Ozempic®

The science, the medicine, and the marketing

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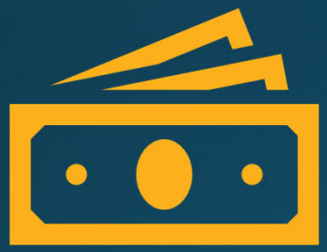
Disclosures



No financial interests to disclose

Not a physician, no medical advice

Ozempic – Today's blockbuster

- Originally designed to treat Type 2 (adult onset) diabetes
- Still widely prescribed for this indication
- Some weight loss was expected, but the actual amount of weight loss surprised physicians and researchers
- Now widely prescribed for weight loss
- One in six Americans now takes one of the drugs in this class

The Ozempic family of drugs

- **Semaglutide**: Brand names Ozempic and Rybelsus
  - Novo Nordisk
- **Dulaglutide**: Brand name Trulicity
  - Eli Lilly
- **Exenatide**: Brand names Byetta and Bydureon
  - Amylin/Bristol Myers Squibb
- **Liraglutide**: Brand names Victoza and Saxenda
  - Novo Nordisk
- **Lixisenatide**: Brand name Adlyxin
  - Sanofi-Adventis
- **Tirzepatide**: Brand name Mounjaro/Zepbound
  - Eli Lilly

The Science

A quick reminder/orientation

- Diabetes comes in two forms
- Type 1
  - Uncommon
  - Typically childhood onset
  - Comes from an autoimmune destruction of the insulin producing cells in the pancreas – no insulin is made
  - Treated with insulin administered by injection
- Type 2
  - Very common
  - Typically adult onset
  - Results from the body being unable to use the insulin that's made
  - "Insulin resistant" diabetes
  - Treatment beyond diet and exercise has been difficult

The beginning – diabetes and the Incretin effect

- It was long recognized that diabetes was a failure to regulate blood sugar, which is normally tightly controlled
- Insulin, produced by the pancreas, was recognized as an important regulator of blood sugar in the 1920's
  - Revolutionary treatment for Type 1 (childhood) diabetes
- However, it was shown early on that the pancreas was not the only organ involved in controlling blood sugar
- Something in the gut (stomach and intestines) also played a major role in this process, as demonstrated by the Incretin Effect

The Incretin Effect

- Having a person drink a dose of glucose produced a very different blood sugar response than giving a person the same dose of glucose by intravenous injection
- In normal people, oral consumption produces a gradual, well controlled rise in blood sugar levels, while intravenous administration leads to a rapid, very large spike in blood sugar
- Something from our gut controls blood sugar
- What was this gut-derived substance?

Human physiology studies

- Two compounds produced by the gut were shown to be (mostly) responsible for the Incretin Effect
- GIP –
  - Glucose-dependent Insulinotropic Polypeptide
  - Shown to be partly responsible for the Incretin Effect in the 1970's
- GLP-1
  - Glucagon-like peptide 1
  - Named because of its similarity to glucagon, a well-known hormone produced by the brain that controls metabolism, appetite, and eating

Interest in GIP and GLP-1 for Type 2 diabetes, but…

- Both are peptides (small proteins)
- Proteins are efficiently digested in the stomach and otherwise rapidly metabolized
- Thought to be not competitive with oral diabetes medications of the time

Enter the Gila Monster

Gila Monsters

- Venomous reptile, native of Mexico and the Southwest United States
- Venom contains a complex mix of substances with a wide array of biological effects
- Jean-Pierre Raufman and John Eng went through these substances looking for those with potential medical uses
- A substance purified from this venom, designated Exendin-4, was shown to produce a slow, extended rise in blood sugar in diabetic mice, mimicking the gut-derived substance responsible of the Incretin Effect
- Exendin is a small protein, and development of Exendin-4 as a treatment for diabetes was undertaken by Amylin Pharmaceuticals

Exendin-4

- Exendin-4 as a drug treatment was initially delayed because it was felt that injecting people with a component of a poisonous venom would have difficulty gaining public acceptance
- Medical institute where Raufman and Eng worked declined to file a patent
- Development of derivatives of Exendin-4 that might possess improved pharmacological effects continued
- Eventually, modified Exendin-4 became Byetta, made by BMS
- In the meantime…..

Glucagon-like peptide (GLP-1)

- Existence of GLP-1 was discovered by Joel Habener
  - He happened upon two cloned genes that were similar to the glucagon gene but unlike glucagon, which is made in the brain, these were made in the gut
  - Named them glucagon-like peptides 1 and 2 (GLP-1 and GLP-2)

- GLP-1 protein (the product of the GLP-1 gene) was first purified in quantity and shown to normalize blood sugar by Svetlana Mojsov
  - Showed it stimulated pancreatic insulin secretion at 1/100th the concentration of GIP
  - Now recognized to be the major contributor to the Incretin Effect

GLP-1 to Ozempic

- GLP-1 itself is not suitable as a drug
- The goal was to make a molecule that acted like GLP-1 but was useful as a drug
- The effort to turn GLP-1 into a usable drug was led by Lotte Knudsen at Novo Nordisk
- Habener, Mojsov, and Knudsen awarded 2024 Lasker Award

GLP-1 receptor

- GLP-1 acts by binding to and turning on a receptor on specific cells in the body beyond the gut
  - GLP-1 is a so-called agonist for the GLP-1 receptor
- The GLP-1 receptor is G-protein coupled receptor (GPCR)
  - An important class of molecules that sense signals outside the cell and cause a change of activity inside the cell
  - Humans have about 1000 different GPCR's, many with multiple effects
  - Over a third of all approved drugs act on a GPCR of one type or another
- Can you make a useful drug that turns on this receptor, and thus mimics the effects of GLP-1 itself?

Modifying GLP-1

- Major work done at Novo Nordisk, the leading producer of insulin
  - Had previously made derivatives of insulin with improved properties
- Natural GLP-1 is a small protein (peptide), a chain of 34 amino acids
- Ozempic has amino acid #8 modified to render it resistant to cleavage that takes place as part of its natural breakdown in the body
- Ozempic also has amino acid #34 modified so it binds to albumin, a major protein in the blood, greatly increasing its persistence in the blood circulation
- It's still a protein, and thus susceptible to digestion in the stomach
  - Weekly injection required

An oral form of Ozempic

- How to overcome digestive enzymes in the stomach?
  - Needs to be absorbed in the stomach
  - Not enteric coated (which causes medicines to bypass the stomach)
  - Contains SNAC that acts as an absorption enhancer in the stomach itself
- Higher dose
- Take it daily rather than weekly
- Commercial name Rybelsus®
- Results in less weight loss than Ozempic

Questions?

The Medicine

Current Medical Practice

- There are now a total of six GLP-1 mimic drugs, put into 10 different formulations, each with a different trade name
- All act by the same biological mechanism – they turn on the GLP-1 receptor
- These drugs were developed for Type 2 diabetes and are widely prescribed for this indication
  - Significantly lower A1C levels – modified hemoglobin, a measure of long-term high blood sugar
- Some are currently approved for weight loss, others are used off-label for weight loss
- The amount of weight loss varies in different individuals
- Ozempic, which many feel has the strongest effects on weight, can result in loss of up to 25% of body mass
- All of these drugs reduce appetite and produce a sensation of satiety
  - You eat less

Side effects

- Many side effects occur at the onset of use
- Gastrointestinal - Nausea, vomiting, diarrhea, constipation
- Less common – pancreatitis, gall bladder problems, low blood sugar
- Loss of hedonic aspects of food
  - The "pleasure of eating"
- Cosmetic changes
  - "Ozempic face"

Ozempic face

You look thinner, but you look older

These drugs have become extremely popular in the entertainment industry, but Ozempic face is seen as a problem

An entire area of cosmetic and plastic surgery has now developed to address Ozempic face

Other clinical issues

- Once someone starts taking these medications, they're on them for life
- Cessation of drug results in re-gain of the weight
- Assuming the drug is effective and well tolerated, patients are committed to continuously paying for them

- These drugs now appear to improve a number of health parameters, even though they're not yet FDA approved for those indications
- Example: December 20, 2024 Zepbound® approved for sleep apnea

Surprising applications

- Ozempic and related drugs act by reducing the craving for food
  - Exactly how they do this is not fully understood
- Could they reduce the craving for other things?
- Animal studies showed administration of Ozempic reduced alcohol consumption
- Studied 1.3 million people taking these drugs over 8 years
- Use was associated with 50% reduction in binge drinking
- Use was associated with 40% reduction in opioid use
- Still an association, rather than a proven cause and effect, but exciting

Questions?

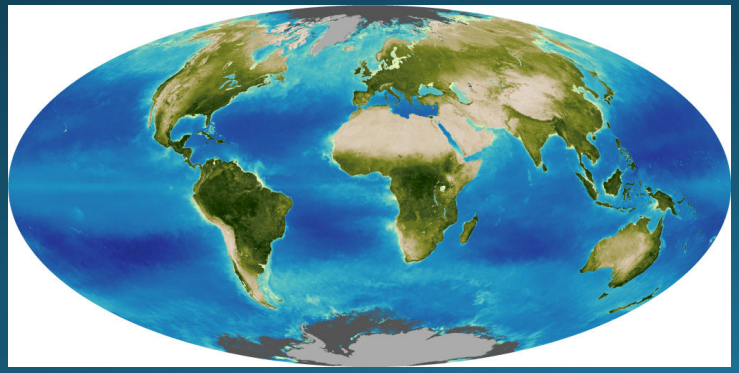
The Marketing

Ozempic and relatives – Economic importance

- Nominally expensive - $2,500 - $12,000 per year
  - Most covered by insurance
  - Out of pocket expenses much lower, often ~ $25/month
- Current annual sales $47 Billion
- Will become the best-selling class of drugs worldwide this year
- Sales are estimated to rise to $135 Billion in the 2030's

But even more…

- An enormous future market
- By 2035 it's estimated that half the world's population will be overweight or obese
  - Ultimate market may be as large as 3.5 billion people



Pharmaceutical marketing

- Direct-to-consumer advertising now widespread in the pharmaceutical industry
- The primary message of most GLP-1 advertisements has been focused on Type 2 diabetes
- However, all make some mention of weight loss, even if they're not approved by the FDA for weight loss
- Ozempic and other GLP-1 drugs have their own internet domain names
- Ozempic.com

From the Ozempic.com website:

The company's website still de-emphasizes weight loss:

"Lowering A1C is an important part of managing type 2 diabetes. But so is managing your potential risk of major cardiovascular (CV) events if you also have known heart disease. **Ozempic®, along with diet and exercise, is proven to improve blood sugar in adults with type 2 diabetes. In adults with type 2 diabetes and known heart disease, Ozempic® reduces the risk of major cardiovascular events such as stroke, heart attack, or death. You may also lose some weight.**"

Future trends

- Manufacturers of these drugs will continue to seek FDA approval for additional indications
- Manufacturers will focus on serious health conditions other than obesity
  - Insurance reimbursement
- These drugs are chemically synthesized. Although these syntheses are complex, generic forms will start to become available
- Approval of generics will bring prices down

Questions?