## GLP-1 Agonists and Their Role in Aesthetics

South Beach Symposium Miami Beach, FL

February 6 - 8, 2024

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Presented by Michael H. Gold, MD Gold Skin Care Center Tennessee Clinical Research Center Nashville, TN 37215

#### Academic Appointments

#### **01.** Assistant Clinical Professor

- Department of Medicine, Division of Dermatology, Nashville, TN USA
- Vanderbilt University School of Medicine: 2006-2014
- Vanderbilt University School of Nursing: 2006-2020

#### **02.** Adjunct Assistant Professor

- Meharry Medical College: 2013 Present
- School of Medicine, Nashville, TN

#### **03.** Visiting Professor of Dermatology

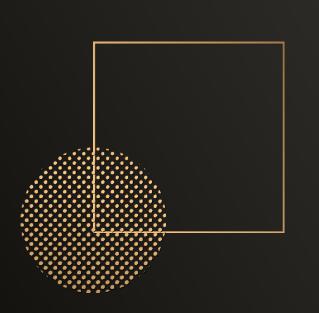
- Huashan Hospital, Fudan University (Shanghai Medical University), Shanghai, China
- The First Hospital of China Medical University, Shenyang, China:
- Guangdong Provincial People's Hospital, Guangzhou, Zhejiang

#### **04.** Visiting Professor of Plastic Surgery

- First People's Hospital of Foshan University, Guangdong, China
- The First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang
- Rongjun Hospital, Jiaxing, China

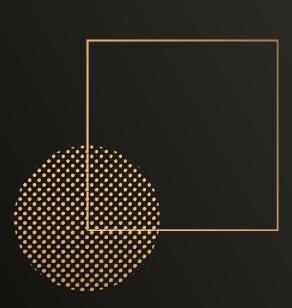
05.

- The People's Hospital of Hunan Province, Changsha, China
- Editor-in-Chief Journal of Cosmetic Dermatology Wiley: 2016-Present
  - Editor-in-Chief- Dermatological Reviews Wiley: 2019 Present



### Conflict of Interest

**01.** Consultant to many pharmaceutical, cosmeceutical, laser and energy-based device companies



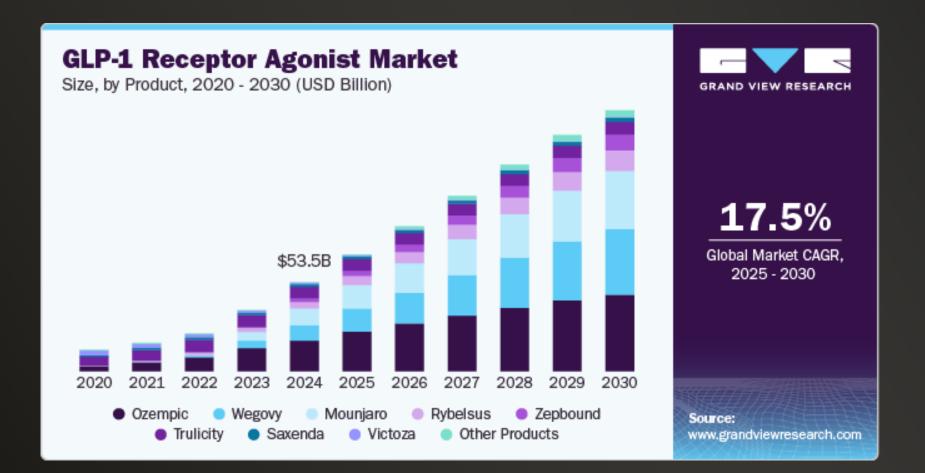
- **02.** Consultant, performs research and speaks on behalf of numerous pharmaceutical and medical device companies
- **03.** For the benefit of this presentation Dr. Gold has no conflicts of interest

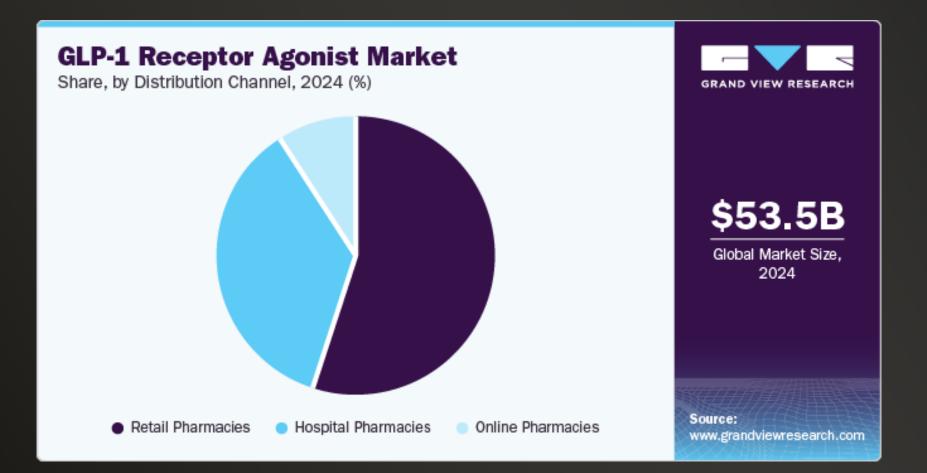
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Drug List for GLP-1s for Diabetes and Weight Loss

GLP-1: Glucagon-like Peptide Receptor Agonists GIP: Glucose dependent Insulinotropic Polypeptide \* Daily Dose Source: Drug Resource: Facts and Comparisons





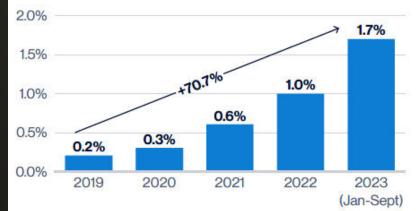




# Figure 1: Semaglutide Prescription Rates in the U.S. (2019 – 2023)

Approximately 1.7% of people in the U.S. who attended a health care visit were prescribed a semaglutide medication in 2023...

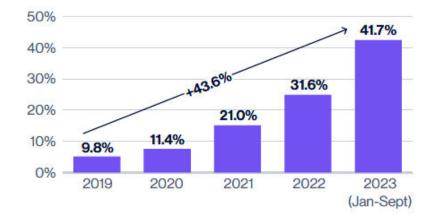
% of people in the U.S. with a health care visit who were prescribed semaglutide



#### Figure 2: Proportion of Semaglutide Prescription for Non-T2DM Indication (2019 – 2023)

... with an increasing proportion of prescriptions going to patients without T2DM – principally to support with weight loss management.

% of patients in the U.S. prescribed semaglutide who do not have a diagnosis of T2DM



Source(s): CNN, Epic Research

Note(s): Figure 1: Includes Ozempic and Rybelsus approved for T2DM and Wegovy approved for chronic weight management Figure 2: 2023 data as of September 21, 2023

- GLP-1 Receptor Agonists = Glucagon-Like Peptide 1 Receptor Agonists
- These medications are transforming the landscape of metabolic treat ment for diabetes and obesity (1)
- Through their incretin effects (hormones that are released into the gut after eating to help regulate blood sugars), GLP-1 agonists regulate blood glucose levels and promote satiety, leading to significant weight loss (2)
- All positive

<sup>1.</sup> Haykal D, Hersant B, Cartier H, Meningaud JP. The Role of GLP-1 Agonists in Aesthetic Medicine: Exploring the Impact of Semiglutide on Body Contouring and Skin Health. J Cosmet Dermatol Dec 2024; https://doi.org/10.1111/jocd.16716

<sup>2.</sup> Ard J, Fitch A, Fruh S, Herman L. Weight Loss and Maintenance Related to the Mechanism of Action of Glucagon-Like Peptide 1 Receptor Agonists. *Adv Ther*. 2021;38(6):2821-2839. doi:10.1007/s12325-021-01710-0

- Recent observations have identified a new aesthetic challenge with the use of these drugs
- The rapid and sometime extreme weight reduction often leaves patients with excess skin, reduced facial volume, and an overall appearance of premature skin aging (3,4)
- Gives increase complexity to the patient experience expected outcome is a more "healthier lifestyle"
- Fueled on by Social Media

Tay JQ. Ozempic face: A new challenge for facial plastic surgeons. J Plast Reconstr Aesthetic Surg JPRAS. 2023;81:97-98. doi:10.1016/j.bjps.2023.04.057
 Mansour MR, Hannawa OM, Yaldo MM, Nageeb EM, Chaiyasate K. The rise of "Ozempic Face": Analyzing trends and treatment challenges associated with rapid facial weight loss induced by GLP-1 agonists. J Plast Reconstr Aesthetic Surg JPRAS. 2024;96:225-227. doi:10.1016/j.bjps.2024.07.051

- The role of SM has further amplified the popularity and visibility of GLP-1 agonists like Semiglutide
- Platforms such as Instagram, TikTok, and X (formerly known as Twitter) filled with testimonials, weight loss transformations, and discussions about the Semiglutide "face" (5)
- The viral nature of this content has raised public awareness but also has made it a trending topic in both the medical and now the aesthetic space

<sup>5.</sup> Carboni A, Woessner S, Martini O, Marroquin NA, Waller J. Natural Weight Loss or "Ozempic Face": Demystifying A Social Media Phenomenon. *J Drugs Dermatol JDD*. 2024;23(1):1367-1368. doi:10.36849/JDD.7613

- While many users celebrate the dramatic weight loss results, the widespread attention has also brought to light the aesthetic conseque nces of rapid weight loss
- This leads to an increasing demand for solutions to counteract these effects (6)

- Semiglutide, one of the more popular GLP-1 agonist medications, enhances glucose-dependent insulin secretion, suppresses glucagon secretion, and delays gastric emptying
- These mechanisms make it an effective tool for controlling blood sugar levels in patients with diabetes

• It also significantly impacts body weight by promoting satiety and reducing food intake, leading to dramatic weight loss in patients with obesity (7-9)

Suran M. As Ozempic's Popularity Soars, Here's What to Know About Semaglutide and Weight Loss. JAMA. 2023;329(19):1627-1629 doi:10.1001/jama.2023.2438.
 Yao H, Zhang A, Li D, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. BMJ. 2024;384:e076410. doi:10.1136/bmj-2023-076410.

<sup>9.</sup> Chao AM, Tronieri JS, Amaro A, Wadden TA. Semaglutide for the treatment of obesity. *Trends Cardiovasc Med*. 2023;33(3):159-166. doi:10.1016/j.tcm.2021.12.008

- Very common with rapidly increasing prevalence
- One of leading causes of cardiovascular disease, blindness, ESRD, amputations, hospitalizations
- Common in Populations with HIV
- Diabetes can be controlled, but management is complicated and requires individualization

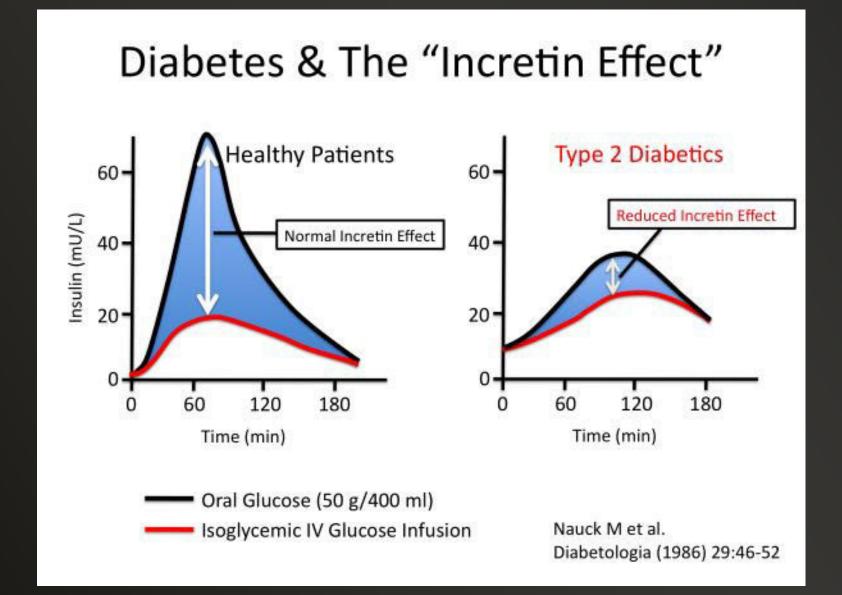
Key Concepts in Diabetes Management

• What should be the glycemic target?

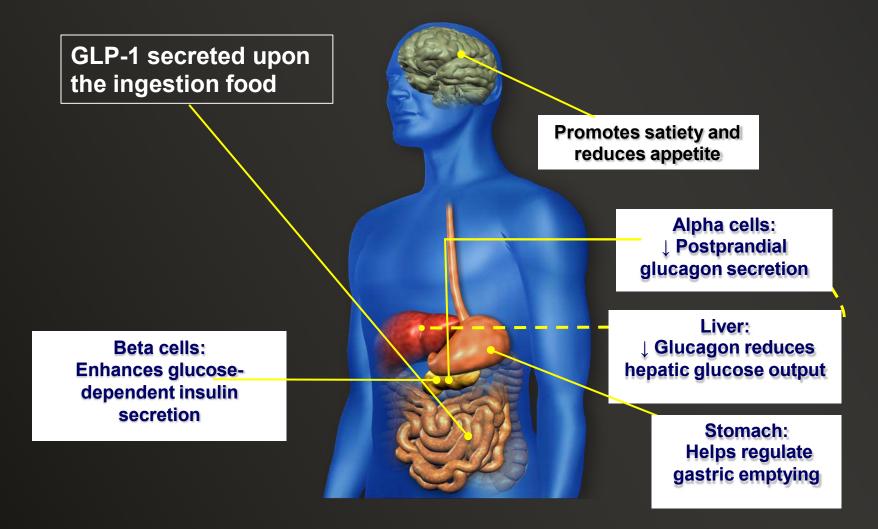
What should be the glycemic target?

HbA1c < 7%

## The Incretin Effect

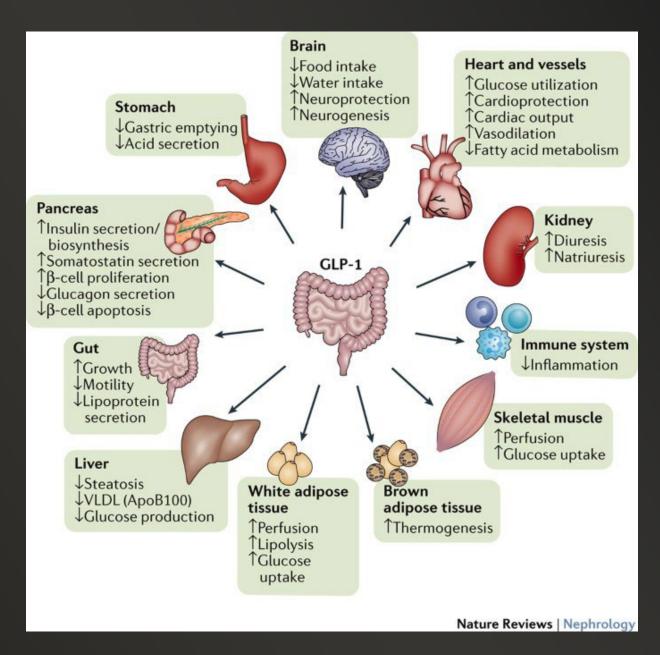


GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins



Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520.; Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422.; Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553.; Adapted from Drucker DJ. *Diabetes*. 1998;47:159-169.

# Multiple Sites of Action of GLP-1 RA



#### GLP1 RAs in Diabetes: Effects on Glucose

Drug	Duration	Glucose Effect
Exenatide	24 weeks	-0.9%
Liraglutide	52 weeks	-1.1 %
Lixisenatide	24 weeks	-0.72%
Dulaglutide	36 weeks	-1.8%
Semaglutide	40 weeks	-2.1%

Glucose and weight data from FDA Package Inserts at highest approved dose

#### GLP1 RAs in Diabetes: Effects on Glucose and Weight

Drug	Duration	Glucose Effect	Weight Effect
Exenatide	24 weeks	-0.9%	-2.9 kg
Liraglutide	52 weeks	-1.1 %	-2.5 Kg
Lixisenatide	24 weeks	-0.72%	-2.7 kg
Dulaglutide	36 weeks	-1.8%	-4.6 kg
Semaglutide	40 weeks	-2.1%	-6.4 kg

Glucose and weight data from FDA Package Inserts at highest approved dose

#### GLP1 RAs in Diabetes: Effects on Cardiovascular Events

Drug	Duration	Glucose Effect	Weight Effect	Reduction in MACE
Exenatide	24 weeks	-0.9%	-2.9 kg	NO
Liraglutide	52 weeks	-1.1 %	-2.5 Kg	↓ 14%
Lixisenatide	24 weeks	-0.72%	-2.7 kg	NO
Dulaglutide	36 weeks	-1.8%	-4.6 kg	↓ 12%
Semaglutide	40 weeks	-2.1%	-6.4 kg	↓ 26%

Glucose and weight data from FDA Package Inserts at highest approved dose

#### GLP1 Receptor Agonists: Pros and Cons

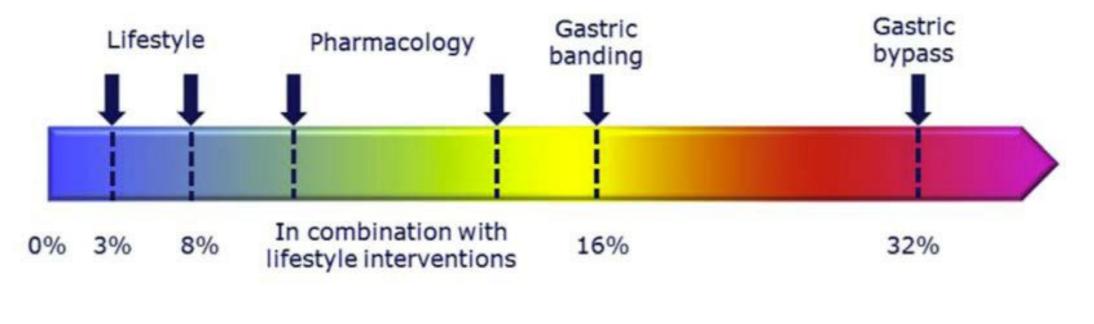
## • <u>Pros</u>

- 🕹 A1c ~1.5%
- No Hypoglycemia
- CVD benefit
- Weight Loss
- $\downarrow$  Liver Fat
- Weekly Administration

## <u>Cons</u>

- Nausea
- ? Pancreatitis
- Cost (NADAC \$~770/month)

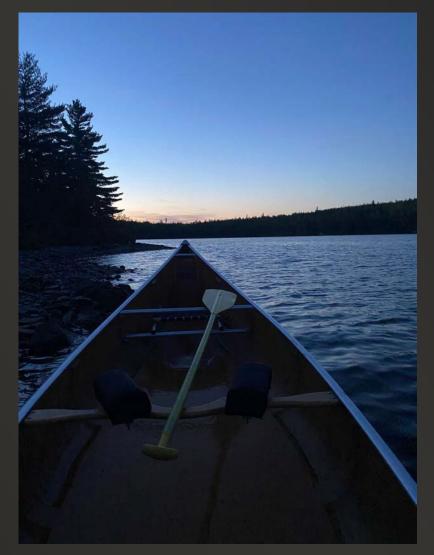
# Weight loss for different treatment interventions

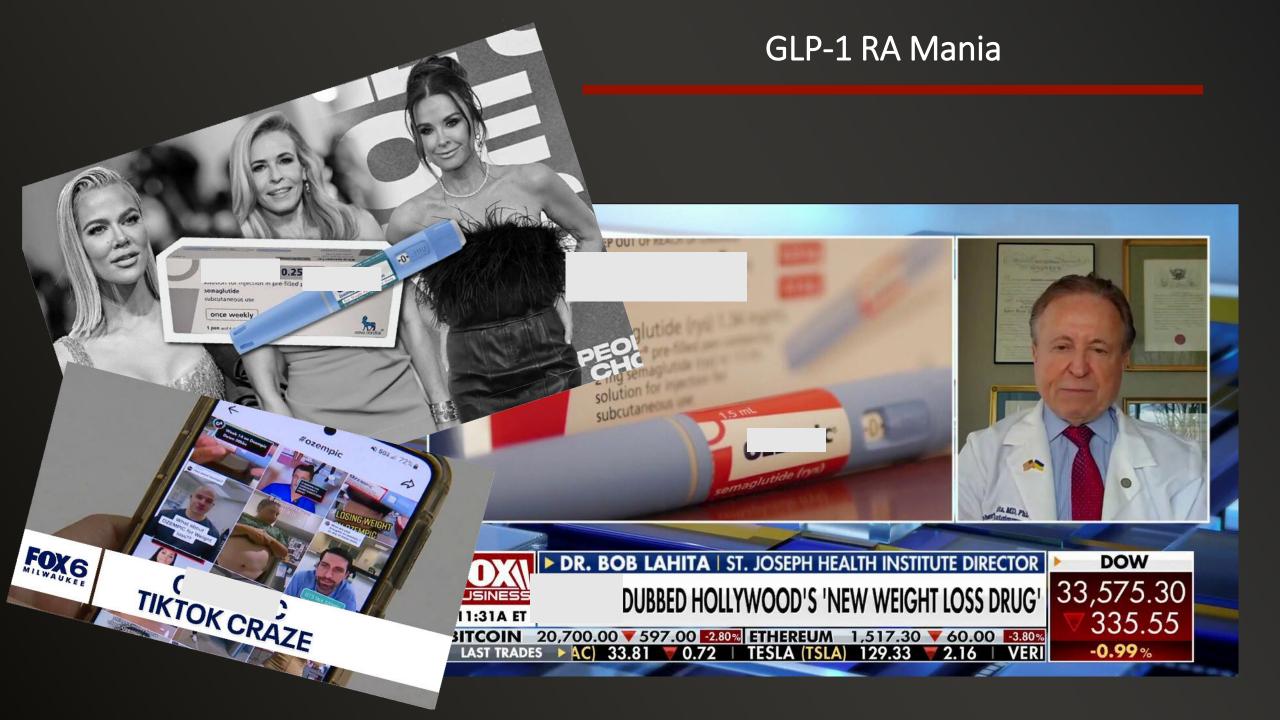


Magnitude of weight loss (%)

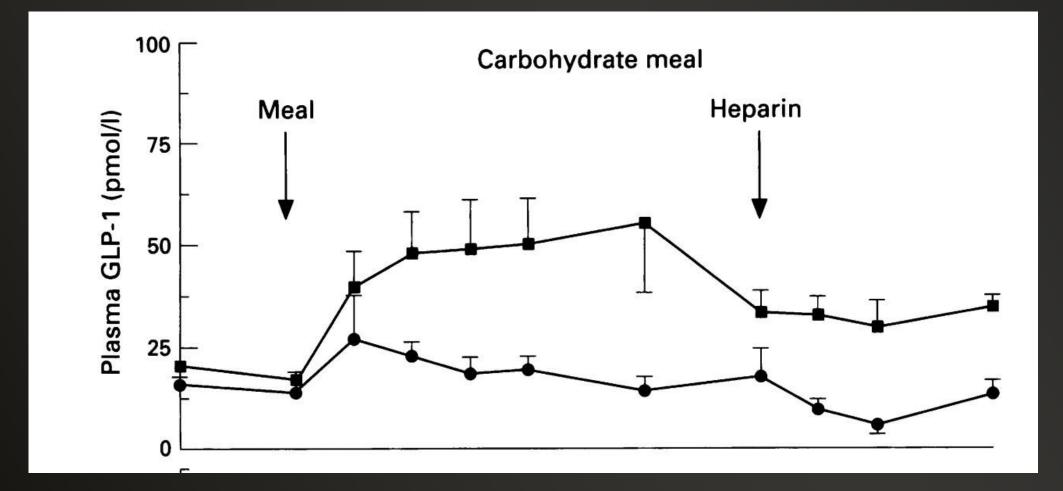
# Next Generation Pharmacologic Treatment for Obesity: GLP-1 RA Dawn of a New Era

Ensign Lake, Boundary Waters Canoe Area, MN





### GLP-1 Secretion is Reduced in Obesity



### GLP1 RA for Obesity

Drug	Duration	Max Dose	Weight Effect	% Non- responder*	% D/C in Treatment Arm
Liraglutide	72 w	3.0 mg	-8.4 kg/-8%	46%	9.9%
Semaglutide	68 w	2.4 mg	-18.4 kg/-16%	13%	5.9%
Tirzepatide	72 w	15 mg	-22 kg/-18.4%	12.5%	10%

\*weight loss < 5%

GLP1 RA: Adverse Effects & Long-Term Benefits

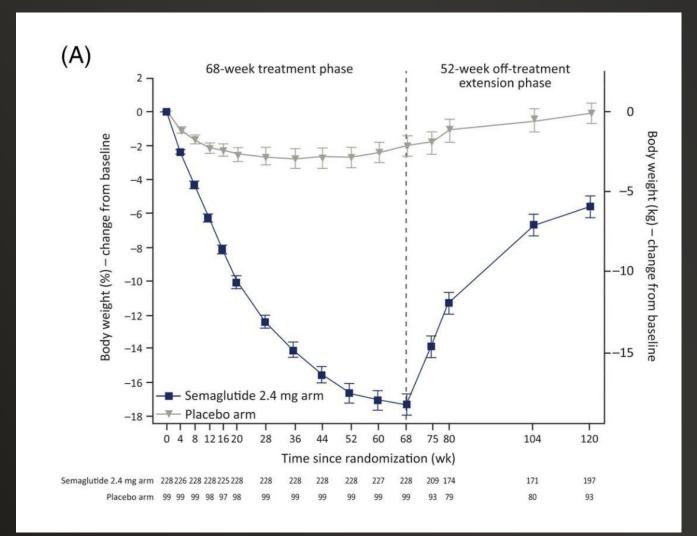
#### Possible Adverse Effects

- Nausea/Diarrhea
- Pancreatitis
- Gastroparesis
- Bowel Obstruction
- Decreased muscle mass
- Facial lipoatrophy ("Ozempic Face")
- Suicidal ideation (Wang, Nat Med, 2024)
- ? Medullary thyroid cancer
- ? Decreased effectiveness of oral contraceptives (tirzepatide)

## **Possible Long-term Benefits**

Diabetes Prevention

#### Weight Rebound After Semaglutide Discontinuation



Wilding, Diab Obes Metab, 2022

• While the effects of GLP-1 agonists in metabolic health are wellestablished, their aesthetic effects, particularly in the context of fat redistribution and skin integrity lack expansive research

• The following are examples of concerns that we may see or have seen with the use of GLP-1 agonists in aesthetics

- Facial Aging & Volume Loss
- Often referred to as the Semiglutide or Ozempic Face
- The face loses its natural volume leading to a hollow or gaunt appearance, especially around the midface, temples, and periorbital areas
- Fat pads also diminish which causes youthful contour support to diminish also exacerbating sagging skin, particularly in and around the mouth, leading to jowling and a less defined facial structure (4,5)

- 4. Mansour MR, Hannawa OM, Yaldo MM, Nageeb EM, Chaiyasate K. The rise of "Ozempic Face": Analyzing trends and treatment challenges associated with rapid facial weight loss induced by GLP-1 agonists. *J Plast Reconstr Aesthetic Surg JPRAS*. 2024;96:225-227. doi:10.1016/j.bjps.2024.07.051
- 5. Carboni A, Woessner S, Martini O, Marroquin NA, Waller J. Natural Weight Loss or "Ozempic Face": Demystifying A Social Media Phenomenon. *J Drugs Dermatol JDD*. 2024;23(1):1367-1368. doi:10.36849/JDD.7613

- This facial volume loss often results in patients appearing older than their biological age, creating a psychological impact that can be discerning, especially for those who have worked so hard to achieve their desired weight goals (10)
- The gaunt appearance, associated with the Semiglutide face, contrasts with the expected benefits of feeling healthier, leaving patients concerned about their facial aesthetics (11)

 Haykal D, Cartier H. Unveiling the psychological and ethical journey of cosmetic dermatology procedures. J Eur Acad Dermatol Venereol JEADV. Published online September 20, 2023. doi:10.1111/jdv.19522
 Mailhac A, Pedersen L, Pottegård A, et al. Semaglutide (Ozempic®) Use in Denmark 2018 Through 2023 ‒ User Trends and off-Label Prescribing for Weight Loss. Clin

Epidemiol. 2024;16:307-318. doi:10.2147/CLEP.S456170

- How to Treat the Semiglutide Face:
- For Restoration of Volume Loss
  - Dermal Fillers
    - HA Fillers
    - Biostimulatory Fillers, such as Calcium Hydroxylapatite (CaHA) and Poly-L- Lactic Acid (PLLA)
  - Fat Grafting or Adipose Derived Matrix
- For Tightening of Lose or Sagging Skin
  - Energy Based Devices including lasers, MFUS (Ulthera and Ulthera Prime), and PRECISE by SofWave
  - RF Microneedling
  - Threads
  - Surgery

#### Skin Laxity

- The skin's ability to retract and conform to a new body image is limited by factors such as age, genetics, and the rate of weight loss
- When weight is lost quickly, the skin does not have time to adjust, leading to sagging areas that are most noticeable in the:
  - Face
  - Neck
  - Arms
  - Abdomen
  - Thighs

- In the face, skin laxity manifests as drooping cheeks, deepened nasolabial folds, and neck sagging
- For the body, patients may experience skin folds that hinder mobility or cause discomfort, particularly in the arms, thighs, and abdominal region
- Can lead to functional challenges (12)

- Treatment Options for Skin Laxity
- Non-surgical skin tightening treatments, such as RF, HIFU or PRECISE ultrasound, or fractional lasers
  - Help stimulate collagen and elastin to improve skin firmness and elasticity
- Surgical approaches

- Body Contouring
- Body contouring has become an essential part of the post-weight loss transformation
- Non-invasive and surgical options exist

# Non-Invasive Options for Body Contouring

- Cryolipolysis
- HIFU or SUPERP
- RF Skin Tightening
- These treatments work by breaking down fat cells or by stimulating collagen production to tighten and firm the skin or fat deposits
- Often need combination therapies for an appropriate effect
- Usually always need multiple treatment sessions

- Surgical Treatment Options for Body Contouring
- For patients with more severe skin laxity issues or large amounts of excess skin
  - Abdominoplasty
  - Body Lifts
  - Thigh Lifts
  - Liposuction (?)
  - Often, surgical and non-surgical approaches work for many

 Further research is needed in all of these areas where we are utilizing aesthetic treatments to determine their long-term effectiveness for our patients

# FDA's Concerns with Unapproved GLP-1 Drugs Used for Weight Loss

- Understanding unapproved versions of these drugs
- FDA is aware that some patients and health care professionals may look to unapproved versions of GLP-1 (glucagon-like peptide-1 (GLP-1) receptor agonists) drugs, including semaglutide and tirzepatide, as an option for weight loss. This can be risky for patients, as unapproved versions do not undergo FDA's review for safety, effectiveness and quality before they are marketed.

#### • FDA recommendations for patients

- Patients should obtain a prescription from their doctor and fill the prescription at a state-licensed pharmacy.
- Visit FDA's <u>BeSafeRx</u> campaign for resources to safely buy prescription medicines online.
- Talk to your doctor if you have questions about your medicines.

## • Concerns with compounded versions of these drugs

- A <u>compounded drug</u> might be appropriate if a patient's medical need cannot be met by an FDA-approved drug, or the FDA-approved drug is not commercially available. However, compounded drugs are not FDA approved. This means the agency does not review compounded drugs for safety, effectiveness or quality before they are marketed.
- The agency has identified some areas of concern for compounded GLP-1 drugs.
   FDA is working with its state regulatory partners and will continue to communicate with compounders regarding these concerns.

#### Dosing concerns with compounded semaglutide and tirzepatide

- FDA received multiple reports of adverse events, some requiring hospitalization, that may be related to <u>dosing</u> <u>errors</u> associated with compounded injectable semaglutide products. These dosing errors resulted from patients meas uring and self-administering incorrect doses of the drug, and in some cases, health care professionals miscalculating d oses of the drug.
- Additionally, the agency has received adverse event reports that may be related to patients prescribed compoun ded semaglutide or tirzepatide products in doses beyond what is in the FDA-approved drug label. This could mean usi ng more product in a single dose, taking doses more frequently or increasing the amount more quickly (titration schedule). Some of the adverse events are serious and some patients reported seeking medical attention for t heir symptoms, including nausea, vomiting, diarrhea, abdominal pain and constipation.
- Health care providers should be vigilant when prescribing compounded semaglutide or tirzepatide products and deter mining appropriate doses and titration and dosing schedules for patients. The agency also encourages patients to talk with their health care provider or compounder about how to measure and administer the intended dos e of compounded semaglutide or tirzepatide.

# Retatrutide cannot be used in compounding

 Retatrutide cannot be used in compounding under federal law. Additionally, it is n ot a component of an FDA-approved drug and has not been found safe and effective for any condition.

## • Salt forms should not be used to compound semaglutide

 The agency is aware that some semaglutide products sold by compounders may be the salt forms. These salt forms, including semaglutide sodium and semaglutide acetate, are different active ingredients than are used in the approved drugs. The agency does not have information on whether these salts have the same chemical and pharmacologic properties as the active ingredient in the approved drug, and we are not aware of any lawful basis for their use in compounding.

# Adverse events related to compounded versions of semaglutide and tirzepatide

- FDA has received reports of adverse events related to compounded versions of semaglutide and tirzepatide. However, federal law does not require state-licensed pharmacies that are not outsourcing facilities to submit adverse events to FDA so it is likely that adverse events from compounded versions of these drugs are underreported. Many of the adverse events reported for compounded products appear to be consistent with adverse events related to the FDA-approved versions of these products.
- As of November 30, 2024, FDA has received:
- more than 392 reports of adverse events with compounded semaglutide.
- more than 215 reports of adverse events with compounded tirzepatide.
- It is not always possible to determine if the adverse event directly resulted from use of the drug
  or if other factors may have contributed to these adverse events

- Illegally marketed versions of these drugs
- Counterfeit semaglutide
- FDA is aware of <u>counterfeit semaglutide</u> marketed in the U.S. <u>Counterfeit</u> dr ugs claim to be authentic, but could contain the wrong ingredients, contain too little, too much or no active ingredient at all or other harmful ingredient s, and are illegal.
- The agency investigates reports of suspected counterfeit drugs to determine the public health risks and the appropriate regulatory response.
   FDA remains vigilant in protecting the U.S. drug supply from these threats.

# • Illegal online sales of these drugs

- FDA monitors the internet for fraudulent or unapproved drugs and has issued <u>warning letters</u> to stop the distribution of illegally marketed semaglutide and tirzepatide. These illegally marketed drugs:
- may be counterfeit
- could contain the wrong ingredients or harmful ingredients
- could contain too little, too much or no active ingredient at all
- The agency urges consumers to be vigilant when purchasing drugs online and only purchase from <u>state-licensed pharmacies</u>.

# FDA reminds compounders of the legal restrictions on making copies of FDA-approved drugs

Compounded drugs are not approved by FDA. FDA-approved drugs go through FDA's rigorous review for safety, effectiveness, and quality as part of the premarket approval process. Compounded drugs must meet conditions to qualify for exemptions under sections 503A and 503B of the Federal Food, Drug and Cosmetic (FD&C) Act. Among the conditions are:

•Section 503A of the FD&C Act includes restrictions on compounding drugs that are <u>essentially copies of a</u> <u>commercially available drug</u>. When a drug shortage is resolved, FDA generally considers the drug to be commercially available. Certain amounts are permissible under the law as long as the compounding is not done "regularly or in inordinate amounts."

•Section 503B of the FD&C Act restricts outsourcing facilities from making compounded drugs that are <u>essentially a</u> <u>copy of one or more FDA-approved drugs</u>. Among other things, this means the compounded drug may not be identical or nearly identical to an FDA-approved drug unless the approved drug is on FDA's drug shortage

A pharmaceutical company has filed lawsuits against compounding pharmacies, medical spas, and

wellness centers for selling products that claim to contain tirzepatide:

•Lawsuits: filed lawsuits against vendors for:

•Selling products that fraudulently claim to be FDA-approved

•Selling products that are not their own branded product

•Selling products that may expose patients to serious health risks

•Settlements: entered into settlement agreements with some vendors, including:

•Totality Medispa: Totality Medispa agreed to make a monetary payment and cannot mislead consumers into

believing that it sells FDA-approved products

A pharmaceutical companyhas filed lawsuits against compounding pharmacies, medical spas, and

wellness centers for selling products that claim to contain tirzepatide:

Cease-and-desist letters: sent cease-and-desist letters to some vendors
 Warnings: warned patients about counterfeit and compounded medicines
 Concerns include:

- •The FDA has not reviewed these products for safety, quality, or efficacy
- •Some products have been found to contain bacteria, high impurity levels, different chemical structures, and different colors than their agent
- Some products are untested and unproven
- •This company also sells tirzepatide under the for diabetes.

- GLP-1 agonists are great drugs that are gaining prominence in the me dical space
- They are also in our space
- How we deal with them is something that is still an open debate
- Treat your patients we have aesthetic options when needed
- If you dispense or want to dispense make sure you have checked all of your boxes