GLP-1 Agonists: Now Basically Indicated for Everything

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MAHC Grand Rounds

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Disclosures

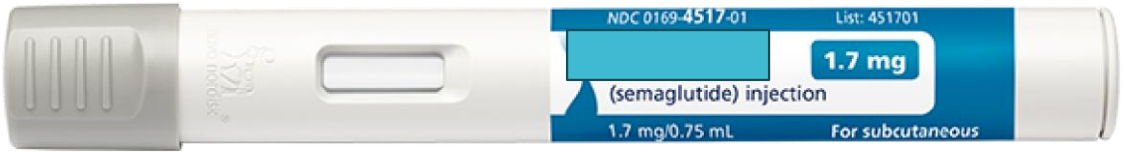
- None

Learning Objectives

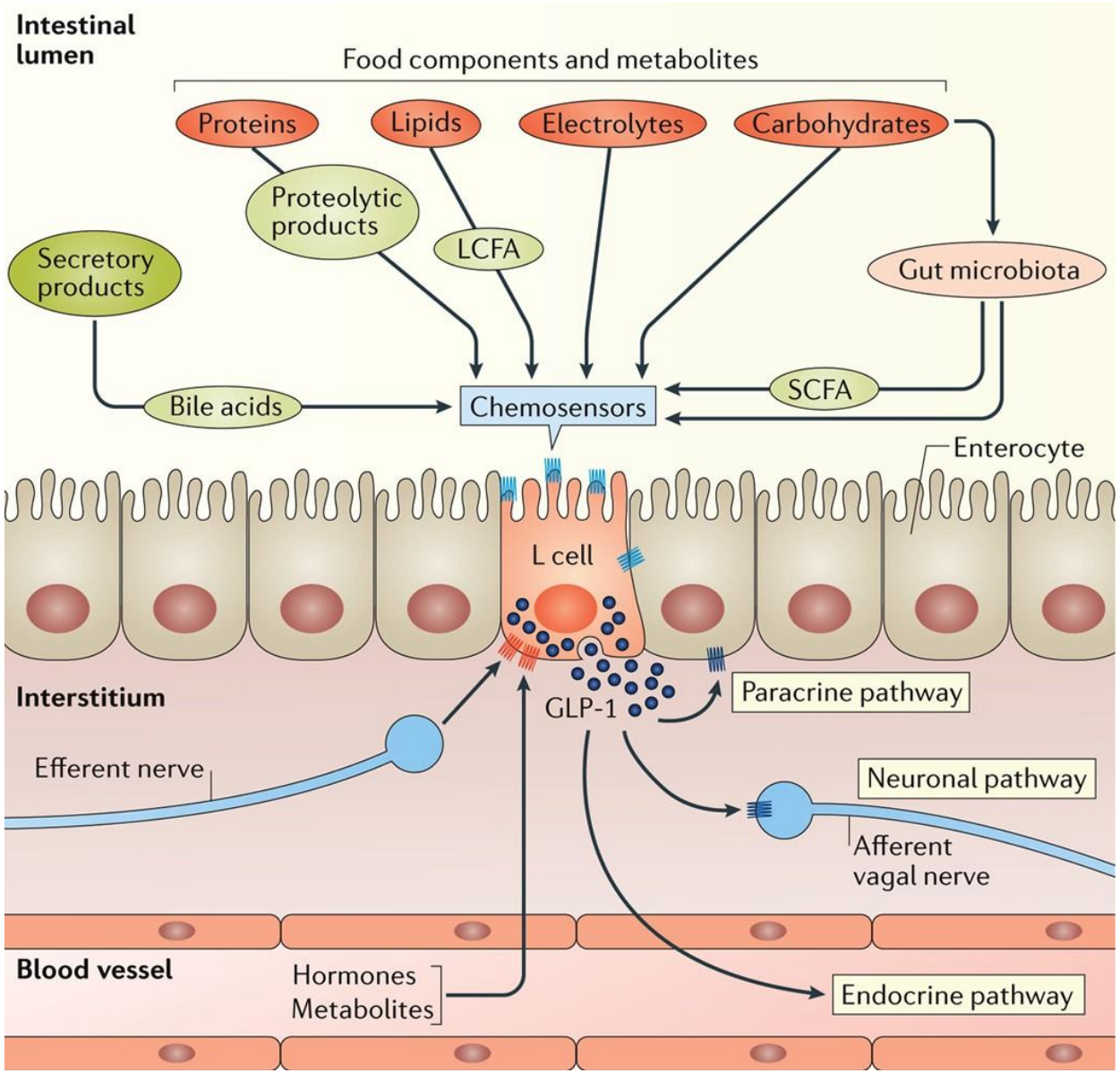
- Apply principles to the safe prescribing and patient counseling of GLP-1 agonists.
- Recognize current approved indications for GLP-1 agonists.
- Evaluate emerging and potential benefits of GLP-1 agonists beyond glycemic control.

History

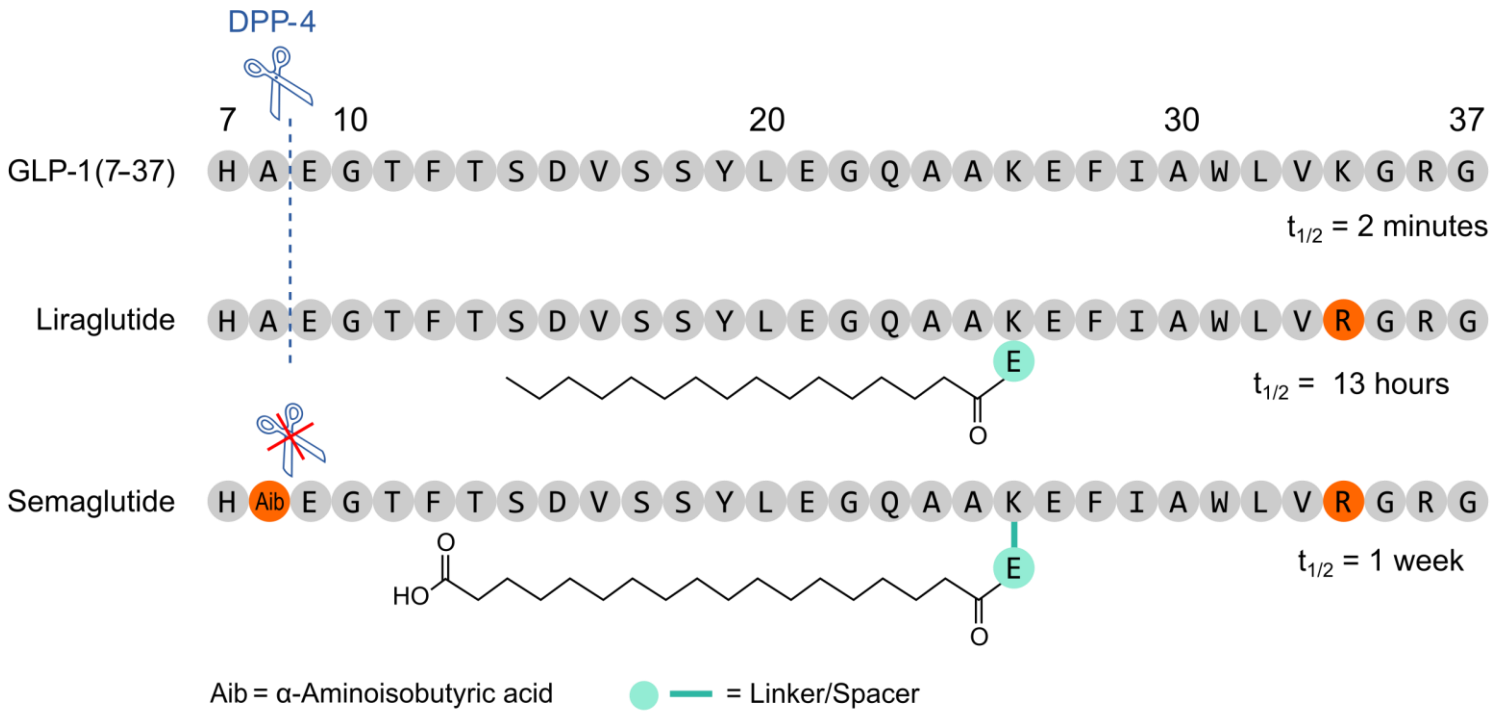
- SubQ approval is the 2010s
- Oral approval 2019-2020



Glucagon Like Peptide-1

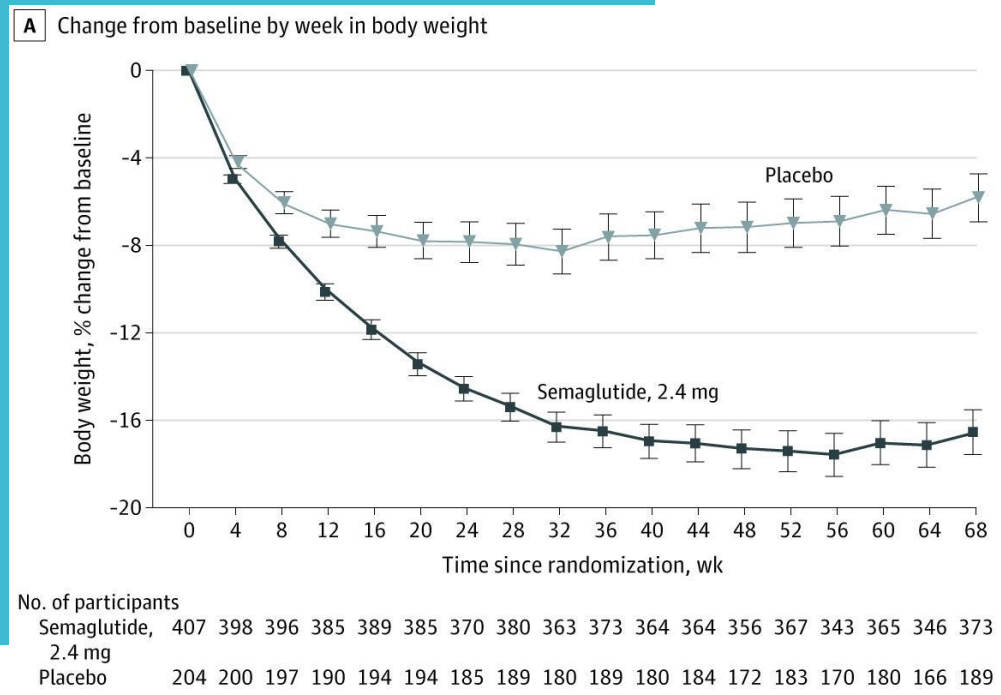


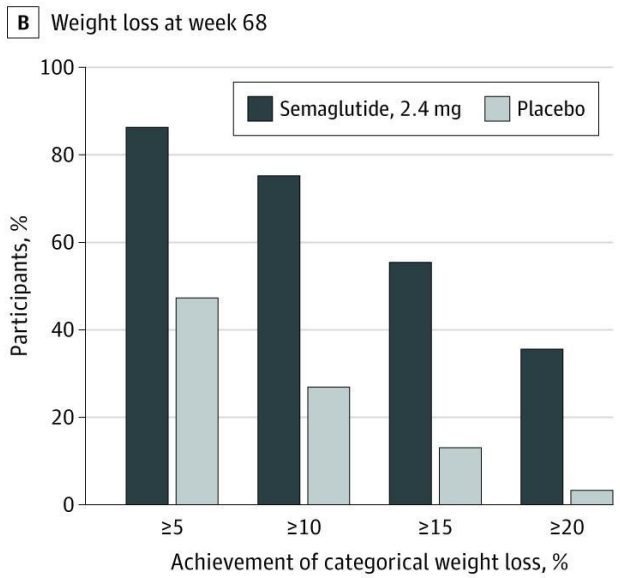
GLP-1 versus the drugs

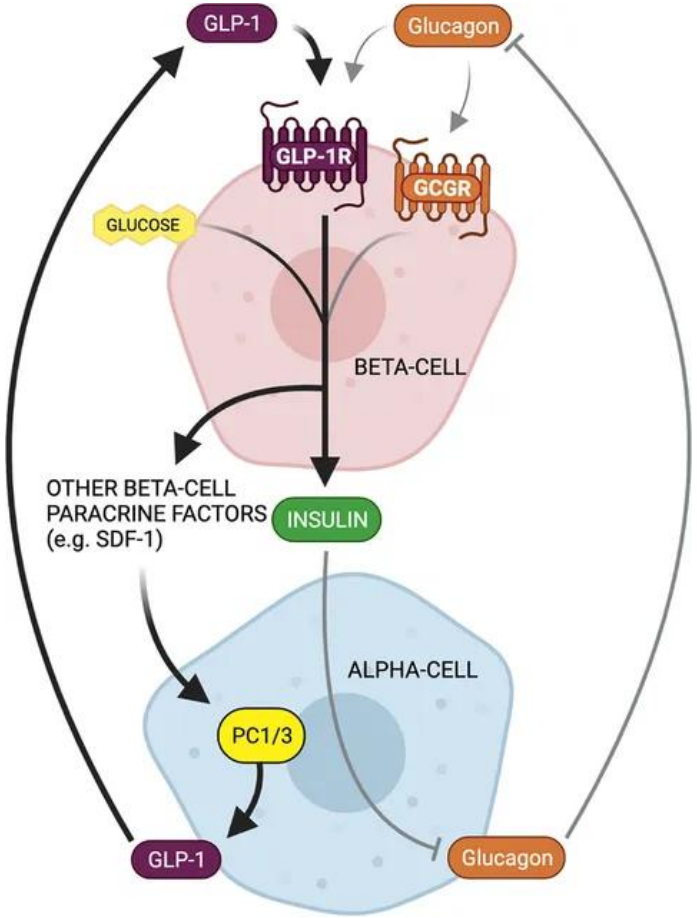


Why GLP-1 Agonists Work

- Stimulates insulin secretion
- Suppresses glucagon release
- Increased satiety, delayed gastric emptying
- Work on neural pathways to increase satiety







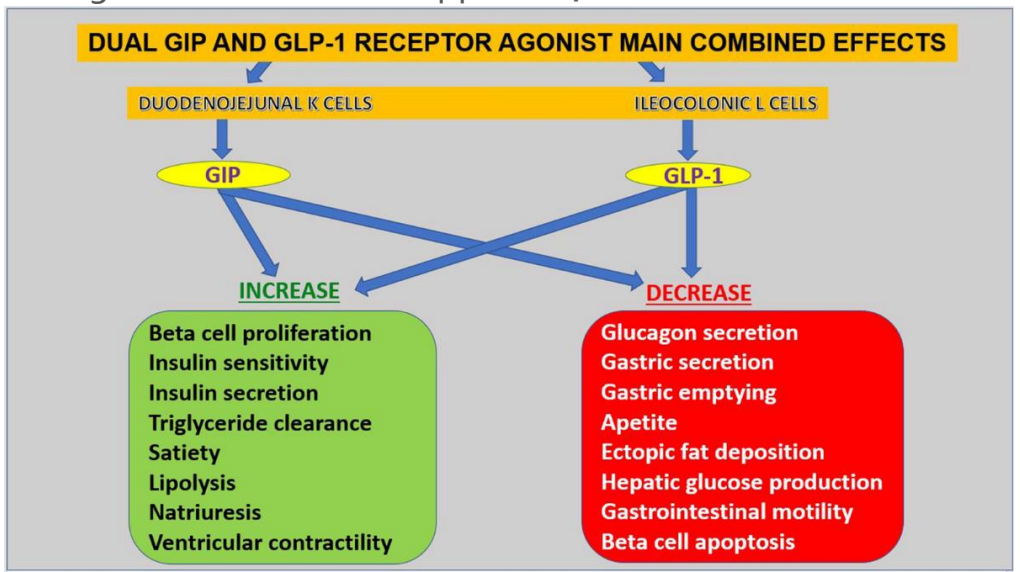
Approved by Health Canada

- Type 2 Diabetes
- Weight loss
  - 30 kg/m² or greater
  - BMI of 27 kg/m² or greater
    - with at least one weight-related condition like hypertension, Type 2 diabetes, dyslipidemia, or obstructive sleep apnea, alongside a reduced-calorie diet and increased physical activity

Classification	BMI category (kg/m²)	Risk of developing health problems
Underweight	< 18.5	Increased
Normal Weight	18.5 - 24.9	Least
Overweight	25.0 - 29.9	Increased
Obese class I	30.0 - 34.9	High
Obese class II	35.0 - 39.9	Very high
Obese class III	>= 40.0	Extremely high

Examples

- Approved for T2DM
  - Liraglutide
  - Semaglutide (injectable and oral)
  - Tirzepatide
  - Dulaglutide
  - Not an exhaustive list
- Approved for Weight loss
  - Liraglutide
  - Semaglutide
  - Tirzepatide
  - Not an exhaustive list
  - Please note: Several different brand names with some being approved by Health Canada and others being off label still
    - Ie. Liraglutide → Saxenda approved, Victoza is off label



Side Effects

- Injection site reactions for subq route
- GI Side effects most common
  - Nausea, vomiting, diarrhea, constipation
  - Dose dependent, start low!
- Severe
  - Gallbladder (ie. Cholelithiasis, cholecystitis)
  - Pancreatitis
  - Bowel obstruction
  - ?Diabetic Retinopathy (SUSTAIN-6 study)
  - AKI
  - MTC

Many others but low risk

For reference in the future!

Table 3. Adverse Events.*

Adverse Event	Semaglutide (N=1306)			Placebo (N=655)		
	No. of participants (%)	No. of events	Events/100 person-yr	No. of participants (%)	No. of events	Events/100 person-yr
Any adverse event	1171 (89.7)	9658	566.1	566 (86.4)	3302	398.0
Serious adverse events	128 (9.8)	164	9.6	42 (6.4)	53	6.4
Adverse events leading to discontinuation of drug or placebo	92 (7.0)	123	7.2	20 (3.1)	23	2.8
Gastrointestinal disorders	59 (4.5)	78	4.6	5 (0.8)	5	0.6
Fatal events†‡	1 (0.1)	1	0.1	1 (0.2)	3	0.3
Adverse events reported in ≥10% of participants§						
Nausea	577 (44.2)	1068	62.6	114 (17.4)	146	17.6
Diarrhea	412 (31.5)	766	44.9	104 (15.9)	138	16.6
Vomiting	324 (24.8)	636	37.3	43 (6.6)	52	6.3
Constipation	306 (23.4)	390	22.9	62 (9.5)	73	8.8
Nasopharyngitis	281 (21.5)	480	28.1	133 (20.3)	216	26.0
Headache	198 (15.2)	387	22.7	80 (12.2)	104	12.5
Dyspepsia	135 (10.3)	179	10.5	23 (3.5)	30	3.6
Abdominal pain	130 (10.0)	175	10.3	36 (5.5)	41	4.9
Upper respiratory tract infection	114 (8.7)	158	9.3	80 (12.2)	116	14.0
Safety focus areas¶						
Gastrointestinal disorders‖	969 (74.2)	4309	252.6	314 (47.9)	739	89.1
Gallbladder-related disorders	34 (2.6)	42	2.5	8 (1.2)	8	1.0
Hepatobiliary disorders‖	33 (2.5)	40	2.3	5 (0.8)	5	0.6
Cholelithiasis	23 (1.8)	24	1.4	4 (0.6)	4	0.5
Hepatic disorders	31 (2.4)	37	2.2	20 (3.1)	24	2.9
Acute pancreatitis**	3 (0.2)	3	0.2	0	—	—
Cardiovascular disorders†	107 (8.2)	134	7.2	75 (11.5)	96	10.5
Allergic reactions	96 (7.4)	108	6.3	54 (8.2)	63	7.6
Injection-site reactions	65 (5.0)	99	5.8	44 (6.7)	82	9.9
Malignant neoplasms†	14 (1.1)	14	0.8	7 (1.1)	7	0.8
Psychiatric disorders‖	124 (9.5)	160	9.4	83 (12.7)	113	13.6
Acute renal failure	3 (0.2)	4	0.2	2 (0.3)	2	0.2
Hypoglycemia	8 (0.6)	15	0.9	5 (0.8)	7	0.8

* Adverse events are shown for the safety analysis population (all randomly assigned participants exposed to at least one dose of trial drug or placebo); since all participants received at least one dose of drug or placebo, the safety population is the same as the full-analysis population. Included are all adverse events that occurred during the on-treatment period (i.e., the period during which any dose of semaglutide or placebo was administered within the previous 49 days, with any period of temporary interruption of a regimen excluded), unless indicated otherwise. Adverse events were classified by severity as mild (causing minimal discomfort and not interfering with everyday activities), moderate (causing sufficient discomfort to interfere with normal everyday activities), or severe (preventing normal everyday activities).

† Included are events that were observed during the in-trial period (the time from random assignment to last contact with a trial site, regardless of treatment discontinuation or rescue intervention).

‡ In the semaglutide group, sudden cardiac death occurred in one participant with a medical history of hypertension and obstructive sleep apnea who had discontinued semaglutide. In the placebo group, death due to glioblastoma, aspiration pneumonia, and severe sepsis occurred in one participant each who had discontinued placebo.

§ Shown are the most common adverse events, according to the preferred term in the Medical Dictionary for Regulatory Activities (MedDRA), version 22.1, reported in 10% or more of participants in either treatment group.

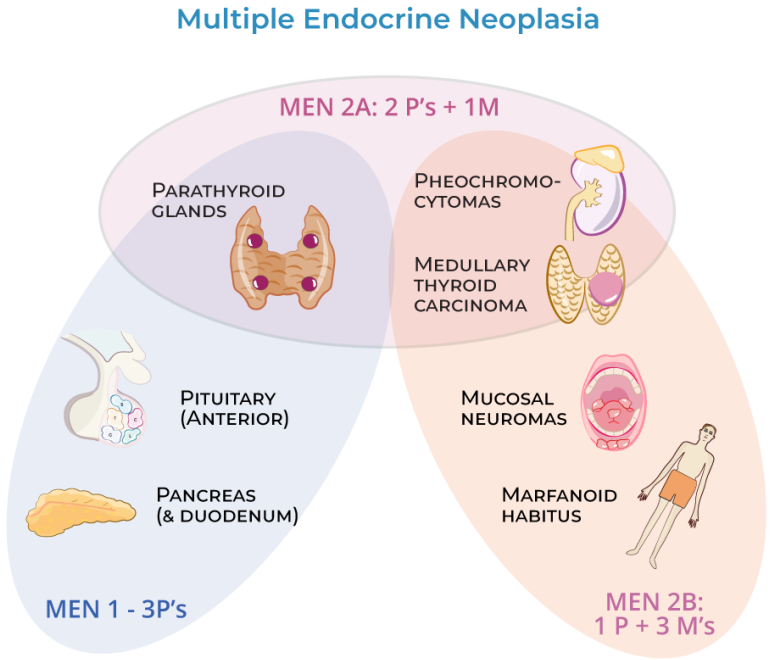
¶ On the basis of therapeutic experience with glucagon-like peptide-1 receptor agonists and regulatory feedback and requirements, a number of safety focus areas were prespecified as being of special interest in the safety evaluation. Identified through searches of MedDRA, these preferred terms were judged to be relevant for each of the safety focus areas.

‖ This is a system organ class. (For gallbladder-related disorders, hepatobiliary disorders is the system organ class and cholelithiasis is the preferred term.)

** Acute pancreatitis was confirmed by the event adjudication committee.

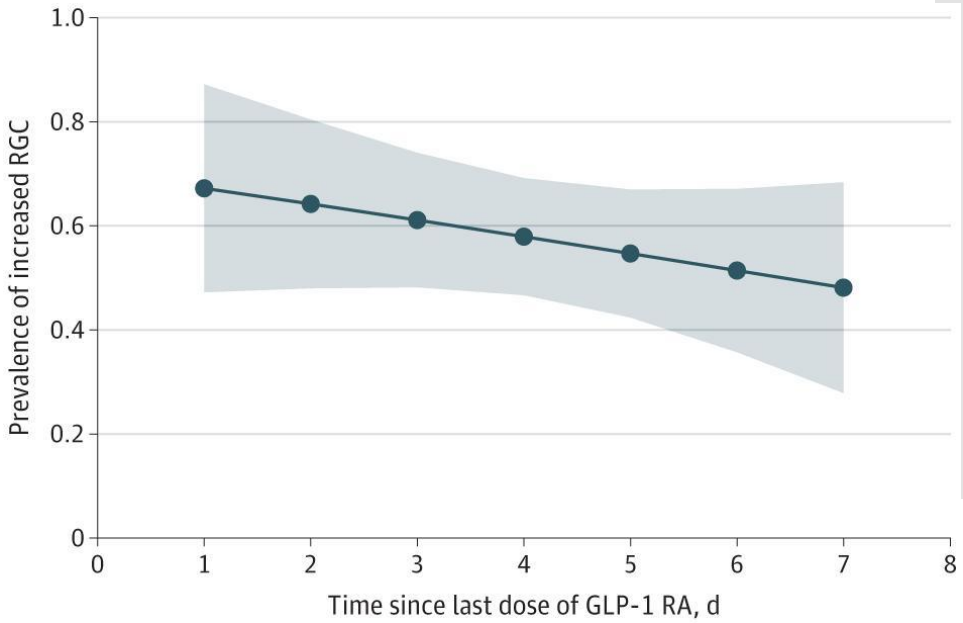
Contraindications

- Dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures
- Contraindicated if:
  - personal or family history of MTC
  - patients with Multiple Endocrine Neoplasia syndrome type 2
- Pregnancy, breastfeeding



Other considerations

- Medications that cause delayed gastric emptying
  - Opioids
  - TCAs
  - Marijuana, Alcohol
  - CCBs
  - Diphenhydramine
  - PPIs
- Patients undergoing surgery, scopes
  - Due to delayed gastric emptying and risk for adverse events, ie. with anesthesia
  - Individualize this
    - Depends on T2DM vs weight loss



Resource for future use! RxFiles

Drug Class	GLP1 Agonists			
Generic → BRAND	Dulaglutide subcut TRULICITY (subcut weekly)	Liraglutide subcut VICTOZA (subcut daily)	Semaglutide subcut OZEMPIC (subcut weekly)	Semaglutide po 14mg RYBELSUS (po daily)
Major trials to support findings/outcomes* Also SHI SR & NMA*	REWIND n=9901 / 5.4 yr	LEADER n=9340 / 3.8 yr GRADE n=5047 / 5 yr	SUSTAIN-6 n=3297 / 2 yr FLOW n=3533 / 3.4 yr stopped early renal dx HFpEF DM n=616 / 1 yr	PIONEER-6 n=3183 / 1.3 yr SOUL n=9650/ 49.5 mo CV&renal
↓ Risk of Major CV - MACE	✓✓ ↓ MACE NNT≈72/5.4yr REWIND ? North America subgroup- neutral HR: 1.14 (0.89-1.47)	✓✓ ↓ MACE NNT≈53/3.8yr LEADER ? North America subgroup – neutral HR: 1.01 (0.84-1.22)	✓✓ ↓ MACE NNT≈44/2.1yr SUSTAIN-6 ? North America subgroup – marginal HR: 0.87 (0.57-1.34)	✓ ↓ MACE NNT≈56/49.5mo SOUL Neutral MACE PIONEER-6 non-inferior to placebo 3.8% vs 4.8%; HR: 0.79 (0.57-1.11) Many trial limitations, e.g. short
↓ Risk of All-Death	HR 0.9 (0.80-1.01) 10.8% vs 12%/5.4yr (NS) REWIND	✓✓ NNT≈72/3.8yr LEADER	HR 1.05 (0.74-1.50) SUSTAIN-6 ✓ 2° endpoint NNT≈34/3.4yr (12.8% vs 15.8%) FLOW	✓? 2° endpoint NNT≈72/1.3yr PIONEER-6
Less Renal Disease (composite/surrogates)	✓ NNT=40/5.4yr (17.1 vs 19.6%) REWIND	✓ NNT=67/3.8yr (5.7% vs 7.2%) LEADER	✓✓ semaglutide NNT≈23/3.4yr (18.7% vs 23.2%) FLOW	HR:0.91 (0.8-1.05) 8.4% vs 9%/49.5mo (NS) SOUL
Effect on A1c**	✓✓	✓✓	✓✓	✓✓
Weight Loss	✓✓ ↓1.3-3 kg/5-52 wk	✓✓ ↓ 2.3 kg/3.8 yr	✓✓ ↓ 3-4kg/2.1 yr	✓✓ ↓ 3.4kg/1.3 yr
Less Risk of Hypoglycemia	✓?	✓ Severe: 2.4% vs 3.3% p=0.02 (placebo group had more insulin)	✓?	✓? Severe: 1.4% vs 0.8%
	Risk when given with sulfonylurea or insulin			
Less Risk of HF see RxFiles Chart: HF pg 23	HR: 0.93 (0.77-1.22)	HR: 0.87 (0.73-1.05)	✓↓HF sx in HFpEF & BMI ≥30 HFpEF DM	HR: 0.86 (0.48-1.55)
	? As a class, ↓ hospitalization for HF. Shi et al. SR & NMA			
Effect on GI & D/C due to Tolerability	X GI (?better tolerated[42]) D/C due to AE 9% vs 6% NNH≈36/5.4yr	X GI D/C due to AE 9.5% vs 7.3% NNH≈46/3.8yr	X GI (?better tolerated[42]) D/C due to AE 11.5-14.5% vs 5.7-7.6% NNH≈14/2yr	X D/C due to GI: 6.8% vs 1.6% D/C due to AE 11.6% vs 6.5%; NNH≈20/1.3yr
? AE Concerns Associated with Class	AEs: GI, dizziness, ↑HR (clinical relevance uncertain for most). Rare/?: bile duct / gallbladder dx;[46]?↑ thyroid cancer (liraglutide rodent data);[41]?retinopathy progression, delayed gastric emptying/aspiration with anesthesia, ?ileus, sema ?self-harm/suicidality, ?↓BMD. Caution: GI e.g. Crohn's, IBS, severe gastroparesis. See AE Infographic.			
Cost – 1 month Some cost programs may be available	XX $288 ✗ ⊗	XX $134-$368 ✗ ⊗	XX $120-$220 ☎ ✆ NIHB	XX $260 ✗ ✆ NIHB
Other	Environmental impact - single use disposable pen	Gallbladder AE: NNH≈84	NIHB open benefit (T2DM, combo with metformin & exercise)	Short trials. SAE lower in treatment group.
Practical / Clinical Considerations	Upper GI effects often worse than lower GI effects; a low fat diet is better (small, frequent meals); gradual dose titration; pt may struggle with AE in first few weeks, but many will adjust diet, gain tolerability, & do OK. Insulin dose can be reduced 20-30% initially; Expert possibly more after that. Discontinue DPP4i or tirzepatide.			
Time Tested	FDA approval since 2010-2017; safety data & real world use still ongoing			
Convenience	✓ Single Use Pen subcut once weekly	subcut once daily	✓ subcut once weekly	✓ 30min pre-am meal; ≤120mL H_2O oral once daily
Overall	✓	✓	✓	✓?

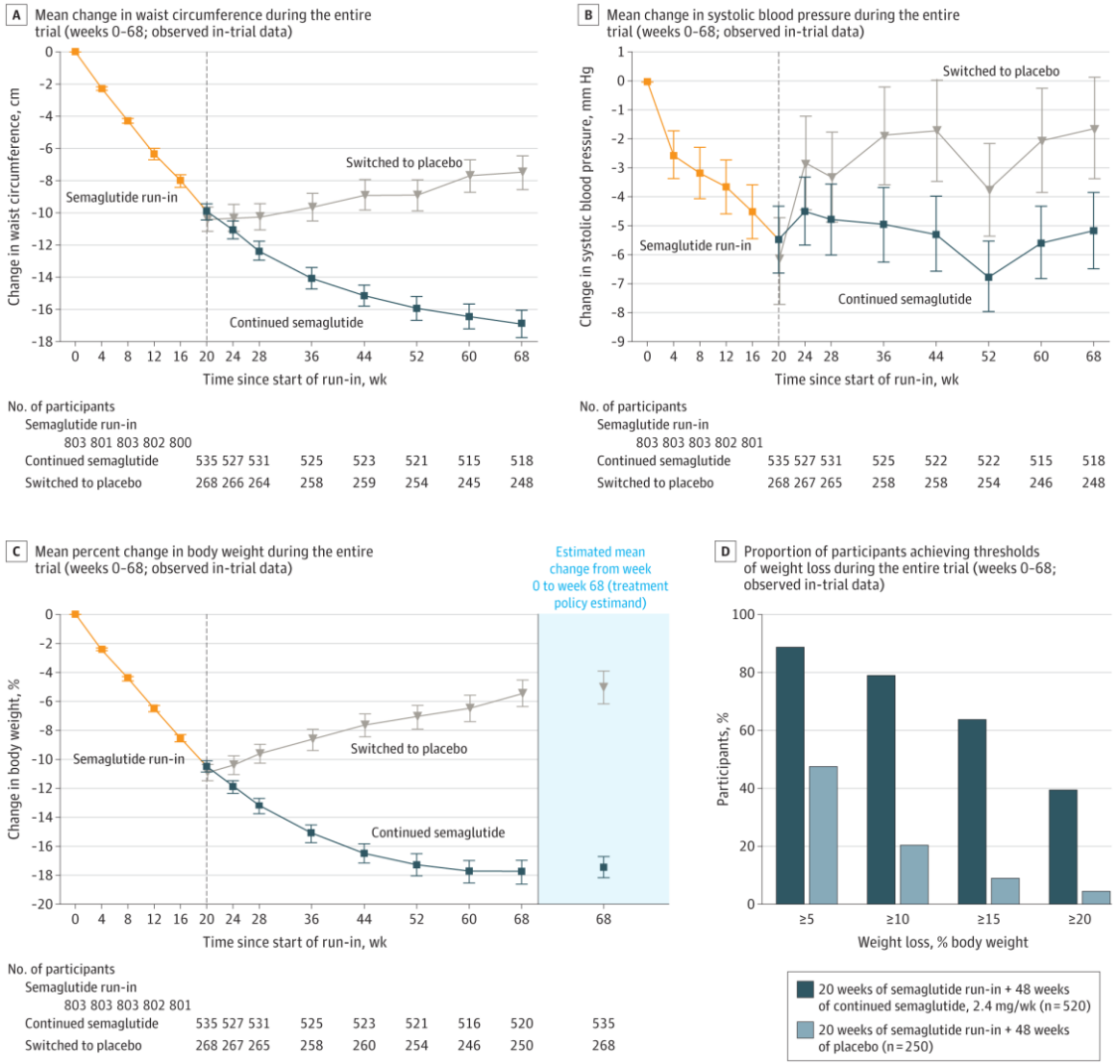
Dosing

- Semaglutide
  - 0.25mg weekly injectable
  - Titrate up every 4 weeks typically, but if SE then consider staying at dose for longer

  - If missed dose:
  - **Taken as soon as possible within 5 days** of the missed dose
  - If more than 5 days have passed since the missed dose, the dose should be skipped and the next dose administered on the regularly scheduled day
  - **Not necessary to return to the lowest dose** after missing a dose but should be strongly considered if 2-3+ doses are missed

Tapering and Stopping

- Do not need to taper off – no withdrawal SE
- But … Weight gain and reversal of cardiometabolic benefits
  - STEP 1 and 4 Trial
  - Generally - patients will regain ½ to 2/3 of the weight lost in 1-2 years



Benefits Beyond Glycemic Control

- **Cardiovascular benefits**
  - reduce MACE, including non-fatal myocardial infarction, stroke, and cardiovascular death
  - LEADER trial, SELECT trial
- **Heart failure**: Semaglutide has shown benefits in obesity-related heart failure with preserved ejection fraction (HFpEF)
  - STEP-HFpEF trial, SUMMIT trial
  - HFrEF → no significant benefit found
- **Renal protection**: GLP-1 RAs reduce albuminuria and slow eGFR decline in patients with type 2 diabetes and chronic kidney disease
  - FLOW trial
- **Metabolic benefits**: These agents improve systolic blood pressure, LDL cholesterol, and may benefit metabolic dysfunction-associated steatohepatitis

Next Steps? Future Research?

- PCOS
  - Increase conception rates through weight loss?
- Substance Use Disorders
  - activation in brain reward circuits, modulating dopaminergic signaling and attenuating reward-driven behaviors?
- Type 1 Diabetes
  - Possibly preserving beta cell function
  - Risk of DKA and hypoglycemia?
  - Weight loss, a1c improvement, reduction of insulin requirements?
- OSA
  - Weight loss
- Knee Osteoarthritis
  - Weight loss, anti inflammatory effects
  - STEP-9 trial

Next Steps? Future Research?

- Parkinson Disease
  - Neuroprotective anti-inflammatory effects?
  - Recent early phase 2 trials showed improvement in motor scores (MDS-UPDRS) but phase 3 showed none
- Alzheimer Disease
  - Reduce neuroinflammation, improve insulin signaling in the brain?
  - May also enhance synaptic plasticity and reduce amyloid-β and tau pathology
- Migraines and IIH
  - ?small study showed potential benefit in obese patients with unresponsive high frequency migraines
- Inflammatory Bowel Disease