Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs): Mechanism, Benefits, and Evidence-Based Clinical Considerations

Mechanism of action

GLP-1 is an incretin hormone secreted by L cells in the small intestine. It binds to GLP-1 receptors expressed in various tissues including pancreas, stomach, heart, kidneys, immune cells, and brain. Synthetic GLP-1 agonists are designed to last longer in the body, so they provide consistent benefits compared to the natural hormone, which breaks down quickly.

- Glucose regulation: GLP-1 helps the pancreas release insulin when blood sugar is high and reduces the release of glucagon, keeping blood sugar stable.
- Appetite & satiety: GLP-1 receptor agonists act on the brain's appetite centers, promoting a sense of fullness and reducing hunger, which helps lower overall calorie intake.
- Gastric emptying: By delaying gastric emptying, it reduces blood sugar spikes after meals.
- Cardiometabolic benefits: GLP-1 agonists can improve cardiac function and reduce cardiovascular risks and mortality.
- Weight loss: GLP-1 helps patients lose weight by delaying gastric emptying, regulating hunger and calorie intake.

Glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonists selectively bind to and activate both receptors, mimicking native GIP & GLP-1. They contain C20 fatty diacid, enabling albumin binding and prolonging half-life. These agents enhance first and second phase insulin secretion, reduce glucagon levels in a glucose-dependent manner, slow gastric emptying, and decrease food intake, likely via appetite regulation. GLP-1 regulates appetite and caloric intake, while studies suggest GIP may further contribute to food intake regulation. Both receptors are present in brain regions involved in appetite control.

Duration of effect

GLP-1 receptor agonists provide sustained benefits in glycemic control, weight reduction, and cardiovascular health as long as treatment is continued. Discontinuation often leads to weight regain and diminished metabolic improvements unless patients maintain consistent lifestyle interventions.

Comparing administration routes - Oral vs injectable GLP-1 RAs

- Administration: Oral GLP-1 (semaglutide) must be taken on an empty stomach at least 30 minutes before consuming any food, beverage, or medications, with no more than 4 oz of plain water. This can be challenging for some patients. Injectable GLP-1 on the other hand is administered weekly and is more straightforward.
- Efficacy: Injectable forms tend to work better overall, with more consistent blood sugar control and weight loss. The oral form (semaglutide) is less predictable as it depends on strict timing & absorption with an oral bioavailability of ~ 0.4 to 1% compared to 89% for subcutaneous injection.
- Convenience & cost: Many patients prefer oral medications to avoid needles, but complex instructions can make adherence challenging. While oral meds may seem less expensive, poor adherence often leads to higher overall costs. Injectables with simpler weekly dosing are typically a better choice for patients who need reliable outcomes. Oral forms are suitable for those who dislike injections and can maintain the required regimen.

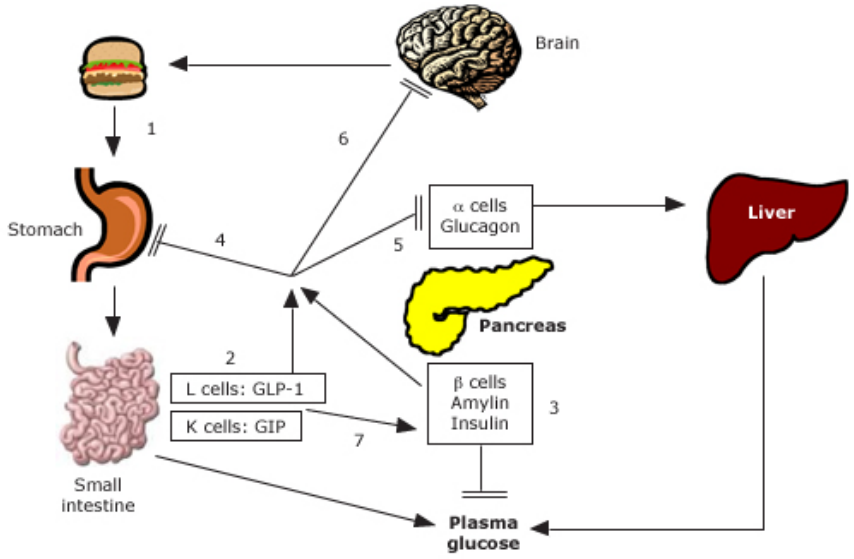
Discontinuation effects

Discontinuing GLP-1 receptor agonists often leads to the return of symptoms including weight regain, worsened glycemic control, and the recurrence of metabolic syndrome features. Appetite regulation diminishes leading to weight gain, while blood sugar levels may rise particularly in patients with diabetes. BP, cholesterol, and inflammatory markers can also worsen. Patients planning to stop GLP-1 therapy should work closely with a healthcare provider to establish a comprehensive plan that prioritizes healthy eating, regular exercise, and other lifestyle modifications to minimize adverse outcomes.

Long-term metabolic benefits & considerations

GLP-1 receptor agonists offer significant benefits for managing metabolic syndrome, but these effects are dependent on consistent use. They improve blood sugar control by enhancing pancreatic function, promoting glucose dependent insulin secretion, and suppressing glucagon. In terms of weight management, GLP-1 receptor agonists target visceral fat and support long term weight loss. While lean muscle loss during weight reduction with GLP-1 receptor agonists varies, evidence suggests these treatments promote adaptive changes in muscle quality, likely improving insulin sensitivity and reducing muscle fat infiltration. Cardiovascular benefits include reduced risk of heart attack and stroke with modest renal protection. The benefits of GLP-1 agonists are time-dependent, with greater improvements with prolonged use. Overall, GLP-1 receptor agonists are a valuable tool in addressing metabolic syndrome, but their success requires adherence to the treatment plan and the incorporation of consistent lifestyle modifications.

Multihormonal regulation of glucose



In healthy individuals, (1) ingestion of food results in (2) release of gastrointestinal peptides (GLP-1 and GIP) as well as (3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on (4) gastric emptying, (5) glucagon release, and (6) appetite. (7) Following the absorption of food, GLP-1 and GIP promote insulin secretion, otherwise known as the incretin effect. In diabetes, these steps are disrupted.

GLP-1: glucagon-like peptide 1; GIP: glucose-dependent insulinotropic polypeptide, gastric inhibitory peptide.

GLP-1 receptor agonists in psychiatry: Evidence for weight and cardiometabolic benefits

A systematic review on the efficacy of GLP-1 receptor agonists in mitigating psychotropic drug-related weight gain (Menon et al. 2024)
Authors analyzed the efficacy of GLP-1RAs in addressing weight gain associated with psychotropic medications, including antipsychotics and antidepressants.

Significant Findings

- Six randomized controlled trials (RCTs) (n=374) met the inclusion criteria, with most demonstrating significant weight reduction following GLP-1RA treatment.
- Liraglutide and exenatide were the most studied GLP-1RAs, with reported weight loss associated with GLP-1RA ranging from 3 to 5.3 kg.
- Metabolic improvements were observed, including reductions in fasting plasma glucose, HbA1c, and lipid levels.
- Both liraglutide and exenatide were effective, with liraglutide demonstrating more pronounced weight reduction in broader populations, while exenatide was particularly beneficial in mitigating metabolic adverse effects in patients with schizophrenia on olanzapine or clozapine.
- Most common AEs were GI symptoms (nausea, vomiting, diarrhea), which were generally mild to moderate and subsided over time.

This review supports GLP-1RAs as effective adjuncts for mitigating psychotropic-induced weight gain and metabolic complications, highlighting their potential for high-risk patients on psychiatric medications.

Glucagon-like peptide agonists for weight management in antipsychotic-induced weight gain (AIWG): A systematic review and meta-analysis (Bak et al., 2024)
This study evaluated the efficacy and safety of exenatide & liraglutide in managing antipsychotic-induced weight gain. It synthesized data from five RCTs and one cohort study involving 269 patients using antipsychotics.

Significant Findings

- Mean weight loss & BMI reduction
  - Exenatide: −2.48 kg & −0.82 kg/m², liraglutide: −4.70 kg & −1.52 kg/m²
  - Liraglutide resulted in more weight loss than exenatide, but the difference was not statistically significant.
- Safety
  - Most common side effects: Nausea (~41% exenatide, 38% liraglutide), vomiting & diarrhea.
  - Side effects were acceptable. No increase in psychopathology was observed.
- BP & metabolic parameters
  - SBP: Exenatide: −5.07 mmHg, liraglutide: −1.45 mmHg
  - Fasting Glucose: Significant reduction only with liraglutide (−0.44 mmol/L)
  - HbA1c: Exenatide: ↑ 2.90, liraglutide: − 2.35
  - LDL: Exenatide: ↑ 0.70, liraglutide ↓ 0.32 mmol/L

    - Liraglutide improved fasting glucose & HbA1c. No significant lipid profile improvements.

Exenatide & liraglutide show promise for AIWG related weight loss with acceptable side effects and no worsening of psychopathology. Liraglutide appears particularly effective, but further research is needed.

Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine or olanzapine treated patients with schizophrenia spectrum disorder (Larsen et al, 2017)
This randomized, double-blind, placebo-controlled study investigated the effects of liraglutide (1.8 mg SQ daily) as an adjunct to clozapine or olanzapine in 103 overweight or obese patients with schizophrenia spectrum disorders and prediabetes. Conducted in Denmark at two sites, the primary endpoint was glucose tolerance estimated by a 75 gm OGTT, with secondary endpoints including weight and cardiometabolic changes.

Significant Findings

- Improved glucose tolerance
    - 30 liraglutide treated pts (~64%) achieved normal glucose tolerance, compared with 8 (16%) placebo treated participants ($P < 0.001$).
    - 23% greater reduction in 2-hour post OGTT plasma glucose levels compared to placebo.
- Significant weight loss
    - Liraglutide led to weight reduction of 5.3 kg (95% CI, −7.0 to −3.7 kg).
    - Waist circumference decreased by 4.1 cm & visceral fat reduced by 250 gm.
- Cardiometabolic benefits
    - LDL decreased by 15.4 mg/dL & SBP by − 4.9 mm Hg
    - Improved beta cell function & glucagon suppression, but no change in insulin sensitivity.
- Safety
    - Most AEs were transient GI effects, mainly nausea (62%), with no correlation between higher nausea in the liraglutide group and greater weight loss.
    - Serious adverse events (including psychiatric exacerbation) were fewer in the liraglutide group compared to placebo.

Liraglutide significantly improved glucose metabolism, reduced weight, and lowered cardiometabolic risk in patients with schizophrenia spectrum disorders treated with clozapine or olanzapine, supporting GLP-1 RAs as adjunctive therapy for antipsychotic induced metabolic side effects.

How to treat antipsychotic related weight gain and metabolic disturbances: Is there a role for GLP-1 receptor agonists? (Fink-Jensen & Correll, 2024)
This review evaluated the potential role of GLP-1 RAs in mitigating weight gain and metabolic disturbances associated with antipsychotics, particularly clozapine and olanzapine. Authors discussed the mechanisms of GLP-1 RAs and their ability to counteract obesity and cardiometabolic risk in psychiatric patients.

Significant Findings

- Nonpharmacological interventions, such as lifestyle changes, are difficult to implement in psychiatric populations, and traditional pharmacological interventions like metformin & topiramate have only modest effects (~3–4 kg weight loss over 12–24 weeks).

- GLP-1 RAs have been used for T2DM since 2007 and obesity since 2020, with newer agents like dulaglutide, semaglutide, and tirzepatide showing stronger weight loss effects.
- Concerns about GLP-1 RAs inducing psychiatric side effects (eg. anhedonia, depression, suicidal ideation) remain unproven, as post hoc analyses and cohort studies have not identified an increased risk.
- High GLP-1 RA costs limit access, but upcoming patent expirations may lower prices, outweighing costs of preventable cardiometabolic diseases.
- More studies specifically in psychiatric populations are needed to confirm both the metabolic benefits and psychiatric safety of GLP-1 RAs.

GLP-1 RAs could be an effective strategy to prevent or reverse weight gain and metabolic complications in antipsychotic treated patients. However, they remain underutilized due to limited psychiatric specific trials and high costs. Ongoing clinical trials will provide further data on their use in this population.

Effect of GLP-1 receptor agonists on obesity in patients with severe mental illness: A state hospital case series of clozapine-treated patients (Ali et al, 2024)
This retrospective case series examined two state hospital patients with obesity who were on clozapine and received dulaglutide alongside dietary counseling.

Significant Findings

- Significant weight reduction: Patient 1 lost 22%, Patient 2 lost 16% of body weight.
- Improved glycemic control: HbA1c levels dropped by 5% in both patients.
- Marked reduction in triglycerides: Patient 1 decreased by 46%, Patient 2 by 68%.

The study provides preliminary evidence supporting the use of GLP-1 RAs for managing AIWG and metabolic issues in psychiatric patients, particularly those on clozapine. However, larger controlled trials are needed to establish long-term safety and efficacy in this population.

The impact of GLP-1 Receptor Agonists on mental health: A systematic review (Tempia Valenta et al, 2024)
Authors reviewed 81 studies on GLP-1 RAs' impact on mental health, assessing therapeutic benefits across psychiatric disorders and potential adverse effects.

Significant Findings

- GLP-1 RAs may improve depressive symptoms, cognitive function, and reduce suicidal ideation through antioxidative, anti-inflammatory, and neurotransmitter-modulating effects.
- Show efficacy in reducing alcohol/substance use and binge eating.
- However, pharmacovigilance data indicate potential psychiatric adverse effects, including depression, anxiety, and suicidal ideation, with variations among agents.

GLP-1 RAs show promise for psychiatric conditions, including depression, anxiety, and substance use disorders. While beneficial, their psychiatric safety profile warrants careful monitoring.

Management of obesity with semaglutide or metformin in patients with antipsychotic-induced weight gain (MOSA): a non-randomized open-label pilot study (Campforts et al, 2024)
This prospective, non-randomized cohort study compared the efficacy and safety of oral semaglutide vs metformin for treating antipsychotic-induced weight gain in a real world outpatient setting. Conducted in

the Netherlands, the study included 37 patients on antipsychotic therapy experiencing significant weight gain.

Significant Findings

- Mean weight loss: Semaglutide -4.5 kg (4%) vs metformin -2.9 kg (2.5%).
- BMI: Semaglutide -1.7 kg/m² & waist circumference -6.8 cm compared to metformin BMI - 0.8 kg/m² & waist circumference -3.4 cm.
  No statistically significant difference between groups.
- Both treatments led to a small but significant reduction in psychiatric symptoms. Semaglutide group reported significant improvement in quality of life.
- Most common AEs were GI symptoms, primarily nausea, occurring mainly at treatment initiation or during dose escalation. However, most were mild, with 2 pts discontinuing treatment and 8 in the metformin group.

Oral semaglutide is an effective and well-tolerated option for psychiatric patients, demonstrating efficacy similar to metformin. Most adverse effects were mild and transient, with positive effects on psychiatric symptoms and quality of life.

Limitations of studies

Limitations include small sample size, short follow-up, and heterogeneity in psychiatric diagnoses, medication regimen, and outcome measures, all of which reduce the generalizability of findings. Adverse event data, particularly on psychiatric effects remain incomplete, while real world evidence on adherence is limited. Also, head-to-head comparisons between GLP-1 RAs are lacking, and many studies cannot perform meta-analyses due to variations in study design and endpoints. These limitations highlight the need for larger, longer-term trials to provide clearer guidance on the use of GLP-1 RAs in psychiatric populations.

Future research

- Investigating slow tapering and low-dose maintenance strategies to prevent rebound.
- Investigating the role of GLP-1 RAs in facilitating adherence to lifestyle interventions in patients with severe mental illness.
- Assess whether early pharmacologic intervention improves motivation and engagement in behavioral modifications for sustained weight and metabolic benefits.
- Extended follow-up needed to assess sustained weight and metabolic benefits. Real world trials needed to evaluate efficacy and tolerability in psychiatric population.
- Further studies required on glycemic control, cardiovascular outcomes, and psychiatric stability.
- Evaluating the efficacy of GLP-1 receptor agonists across psychiatric conditions and metabolic complications, while assessing their prophylactic use in high-risk patients on antipsychotics.
- Investigating GLP-1 RAs and other gut-derived peptides for both metabolic and psychiatric benefits, including their potential as antidepressants and opportunities for drug repurposing.
- Conducting head-to-head trials of GLP-1 receptor agonists to compare efficacy and safety in managing antipsychotic associated metabolic adverse effects.

Safety of GLP-1 RAs and Dual GIP + GLP-1 RA

Class	GIP + GLP-1 RA	GLP-1 RAs		
Product	**Zepbound (tirzepatide)**	**Wegovy (semaglutide)**	**Saxenda (liraglutide)**	**Trulicity (dulaglutide)**
Market Experience	15 months	< 3 years	10 years	10 years
Boxed Warnings	• Risk of thyroid C-cell tumors • Contraindicated in pts with a personal or family history of MTC or in pts with MEN 2 • Counsel patients on MTC risk & thyroid tumor symptoms			
Contraindications	• Known serious hypersensitivity to molecular entity or excipients • Personal or family history of MTC or in patients with MEN 2			
			Pregnancy	
Warnings & Precautions	**-** Pancreatitis **-** Hypoglycemia when used with insulin secretagogues or insulin **-** Acute gallbladder disease **-** Pulmonary aspiration during general anesthesia or deep sedation **-** Hypersensitivity reactions			
	AKI - Severe GI adverse reaction - Diabetic retinopathy complications in T2DM **-** Suicidal behavior & ideation	AKI - Heart rate increase - Severe GI adverse reaction **-** Diabetic retinopathy complications in T2DM **-** Suicidal behavior & ideation	Thyroid C-cell tumors - Heart rate increase - Renal impairment **-** Suicidal behavior & ideation	AKI - Severe GI adverse reaction - Diabetic retinopathy complications in T2DM, **-** Thyroid C-cell tumors
Most Common AEs (≥ 5%)	- injection site reactions - hypersensitivity reactions - eructation - hair loss – GERD - constipation - dyspepsia - fatigue	– headache – dizziness - abdominal distension – eructation - hypoglycemia in T2DM – flatulence - gastroenteritis – GERD – nasopharyngitis - constipation - dyspepsia - fatigue	- injection site reactions - headache – hypoglycemia - dizziness - increased lipase – upper abdominal pain – pyrexia – gastroenteritis - constipation - dyspepsia - fatigue	- decreased appetite
	- nausea - diarrhea - vomiting - constipation - abdominal pain - dyspepsia - fatigue			
Monitoring	- BG - efficacy of PO meds (especially narrow therapeutic index) - GI adverse reactions – S/Sx of pancreatitis & gallbladder disease - heart rate - body weight			
	-renal function in pts reporting AEs that could lead to volume depletion – worsening of diabetic retinopathy - depression or suicidal thoughts	- renal function – triglycerides – worsening of diabetic retinopathy - depression or suicidal thoughts	- renal function – triglycerides - depression or suicidal thoughts	- renal function - worsening diabetic retinopathy
Pregnancy	May cause fetal harm. D/C if pregnant	- May cause fetal harm. D/C if pregnant - Discontinue Wegovy ≥2 months before planned pregnancy due to semaglutide's long half life (both females & males)	Contraindicated	Should be used only if benefit outweighs fetal risk
Breastfeeding	No data. Weigh infant risk vs. maternal benefit when determining treatment	No human data. Present in rat milk; weigh benefits of breastfeeding against potential risks	No human data. Present in rat milk; weigh benefits of breastfeeding against potential risks	No data. Weigh breastfeeding benefits vs maternal need & infant risk
Significant Drug-Drug or Drug-Food Interactions	**-** When initiating drug, consider dose reduction of concomitantly administered insulin secretagogues (eg. sulfonylureas) or insulin to reduce the risk of hypoglycemia **-** Delays gastric emptying; may affect absorption of concomitantly administered oral meds. Monitor narrow TI meds (e.g. warfarin) or meds dependent on threshold concentrations for efficacy			
	- Use non-oral contraceptive or add a barrier method of contraception for 4 weeks after initiation and dose escalation			
Geriatric Considerations	No safety/efficacy differences in geriatrics or younger pts, but some older individuals may have greater sensitivity			
Pediatric Considerations	Safety & effectiveness have not been established in pediatric patients	Approved for weight management in obese pts ≥12 years when used with diet & exercise	Approved for weight management in pts ≥12 years weighing over 60 kg, with diet & exercise	- Approved for ≥10 years as adjunct to diet & exercise for glycemic control - More injection site reactions vs. adults

Summary of GLP-1 RAs and Dual GIP + GLP-1 RA

Characteristic		GLP-1 Ras	Dual GIP + GLP-1 RA
Drugs		Exenatide SQ (Byetta 2005) BID Exenatide ER SQ (Bydureon Bcise 2017) Weekly Liraglutide SQ (Victoza 2010 and Saxenda 2014) Daily Dulaglutide SQ (Trulicity 2014) Weekly Semaglutide SQ (Ozempic 2017 and Wegovy 2021) Weekly Semaglutide PO (Rybelsus 2019, 2024) Daily	Tirzepatide SQ (Mounjaro 2022 and Zepbound 2023) Weekly injection
Efficacy in DM		High to very high	Very high
Hypoglycemia		When used with insulin secretagogues or insulin	
Weight change[#]		Loss (intermediate to very high)	Loss (very high)
CV effects	Effect on MACE	• Benefit: dulaglutide (Trulicity), liraglutide (Victoza), semaglutide SQ (Ozempic) • Neutral: exenatide once weekly (Bydureon Bcise)	Under investigation
	HF	Neutral	Under investigation
Renal effects	Progression of CKD	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide (Trulicity), liraglutide (Victoza), semaglutide SQ (Ozempic)	Under investigation
	Dosing/use considerations	• Renal dose adjustment needed for exenatide (Bydureon Bcise & Byetta) • No dosage adjustment for dulaglutide (Trulicity), liraglutide (Victoza), semaglutide (Ozempic & Rybelsus) • Trulicity: Monitor renal function in pts with renal impairment reporting severe GI reactions; use cautiously in ESRD • Victoza: Limited ESRD data; post marketing reports of ARF & worsening of chronic renal failure. Use cautiously in dehydration	• Mounjaro: Not recommended in pts with end stage renal impairment due to limited clinical data • Zepbound: Monitor renal function in pts reporting adverse reactions that could lead to volume depletion
Clinical considerations		• Counsel patients about potential for ileus • Not recommended for individuals with history of gastroparesis	
		• Risk of thyroid C-cell tumors in rodents: human relevance not determined (liraglutide (Victoza), dulaglutide (Trulicity), exenatide ER (Bydureon BCise), semaglutide (Ozempic & Rybelsus), tirzepatide (Mounjaro & Zepbound) • Pancreatitis has been reported in clinical trials but causality has not been established. D/C if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected	

AKI: Acute kidney injury, ARF: acute renal failure, BG: blood glucose, CV: cardiovascular, CVOT: cardiovascular outcomes trial, D/C: Discontinue, DKA: diabetic ketoacidosis, DKD: diabetic kidney disease, DM: Diabetes Mellitus, eGFR: estimated glomerular filtration rate, GI: gastrointestinal, GIP: glucose-dependent insulinotropic polypeptide, GLP-1 RA: glucagon-like peptide 1 receptor agonist, HF: heart failure, H/o: History of, NASH: nonalcoholic steatohepatitis, MACE: major adverse cardiovascular events, SQ: Subcutaneous, T1DM: Type 1 daibetes mellitus, T2DM: Type 2 diabetes mellitus, pts: Patients, MEN2: Multiple Endocrine Neoplasia syndrome type 2, OSA: Obstructive sleep apnea, S/Sx: Signs/symptoms, TI: Therapeutic index

#Based on secondary endpoints, Mounjaro provided short-term weight loss of about 5.4 kg to 11.4 kg which is greater than all other GLP-1 RAs. Weight loss is an average value and will vary among patients.

Current FDA-Approved GLP-1 RAs for T2DM in Adults (excluding Insulin + GLP-1 RA)

Drug Products	FDA Approval[a]	FDA-Approved Indications[b]	Dosage Form & Strength	Dosing[c]	Cost per 28 days[d]	Other FDA-Approved Indications, comments & Potential Off-label Uses[e]	Shortages Update
Bydureon BCise (exenatide ER) *[AstraZeneca Pharmaceuticals LP]*	2017	Adjunct to diet & exercise to improve glycemic control in adults & pediatric patients aged ≥10 with T2DM	SQ injection: 2 mg of exenatide in a 0.85 mL single dose autoinjector	• 2 mg SQ once weekly. • Administer with or without meals immediately after the dose is prepared.	$827	N/A	--
Byetta (exenatide) *[AstraZeneca Pharmaceuticals LP]*	2005	Adjunct to diet & exercise to improve glycemic control in adults with T2DM	SQ injection: 250 mcg/mL in 5 mcg per dose, 60 doses, 1.2 mL single-patient-use prefilled pen or 10 mcg per dose, 60 doses, 2.4 mL single-patient-use prefilled pen	• Start at 5 mcg SQ bid. Increase to 10 mcg SQ bid after 1 month based on clinical response. • Administer within 60 minutes prior to morning & evening meals (or before 2 main meals ≥ 6 hours apart)	$793	Comments: - Concurrent use of Byetta with insulin cannot be recommended (not studied) - Not a substitute for insulin & is not for type 1 diabetes or diabetic ketoacidosis	--
Ozempic (semaglutide) *[Novo Nordisk]*	2017	• Adjunct to diet & exercise to improve glycemic control in adults with T2DM • Reduce the risk of major cardiovascular events (cardiovascular death, nonfatal MI/stroke) in adults with T2DM & established CVD • Reduce the risk of sustained eGFR decline, end-stage kidney disease & cardiovascular death in adults with T2DM & CKD	SQ injection • 2 mg/3 mL (0.68 mg/mL) delivers 0.25 mg or 0.5 mg per injection • 4 mg/3 mL (1.34 mg/mL) delivers 1 mg per injection, and 8 mg/3 mL (2.68 mg/mL) delivers 2 mg per injection	• 0.25 mg to 2 mg SQ once weekly. • Increase dose ≥ 4 weeks if additional glycemic control is needed. • To reduce the risk of sustained eGFR decline, end-stage kidney disease & cardiovascular death: 0.5 mg to 1 mg once weekly • Administer subcutaneously at any time of the day with or without meals.	$967	Potential off-label uses: • Heart failure with normal ejection fraction – obesity • Weight reduction in overweight or obese pts • Nonalcoholic fatty liver disease • Nonalcoholic steatohepatitis Comments: If a dose is missed, administer within 5 days of missed dose	1/14/2025: Novo Nordisk has Ozempic available. Novo Nordisk discontinued Ozempic 0.25 mg and 0.5 mg dose strength in the 2 mg/1.5 mL presentation.
Rybelsus (semaglutide) *[Novo Nordisk]*	2019 Formulation R2: 2024	Adjunct to diet and exercise to improve glycemic control in adults with T2DM	• Tablets (formulation R1): 3 mg, 7 mg & 14 mg • Tablets (formulation R2): 1.5 mg, 4 mg & 9 mg	• Formulation R1: 3 mg to 14 mg PO QAM • Formulation R2: 1.5 mg to 9 mg PO QAM • Increase dose every 30 days, if additional glycemic control is needed • Administer on an empty stomach at least 30 minutes before the first food, beverage, or other oral meds of the day with no more than 4 ounces of plain water only. Swallow	$904	Potential off-label uses: • Weight reduction in overweight or obese pts • Nonalcoholic steatohepatitis • Reduce the risk of major adverse cardiovascular events in adults with T2DM & established CVD[g] Comments: Rybelsus formulation R2 is not interchangeable with R1. Use either formulation	1.5 mg, 4 mg, 9 mg tablets (formulation R2): current anticipated availability unknown

Drug Products	FDA Approval[a]	FDA-Approved Indications[b]	Dosage Form & Strength	Dosing[c]	Cost per 28 days[d]	Other FDA-Approved Indications, comments & Potential Off-label Uses[e]	Shortages Update
				tablets whole. Do not split, crush or chew		but not both at the same time.	
Trulicity (dulaglutide) *[Eli Lilly and Company]*	2014	• Adjunct to diet & exercise to improve glycemic control in adults & pediatric pts 10 years of age & older with T2DM • Reduce the risk of major adverse CV events in adults with T2DM who have established CVD or multiple CV risk factors	SQ injection: 0.75 mg/0.5 mL, 1.5 mg/0.5 mL, 3 mg/0.5 mL, 4.5 mg/0.5 mL in a single-dose pen	• 0.75 mg to 4.5 mg SQ once weekly • Pediatrics: 0.75 mg to 1.5 mg SQ once weekly • Increase dose ≥ 4 weeks, if additional glycemic control is needed • Administer at any time of day with or without food	$977	Comments: Administer the missed dose as soon as possible if there are at least 3 days until the next scheduled dose	1/9/25: Lilly has Trulicity available
Victoza (liraglutide) *[Novo Nordisk]*	2010	• Adjunct to diet & exercise to improve glycemic control in adults & pediatric pts 10 years & older with T2DM • Reduce the risk of major adverse CV events in adults with T2DM & established CVD	SQ injection: 6 mg/mL in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg	• Adults & pediatrics: 0.6 mg to 1.8 mg SQ once daily • Increase dose ≥ 1 week, if additional glycemic control is needed • Administer at any time of day with or without meals.	$657 (brand: $761)	Potential off-label uses: • Non-alcoholic fatty liver • Nonalcoholic steatohepatitis • Polycystic ovary syndrome • Antipsychotics induced weight gain Comments: • Administer as separate injections when using with insulin. Never mix • Inspect before injection; use only if clear, colorless, & particle-free.	1/27/25: Novo Nordisk has Victoza on shortage due to manufacturing delays Estimated Resupply: Mid-February 2025
GIP + GLP-1 RA							
Mounjaro (tirzepatide) *[Eli Lilly Co]*	2022	Adjunct to diet and exercise to improve glycemic control in adults with T2DM	SC injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen	• 2.5 mg to 15 mg SQ once weekly • Increase dose ≥ 4 weeks, if additional glycemic control is needed • 2.5 mg dose is for initiation, not glycemic control • Administer at any time of day with or without meals • Inspect & use only if clear, colorless to slightly yellow, without particles • Do not mix with insulin; inject separately	$1,069	<u>Potential off label uses</u> • Weight reduction in overweight or obese pts • Reducing risk of major CV events in T2DM • Heart failure with preserved ejection fraction • Nonalcoholic steatohepatitis <u>Comments</u> • If a dose is missed, take within 4 days; if >4 days, skip & resume schedule	1/9/2025: Lilly states Mounjaro is available

[a] Date applies to approval date for the original brand name medication. [b] FDA-approved indications in scope of therapeutic class review. [c] Dosing regimen for disease state(s) in scope of therapeutic class review. [d] Estimated cost based on WAC per Medispan as of 8/282024 for estimated 28 day supply based on the prescribing information. [e] As listed in MICROMEDEX database (or as referenced). [f] For brand or biologic products with no generic available only; as listed in the Orange or Purple Book. [g]Cardiovascular disease

FDA-approved GLP-1 RAs for chronic weight management in adults with obesity or overweight

Drugs	FDA Approval[a]	FDA-Approved Indications[b]	Dosage Form & Strength	Dosing[c]	Cost per 30 days[d]	Other FDA-Approved Indications & Potential Off-label Uses[e]	Latest Shortages
GIP/GLP-1 Receptor Agonist: Selectively binds to and activates both GIP and GLP-1 receptors, mimicking native hormones. GLP-1 regulates appetite and caloric intake, while studies suggest GIP may enhance metabolic regulation and support weight loss.							
Zepbound (tirzepatide) *Eli Lilly and Company*	2023	Adjunct to reduced-calorie diet & increased physical activity for chronic weight management in adults with BMI ≥30 kg/m^2 (obesity) or ≥27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., HTN, dyslipidemia, T2DM, OSA or CV disease)	Single-dose pens or vials: 2.5 mg/0.5 ml, 5 mg/0.5 ml, 7.5 mg/0.5 ml, 10 mg/0.5 ml, 12.5 mg/0.5 ml, 15 mg/0.5 ml	2.5 mg to 15 mg SQ once weekly • 2.5 mg dose is for initiation, not glycemic control • Increase dose ≥ 4 weeks, if additional glycemic control is needed • Administer at any time of day with or without meals • Inspect & use only if clear, colorless to slightly yellow, without particles	$1,272.84	<u>Other FDA approved indications</u> • Treatment for moderate to severe OSA in adults with obesity <u>Potential off-label uses</u> • T 2DM • In combination with a reduced calorie diet & increased physical activity to reduce the risk of major adverse CV events (cardiovascular death, non-fatal MI/stroke) in adults with established cardiovascular disease and either obesity or overweight	1/9/2025: Lilly states Zepbound is available
GLP-1 Receptor Agonists: Selectively binds to and activates GLP-1 receptor, regulating appetite and caloric intake							
Wegovy (semaglutide) *Novo Nordisk*	2021	In combination with a reduced calorie diet & increased physical activity for chronic weight management in adults & pediatric pts ≥12 yrs with obesity or adults with overweight in the presence of at least one weight related comorbid condition (eg, HTN, T2DM, dyslipidemia) Risk reduction of major adverse cardiovascular events (cardiovascular	Single-dose, single use Pen for SQ injection that delivers 0.25 mg, 0.5 mg, 1 mg, 1.7 mg or 2.4 mg dose	• 0.25 mg to 2.4 mg SQ once weekly • follow the dosage escalation schedule, titrating Q4 weeks to achieve maintenance dose of 2.4 mg (recommended) or 1.7 mg once weekly	$1,618.82	<u>Potential off label use</u> T2DM	1/14/2025: Novo Nordisk has Wegovy available

		death, non-fatal MI or non-fatal stroke) in adults with established CVD and either obesity or overweight					
Saxenda (liraglutide) *Novo Nordisk*	12/23/2014	Adjunct to a reduced-calorie diet & increased physical activity for chronic weight management in adults with initial BMI ≥30 kg/m^2 (obesity) or ≥27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., HTN, T2DM, or dyslipidemia). Pediatric pts ≥ 12 yrs with • weight >60 kg and • initial BMI corresponding to 30 kg/m2 for adults (obese) by international cut-offs	Single-patient-use Pen for injection: 6 mg/ml in 3 ml that delivers 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3 mg dose	Start at 0.6 mg/day, increase weekly to 3 mg. Pediatric escalation may take up to 8 weeks; if not tolerated, reduce to prior dose or 2.4 mg	$1,618.82	Potential off-label uses: T2DM	1/27/2025: Novo Nordisk has Saxenda available. Teva launched the authorized generic of liraglutide in late-June 2024

[a] Date applies to approval date for the original brand name medication. [b] FDA-approved indications in scope of therapeutic class review. [c] Dosing regimen for disease state(s) in scope of therapeutic class review. [d] Estimated cost based on AWP for brands per Medispan as of 05/08/2024 for estimated 30 day supply based on the prescribing information. [e] As listed in MICROMEDEX database (or as referenced).

References available upon request

Formulary	Covered Drug	Brand & Dosage Strengths	Diagnosis	Restrictions
DHCS MediCal	Exenatide	Byetta 250 mcg/ml, 1.2 ml 250 mcg/ml, 2.4 ml	Type 2 Diabetes Mellitus	
	Exenatide	Bydureon Bcise 2 mg/pen, 0.85 ml	Type 2 Diabetes Mellitus	
	Liraglutide	Victoza 18mg/3ml	Type 2 Diabetes Mellitus	
	Liraglutide	Saxenda 18mg/3ml	Chronic weight management	5 prefilled pens Per 28 days
	Semaglutide	Ozempic 0.25-0.5 mg/dose (2 mg/1.5 ml) 0.25-0.5 mg/dose (2 mg/3 ml) 1 mg/dose (2 mg/1.5 ml) 1 mg/dose (4 mg/3 ml) 2 mg/dose (8 mg/3 ml)	Type 2 Diabetes Mellitus	
	Semaglutide	Rybelsus tablets 3 mg, 7 mg, 14 mg	Type 2 Diabetes Mellitus	
	Semaglutide	Wegovy 0.25 mg/0.5 ml 0.5 mg/0.5 ml 1 mg/0.5 ml 1.7 mg/0.75 ml 2.4 mg/0.75 ml	Chronic weight management	4 single dose Pens per 28 days
	Tirzepatide	Zepbound 2.5 mg/0.5 ml 5 mg/0.5 ml 7.5 mg/0.5 ml 10 mg/0.5 ml 12.5 mg/0.5 ml 15 mg/0.5 ml	Chronic weight management	4 single dose pens per 28 days
CareAdvantage & HealthWorx	Dulaglutide (Trulicity)	Trulicity	Type 2 DM at high risk of MACE or have established CVD	Quantity Limit
	Semaglutide	Ozempic	Type 2 DM at high risk of MACE or have established CVD	Quantity Limit
	Semaglutide	Rybelsus	Type 2 DM high risk of MACE or have established CVD	Quantity Limit
	Tirzepatide	Mounjaro	Type 2 DM high risk of MACE or have established CVD	Quantity Limit
HealthWorx	Tirzepatide	Zepbound	ALL the following must be met: 1) BMI ≥30 or ≥27 in the presence of at least ONE weight-related comorbidity 2) used with a reduced calorie diet, increased physical activity and behavioral counseling; and 3) t/f or intolerant to BOTH Contrave and Qsymia.	Quantity Limit