



ADVISORY COUNCIL

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Unlocking the Potential of GLP-1/GIP Receptor Agonists: A New Horizon in Managing Complex Health Conditions?

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Today's Discussion

1. Evolution of Obesity Treatment Approaches
2. Overview Of GLP-1/GIP Agonists
3. Emerging Evidence for Broader Applications in Complex Health Conditions
4. Challenges and Considerations
 - Economic And Accessibility Issues





The Evolution of Treatment Approaches in Obesity Management

Roughly **3 out of 4**
American adults
are overweight¹

40% of American
adults are obese²





1 Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. NCHS Health E-Stats. 2020.

2 Emmerich SD, Fryar CD, Stierman B, Ogden CL. Obesity and severe obesity prevalence in adults: United States, August 2021–August 2023. NCHS Data Brief, no 508. Hyattsville, MD: National Center for Health Statistics. 2024.

Lifestyle / Behavior Modification

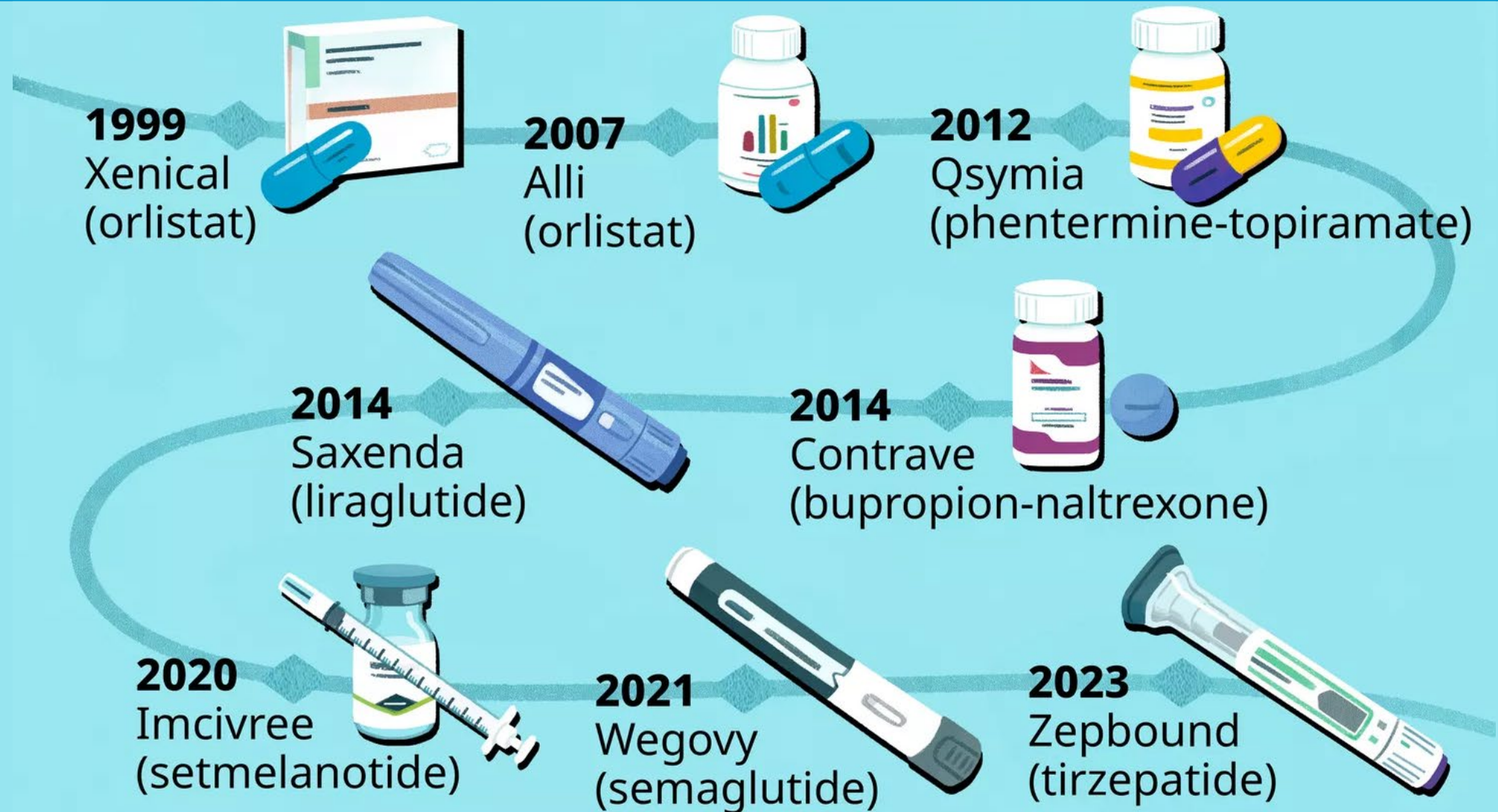


Surgery Comparison Chart

Type of Surgery	Roux-EN-Y Gastric Bypass	Vertical Gastrectomy With Duodenal Switch (DS)	Vertical Gastrectomy (VG)	Adjustable Gastric Band (Lap-band)
				
What Surgery Entails	Small pouch (about 1 ounce/20-30cc). Pouch is connected to the small intestine where food and digestive juices are separated for the first 3 to 5 feet. The RnY significantly restricts the volume of food that can be eaten.	Long vertical pouch (about 4-5 oz or 120-150cc). The duodenum (first portion of the small intestine) is attached to the last 6 feet of small intestine, where food and digestive juices are rejoined after 12 feet. Moderate restriction of volume of food that can eaten. Provides moderate malabsorption of fat, which can cause diarrhea and bloating.	Long narrow vertical pouch (about 2-3 oz or 60-100cc). Same shape as the duodenal switch pouch but smaller. No intestinal bypass. The VG significantly restricts the volume of food that can be eaten. There is no malabsorption of nutrients or dumping.	The Lap-Band is an adjustable silicone ring that is placed around the top part of the stomach creating a small (1-2 ounce or 15-30cc) pouch. The Lap-Band moderately restricts the volume and type of foods the patient is able to consume. The Band delays emptying of the pouch and creates the sensation of satiety. There is no malabsorption of nutrients.
Realistic Expectations	Provides mild malabsorption of nutrients. Patients can expect to lose 70% of excess weight. Less effective (patients who lose <50% excess weight) than with the DS.	Patients can expect to lose 75%-80% of excess weight. Some patients can lose too much weight. More risk of nutritional deviancies than with the RnY.	Patients can expect to lose 60%-70% of excess weight loss at about 2 years. Long term results not available at this time. Easily converted to DS or RnY, if needed.	Patients can expect to lose 60% of their excess weight. This procedure requires the most effort of all of the procedures in order to be successful. Patient must be committed to good eating habits and exercise.
Post-Surgery Eating and Required Supplements	Patients must eat 3 small meals a day. Patients must avoid sugar and fats to prevent "Dumping Syndrome". Patients must take vitamin and protein supplements to avoid deficiency. (Multivitamin, Calcium, Vitamin B12 and Iron - for menstruating women)	Patients must eat 3 meals a day. Patients must strictly adhere to protein and vitamin supplements to avoid deficiencies. (Multivitamins, ADEK vitamins, Calcium and Iron for menstruating women).	Patient must eat 3 meals a day containing 600-800 calories per day (recommended for the first 24 months) and about 1000-1200 thereafter. There is no dumping or diarrhea.	Patients must eat 3 meals per day consisting of less than 1000 calories per day during weight loss. Patients will need to avoid certain foods that can become "stuck" such as bread, rice, nuts, dense meats that may cause pain and vomiting. Patients must not drink fluids with meals.
How Effective is This Surgery?	The RnY is effective for patients with a BMI of 35-55 and those with a "sweet tooth".	The DS is effective for patients with a BMI of >50 kg/m2. Those with BMI of <45 kg/m2 may lose too much weight. The DS has a higher incidence of complications than any of the other procedures.	The VG is effective for high risk or very high BMI patients (BMI > 60 kg/m2) patients as a "first-stage" procedure. Much lower complication rate than the RnY or DS due to there being no intestinal bypass performed.	The Lap-Band is most effective for patients that are more disciplined in following a strict diet and will commit to an exercise program.

Source: <https://nationalbariatriclink.org/bariatric-surgery/bariatric-surgery-basics/types-of-bariatric-surgery>

FDA-Approve Weight Loss Drugs



Source: <https://www.verywellhealth.com/whats-new-in-obesity-treatment-7556082>



News Release

Lilly's Zepbound® (tirzepatide) superior to Wegovy® (semaglutide) in head-to-head trial showing an average weight loss of 20.2% vs. 13.7%

December 4, 2024

Source: <https://investor.lilly.com/news-releases/news-release-details/lillys-zepboundr-tirzepatide-superior-wegovyr-semaglutide-head>



Overview Of GLP-1/GIP Agonists

Centrally Acting Medications

Medications

Phentermine

Thought to work centrally and stimulate CNS activity (increasing norepinephrine, dopamine and serotonin)

- Reduces appetite
- Adverse effects may include xerostomia, insomnia, headache, and constipation

Phentermine-Topiramate

Topiramate is thought to augment GABA activity and inhibit carbonic anhydrase

- Reduces appetite
- Adverse effects may include paresthesia, xerostomia, constipation, and dysgeusia

Naltrexone-Bupropion

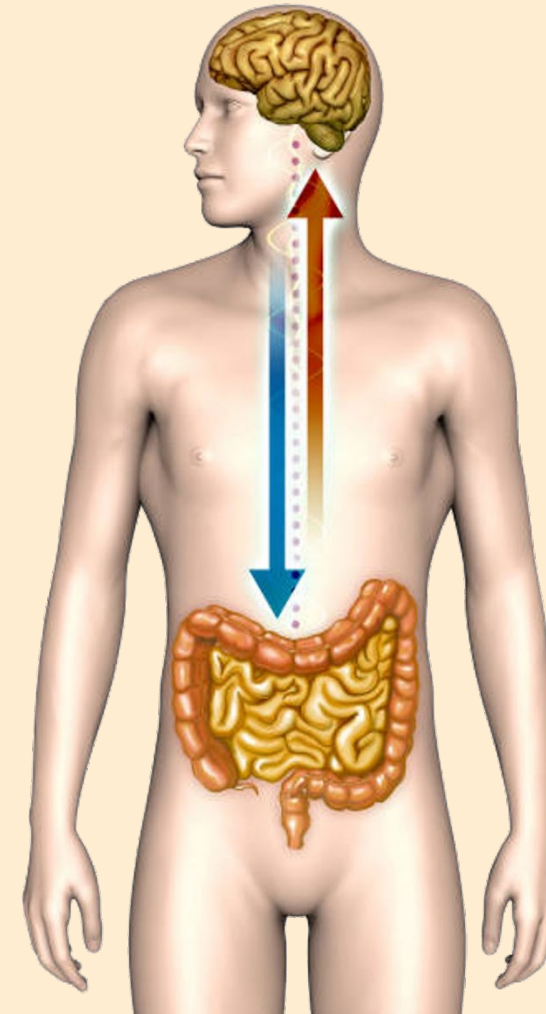
Wellbutrin inhibits uptake of norepinephrine and dopamine.

Naltrexone is an opioid antagonist

- Reduces appetite
- Adverse Effects may include nausea, constipation, headache, vomiting, dizziness, insomnia, and xerostomia

The Gut-Brain Axis

The gut-brain axis is an integrated and bidirectional communication system that links the central nervous system with the gastrointestinal tract, involving neuroendocrine signaling pathways



GLP-1 receptor agonists trigger insulin release from the pancreas and block glucagon secretion. Also thought to slow stomach emptying and increase how full one feels after eating (through affecting areas of the brain that process hunger)

GIP receptor agonists are thought to enhance the effects of GLP-1 RAs through increasing satiety (by acting centrally)

Cellulose-Citric Acid Hydrogel expand in the stomach and intestines to create a feeling of fullness

Orlistat inhibit gastric & pancreatic lipases



Emerging Evidence for Broader Applications in Complex Health Conditions

GLP-1 Impacts Beyond Diabetes, Obesity, CV Risk, and OSA

While GLP-1 receptors are concentrated in the pancreas, they are spread throughout the body-and evidence is growing that GLP-1 drugs can interact directly with GLP-1 receptors found in other organs.

Brain

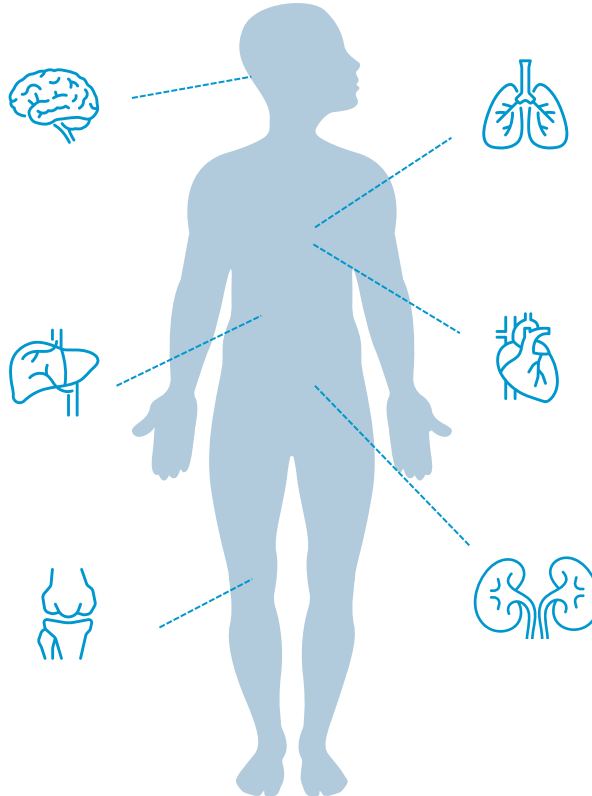
May reduce addictive disorder and potentially play a role in slowing neurodegenerative diseases such as Alzheimer's

Liver

May reduce progression to cirrhosis in patients with fatty liver disease

Bone

May positively impact joint pain and function



Respiratory

May reduce symptoms of obstructive sleep apnea

Heart

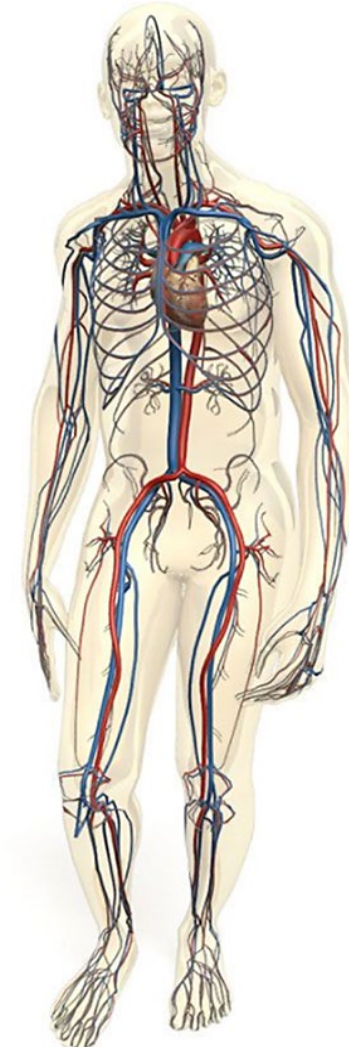
May reduce inflammation in the heart and circulatory system

Kidneys

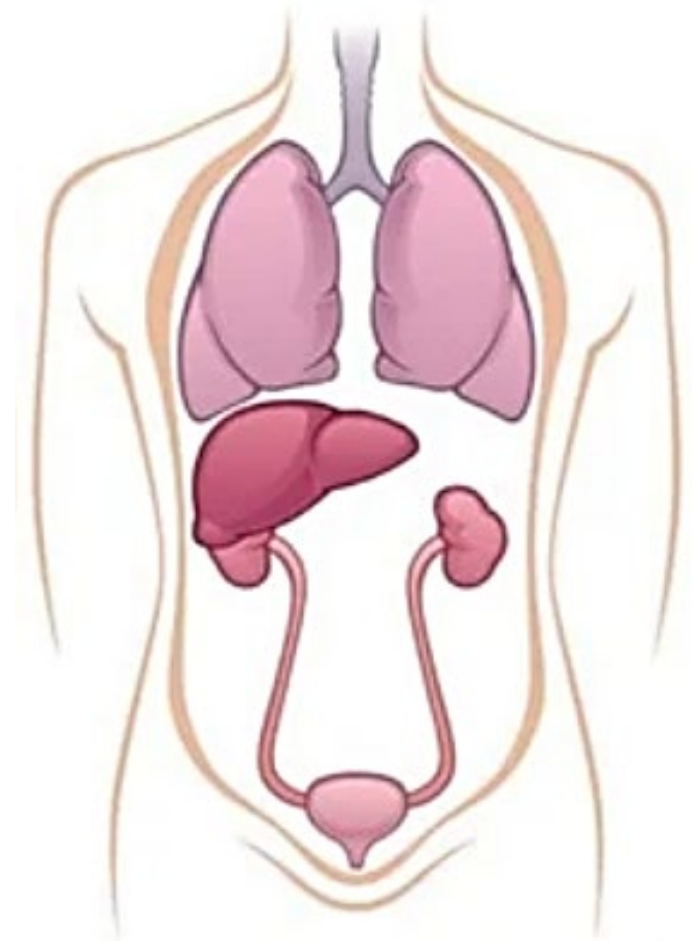
May reduce risk of kidney failure in those with chronic kidney disease

Source: Adapted from <https://www.troweprice.com/personal-investing/resources/insights/new-diabetes-and-obesity-drugs-show-promise-for-patients-and-investors>.

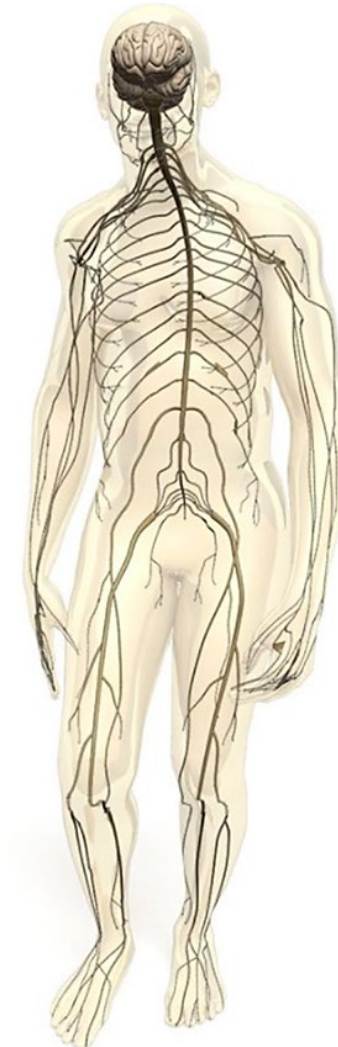
- Improved glycemic control in type 2 diabetes
 - Lowered HbA1c by $\approx 1\%$
- Reduced major CV events by 20% (SELECT trial)
 - CV-related death
 - Nonfatal MI
 - Nonfatal CVA
- Reduced blood pressure & cholesterol



- Decreased risk of major kidney events by 24% (FLOW trial)
 - Kidney failure
 - Dialysis
 - Transplant
- Decreased progression to cirrhosis in fatty liver disease
- Reduced symptoms of obstructive sleep apnea



- May impact addictive behavior
 - Drug/opioid
 - Alcohol
 - Smoking
- Reduce Hunger (centrally acting)
- May slow progression of Alzheimer's disease
 - Evoke & evoke+ are assessing the potential neuroprotective effects of semaglutide in early Alzheimer's



- Impact on musculoskeletal pain
- Impact on physical function
- May impact bone metabolism
 - Inhibit osteoclast function
 - Promote bone formation





Challenges and Considerations

Per data presented at an obesity conference in November,
Semaglutide in people with overweight/obesity and cardiovascular disease
was associated with:

11%
less likely to be
hospitalized
for any reason

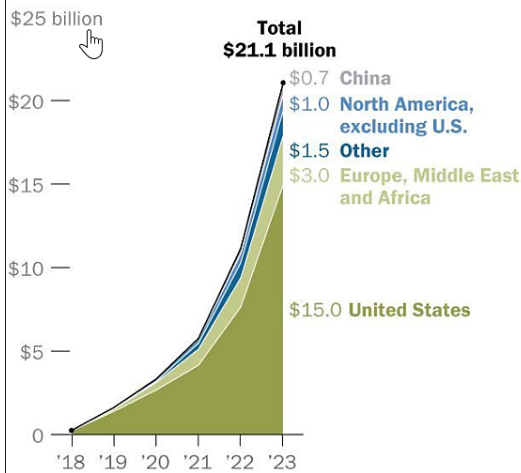
Decreased
hospitalizations
for CV causes by
17%



\$100 Billion Dollar Market Share Opportunity

Weight-loss drug sales reach 5-year high

Combined annual sales for Ozempic, Rybelsus and Wegovy, in billions of U.S. dollars



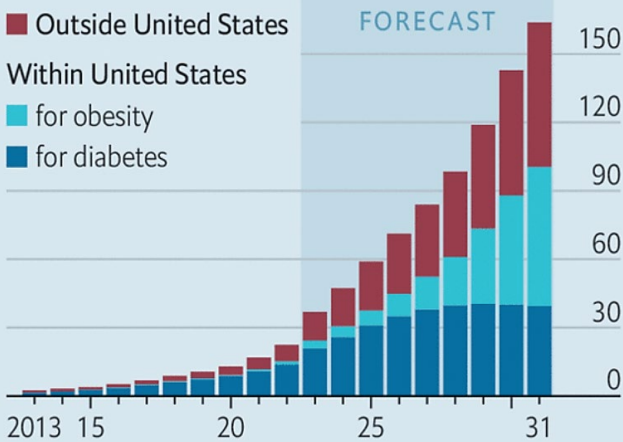
Note: Figures converted from Danish kroner to U.S. dollars, at rate of 1 krone = \$0.145.

Source: Novo Nordisk annual reports, accessed through U.S. Securities and Exchange Commission's EDGAR database.

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Insatiable appetite

GLP-1* sales, \$bn



Source: Jefferies

*Glucagon-like peptide-1 receptor agonist

The Economist

Driving Non-pharmaceuticals Market Entrance



[V] I V I M

Compounded tirzepatide \$375
now **\$299**/mo

Schedule Free Consult



TelyRx
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bound™ (tirzepatide) presc...

Prescribed 100% online

No appointments

No insurance

Next-day delivery



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delivered next d...
Starting at \$1379...

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LifeMD[®]
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Your Body
Weight
Only \$129[^]/month**

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Questions?





Thank you!



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