as an add on (Miller).
- Provider issues: Long, complex discussion with patients, lack of training

Physician Attitudes Towards Prescribing

- "Promoting and prescribing drugs to treat obesity does a disservice to our patients, society, and ourselves. Such prescriptions may help patients lose a few pounds in the short run, but these drugs violate nearly every principle of careful, conservative prescribing, and they may well put patients at risk"
- 31% say they do not prescribe this class of medications.
- Experimental studies have found that physicians see patients with obesity as being less compliant, having less self-discipline and being more annoying.

N Engl J Med. 2016 Sep 22;375(12):1187-9
Obesity (2009) 17, 941–964.

Medications in the pipeline

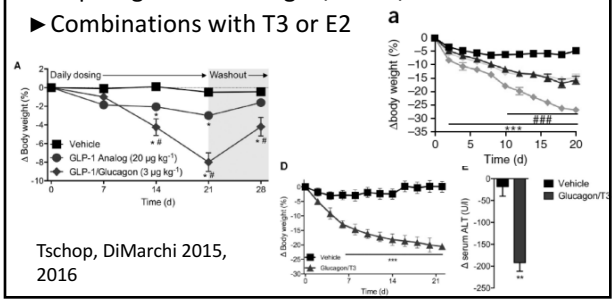
Drug	Mechanism	Mfg	Trials	Status
Velneperit	NPY5R antagonist	Shionogi	Phase 2	Discontinued
Obinepitide	dual NPY2/Y4 R agonist	7TM Pharma	Phase 2	No info since 2010
Tesofensine	DA, NE, S re-uptake inhib	Saniona	Phase 2	In development
Bupropion + zonisamide	DA re-uptake inhib, GABA	Orexigen	Phase 2	No info since 2009
Beloranib	MetAP2 inhib	Zafgen	Phase 3	halted
Cetilistat	Lipase inhib	Norgine BV	Phase 3	Approved in Japan
Setmelanotide	MC4R agonist	Rhythm Pharm	Phase 2	Genetic obesity

Novel Combinations

- Canagliflozin 300 mg and Phentermine 15 mg 26 wk phase 2 trial, n=335, 6.9% placebo subtracted weight loss, reduced blood pressure (Hollander P; Diabetes Care. 2017 Mar 13)
- Dapagliflozin plus exenatide 28 wk trial, n=695, 3.4 kg weight loss (Lancet Diab Endo. 2016 Dec;4(12):1004-1016)
- Pramlintide with phentermine 24 wk trial, n=244, 11.3% weight loss (Obesity 2010 Sep;18(9):1739-46)

Unimolecular Polypharmacy

- Dual agonists: glucagon/GLP-1
- Triple agonists: Glucagon/GLP-1/GIP
- Combinations with T3 or E2



Tschop, DiMarchi 2015, 2016

Conclusions

- We have a number of safe and effective weight loss agents
- They are not prescribed very often
- The market is challenging currently
- We need a 'statin'
- In the mean time, the goal is to have an honest, productive conversation with patients about the risks and benefits of these agents