GLP-1 AGONISTS: A NEW FRONTIER IN MEDICINE

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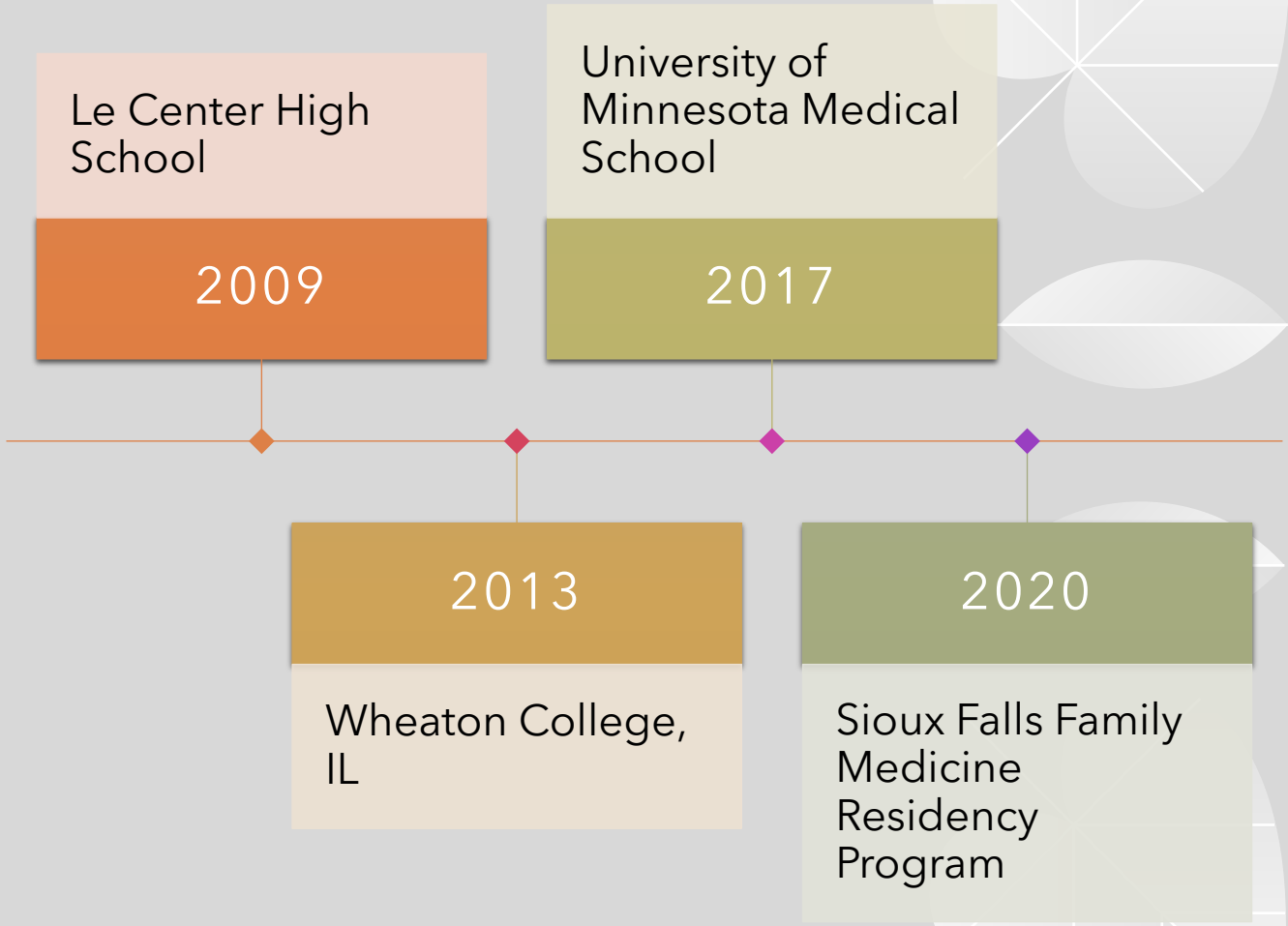
WHO ’S THIS GUY?

Hello, my name is Jay Joseph Allen



Yeah, but what do you do?

- Family Physician with Obstetrics at Essentia Health, Duluth
- Started as core faculty at the Duluth Family Medicine Residency Program in 2022
- Currently split my time 50/50 between the two roles

I'VE ALSO GOT AN AMAZING WIFE AND SOME PRETTY GREAT KIDS

DISCLOSURES

I have no relevant disclosures.

WHY THIS LECTURE?

Why is there so much press coverage?

I'm not going to…

Educate on prescription patterns or how to counsel patients on GLP-1's.

Talk about dose adjustments and micromanagement.

Discuss side effects, contraindications, safety in pregnancy/lactation etc.

Say anything about why you should prescribe these medications (pet peeve).

I'm going to…

Show why it feels that these medicines are overwhelming.

Explain how these medicines have evolved over time.

Review substantial evidence on GLP-1 agonist efficacy across the spectrum of indications.

Raise concern on how these medicines offer some significant societal challenges.

A brief word on biostats…

- Hazard Ratio (HR): The chance of a chosen event over the study period.
  - HR 0.5 = 50% less likely to happen
  - HR 2.0 = 2x more likely to happen
- Odds Ratio (OR): A measure of the odds of an event happening in one arm of the study compared to the other.
  - OR >1: More likely to happen
  - OR <1: Less likely to happen

Outline

- A Brief History of GLP-1 Agonists' brief history
- Physiology/Pharmacology of GLP-1
- Diabetes management with GLP-1 agonists
- Mounting Weight-based Indications from the Literature
- Addiction Medicine
- Pitfalls

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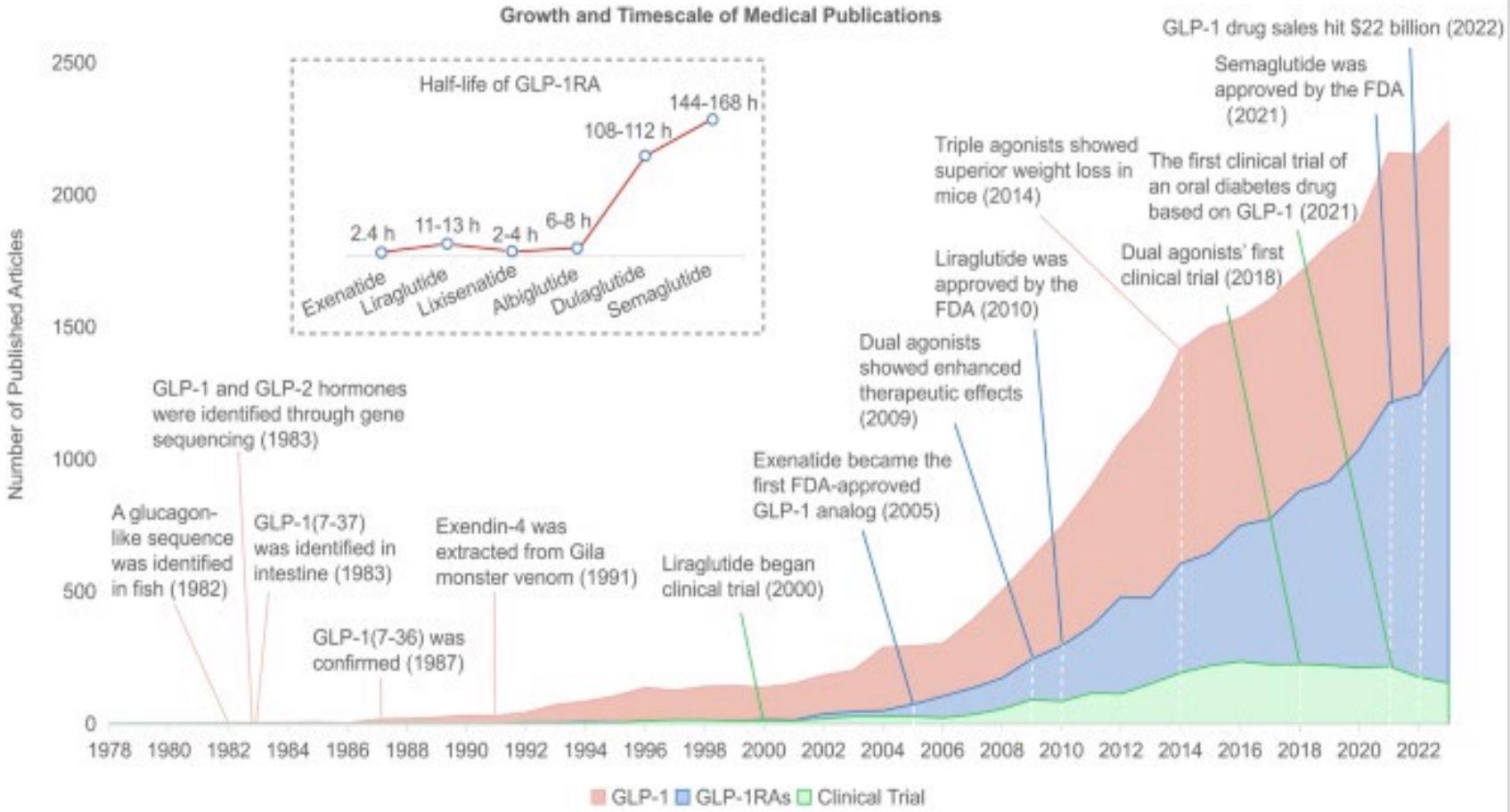
What is your opinion of GLP-1 agonists?

ⓘ Start presenting to display the poll results on this slide.

BACK IN MY DAY…

….2014

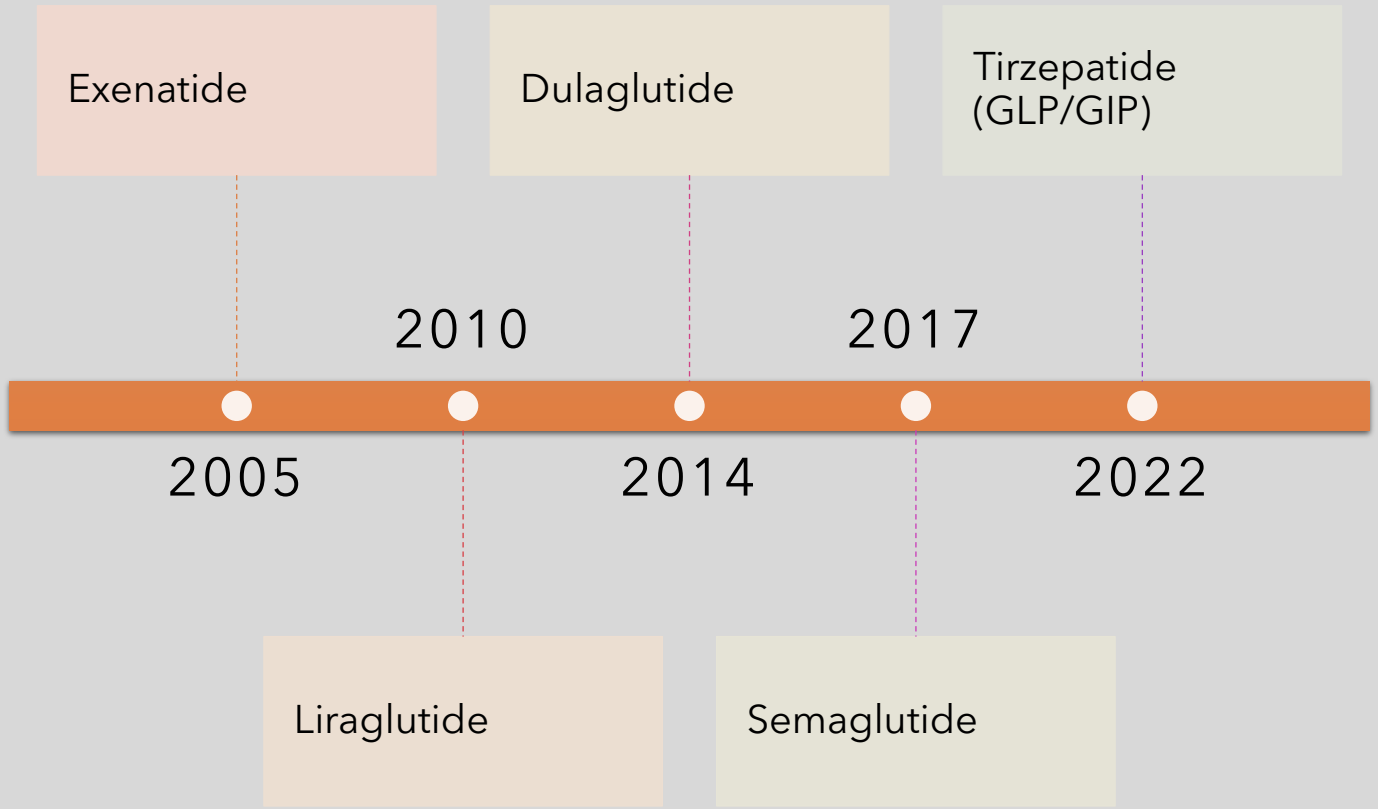


SINCE THEN, RESEARCH HAS

EXPLODED

NATURE, GLUCAGON-LIKE PEPTIDE-1 RECEPTOR: MECHANISMS AND ADVANCES IN THERAPY. SEPTEMBER 2024

FDA Approval Dates for Diabetes



Why do they seem better now?

GLP-1RA Agents Suggested Comparative Doses for Treating Type 2 Diabetes												
Medication	**Dosing Route and Interval**	**Comparative doses**										
Tirzepatide¶	SC Weekly			2.5mg			5mg		7.5mg	10mg	12.5mg	15mg
Semaglutide*	SC Weekly		0.25mg	0.5mg		1mg		2mg				
Dulaglutide*	SC Weekly		0.75mg‡	1.5mg	3mg	4.5mg						
Exenatide XR	SC Weekly			2mg								
Semaglutide	PO Daily	3mg	7mg	14mg								
Liraglutide*	SC Daily	0.6mg	1.2mg	1.8mg								

Adapted from: Whitley HP. *Clinical Diabetes*. 2023;41(3):467-473.

Indicates an initiation dose **NOT** meant for glycemic control. Requires titration.

Indicates a therapeutic dose

*** Indicates a medication with proven cardiovascular disease (CVD) benefits**

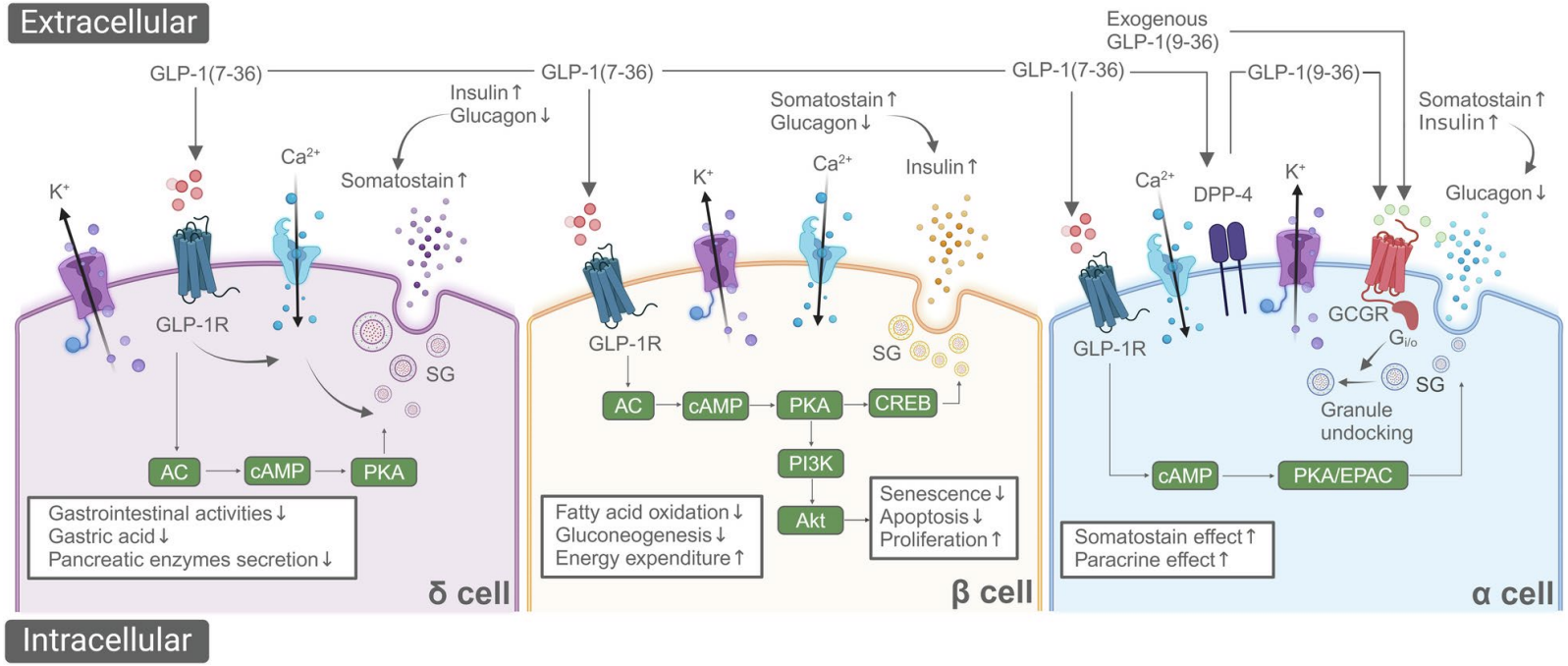
¶ Tirzepatide has **NOT** yet been shown to benefit CVD. Studies are ongoing.

‡ Dulaglutide 0.75mg has **NOT** been shown to benefit CVD

Beth Israel Lahey Health Conversion and Therapy Gap Management Guide

BILH-GLP1RA-Conversion-Guide.pdf

HOW DO THEY WORK?



BUT HOW DO THEY WORK?!

NATURE, GLUCAGON-LIKE PEPTIDE-1 RECEPTOR: MECHANISMS AND ADVANCES IN THERAPY. SEPTEMBER 2024

Psst…

You'll lose them if you talk about that basic science stuff.

You don't really understand it, anyway.

Focus on the effects.

BUT HOW DO THEY WORK?!

NATURE, GLUCAGON-LIKE PEPTIDE-1 RECEPTOR: MECHANISMS AND ADVANCES IN THERAPY. SEPTEMBER 2024

But how do they work?

Focusing on effects

Actions of GLP -1 and GIP Relevant to Glucose Control	GLP-1	GIP
Pancreas		
Stimulates glucose-dependent insulin release	+	+
Increase insulin biosynthesis	+	+
Inhibits glucagon secretion	+	-
Stimulates somatostatin secretion	+	-
Induces β-cell proliferation	+	+
Inhibits β-cell apoptosis	+	+
Gastrointestinal Tract		
Inhibits gastric emptying	+	-
Inhibits gastric acid secretion	+	+
Central Nervous System		
Inhibits food and water intake	+	-
Promotes satiety and weight loss	+	-
Cardiovascular System		
Improves cardiovascular function after ischemia	+	-
Adipose Tissue		
Insulin-like lipogenic actions	-	+
Lipid storage	-	+

Source: Marks Basic Medical Biochemistry

BUT…
DO THEY WORK?

Do you have any evidence, sir?

EVIDENCE FOR GLP-1 AGONISTS IN DIABETES

Indication	Medicine	Study (Date published)	Key Outcome
A1c reduction			
	Liraglutide	LEAD (2009)	- 1.0%
	Dulaglutide	AWARD (2014)	- 1.59%
	Semaglutide (1.0 mg)	SUSTAIN (2017)	- 1.53% (-1.86% in SURPASS-2)
	Tirzepatide	SURPASS-2 (2021)	- 2.30%
Adverse Cardiac Outcomes (in DM)			
	Liraglutide	LEADER (post-hoc)	0.78 HR CV Death
	Dulaglutide	REWIND (2019)	0.88 HR Composite
	Semaglutide	SUSTAIN-6 (2016)	0.74 HR Composite
Renal Protection (in DM)			
	Liraglutide	LEADER (post-hoc)	0.78 HR Nephropathy
	Dulaglutide	REWIND (2019)	0.85 HR Nephropathy
	Semaglutide	FLOW (2024)	Lower rate of EGFR change (1.16 eGFR/yr)

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Each medicine has shown reduction in all-cause mortality

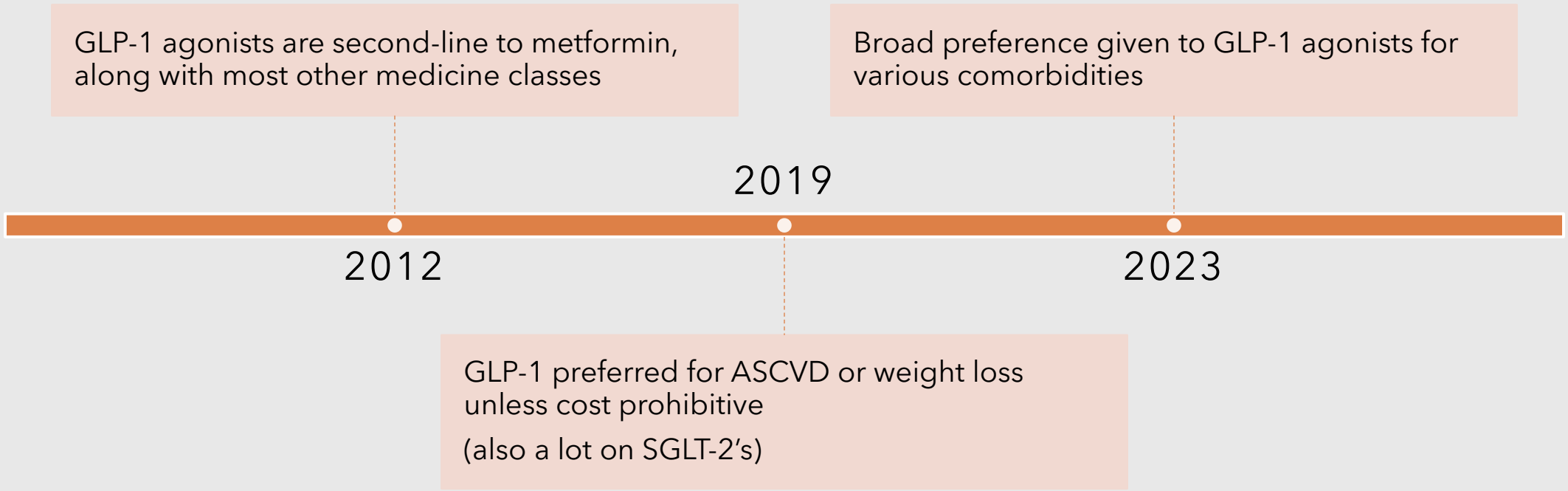
But more importantly…

EVIDENCE
GLP-1
NISTS
ABETES

All-Cause Mortality Reduction

Medicine	All-Cause Mortality Reduction
Liraglutide	0.85 HR
Dulaglutide	0.90 HR (p=0.067)
Semaglutide	0.80 HR
Tirzepatide	0.58 AHR (retrospective cohort study)

ADA Guideline Implementation



AND THEN CAME THE WEIGHT LOSS STUDIES

They're pretty significant.

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Which adverse outcome(s) associated with obesity have GLP-1 agonists been shown to improve?

ⓘ Start presenting to display the poll results on this slide.

Which adverse outcome(s) associated with obesity have GLP-1 agonists been shown to improve?

- Coronary artery disease
- Congestive Heart Failure
- Hypertension
- Obstructive Sleep Apnea
- Osteoarthritis
- Type 2 Diabetes Mellitus
- Metabolic Dysfunction Associated Steatohepatitis (MASH)

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Obesity and its many risks

- Coronary artery disease
- Congestive Heart Failure
- Hypertension
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- Most studies published in NEJM or BMJ

OF NOTE

I am not going to focus on weight loss as a benefit of these trials, despite all showing significant weight loss.

All statistically significant improvements will focus on other patient-oriented outcomes associated with obesity.

Obesity and its many risks

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SELECT Trial (2023)

Semaglutide

- Inclusion Criteria
  - Patients with BMI >27
    - Average BMI 33.3
  - CV Disease
    - 68% with prior MI
    - 18% with prior stroke
    - 8% with more than one
  - NO diabetes

Obesity and its many risks

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SELECT Trial (2023)

Semaglutide

- Lower Composite CV End Point (HR 0.80)
- Lower Heart failure composite end point (HR 0.82)
- Lower All cause mortality (HR 0.81)
- Almost significant lower CV mortality (HR 0.85, p=0.07)

TAKE A BREAK SLIDE – DULUTH FAUNA

Obesity and its many risks

- Coronary artery disease
- Congestive Heart Failure
- Hypertension
- Obstructive Sleep Apnea
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SUMMIT Trial (2025)

Tirzepatide

- Inclusion Criteria
  - 40 years and older
    - Average 65
  - BMI >30
    - Average 38
  - EF >50%
    - Average 61
  - Decompensation episode within the last 12 months OR EGFR <70 ml/m/1.73m2

Obesity and its many risks

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- Osteoarthritis
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SUMMIT Trial (2025)

Tirzepatide

- Lower Composite (0.62 HR)
- Decreased Hospitalization (0.44 HR)
- Improved KCCQ-CSS Score (+6.9)
- 6-minute walking distance (+18.3 m)

Obesity and its many risks

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- Congestive Heart Failure
- Hypertension
- Obstructive Sleep Apnea
- Osteoarthritis
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SUMMIT Trial (2025)

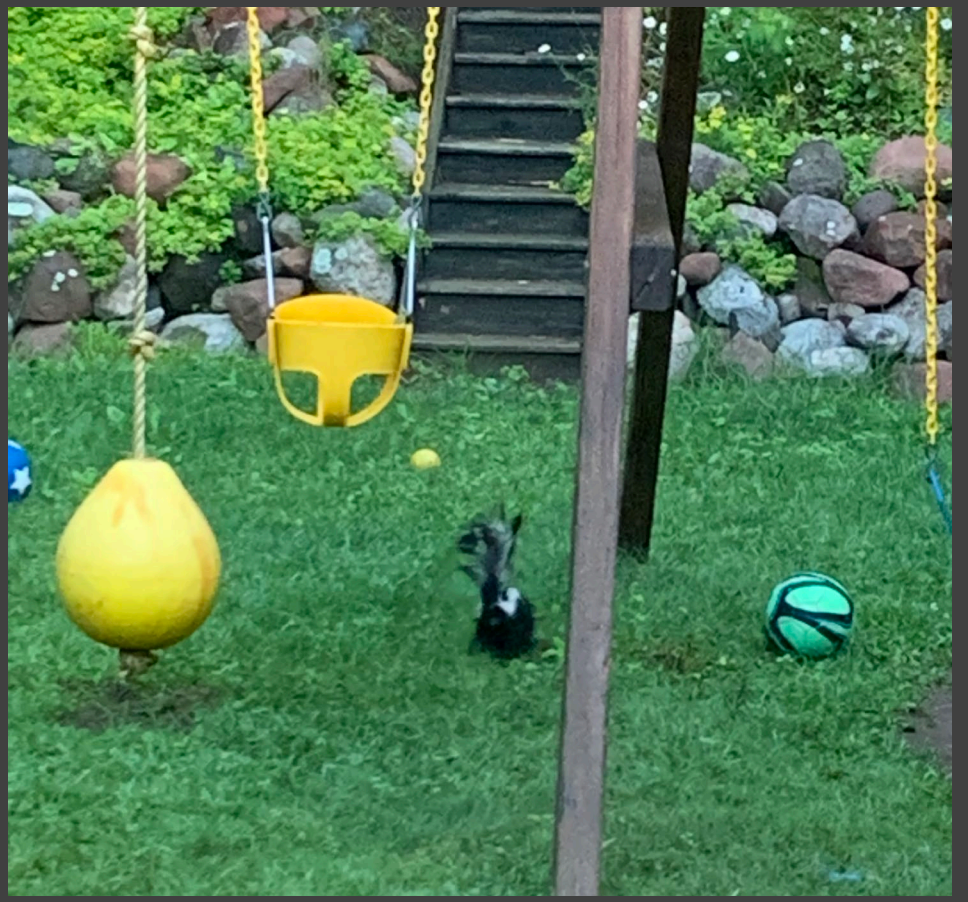
Tirzepatide

- Systolic BP reduction (- 4.6 mmHg)

SELECT Trial (2023)

Semaglutide

- Systolic BP reduction (- 3.31 mmHg)
- Diastolic BP reduction (- 0.55 mmHg)



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Obesity and its many risks

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SURMOUNT-OSA Trial (2024)

Tirzepatide

- Apnea-Hypopnea index
  - Tirzepatide: - 25.3 events/hr
  - Placebo: - 5.3 events/hr
- Systolic blood pressure
  - Tirzepatide: - 9.5 mmHg
  - Placebo: - 2.1 mmHg

Obesity and its many risks

- Coronary artery disease
- Congestive Heart Failure
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- Obstructive Sleep Apnea
- Osteoarthritis
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STEP 9 Trial (2024)

Semaglutide

- Reduction in WOMAC score (Max 96)
- Percentage of participants with
  - >30 point reduction
    - Semaglutide: 77.6
    - Placebo: 57.8
  - >50 point reduction
    - Semaglutide: 65.2
    - Placebo: 35.3

Obesity and its many risks

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- Congestive Heart Failure
- Hypertension
- Obstructive Sleep Apnea
- Osteoarthritis
- Type 2 Diabetes Mellitus
- Metabolic Dysfunction Associated Steatohepatitis (MASH)

SURMOUNT-1 Trial (2024)

Tirzepatide

- PREVENTION (over 176 weeks)
- New onset Type 2 Diabetes Mellitus
  - Tirzepatide: 1.3%
  - Placebo: 13.3%
  - Tirzepatide HR: 0.07
  - Metformin HR: 0.83

TAKE A BREAK SLIDE – DULUTH FAUNA

Obesity and its many risks

- Coronary artery disease
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- Metabolic Dysfunction Associated Steatohepatitis (MASH)
  - AKA NASH
    - Non-alcoholic steatohepatitis
  - I'm gonna focus on this for a minute.
  - Prevalence increasing
    - 2010: 1.51%
    - 2020: 2.79%
  - And most of all…

Obesity and its many risks

- Coronary artery disease
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Notoriously difficult to treat

Obesity and its many risks

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Newsome et al. 2020

Semaglutide (0.4 mg max dose)

- Resolution of NASH with no worsening of fibrosis (6.87 OR)
  - 59% with 0.4 mg
  - 36% with 0.2 mg
  - 40% with 0.1 mg
  - 17% with placebo

ANOTHER FRONTIER: ADDICTION

How do these medicines help addiction? I thought they were just endocrine?

How GLP-1 is related to addiction

"Several preclinical studies have described the role of GLP-1 in reward processing, stress regulation, and cognitive function, collectively suggesting that targeting the GLP-1 system may represent a novel pharmacotherapeutic approach for ASUDs." – Bruns et al

What research exists?

- Alcohol use disorder: Studies are mounting
- Stimulant use disorder: Lots of animal studies
- Opioid use disorder: Lots of animal studies

Alcohol use disorder

Cohort study in Nature 2024: 0.44 HR recurrent AUD diagnosis in 12 months (semaglutide)

RCT Feb 2025 in JAMA: significantly less alcohol consumption at 8 weeks (semaglutide)

Cohort study in JAMA psych Nov 2024:

0.64 aHR (semaglutide) and 0.72 (liraglutide) decreased risk hospitalization

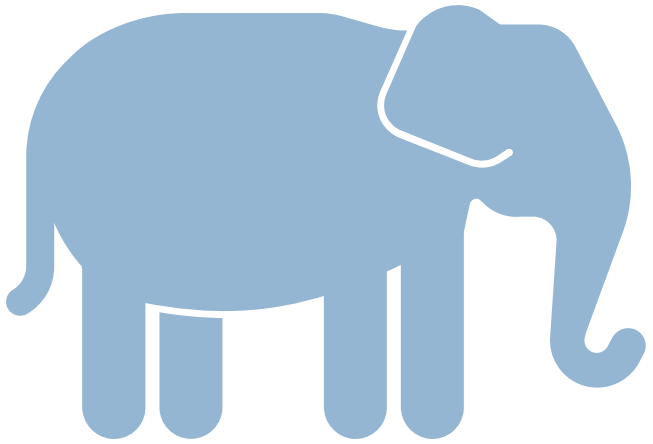
Disulfiram: 0.98 (0.96-1.00) aHR

Acamprosate 1.11 aHR

Naltrexone: 0.86 aHR

Summary

- GLP-1 agonists have clinical trials to demonstrate benefit in:
  - Diabetes (all-cause mortality)
  - Many conditions associated with obesity
  - Alcohol use disorder (with more to come on other addictions)



TO ADDRESS THE ELEPHANT IN THE ROOM…

Pitfalls

- Cost
  - Individually
  - Societally
- Novelty
- Cultural effect

Pitfall: Cost per month

Diabetes

Victoza (liraglutide): $857

Trulicity (dulaglutide): $977

Ozempic (semaglutide): $997

Mounjaro (tirzepatide): $1069

Weight loss

Zepbound (tirzepatide): $1,060

Saxenda (liraglutide): $1,349

Wegovy (semaglutide): $1,349

Justice issue.

Individually

This is a justice and equity issue

- Not all insurances are the same
- Preferentially cares for the highest income brackets

Societally

IF we decided to cover this from a single-payer perspective, the cost would be cataclysmic.

Some back of the napkin math:

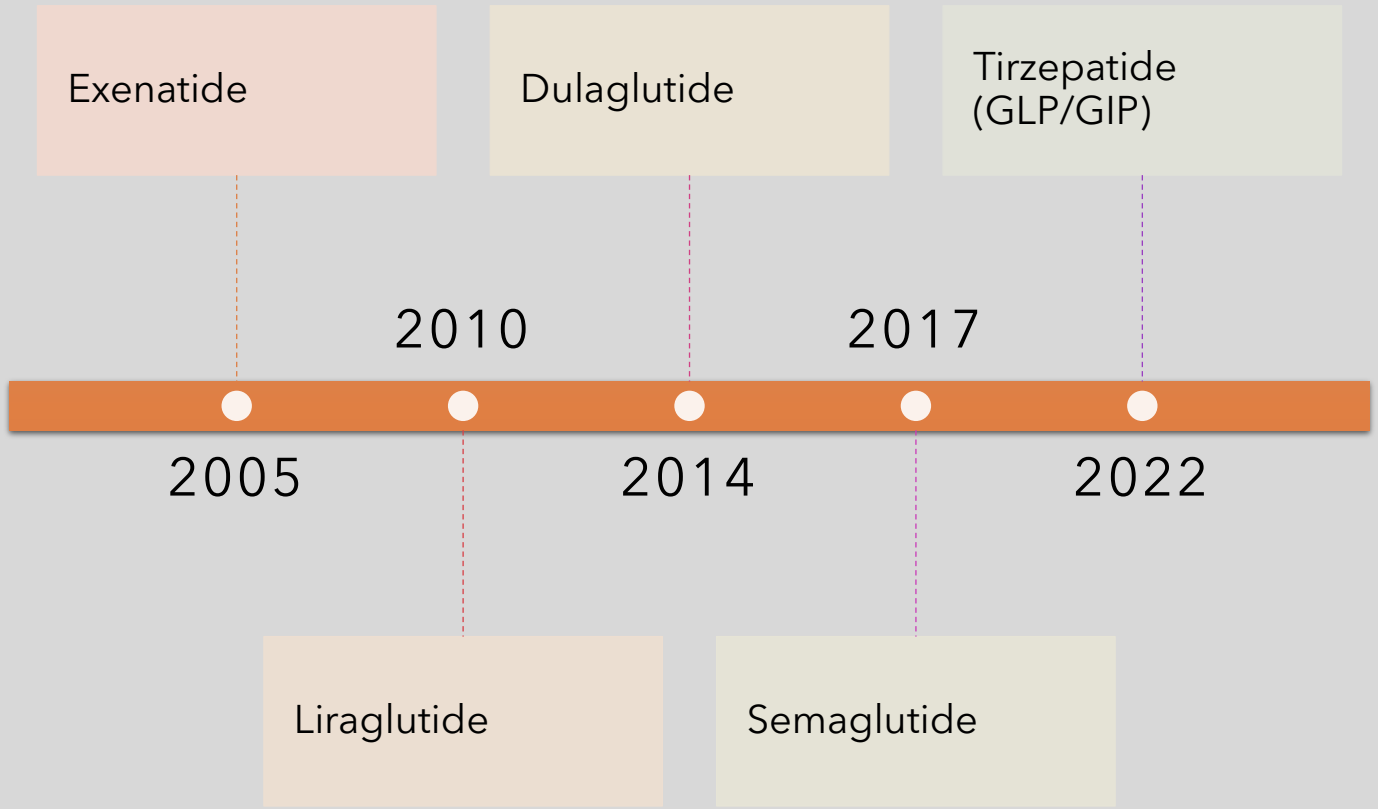
- Diabetes cost
  - ~35 million people with diabetes in the USA
  - Let's say half should be on a GLP-1
  - 17.5 million x $1,069 (mounjaro) = $18.7 billion monthly or $224.4 billion annually

- Predicted 2025 Medicare Part D expenditure
  - $137 billion
  - Source: A Current Snapshot of the Medicare Part D Prescription Drug Benefit | KFF

Another pitfall:

Novelty

Once upon a time…



ANOTHER PITFALL: CULTURAL

"All my friends are on Ozempic... And they look GREAT!"
- BMI 23

Inducing eating disorders for patients?

Increase anti-obese rhetoric?

Fat shaming?

THE PITFALLS ARE NUMEROUS, BUT SO ARE THE BENEFITS.

This is where shared decision-making comes into play.

THANK YOU!

Questions?

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