New Weight Loss Drugs in Psychiatry

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Dr. Liebers has no financial relationships with companies related to this material.

Introduction

From liraglutide (Saxenda) to tirzepatide (Mounjaro), new weight loss medications are reshaping the treatment of diabetes and obesity. But what's their impact in psychiatry? In this article, I'll look at the promise and peril of using these glucagon-like peptide-1 receptor agonists (GLP-1 RA) to treat metabolic side effects and will explore other potential uses in psychiatry.

How they work

GLP-1 is a short-lived hormone released in the gut when we eat. The new weight loss medications mimic this hormone but are engineered to last a lot longer. They slow stomach emptying, causing the vagal nerve to signal fullness to the brain. At the same time, these medications cross the blood-brain barrier and directly signal satiety at the hypothalamus. They stimulate the growth of new neurons in the hippocampus and improve brain metabolism, attracting the attention of Alzheimer's researchers. Their anti-inflammatory and insulin sensitization properties in the brain may help explain antidepressant effects seen in some patients. They also promote the growth of dopaminergic neurons and have been tested in Parkinson's disease.

Obesity

Three of the GLP-1 RAs are FDA approved for obesity: liraglutide (Victoza, Saxenda), semaglutide (Ozempic, Wegovy), and tirzepatide (Mounjaro, Zepbound) (these have separate

brands for diabetes and obesity, and we have listed the diabetes brand first). Specifically, they are approved in patients who have a BMI > 30 kg/m2 or who have a BMI > 27 kg/m2 and an obesity related health condition (eg diabetes, hypertension, or dyslipidemia).

Among them, tirzepatide is the most effective, with average weight loss of about 20% of body weight (Jastreboff AM et al, *N Engl J Med* 2022;387(3):205-216). Tirzepatide targets both GLP-1R and the glucose-dependent insulinotropic peptide receptor (GIPR), while the older two medications focus on GLP-1R alone. Between those, semaglutide appears most effective with an average ~10-15% of body weight loss over a year, followed by liraglutide with ~5-10% of body weight lost.

Among the GLP-1RAs that lack approval in weight loss, exenatide (Bydureon) is slightly less effective than liraglutide, and dulaglutide (Trulicity) has not been tried in a randomized study of patients without diabetes.

Even stronger drugs are on the horizon. Retatrutide, with triple-target effects (it works at the two receptors mentioned above and the glucagon receptor) caused people to lose about a quarter of their body weight after a year in phase II study published last year (Jastreboff AM et al, *N Engl J Med* 2023;389(6):514-526).

Antipsychotic weight gain

What sets the GLP-1 RAs apart from alternatives for antipsychotic-induced weight gain (like metformin and samidorphan in its combination formulation with olanzapine) is their ability to reverse weight gain after it has already started to get out of control. In a small open-label trial of exenatide in people with clozapine-associated obesity (BMI between 30kg/m2 and 45kg/m2), the group on that drug had ~10 lbs more weight loss than placebo at 24-weeks (Siskind D et al, *J Psychiatr Res* 2020;124:9-12). Liraglutide worked even better with a mean difference of ~12lbs

in a 16-week study in patients either on clozapine or olanzapine. While more studies in psychiatric populations are needed, obesity and antipsychotic-induced obesity are more alike than different, and it is likely that other GLP-1 RAs will work in this population as well.

By comparison, the opioid antagonist samidorphan combination with olanzapine, Lybalvi, has only been tested for its ability to reduce weight gain in non-obese patients, compared to olanzapine alone. Similarly, metformin is most effective when starting a new antipsychotic. In one meta-analysis of RCTs, metformin worked about three times as well when starting a new antipsychotic in first episode psychosis (~13 lbs difference from placebo) compared with its use after chronic antipsychotic treatment (~4 lbs difference from placebo) (De Silva VA et al, *BMC Psychiatry* 2016;16(1):341). Between these two, metformin is my first-line preference as it not only helps with antipsychotic-related weight gain but also with the metabolic side effects of antipsychotics (insulin resistance, fasting glucose, triglycerides, as well as hyperprolactinemia), earning it a recommendation from the APA for this purpose. It also has evidence in patients with BMI >30 kg/m2. But neither can match the effects of GLP-1 RAs in patients with high BMIs after chronic antipsychotic use.

Psychiatric effects

Substance use

As the use of GLP-1 RAs expanded, clinicians noticed that some patients taking them had decreased cravings for alcohol. This made sense to researchers who had seen them dial down reward-response circuitry in animal models. So far, the clinical data is mixed but intriguing. Dulaglutide did not work in an RCT in smoking cessation in mostly obese adults, but alcohol consumption decreased in the treatment group (Lengsfeld S et al, *eClinicalMedicine* 2023;57:101865; Probst L et al, *JCI Insight* 2023;8(22):e170419). Exenatide did not work in

cocaine use disorder, but did reduce drinking in obese patients with alcohol use disorder (Klausen MK et al, *JCI Insight* 2022;7(19):e159863). Though promising, these results were arrived at by data fishing techniques, which makes them too preliminary to recommend for substance use disorders.

Mood symptoms

Animal studies, case reports and a meta-analysis of RCTs of GLP-1 RAs suggest that these medications might help with depression (Chen X et al, *Am J Geriatr Psychiatry* 2023:S1064748123003949 (online ahead of print)). At the same time, they worsened mood symptoms in case reports. We have not yet seen any actual clinical trials of a GLP-1 RA for depression to help clear up their role here.

Binge Eating disorders

There is currently only one FDA approved medication for binge eating disorder (BED): lisdexamfetamine. Case reports and a cohort study suggest GLP-1 RAs may work for BED (Richards J et al, *Obes Pillars* 2023;7:100080). Liraglutide 3 mg/day reduced binge eating in a small RCT of stable bipolar patients with obesity, both on and off antipsychotics, without changing mood symptoms (McElroy SL et al, J Clin Psychopharmacol. Published online January 16, 2024. doi:10.1097/JCP.0000000000001803).

Cognition

Animal studies suggested the GLP-1 RAs may improve cognition, but results in humans are inconclusive. Liraglutide improved cognition in an open label study of mood disorders, but exenatide failed to do the same in a small RCT of schizophrenia with obesity (Mansur RB et al, J

Affect Disord 2017;207:114-120; Ishøy PL et al, Acta Psychiatr Scand 2017;136(1):52-62). Likewise, studies in dementia have been mixed, but more definitive trials are underway.

Risks

Nausea, vomiting, constipation and diarrhea are the most common side effects, but they tend to improve with time. In trials, these side effects occurred about twice as often with GLP-1 RAs than with placebo, and in about a third of patients on the active drug. Patients with a history of pancreatitis, medullary thyroid cancer or a personal or family history of multiple endocrine neoplasia 2 (MEN2) are advised not to take these drugs. The concern about thyroid tumors comes from animal data and it's not clear whether there is an elevated risk in people. Some people have reported worsening suicidal ideation and given the known association between bariatric surgery and suicidality, these reports should be taken seriously and discussed with patients while we wait further research on this potential connection (recent studies have started to allay these fears; if anything, the GLP-1 RAs may be protective). The risk of gastroparesis has prompted some surgeons to recommend stopping it altogether around the time of some procedures.

How to use them

So which should you prescribe: liraglutide, semaglutide or tirzepatide? The choice often comes down to cost and availability. Liraglutide is the best studied in psychiatric populations and came off patent in December 2023 but the downside is that it requires daily injections. Semaglutide and tirzepatide are more effective for weight loss and are weekly injections. Educate your patients in advance about the GI side effects and titrate slowly if those symptoms come up. If slow titration does not work to minimize side effects, suggest small food portions, and make sure

any reflux symptoms are appropriately treated (a short course of a proton pump inhibitor is most commonly recommended) (Gorgojo-Martínez JJ et al, *J Clin Med* 2022 Dec 24;12(1):145). If all that fails, you can switch to another GLP-1 RA. In the general population, most people come off these drugs after a year (in line with the duration of most trials), although when effective, patients can stay on them for longer—which may be required for patients on long-term antipsychotic therapy.

When medications are added to the FDA's shortage list (which is the case for semaglutide and tirzepatide), drug compounders are allowed to prepare them at a lower cost. This means that some specialty pharmacies have started selling replications of the patented medications, with an unclear source. Given how hard it is to get these medications for some patients, this can be an attractive alternative, but the FDA has expressed concern at the frequency of -glutide salts turning up in compounded formulations, which are not present in any of the FDA-approved drugs, and thus have an unknown safety and efficacy profile.

Many psychiatrists—particularly those treating patients with serious mental illness on long-term antipsychotic therapy—have started prescribing these medications. For mental health practitioners with less experience prescribing antidiabetic and weight loss medications, it may be appropriate to coordinate with primary care colleagues.

Carlat Take

To prevent metabolic side effects when beginning an antipsychotic, start with metformin, but consider a GLP-1 RA for patients who have already been on antipsychotics for a while with a BMI > 30 kg/m2 (or > 27 kg/m2 and obesity-related health problems). GLP-1 RAs can be safely combined with metformin or used on their own.

GLP-1 RAs: Quick Guide			
Medication	**Mean Weight Loss***	**Dosing (SC injection)**	**Notes**
Approved for Weight Loss and Diabetes			
Liraglutide (Victoza, Saxenda)	Obesity: ~5-10% at max dose, in 52-72 weeks Antipsychotic-related weight gain: 5% at 16 weeks	Daily Start: 0.6 mg Target: 3mg, after increasing by 0.6mg weekly	Higher risk of biliary disease and pancreatitis
Semaglutide (Ozempic, Wegovy)	Obesity: ~10-15% at max dose, in 52-72 weeks	Weekly Start: 0.25mg Target: 2.4mg, after dose increases every 4 weeks	An oral version, not approved for weight loss, works about as well as the SC. Higher risk of gastroparesis
Tirzepatide (Mounjaro, Zepbound)	Obesity: ~18% at 72 weeks on max dose	Weekly Start: 2.5mg Target: 5, 10 or 15mg, increasing in 2.5mg increments every 4 weeks	Not yet studied in psychiatric patient populations. FDA approved in obesity with sleep apnea. Higher risk of nausea and vomiting
Approved for Diabetes			
Dulaglutide (Trulicity)	Untested in patients without diabetes	Weekly Start: 0.75mg Target 1.5mg, dose increase after 4 weeks	
Exenatide (Byetta)	Obesity: About 5% at 6 months Antipsychotic induced weight gain: 5% weight loss at 24 weeks	Twice daily before meals Start: 5 mcg Target: 10mcg after one month	
*Difference in weight compared to placebo			