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Embracing the Pros and Cons of the New Weight Loss Medications (Semaglutide, Tirzepatide, Etc.)

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Abstract

Purpose of Review The history of multiple weight loss medications has been a concerning paradox based on an increased cardiovascular risk despite significant reductions in adipose tissue and weight. A new class of weight loss medications could change this past narrative based on early preliminary results of cardiovascular risk (not events—still need to be determined) and weight reduction in non-diabetics that acutely competes with results achieved with bariatric surgery. The purpose of this review is to provide a comprehensive summary of the advantages and disadvantages of these newer medications, and how they could impact urology.

Recent Findings Weight loss of − 15 to − 20% compared to baseline has become plausible in the short-term and preliminary guidance to reduce acute and chronic adverse events are receiving attention. However, the cost, access, conflicts of interest, supply chain, life-long adherence issues, and the long-term diverse implications on mental and physical health when exposed to this class of medications (GLP-1 agonists) are unknown. The profound caloric reductions should also result in baseline or ongoing nutritional deficiency testing, and general and specific dietary recommendations, which could theoretically mimic some bariatric surgery pre- and post-surgical protocols but has yet to be studied. Regardless, the potential impact of these medicines within a variety of medical specialties needs clinical research.

Summary Current and future lifestyle interventions, dietary patterns, and medicines in the weight loss category need to be held to a paradigm whereby cardiovascular health should improve with significant weight loss without a negative impact on mental health. In urology, the ability to impact cancer risk, ED, FSD, incontinence, infertility, nephrolithiasis, and multiple other endpoints are plausible (based on bariatric surgery data) but need preliminary clinical research. Other medicines with a similar or even larger potential impact are in clinical trials, and thus, a concise overview for clinicians and researchers was needed for objective guidance. Currently, comprehensive lifestyle changes utilized with and without these medications continue to garner positive mental, physical, and legacy effects, which suggest that they are as necessary as ever in the treatment of the numerous conditions impacted by unhealthy weight gain.

Keywords Semaglutide · Tirzepatide · Urology · GLP-1 agonist · Bariatric surgery · Lifestyle changes · Weight loss

Introduction

Weight loss medications, in some notable cases (fenfluramine/phentermine and sibutramine), are part of a historical dubious paradox, whereby an increased cardiovascular risk or events occurred despite significant reductions in adipose tissue [1]. A more recent concern in this category was expressed over lorcaserin, which appeared to not only increase the risk of several different cancers [2] but had questionable mental health impacts [3]. All these past examples resulted in the removal of these options from the prescriptive marketplace. Smoking or nicotine exposure is somewhat crudely analogous to this past concerning situation since patients could lose weight or prevent gain, but it has detrimental impacts on cardiovascular and other health outcomes [4–6]. In other words, just because a product can assist with weight loss does not immediately suggest it simultaneously provides a heart or mentally healthy impact. Current and future lifestyle interventions, dietary patterns, and medicines in the weight loss category should be held to

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a paradigm whereby cardiovascular health (risk and events) and even all-cause morbidity and mortality should simultaneously improve with weight loss [7].

Bariatric surgery appears to have met these impressive standards [8–10], including substantial reductions in the risk and mortality of multiple cancers [10], which is why it should continue to be a primary option for those patients requiring substantial weight loss to improve a variety of health risks and outcomes. Regardless, a salubrious source of past skepticism existed over whether a non-surgical intervention could result in profound weight loss while simultaneously improving cardiovascular and all-cause risk, mortality, and their relevant clinical endpoints (myocardial infarction, stroke, cancer, etc.). Today, this historical narrative could be in flux.

Incretin mimetics were originally conceived for the treatment of type 2 diabetes via insulin production stimulation and glucose regulation, but when diabetics began to lose weight with the potential for major adverse cardiovascular event (MACE) reduction in patients with confirmed cardiovascular disease (CVD), they were then repurposed for weight reduction [11, 12]. Semaglutide and tirzepatide are glucagon-like peptide-1 (GLP-1) agonists, which are hormones naturally produced by the human body in small dosages to slow gastric emptying and impact the brain to reduce appetite and energy intake [13–15]. GLP-1 is secreted by enteroendocrine L-cells in the small and large intestine when glucose or fat encounters the intestinal lumen. Higher concentrations of L-cells are found in the latter section of the ileum and colon. Specific cells in the nucleus tractus solitarius in the brainstem also appear to secrete GLP-1 [16•]. Interestingly, bariatric surgery with a malabsorption and restrictive component has also been found to increase GLP-1 [17], but caloric restriction (CR) without surgery has no consistent pattern from preliminary research, and some studies even suggest a reduction in this compound [18]. Moderate- and high-intensity exercise appears to acutely increase GLP-1 [19], which when combined with CR or fasting could be helpful for weight loss [20]. It is of interest many of the weight loss trials of semaglutide utilize caloric reduction and physical activity in the intervention and placebo groups [16•]. Still, one major limitation with endogenously synthesized GLP-1 is the brief plasma half-life of 1.5 to 2 min due to enzymatic elimination via dipeptidyl peptidase-4 (DPP-4) [16•]. Thus, the previous and ongoing research had led to novel GLP-1 agonists that can be exogenously delivered with longer and more sustainable half-lives. For example, semaglutide is a modified version of GLP-1 to protect it from immediate degradation and contains strong affinity to albumin with a half-life of approximately 1 week.

Tirzepatide contains an additional incretin agonist known as "gastric inhibitory polypeptide" (GIP) or "glucose-dependent insulinotropic polypeptide" [21], which could be one explanation of its preliminary greater reduction in body weight of approximately − 20% with this dual acting agonist vs semaglutide (single agonist) of − 15% in non-diabetic overweight and obese patients who qualified for these medications in clinical trials. Another explanation could be the need for more phase 3 trials with tirzepatide or a head-to-head study to appreciate the mean percentage weight reduction with this medication. It should also be noted that tirzepatide was not FDA approved for weight loss at the time of manuscript submission to this journal, but the potential for approval in 2023 or early 2024 appears optimistic. This dual agonist has also brought attention to GIP, which is also secreted endogenously in humans in response to nutrient consumption, and both hormones also result in pancreatic beta-cell stimulation to release insulin in a glucose-dependent pathway [21]. GIP is secreted by K cells in the proximal portion of the small intestine. These agents represent one of the most acutely impactful weight loss interventions ever conceived and their results are superior to what has been achieved thus far in this specific and general class of medications [22], but what are the current and potential advantages and disadvantage of these novel agents?

Acute and Chronic Adverse Effects and Medication Discontinuation Before Some Procedures

Gastrointestinal adverse effects are concerning with these medications despite being mild-to-moderate and transient especially during dose-escalation periods. For example, prescribing information for semaglutide currently lists nausea (44%), diarrhea (30%), vomiting (24%), constipation (24%), abdominal pain (20%), headache (14%), and fatigue (11%) [23]. A recent "real-life" Mayo Clinic cohort study of 175 patients found that an approximate 49% experienced adverse effects with nausea and vomiting (37%) and then diarrhea (9%) and fatigue (6%), constipation (6%), and abdominal pain (5%) less common [24]. A total of 3% discontinued the drug due to adverse effects and 9% required dose-reduction or non-dose escalation. The issue of chronic or long-term exposure to these agents has yet to be answered, except for the real observed issue of two-third weight regain from baseline after 1 year of medication cessation along with the regression of multiple metabolic markers [25••]. There is also the issue of laboratory animal studies suggesting thyroid C-cell tumor initiation in mice and rats, which was dose- and treatment-duration dependent, and how this could potentially translate to humans [23]. Currently, semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC), or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Semaglutide cessation should also occur at least 2 months—due to the extended half-life, before a planned pregnancy in females and males because of the concern for fetal injury.

Gastric emptying appears to be delayed with these agents, which raises the question of the potential of intraoperative pulmonary aspiration [26], regurgitation under anesthesia [27], upper endoscopy procedural concerns [28], and other yet to be appreciated issues. Recently, the American Society of Anesthesiologists (ASA) Task Force on Preoperative Fasting suggested patients undergoing elective procedures to temporarily discontinue GLP-1 agonists for 1 day to 1 week depending on the dosing schedule of the specific product being utilized (see consensus guideline) [29••]. This "suggestion" applies regardless of the dose, indication, or surgery/procedure. They also offer recommendations on when to consider delaying the elective procedure based on gastrointestinal symptoms, and recommendations of what to consider even if no symptoms are occurring, but the medication was not withheld. This guidance statement also acknowledges preliminary research, which suggests that gastric emptying issues appear to decrease with long-term utilization [29••, 30].

A separate expert multidisciplinary expert consensus manuscript was also recently published on how to prevent and manage gastrointestinal issues in patients on GLP-1 agonists [31••]. This manuscript is a preliminary guide on dealing with the most common adverse effects of these medications. Again, these issues are prevalent regardless of the half-life, duration, or route of exposure (oral/subcutaneous). Gastrointestinal (GI) side effects are usually temporary and occur often during dose-escalation periods and when the maintenance dosage is achieved it is less prevalent in incidence and severity. Some of the many dietary suggestions proffered to decrease the intensity of GI issues include the following (see the publications for more detailed information):

- Consume smaller portion meals more often, eat slowly, only when hungry, and feeling of satiety should cause eating cessation
- Sitting or standing after a meal (avoid lying down)
- Do not consume food near bedtime, be less active after eating, and avoid drinking with a straw
- Low-fat diets and water-based salubrious foods (soups, gelatin etc.) are more ideal
- Avoid high-fat and processed or refined foods
- Try to limit or avoid sweets, spices, dressings, and canned food
- Maintain a food diary to determine personal food triggers and relievers of adverse effects

There are also added recommendations for those with nausea (ginger-based drinks, etc.), vomiting (hydrate, smaller meals, etc.), diarrhea (hydration, electrolyte beverages, avoid high fiber and sugar alcohols, etc.), or constipation [31••]. It should also be noted that weight loss has currently not been correlated with the extent of GI side effects with these newer GLP-1 agonists [32, 33], which may be another advantage compared to some older medications in this class [34], but this issue requires more analysis. Separately, the recent FDA approval of semaglutide in adolescents (age 12 or older) suggests the short-term safety of this and potentially other newer agents in this class are still notable [23, 35]. In general, side effects in teenagers from a phase 3 trial occurred early and began to dissipate over time [36]. In adults semaglutide 2.4 mg once weekly was approved for weight management in patients with a BMI of 27 or more who have at least one or more weight-associated health issues, or in patients with a BMI of 30 or more [23, 37]. In teens it was approved for aged 12 and older who are at the 95th percentile or higher for sex and age (obesity)-based on growth chart criteria from the Centers for Disease Control (CDC) [35]. In adults and teens the FDA approval also includes the language to include a caloric reduction meal plan and increased physical activity in addition to the medication for optimal efficacy.

Appetite, Cravings, Energy Intake, Food Preferences, Satiation, Taste, and Addictions?

The old adages of "calories in versus out" or "calorie intake versus caloric burn" although often criticized do have some merit regarding dramatic weight reduction. This was identified in bariatric surgery patients in whom the procedure has short- and long-term success with greater sustained reductions in energy intake [38•]. Interestingly, energy or caloric reductions of more than 50–66% from baseline can be observed initially post-surgery, but over the next several years this percentage tends to decrease to less than 50%, and after 10 years there appears to be tremendous latitude in patient energy intake ranging from less than 10 to 45% reductions [38•, 39]. Again, some of the largest reductions in weight in men and women over short and long periods occur in those able to achieve the largest caloric reductions along with appropriate macronutrient intakes. Some of the largest caloric reductions in the first year are predictive of long-term success, and the mean weight loss appears greatest after year 1 compared to any other year up to a decade later. It appears over time that most patients cannot sustain such profound caloric restrictions, and this is reflective in the percentage weight changes from baseline. For example, after 1 year of follow-up in a notable study men and women lost approximately 24% and 26% of their baseline weight, but after 10 years of follow-up this was reduced to 15% and 17%, respectively [38•]. However, the plus or minus standard deviation around these mean reductions from baseline in the first- to the tenth-year post-surgery was approximately

9–12%. This would in part (not fully) explain why weight regain occurs in many patients as well as one reason a small percentage of patients do not experience significant weight loss over time, which is why other competitive non-surgical options would also be beneficial, or even perhaps some select patients could synergistically utilize a procedure with a medication. Additionally, with increasing age and reductions in weight there is a reduction in basal metabolic rate (BMR) with an increase in appetite, which partly explains why some partial weight regain over time is the rule and not the exception regardless of the past diet or surgical intervention studied [40–42].

Preliminarily, the dramatic acute caloric reduction situation has also been observed regarding the newer GLP-1 medications [43]. Appetite, energy intake, and fat mass reductions occur including in those with type 2 diabetes, but remarkably there has been minimal published overall on the quantity and quality of calories impacted upon medication initiation, continuation, or cessation. For example, on a subcutaneous low dose (1 mg) of semaglutide a 24% reduction in total caloric intake was noted at 12 weeks from baseline [44]. A trial of standard dosage of semaglutide for weight loss observed a − 47.1% mean energy intake versus − 18.6% with placebo at week 20 from baseline with increases in satiation [45]. In a study of type 2 diabetics on oral semaglutide (14 mg) after 12 weeks, energy intake was reduced by approximately 39% versus placebo (− 1217 cal) [46]. Thus, preliminary data suggests that profound caloric reduction occurs with higher oral and injectable dosages of these medications. It appears reasonable to predict that 25–50% energy intake decreases with the conventional weight loss dosages of the GLP-1 agonists. Whether or not this can continue long term is unknown. One interesting differential impact of these agents is the ability for those without diabetes or simply less insulin resistance to experience larger reductions in weight [16•].

Another preliminary observation is the impact of these medications on food preferences or cravings. A recent systematic review of 12 GLP-1 agonist studies meeting the inclusion criteria ($n = 445$) found appetite and craving reductions, food preference and taste changes, and altered gastric emptying were noteworthy [47]. In the STEP 5 trial of semaglutide at 104 weeks there was a significant reduction in the penchant for salt, spicy, dairy, and starchy foods [48]. Perhaps another mechanism of interest is the ability of these agents to impact foods or behaviors associated with greater caloric intake or adipose tissue storage. Thus, it is plausible that some addictive behaviors or self-medicating tendencies with certain foods and other substances could be favorably impacted. Recent laboratory evidence suggests that GABA neurotransmission could be affected, which could result in a reduction in alcohol intake or other addictive behaviors [49]. It is for this reason clinicians may not only be able to prevent smoking cessation weight gain on these agents, but the desire for tobacco intake itself, if future studies suggest a benefit in this area. This would be one area of research interest in urology or other specialties where immediate smoking cessation could provide a morbidity and mortality advantage (bladder cancer treatment, etc.).

Adipose Tissue (Fat Mass) vs Lean Muscle Mass Lost and Resistance Exercise?

Body weight changes appear to be primarily the result of fat mass reduction with GLP-1 agonists, although lean muscle mass loss also occurs. A subgroup of the STEP 1 study (95 on semaglutide and 45 on placebo) utilized DEXA (dual-energy X-ray absorptiometry) imaging to monitor body mass after 68 weeks [50•]. Total and regional fat mass decreases from baseline were found with semaglutide along with total lean mass (kg), but the percentage of lean body mass in relation to total body mass increased. For example, the kilogram change in total fat mass was approximately − 10.40 with semaglutide vs − 1.17 with placebo, and for total lean body mass it was − 6.92 vs − 1.48. Thus, the fat to lean mass loss was a ratio of 1.5 vs 0.79 and suggests that participants on placebo experienced a greater loss in lean versus fat mass.

Regardless of the DEXA mathematics involved, it has been appreciated that with any acutely effective weight loss method, including bariatric surgery, the loss of some lean muscle mass or fat free mass (20–40%) is expected, but there tends to be more substantial loss of fat mass [51]. Why lean muscle mass is lost universally in these situations harbors many theories, but it appears that muscle protein synthesis (MPS) is not impaired; rather, an accelerated muscle proteolysis occurs. This would continue to suggest aerobic physical activity with an emphasis on regular resistance exercise, and appropriate (not extreme) protein intakes could be of benefit, but this has not been adequately studied with the newer GLP-1 agonists as with multiple other caloric reduction scenarios. Obesity harbors more muscle mass, but of less quality vs healthy weight individuals, and weight loss with resistance exercise is an opportunity to improve quality, maintain strength, and potentially preserve greater lean mass during profound or even moderate weight reduction. Macronutrient intake in the bariatric literature also appears to suggest protein intake maintained or appropriately improved is a greater predictor of sustained weight loss [38•, 52], and greater intake of carbohydrates and/or alcohol could be associated with a greater weight gain post-procedure [53]. Still, greater overall energy or caloric consumption continues to be correlated with less than substantial weight loss after these procedures [54], and how this relates to GLP-1 agonist sub-optimal weight changes needs further investigation.

BMI Controversial Indication

Whether or not a patient qualifies for these newer weight loss medications is based on BMI-based criteria [23]. This is controversial because BMI alone is an inconsistent measure of overweight and obesity [55], and recently major medical groups such as the American Medical Association (AMA) are requesting reevaluation or additional evaluations of this parameter based on a variety of issues [56]. There is also the concept of BMI healthy but metabolically unhealthy especially with aging and co-morbidities, which suggest that certain individuals are prone to losing muscle and bone, but simultaneously gain adipose tissue, which may not appreciably alter their total weight or BMI [57]. A reliance on additional cardiovascular and metabolic markers, and the potential use of waist circumference (WC), waist-to-hip ratio (WHR), or other BMI-adjunct parameters, is paramount. Where do these other individuals fit in the paradigm for the new weight loss medications? BMI benefit appears more correlative at the larger values (≥ 30) and this is one advantage of such a rapid simplistic measurement. However, since it cannot establish where the distribution of adipose tissue resides, and it cannot precisely define morbidity and mortality risk, it appears imperative not only to incorporate other risk markers in these other individuals, but also to advocate for more trials to address the issue of optimal medication candidacy.

Cardiovascular Risk and Event Reduction? SELECT Trial

In patients with type 2 diabetes on GLP-1 agonists the evidence continues to accumulate over cardiovascular marker improvement as well as a reduction in events [16•]. This is encouraging based on the forementioned dubious history of effective weight loss drugs eventually removed from the market. In patients without diabetes there is also the preliminary suggestion of favorable changes in cardiovascular markers from blood pressure, glucose, lipids, inflammation, and WC [16•, 58, 59]. Even in normotensive patients systolic (approximately − 5 mm Hg) and diastolic (− 2.5 mm Hg) reductions were observed. An improvement in physical function and mood has also been preliminarily cited, but short- and long-term diverse mental and physical health impacts need to be better clarified. Also, whether medication changes, cessation, dosage reduction of other conventional medicines, and reductions in microvascular and macrovascular issues occur need more research. For example, bariatric surgery is currently well known to impact not only risk parameters, but also medication utilization rates, microvascular and macrovascular events, and all-cause morbidity and mortality [8–10, 60].

SELECT was the name of a well-known trial of selenium and/or vitamin E for the prevention of prostate cancer that did not demonstrate benefit, but rather the potential for harm [61]. However, SELECT is also the name of a potentially transformative trial (in a positive or negative manner) with semaglutide on the impact of cardiovascular events in non-diabetic patients ($n = 17{,}605$) with overweight or obesity with documented cardiovascular disease and a history of a cardiovascular event [62]. Arguably, this trial should report interim results in 2023–2024, and is the first major test of whether these medications change cardiovascular outcomes and event rates.

Cost, Conflict of Interest, Compounding, Competition (Head-to-Head), and Priority Review Voucher Programs

The cost and access issues of these potentially life-long medications without knowledge of long-term adverse events are concerning [63•], as is the potential for conflict of interest [64], and even the recent concern over the safety of some compounding pharmacies formulating these medications [65]. Compounded medications are not FDA-approved, and the safety or impact of these drugs is not validated by the agency. The FDA has received some safety signals with some forms of compounded semaglutide. On an optimistic note, there are numerous phase 3 trials ongoing of various diverse drugs in the GLP-1 agonist and associated classes, which in the next few years if long-term safety prevails should add to a keen and intense competition pool [63•]. This could impact not only availability, but also insurance coverage, access issues, out-of-pocket costs, and an eventual generic lower cost option(s).

The intense competition to become the medication of choice in the weight loss milieu cannot be understated. Older weight loss medications from different classes achieved approximately 5% (plus or minus several percentage points) of weight loss over placebo, which places the current results with the newer GLP-1 agonists in a unique efficacy category [66]. Semaglutide has been tested against an older GLP-1 agonist, liraglutide (approved for weight loss in 2014), and after 68 weeks mean body weight changes of − 15.8% versus − 6.4% significantly favored semaglutide [22]. Although, tirzepatide appears to have achieved greater weight loss versus semaglutide when indirect studies are analyzed [67, 68]. Interestingly, a recent phase 3 trial (NCT05822830) sponsored by Eli Lilly known as "SURMOUNT-5" was announced at the time of this manuscript's submission, which will utilize semaglutide versus tirzepatide in non-diabetic adults ($n = 700$) with a primary endpoint of a percentage change in body weight from baseline over 72 weeks [69]. This study is expected to be completed in late 2024. Of further interest, Eli Lilly recently appeared to utilize a "priority review voucher," which cost over 100 million US dollars

in order to accelerate the review of tirzepatide for weight loss [70]. Priority review vouchers are not created to increase the probability of FDA acceptance, but rather to move up in que, or shorten the time interval before a decision is proffered [71].

Dietary Deficiency/Insufficiency, Laboratory Testing, and Supplementation?

Bariatric surgery contains multiple clinical guidelines concerning the potential for nutrient deficiency or insufficiency and procedures involved in repletion [72, 73]. No such standards exist yet with these novel medications except for the previously mentioned 2023 dietary expert guidance for preventing or managing gastrointestinal issues [31••]. This is partially understandable based on their recent approval, but at the same time concerning since the weight loss achieved initially competes with bariatric surgery. Issues of malnutrition with these medications could be an ongoing and future concern [74]. What should protein or macronutrient intake, in general, be when initiated and maintained on these medications? What about nutrient testing? It would appear standard to ingest a daily multivitamin, pay attention to macronutrient intakes, and ideally meet with a dietician and other health professionals on regular intervals, but again all these issues remain at an embryonic stage, and would appear to require immediate attention, awareness, and research.

Urologic Opportunities and Concerns (Bariatric Surgery Lessons and Comparisons)

The potential to investigate the benefits and limitations of these medications in a variety of specialties, including urology, abounds. The known improvements in some urologic conditions with bariatric surgery should also be appreciated and provide guidance for what could be researched, expected, or even dissimilar with the newer long-acting GLP-1 agonists.

Interestingly, at the time of this manuscript's submission there has been essentially minimal data published on the impact of GLP-1 agonists on diverse urologic disease risk or outcomes. Bariatric surgery results could provide a partial guide of potential expectations. For example, the reduction in the risk of multiple cancers was mentioned [10], including some urologic cancers in specific patient populations [75], and cancer-related mortality also appears to be impacted [76]. Minimal past laboratory data exists to suggest that some GLP-1 agonists could inhibit prostate cancer proliferation [77]. It would also be of interest as to whether aggressiveness, progression, recurrence, or urologic cancer mortality could be impacted, as well as reducing the conventional medicine issues exacerbated by unhealthy weight status. Preventing the impact of smoking cessation weight gain for example [5], especially in a patient already dealing with an unhealthy weight status after certain urologic procedures and treatments, such as cystectomy or intravesical therapy could be an avenue of interest.

Sexual function and incontinence should be other areas of interest based on recent data. For example, a summary of 14 studies ($n = 508$) found a mean testosterone increase of 156.3 pg/ml (95% CI 84.78–227.86; $p < 0.0001$) in men receiving bariatric surgery [78]. The reported increases found in this analysis varied from less than 100 to 350 pg/ml. Improvements in erectile function, desire, intercourse, and overall satisfaction were also noted. A meta-analysis in women found a 76% decrease in female sexual dysfunction (FSD), and improvements in the female sexual function index (FSFI) in all domains, except pain, from 16 observational studies ($n = 953$) [79]. Significant short- and long-term benefits in improving urinary continence (stress, urge, mixed) have already been noted for male and female patients undergoing bariatric surgery [80, 81]. It would also be of interest in patients needing various urologic surgery procedures if significant weight loss before or after the procedure would further improve surgical outcomes. Would BPH outcomes improve with medications, or with minimally invasive procedures when substantial weight loss is accomplished [82–84]? There is also the issue of male and female fertility and whether weight loss via bariatric procedures has resulted in improved fertility parameters and outcomes [85–88]. In fact, the impact of GLP-1 agonists on sperm quality and quantity is unknown, and currently pregnancy or considering pregnancy is reason for discontinuation of these medications.

Nephrolithiasis risk after bariatric surgery is concerning, regardless of the procedure utilized, although biliopancreatic diversion with duodenal switch (BPD-DS) appears to be associated with the highest risk versus Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) in some notable observational series [89]. Age, comorbidities, and stone history prior to the procedure could also impact risk, but one could argue that weight loss of these magnitudes could reduce the risk of stone disease in some patients [90]. Interestingly, at the time of the submission of this manuscript there was a dearth of data on GLP-1 agonists and kidney stone risk or recurrence. Nephrolithiasis has not been associated with semaglutide or other novel GLP-1 agonists in past phase 3 trials, but in general these trials are of a short duration. Could this be an advantage over bariatric surgery, at least in the short term, or has this issue or awareness not been recognized until now? Additionally, one of the more notable postoperative issues in bariatric surgery are urinary tract infections (UTIs), and this risk is impacted by a variety of factors [91, 92]. Again, a dearth of data exists in GLP-1 agonist literature in terms of UTI risk (increase, decrease,

no impact) before, during, and after profound weight loss is achieved. The list of opportunities in determining the true effects of GLP-1 agonists on urologic risks and outcomes appear boundless and should be determined if these agents remain a mainstay of weight management.

Conclusion

Weight loss, at least in the first 2 years of semaglutide or tirzepatide utilization, is unprecedented in medicine with a non-surgical option. It is imperative that clinicians and researchers throughout medical specialties become accustomed to the evolving potential advantages and disadvantages of these products within their respective disciplines [29••, 31••], and even from case series [93]. What clinically occurs with long-term utilization of these agents from side effects to efficacy is unknown, but thus far the ability to reduce weight, and cardiovascular risk appears impressive enough to consider studying their impacts, even observationally, in urologic settings. What should also be appreciated is the pipeline of these and related medications. Results suggest that similar or even greater weight reduction to injectable semaglutide or tirzepatide is occurring at this moment [63•]. Oral orforglipron (− 15% weight loss) [94] and once-weekly subcutaneous retatrutide are two of the many examples [95]. For example, retatrutide, a triple agonist (GLP-1, GIP, and glucagon receptor), recently demonstrated the most profound percentage weight loss from baseline of any trial to date with an impressive − 24.2% after 48 weeks in the 12-mg dosage group. Drug delivery advances and options also recently occurred in a phase 3 trial of high-dose (50 mg) oral semaglutide, which appeared to provide weight loss identical to their injectable product [96]. Perhaps we need to visualize these novel medications indifferently if they indeed remain on the market for the long term. It was not long ago the idea of controlling blood pressure, cholesterol, or glucose and reducing morbidity and mortality with a potentially lifelong medication would have seemed innovative and today it has become an untenable evidence-based foundation of preventive medicine. So, why not weight loss medication? Could this be the moment they prevail or will compliance [97], or another physical or mental health issue alter the fate of these newer medications [98], somewhat akin to what was forementioned with some past notable medications?

Finally, what will be the fate of diet and exercise if the situation remains optimistic for these medications? Lifestyle or behavioral changes impact some of the same established cardiovascular parameters, and they can enhance conventional treatment outcomes, reduce the dosage of some medications, and improve mental health outcomes [7]. Could this be the case with the weight loss medications? It is the hope of this author, especially if safety and efficacy continue, and cost and access issues profoundly change. In the meantime, lifestyle changes from aerobic to resistance exercise in conjunction with proper dietary changes are also what appear to result in enhanced efficacy and reduced adverse effects from these novel medications. Thus, lifestyle changes and traditional proven medications will be as critical as ever, because they also have legacy effects on their own, even when reduced or discontinued that need to be embraced [99–103], just as much as these novel pharmacologic weight loss interventions, which as of this moment have not demonstrated similar such effects when medication cessation occurs.

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Compliance with Ethical Standards

Competing Interests Dr. Moyad was a quality control consultant for Max International Beauty (Cosmetics).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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