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Obesity: Pharmacological Management

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Disclosures

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Disclosures

Vicki Shah, PA-C, MMS

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- Consultant: AbbVie, Clinical Area- HCV

Why Use Medications?

Objectives:

- Treat diseases
  - 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

Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA*. 2014;311:74–86. 35; Avenell A, Brown TJ, McGee MA, et al. What interventions should we add to weight reducing diets in adults with obesity? A systematic review of randomized controlled trials of adding drug therapy, exercise, behaviour therapy or combinations of these interventions. *J Hum Nutr Diet.* 2004;17:293–316; Wadden TA, Berkowitz RI, Womble LG, et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med.* 2005;353:2111–2120.

Indications

- Patients with obesity (e.g., BMI ≥ 30kg/m^2)*
- Patients who are overweight (e.g., BMI ≥ 27kg/m^2) with presence of increased adiposity complications (e.g., type 2 diabetes mellitus, hypertension, dyslipidemia)
- Consider pharmacotherapy when diet, exercise, and behavior modification do not produce sufficient weight loss

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Considerations

- Variable weight loss over variable duration.
- Average of around 5 – 10% weight loss, with greater weight loss in hyper-responders, and less than 5% weight loss (or even weight gain) in hypo-responders.
- Choice of medication should be tailored to the patient with consideration of co-morbid conditions and DDI
- Assess safety and efficiency every month for 3 months, then every 3 months
- Continue an anti-obesity medication if it is deemed effective and well tolerated.

Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA. 2014;311:74–86. 35; Avenell A, Brown TJ, McGee MA, et al. What interventions should we add to weight reducing diets in adults with obesity? A systematic review of randomized controlled trials of adding drug therapy, exercise, behaviour therapy or combinations of these interventions. *J Hum Nutr Diet.* 2004;17:293–316; Wadden TA, Berkowitz RI, Womble LG, et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med.* 2005;353:2111–2120.

Considerations

- If no clinical improvement (4 - 5% weight loss) after 12-16 weeks with one anti-obesity medication, then consider
  - Increasing anti-obesity medication dose (if applicable)
  - Giving alternative anti-obesity medication
- If weight loss plateaus, then consider
  - Setting new lower set point?
  - Adding a second medication
  - Increasing physical activity and reviewing diet

Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA. 2014;311:74–86. 35; Avenell A, Brown TJ, McGee MA, et al. What interventions should we add to weight reducing diets in adults with obesity? A systematic review of randomized controlled trials of adding drug therapy, exercise, behaviour therapy or combinations of these interventions. *J Hum Nutr Diet.* 2004;17:293–316; Wadden TA, Berkowitz RI, Womble LG, et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med.* 2005;353:2111–2120.

Considerations

- Rebound post-treatment: If medication stopped many patients will rebound to a new higher set point
- Treatment course of most studies was around 52 weeks, causing uncertainty in the description of drug rebound trends after 1 year
- When long-term weight loss drugs reached their maximum effects, their drug rebound effects appeared

Dong, Z., Xu, L., Liu, H., Lv, Y., Zheng, Q., and Li, L. (2017) Comparative efficacy of five long-term weight loss drugs: quantitative information for medication guidelines. Obesity Reviews, 18: 1377– 1385. doi: 10.1111/obr.12606.

Phentermine

- Approved in 1959, for short term use 12 wks
- Good candidates: Younger patients who need assistance with appetite suppression
- Do not use: hyperthyroid, uncontrolled HTN, seizure disorder, CVD, glaucoma, drug abuse
- DDI: Monoamine oxidase inhibitors, sympathomimetics, antidepressants, alcohol, adrenergic neuron blocking drugs, and some anesthetic agents

Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA*. 2016;315:2424–34. doi: 10.1001/jama.2016.7602; Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA*. 2014;311(1):74-86. doi:10.1001/jama.2013.281361.

Phentermine

Medication	Mechanism, dosage, and available formulations	Trial and duration	Trial arms	Weight loss (%)	Most common adverse effects
Phentermine (Adipex-P,[15] Ionamin,[16] Lomaira,[17] Suprenza[18]) Schedule IV controlled substance NOTE: Approved for short-term use	Adrenergic agonist 8–37.5 mg/d Capsule, tablet	Aronne LJ, et al[19] 28 weeks	15 mg/d 7.5 mg/d Placebo (topiramate ER and phentermine/ topiramate ER arms excluded)	6.06[a] 5.45[a] 1.71	Dry mouth, insomnia, dizziness, irritability

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Orlistat

- Approved in 1999, take multivitamin daily
- Good candidates: Patients with hypercholesterolemia and/or constipation who can limit their intake of dietary fat
- Do not use: Chronic malabsorption syndrome, cholestasis
- DDI: Cyclosporine, hormone contraceptives, seizure medications, thyroid hormones, warfarin

Davidson MH, Hauptman J, DiGirolamo M, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized, controlled trial. *JAMA.* 1999;281:235–242; Xenical (orlistat) [prescribing information]. South San Francisco, CA: Genentech USA Inc. http://www.gene.com/download/pdf/xenical_prescribing.pdf; Alli (orlistat) [label]. Moon Township, PA: GlaxoSmithKline. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021887lbl.pdf. Approved February 7, 2007. Accessed July 2, 2014.

Orlistat

Medication	Mechanism, dosage, and available formulations	Trial and duration	Trial arms	Weight loss (%)	Most common adverse effects
Orlistat (Alli,[20] Xenical[21])	Lipase inhibitor 60–120 mg three times per day with meals Capsule	XENDOS[22] 208 weeks	120 mg three times per day Placebo	9.6 (Week 52)[a] 5.25 (Week 208)[a] 5.61 (Week 52) 2.71 (Week 208)	Fecal urgency, oily stool, flatus with discharge, fecal incontinence

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Lorcaserin

- Approved in 2012
- Good candidates: Patients who report inadequate meal satiety
- Do not use: serotonin syndrome, heart failure, psychiatric disorders, and priapism
- DDI: SSRI's, SNRI's, MAO inhibitors, anti-dopaminergic medications, St John's wort, triptans, bupropion, dextromethorphan, CYP 2D6 substrates

Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med.* 2010;363:245–256; **Fidler MC, Sanchez M, Raether B, et al.** A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab.* 2011;96:3067–3077; Belviq (lorcaserin) [prescribing information]. Zofingen, Switzerland: Arena Pharmaceuticals GmbH. https://www.belviqhcp.com/media/1001/belviq_prescribing_information.pdf.

Lorcaserin

Medication	Mechanism, dosage, and available formulations	Trial and duration	Trial arms	Weight loss (%)	Most common adverse effects
Lorcaserin (Belviq, Belviq XR)[27] Schedule IV controlled substance	Serotonin 5-HT2C receptor agonist 10 mg twice per day or 20 mg/d ER Tablet	BLOOM[28] 52 weeks	10 mg twice per day Placebo	5.8[a] 2.2	Headache, dizziness, fatigue, nausea, dry mouth, constipation
		BLOSSOM[29] 52 weeks	10 mg twice per day 10 mg/d Placebo	5.8[a] 4.7[a] 2.8	
		BLOOM-DM[30] 52 weeks	10 mg twice per day 10 mg/d Placebo	4.5[a] 5.0[a] 1.5	

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Liraglutide

- Approved in 2014, lower dose1.8mg used for DM
- Good candidates: Patients who report inadequate meal satiety, and/or have type 2 diabetes, prediabetes, or impaired glucose tolerance; patients requiring use of concomitant psychiatric medications
- Do not use: personal or family hx of medullary thyroid cancer or Type 2 Multiple Endocrine Neoplasia syndrome. Discontinue with suspected pancreatitis, gallbladder disease, or suicidal behavior and ideation
- DDI: May slow gastric emptying

Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes (Lond) [Errata (2012) 36:890 and (2013) 37:322]. 2012;36:843–854;
Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond).* 2013;37:1443–1451.

Liraglutide

Medication	Mechanism, dosage, and available formulations	Trial and duration	Trial arms	Weight loss (%)	Most common adverse effects
Liraglutide 3 mg (Saxenda)[36]	GLP-1 receptor agonist 0.6–3 mg/d Prefilled pen for subcutaneous injection	SCALE Obesity and Prediabetes[37] 56 weeks	3 mg/d Placebo	8.0[a] 2.6	Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain
		SCALE Diabetes[38] 56 weeks	3 mg/d 1.8 mg/d Placebo	6[a] 4.7[a] 2	
		SCALE Maintenance[39] 56 weeks (after initial ≥5% weight loss with LCD)	3 mg/d Placebo	6.2[a] 0.2	

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Naltrexone/Bupropion

- Approved in 2014, separately used for addiction or depression/smoking cessation
- Good candidates: Patients who describe cravings for food and/ or addictive behaviors related to food; patients who are trying to quit smoking, reduce alcohol intake, and/or have concomitant depression
- Do not use: uncontrolled HTN, seizure disorders, drug/alcohol withdrawal
- DDI: Opioid pain medications, anti-seizure medications, MAO inhibitors

Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)*. 2011;19:110–120;
Greenway FL, Fujioka K, Plodkonski RA, et al. COR I Study Group. *Lancet*. 2010;376:595–605.

Naltrexone/Bupropion

Medication	Mechanism, dosage, and available formulations	Trial and duration	Trial arms	Weight loss (%)	Most common adverse effects
Naltrexone SR/bupropion SR (Contrave)[31]	Opioid receptor antagonist/ dopamine and norepinephrine reuptake inhibitor 8/90 mg/d–16/180 mg twice per day Tablet	COR-I[32] 56 weeks	16/180 mg twice per day 8/180 mg twice per day Placebo	6.1[a] 5.0[a] 1.3	Nausea, vomiting, constipation, headache, dizziness, insomnia, dry mouth
		COR-II[33] 56 weeks	16/180 mg twice per day Placebo	6.4[a] 1.2	
		COR-BMOD[34] 56 weeks	16/180 mg twice per day Placebo	9.3[a] 5.1	
		COR-DIABETES[35] 56 weeks	16/180 mg twice per day Placebo	5.0[a] 1.8	

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Phentermine/Topiramate

- Approved 2012, topiramate used for seizures and migraine
- Good candidates: Younger patients who need assistance with appetite suppression
- Do not use: glaucoma, uncontrolled HTN, heart disease, or hyperthyroidism. Topiramate can cause birth defects
- DDI: Monoamine oxidase inhibitors. May alter oral contraceptive blood levels

Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/ topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr*. 2012;95:297–308; Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity (SilverSpring).* 2013;21:2163–2171; Qsymia (phentermine and topiramate extended-release) [prescribing information]. Mountain View, CA: Vivus Inc. http://www.qsymia.com/pdf/prescribinginformation.pdf.

Phentermine/Topiramate

Medication	Mechanism, dosage, and available formulations	Trial and duration	Trial arms	Weight loss (%)	Most common adverse effects
Phentermine/ topiramate ER (Qsymia)[23] Schedule IV controlled substance	Adrenergic agonist/ neurostabilizer 3.75/23–15/92 mg/d Capsule	EQUIP[24] 56 weeks	15/92 mg/d 3.75/23 mg/d Placebo	10.9[a] 5.1[a] 1.6	Paresthesias, dizziness, dysgeusia, insomnia, constipation, dry mouth
		CONQUER[25] 56 weeks	15/92 mg/d 7.5/46 mg/d Placebo	9.8[a] 7.8[a] 1.2	
		SEQUEL[26] 108 weeks (52-week extension of CONQUER trial)	15/92 mg/d 7.5/46 mg/d Placebo	10.5[a] 9.3[a] 1.8 (Weeks 0–108)	

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Metformin

- Reduce appetite, effects of GI hormones applicable to weight loss
- Improving insulin sensitivity, leptin sensitivity, reduce neuropeptide Y levels, and increase GLP-1 activity
- 5.8±7.0 kg weight loss with dosage up to 2,500 mg per day
- May help improve: Insulin resistance, PCOS, NAFLD/NASH, CVD, Antipsychotic-related weight gain, HIV protease inhibitor-associated abnormalities (i.e., HIV lipodystrophy), reduce the overall cancer rate and help improve the treatment of multiple cancers

Seifarth C, Schehler B, Schneider HJ. Effectiveness of metformin on weight loss in non-diabetic individuals with obesity. *Exp Clin Endocrinol Diabetes*. 2013;121(1):27-31; Desilets AR, Dhakal-Karki S, Dunican KC. Role of metformin for weight management in patients without type 2 diabetes. *Ann Pharmacother*. 2008;42(6):817-826.

Conclusions

- Weight loss is single most important intervention and requires lifelong monitoring
- 10% weight loss helps with HTN, insulin resistance, hyperlipidemia, OSA, mood in addition to NAFLD/NASH
- Definition from the Obesity Medical Association:

*"Obesity is defined as 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."*

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