GLP-1 AGONISTS: A NEW FRONTIER IN MEDICINE

Jay Allen MD
Duluth Family Medicine Residency Program
Essentia Health

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WHO'S THIS GUY?

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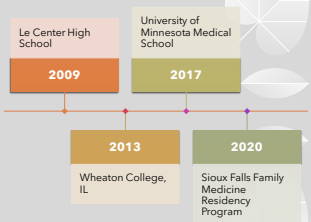
Hello, my name is Jay Joseph Allen



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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

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

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DISCLOSURES

I have no relevant disclosures.

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WHY THIS LECTURE?

Why is there so much press coverage?

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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).

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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.

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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

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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.

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BACK IN MY DAY…

….2014

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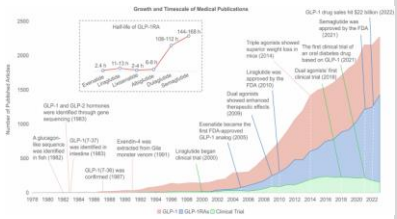

SINCE THEN, RESEARCH HAS

EXPLODED

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

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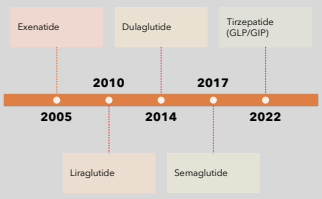
FDA Approval Dates for Diabetes



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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

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HOW DO THEY WORK?

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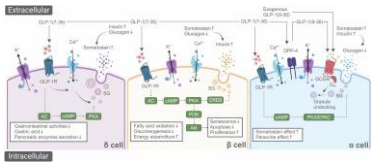

BUT HOW DO THEY WORK?!

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

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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

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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

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BUT…
DO THEY WORK?

Do you have any evidence, sir?

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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)

EVIDENCE FOR GLP-1 AGONISTS IN DIABETES

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Each medicine has shown reduction in all-cause mortality

But more importantly…

EVIDENCE
GLP-1
NISTS
ABETES

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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)

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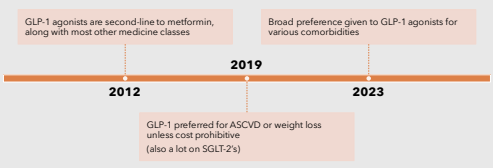
ADA Guideline Implementation



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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.

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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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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**
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Obesity and its many risks

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

- Most studies published in NEJM or BMJ

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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.

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Obesity and its many risks

- **Coronary artery disease**
- Congestive Heart Failure
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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

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Obesity and its many risks

- **Coronary artery disease**
- Congestive Heart Failure
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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)

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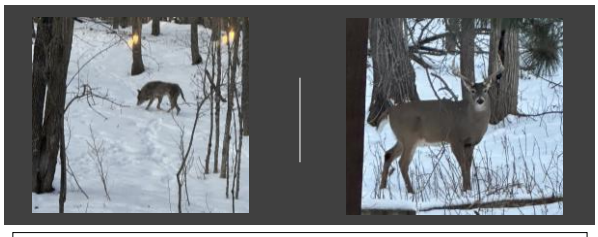

TAKE A BREAK SLIDE – DULUTH FAUNA

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Obesity and its many risks

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

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

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Obesity and its many risks

- Coronary artery disease
- **Congestive Heart Failure**
- Hypertension
- Obstructive Sleep Apnea
- Osteoarthritis
- Type 2 Diabetes Mellitus
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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)

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Obesity and its many risks

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

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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TAKE A BREAK SLIDE – DULUTH FAUNA

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Obesity and its many risks

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

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

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Obesity and its many risks

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

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

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Obesity and its many risks

- Coronary artery disease
- 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*

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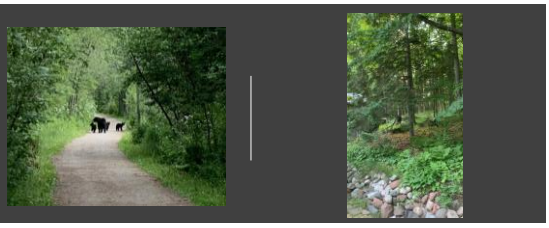

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- Osteoarthritis
- Type 2 Diabetes Mellitus
- **Metabolic Dysfunction Associated Steatohepatitis (MASH)**

- 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…

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Obesity and its many risks

- Coronary artery disease
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- Hypertension
- Obstructive Sleep Apnea
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- Type 2 Diabetes Mellitus
- **Metabolic Dysfunction Associated Steatohepatitis (MASH)**

Notoriously difficult to treat

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Obesity and its many risks

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- Type 2 Diabetes Mellitus
- **Metabolic Dysfunction Associated Steatohepatitis (MASH)**

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

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ANOTHER FRONTIER: ADDICTION

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

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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

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What research exists?

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

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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

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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)

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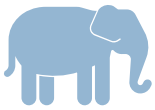

TO ADDRESS THE ELEPHANT IN THE ROOM…

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Pitfalls

- Cost
  - Individually
  - Societally
- Novelty
- Cultural effect

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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

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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.

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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

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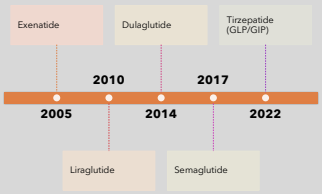
Another pitfall:

Novelty

Once upon a time…



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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?

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THE PITFALLS ARE NUMEROUS, BUT SO ARE THE BENEFITS.

This is where shared decision-making comes into play.

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THANK YOU!

Questions?

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Citations

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