Clinical Pharmacology & Toxicology Pearl of the Week

~Tirzepatide~

Background

- The first "dual agonist" GLP-1 receptor medication on the market
- First became available in Canada in November 2023
- Only approved in Canada for use in Type 2 diabetes
- Marketed under the trade name "Mounjaro" in Canada (also sold under the name "Zepbound" in the USA when used for weight loss or OSA)
- Listed cost in Canada is approximately $400 - $530 (per 5-vial carton)
- Currently not covered by AB Blue Cross, but may be covered by some private insurance plans for on-label use only (diabetes)

Indications

- Type 2 diabetes (Canada)
- Weight loss (USA)
- Moderate to severe OSA (USA)

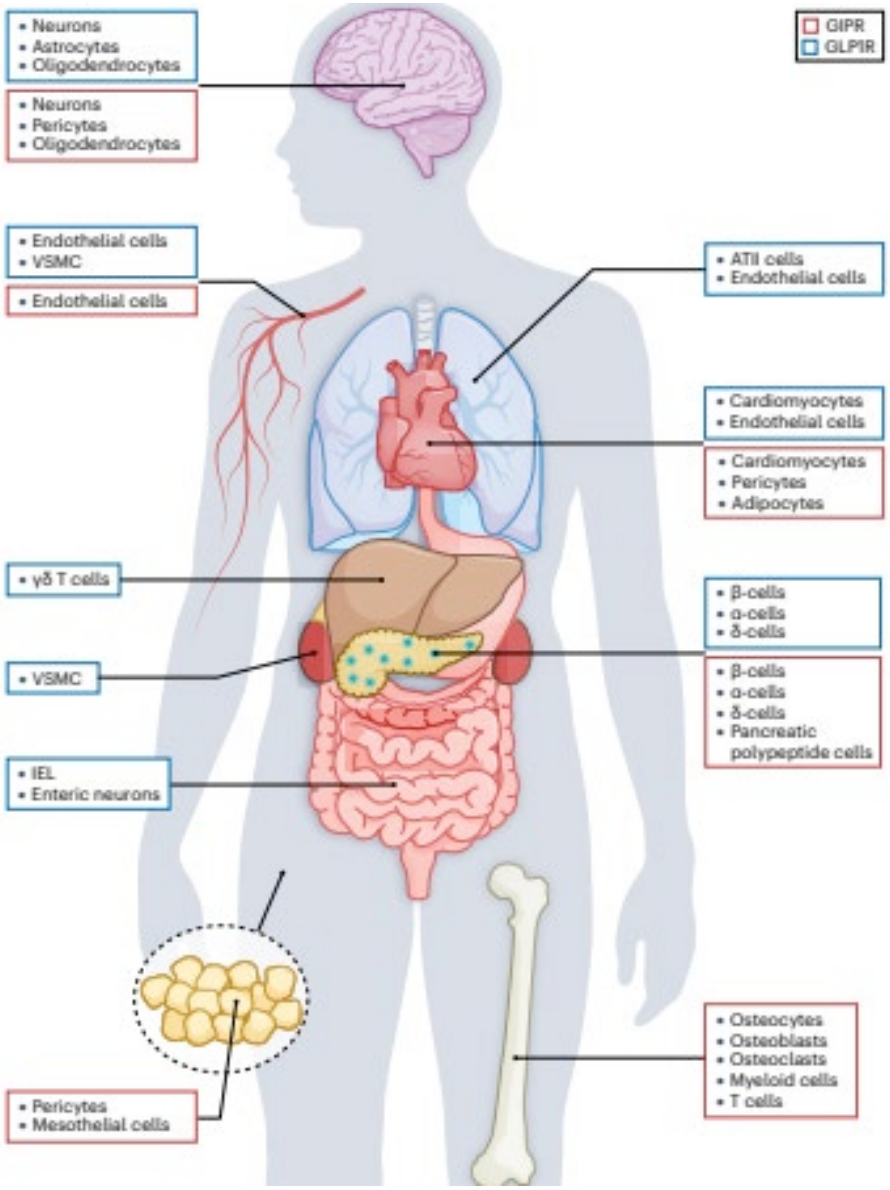
Dosing

- 2.5 mg subcutaneously once weekly for 4 weeks, then increase to 5 mg once weekly. May increase dose in 2.5 mg/week increments every 4 weeks if needed to achieve glycemic goals (maximum weekly dose is 15 mg/week)
- No dose adjustments are necessary in liver or kidney dysfunction

Mechanism of Action

- Acts on both glucagon-like peptide-1 (GLP-1) receptors AND glucose-dependent insulinotropic polypeptide (GIP) receptors, reportedly resulting in a more potent effect than "classic" GLP-1 medications (ie. semaglutide, liraglutide, dulaglutide).
- Stimulation of these receptors slows gastric emptying, inhibits the release of glucagon, and stimulates insulin production, therefore reducing hyperglycemia in people with type 2 diabetes.
- Stimulation of these receptors also reduces food intake and therefore body weight, making this class of medications an effective treatment for obesity

- Beyond this, these receptors are widely expressed throughout the body and exert multiple extra-pancreatic actions. These actions affect inflammation, cardiovascular and renal function, gastrointestinal motility, bone and mineral homeostasis and neurological function.



Hammoud, R., Drucker, D.J.
Beyond the pancreas: contrasting cardiometabolic actions of GIP and GLP1
Nat Rev Endocrinol **19**, 201–216 (2023)
https://doi.org/10.1038/s41574-022-00783-3

Pharmacokinetics

- Bioavailability: 80%
- Half-life elimination: approximately 5 days
- Time to peak: 8 to 72 hours

Important Studies

- **The SURPASS-2 trial**: Tirzepatide was found to be superior to semaglutide with regards to lowering Hgb A1c at 40 weeks.
    - Frías JP, et al. SURPASS-2 Investigators. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med. 2021 Aug; 385(6):503-515.
- **The SURPASS-3 trial**: Tirzepatide was superior to degludec insulin, with greater reductions in Hgb A1c and bodyweight at 52 weeks and a lower risk of hypoglycemia.
    - Ludvik B, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. The Lancet. 2021 Aug; 398:583 – 598
- **The SYNERGY-NASH trial:** Tirzepatide was found to improve, and even resolve in some, features of liver fibrosis on liver biopsy in patients with moderate to severe metabolic associated steatohepatitis (MASH) after 52 weeks.
    - Loomba R, et al. Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis. N Engl J Med 2024; 391:299-310
- **The SURMOUNT-OSA trial:** Among patients with moderate-to-severe OSA and obesity, tirzepatide reduced the AHI, body weight, hypoxic burden, CRP, and systolic blood pressure and improved sleep-related patient-reported outcomes after 52 weeks.
    - Malholtra A, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. N Engl J Med 2024;391:1193-120
- **The SUMMIT trial:** Treatment with tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo and improved health status in patients with heart failure with preserved ejection fraction (HFpEF) and obesity.
    - Packer M, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med 2025;392:427-437

Medication Safety Issues & Considerations

- Contraindicated in people with a personal or family history of medullary thyroid carcinoma or in those with multiple endocrine neoplasia syndrome type 2, and in pregnancy.
- Common side effects include gastrointestinal symptoms such as diarrhea, constipation, nausea and vomiting
- Serious adverse effects that have been reported include AKI secondary to volume contraction in the setting of GI upset, worsening of diabetic retinopathy in the setting of rapid glucose reduction, medullary thyroid cancer, gallbladder disease, pancreatitis, hypoglycemia, and hypersensitivity reactions including angioedema and anaphylaxis.
- Shown to be teratogenic in animal studies, unknown if passed through breastmilk

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral, Specialist Link and through RAAPID. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

Created and Reviewed: March 5, 2025