Safety and Efficacy of GLP-1 Receptor Agonists: What Don't They Treat?

Kathryn Pinkney, PharmD, BC-ADM, TTS

Alexis Bogannam, PharmD

Beth Israel Lahey Health
Performance Network

Disclosures

- Kathryn Pinkney: No disclosures
- Alexis Bogannam: No disclosures
- This presentation will include discussion of off-label medication use

Objectives

- Review mechanism of action & metabolic effects of Glucagon-Like Peptide-1 Receptor Agonist Agents (**GLP-1 RA Agents**)
  - Including **both** GLP-1 RA & Dual Glucose-dependent Insulinotropic Polypeptide (GIP)/GLP-1 RA Agents
- Identify FDA-Approved Indications for GLP-1 RA Agents
- Discuss emerging evidence for GLP-1 RA Agent use in non-FDA approved conditions
- Recognize key safety considerations to discuss with patients when initiating a GLP-1 RA Agent
- Apply clinical trial data & guideline recommendations to patient-specific case scenarios

Abbreviations

ADA: American Diabetes Association

ADE: adverse drug effect

ASCVD: atherosclerotic cardiovascular disease

AUD: alcohol use disorder

BMI: body mass index

CV: cardiovascular

CVD: cardiovascular disease

CVOT: Cardiovascular Outcomes Trial

EGFR: estimated glomerular filtration rate

GERD: gastrointestinal reflux disease

GI: gastrointestinal

HF: heart failure

HFpEF: Heart failure with preserved ejection fraction

HFrEF: heart failure with reduced ejection fraction

HLD: hyperlipidemia

KCCQ: Kansas City Cardiomyopathy Questionnaire

MACE: major adverse cardiovascular events

MASH: Metabolic dysfunction-Associated Steatohepatitis

MASLD: Metabolic dysfunction-Associated Steatotic Liver Disease

MEN 2: multiple endocrine neoplasia syndrome type 2

MI: Myocardial infarction

MOA: mechanism of action

MTC: medullary thyroid carcinoma

NYHA: New York Heart Association

OSA: obstructive sleep apnea

PCOS: polycystic ovarian syndrome

RCT: randomized control trial

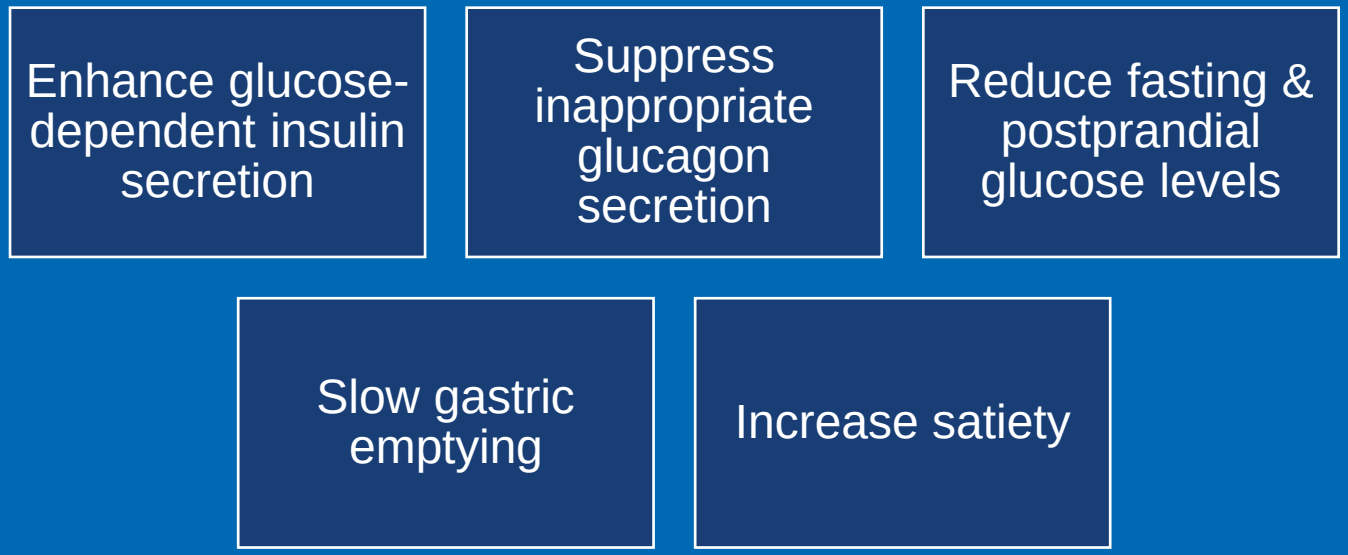
SGLT2: Sodium-Glucose Cotransporter 2

T2DM: type 2 diabetes

MOA of GLP-1 RA Agents

GLP-1 RA Agents known as "Incretin Mimetics"

- Mimic actions of endogenous incretin hormone **Glucagon-like Peptide 1**
- The dual **GIP**/GLP-1 RA Agent **tirzepatide** is also known as a "twincretin" or "dual incretin mimetic"
  - Synergistically amplifies benefits by *also* mimicking **Glucose-dependent Insulinotropic Polypeptide**



MOA of GLP-1 RA Agents, cont.

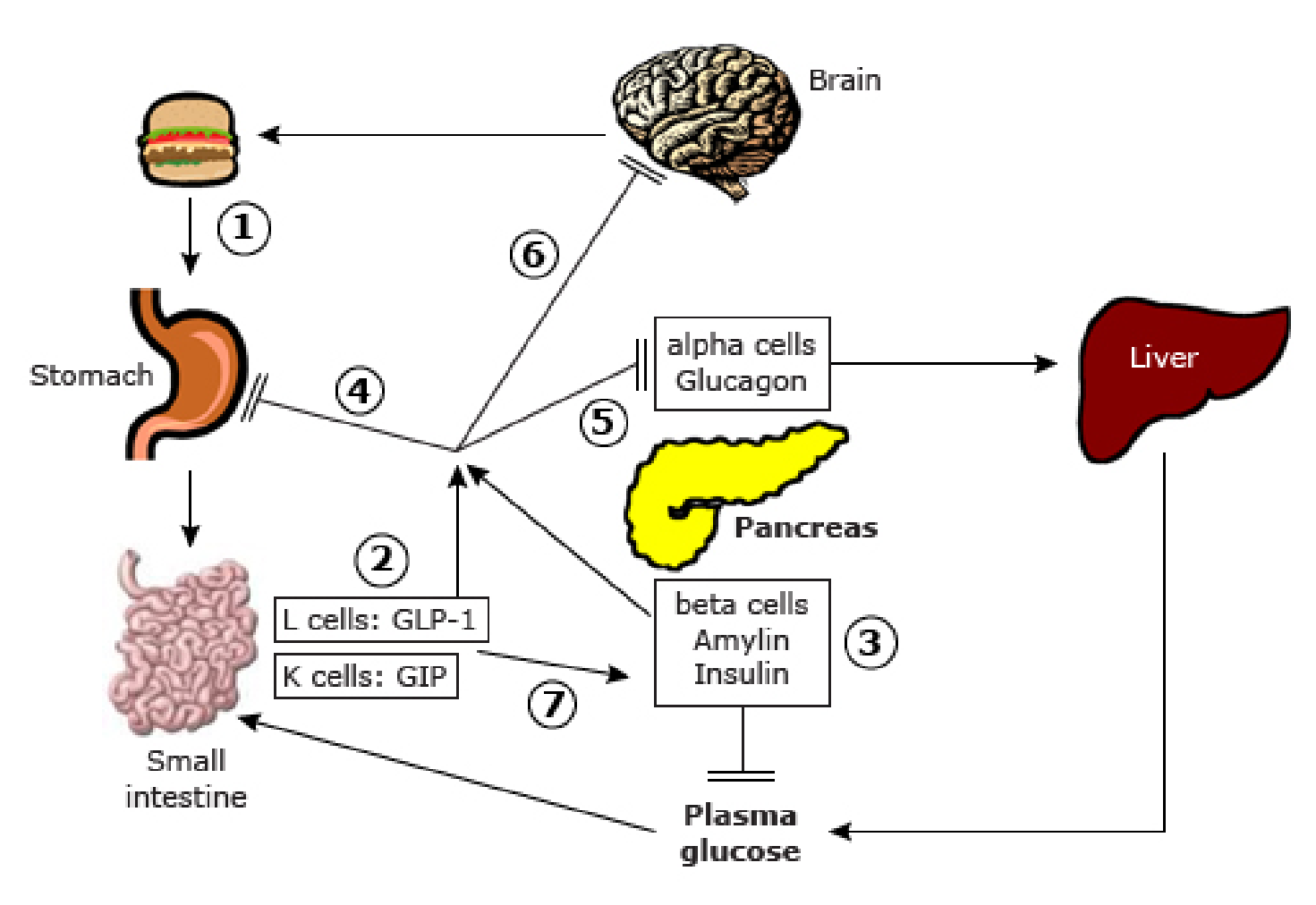


Image courtesy of UpToDate™: "Multihormonal regulation of glucose"

FDA-Approved Indications

Labeled Uses for GLP-1 RA Agents

GLP-1 RA Agents

Generic Name	Brand Name Indicated for T2DM	Brand Name Indicated for Obesity
Tirzepatide	Mounjaro™	Zepbound™
Semaglutide	Ozempic™	Wegovy™
Liraglutide	Victoza™	Saxenda™
Dulaglutide	Trulicity™	N/A

Type 2 Diabetes Mellitus

Efficacy: A1C reduction of **~1 to 2.3%** depending on agent/strength

FDA-Approved Indication for T2DM

- Tirzepatide, Semaglutide (injectable & oral), Dulaglutide, Liraglutide

Key Advantages

- Notable weight loss benefit
- Generally low risk of hypoglycemia
- First line for certain high-risk individuals

Obesity

Efficacy: Mean weight loss of **~7 to 22%** depending on agent/strength

FDA-Approved Indication for Obesity

- Tirzepatide, Semaglutide (injectable only), Liraglutide

Indicated for Adults with Elevated BMI	
BMI $\geq$ 30 kg/m^2	...or BMI $\geq$ 27 kg/m^2 and $\geq$ 1 weight-related comorbidity

Comorbidities
T2DM
HTN
HLD
OSA
CVD

Chronic Kidney Disease

Efficacy: Slowed kidney disease progression, reduced albuminuria, and preserved estimated glomerular filtration rate

FDA-Approved Indication for CKD + T2DM

- **Semaglutide** (injectable only) has shown 24% relative risk reduction in composite renal endpoints including benefit for disease progression
- Consider for T2DM w/CKD regardless of ASCVD

Secondary Endpoint Improvement

- **Dulaglutide & Liraglutide** have shown benefit for secondary renal endpoints; driven mainly by reduction in albuminuria

Under Investigation: Tirzepatide has emerging data to suggest similar benefit in secondary endpoints

Perkovic 2024; Tuttle 2018; Marso 2016; Del Prato 2021

Chronic Kidney Disease

Approved for CKD + T2DM	Encouraging Data	Emerging Data
• Semaglutide (injectable)	• Dulaglutide • Liraglutide	• Tirzepatide

Obstructive Sleep Apnea

Efficacy: Reduction of the **Apnea-Hypopnea Index (AHI)** and of disease severity

FDA-Approved Indication for OSA + Obesity

- **Tirzepatide (Zepbound™ brand only)**
- Benefit seen regardless of baseline characteristics or Continuous Positive Airway Pressure (CPAP) machine use

Under investigation

- **Semaglutide**: Ongoing trial studying 2.4 mg dose (injectable) in patients with obesity & moderate to severe OSA

Malhotra 2024; Wilding 2021

Obstructive Sleep Apnea

Approved for OSA + Obesity	Emerging Data
• Tirzepatide (Zepbound™)	• Semaglutide (injectable)

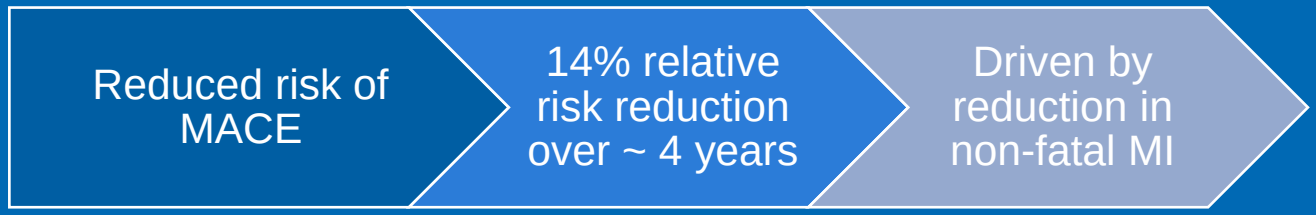
Cardiovascular Disease

Efficacy: Reduced risk of Major Adverse Cardiovascular Events

FDA-Approved Indication for CV Risk Reduction in ASCVD + T2DM

- Semaglutide (injectable), Liraglutide, Dulaglutide*
- **Dulaglutide is also approved for CV risk reduction with multiple CV risk factors + T2DM*

Encouraging data: Oral Semaglutide 14 mg for ASCVD + T2DM



Under investigation, but similar benefits expected

- Tirzepatide: As of now there is positive data for MACE & potential benefit for cardiometabolic risk factors, but there is ongoing CVOT

McGuire 2025; Del Prato 2021; Nicholls 2023

Cardiovascular Disease

Approved for CV risk **or** ASCVD + T2DM	Approved for ASCVD + T2DM	Encouraging Data	Emerging Data
• Dulaglutide	• Semaglutide (injectable) • Liraglutide	• Semaglutide (oral)	• Tirzepatide

Patient Case: 62-year-old woman with T2DM

CC: "I've gained weight despite trying to eat less. My blood sugars have been high."

PMH: T2DM, Hyperlipidemia, ASCVD (MI 5 years ago), CKD stage 3b, GERD, Obesity

Relevant Vitals/Labs

- BMI: 34 kg/m^2
- A1C: 8.3%
- eGFR: 42 mL/min/1.73 m^2

Current Medications

- Metformin 500 mg daily, Sitagliptin 50 mg daily
- Atorvastatin 40 mg nightly
- Omeprazole 20 mg daily

Questions to consider...

- **Which indications for GLP-1 RA Agent use does this patient possess?**
- Which agents might you consider when treating this patient?

Patient Case: 62-year-old woman with T2DM

CC: "I've gained weight despite trying to eat less. My blood sugars have been high."

PMH: T2DM, Hyperlipidemia, ASCVD (MI 5 years ago), CKD stage 3b, GERD, Obesity

Current Medications

- Metformin 500 mg daily, Sitagliptin 50 mg daily
- Atorvastatin 40 mg nightly
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T2DM	ASCVD	CKD	Obesity
• *Semaglutide* • Dulaglutide • Liraglutide • Tirzepatide	• *Semaglutide* • Dulaglutide • Liraglutide	• *Semaglutide*	• *Semaglutide* • Liraglutide • Tirzepatide

Questions to consider...

- Which indications for GLP-1 RA Agent use does this patient possess?
- **Which agents might you consider when treating this patient?**

Pipeline Indications

Indications for GLP-1 RA Agents with Encouraging Data

Metabolic Dysfunction-Associated Steatohepatitis

Benefits: Steatosis, inflammation, & fibrosis resolution

- Thought to be driven by weight loss, improved insulin resistance, & reduced inflammation

Encouraging data in phase 2 trials

- **Tirzepatide**: Resolution of MASH in ~44 to 62% of patients vs. ~10% with placebo
- **Liraglutide**: Resolution of MASH in ~39% of patients vs. 9% with placebo

RECENT UPDATE: Accelerated approval for injectable Semaglutide for MASH with liver fibrosis

- **Semaglutide 2.4 mg** (Wegovy™): Resolution of MASH in ~63% of patients vs. ~34.3% with placebo in phase 3 trial

Loomba 2024; Armstrong 2015; Sanyal 2025

Exiting the Pipeline: Injectable Semaglutide for MASH

ent for Serious Liver Disease Known as 'MASH'

FDA Approves Treatment for Serious Liver Disease Known as 'MASH'

Action Will Provide New Therapy for Growing Public Health Issue

Action

The U.S. Food and Drug Administration has approved Wegovy (semaglutide) injection to treat metabolic-associated steatohepatitis (MASH) in adults with moderate-to-advanced fibrosis (excessive scar tissue in the liver). MASH, also known as nonalcoholic steatohepatitis, is a se
also approved for obes
as heart attacks, in ind
adults (14.9 million pe

Content current
08/15/2025

Novo Nordisk's Wegovy Receives Accelerated Approval for MASH with Liver Fibrosis

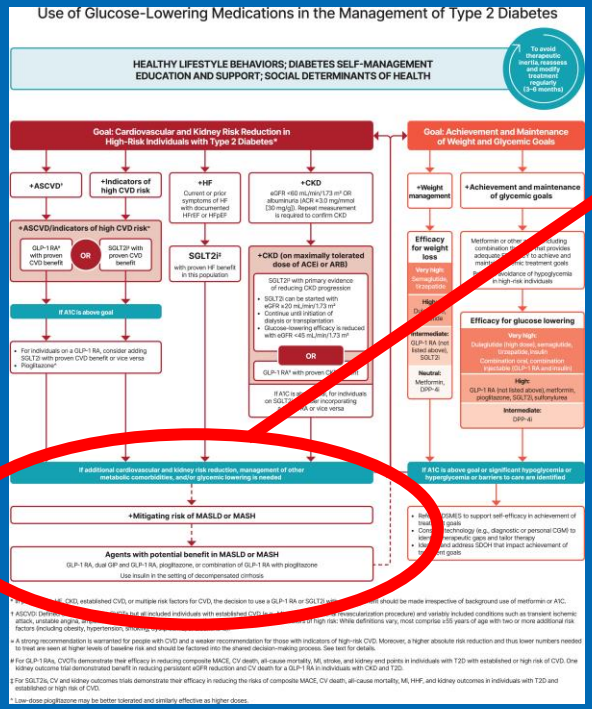
On August 15, 2025, the FDA granted accelerated approval to Novo Nordisk's Wegovy (semaglutide) 2.4 mg injection for the treatment of adults with noncirrhotic metabolic dysfunction–associated steatohepatitis (MASH) with moderate to advanced fibrosis (consistent with stages F2–F3 fibrosis), in combination with a reduced-calorie diet and increased physical activity.

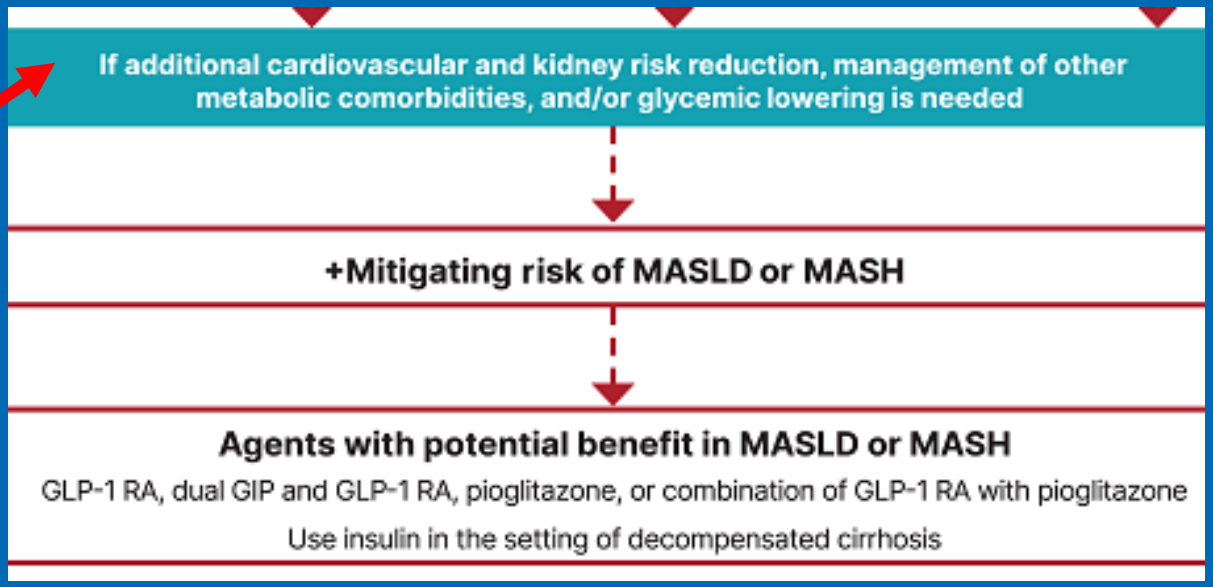
MASH (formerly known as nonalcoholic steatohepatitis [NASH]) affects approximately 5% of U.S. adults. Wegovy is the first and only glucagon-like peptide-1 receptor agonist (GLP-1 RA) approved for this indication; it is also approved for chronic weight management in adults and adolescents 12 years of age and older and to reduce the risk of major adverse cardiovascular events (MACE) in adults with cardiovascular disease and either obesity or overweight.

The accelerated approval in MASH was based on Part 1 of the ongoing two-part ESSENCE trial. At Week 72, 63% of

Metabolic Dysfunction-Associated Steatohepatitis

ADA Standards of Care 2025 highlights these benefits





GLP-1 RA Agents recommended as preferred option for T2DM + biopsy-proven MASH or those with MASLD (at high risk for liver fibrosis)

Beth Israel Lahey Health Performance Network

Image courtesy of the ADA, excerpt from Figure 9.3 "Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes"

Metabolic Dysfunction-Associated Steatohepatitis

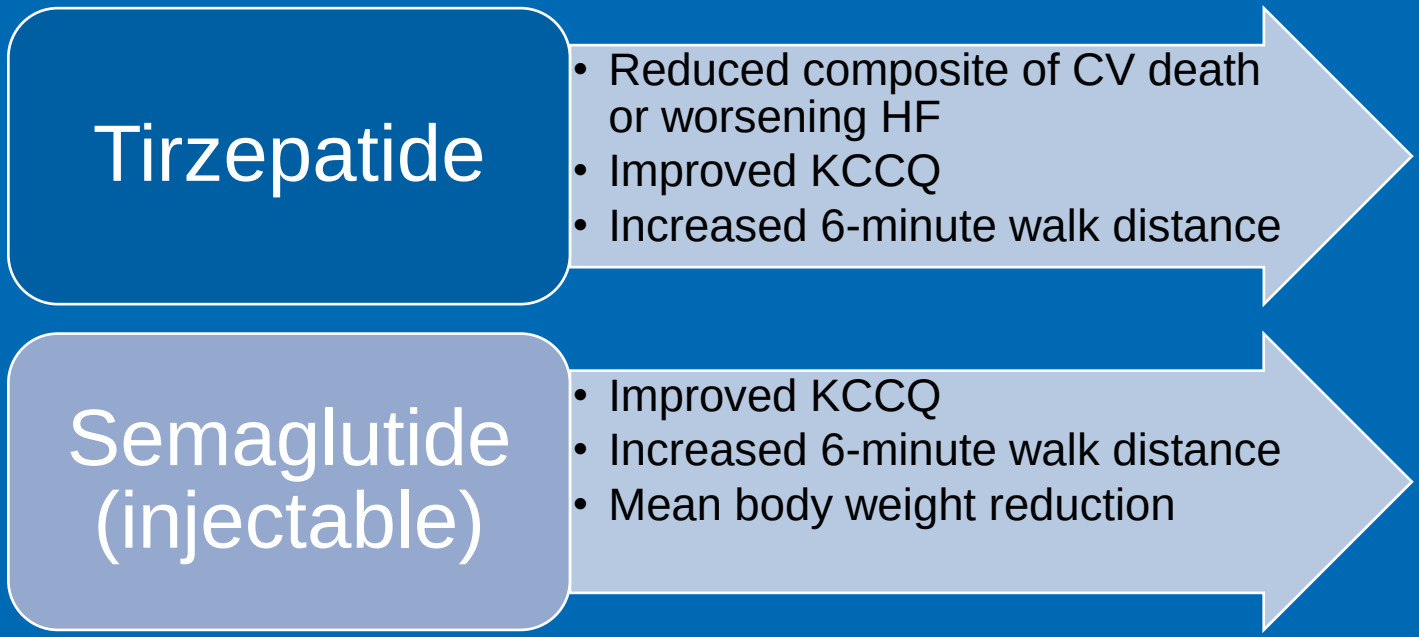
Newly Approved for MASH with liver fibrosis	Encouraging Data
• Semaglutide (injectable) [Wegovy™]	• Tirzepatide • Liraglutide

Heart Failure

Benefits: Secondary data shows improved cardiac structure and function in adults with HFpEF* & Obesity

**NOT currently recommended for HFrEF*

Encouraging data in phase 3 trials



Packer 2024; Kosiborod 2023

Patient Case: 58-year-old man with HFpEF

CC: "I get out of breath walking to the mailbox & my liver doctor says I have inflammation"

PMH: Pre-diabetes, HFpEF, Obesity, MASH, HTN, OSA, HLD, Gout

Relevant Vitals/Labs

- BMI: 36 kg/m^2
- A1C: 5.9%

Current Medications

- Lisinopril 20 mg daily
- Rosuvastatin 20 mg nightly
- Uses CPAP

Questions to consider...

- **Which indications does this patient have that might prompt you to consider GLP-1 RA Agent (labeled or "off-label")**
- Which agents might you consider when treating this patient?

Patient Case: 58-year-old man with HFpEF

CC: "I get out of breath walking to the mailbox & my liver doctor says I have inflammation"

PMH: Pre-diabetes, HFpEF, Obesity, MASH, HTN, OSA, HLD, Gout

Current Medications

- Lisinopril 20 mg daily
- Rosuvastatin 20 mg nightly

Obesity	MASH	OSA	HFpEF (**off label**)
• *Tirzepatide* • *Semaglutide* • Liraglutide	• *Semaglutide*	• *Tirzepatide*	• *Tirzepatide* • *Semaglutide*

Questions to consider...

- Which indications does this patient have that might prompt you to consider GLP-1 RA Agent (labeled or "off-label")
- **Which agents might you consider when treating this patient?**

Efficacy Summary of GLP-1 RA Agents for Approved and Pipeline Indications

GLP-1 RA Agent	T2DM	Obesity	CKD + T2DM	OSA	CV risk or ASCVD + T2DM	ASCVD + T2DM	MASH + T2DM	HFpEF + Obesity
Tirzepatide (Mounjaro™)	✓		○			#	#	#
Tirzepatide (Zepbound™)		✓		✓				
Semaglutide (Ozempic™)	✓		✓		#	✓		
Semaglutide (Wegovy™)		✓		○			✓	#
Semaglutide (Rybelsus™)	✓					#		
Liraglutide (Victoza™)	✓				#	✓	#	
Liraglutide (Saxenda™)		✓	#					
Dulaglutide (Trulicity™)	✓		#		✓	✓		

✓	**FDA-Approved Indication**
#	**Encouraging Data Confirmed**
○	**Under Investigation, Studies Ongoing**

Future Potential

Non-FDA Approved

Off-Label Use: Polycystic Ovarian Syndrome (PCOS)

2023 International Evidence Based Guidelines for the Assessment and Management of PCOS

Liraglutide and semaglutide can be considered in addition to lifestyle intervention for higher weight adults with PCOS

Off-Label Use: PCOS Relevant Studies

Effects of liraglutide on ovarian dysfunction in PCOS

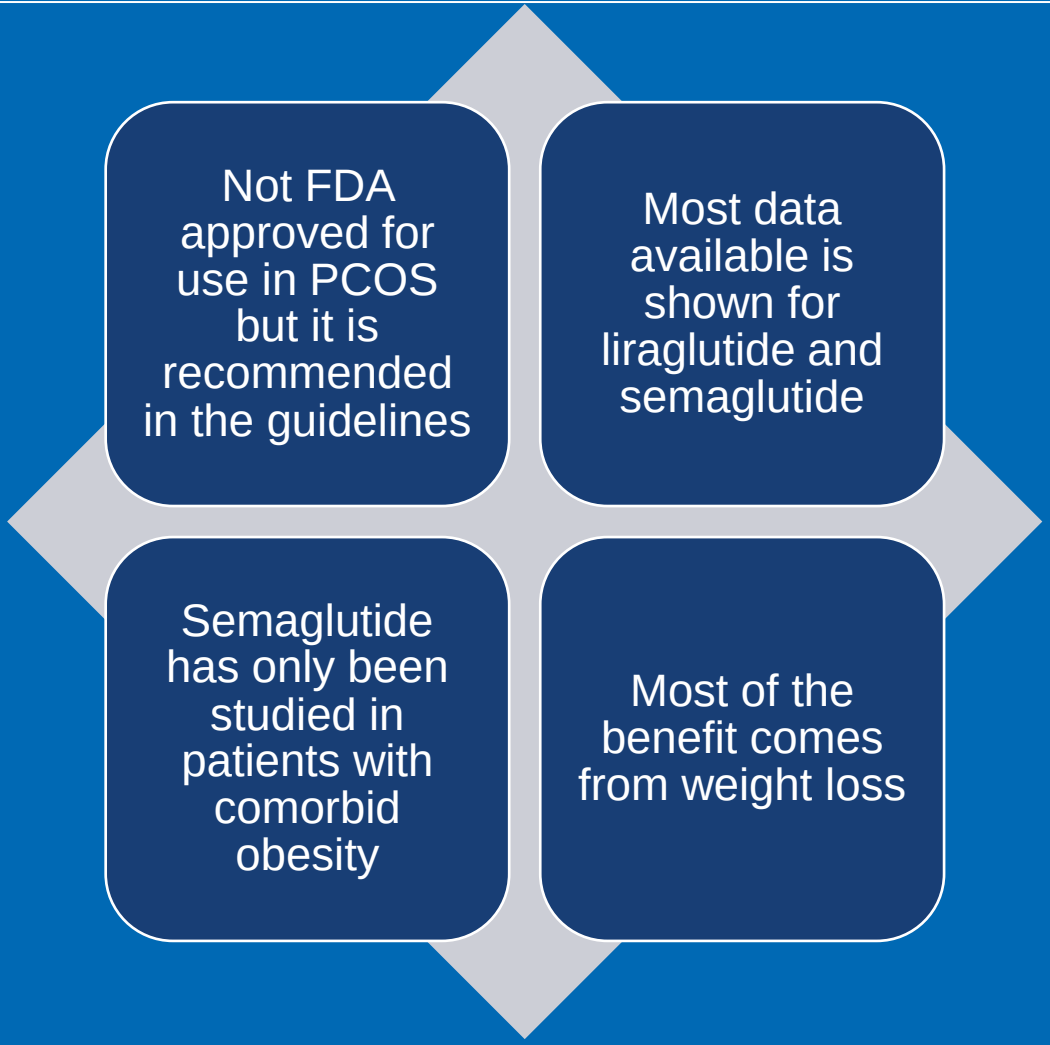
- Double-blind RCT in 72 women with PCOS for 26 weeks
- Received liraglutide 1.8 mg daily or placebo
- **Liraglutide use showed improvement in bleeding ratio, increase in sex hormone binding globulin (SHBG) and decrease in free testosterone and ovarian volume** compared to placebo

Meta-analysis assessing the use of semaglutide or liraglutide in patients with PCOS and obesity

- **GLP-1 RA Agent use resulted in a significant reduction in waist circumference, BMI, triglycerides and total testosterone** when compared to placebo

Nylander 2017; Lin 2024

Summary: PCOS



How About Alzheimer's?

The 2024 Alzheimer's Association International Conference (AAIC)

- Phase IIb multi-center double blind placebo RCT in the UK in patients with mild Alzheimer’s
  - Liraglutide appears to **reduce shrinking in parts of the brain by 50% compared to placebo and may reduce cognitive decline by up to 18% after one year of treatment**

Current studies are ongoing to assess use of GLP-1 RA Agents in patients with Alzheimer's

- Evoke and Evoke + phase III trials
  - Use of semaglutide 14 mg orally daily to be completed later in 2025

What about impact on Addiction?

Stanford MEDICINE News Center

Topics A-Z Latest Articles

Stanford Medicine / News Center / 5 Things: GLP-1s and addiction

INSIGHTS

Five things to know about GLP-1s and addiction

By Mark Conley

Stanford Medicine psychiatrist Anna Lembke unpacks the potential of FDA-approved weight-reducing GLP-1 drugs like Ozempic as tools in treating addiction.

Addiction | April 01, 2025

Forbes

Hype Or Hope? Latest Research On GLP-1 Receptor Agonists And Addiction

By Lipi Roy, MD, MPH, Contributor. ⊙ Dr. Lipi Roy writes about addiction, me... Follow Author

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HEALTH NEWS ✓ Fact Checked

Ozempic May Help Curb Addictive Behaviors Like Drinking and Smoking

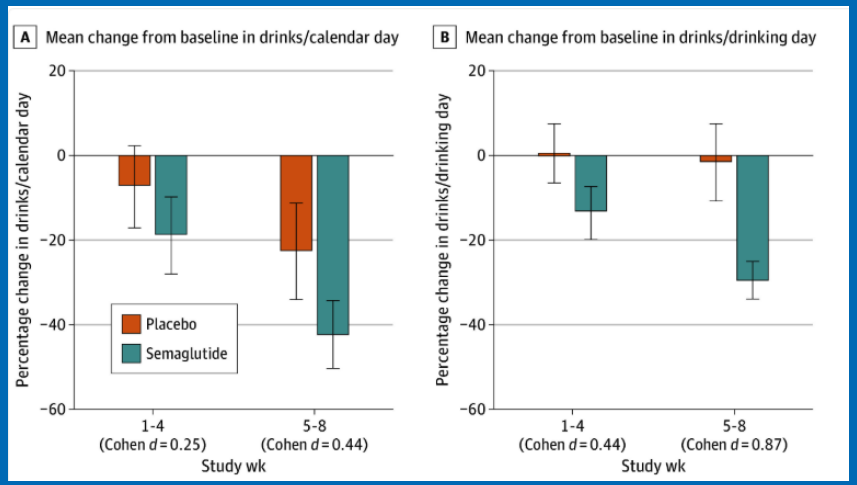
People claim that GLP-1 drugs like Ozempic and Wegovy have helped them overcome addictive behaviors like drinking, smoking, and shopping. Anchiy/Getty Images Anchiy/Getty Images

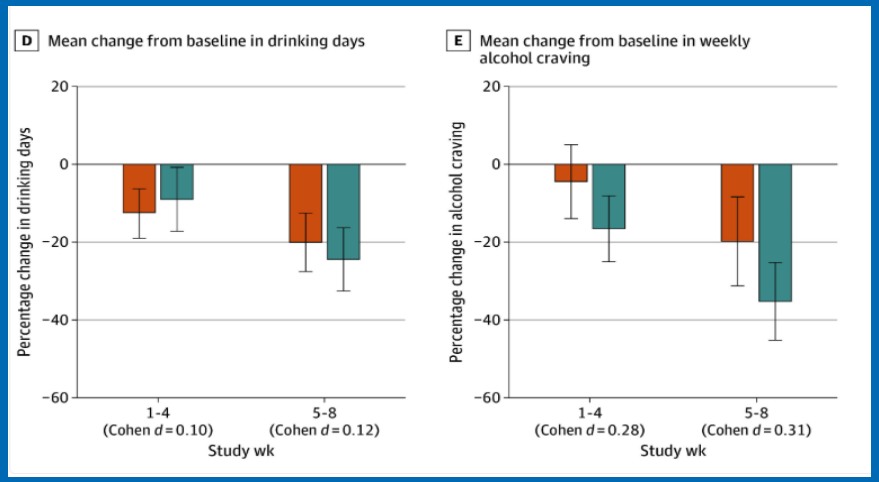
- Some Ozempic users report that the drug has helped them control addictive behaviors like drinking.
- In testimonials shared online, some users claim they no longer feel the same desire for habits like smoking, drinking alcohol, and gambling.
- Current research on the addiction-curbing effects of GLP-1 drugs like Ozempic is

What about impact on Addiction?

Phase II RCT using weekly semaglutide in adults with AUD

- Semaglutide use did not affect the average drinks per calendar day or number of drinking days
- Semaglutide significantly **reduced drinks per drinking day and weekly alcohol craving**



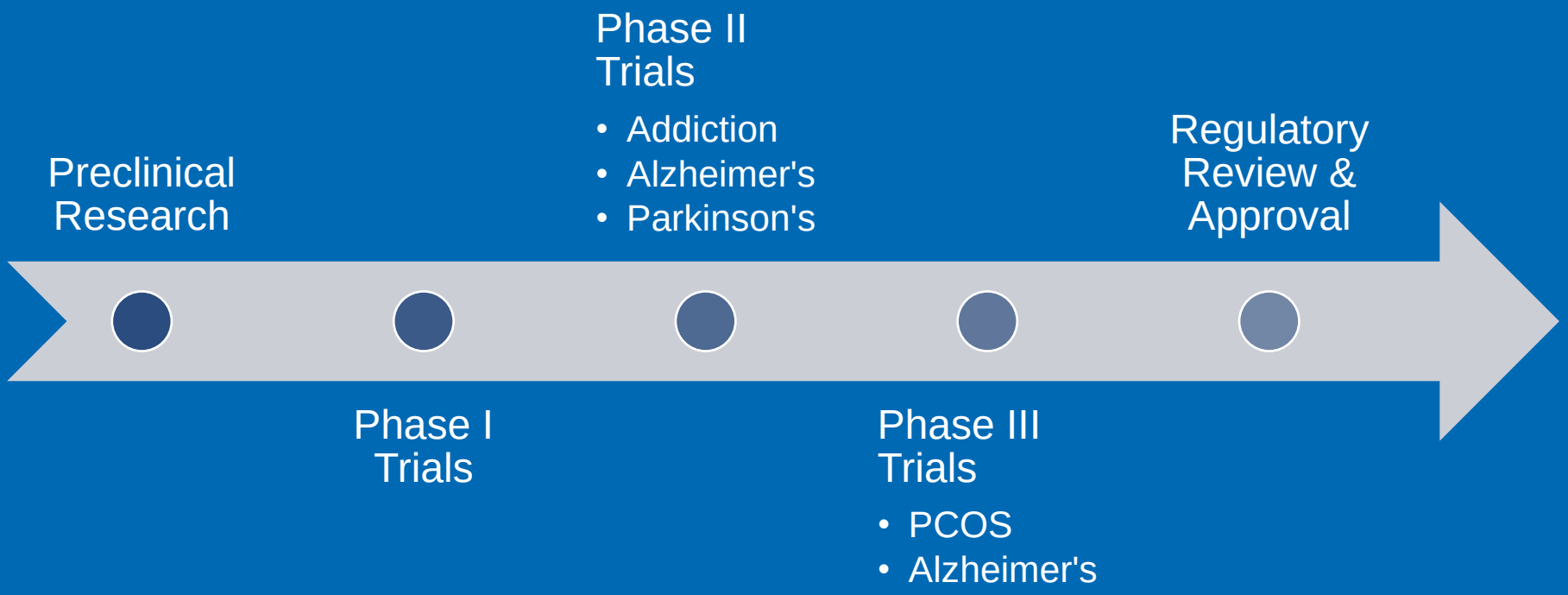


Current studies are ongoing to further assess GLP-1 RA Agent use in these patients

Thoughts on Parkinson's?

Current studies are ongoing to further assess the use of liraglutide and semaglutide

Summary of Future Use



Safety Considerations

Common Adverse Effect Management

Common ADE may include: nausea, vomiting, GI pain, diarrhea and constipation

Dose adjustment considerations:

- GLP-1 RA Agents may be titrated every 4 weeks
- For minor GI effects consider:
  - Extending the titration window another 2 - 4 weeks
- If GI symptoms persist consider:
  - Switching to another GLP-1 RA Agent
  - Decreasing to the previously tolerated dose

Common Adverse Effect Management

Patient Counseling Points

- Eat slower and smaller portions
- Increase water and fiber intake
- Most adverse effects are seen after initiation and dose titration

Use of Anti-emetics

- May potentially be useful for nausea but data is limited (off-label use)
- Use should be limited to short term

BILH Conversion Guide for GLP-1 RA Agents

GLP-1RA Agents Suggested Comparative Doses for Treating Type 2 Diabetes

Medication	Dosing Route and Interval	Comparative Doses										
Tirzepatide¶ (Mounjaro)	SC Weekly			2.5mg			5mg		7.5mg	10mg	12.5mg	15mg
Semaglutide* (Ozempic)	SC Weekly		0.25mg	0.5mg		1mg		2mg				
Dulaglutide* (Trulicity)	SC Weekly		0.75mg‡	1.5mg	3mg	4.5mg						
Exenatide XR (Bydureon)	SC Weekly			2mg								
Semaglutide (Rybelsus)	PO Daily	3mg	7mg	14mg								
Liraglutide* (Victoza)	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

GLP-1RA Agents Suggested Comparative Doses for Weight Management

Medication	Dosing Route and Interval	Comparative Doses								
Tirzepatide (Zepbound)	SC Weekly			2.5mg		5mg	7.5mg	10mg	12.5mg	15mg
Semaglutide* (Wegovy)	SC Weekly		0.25mg	0.5mg	1mg	1.7mg	2.4mg			
Liraglutide (Saxenda)	SC Daily	0.6mg	1.2mg	1.8mg	2.4mg	3mg				

Indicates an initiation dose. Titration is required.

Indicates an intermediate dose to minimize GI side effects. Titration is recommended.

Indicates a maintenance dose.

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

Patient Case: 54-year-old man with history of pancreatitis

CC: "My A1C is climbing again, Metformin isn't working"

PMH: T2DM, Obesity, HTN, HLD, GERD, history of alcohol-associated pancreatitis (hospitalized ~1 year ago), former smoker, social alcohol use (2-3 drinks per week)

Relevant Vitals/Labs

- BMI: 32 kg/m^2
- A1C: 8.1%
- Triglycerides: 140 mg/dL

Current Medications

- Metformin 1000 mg BID
- Lisinopril 20 mg daily
- Atorvastatin 20 mg nightly
- Omeprazole 20 mg daily

Questions to consider...

- Is a GLP-1 RA Agent contraindicated in this patient?

Pancreatitis

Pancreatitis has been reported in clinical studies with all GLP-1 RA Agents

Risk Factors

- Diabetes
- Heavy alcohol use
- High triglyceride levels
- Gallbladder disease

Elevations in amylase and lipase levels

Risk of Pancreatitis Reported in Clinical Trials

Liraglutide

- 2.7 versus 0.5 cases per 1000 patient years compared to glimepiride

Tirzepatide

- 0.23 versus 0.11 cases per 100 patient years compared to a comparator therapy

Semaglutide

- 0.3 versus 0.2 cases per 100 patient years compared to a comparator therapy

Dulaglutide

- 3.4 versus 2.7 cases per 1000 patient years comapred to a non-incretin comparator

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Questions to consider...

- Is a GLP-1 RA Agent contraindicated in this patient?

Black Box Warning: Risk of Thyroid C-cell Tumors

Included in all GLP-1 RA Agent package inserts

- Use is **contraindicated** in patients with a family or personal history of MTC and MEN 2
- Result of preclinical, carcinogenic studies in mice and rats
  - A dose and time dependent effect was seen showing an increased risk of medullary carcinomas
  - Subsequent studies did not show statistical significance due to poor trail design
  - Risk in humans has not been determined

Black Box Warning: Risk of Thyroid C-cell Tumors

Consideration for use of GLP-1 RA Agent in those **without** a personal or family history of MEN 2 or MTC

- Lifetime risk of CV complications in patients with T2DM is 73% for men and 67% for women
- The lifetime thyroid cancer risk is estimated to be 1.1%
  - **The benefits of use of a GLP-1 RA Agent will typically outweigh the risk**

Retinopathy

May be a transient effect related to the rapid reduction in blood glucose levels in those with pre-existing and advanced retinopathy, poor glycemic control and concurrent insulin use.

SUSTAIN-6 – Semaglutide CVOT

- Higher incidence of diabetic retinopathy was seen in the semaglutide group compared to placebo

Other analyses with various GLP-1 RA Agents have produced mixed results

Retinopathy

The American Academy of Ophthalmology (AAO):

- Maintaining control of glucose is crucial for lowering the risk of diabetic retinopathy development and progression

The American Diabetes Association (ADA):

- Retinopathy should be assessed when intensifying glucose lowering therapy
- Regular yearly eye exams are recommended

GLP-1 RA Agent use is **not contraindicated** in patients with diabetic retinopathy

Patient Case: 33-year-old woman with PCOS

CC: "I want to lose weight before I am ready to try to get pregnant in a couple years"

PMH: Obesity, PCOS with irregular menses, Pre-diabetes, HLD, Anxiety

Relevant Vitals/Labs

- BMI: 36.5 kg/m^2
- A1C: 5.8%

Current Medications

- Ethinyl estradiol/norgestimate daily
- Atorvastatin 10 mg nightly
- Vitamin D3 2000 IU daily

Questions to consider...

- Would you recommend initiating a GLP-1 RA Agent in this patient?

Oral Contraceptive Use

Most GLP-1 RA Agents have not been found to have a significant effect on oral contraceptives including liraglutide, dulaglutide and semaglutide

Tirzepatide requires a back up contraceptive method be used for 4 weeks after initiation or dose titration

Tirzepatide 5 mg reduced the maximum concentration of ethyl estradiol and norgestimate by 59% and 66% respectively

Patient Case: 33-year-old woman with PCOS

CC: "I want to lose weight before I am ready to try to get pregnant in a couple years"

PMH: Obesity, PCOS with irregular menses, Pre-diabetes, HLD, Anxiety

Relevant Vitals/Labs

- BMI: 36.5 kg/m^2
- A1C: 5.8%

Current Medications

- Ethinyl estradiol/norgestimate daily
- Atorvastatin 10 mg nightly
- Vitamin D3 2000 IU daily

Questions to consider...

- Would you recommend initiating a GLP-1 RA Agent in this patient?
- What counseling points would you review if you initiated tirzepatide in this patient?

Periconception

Observational studies in pregnant woman with type 2 diabetes have not shown a significantly increased risk of congenital malformations

AJOG Considerations:

- There is not enough evidence to predict any adverse effects to periconception exposure of GLP-1 RA Agent use
- Recommend use of contraception to prevent unintended pregnancy while taking GLP-1 RA Agents

Pregnancy

Use in pregnancy is not recommended, therapy should be discontinued when pregnancy is recognized

Semaglutide

- Discontinue at least 2 months before planned pregnancy due to long washout period

Tirzepatide

- If taking oral contraceptives use a backup contraceptive method for 4 weeks after initiation and dose escalation

No specific guidance provided for dulaglutide or liraglutide

Lean Muscle Loss

Systematic Reviews of GLP-1 RA Agent use has shown that lean mass contributes to 20-50% of total weight lost

Strategies to reduce muscle loss during weight loss therapies

- Dietary modifications
  - Increased intake of proteins
    - Preserves lean mass
    - Reduces adaptive thermogenesis
    - Causes negative energy balance
  - Whey proteins
    - Can increase the secretion of insulin and GLP-1
    - High dosage requirements restrict regular use
  - Branched-chain amino acids
    - Aided the maintenance of muscle mass and improved muscle strength in post-menopausal women with sarcopenic obesity
- Exercise
  - Endurance and resistance-type exercises aid in preserving muscle mass
  - Resistance-based exercises improve muscle strength

Combining protein supplementation with resistance training exercises may further induce increases in lean body mass

Dietician Referral

- Should be recommended for any patient starting GLP-1 RA Agent therapy
  - Allows for more frequent check-ins and individualized counseling
  - Patients need to maintain a well-balanced diet

Retrospective observational studies have shown patients on GLP-1 RA Agents have a higher incidence of nutritional deficiencies

- Over 20% of patients had nutritional deficiencies diagnosed within one year of starting GLP-1 RA Agent therapy

Safety Take Home Points

Pancreatitis

- History of pancreatitis with an unknown cause warrants a risk versus benefit discussion with provider

Thyroid C-cell tumors

- Lifetime risk of CVD is significantly higher than lifetime risk of thyroid cancer for those without a family or personal history of MEN 2 or MTC

Retinopathy

- May be due to rapid lowering of blood glucose levels
- Consider a risk versus benefit discussion for those with pre-existing disease

Discontinuation of Therapy

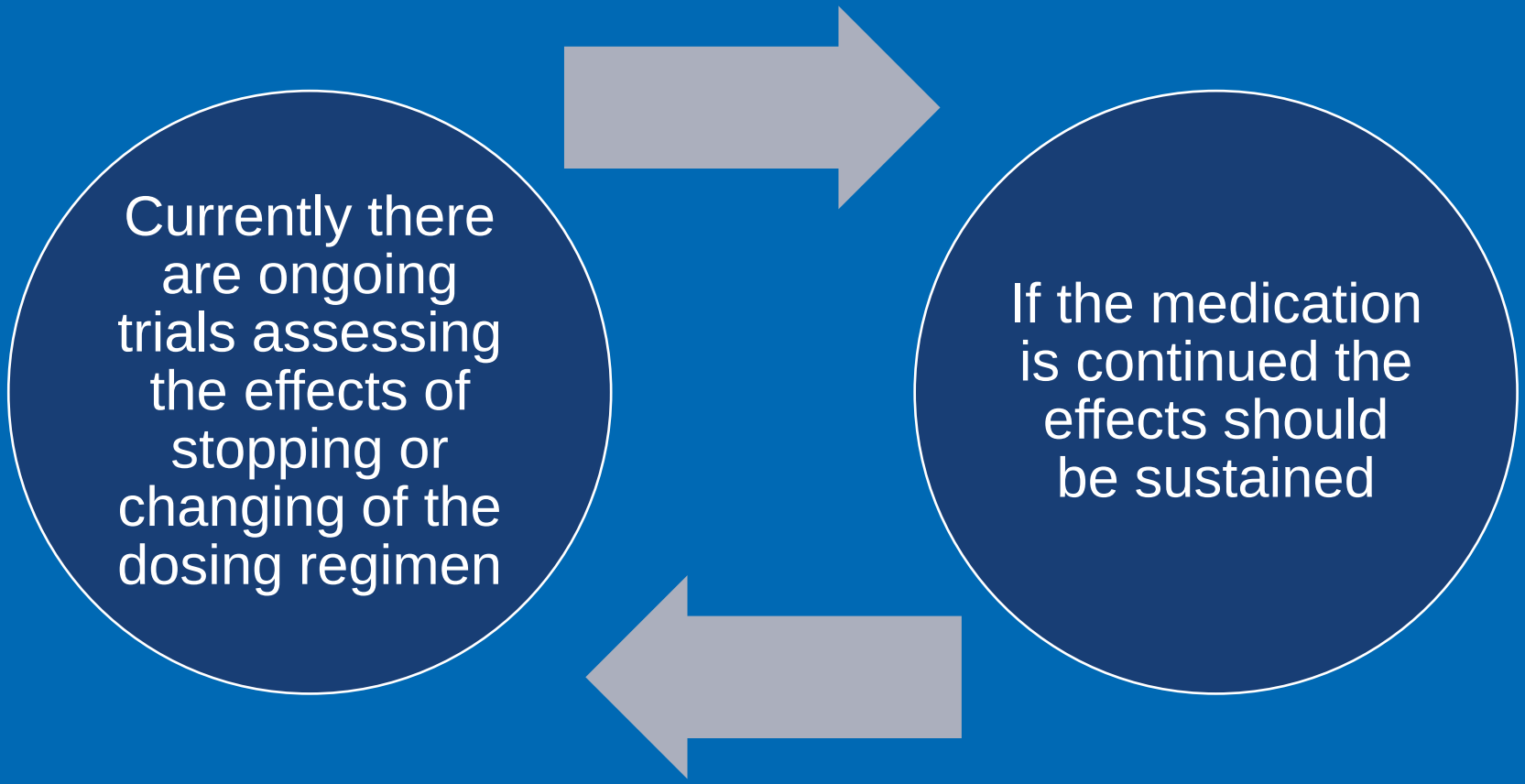
Concern for Weight Gain with Discontinuation?

Extension of Step 1 Semaglutide trial:

- Semaglutide was stopped at week 68 and patients were followed through week 120
  - Patients regained 11.6% of the weight lost by week 120
    - Resulted in a net weight loss of 5.6% from weeks 0 – 120
  - Cardiometabolic improvements seen in weeks 0-68 had reverted towards baseline at week 120

This suggests the need for ongoing treatment in order to maintain improvements in weight and health outcomes

Is Long Term Use Needed?



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