Healthcare

ALERTBULLETIN®

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Weight-loss Medications: A Risk Management Overview

More than two in five adult Americans (40 percent) are obese, while almost one in 10 suffers from severe obesity, making this one of the biggest health-related challenges facing our society. Obesity generates $173 billion in annual medical costs and is associated with several comorbidities – including type 2 diabetes, heart disease, stroke and cancer – which significantly increase the risk of premature death.

In response to this epidemic, the U.S. Food and Drug Administration (FDA) has approved a number of medications designed to treat obesity and related conditions. (See the box to the right.) Because these drugs are designed to produce rapid weight loss, they have attracted increasing attention from non-diabetic, non-obese consumers who wish to slim down for aesthetic reasons. As of May 2024, about 15 million people are currently taking a prescription weight-loss drug. According to the Swiss Re Institute, global sales of weight-loss medications are expected to reach $150 billion by 2031, as weight-conscious individuals discover a pharmacological means of shedding pounds.

While weight-loss drugs have transformed the lives of many people, the off-label use of brand-name drugs, or use of the compounded versions of branded drugs, is not without risk. Compounded formulas, most often sold in wellness centers or through direct-to-consumer online outlets, are currently flooding the marketplace due to surging consumer demand and shortages of brand-name drugs.

Common Weight-loss Medications

- **Semaglutide** – A weekly injectable medication that mimics the action of glucagon-like peptide 1 (GLP-1), a natural metabolic hormone produced by the lining of the stomach. The drug is a GLP-1 receptor agonist, which controls high blood sugar in type 2 diabetics by increasing insulin secretion, improving blood glucose removal and regulating glycemic levels. Semaglutide is effective in suppressing appetite and reducing body weight for adults and adolescents ages 12 years and older.
- **Liraglutide** – Also a GLP-1 receptor agonist, this injectable drug treats type 2 diabetes and obesity by aiding insulin release and slowing gastric emptying, which help control both blood sugar levels and appetite sensation. In higher doses, the drug aids weight management in both adults and adolescents.
- **Tirzepatide** – A dual agonist of both GLP-1 receptors and glucagon inhibitory peptides – i.e., hormones released by the stomach lining to regulate blood glucose and nutrient balance – this weekly injectable drug increases insulin secretion and sensitivity, reduces glucagon secretion and slows gastric emptying. It is approved for adults with insufficiently controlled type 2 diabetes, as well as for weight loss.
- **Phentermine** – Like an amphetamine, this oral medication speeds up weight loss by stimulating the central nervous system. Phentermine may be combined with other drugs, such as the anticonvulsant topiramate, for increased efficacy. The combination is approved for long-term use, under close medical observation, for patients/clients ages 17 and up.

Sources: "Top Weight Loss Medications," posted by the Obesity Medicine Association, January 26, 2024, and Windle, M.L., "Rapid Rx Quiz: Most Effective Obesity Drugs," posted on *Medscape*, September 3, 2024.

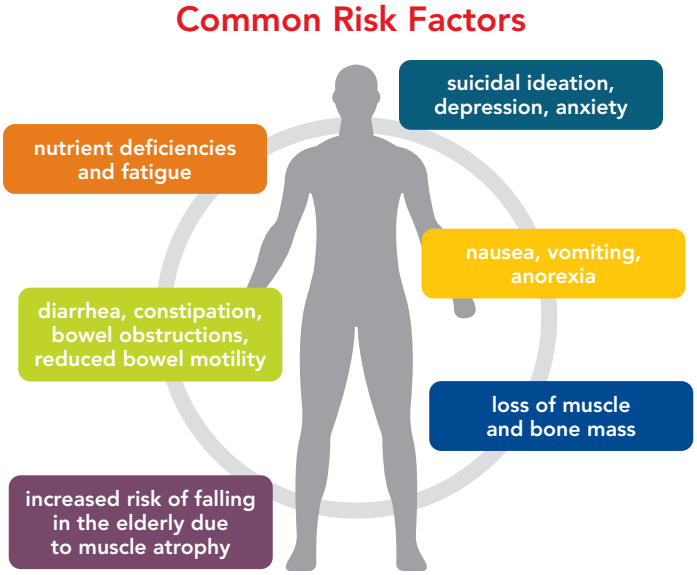
It should be noted that there have been media reports of deaths linked to the use of compounded semaglutides. While these accounts are still under investigation by the FDA, they serve to illustrate the liability exposures confronted by providers who haphazardly prescribe weight-loss medications, as well as the companies and pharmacies that distribute and compound them.

This *AlertBulletin*® examines the risks associated with the prescribing and compounding of weight-loss medications and offers a variety of suggestions designed to limit potential liability. In addition, the article provides a brief overview of the drugs' benefits and dangers, addresses cost and accessibility concerns, and notes some of the specific issues related to compounded drugs.

Clinical Benefits and Risks

The majority of patients/clients who take weight-reducing drugs lose, on average, 10 percent or more of their initial body weight within six months of starting. The drugs also may help improve other conditions, such as high blood pressure and elevated triglyceride levels, which in turn may decrease the risk of heart attack and stroke. Improvements in joint pain and sleep apnea have been noted, as well.

Observed side effects vary by type of medication and can range from relatively mild and transient to more serious. The graphic below notes some of the most common hazards associated with weight-loss drugs:



Although rare, serious complications have been known to occur, including pancreatitis, gallbladder disease, acute kidney injury, thyroid cancer and allergic reactions. In addition, weight loss may be temporary, as clinical test subjects frequently regained lost pounds once they ceased taking the drug.

Accessibility and Cost Concerns

Some weight-loss medications, such as semaglutide and tirzepatide, are unavailable to large numbers of potential users due to their high cost (approximately $1,000 or more per month) as well as insurance coverage restrictions. Access is also limited by periodic shortages of many popular brand-name drugs, due in part to ever-higher levels of off-label use by individuals paying out of pocket.

The combination of avid consumers, high prices and supply problems has led to a proliferation of illegally marketed versions of weight-loss medications. While the FDA monitors the Internet for fraudulent and/or unapproved drugs, and issues warning letters or takes other enforcement actions when appropriate, prescribers should remind patients/clients to remain vigilant when accessing compounded weight-loss medications and to purchase drugs only from state-licensed compounding pharmacies that require a medical prescription for dispensing. (For a checklist of additional measures that patients/clients can take to guard against illicit or unsafe forms of these drugs, see Tchang, B. "A Checklist for Compounded Semaglutide or Tirzepatide," posted on *Medscape*, August 12, 2024.)

Compounding Risks

Compounding pharmacies – which specialize in small-scale production of custom-tailored medications – have partly filled the gap between supply and demand by offering their own version of costly FDA-approved GLP-1 drugs, often at a lower price.

The FDA permits the marketing of compounded drugs under specified conditions, notably when shortages of brand-name products occur. Of note, compounding pharmacies should regularly review FDA status reports concerning GLP-1 shortages, in order to remain compliant with agency conditions. (See "FDA Clarifies Policies for Compounders as National GLP-1 Supply Begins to Stabilize.") Should pharmacies and telehealth companies persist in making and selling compounded formulas of GLP-1 medications after their removal from the FDA's shortages list, they may be subject to enforcement actions by the agency, as well as potential civil liability claims from the brand name drug manufacturer.

Although the FDA does not approve the formulas of compounded medications, certain legal restrictions are in force, as described in the resources listed below:

- "Compounding When Drugs Are on FDA's Drug Shortages List"
- "Compounding and the FDA: Questions and Answers"
- Federal Food, Drug, and Cosmetic (FD&C) Act, sections 503A and 503B

Prescribing Safeguards

Providers should prescribe weight-loss medications only after careful analysis of relevant scientific evidence, documentation of the product's proposed purpose, and consideration of benefits and risks. The following list of clinical safeguards is intended to help healthcare organizations and providers protect patients/clients and minimize potential liability exposure. While these strategies are aimed primarily at reducing risks associated with off-label use of branded medications and compounded weight-loss drugs, some also apply to medications prescribed for their intended FDA purpose.

1. Review federal and state regulations and guidance relating to off-label prescribing of weight-loss medications, and consult state medical licensing boards regarding applicable clinical standards for patient/client screening and monitoring, informed consent, remote prescribing and other aspects of care.

2. Remain abreast of research into the long-term effects of GLP-1 use, including pancreatitis, intestinal blockage, thyroid cancer and mood changes, among other conditions, and promptly cease prescribing drugs associated with adverse effects.

3. Treat only those patients/clients who meet strict weight-related selection criteria, such as:

- Adults with a BMI of 30 or greater.
- Adults with a BMI of 27 or greater with weight-related health problems, such as high blood pressure or type 2 diabetes.
- Adolescents, ages 12 and older, who have a BMI of 30 kg/m2 or greater and who weigh more than 60 kg (132 pounds).

4. Adopt sound assessment protocols, addressing such issues as frequency of blood testing, tracking of lab results, adjustment of doses and communication with patients/clients. Also, provide an updated medication history, including supplements and OTC drugs, when documenting assessments.

5. Do not prescribe weight-loss drugs to patients/clients who are breastfeeding; are pregnant or plan to become pregnant; or have known allergies, uncontrolled hypertension (if prescribing phentermine) or a history of medullary thyroid cancer (if prescribing semaglutide).

6. Be cognizant of common side effects and inform patients/clients of the need to promptly convey any signs or symptoms to the provider or healthcare facility. In addition, explain that if desired weight loss is not achieved within the drug's expected time frame, a different approach may need to be taken. Document all discussions in the healthcare information record.

7. Conduct a comprehensive, well-documented informed consent discussion, which covers the following issues, at a minimum:

- **Rationale for choosing off-label use of a brand-name drug or a compounded formula** of the weight-loss medication.
- **Benefits and risks of the proposed medication,** as well as alternative treatment options.
- **Short- and long-term effects** of the chosen drug's use, including potentially serious complications.
- **Importance of combining medication therapy with physical activity** and healthy eating habits.
- **Health conditions that may pose risks,** as well as relevant family medical history, such as thyroid cancer or kidney disease.

8. Monitor safety-related alerts from the FDA and adjust clinical practices accordingly. Of note, the FDA recently updated labeling requirements for GLP-1 weight-loss drugs with a warning about pulmonary aspiration during general anesthesia or deep sedation, due to the drug's effect on gastric emptying. Facilities that administer anesthesia or sedation should routinely ask patients/clients about use of GLP-1 medications.

9. Implement a reporting mechanism for adverse events relating to use of weight-loss medications. Ensure that internal reporting mechanisms comply with the FDA's Adverse Event Reporting System (FAERS), as well as state licensing board requirements.

10. Notify the facility or practice of any off-label prescribing of weight-loss drugs, in order to ensure compliance with facility protocol. Inform professional liability insurers as well, so they can verify the adequacy of existing coverage.

Sources of Liability

Medical providers and pharmacists should be aware of basic hazards and sources of liability associated with compounded weight-loss drugs, including the following, among others:

Dosing errors. Unlike brand-name drugs, compounded formulas may lack safety packaging in the form of a pre-filled injection pen, resulting in potential dosing errors. Drug packaging should specify the appropriate dose and titration of the medication, dosing schedules, and instructions on how to measure and administer the intended dose.

Inclusion of unapproved derivatives. Compounded formulas may or may not include the same active ingredients found in branded products. In some cases, derivative forms of a drug – such as semaglutide sodium and semaglutide acetate – are added. Per FDA guidance, the use of salt forms in semaglutide injectables does not meet the conditions of section 503A of the FD&C Act. In order to ensure formulas are free of dangerous impurities, compounding pharmacies are expected to dispense weight-loss drugs with an accompanying list of ingredients, as well as provide prescribers with access to the certificate of analysis for the active pharmaceutical ingredient, if requested.

Use of prohibited substances. Section 503A of the FD&C Act restricts bulk drug ingredients that may be used to compound human medications. The FDA requirements are summarized in the pullout to the right; however, these rules are somewhat complex and readers should consult the cited online sources.

The development of semaglutide and related weight-loss medications has revolutionized treatment of obesity, diabetes and other related conditions. However, off-label use of branded drugs, as well as the use of their compounded counterparts, is not without risk. By being aware of the hazards associated with these products and adopting effective selection, assessment and documentation policies and procedures, prescribers can help patients/clients achieve their weight-reduction goals in a safe, controlled manner.

Compounded Drug Ingredients: Basic Requirements

Section 503A of the FD&C Act governs the bulk drug substances that may be used to compound human medications. The ingredients used in such formulations must meet the following standards, among others:

1. Substances used in compounded medications must be included in the *United States Pharmacopeia* and its chapter on pharmacy compounding or, alternatively, in a National Formulary monograph.
2. If such a monograph does not exist, bulk drug substances must be components of drugs already approved by the FDA.
3. In addition to the above requirements, bulk drug substances must appear on the FDA's 503A Bulks List.

Note that, under federal law, use of the component *retatrutide* in compounded drugs is illegal, as it is not an FDA-approved drug.

Quick Links

- "FDA Clarifies Policies for Compounders as National GLP-1 Supply Begins to Stabilize," issued by the U.S. Food and Drug Administration, updated December 19, 2024.
- CNA *inBrief*® 2022-Issue 1, "Off-label Product Use: Basic Risk Management Considerations."

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