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Pharmacotherapy Principles & Considerations for Weight Management

2021

Learning Objectives

- Discuss the rationale behind and the indications for the use of anti-obesity pharmacotherapies
- Describe the mechanisms of action of anti-obesity pharmacotherapies
- Review the current FDA-approved medications for weight loss and newer medications that have weight-loss-promoting potential
- Identify the pharmacotherapies that are part of a successful medical weight loss (MWL) program

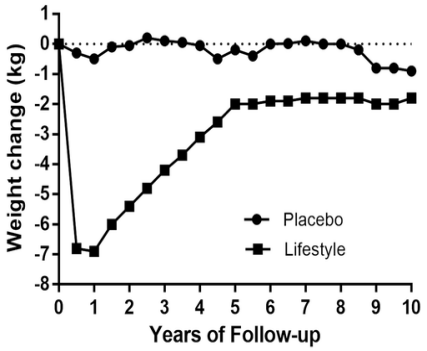
Throughout the presentation will highlight those that are part of our intervention

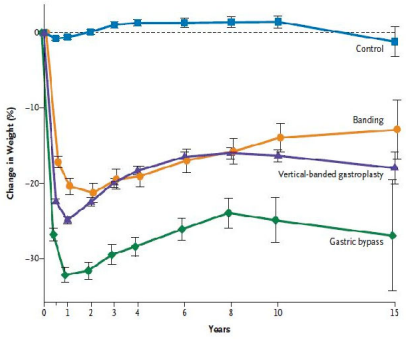
The Current State of Obesity Management

- Indicated for individuals with BMI ≥30 kg/m^2 or BMI > 27 kg/m^2 with co-morbidity
  - **Less than 2% of eligible people are on anti-obesity medications[1]**
- Medications allow people to better adhere to lifestyle changes by:
  - Addressing the different physiologic mechanisms that promote weight gain or make it more difficult to lose weight

1. Thomas CE, Mauer EA, Shukla AP, Rathi S, Aronne LJ. Low adoption of weight loss medications: A comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT2s. Obesity (Silver Spring). 2016 Sep;24(9):1955-61. doi: 10.1002/oby.21533. PMID: 27569120; PMCID: PMC5669035.

Obesity is a relapsing chronic disease





Adapted from Venditti et al Int J Obes 2008;32:1537-44

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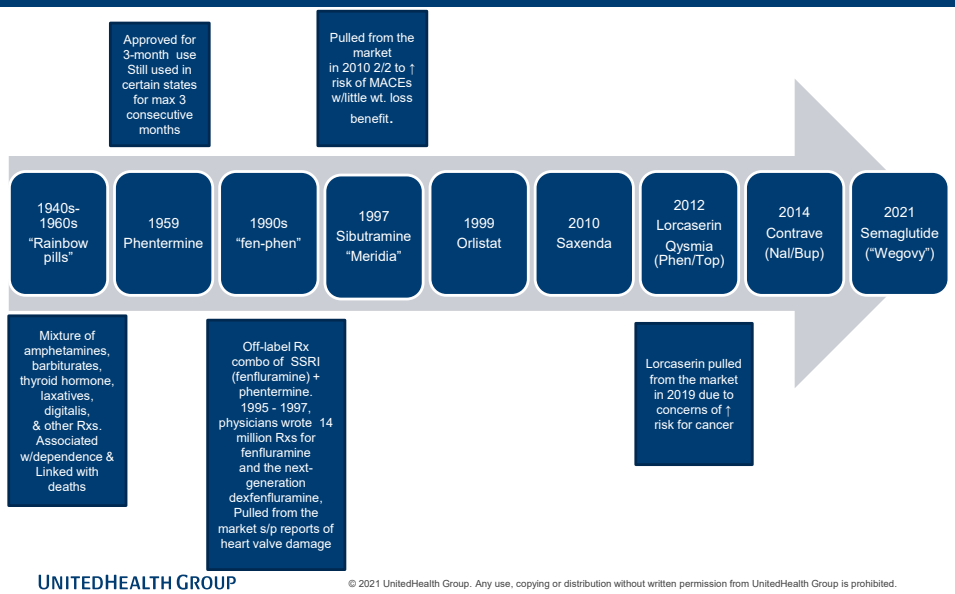
Bray GA, Kim KK, Wilding JPH; World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev. 2017 Jul;18(7):715-723. doi: 10.1111/obr.12551. Epub 2017 May 10. PMID: 28489290.

10 year data cited from the Diabetes Prevention Program

Source for bariatric curve: https://www.georgiasurgicare.com/advanced-weight-loss-center/weight-regain-care-after-weight-loss-surgery-postbariatric-care/

History of anti-obesity medicines (AOMs)



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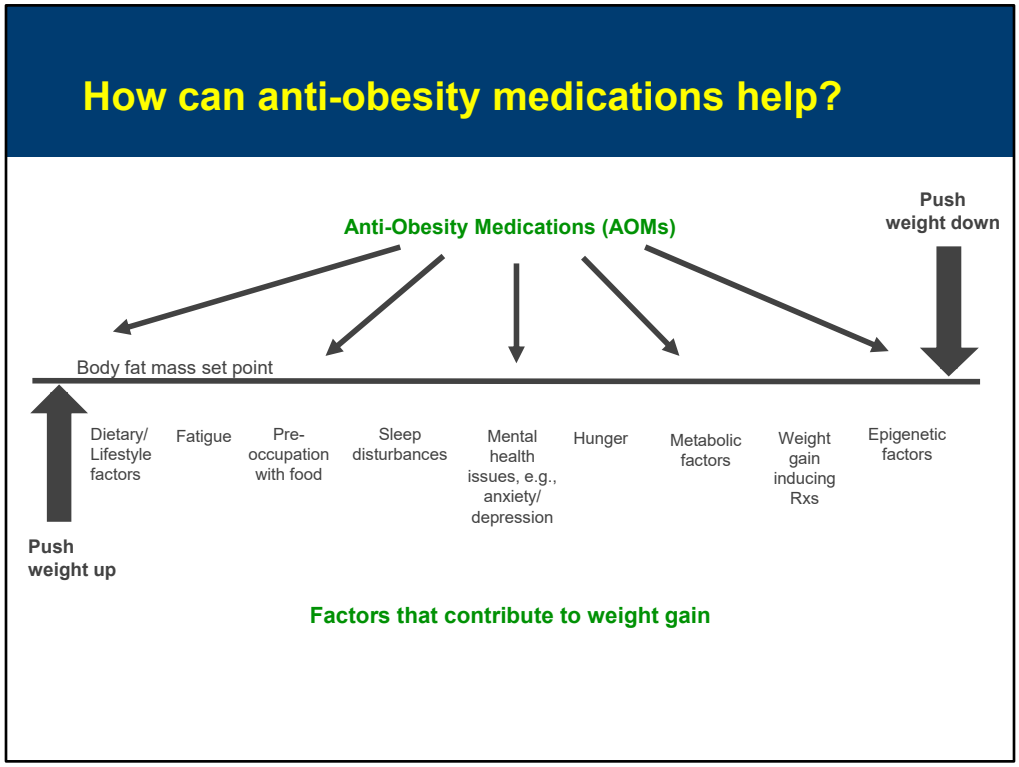


Adapted from the Kaplan, Blackburn slide deck. Blackburn Obesity Medicine Conference, June 2020.

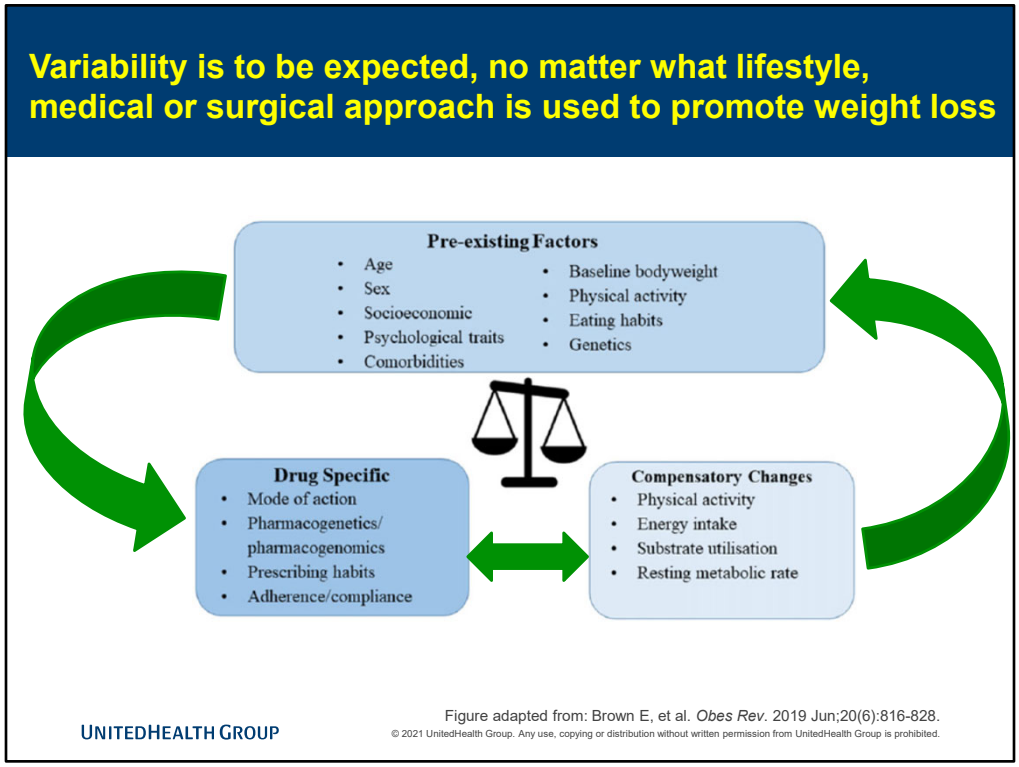


Figure adapted from: Brown E, Wilding JPH, Barber TM, Alam U, Cuthbertson DJ. Weight loss variability with SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes mellitus and obesity: Mechanistic possibilities. Obes Rev. 2019 Jun;20(6):816-828. doi: 10.1111/obr.12841. Epub 2019 Apr 10. PMID: 30972878.

FDA-Approved Medications/Device for Weight Loss

Drug	Status
Phentermine	Approved in 1955
Orlistat (Rx & OTC)	Approved in 1999
Phentermine/Topiramate (Qysmia®)	Approved in 2012 (Components available in generic formulation)
Naltrexone/bupropion (Contrave®)	Approved in 2014 (Components available in generic formulation)
Liraglutide (Saxenda®/Victoza®)	Approved in 2014 (Will become generic for tx of T2DM in 2023 and for obesity in 2025)
Plenity® (device)	Approved in 2019
Semaglutide (Ozempic®/Wegovy®)	Approved in 2017 for the tx of T2DM and for obesity in June 2021

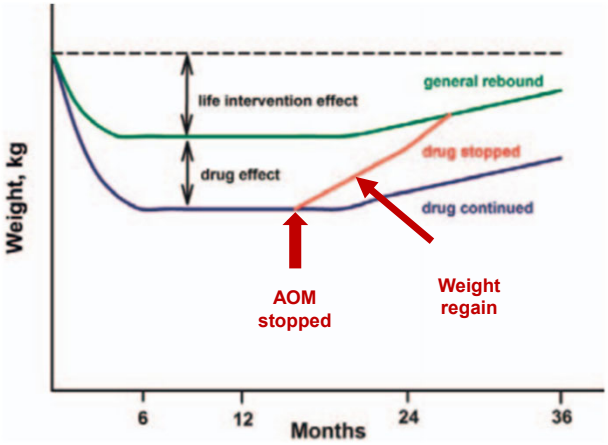
Apovian

Medications that promote weight loss (off-label)

- **Metformin**
- **Topiramate**
- **Bupropion**
- **Naltrexone**
- Zonisamide
- Dulaglutide
- Liraglutide
- Exenatide
- Pramlintide
- Canagliflozin
- Dapagliflozin
- Empagliflozin

Weight loss over time +/- lifestyle intervention and AOMs

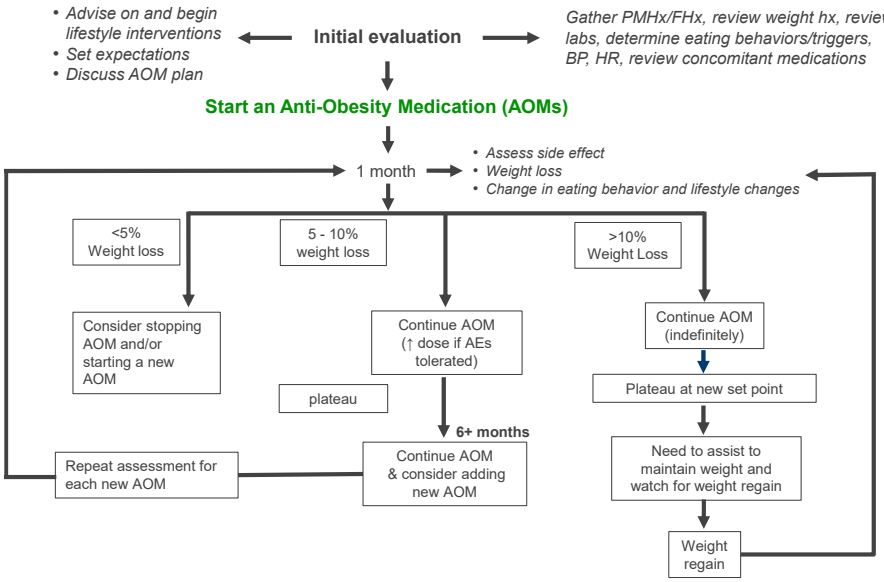
AOMs are not a temporary solution.
Must manage expectations.



Schultes B. *Visc Med*. 2016 Oct;32(5):347-351.

Schultes B. Pharmacological Interventions against Obesity: Current Status and Future Directions. *Visc Med*. 2016 Oct;32(5):347-351. doi: 10.1159/000450904. Epub 2016 Oct 7. PMID: 27921047; PMCID: PMC5122991.

Treatment Algorithm



Adapted from Pharmacology talk, Blackburn Obesity June 2020

Considerations when deciding what to start

Persons with insulin resistance/ prediabetes OR Rx-induced weight gain

- Consider starting **metformin**, if not already on metformin as the foundation
- Need to set expectations:
  - May help curb cravings/hunger
  - May not result in significant or rapid weight loss
  - Will work to stabilize insulin levels
- Benefits:
  - "Anti-aging" effect:
    - Improves mitochondrial function
    - Decreasing telomere attrition and senescence
  - Cardioprotective effects
  - Anti-inflammatory effects/anti-cancer
- Will need to monitor B12 levels

After consideration of metformin …

Person with NO history of significant cardiovascular disease

Depending on co-morbidities

- Consider phentermine +/- topiramate
- Can prescribe phentermine in the morning and topiramate with or around evening meal

- Obtain baseline BP
  - Monitor periodically
- **No need for an EKG in an otherwise healthy adult with no cardiovascular history**
- If topiramate is added (for Qysmia®), discuss potential for teratogenic effects and document current method of contraception
- Consider titrating phentermine dose up from 4mg to 8mg before considering higher dose
  - ***For most people, there is not a significant difference between the effect of 8mg and a higher dose***
- As a controlled substance, phentermine will need an in-person visit to initiate treatment

Person who struggles with night or binge eating

Depending on co-morbidities

- Would also be useful in people with a:
  - History of migraines
  - History of insomnia or sleep disturbances
  - History of alcohol dependence

- **Consider topiramate**
- Time in evening to reduce sedating effect
- Time with or before evening meal to target evening hunger and binges

- Not as effective for appetite/craving control if taken right before bed
  - May ↑ risk for lingering sedating effects in the AM
- Discuss the potential for teratogenic effects and document current method of contraception while on this medication
- If discontinued, will need to titrate dose down

Person with history of depression, fatigue, tobacco dependence

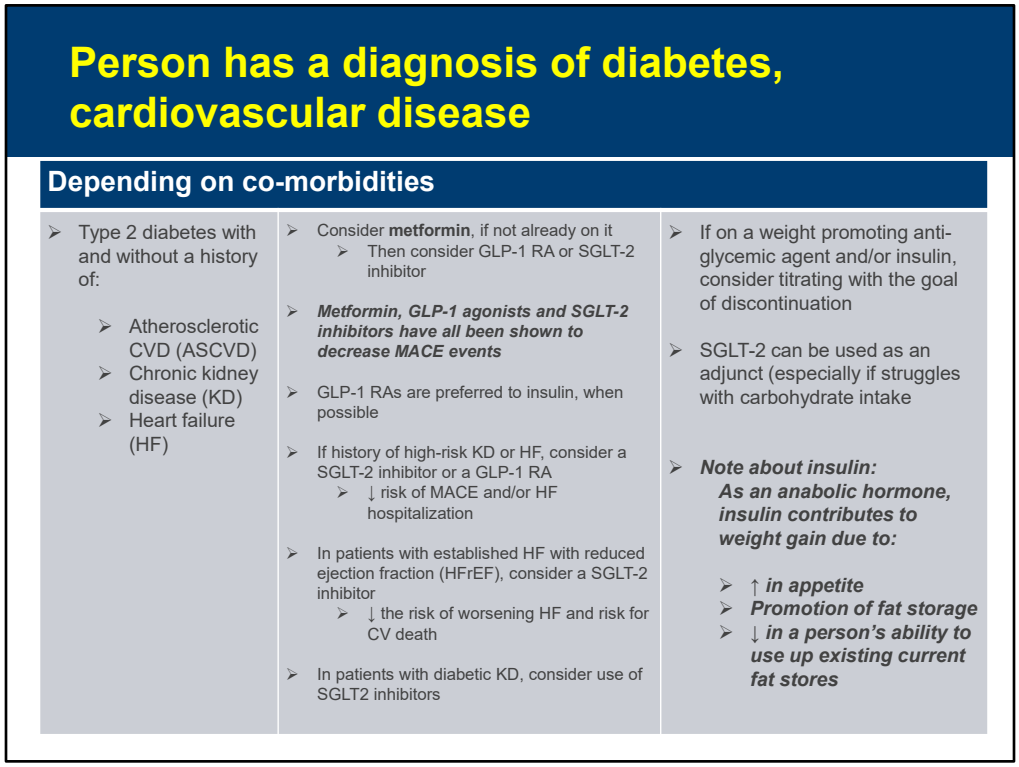
Depending on co-morbidities

- If has a hx of depression
- Has a hx of a "hungry mind"
- Has a hx of tobacco dependence/vaping and is open to quitting
  - Smokers are often reluctant to quit due to concerns of weight gain (~1-10kg within 2 years of quitting)*

- Consider **bupropion +/- naltrexone**
- Would dose bupropion in the morning and naltrexone in the evening

- Obtain baseline BP, monitor periodically
- Bupropion can have a stimulating effect
- If person is on another antidepressant that is weight promoting have a discussion with them about speaking to their PCP/provider about considering a more weight neutral Rx and/or switching to bupropion
- Would not recommend in people with:
  - Uncontrolled HTN
  - Hx of seizures
  - Hx of anorexia nervosa/ bulimia
  - Hx of anxiety disorder
- May also consider the use NRT therapies when helping people to quit smoking as an additional tool to mitigate weight gain

*Sahle BW, Chen W, Rawal LB, Renzaho AMN. Weight Gain After Smoking Cessation and Risk of Major Chronic Diseases and Mortality. *JAMA Netw Open.* 2021;4(4):e217044. doi:10.1001/jamanetworkopen.2021.7044



Standards of Medical Care in Diabetes—2021 Abridged for Primary Care Providers
American Diabetes Association
Clinical Diabetes Jan 2021, 39 (1) 14-43; **DOI:** 10.2337/cd21-as01

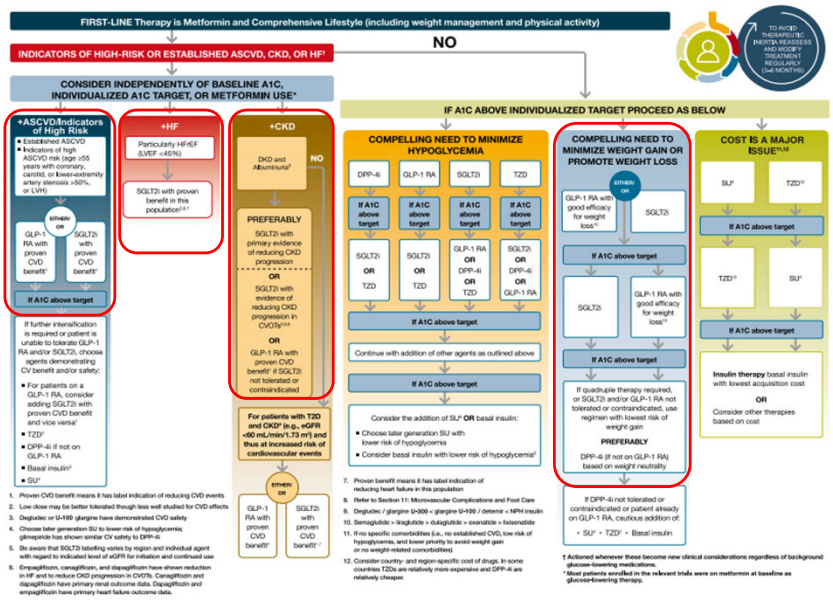


FIGURE 9.1 Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee adaptation of Davies MJ, D'Alessio DA, Fradkin J, et al. Diabetes Care 2018;41: 2669–2701 and Buse JB, Wexler DJ, Tsapas A, et al. Diabetes Care 2020;43:487–493. For appropriate context, see Figure 4.1. In this version, the "Indicators of high-risk or established ASCVD, CKD, or HF" pathway was adapted based on trial populations studied. DPP-4i, DPP-4 inhibitor; GLP-1 RA, GLP-1 receptor agonist; LVEF, left ventricular ejection fraction; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

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Standards of Medical Care in Diabetes—2021 Abridged for Primary Care Providers
American Diabetes Association
Clinical Diabetes Jan 2021, 39 (1) 14-43; **DOI:** 10.2337/cd21-as01

Person has a history of cancer and/or use of psychoactive (weight promoting) drugs

Depending on co-morbidities

➢ History of breast, colorectal, endometrial, and prostate cancer[1-6]	➢ Consider adding **metformin**, if not already on it ➢ Can then add other medications per clinical judgment	➢ Metformin will mitigate weight gain from taking these medications, as from as from changes secondary to chemotherapy for cancer

➢ If on a weight promoting psychoactive drug for which there is no other alternative[7-10]	➢ Consider adding **metformin** or **topiramate**	➢ Metformin mitigates weight gain from taking these medications
		  ➢ *Greatest efficacy when started soon after commencement of weight promoting drug*
		➢ Topiramate can mitigate weight gain from taking these medications.
		  ➢ Added potential for mood stabilization
		➢ ***Would require input from prescribing team***

1. Roshan MH, Shing YK, Pace NP. Metformin as an adjuvant in breast cancer treatment. *SAGE Open Med*. 2019;7:2050312119865114. Published 2019 Jul 16. doi:10.1177/2050312119865114

2. Ashamalla M, Youssef I, Yacoub M, Jayarangaiah A, Gupta N, et al. (2018) Obesity, Diabetes and Gastrointestinal Malignancy: The role of Metformin and other Anti-diabetic Therapy. Glob J Obes Diabetes Metab Syndr 5(2): 008-014. DOI: 10.17352/2455-8583.000032

3.Kamarudin, M.N.A., Sarker, M.M.R., Zhou, JR. *et al.* Metformin in colorectal cancer: molecular mechanism, preclinical and clinical aspects. *J Exp Clin Cancer Res* **38,** 491 (2019). https://doi.org/10.1186/s13046-019-1495-2

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5. Mu, N., Xu, T., Gao, M., Dong, M., Tang, Q., Hao, L. ... Hou, J. (2020). Therapeutic effect of metformin in the treatment of endometrial cancer (Review). Oncology Letters, 20, 156. https://doi.org/10.3892/ol.2020.12017

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Antipsychotic-Induced Metabolic Dysfunction: The Potential Role of Gut-Brain Axis. *Front Pharmacol*. 2019;10:371. Published 2019 Apr 9. doi:10.3389/fphar.2019.00371

9. Wang, C., Shi, W., Xu, J. *et al.* Outcomes and safety of concomitant topiramate or metformin for antipsychotics-induced obesity: a randomized-controlled trial. *Ann Gen Psychiatry* **19,** 68 (2020). https://doi.org/10.1186/s12991-020-00319-x

10. Ellinger LK, Ipema HJ, Stachnik JM. Efficacy of Metformin and Topiramate in Prevention and Treatment of Second-Generation Antipsychotic–Induced Weight Gain. *Annals of Pharmacotherapy*. 2010;44(4):668-679. doi:10.1345/aph.1M550

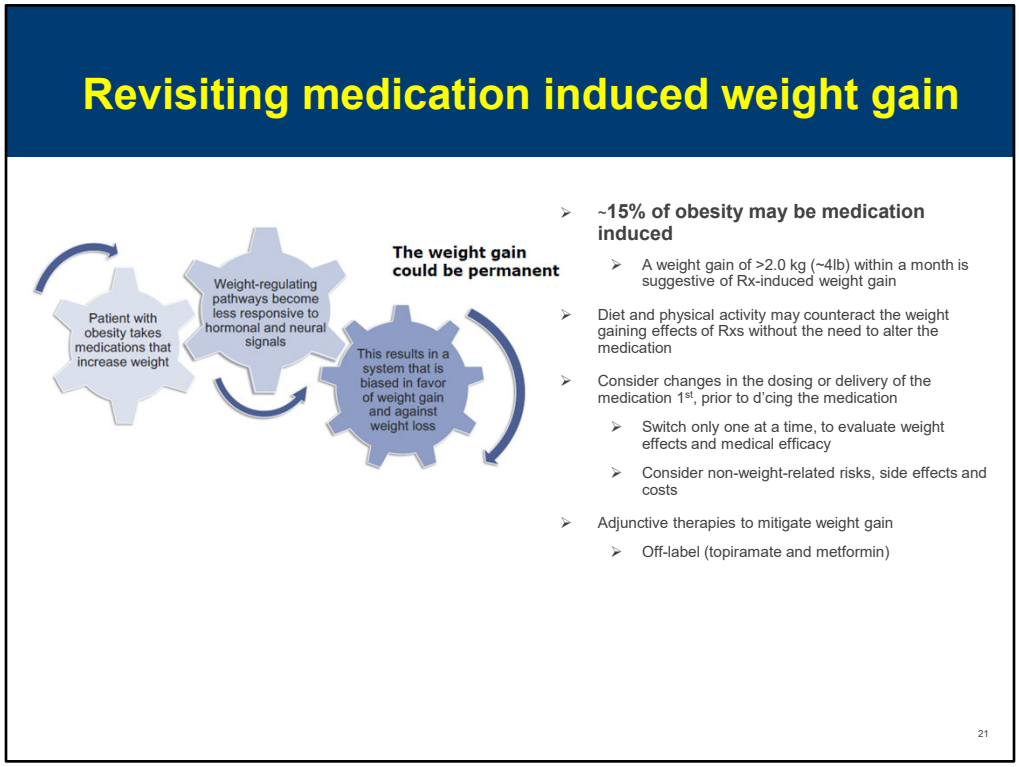

Figure from: Drug Induced Weight Gain Louis J. Aronne, MD, FACP, FTOS, DABOM Blackburn Obesity Conference, June 15, 2021

Ellinger LK, Ipema HJ, Stachnik JM. *Ann Pharmacother*. 2010;44(4):668-679.
Fiedorowicz JG, et al. *Curr Psychiatry Rev*. 2012;8(1):25-36.
Maayan L, VakhrushevaJ, Correll CU.*Neuropsychopharmacology*. 2010;35(7):1520-1530.
Baptista T, ElFakih Y, Uzcátegui E, et al. *CNS Drugs.* 2008;22(6):477-495.

How do these medications work?

Metformin

Mechanism of Action[1]	Dose	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
➢ ↓ gluconeogenesis ➢ ↓insulin resistance ➢ ↑ levels of GLP-1 **Mechanism for weight loss:** ➢ Induces ↑ GDF 15 levels in the small and large intestine → ↓food intake and ↑ energy expenditure	➢ Start with 500mg in the AM with meals, and in one week may ↑ to BID. ➢ Can ↑ to 1000mg BID, as tolerated ***Use ER formulation due to improved tolerability*** ➢ May time pill prior to or with meal to maximize appetite suppressing effect	➢ Diarrhea ➢ Abdominal cramping ➢ Flatus ➢ Vitamin B12 deficiency *(Metformin acts as a direct competitor to B12 absorption and impairs intrinsic factor)* ➢ Lactic acidosis in the presence of renal insufficiency ➢ Allergic reaction (rare) ➢ Hypoglycemia (rare) ➢ Altered taste	➢ History of ketoacidosis ➢ History of heart failure ➢ GFR < 30 (Stage IV CRF) ➢ History of hepatic failure ***Will need to discontinue up to 48-72 hours prior to a procedure requiring contrast or planned surgery due to risk of metabolic acidosis/ acute renal injury***	➢ ↓ risk of adverse cardiovascular events[2] ➢ Can mitigate weight gain due to psychoactive Rxs[3] ➢ Has anti-cancer effect[4] ➢ ↓ mortality due to COVID[5] ➢ Key to tx of women with PCOS and infertility issues[6] ➢ Can be used during pregnancy to mitigate weight gain ***Even if not very effective in promoting weight loss, would still continue low dose to stabilize insulin levels.***

1. Coll AP, Chen M, Taskar P, Rimmington D, Patel S, Tadross JA, Cimino I, Yang M, Welsh P, Virtue S, Goldspink DA, Miedzybrodzka EL, Konopka AR, Esponda RR, Huang JT, Tung YCL, Rodriguez-Cuenca S, Tomaz RA, Harding HP, Melvin A, Yeo GSH, Preiss D, Vidal-Puig A, Vallier L, Nair KS, Wareham NJ, Ron D, Gribble FM, Reimann F, Sattar N, Savage DB, Allan BB, O'Rahilly S. GDF15 mediates the effects of metformin on body weight and energy balance. Nature. 2020 Feb;578(7795):444-448. doi: 10.1038/s41586-019-1911-y. Epub 2019 Dec 25. Erratum in: Nature. 2020 Feb 13;: PMID: 31875646; PMCID: PMC7234839.

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3. de Silva VA, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. *BMC Psychiatry*. 2016;16(1):341. Published 2016 Oct 3. doi:10.1186/s12888-016-1049-5

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5. Crouse AB, Grimes T, Li P, Might M, Ovalle F and Shalev A (2021) Metformin Use Is Associated With Reduced Mortality in a Diverse Population With COVID-19 and Diabetes. Front. Endocrinol. 11:600439. doi: 10.3389/fendo.2020.600439

6. Sharpe A, Morley LC, Tang T, Norman RJ, Balen AH. Metformin for ovulation induction (excluding gonadotrophins) in women with polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2019;12(12):CD013505. Published 2019 Dec 17. doi:10.1002/14651858.CD013505

Phentermine

Mechanism of Action	Dose	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
➢ Norepinephrine (NE) releasing agent	➢ Adipex-P® 37.5mg/day ➢ Lomaira® 4-8mg/day ➢ Start with 4mg (1/2 tab of Lomaira) and ↑ to 8mg in one week ➢ **Do not start with 37.5mg** ➢ If need more than 8mg, may consider ½ tab of 37.5mg (18.75mg)	➢ Headache ➢ ↑ BP ➢ Anxiety ➢ Tachycardia ➢ Dry Mouth ➢ Insomnia ➢ Tachycardia	➢ History of cardiac disease ➢ Uncontrolled HTN ➢ Hyperthyroidism ➢ Anxiety ➢ Glaucoma ➢ Already on sympathomimetic amines (e.g., as those with ADD/ADHD) ➢ History of substance abuse	➢ Mean Weight Loss: 5-7.8% ➢ Best used in the morning up to mid day ➢ Can be used prn ➢ Can help those with "insatiable hunger" and/or "appetite" ➢ When combined with topiramate has even better weight loss promoting effects ➢ Monitor BP and HR ➢ **Do not need to get an EKG in an otherwise healthy person, with no cardiac history** ➢ **May not initiate phentermine in person who has not been seen in-person at least once**

Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, Ryan DH, Still CD; Endocrine Society. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Feb;100(2):342-62. doi: 10.1210/jc.2014-3415. Epub 2015 Jan 15. Erratum in: J Clin Endocrinol Metab. 2015 May;100(5):2135-6. PMID: 25590212.

Topiramate

Mechanism of Action	Dose	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
➢ GABA receptor modulation: ➢ ↓ glutamate release by blocking voltage gated Na channels ➢ Enhances GABA release ➢ Carbonic anhydrase inhibition	➢ Starting dose 25mg. May titrate to 100 mg in 25mg increments per week, as tolerated. ➢ Because of its possibly sedating effects, best taken in the evening. ➢ ***Once reach a maintenance dose, may prescribe larger dose pill (50mg, 100mg) to improve adherence and ↓ pill burden*** ➢ If has a sleep-related eating disorder, can consider ↑ dose to 300mg/day	➢ Sedation ➢ "Brain-fog" ➢ Word finding difficulties ➢ ↓ desire for alcoholic beverages ➢ Paresthesias ➢ Dysgeusia ➢ Hair loss ➢ May have a diuretic effect → urination and/or dizziness ➢ Nephrolithiasis	➢ Pregnancy ➢ Breast feeding ➢ Glaucoma ➢ MAOi inhibitors ➢ May ↓ efficacy of OCPs	➢ Can be a mood stabilizer ➢ Enhances appetite suppression ➢ Consider in those who suffer from migraines ➢ Good choice for those who binge or partake in night eating ➢ Excellent choice for those who suffer from insomnia ➢ Consider in those who have high alcohol consumption ➢ Most effective in curbing hunger if timed before and/or with meal ➢ ***Before starting in woman of child-bearing age, document form of contraception use***

Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, Ryan DH, Still CD; Endocrine Society. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Feb;100(2):342-62. doi: 10.1210/jc.2014-3415. Epub 2015 Jan 15. Erratum in: J Clin Endocrinol Metab. 2015 May;100(5):2135-6. PMID: 25590212.

Bupropion

Mechanism of Action	Dose	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
➢ ↓ uptake of DA (and NE) ➢ Activates POMC neurons ➢ Modulates reward pathways ➢ Dopamine and norepinephrine reuptake inhibitor	➢ Start with 100-300 mg SR or 150-300 mg XL ***Once reach a maintenance dose, may prescribe larger dose pill (300 mg) to improve adherence and ↓ pill burden***	➢ Dry mouth, ➢ Constipation ➢ Headache ➢ Nausea ➢ Dizziness ➢ Insomnia ➢ Agitation	➢ Hx of seizures ➢ Anxiety ➢ Active or recent history of *bulimia* or *anorexia nervosa* ➢ Pregnant or breastfeeding	➢ Less likely to cause sexual dysfunction compared to other anti-depressants ➢ Consider in people with concomitant tobacco/nicotine dependence

Naltrexone

Mechanism of Action	Dose	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
Blocks the feedback inhibition of by β-endorphin	➢ Start with ¼ tab of 50mg of naltrexone once daily ➢ May ↑ to ½ tab	➢ Gastrointestinal discomfort ➢ **Dose dependent*	Caution in those with pain disorders → may heighten perception of pain	Use in conjunction with bupropion to make the generic formulation of Contrave®

Qysmia® (phentermine/topiramate)

Mechanism of Action	Dose	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
➢ Phentermine: NE releasing agent ➢ Topiramate: GABA receptor modulation	➢ Start with 3.75/23 and can ↑ to as high as 15/92 ➢ *(Most common dose is 7.5/46 mg daily)*	➢ Insomnia ➢ Dry mouth ➢ Constipation ➢ Headache ➢ Parethesias ➢ Dizziness ➢ Mental fog	➢ Pregnancy ➢ Breast feeding ➢ Hyperthyroidism ➢ Glaucoma ➢ MAOi inhibitors (due to risk of hypertensive crisis)	➢ Mean Weight Loss: 6.6 – 8.6% ➢ ***Before starting in woman of child-bearing age, document form of contraception use*** ➢ **May not initiate in person who has not been seen in-person at least once**

Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, Ryan DH, Still CD; Endocrine Society. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Feb;100(2):342-62. doi: 10.1210/jc.2014-3415. Epub 2015 Jan 15. Erratum in: J Clin Endocrinol Metab. 2015 May;100(5):2135-6. PMID: 25590212.

Contrave® (naltrexone/bupropion)

Mechanism of Action	Dose	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
➢ Opiate antagonist– blocks the feedback inhibition of the ß-endorphin ➢ ↓ reuptake inhibitor of dopamine and norepinephrine	➢ Each tab: 8mg naltrexone/ 90mg bupropion ➢ Week1: Start with 1 tab daily ➢ Week2:1 tab BID ➢ Week3: 2 tabs in AM 1 tab in PM ➢ Week 4: 2 tabs BID ➢ *Do not take with a high fat meal due to increased absorption	➢ Nausea ➢ Constipation ➢ Headache ➢ Vomiting ➢ Dizziness	➢ Uncontrolled HTN ➢ Seizure disorder ➢ Anorexia ➢ Bulimia nervosa ➢ Drug or alcohol withdrawal ➢ MAO inhibitors (*due to risk of hypertensive crisis*) ➢ Pain syndromes (*naltrexone can potentiate pain signals and offset the impact of opioids*)	➢ Mean weight loss: 4.8-6% ➢ Many do not need to use the full dose of 4 tabs per day

Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, Ryan DH, Still CD; Endocrine Society. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Feb;100(2):342-62. doi: 10.1210/jc.2014-3415. Epub 2015 Jan 15. Erratum in: J Clin Endocrinol Metab. 2015 May;100(5):2135-6. PMID: 25590212.

Orlistat

Mechanism of Action	Dose	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
➢ Lipase inhibitor ➢ Inhibits gastric and pancreatic lipase ➢ Causes malabsorption of 30% of ingested fat	➢ Alli® 60mg (OTC) ➢ Xenical® 120mg (Rx) ➢ 60-120 mg 3x/day	➢ Steatorrhea ➢ Fecal urgency/ incontinence ➢ Oily spotting ➢ ↓ absorption of fat-soluble vitamins (A,D,E,K) ➢ Flatulence	➢ Pregnant ➢ Breast feeding ➢ Cholestasis ➢ Malabsorption syndrome ➢ Warfarin ➢ Antiepileptic drugs	➢ Does not affect appetite regulatory systems ➢ No systemic absorption ➢ Mean weight loss: 2.9-3.4% ➢ Consider in those who struggle with constipation (possible adjunct to those on GLP-1 who struggle with constipation)

Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, Ryan DH, Still CD; Endocrine Society. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Feb;100(2):342-62. doi: 10.1210/jc.2014-3415. Epub 2015 Jan 15. Erratum in: J Clin Endocrinol Metab. 2015 May;100(5):2135-6. PMID: 25590212.

Glucagon-like peptide-1 (GLP-1) receptor agonists

Mechanism of Action	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
Expressed in cells of the pancreas, the intestine, and neurons located in the caudal brainstem and hypothalamus. ↓ gastric emptying and gut motility ↓ food intake ↑ satiety	➢ Nausea ➢ Emesis ➢ Cramps ➢ Constipation ➢ Dizziness ➢ Pancreatitis ➢ Hypoglycemia (rare)	➢ Hx of pancreatitis ➢ Gallbladder disease ➢ Medullary Thyroid cancer/ MEN2	➢ Each click is on the pen is a dose. May slowly titrate one click at a time to facilitate tolerability ➢ Have been shown to ↓ cardiovascular adverse events

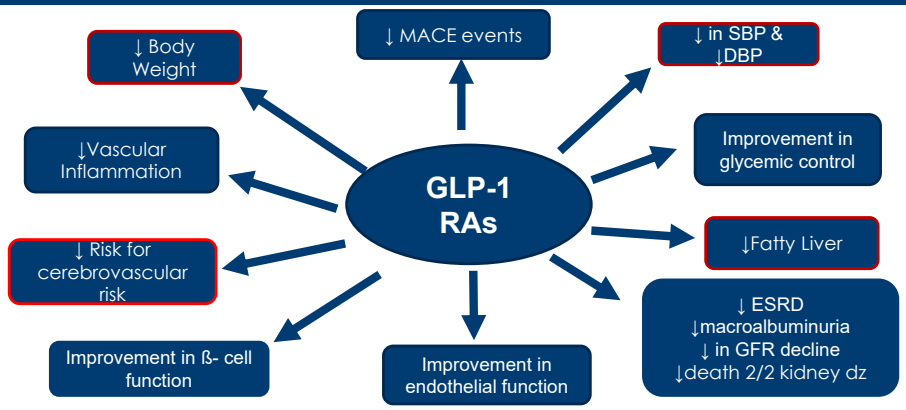
Agent	Dose	Comments
Liraglutide	Start with 0.6mg daily for first week and may increase by 0.6mg each week up to a max dose of 1.8mg (Victoza®) and 3.0mg (Saxenda®)	Commercially available as: ➢ Victoza® (FDA-approved for tx of T2DM) ➢ Saxenda® (FDA-approved for tx of obesity) (Up to 7% weight loss)
Semaglutide	Injectable: Start with 0.25 mg weekly for 4 weeks, after 4 weeks may increase to 0.5mg weekly up to 1 mg (Ozempic) and up to 2.4mg (Wegovy) over 16 weeks. ***In the real world, may do titration over longer periods of time and base dose increases based on need for greater efficacy.*** Pill: Start with 7mg daily for 4 weeks. May ↑ to 14mg for greater effect as tolerated	Formulation has greatest penetration into the brain (i.e. fat soluble) Commercially available as: ➢ Ozempic® (FDA-approved for tx of T2DM) ➢ Wegovy® (FDA-approved for tx of obesity) (Up to 20% weight loss) ➢ Rybelsus®: Oral formulation has more modest weight loss as compared to injectable formulation (5-8lbs after 6 months) ➢ After 6 months, ↓ A1c by 1.2% -1.4%
Dulaglutide	Start with 0.75mg subcutaneously weekly Can ↑ to 1.5 → 3.0 → 4.5 mg as tolerated Recommend 4 weeks at each dose before ↑ dose	➢ Trulicity®: Auto-inject pen ➢ In fall of 2020, received FDA-approval for 3.0mg and 4.5mg weekly. Effect on glucose and weight is dose dependent ➢ Can help to promote modest weight loss (2-6lbs)

Mechanism citation:
Shah M, Vella A. Effects of GLP-1 on appetite and weight. *Rev Endocr Metab Disord*. 2014;15(3):181-187. doi:10.1007/s11154-014-9289-5
Stp trial:
Kushner RF, Calanna S, Davies M, Dicker D, Garvey WT, Goldman B, Lingvay I, Thomsen M, Wadden TA, Wharton S, Wilding JPH, Rubino D. Semaglutide 2.4 mg for the Treatment of Obesity: Key Elements of the STEP Trials 1 to 5. Obesity (Silver Spring). 2020 Jun;28(6):1050-1061. doi: 10.1002/oby.22794. PMID: 32441473; PMCID: PMC7318657.

*Major Breakthrough in Weight Loss With Semaglutide? - Medscape - Nov 12, 2020.*https://www.medscape.com/viewarticle/940841#vp_3, downloaded Feb 2021
www.rybelsus.com

Cardiovascular benefit:
: Sheahan KH, Wahlberg EA, Gilbert MP. Postgrad Med J 2020;96:156–161.

Pleiotropic effects of GLP-1 Receptor Agonists



Sodium-glucose linked transporter (SGLT) 2-inhibitors

Mechanism of Action	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
Inhibits Na+ glucose co-transporter 2 (SGLT-2) → prevent resorption of glucose as well as water in the renal tubules → promoting approximately: ➢ 75 g of urinary glucose excretion with an associated caloric loss (approximately 300 kcal/ day	➢ Recurrent genitourinary infections ➢ Dehydration/ hypotension/ hyperkalemia ➢ Normoglycemic ketoacidosis ➢ ↑ risk of amputations ➢ DKA risk ➢ Risk of bone fractures (canagliflozin) ➢ ↑LDL	➢ Type 1 diabetes ➢ Less effective in those with renal insufficiency ➢ GFR <45 (caution) ➢ GFR < 30 (contraindication) ➢ History of diabetic ketoacidosis ➢ Should be d'cd prior to surgery due to potential risk for DKA	➢ ***Does not affect appetite*** ➢ Variable weight loss depending on agent ➢ Improved CVD mortality ➢ Outcomes ➢ Weight loss is dose dependent ➢ Can also be used prn in anticipation of a carbohydrate rich foods

Agent	Dose	Comments
Canagliflozin	100-300 mg daily	Invokana® ➢ Can induce 2.5-4 kg weight loss
Dapagliflozin	5-10 mg daily	Farxiga® ➢ Can induce 2.65 to 3.2 kg of weight loss
Empagliflozin	10-25 mg daily	Jardiance® ➢ Can induce 2.08-2.5 kg of weight loss

Brown E, Wilding JPH, Barber TM, Alam U, Cuthbertson DJ. Weight loss variability with SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes mellitus and obesity: Mechanistic possibilities. Obes Rev. 2019 Jun;20(6):816-828. doi: 10.1111/obr.12841. Epub 2019 Apr 10. PMID: 30972878.

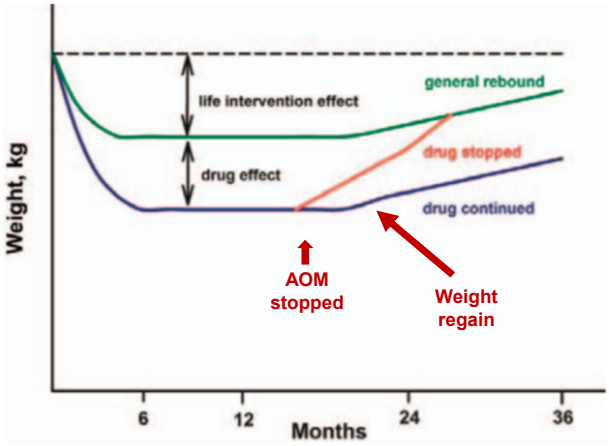
Plenity® (formerly known as Gelesis-100)

Mechanism of Action	Dose	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
➢ Hydrogel composed of cellulose and citric acid ➢ Capsule dissolves in the stomach and the particles released can expand up to 100x their original weight in the stomach → ↑ satiety ➢ Particles remain hydrated in the small intestine until they reach the large intestine. Water is released from the particles and reabsorbed in the colon.	➢ Take 3 capsules two times a day (before lunch and dinner) ➢ Take 20 min prior to a meal with 16 ounces of water. ➢ With or after meal drink an additional 2 glasses of water. ➢ If taking with a concomitant medication with meals or close to meals should be taken after the meal has started	➢ Diarrhea ➢ Distended abdomen ➢ Abdominal discomfort ➢ Flatulence ➢ Constipation	➢ Pregnancy ➢ Allergic reactions to cellulose, citric acid, sodium stearyl fumarate, gelatin ➢ Hx of esophageal disease ➢ Hx of GI disorders that affect motility through the GI system	➢ Not absorbed systemically ➢ Eliminated in the same manner as food ➢ Medical device, not a systemic agent ➢ Indicated for people with BMI 25 – 40 kg/m^2 ➢ When combined with diet and exercise, can help achieve > 5-10% weight loss ➢ Caution with medications that are normally taken with or around meals

Weight regain and plateaus

HOW ANTI-OBESITY MEDICATIONS CAN HELP

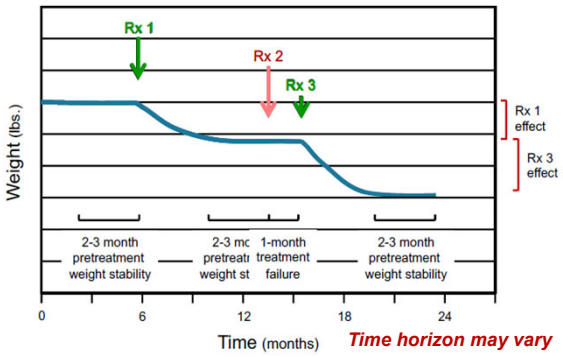
Weight loss over time +/- lifestyle intervention and AOMs



Schultes B. *Visc Med*. 2016 Oct;32(5):347-351. doi: 10.1159/000450904.

Schultes B. Pharmacological Interventions against Obesity: Current Status and Future Directions. *Visc Med*. 2016 Oct;32(5):347-351. doi: 10.1159/000450904. Epub 2016 Oct 7. PMID: 27921047; PMCID: PMC5122991.

Plateaus and escalation of AOMs



Time horizon may vary

These are inevitable and will happen at some point during a person's weight loss journey.

Adapted from Blackburn, Pharmacotherapy talk (June 2020)

Adapted from Blackburn, Pharmacotherapy talk (June 2020)

Promising therapies in development

Class of agents in development:	Mechanism	Comments
Glucagon (GCG) receptor agonist	➢ ↑ glucose levels via gluconeogenesis and inhibits insulin ➢ ↑ satiety ➢ ↑ thermogenesis ➢ ↑ energy expenditure ➢ ↑ lipolysis and fatty acid oxidation → ↓ cholesterol and TG level	
Glucose-dependent insulinotropic peptide (GIP) antagonists	➢ ↑ glucagon secretion ➢ Improves insulin resistance ➢ ↑uptake and rapid oxidation of fatty acids by muscle and liver	
Areas of promising new combinations:	GLP-1 combined with: ➢ GLP-1 + GIP = Tirzepatide (duo-agonist) ➢ GLP-1 + GIP + GCG (tri-agonist) ➢ GLP-1 + SGLT-2 inhibitors	Tolerability may be limited due to gastrointestinal effects. Phase 2 and 3 studies are in process.

Once-Weekly Semaglutide in Adults with Overweight or Obesity
Publication: The New England Journal of Medicine
Publisher: Massachusetts Medical Society
Date: Feb 10, 2021

Adult Obesity Algorithm eBook: Detailed Overview of Obesity Medicine.
Bays HE, McCarthy W, Christensen S, Tondt J, Karjoo S, Davisson L, Ng J, Golden A, Burridge K, Conroy R, Wells S, Umashanker D, Afreen S, DeJesus R, Salter D, Shah N. Obesity Algorithm eBook, presented by the Obesity Medicine Association, www.obesityalgorithm.org. 2020. https://obesitymedicine.org/obesity-algorithm/ (Accessed February 2021)

Michałowska J, Miller-Kasprzak E, Bogdański P. Incretin Hormones in Obesity and Related Cardiometabolic Disorders: The Clinical Perspective. Nutrients. 2021 Jan 25;13(2):351. doi: 10.3390/nu13020351. PMID: 33503878.

Killion EA, Wang J, Yie J, Shi SD, Bates D, Min X, Komorowski R, Hager T, Deng L, Atangan L, Lu SC, Kurzeja RJM, Sivits G, Lin J, Chen Q, Wang Z, Thibault SA, Abbott CM, Meng T, Clavette B, Murawsky CM, Foltz IN, Rottman JB, Hale C, Véniant MM, Lloyd DJ. Anti-obesity effects of GIPR antagonists alone and in combination with GLP-1R agonists in preclinical models. Sci Transl Med. 2018 Dec

19;10(472):eaat3392. doi: 10.1126/scitranslmed.aat3392. PMID: 30567927.

Questions?

Zonisamide

Mechanism of Action	Dose	Commonly Experienced Side Effects	Cautions/ Contraindications	Comments
➢ GABA receptor activator → Inhibits glutamate activity ➢ Carbonic anhydrase inhibitor	➢ Start with 100mg/day ➢ ↑ to 400mg/day	➢ Drowsiness ➢ Dizziness ➢ Headache ➢ Diarrhea ➢ Ataxia ➢ Renal calculi	➢ Pregnancy ➢ Breast feeding	➢ Less sedating than topiramate ➢ Mean weight loss: 6% ➢ Mood stabilizer ➢ ↓ hunger

Gadde KM, Kopping MF, Wagner HR 2nd, Yonish GM, Allison DB, Bray GA. Zonisamide for weight reduction in obese adults: a 1-year randomized controlled trial. *Arch Intern Med*. 2012;172(20):1557-1564. doi:10.1001/2013.jamainternmed.99

There are many medications that have the potential to promote weight gain

Class of medication	Alternative Agents
Weight Promoting	May promote weight loss +/- weight neutral
Cardiovascular:	
Beta-blockers: ➢ Propranolol ➢ Atenolol ➢ Metoprolol	➢ Carvedilol
Older and more lipophilic CCBs may ↑ body weight 2/2 edema, e.g. nifedipine, amlodipine	
Diabetes medications:	
Insulins ➢ Sulfonylureas ➢ Thiazolidinediones ➢ Meglitinides (e.g. nateglinide, repaglinide)	May ↓ weight: ➢ Metformin ➢ GLP-1 agonists ➢ SGLT2-inhibitors ➢ Alpha glucosidase inhibitors (e.g. acarbose, miglitol) ➢ Pramlintide Weight neutral: ➢ DPP4 inhibitors (e.g. "-gliptins")

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Class of medication	Alternative Agents
Weight Promoting	May promote weight loss +/- weight neutral
Steroids:	
Contraceptives: ➢ Progestin contraceptives (injectable or implantable) ➢ OCPs ➢ IUDs	➢ Copper IUD ➢ Testosterone (helpful in men, facilitates ↑ in lead body mass)
Anti-seizure medications:	
➢ Carbamazepine ➢ Gabapentin ➢ Valproate ➢ Pregabalin	➢ Topiramate ➢ Zonisamide

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There are many medications that have the potential to promote weight gain

Class of medication	Alternative Agents
Weight Promoting	May promote weight loss +/- weight neutral
Antidepressants	
Tricyclic antidepressants: ➢ Amitriptyline ➢ Doxepin ➢ Imipramine ➢ Dosulepin	Variable effect on body weight: ➢ Desipramine ➢ Nortriptyline
SSRIs ➢ Paroxetine ➢ Citalopram	Variable effect on body weight: ➢ Escitalopram ➢ Sertraline
SNRIs ➢ Venlafaxine	➢ Desvenlafaxine ➢ Duloxetine
➢ Trazodone	Decrease weight: ➢ Bupropion ➢ Fluoxetine

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Bays HE, McCarthy W, Christensen S, Tondt J, Karjoo S, Davisson L, Ng J, Golden A, Burridge K, Conroy R, Wells S, Umashanker D, Afreen S, DeJesus R, Salter D, Shah N. Obesity Algorithm eBook, presented by the Obesity Medicine Association, www.obesityalgorithm.org. 2020. https://obesitymedicine.org/obesity-algorithm/ (Accessed February 2021)

There are many medications that have the potential to promote weight gain

Class of medication	Alternative Agents
Weight Promoting	May promote weight loss
Mood stabilizers	
➢ Gabapentin ➢ Divalproex ➢ Lithium ➢ Valproate ➢ Carbamazepine ➢ Lamotrigine ➢ Oxcarbazepine	➢ Topiramate ➢ Zonisamide

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