Updated August 2025
Educational Infographic for Healthcare Providers

GLP1 AGONISTS adverse events

dulaglutide TRULICITY - liraglutide VICTOZA - semaglutide subcut OZEMPIC - semaglutide oral RYBELSUS

common <10% ~ less common <1% ~ ? uncertain

nausea diarrhea vomiting dyspepsia constipation

while common, especially early on, some tolerate:
- Discontinuation due to GI: ~4% subcut GLP1 agonist vs 0.9% placebo
NNH=32 / 1.7 year Alexander'21
- T2DM cohort: ~40% discontinue GLP1 agonist at 12 months Weis'22, Do'24

To help with GI effects:
- start low, titrate slow;
- flexible dose escalation strategies ("counting pen clicks" for less conventional doses, off-label)
- eat smaller, more frequent, & low fat meals slowly
- HS dosing for once daily options
- may use loperamide or anti-nauseant during titration period

dizziness

injection site irritation

semaglutide 1mg/wk subcut 1.1% vs 1.5% placebo
SUSTAIN-6 2016

increased heart rate

clinical relevance uncertain in most;
-potential caution HFrEF, tachyarrhythmias

GLP1 agonist vs placebo RR 1.37 (1.23-1.52) (higher doses and longer duration associated with increased risk) He'22
-Acute gallstone disease:
liraglutide 3.1% vs placebo 1.9%
NNH=84/3.8 year LEADER 2016
(majority required hospitalization or surgery)
- Gallbladder disorder:
semaglutide 3.2% vs placebo 2.8% SUSTAIN-6 2016

bile duct & gall bladder disease

risk remains for patient who has had gallbladder removed

Cohort - increased residual gastric content semaglutide 25.2% vs control (no GLP1 use) 5.1% & found current GI symptoms were postively associated with greater risk. Silveria'23
Based on individual risk assessment, ISMP Canada:2023 consider holding semaglutide subcut 3 weeks prior to procedure (USA: hold for 1 week) American Society of Anesthesiologists'24

aspiration with anesthesia & ? ileus / bowel obstruction

Retinopathy progression: semaglutide subcut (possibly others) complications (e.g. need for intravitreal agent) semaglutide 1mg/wk subcut 3% vs placebo 1.8% NNH=83/2.1 year, SUSTAIN-6 2016 but some mixed findings; Albert'23,Chou'25 risk associated primarily with diabetic retinopathy history

NAION: T2DM cohort, semaglutide ↑risk of non-arteric ischemic neuropathy vs placebo; absolute risk is low ~ 1 in 10,000 people EMA'25

liraglutide most data FDA2017/HC2018 warning (based on rodent studies) GLP1 agonists contraindicated if personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2; observational data suggests small ↑risk of all thyroid cancer types in humans Bezin'22 HR 1.58 (1.27-1.95) while other studies found a small increase only in the first year; **overall, absolute risk remains low**

? retinopathy progression
? ischemic optic neuropathy (NAION)
baseline eye exam and monitor

? thyroid cancer

? reduced BMD
- liraglutide associated with a reduction in BMD (hip & spine); moderate-intense exercise with liraglutide maintained BMD Jensen'24

? reduced lean body mass

? self-harm / suicidality
- Health Canada2025/FDA2024: no association based on available evidence (2 observational trials Wang'24, Gamble'18); monitoring is ongoing; risk appears higher in those with a history of suicidal ideation but overlapping confidence intervals Wang'24

Of note, serious adverse event (SAE) rates were typically lower in GLP1 agonist treatment groups vs placebo.
For detailed references and list of abbreviations, please see www.RxFiles.ca/kidney.

Online Extras: GLP1 Agonists Adverse Events Healthcare Provider Infographic:

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Abbreviations: **BMD**=bone mineral density **FDA**=Food & Drug Administration **GI**=gastrointestinal **GLP1a**=glucagon-like peptide-1 receptor agonist **HFref**=heart failure reduced ejection fraction **HR**=hazard ratio **HR**=heart rate **HS**=bedtime **IMSP**=Institute for Safe Medication Practices **NAION**=non-arteric ischemic neuropathy **NNH**=number needed to harm **RR**=relative risk **SAE**=serious adverse events **subcut**=subcutaneous **T2DM**=type 2 diabetes mellitus **USA**= United States **wk**=week(s) **yr**=year(s)

Available GLP1 agonists in Canada:
Dulaglutide (**TRULICITY**)
Liraglutide (**VICTOZA**, **SAXENDA**)
Semaglutide subcut (**OZEMPIC**, **WEGOVY**)
Semaglutide po (**RYBELSUS**)
Insulin degludec / Liraglutide (**XULTOPHY**)
Insulin glargine / Lixisenatide (**SOLIQUA**)

Not available in Canada:
- Lixisenatide: **USA** **ADLYXIN**, **EU** **LYXUMIA**
- Exenatide: **USA** **BYETTA**, **BYDUREON**

Discontinued:
- Exenatide: discontinued in Canada 2022
- Abiglutide: EPERZAN (Canadian brand name) & TANZEUM (USA brand name)

Detailed Evidence Summary & Supplementary Notes

Current AE Listed	Information
Nausea, Vomiting, Diarrhea, Dyspepsia, Constipation	**Alexander '21:** Systematic review & meta-analysis (N = 45 trials comparing GLP-1RAs to placebo or other anti-hyperglycemic medication), n = 71,517 patients with T2DM); stopping subcut GLP-1RA due to GI affects higher than placebo (~4% vs. ~0.9%, NNH = 21/1.7 yr) **Do '24**: Retrospective cohort (USA) analyzing patients taking a GLP-1RA for T2DM or obesity treatment, n = 195 915; discontinuation of GLP-1RA was 36.5% at 12 months based on prescription fill data. Reason for discontinuation was not assessed. However, patients had significantly higher odds of discontinuation at 12 months if they were Black or Hispanic, male, and Medicare or Medicaid enrollees; lived in areas with very high levels of social needs; had obesity only, HF, or other CVD conditions besides HF at baseline; and had new gastrointestinal adverse effects at follow-up. Older patients had lower odds of discontinuation than younger patients. Furthermore, each 1–percentage point increase in OOP cost per a 30-day supply of GLP-1 agonist was associated with increased odds of discontinuation (odds ratio, 1.02; 95% CI, 1.02-1.03). **Weiss '22:** Retrospective cohort (UK) analyzing patients taking an injectable GLP-1RA for treatment of T2DM, n = 549; discontinuation of GLP-1RA was 45% at 12 months, 65% at 24 months based on prescription fill data. Reason for discontinuation was not assessed. Counting pen clicks for less conventional doses: BC Childrens ENDOCRINOLOGY & DIABETES UNIT, BC Diabetes Semaglutide for weight loss and better sugar control, One Size Does Not Fit All: Understanding Microdosing Semaglutide for Diabetes in Multidose Pens | Diabetes Care | American Diabetes Association
Dizziness	As per subcut Semaglutide monograph: "dizziness can be experienced initially during dose escalation. Driving or use of machines should be avoided if dizziness occurs." Hypoglycemia may worsen dizziness – greater risk when GLP-1RA used in combo with a sulphonylurea or insulin (liraglutide monograph)
Injection Site Irritation	SUSTAIN-6 '16: Occurrence of injection site reactions for semaglutide 1mg subcut similar to placebo (1.1% vs. 1.5%)
Increased Heart Rate	Product monograph: In placebo- and active-controlled trials, Ozempic® 0.5 mg and 1 mg resulted in a mean increase in heart rate of 1-6 beats per minute. There was a mean decrease in heart rate of 0.3 beats per minute in placebo-treated patients. In a 2-year trial in patients with cardiovascular risk factors, 28.8% of Ozempic®-treated subjects had an increase in pulse rate of >5 bpm compared to 22.1% on placebo. Wei '22: Systematic review & meta-analysis (N = 8 RCTs studying GLP-1RA CV outcomes, n=60,081 patients with T2DM); concluded no significant effect on total arrythmia (RR = 0.96, 95% CI; 0.96-1.05) from GLP-1RA vs. placebo Wu '22: Systematic review & meta-analysis (N = 56 RCTs comparing GLP-1RAs to placebo or active control (insulin, DPP4i, SGLT2i), n = 79,720 patients with T2DM or obesity); GLP-1RA did not significantly increase the risk of AF (RR 0.97; 95% CI; 0.83-1.12), atrial flutter (RR 0.83; 95% CI; 0.59-1.17), ventricular arrhythmias (RR 1.24; 95% CI; 0.92-1.67) or sudden cardiac death (RR 0.89; 95% CI; 0.67-1.19) • Subgroup analysis showed increasing trend toward incident of atrial fibrillation with dulaglutide (RR 1.40; 95% CI; 1.03-1.90), inverse trend was seen with oral semaglutide (RR 0.43; 95% CI; 0.21-0.87), higher dose of GLP1-RA may increase the risk of ventricular arrythmias (RR 1.63; 95% CI; 1.11-2.40) as well as higher baseline BMI (> 32.38 kg/m^2) (RR 1.60; 95% CI; 1.04-2.48)

Bile Duct & Gall Bladder Disease	He ’22: Systematic review & meta-analysis (N = 76 RCTs studying GLP-1RA vs. placebo, n = 103, 371 patients with T2DM or obesity); concluded GLP1-RAs were associated with an increased use of gallbladder or biliary disease (RR 1.37; 95% CI; 1.23 – 1.52), higher doses and longer treatment duration both associated with increased risk LEADER ’16: RCT studying liraglutide vs. placebo in patients with T2DM; NNH=84/3.8 years for occurrence of cholelithiasis or cholecystitis (with majority of events requiring hospitalization or surgery) SUSTAIN-6 ’16: RCT studying subcut semaglutide vs. placebo in patients with T2DM; no significance difference in the rates of gallbladder disease between semaglutide 1mg and placebo (3.2% vs. 2.8%)
Aspiration with Anesthesia	ISMP Canada Safety Bulletin (September 2023): GLP-1RA Risk of Aspiration during Anesthesia (Delayed Gastric Emptying) • Discusses Canadian Journal of Anesthesiology editorial recommendation (2023): “Consider holding the GLP-1 receptor agonist for at least 3 half-lives ahead of the procedure to clear approximately 88% of the drug. For example, semaglutide has a half-life of 1 week and would therefore need to be **held for 3 weeks**.” • Bulletin references Silveira '23: retrospective analysis of patients undergoing elective upper endoscopy (n=404 patients, 33 in the semaglutide group (using for T2DM or obesity), 371 comparator group (no use of pre-op medications that impact GI emptying, including no use of other GIP1 agonists); increased residual gastric content seen in the semaglutide group (24.2% vs. 5.1%) - digestive symptoms prior to endoscopy was predictive of increased residual gastric content American Society of Anesthesiologists: Involved in publication of this Multisociety clinical practice guidance for the safe use of glucagon-like peptide-1 receptor agonists in the preoperative period; recommends that use of GLP-1ARA in the preoperative period should be based on **shared decision making** after considering variable that may elevated the risk of delayed gastric emptying and aspiration with anesthesia (escalation phase of treatment rather than maintenance phase, higher GLP-1RA dose, weekly dose vs. daily, presence of GI symptoms at baseline, other conditions that may exacerbate delayed gastric emptying such as Parkinson’s or gastroparesis) If decision to hold GLP-1RA is made, hold daily formulations the day of surgery and **weekly formulations for 1 week prior** to surgery
? Ileus	**Ileus was reported during post-approval use of semaglutide**. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. - on September 22, 2023 the U.S. Food and Drug Administration added ileus—which can result in intestinal blockage—as a possible serious adverse event to the monograph. - At least 20 people have reported experiencing blocked intestines to the FDA’s Adverse Events Reporting System. There have also been two deaths reported as a result.
? Retinopathy Progression	may be attributable to the magnitude and rapidity of A1c reductions, as has been seen in previous studies with insulin (theoretical) SUSTAIN-6 ’16: RCT studying subcut semaglutide vs. placebo in patients with T2DM; retinopathy complications (photocoagulation tx) NNH = 83/2.1 years Albert ’23: Meta-analysis of 7 cardiovascular outcome trials studying GLP-1RA (n = 56 004 patients) with a second analysis of 11 studies (n = 11 894) with semaglutide documented diabetic retinopathy; concluded **risk associated primarily with history of diabetic retinopathy**

	Chou '24: Retrospective cohort study investigating whether semaglutide is associated with increased risk of non-arteritic anterior ischemic optic neuropathy in patients with T2DM or obesity (n = 297,220) compared to other glucose lowering or weight loss medications; **concluded that semaglutide was not associated with the development of neuropathy**; T2DM-only group (1-year follow-up: HR, 2.32; 95% CI, 0.60-8.97), obesity-only group (1-year follow-up: HR, 0.41; 95% CI, 0.08-2.09, T2DM with obesity group (1 year follow-up: HR, 0.81; 95% CI, 0.42-1.57) **Diabetes Canada: Screening for retinopathy** **When to initiate screening** • Type 1 diabetes: 5 years after diagnosis in all individuals ≥15 years • Type 2 diabetes: children, adolescents and adults at diagnosis **Screening methods** • 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard) • Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil • Digital fundus photography **If retinopathy is present** • Diagnose retinopathy severity and establish appropriate monitoring intervals (1 year or less) • Treat sight-threatening retinopathy with laser, pharmacological or surgical therapy • Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines* • Screen for other diabetes complications **If retinopathy is not present** • Type 1 diabetes: rescreen annually • Type 2 diabetes: rescreen every 1 to 2 years • Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines* • Screen for other diabetes complications
? Non-arteric ischemic neuropathy (NAION)	EMA (June 2025): Results from several large epidemiological studies suggest that exposure to semaglutide in adults with type 2 diabetes is associated with an approximately two-fold increase in the risk of developing NAION compared with people not taking the medicine. This corresponds to approximately one additional case of NAION per 10,000 person-years of treatment; one person-year corresponds to one person taking semaglutide for one year. https://www.uptodate.com/contents/glucagon-like-peptide-1-based-therapies-for-the-treatment-of-type-2-diabetes-mellitus/abstract-text/39696569/pubmed

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? Other eye concerns	AMD Glucagon-Like Peptide-1 Receptor Agonists and Risk of Neovascular Age-Related Macular Degeneration | JAMA Ophthalmology | JAMA Network
? Thyroid Cancer	Brito '25: Prespecified secondary analysis of a retrospective target trial, n=351 913 patients with T2DM at moderate risk for CV disease, without a history of thyroid cancer who had newly filled GLP-1RA, SGLTI2, DPP4i, or SU; found no significant increased overall risk of thyroid cancer in patients treated with a GLP-1RA (HR 1.24, 95% CI; 0.88 - 1.76) but **increased risk in the first year of treatment relative to DPP4i/SGLT2i/SU** (HR 1.85, 95% CI; 1.11 - 3.08) Silverii '23: Systematic review & meta-analysis of 26 RCTs comparing GLP-1RA with any comparator lasing at least 52 weeks, n = 69 909; concluded that GLP1-RA treatment was **associated with an increase in the risk of thyroid cancer** (OR 1.52; 95% CI; 1.01-2.29) Pasternak '24: Scandinavian cohort study of patients taking GLP1-RA (n = 149,469) compared to DPP4i (n = 296 573); concluded that GLP-1RA use **was not associated with an increased risk of thyroid cancer** (HR 0.93; 95% CI; 0.66 - 1.31) over a mean follow-up of 3.9 years Bezin '22: Nested case-control analysis of French patients with T2DM treated with second-line antidiabetic agents (n = 2562 cases, n = 45,184 controls); found small **increased risk of thyroid cancer** (HR 1.58; 95% CI; 1.27 – 1.95)
? Reduced BMD	Jensen '24: Pre-defined secondary analysis of an RCT (n = 195, excluded patients with T2DM); randomized patients into four groups x 52 weeks (moderate-to-intense exercise, 3mg liraglutide daily, combination of exercise and liraglutide, placebo), outcome was change in bone mineral density from before the study to the end of the 52-week study period; concluded that combination of exercise and liraglutide was the most effective weight loss strategy while preserving bone health • BMD was unchanged in the combination group compared to placebo; compared to the exercise group, BMD decreased for the liraglutide group (mean change -0.013 g/cm2; 95% CI; (-0.024) – (-0.001)) at the hip and -0.016 g/cm2; 95% CI; (-0.032) – (-0.001)) • Total estimated mean change in weight losses during the study was 7.03 kg (95% CI, 4.25-9.80 kg) in the placebo group, 11.19 kg (95% CI, 8.40-13.99 kg) in the exercise group, 13.74 kg (95% CI, 11.04-16.44 kg) in the liraglutide group, and 16.88 kg (95% CI, 14.23-19.54 kg) in the combination group
? Reduced Lean Body Mass	Challenges with assessment e.g. DXA (indirect / surrogate measure of skeletal muscle mass leading to heterogeneity in data), MRI is preferred with functional testing. Dubin'24. Neeland '24: There is heterogeneity in the reported effects of GLP-1-based therapies on lean mass changes in clinical trials: in some studies, reductions in lean mass range between 40% and 60% as a proportion of total weight lost, while other studies show lean mass reductions of approximately 15% or less of total weight lost. Limitations: changes in lean mass may not always reflect changes in muscle mass as the former measure includes not only muscle but also organs, bone, fluids, and water in fat tissue. - Based on contemporary evidence with the addition of magnetic resonance imaging-based studies, skeletal muscle changes with GLP-1RA

	treatments appear to be adaptive: reductions in muscle volume seem to be commensurate with what is expected given ageing, disease status, and weight loss achieved, and the improvement in insulin sensitivity and muscle fat infiltration likely contributes to an adaptive process with improved muscle quality, lowering the probability for loss in strength and function.
? Self-Harm & Suicidality	Health Canada Summary Safety Review (accessed April 25/25): assessed the potential safety issues of suicide and self-harm related to GLP1-Ras; did not find evidence to support a link between GLP-1Ras and the risk of suicide and self-harm, but will continue monitoring Canadian Network for Observational Drug Effect Studies (May 2024): assessed the risk of suicidality and self-harm related to GLP1-RA; after appraising the available real-world evidence to evaluate the risk of suicidality and self-harm related to GLP-1RA use (only 2 observational studies have been published assessing the potential association, Network noted that both studies had limitations to the methods utilized), the Network concluded that there is limited evidence demonstrate whether there is a link between the use of GLP-1RAs and the risk of self-harm ▪ Wang '24: Retrospective cohort study of American health records; studied two cohorts (n = 105,566 obesity cohort, n = 55,452 T2DM cohort), mean follow-up ~ 150-172 days; outcome was incident or recurrent suicidal ideation; incident obesity HR 0.27 95% CI; 0.20 - 0.36, recurrent obesity HR 0.44; 95% CI; 0.32 - 0.60, incident T2DM HR 0.36; 95% CI; 0.25 - 0.53, recurrent T2DM HR 0.51; 95% CI; 0.31 - 0.83 ▪ Gamble '18: Retrospective cohort study of UK primary care database (n = 16,190) investigating new onset of depression or self-harm in patients newly exposed to GLP-1RA vs. SU, mean follow-up 292 days (SU) – 397 days (GLP-1RA); composite outcome of new-onset depression or self-harm (including suicide) HR 1.25; 95% CI; 0.63-2.50 FDA: Ongoing evaluation of the link between GLP-1RA and self-harm/suicide – preliminary evaluations have not found evidence of association but investigation ongoing
Removed AE from Infographic (May 2025)	
? Pancreatic Cancer	Health Canada issues a warning in 2014 due to suspicion that n = 13 cases of pancreatic cancer were associated with incretin-based therapy (DPP4i + GLP1 agonists); causal relationship not established and multiple meta-analysis since suggested no increased risk. Cao '20: Meta-analysis of 7 RCTs studying GLP-1RA vs. placebo in T2DM (n = 56,004) **did not suggest increased risk of pancreatic cancer** or acute pancreatitis Dankner '24: Cohort review, n = 543,595 patients with T2DM followed up over 9 years comparing the occurrence of pancreatic cancer in T2DM with GLP-1RA vs. basal insulin; **did not find an increased risk of pancreatic cancer** in patients using a GLP-1RA (HR 0.50; 95% CI; 0.15 - 1.71)
? Pancreatitis	FDA Issues a warning in 2013 regarding GLP-1RA use and the risk of pancreatitis after 30 cases reports of pancreatitis with exenatide were reported (n = 21 hospitalized). Since then **several meta-analysis have suggested no increased risk of pancreatitis** (Cao '22, Storgaard '17, Monami '17) Ayoub '25: Compared two cohorts of patients with T2DM – those who were prescribed a GLP-1RA and those were not (81,872 patients in each cohort); found no difference in the risk of pancreatitis between the cohorts at months 6, 12, 36, and 60, **lifetime risk of developing pancreatitis was lower among the GLP-1RA user cohort** (0.3 vs. 0.4%)

	Lomeli ' 24: Retrospective chart review (n = 161) analyzing incidence of acute pancreatitis with GLP-1RA therapy in patients with a known history of pancreatitis, only 9.9% of acute pancreatitis cases documented after GLP-1RA exposure; concluded overall frequency of recurrent acute pancreatitis in this cohort of patients exposed to GLP-1RA is similar to the overall frequency of recurrent acute pancreatitis in the literature

AE Infographic & Online Extras References

Nausea, Vomiting, Diarrhea, Dyspepsia

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Injection Site Irritation

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Increased Heart Rate

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Bile Duct & Gall Bladder Disease

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Ileus

FDA Adds Warning To Ozempic Label About Ileus, Intestinal Blockage

U.S. Food and Drug Administration. Ozempic (Semaglutide). Safety-related labeling changes approved by FDA Center for Drug Evaluation and Research (CDER). September 22, 2023.https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail. page&DrugNameID=2183

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