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Perspective

The societal implications of using glucagon-like peptide-1 receptor agonists for the treatment of obesity

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SUMMARY

Glucagon-like peptide-1 receptor agonists (GLP1-RAs) are weight management medications, achieving up to 15%–25% weight loss in clinical trials. Given their effectiveness and potential for scalability, GLP1-RAs are a welcome treatment option for obesity. However, not everyone who could benefit may be able to afford or want to use GLP1-RAs. There are limited data on adherence beyond clinical trials or on how to optimize adjunct behavioral therapy. There is little support offered after GLP1-RA cessation, where weight regain is marked. Without increased accessibility and lower costs, the rollout of GLP1-RAs may widen inequalities. Currently, GLP1-RAs do not offer a sustainable solution to the public health pressures caused by obesity, where prevention remains crucial. To take the best advantage of GLP1-RAs, we need to deploy them in ways that are cost effective, sustainable for healthcare systems, and equitable for societies.

INTRODUCTION

Globally, around 1 in 7 people live with obesity, which is projected to increase to 1 in 4 by 2035.[1] Without intervention, weight-related comorbidities, including type 2 diabetes (T2D) and cardiovascular disease, will follow,[2] placing an increasing burden on healthcare systems, constraining economic growth, and impairing the quality of life (QoL) of individuals. For example, a recent forecast of the costs of obesity and overweight in the UK predicted annual costs to rise around 10% in real terms, from £97.9 billion now to around £109.4 billion by 2040, equivalent to approximately 27% of projected total healthcare spending,[3–5] making it clear that there is a pressing need to develop and implement new treatment strategies for obesity that can be delivered cost effectively and at scale. In England, where the prevalence of obesity is greater than in most other parts of Europe, though less than in North America, approximately 26% of adults have obesity, with a further 38% living with overweight. Data from the Health Survey for England show that about half the adult population is trying to lose weight at any given moment.[6,7] Globally, estimates suggest that around 42% of the world's population tries to lose weight every year.[8]

The development of glucagon-like peptide-1 receptor agonists (GLP1-RAs) for the treatment of obesity has energized the therapeutic management of this condition, representing the first highly effective and safe pharmacotherapeutic option. Originally introduced for the management of T2D in 2005, the first GLP1-RA, liraglutide (Saxenda), was licensed for weight loss in adults in 2014 by the US Food and Drug Administration (FDA) and, a year later, by the European Medicines Agency (EMA). Subsequently, this class of medication has been rapidly growing, with several new drugs approved for T2D, of which two have also been approved for the treatment of obesity, namely semaglutide (Wegovy), a long-acting GLP1-RA, and tirzepatide (Mounjaro), a hybrid glucose-dependent insulinotropic polypeptide (GIP)/GLP1-RA. Many other mediations based on GLP1-RAs are currently in development, with positive results from phase 3 trials for semaglutide in combination with the amylin analog cagrilintide (CagriSema) and for orforglipron, an oral non-peptide small-molecule GLP1-RA,[9,10] among others. This rapid expansion in the range of GLP1-RAs, including the introduction of non-peptide agonists together with the expiration of patents for existing GLP1-RAs, will drive down costs and likely increase availability, with the potential to offer effective treatments at scale, marking a major change in the future management of obesity.[11]

As is often true with any new breakthrough, there is a pervasive positivity bias about the impact GLP1-RAs will make. However,

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reservations have already been expressed in relation to the potential unintended consequences. This perspective aims to appraise some of the potential broader implications of the rollout of GLP1-RAs—not to denigrate the potential benefits but to highlight that these risks need to be mitigated so that we can achieve the best outcomes from these new medications.

GLP1-RAs ARE HIGHLY EFFECTIVE FOR WEIGHT LOSS

In clinical trials of newer GLP1-RAs, patients without diabetes typically lose 15%–25% of their body weight over a period of 12–18 months, after which weight loss tends to plateau and is accompanied by dose-response improvements in cardiometabolic markers and endpoints.[12–14] When compared directly in the recent SURMOUNT-5 trial, 10 or 15 mg tirzepatide achieved 20.2% weight loss vs. 13.7% weight loss with 1.7 or 2.4 mg semaglutide after 72 weeks of treatment (treatment difference: 6.5% [4.9–8.1]).[15] Of particular interest, the SELECT trial examined the cardiovascular efficacy of 2.4 mg semaglutide once weekly in more than 17,600 individuals with overweight or obesity and pre-existing cardiovascular disease, demonstrating a 20% risk reduction for the primary cardiovascular endpoint after 34.2 months despite a somewhat smaller weight loss (9.4%) than seen in most other trials.[12]

The safety profile of GLP1-RAs is generally favorable with predictable gastrointestinal (GI) adverse effects that often wane over time but, in some, may lead to discontinuation of treatment.[16] In the STEP trials, GI adverse events were more common in the semaglutide groups compared with the placebo group, leading to discontinuation of treatment in 3.4%–4.5% and 0%–0.8% of participants, respectively.[17–20] In the SELECT trial, the discontinuation rate of those receiving semaglutide was 16.6% compared to 8.2% in the placebo group, mainly driven by a difference in GI adverse events (10.0% vs. 2.0%).[12,16] In SURMOUNT 1, which tested a dual agonist for both GLP1 and GIP, a similar safety profile was seen with adverse-event-driven discontinuation of treatment after 72 weeks in 4.3%–7.1% of participants in the active treatment groups compared to 2.6% in the placebo group, which increased to 7.3%–12.3% and 5.9%, respectively, after 176 weeks of treatment. Of note, in the SURMOUNT-5 trial with a head-to-head comparison of tirzepatide vs. semaglutide, dropouts due to GI adverse events were 2.7% and 5.6%, respectively.[15] This difference could be due to an anti-emetic effect of GIP that might somewhat ameliorate the GI adverse effects of GLP1-RA agonism.[21]

Another concern related to the use of GLP1-RAs is the loss of lean body mass, especially skeletal muscle, following weight loss. In the SURMOUNT 1 and STEP 1 dual-energy X-ray absorptiometry (DXA) substudies, weight loss was accompanied by reductions in lean body mass of 10.6% and 9.7%, respectively.[22,23] However, this loss was proportionate to total weight loss and corresponds to similar changes seen following substantial weight loss after total dietary replacement (TDR) programs and bariatric surgery.[24,25] Further, the relative reduction of lean body mass is smaller than the relative reduction in fat mass, which could result in an improvement of physical function, although this remains speculative.[26] Resistance exercise has been shown to attenuate the proportion of weight loss composed of lean mass and, together with sufficient protein intake, may be a useful mitigation strategy where there is clinical concern of frailty.[27]

In short, GLP1-RAs have set a precedent for what can be achieved through medically supported weight loss.[28]

BEHAVIORAL SUPPORT IMPROVES TREATMENT OUTCOMES BUT HAS NOT BEEN OPTIMIZED

Most trials provide GLP1-RAs with adjunct behavioral therapy, with similar support also offered to participants randomized to a placebo treatment. Details are often scant, and this aspect of the intervention has received relatively little attention. The STEP trials compared 2.4 mg semaglutide once weekly with placebo. Adjunct behavioral support programs mostly comprised advice to follow a 500 kcal/day energy-deficit diet and increase physical activity, with the support of a dietitian or equivalent every 4 weeks.[29] In STEP 1, this resulted in an absolute weight loss of 14.9% after 68 weeks of treatment.[30] STEP 3 comprised a more intensive behavioral support program, with a hypoenergetic diet (1,200–1,800 kcal/day), increased physical activity, and 30 intensive behavioral therapy visits across the 68 week duration of the study, and achieved a somewhat greater weight loss of 16%.[18] In STEP 5, with a longer duration of 104 weeks, weight loss was 15.2%.[17] Tirzepatide administered at doses of 5, 10, and 15 mg once weekly in adjunct with a behavioral intervention comprising an energy-deficit diet and increased physical activity appears to be even more effective, with absolute weight losses of 15.0%, 19.5%, and 20.9% after 72 weeks in the SURMOUNT-1 trial[31] that was largely maintained when treatment was continued in a subset of participants for 176 weeks.[32] All aforementioned STEP and SURMOUNT trials recruited adults with a BMI $\geq$ 30 kg/m^2 ($\geq$27 kg/m^2 in persons with $\geq$1 weight-related coexisting condition) without diabetes.

Of special note, in the SELECT trial, which recruited people with pre-existing cardiovascular disease, aged $\geq$45 years, $\geq$27 kg/m^2, and with no history of diabetes, semaglutide treatment was delivered without structured adjunct behavioral therapy. Average weight loss was 9.4% after 104 weeks, somewhat lower than in the STEP trials, suggesting that behavioral therapy brings important additional weight loss in the short term, though it is not essential to achieve clinical benefits.[12] However, the SELECT trial recruited a generally older population with a higher proportion of males compared with the STEP trials, both of which are associated with attenuated responses to GLP1-RA therapy and may have contributed to the lower weight loss.[33,34]

Clinical guidelines recommend support without specifying the details.[35,36] Given the additional costs of providing adjunct behavioral therapy, further detailed consideration is needed about the most effective and cost-effective support. To best inform the most effective adjunct behavioral therapy, more evidence is needed from real-world data, describing the behavioral therapy provided alongside GLP1-RA prescriptions. Pragmatic RCTs that trial adjunct behavioral therapy could clarify three things: (1) which kind of support works best—routine dietary counseling or more targeted psychological interventions, (2) which patients benefit the most—for instance, those with disordered-eating symptoms, and (3) when to offer it—at treatment

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initiation, when weight loss stalls, or after medication stops. Such evidence would help deliver the right support at the right time, in a way that is cost effective for health services.

HEALTHCARE PROFESSIONALS FACE CHALLENGES PROVIDING OBESITY MANAGEMENT

There is considerable potential that these new medications will become a cornerstone of weight management in the coming years. In the USA, one estimate suggests that 9% of the total population will be using GLP1-RAs by 2030.[37] Indeed, the advent of a new, more effective and safe therapy would usually be rapidly adopted into routine care in some countries, but it is likely to be very challenging for resource-constrained healthcare systems.[38,39]

However, the current provision of specialist weight management services is limited in most healthcare systems, and primary care practitioners have limited knowledge of existing resources and how to access them,[40] lack confidence when discussing weight,[41] and lack the time.[42] In the UK, for example, referral to existing weight management interventions is the exception rather than the norm,[43] with substantial variability in available weight management services, with some regions having no local access to specialist services.[44–46] These may range from digital health coaching to the provision of pharmacotherapy or bariatric surgery, and this makes it particularly challenging for non-specialist clinicians to know how or where to refer their patients. Many services have long waiting lists, and there is evidence of marked inequalities in access to care.[46,47] Given that current clinical guidelines for the management and treatment of obesity are not fully implemented and widely debated, the same is likely to be true for new treatments, including pharmacotherapy and adjunct behavioral support.[48,49] The integration of new pharmacotherapy for the management of obesity is particularly challenging because it needs to be prescribed by a physician, offered with adjunct behavioral support, and regularly reviewed. This will place additional burdens on physician time and already overstretched services for behavioral support.

Successful deployment of these medications will also hinge on the attitudes of clinicians and other healthcare professionals (HCPs) involved in providing treatment for patients seeking support for weight management. Qualitative research based on data from general practitioners (GPs), nurses, dietitians, and clinical psychologists has consistently found mixed and sometimes ambivalent attitudes toward weight management within primary healthcare.[50–52] In some countries, such as the UK, GLP1-RAs are now used in primary care settings for weight management, and early evidence suggests that clinicians are largely optimistic about the rollout of GLP1-RAs. Those who welcome them have described these medications as familiar, given many clinicians already prescribe them for the management of T2D[53] and are pleased to have the opportunity to offer a new, effective treatment for obesity to their patients.

However, there are also many concerns. The widespread media coverage has reportedly encouraged more patients to initiate conversations with their healthcare providers about weight management, and some physicians feel ill-equipped to handle these conversations.[54] Clinicians describe patients seeking access to GLP1-RA medications as "eager" and proactively booking appointments, increasing pressures on the system.[53] This may suggest that patients are more interested in seeking treatments that they perceive to be more useful and beneficial than previous weight loss options or that the likelihood of consulting a clinician for weight management support is higher than it was previously. However, HCPs know that they will be responsible for the prescription and ongoing monitoring of these medications and are cautious about managing this new wave of pharmacotherapy within their current capacity[53] and taking on additional responsibilities for a chronic relapsing condition.[53,55] Some, though not all, worry that these medications are a "short-term" solution and are concerned about weight regain following cessation of medication.[30] Some HCPs express ethical concerns about the medicalization of obesity, and some believe wider societal action is needed to take a more preventative approach toward obesity and see treatment as diverting attention from primary prevention.[56]

The ongoing debate on the definition, diagnostic criteria, and staging for obesity makes it difficult for physicians without specialist backgrounds or sufficient resources to decide when and for whom the prescription of pharmacotherapy might be relevant, and detailed guidance is needed to support physicians in making appropriate decisions and communicating this sensitively to their patients.[48,57,58] There is currently a scarcity of training available for undergraduate medical students and other HCPs.[59] Core skills for obesity management, such as the ability to hold sensitive conversations with patients about their body weight and confidence to discuss obesity management, do not appear to have been widely instituted.[60–62] An improvement in training on weight management to better equip healthcare providers with the necessary skills is therefore needed. This will enable better identification of patients for treatment with these medications rather than other weight loss options and improved support to patients during therapy and when medication ceases.

SOME PATIENTS MAY NOT WANT TO USE GLP1-RAs AT ALL OR OVER THE LONGER TERM

Despite their efficacy and safety, these treatments will not be the right option for everyone. Participants in clinical trials investigating GLP1-RAs represent a group of people who are motivated to consent to join a research study of a new weight loss medication, but not all people living with overweight and obesity may want to consider medication.[63] Many trials do not report the number of participants approached and invited to take part, so there is a lack of data on the acceptability of taking part in such trials. Weight loss may not be the goal for some patients, and many people are actively seeking to reduce the number of medications that they take. Indeed, in a diabetes remission trial, the possibility of medication reduction was a key motivator to take part in a study trialing an intensive dietary intervention.[64,65] Qualitative data focused on patient perspectives of less contemporary weight loss medications describe perceptions that weight loss medications are "unnatural" or a "band-aid solution," with concerns raised about weight regain post-cessation.[66] A recent survey found that while 45% of USA adults were interested in the use of GLP1-RAs for weight management, this number declined

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to 14% when individuals were informed about weight regain after discontinuing therapy.[67]

Currently, data are sparse on discontinuation rates for GLP1-RAs in routine care when prescribed specifically for weight management. However, extrapolating the data available for people with T2D suggests that a high proportion of people experience unacceptable side effects and stop treatment.[68–70] In the USA, continuous use beyond 6 months for injectable GLP1-RAs ranged from 32% to 74%, and nearly 40% of patients with T2D discontinued their second-line antidiabetic medication over a 12 month period, most commonly GLP1-RAs.[71] Overall, around 70% of all GLP1-RA users discontinue within 2 years.[68–71] In Denmark, approximately half of GLP1-RA users with T2D discontinue treatment within 5 years from the initial prescription,[72] and out of more than 110,000 individuals filling a prescription for semaglutide (Wegovy) for weight management within the first year after its release in Denmark in December 2022, only 10% followed the recommended dose titration scheme with an increase every 4 weeks until reaching the recommended dose of 2.4 mg weekly, while 5.7% stopped treatment after their first prescription and 1 in 4 discontinued treatment before their sixth prescription.[63] In this study, 33%–48% of users continued with the 1.0 mg dose from the fourth prescription onwards, illustrating that the real-world use of these medications may not resemble what has been tested in premarket clinical trials. However, as newer oral non-peptide GLP1-RAs that are currently in the pipeline come to the market, attitudes toward these medications may change, with potentially lower discontinuation rates due to injection-based side effects.

We know, from other conditions, that medication adherence is often poor. For example, adherence rates for major antidiabetic medications and antihypertensive medications are approximately 68% and 55%, respectively, and it is reasonable to assume the use of GLP1-RAs for weight management may be similar.[73,74] For patients taking these medications for the treatment of obesity, there may be a particular reluctance to continue when weight loss plateaus or weight loss goals are reached,[75] e.g., in a Danish survey including 1,013 individuals filling a prescription for semaglutide for weight management, almost half only expected to take the treatment for a limited time period, and just 11% expected lifelong treatment.[54]

Patients who are overweight and living with obesity may set unrealistically high goals (22%–34% of starting weight) beyond what current medications can achieve.[76–80] Observational data suggest that while setting high goals is associated with greater weight loss, those who set higher goals may be more likely to withdraw from weight loss programs than those who set medium goals.[76] Patients interested in using GLP1-RAs may be disappointed if their expectations for weight loss are not met, prompting discontinuation.

WEIGHT REGAIN WHEN TREATMENT ENDS IS COMMON

A small proportion of people may sustain long-term weight loss after discontinuation of treatment with GLP1-RAs, but current data from trials and cohort studies tell us that average regain is often substantial and occurs at a rate that appears to be faster than following the end of behavioral weight management programs. Indeed, our systematic review of weight change in RCTs after the cessation of behavioral weight management programs estimated weight regain to be between 0.12 and 0.32 kg/year.[81] For comparison, a post-treatment extension of the STEP 1 trial in a subset of participants reported the regain of, on average, two-thirds of the weight lost at 1 year post-cessation of semaglutide and adjunct behavioral support (approximately 11.5 kg).[30] In STEP 4 and SURMOUNT 4, participants switching to placebo treatment after 20 weeks of semaglutide or 36 weeks of tirzepatide treatment, respectively, gradually regained weight despite ongoing behavioral support, whereas those who continued active treatments continued to lose weight.[13,19,30]

To date, the majority of the literature on weight regain physiology is based on dietary or surgically induced weight loss.[82,83] People with obesity likely have genetic susceptibility and physiological mechanisms favoring regain, which would likely impact weight regain after pharmacotherapeutic and other weight loss interventions alike.[84,85] Potential physiological adaptations that may contribute to weight regain after energy restriction include, but are not limited to, changes in hormone-related homeostatic appetite regulation as well as adipocyte reduction and shrinkage, markedly decreasing lipolysis and increasing triglyceride synthesis.[86–88] Crucially, these compound with living in an environment that promotes weight gain.

Weight regain after the cessation of GLP1-RAs for weight loss is not surprising. Behavioral weight management programs help provide people with the practical coping skills to change their eating behavior.[66,89] However, the mechanism of action of GLP1-RAs is primarily to boost satiety and reduce appetite, meaning there is less of a need for people to learn the cognitive strategies to curtail their appetite, and they may be less likely to be able to manage their weight when treatment ends. Of course, GLP1-RAs should be used in conjunction with support for dietary change, but it is plausible that the extrinsic control of appetite provided by the medication may undermine the perceived value of conscious dietary and physical activity changes and limit their adoption. As a consequence, weight regain may be greater after the use of GLP1-RAs compared to behavioral weight management programs. However, to best inform long-term management plans for weight management, better follow-up data after cessation of GLP1s from trials and from real-world healthcare records are needed.

A key reason to treat obesity is to prevent or treat obesity-related conditions. In the SELECT trial, GLP1-RAs were highly effective with sustained intervention, with a number needed to treat (NNT) to prevent one cardiovascular event of 67 patients following a mean duration of treatment of 34.2 ± 13.7 months.[12,90] SURMOUNT-1 showed the NNT with tirzepatide to prevent one case of T2D was 9 patients.[32] However, little is known about time-limited treatment. A review of behavioral weight management programs found benefits for cardiometabolic health lasting ~5 years after program end, which has so far not been indicated following the cessation of weight loss using the new pharmacological agents.[81] Specifically, the STEP 1 extension showed that 1 year after cessation of semaglutide, glycated hemoglobin (Hba1c) returned to 5.6% (baseline was 5.7% and post-treatment was 5.2%) and systolic blood pressure (SBP) increased to 131 mmHg (baseline was 129 mmHg and post-treatment was 121 mmHg), and blood lipid markers showed similar patterns.[30]

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In the STEP 4 and SURMOUNT 4 trials, switching from initial active treatments to placebo also led to a relapse in important cardiovascular risk markers such as Hba1c, SBP, and low-density lipoprotein (LDL)-cholesterol.[13,19]

One easily argued solution is to continue the use of GLP1-RAs chronically. However, that poses challenges to adherence and has significant financial implications for individuals or healthcare systems. In accordance, early data from the USA suggest that, among those who self-fund, prolonged use is uncommon and approximately half discontinue within the first year when prescribed solely for obesity.[91] In a Danish survey, only a small minority of people redeeming a prescription for semaglutide expected to continue treatment lifelong.[54] For insurers or publicly funded healthcare systems to treat people lifelong would be costly at the current cost of the GLP1-RAs, but this will likely change in the future as current medications go off patent and new and simpler non-peptide medications become available. In the current scenario, another option could be to consider a pulsed treatment, or rescue therapy, similar to that currently seen in programs of TDR, where a TDR is reinstated after weight regain over a certain threshold.[92] However, it is currently unclear if a second course of GLP1-RA treatment would achieve the same result as the first or would be acceptable to patients, and this may raise concerns about "yo-yo dieting."

GLP1-RAs OR BARIATRIC SURGERY?

Individuals with severe and complex obesity who are likely to be prioritized for GLP1-RA medications are often also eligible for bariatric surgery. GLP1-RAs may also be used as part of the care pathway toward bariatric surgery, to aid preoperative weight loss, potentially improving safety outcomes in surgery.[93]

Bariatric surgery consistently achieves substantial weight losses beyond that achieved by the GLP1-RAs currently on the market and, though invasive, in general has a good safety record in experienced hands, although there is a risk of long-term complications, such as micronutrient deficiencies, chronic abdominal pain, and post-bariatric hypoglycemia.[94] There are no randomized controlled trials directly comparing the two options, though one is currently underway.[95] In a recent non-randomized study, 75 patients without diabetes but eligible for bariatric surgery were assigned 1:1:1 to sleeve gastrectomy or 4 week TDR followed by an energy-reduced diet and increased physical activity with or without daily injection of 3.0 mg liraglutide.[96] After 1 year, surgery resulted in the greatest weight loss (43.4 kg [32%]), but behavioral modifications with 3.0 mg liraglutide also resulted in a significantly greater weight loss (26.3 kg [24%]) than behavioral modifications alone (15.4 kg [14%]). Despite the greater weight loss with bariatric surgery, changes in fasting plasma glucose and lipid profiles favored the liraglutide-treated group.

A recent qualitative trial explored patient perspectives comparing bariatric surgery to intensive weight loss interventions comprising GLP1-RAs.[97] Here, patients raised concerns about adverse events from both surgery and pharmacotherapy, the costs associated with GLP1-RA therapy, and the perceived "extra work" required to take part in a program based on GLP1-RAs. However, based on past experiences from other surgical procedures, some patients preferred the idea of GLP1-RA treatment, reflecting that the ability to stop GLP1-RA therapy at any time is a positive attribute. For others, the permanency of surgery was appealing, with some reflecting that surgery may take away the ability to "cheat."[97]

A particular advantage of bariatric surgery is the successful long-term maintenance of large weight losses, with data showing a mean BMI reduction of approximately 11 kg/m^2 at 1 year post-surgery, followed by a gradual weight regain on average until year 8, where it stabilized at approximately 7 kg/m^2 less than the baseline BMI until 20 years post-surgery.[98] This large and sustained weight loss is accompanied by 23% and 30% reductions in all-cause and cardiovascular mortality, respectively, and a 3 year increase in life expectancy.[98] Despite promising data showing 20%–26% reductions in cardiovascular and some diabetes-related microvascular outcomes in high-risk populations with T2D or established cardiovascular disease treated with semaglutide for 1.3–3.3. years,[12,99] long-term results with GLP1-RAs are still not comparable to surgical outcomes. Moreover, the newer co-agonist GLP1-RA/GIP medications, such as tirzepatide, or triple-agonist medications in development, such as retatrutide, have consistently shown weight losses beyond 20% in adults without diabetes, thus moving very close to the range of bariatric surgery.[100] Though difficult to appraise for the newer, more effective treatments that will soon come to the market, cost comparisons in the USA suggest that after around 1.5 years, GLP1-RAs, comprising semaglutide, liraglutide, and exenatide, become costlier than bariatric surgery.[101,102] Accordingly, greater investment in bariatric surgery should be considered alongside funding for GLP1-RA provision.

GLP1-RAs MAY RISK WIDENING INEQUITIES AND INEQUALITIES IN WEIGHT MANAGEMENT

Marked inequalities exist in the treatment of obesity,[103,104] and the disconnect between accessibility to these new treatments and need risks exacerbating this problem. In countries where GLP1-RA therapy is most available, such as the USA, Canada, Australia, New Zealand, and parts of Europe, the prevalence of obesity is more common in minority ethnic groups and people within low socioeconomic positions. Yet, at present, access to GLP1-RA therapy for obesity is largely limited to people who can afford to pay for the treatment directly or via insurance schemes or who can access treatment through occupational or state-funded healthcare.[105] Cost has consistently been cited as one of the most common barriers toward initiating and continuing GLP1-RA treatment, though there are still limited data on GLP1-RAs used solely for weight management.[75,97,106] Currently, GLP1-RAs are manufactured by three main providers, and this oligopoly likely contributes to the elevated costs, as seen with other pharmaceutical agents.[107] While availability is limited and treatments are not offered routinely, it is likely that the people who are best able to navigate health systems and advocate for their treatment of choice will be the best served.

With time and as providers of weight loss medications are introduced to the market, availability will improve, and it is likely that the price will decrease, particularly as existing patents begin to expire.[11] Similarly, novel medications in development may

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further broaden availability, with simpler oral administrations and lower production costs.[28,108] However, the prospect of affordability for everyone living with obesity is likely in the far distance, even in wealthy countries. Health systems with very limited funding and grappling with the double burden of under- and over-nutrition will struggle to offer these treatments, likely exacerbating inequity at a global level. It is essential that we much better understand the cost effectiveness of different treatment options to optimize the use of limited healthcare budgets.

To date, there are no reports of the outcomes of GLP1-RAs in randomized controlled trials (RCTs) in relation to socioeconomic status (SES) or ethnicity when used exclusively for weight management. Some observational data suggest that adherence to GLP1-RAs for weight loss is higher in patients with a higher socioeconomic position,[109] which reflects the findings from behavioral therapies.[110,111] Behavioral therapies for weight management require high levels of personal agency and cognitive resources, and it is this demand that typically reduces adherence.[112] On the other hand, data from the English National Health Service Digital Weight Management Programme has shown that greater support provided to more deprived communities equalized weight loss outcomes.[113] This may indicate that the provision of extra behavioral support may be beneficial to equalize weight loss outcomes following GLP1-RA therapy. Pharmacological treatments also require personal agency but to a lesser extent, so it is plausible that these treatments may be less likely than behavioral interventions to increase disparities. However, perception of non-adherence has been associated with a reduced provision of guideline-recommended care in other health conditions and may mean that clinicians are less likely to prescribe pharmacotherapy for weight management to those with lower executive functioning.[114–116] Patients living with obesity and severe mental illness have a markedly higher risk of obesity and associated cardiovascular disease yet are often excluded from clinical trials. People with severe mental illness have reported challenges in persisting with weight loss interventions, potentially due to decreased motivation and concentration. However, evidence shows that GLP1-RA therapy does not increase the risk of psychiatric adverse events, and it is associated with improvements in physical and mental health-related QoL and reduced emotional eating behaviors.[117–120] As such, this may represent a patient group who may specifically benefit from GLP1-RA therapy. More research is needed to inform the best support to offer patients with severe mental illness to enable them to access and sustain GLP1-RA therapy.

GLP1-RAs MAY FURTHER MEDICALIZE OBESITY

Whether or not obesity should be considered a disease is contentious, but management of obesity through weight loss is widely recognized as an important intervention to prevent or treat many obesity-related diseases. There is general acceptance that the recent rapid increase in obesity at the population level is due to changes in the environment, exposing a genetic susceptibility.[121] We live in a world that bears little resemblance to the world in which we evolved, where food was scarce and the energy cost of acquiring it was high. Obesity is arguably a normal physiological response to an abnormal environment where food is abundantly available and individual decision-making is consistently shaped by marketing campaigns and food purchasing systems designed to maximize profit rather than health. There is, therefore, a risk that turning to a medical solution for obesity may distract from public health efforts to prevent obesity.

Arguments for the classification of obesity as a disease suggest that this would reframe the interface between patients feeling too stigmatized to seek help and clinicians feeling unable to provide the right support by helping to reduce stigma and giving doctors new tools for weight management. However, there is little direct evidence that classifying obesity as a disease will help to reduce stigma.[122] Many diseases are still highly stigmatized even when medical treatments are available, such as psoriasis and epilepsy.[123,124] Even where obesity is recognized as a chronic disease, people living with overweight and obesity still report stigmatizing comments from HCPs and experience significant internalized stigma.[125,126]

THE WIDESPREAD USE OF GLP1-RAs MAY NOT REDUCE WEIGHT-RELATED STIGMA

Weight stigma, most commonly experienced by people living with obesity, refers to negative attitudes and beliefs that devalue people based on their weight status and may include bias, discrimination, stereotyping, and social exclusion.[127] People living with obesity experience wage and employment penalties due to weight stigma.[128–131] This likely relates to body weight during childhood and adolescence, and the stigma endured may carry over into adulthood, and some evidence suggests that it persists even after weight loss.[132]

Some people think that as these novel pharmacological treatments become more normalized, weight stigma will subside. This may occur if obesity is more broadly regarded as a disease that can be treated with biological agents, encouraging more people to seek interventions.[121] There is also the hope that successful weight loss, supported by these new and more effective treatments, will reduce weight stigma experienced by an individual and may improve QoL. However, data from bariatric surgery suggest that this may not be the case.[122] In the immediate 1–2 years after bariatric surgery, there is an improvement in QoL, with greater improvements in physical QoL than mental QoL, but this typically does not continue, despite subsequent weight loss.[133–135] However, evidence suggests that postoperative QoL remains greater than preoperative QoL. Early evidence points to similar outcomes following GLP1-RA-supported weight loss.[136] Qualitative research tells us that people who have undergone bariatric surgery for weight loss experience ongoing stigma even after substantial weight loss.[137] This may be because for people living in much larger bodies experiencing the most marked weight stigma, losing even 15% of their weight, as in the clinical trials of GLP1-RAs, is unlikely to relieve them of the physical manifestations of excess weight, which are the root of much of the weight bias. Moreover, after bariatric surgery, people report that they feel judged for "choosing an easy option."[137] This may further lead to a "double stigma," where patients are offered the best available therapy but do not achieve their goals. People using GLP1-RAs have reported similar reactions from others.[136] If we look further ahead, stigma may be further

exacerbated because there will be more treatments available, and those who do not engage with them may be blamed for not acting to manage their weight.[122] In addition to persistent stigma, future research should therefore investigate whether GLP1-RA-supported weight loss changes patients' internal relationship with food and body image, including risk for disordered eating or identity confusion following significant weight loss.

GLP1-RAs ARE EFFECTIVE FOR WEIGHT LOSS BUT MAY DISTRACT FROM OBESITY PREVENTION

There are genuine prospects that this new generation of highly effective weight loss therapies will lead to improved obesity treatment. However, the rapid uptake and promotion of GLP1-RAs may reflect broader structural factors, including pharmaceutical industry influence over public discourse and clinical priorities, which risks shaping obesity primarily as a pharmacological challenge rather than a societal one.

It is already clear that these treatments will not be universally available, appropriate, or acceptable, and the cost of long-term provision will likely be too high to be a sustainable option for most individuals or healthcare systems to make available for all people who may benefit, so the primary prevention of weight gain and the secondary prevention of weight regain are as important as ever. Simply put, this will require either a substantial overhaul of our food environment to one that does not encourage overconsumption and does not rely on individuals having the material or cognitive resources to specifically seek out healthy eating and physical activity or reframing the food purchasing environment to one that prioritizes health over profit.[138,139] Population-level interventions must also address the primary prevention of excess weight gain in childhood, which is a major predictor of obesity in adulthood and obesity-related comorbidities.[140]

Actions to prevent or treat obesity are not mutually exclusive. There is some evidence that people taking these new medications may develop healthier eating habits, with stores in the USA reporting declining food sales as GLP-1RA medication use rises.[141] Taking a positive perspective, this could mean healthier family environments that could support primary prevention in other household members, including children. However, there is a concern that while attention is focused on exciting MedTech solutions for patients, generating profits for industry and boosting gross domestic product (GDP), there is a real risk that we turn our backs on the need to put guardrails around the actions of the food industry in ways that are often not immediately appealing to the public or policymakers and that prompt opposition from the industry, who perceive them as a threat to growth.

CONCLUSION

The burden of established obesity is so high that new effective and safe medications, such as GLP1-RAs, are a welcome new tool to treat obesity. However, they may not be appropriate for everyone, and not everyone who could benefit may want or be able to afford to use them. We need to find ways to deploy them that are cost effective, sustainable for healthcare systems, and equitable for societies. As they roll out, we need to look beyond the medications themselves and think about the dynamic ecosystem into which we are launching them. We need to deploy them alongside other treatment options, carefully considering their acceptability over the longer term and their implications for weight stigma and inequalities in healthcare. None of this is easy, and the complexity of doing so should remind us that we need to redouble our efforts on obesity prevention.

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