Ensuring the Appropriate Use of Glucagon-Like Peptide-1 Receptor Agonists

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ACCP CALL TO ACTION

The American College of Clinical Pharmacology (ACCP) strongly encourages healthcare professionals who provide chronic weight management therapy and are considering the use of glucagon-like peptide-1 (GLP-1) receptor agonists, to ensure these emerging medications are appropriately prescribed, supplied, and filled per the approved labels. Healthcare professionals should also ensure that patients are clinically monitored, and these agents are utilized as part of a well-balanced treatment plan which includes a comprehensive, multi-method approach emphasizing coaching for positive lifestyle changes and enhancing health literacy to maximize benefits and mitigate risks for patients. Additionally, we encourage regulatory agencies to utilize all available means to prevent the manufacturing and importation of unapproved GLP-1 receptor agonists and to stop dangerous prescribing behaviors of these products.

Introduction

Obesity is a multifaceted disease with increasing prevalence and profound implications for both the individual and society. In the United States alone, from 2017 to 2020, the prevalence of obesity was approximately 42% in adults aged ≥20 years and approximately 20% in children and adolescents aged 2 to 19 years.[1] The significance of obesity as a disease is linked to a myriad of associated health disorders, which include metabolic complications (e.g., diabetes, dyslipidemias, hyperuricemia, and metabolic syndrome), cardiovascular diseases (e.g., hypertension, atherosclerosis, heart failure, and atrial fibrillation), and certain cancers (e.g., breast cancer, esophageal, liver cancer, colorectal, prostatic, thyroid, pancreatic adenocarcinoma, renal, and multiple myeloma), resulting in higher rates of morbidity and mortality.[2] Moreover, obesity also takes its toll on the mental health of patients, contributing to depression, anxiety, and low self-esteem.[3]

The typical treatment paradigm for obesity generally includes lifestyle modifications such as dietary changes and increased physical activity, behavioral therapy, medications, and in some severe cases, bariatric surgery, with an aim of sustainable weight loss and improved overall health. Unfortunately, many people are unable to achieve clinically meaningful and sustained weight loss with lifestyle modifications alone, and until recently, successful pharmacological treatments for chronic weight management were lacking. The history of pharmacotherapy for weight loss in the United States has been riddled with failures, be it the "rainbow diet pills" of the 1940s, which were essentially mixtures of amphetamines and diuretics to the "fen-phen" (combination therapy fenfluramine/phentermine) enthusiasm of the 1990s, which was later linked to significant cardiovascular and respiratory complications.[4]

However, not all therapies were failures and there have been some successfully marketed treatments. The amphetamine derivatives phentermine, benzphetamine, and diethylpropion, which were developed in the late 1950s/early 1960s, are sympathomimetics which act to increase levels of norepinephrine and to a lesser extent, dopamine, and serotonin.[5,6] However, these medications were approved for only short-term use. These derivatives were then followed in the 1990s by a few compounds designed for the long-term management of obesity. These include orlistat (lipase

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inhibitor), and the combination therapies phentermine/topiramate (sympathomimetic/antiepileptic), and bupropion extended release/naltrexone extended release (norepinephrine and dopamine reuptake inhibitor/mu opioid receptor antagonist).[7]

Recent research into new treatments for type 2 diabetes recognized the role that incretin hormones play in both diabetes and obesity. These hormones are released in the intestines in response to the presence of nutrients. The two main incretins involved in this process are glucagon-like peptide-1 (GLP-1), produced by the L cells (located in the distal ileum and colon), and glucose-dependent insulinotropic polypeptide (GIP), produced by the K cells (located in the duodenum and jejunum). Both are part of the entero-insular axis of glucose homeostasis.[8,9] When released, both hormones stimulate insulin production in pancreatic β cells in a glucose-dependent manner.[8] Additionally, GLP-1 was found to have a direct suppressive effect on appetite and slowing gastric emptying.[8] From a pathophysiology standpoint, normal GLP-1 secretion in the gut appears to be impaired in both individuals with type 2 diabetes and obesity.[9]

Currently, there are eight approved GLP-1 receptor agonists (RA), six of which are indicated for the improvement of glycemic control and two indicated for chronic weight management. There are also two approved combined GIP/ GLP-1 receptor agonists, one for the treatment of glycemic control and one for chronic weight management. The two GLP-1 RAs approved for chronic weight management in both adults and children include liraglutide (SAXENDA) and semaglutide (WEGOVY).[10,11] The one approved GIP/GLP-1 RA for chronic weight management in adults is tirzepatide (ZEPBOUND).[12] All three are indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in individuals with a body mass index (BMI) $\geq$30 or $\geq$ 27 kg/m^2 in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, dyslipidemia, obstructive sleep apnea, or cardiovascular disease). It is important to note that for the GLP-1 RAs approved for the treatment of both chronic weight management and type 2 diabetes, a lower dose formulation is indicated for type 2 diabetes.

Although the GLP-1 RAs have been on the market since 2005 with the approval of exenatide (BYETTA) for the improvement of glycemic control, the regulatory approvals of the GLP-1 RAs and the GIP/GLP-1 RA for chronic weight management are more recent and have been well received by physicians and patients.[13] With pivotal clinical trial results reporting a placebo adjusted weight loss that ranged from approximately 12% (semaglutide) to 18% (tirzepatide), which surpassed other marketed therapies that typically have a weight loss range of 4% to 11%, commercial demand has grown rapidly.[14,15] Additionally, when considering the findings of improvement in cardiometabolic risk factors for these compounds, it is understandable that there is great excitement around this class of drugs.[14–16] However, like all new products that show a significant impact in global healthcare, the excitement and demand for GLP-1 RAs and GIP/GLP-1RA has led to potential abuses and treatment paradigms that neither follow regulatory labeling nor are grounded in the known science that led to their approval. There may not be proper appreciation of the limits to the available data, the short-term and/or long-term adverse effects of these drugs, nor the potential for weight rebound and loss of cardiovascular benefits if treatment is stopped. Additionally, the availability of counterfeit or adulterated versions of these medications, the misuse or abuse by the general public, and exacerbation of drug shortages for those GLP-1 RAs and GIP/GLP-1 RA labeled for type 2 diabetes when they are used off-label for weight loss, should also be considered. The following is a brief review of these potential concerns that ultimately support the position of the American College of Clinical Pharmacology (ACCP) in this paper.

Recognizing Potential Safety Issues

Obesity is often associated with stigma and discrimination. While the thoughts and feelings regarding this issue often go unspoken, psychologists have recently brought to attention the importance of how weight lowering medications may further drive these discriminatory views.[17] As such, the population in general may feel undue pressure to take these newer weight lowering medications when they may not be indicated. In addition, those obese individuals that do meet the criteria for pharmacotherapy, may solely rely on this intervention rather than balancing this treatment with lifestyle changes that incorporate a healthy diet and exercise to help support their continued weight management and improve their overall health.

With the growing media attention and the rapidly increasing number of individuals taking GLP-1 or GIP/GLP-1 RAs, some physicians and researchers have started to raise concerns about the indiscriminate use of this class of medication, as they are not free of potential short-term or long-term toxicities and the risk–benefit ratio may not be adequately appreciated by those seeking only short-term, even cosmetic, weight loss. It is important to point out that some adverse effects may also be serious and require the timely identification and prompt response by the treating physician to either reduce the dosage or stop the medication. In other situations, additional pharmacotherapy or hospitalization may become necessary to treat patients with these adverse effects. Concerningly, it is also likely that some

of these adverse effects may be misinterpreted as a new medical condition, thus increasing the possibility of an unnecessary prescribing cascade.

The most reported adverse events associated with GLP-1 RA administration tend to be gastrointestinal in nature and commonly occur at the onset of therapy, prompting gradual up-titration of these compounds, at least for those being treated for type 2 diabetes. In the phase 3 clinical trials involving semaglutide, liraglutide, dulaglutide, exenatide, and lixisenatide, in obese and/or type 2 diabetes patients, the most common GI side effects experienced were nausea, vomiting, diarrhea, and constipation.[18] Nausea was the most frequently reported adverse event, with a frequency of 5% to 59% across the different compounds, irrespective of the respective half-life or route of administration.[18] While these adverse events are typically transient, other more serious gastrointestinal events have been reported.

For example, in a recently published health claims database study, researchers investigated the incidence of gastrointestinal adverse effects in patients with obesity prescribed the GLP-1 RAs semaglutide and liraglutide or the combination therapy bupropion–naltrexone, from 2006 to 2020.[19] The incidence of biliary disease (per 1000 person years) was 11.7 for semaglutide, and 18.6 for liraglutide compared to 12.6 for bupropion–naltrexone. The incidence of pancreatitis was 4.6, 7.9, and 1.0; the incidence of gastroparesis was 9.1, 7.3, and 3.1; and the incidence for bowel obstruction was 0.0, 8.1, and 1.7 for semaglutide, liraglutide, and bupropion–naltrexone, respectively.[19] While this real-world evidence study assessed GLP-1 RA use in patients with a record of obesity (and without a diagnosis of diabetes), whether the use was solely for weight loss is uncertain and dosage was not reported.

These types of adverse events and their respective frequency should be carefully considered when prescribing this class of agents. Pancreatitis can cause severe abdominal pain and may be life-threatening, sometimes necessitating surgery. Gastroparesis and bowel obstruction have been linked to a poor quality of life.[20] Additionally, while gastroparesis primarily causes bloating, cramping, nausea, and vomiting, these side effects may also lead to more severe outcomes. In September 2023, the Food and Drug Administration (FDA) required the Adverse Reactions Section of the semaglutide label to include the potential for ileus.[21] At the time of this label update, there were approximately 20 reported cases of ileus, including two deaths, after its use.[22] Although the occurrence of this event is very rare, its severity cannot be ignored. Thus, health practitioners should be mindful of this rare, but serious, adverse effect when educating patients on the risks and benefits of these medications.

Beyond the gastrointestinal side effects, there has also been increased attention placed on some of the potential psychological adverse effects, such as depression and suicidal ideation. While clinical trial data can be a source for this type of information, many times such events are not adequately identified until its use in a broader, real-world setting. A recent retrospective pharmacovigilance study of the European Pharmacovigilance database by Ruggiero et al assessed the reports of suicidal events (ideation and attempts) from 2018 to 2023 among those using GLP-1RAs.[23] A total of 236 suicidal events were identified, with suicidal ideation accounting for approximately 65% and suicidal attempts accounting for approximately 20%.[23] The events of ideation occurred most frequently with the use of liraglutide and semaglutide, while the events of suicidal attempt were primarily observed with dulaglutide and liraglutide. Both types of suicidal events were mainly reported in female patients.[23] An accurate assessment of causation would require further investigation, likely by the EMA Pharmacovigilance Risk Assessment Committee (PRAC) in the future.[23]

These types of adverse events are also closely being watched by the US FDA. Although a preliminary review of the FDA's Adverse Event Reporting System has found no causal link between use of GLP-1 RAs and suicidal thoughts or actions, the agency recognizes that current data are limited and had the potential for confounding factors.[24] Thus, the FDA will continue their investigation with a meta-analysis of all clinical trial data and a sentinel system post-marketing data analysis.[24] Such concerns by both regulatory agencies are not surprising, since most centrally acting antiobesity drugs, like the GLP-1 RAs, raise attention to the potential for neuropsychiatric safety issues.[23] In fact, the labels for weight management products carry a class warning that advises healthcare professionals to monitor patients for the emergence of worsening depression, suicidal thoughts or behaviors, or any unusual changes in mood or behavior.[24] Interestingly, the cases of suicidal events appear to be related to dose, with higher doses (those typically used for weight management) displaying a greater frequency.[23] Importantly, only those GLP-1 RAs indicated for chronic weight management have this required class warning included in the approved label, while those indicated for glycemic control do not, although many are used off-label for this same purpose. This raises the question if healthcare professionals prescribing GLP-1 RA formulations that are indicated for glycemic control but are prescribing them for off-label chronic weight management, are informed of this potential, albeit rare, serious risk and are properly monitoring their patients, particularly those with prior mental health conditions.

Another adverse event which healthcare practitioners should be aware of when prescribing these new weight loss medications is the potential for the loss in lean (muscle, bone, and organ) body mass.[25] Rapid loss of lean body mass ultimately results in sarcopenia and a loss of bone density, which is particularly concerning for older individuals and perimenopausal women. A recent systematic literature review conducted by Bikou et al, assessed the effect of semaglutide on lean body mass across the various clinical trials conducted from January 2014 to July 2023. The authors note, that "while the overall reduction in weight was primarily attributed to the loss of fat mass, noteworthy reductions in lean mass were observed in the larger randomized controlled trials conducted by Wilding et al.[14] and McCrimmon et al."[26] Importantly, while both these trials noted that the total lean body mass decreased in absolute terms (kg change), the proportion of lean body mass relative to total body mass increased, suggesting a positive trend. Ultimately, not enough data is available yet to truly determine the impact on lean body mass and further investigation into this potential effect is warranted.

Finally, obese individuals can often suffer from nutritional deficiencies due to poor ingestion of minerals and vitamins which may have serious consequences to their overall health. These micronutrients play an important part in maintaining both the physical and mental well-being of the patient, as they not only act as cofactors in metabolic reactions but also play a vital role in proper functioning of various organ systems.[27] When the treatment of obesity solely focuses on reducing food intake through direct suppressive effects without balancing for other dietary and nutritional changes, health practitioners have seen an increase in the number of undernutrition cases and nutrition-related adverse events. Although obesity results from an imbalance between caloric intake and expenditure, the factors causing this imbalance are not the same for all patients. Therefore, obese patients need individualized care and a tailored approach from their prescribing physicians with a careful consideration of concomitant medication, diet, exercise, and lifestyle changes.

Concerns Regarding Advertising and Medication Product Quality

While direct-to-consumer advertising for pharmaceutical products is a common marketing approach, the increased volume of consumer-directed advertising through TV, radio, and social media platforms by various physical retail and online businesses operating under the category of weight loss clinics, telehealth services, specialty/compounding pharmacies, medical/wellness spas, and digital health applications has become concerning. It has been reported that on the social media platforms Facebook and Instagram alone, there were more than 4000 active ad campaigns in the United States promoting the use of semaglutide (Ozempic and Wegovy).[28] Most of these advertisements are neither funded nor supported by the sponsor pharmaceutical companies manufacturing these drugs, but rather by independent businesses supplying the medications directly to the consumer.

This type of advertising raises concerns, as sponsor drug companies must disclose the potential risk information for their products when advertising claims are made. According to federal law, it is imperative that drug companies provide consumers a "fair balance" of information when addressing the risk to benefit ratio for their products. Additionally, any statements relating to side effects and contraindications must be presented in a clear, conspicuous, and neutral manner.[29] The majority of these new non-sponsor-related GLP-1 RA ads do not adequately present the required risk information listed in the drug's prescribing information and in many such ads no safety information is included at all. Additionally there have been reports that some of these companies utilize different salt forms of the active pharmaceutical ingredient (API) than what is contained in the approved marketed product, as well as non-pharmaceutical grade API intended for "research use only," or products sourced from establishments not registered with the FDA, as required under Section 510 of the Food, Drug & Cosmetic (FD&C) Act § 503A(b)(1)(A)(ii)–(iii). [30–34] There have also been reports of these companies supplying adulterated products containing significant levels of both known and unknown impurities and selling products containing lower doses or different compounds than what is labeled.[35,36]

Attention to Proper Prescribing, Use Behavior, and Therapeutic Management

The FDA-approved drug labeling is the primary tool for communicating essential information regarding the safe and effective use of a drug product.[37] The approved drug label provides essential information about the appropriate patient population for which the drug is indicated, the approved dose and regimen, contraindications, warning and precautions, adverse reactions, and the clinical studies which supported the approval of drug.[37]

The FDA-approved labels of GLP-1 RA drugs for chronic weight management have clearly defined patient populations for which they are indicated:

- Adult patients with BMI of 30 kg/m^2 or greater (obesity);[10–12]
- Adult patients with BMI of 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia);[10–12]

- Pediatric patients aged 12 years and older with an initial BMI at the 95th percentile or greater for age and sex (obesity).[10,11]

The indication statements for these drugs also make it clear that they are to be used as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management. Lifestyle interventions including diet and exercise are the cornerstone of weight loss management.[38,39] In the phase 3 trials of GLP-1 RA drugs Wegovy and Zepbound, all patients received lifestyle intervention in addition to the drug intervention.[14,15]

Off-label prescribing refers to actions that are not concordant with the indications, doses, routes of administration, or patient groups included in the approved label.[40] There are reports where GLP-1 RA drugs have been prescribed off-label to healthy subjects who do not meet the criteria of the indicated patient populations, but simply wish to lose weight for image-enhancing (i.e., non-medical) reasons.[41] The evidence supporting off-label use of a drug has generally been less thoroughly scrutinized than for FDA-approved uses and the balance of benefits and risks may not be as well known. As noted above, acute pancreatitis, acute gallbladder disease, hypoglycemia, acute kidney injury, and hypersensitivity have been reported at a higher rate than placebo in clinical trials of both Wegovy and Zepbound.[11,12] While the benefit of GLP-1 RA drugs may outweigh the risk in the indicated patient population, the same may not be true in healthy individuals who are not obese and desire to lose weight for cosmetic reasons. Additionally, off-label use and the potential for abuse could be increased in those individuals considered vulnerable or have a body dysmorphic disorder, thus healthcare professionals should be carefully assessing this risk.

Off-label use of these drugs can also contribute to critical drug shortage and put patients correctly indicated for these drugs on significantly long waitlists. This is particularly concerning for those GLP-1 RAs formulated for type 2 diabetes but being used for off-label for short-term/cosmetic weight loss. Additionally, while these compounds fall within the same drug class, their pharmacological and safety profiles differ and switching from one drug to the next is common. Thus, it is critically important for these drugs to be properly prescribed and attention given to their pharmacological profiles. This will take the concerted effort of healthcare professionals, manufacturers, health insurance companies, Medicare and Medicaid, and society alike, to ensure their appropriate use and access for patients in need.

While the advent of telehealth has certainly enhanced and improved healthcare access, questions are now arising regarding the lack of appropriate medical professional/patient relationships, particularly with the rise of GLP-1 and GIP/GLP-1 RA therapies used for chronic weight management. Establishing these relationships are critically important and initial interactions should include a through medical assessment to ensure potential patients meet the appropriate indications for therapy, including evaluating for risks of drug/disease interactions as well as routine, long-term clinical monitoring of patients for adverse events and proper medication usage. Concerningly, most of these businesses which advertise their services, frequently through internet websites and telemarketing activities, to supply GLP-1 and GIP/GLP-1RAs for weight loss, are not engaged in appropriate medical management of their consumers. In most cases, there is no communication between the medication suppliers and the patient's primary healthcare provider, nor any follow-up communication or medical assessments to ensure proper medical monitoring is being performed. The use of telehealth companies may also allow individuals to obtain this product through multiple sources, potentially increasing safety concerns and the risk for abuse. While some of these businesses offer virtual dieticians and lifestyle coaching in conjunction with prescriptions, many do not. There have also been reports of some of these businesses providing prescriptions for GLP-1 RAs to consumers without any clinician-patient interaction, instead relying solely on the use of automated surveys/chat communication. Additionally, because many of these companies are supplying their medication directly to the consumer, there is often a limited opportunity for a pharmacist's evaluation of potential drug–drug and drug–disease interactions. This combination of rampant inappropriate advertising and often blatant failure to ensure proper clinical patient evaluation and medication management creates an environment for misuse and represents an increasingly growing threat to public health safety.

Discussion

Obesity is more than just a physical condition; it is a multifaceted medical disease with profound implications for both individuals and societies. Beyond its visible impact on weight, obesity is intricately linked to a myriad of health complications, including diabetes, cardiovascular disease, hypertension, and certain cancers. Its prevalence has reached alarming levels globally, making it a critical public health concern.

By acknowledging obesity as a disease rather than merely a lifestyle choice, we validate the complex interplay of genetic, environmental, and socioeconomic factors that contribute to its development. This acknowledgement also helps change our mindset in how we approach prevention, treatment, and public

health policies. Pharmaceutical interventions can play an important part in this treatment paradigm but should not be the sole factor involved. A comprehensive approach that includes prevention strategies in the form of lifestyle changes (incorporating healthy dietary habits and regular exercise) should be implemented and when appropriate, behavioral therapy should also be considered.

The advent of the GLP-1 and GIP/GLP-1 RAs as a treatment for obesity not only provides a vital tool in the physician's armamentarium for obesity but requires a well-needed public attention to this disease state. The current excitement that healthcare practitioners, regulators, researchers, and patients have for this class of medication is certainly justified. As more research is performed, additional potential benefits of this mechanism of action that go beyond glycemic control shall continue to be uncovered. For example, its potential use in obese patients with heart failure with preserved ejection fraction is currently being investigated in the STEP-HFpEF Trial.[42] However, this fervor should be tempered and properly balanced with an understanding of our still limited scientific and medical knowledge with this class of compounds. Short- and long-term side effects should be considered, clinically monitored, and the potential for weight rebound and loss of beneficial cardiovascular effects when stopping these medications should be discussed with the patients. Additionally, our healthcare society needs to consider the potential for significant abuse and misuse as the demand for these compounds grows and must take steps to ensure that patients are appropriately informed regarding the medical risks and proper usage of these compounds and are only receiving FDA-approved medication products.

Thus, the ACCP strongly encourages Healthcare Professionals who provide chronic weight management therapy and are considering the use of GLP-1 receptor agonists, to ensure these emerging medications are appropriately prescribed, supplied, and filled per the approved labels. Healthcare professionals should also ensure that patients are clinically monitored and that these agents are utilized as part of a well-balanced treatment plan which includes a comprehensive, multi-method approach emphasizing coaching for positive lifestyle changes and enhancing health literacy to maximize benefits and mitigate risks for patients. Additionally, we encourage regulatory agencies to utilize all available means to prevent the manufacturing and importation of unapproved GLP-1 receptor agonists and to stop dangerous prescribing behaviors of these products.

Conflicts of Interest

Kenneth Todd Moore is an employee and stockholder of Janssen Pharmaceuticals. Parag Kumar is an employee and stockholder of Gilead Sciences. Aman Gupta discloses no conflicts of interest. Jinshan Shen is an employee and stockholder of Relay Therapeutics.

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This will not be Open Access.

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