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EDITORIAL

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"From evidence to practice" – Insights from the multidisciplinary team on the optimal integration of GLP-1 receptor agonists in obesity management services

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have captured the media and public imagination with suggestions that they offer a simple solution to the complex, relapsing, chronic condition that is living with overweight and obesity. We should, of course, be open to all possible treatment options given the increasing number of people living with overweight and obesity globally (Baker, 2023; World Health Organization, 2022) and consider how GLP-1 RA can be used as part of a toolkit-style approach within the shared decision making with our patients. To this effect, the British Nutrition Foundation and British Dietetic Association recently published a position statement regarding the use of GLP-1 RA therapies (British Dietetic Association and British Nutrition Foundation, 2024).

Dietary advice alone has been shown to have limited effects on weight loss and obesity-related outcomes. Although approaches, including total diet replacement, have been shown to achieve clinically significant (10%–15%) weight loss over the shorter term, long-term weight maintenance remains a challenge (Brown & Leeds, 2019). Dietary advice has been shown to be more effective when combined with physical activity, and further enhanced with the inclusion of behaviour change strategies.

As a chronic condition, with a remitting and relapsing nature, obesity requires a multi-component, multidisciplinary team (MDT) approach to support people in achieving their goals in variable settings (World Health Organization, 2024).

There is a need to acknowledge that enacting dietary and lifestyle change is challenging and people living with obesity seeking to change their dietary habits require continued support. This might include, where indicated, additional psychological, pharmacological, or surgical treatment options; it is our view no option should be excluded. When considering options, it is key for the members of the multidisciplinary obesity management team to be able to set out and discuss with people living with obesity how the different treatment options can combine and work together. These should be discussed in an empathetic manner so that individuals are fully informed and involved in their care.

For those currently using GLP-1 RAs, there has been little focus on optimal dietary approaches to support individuals who are taking these therapies, how best to combine a multimodal approach, and how to effectively manage side effects. Despite substantial empirical evidence on their use and outcomes, questions remain about how healthcare professionals and systems can best use these in practice. This editorial aims to explore the different perspectives of the multidisciplinary team and how we can take the published evidence and apply it to real-world holistic care.

THE EMERGENCE OF GLP-1 RAS AND THEIR CURRENT ROLE AS A TREATMENT FOR OBESITY – THE PHYSICIAN'S VIEW

For years, metabolic/bariatric surgery has been the most effective treatment modality for people living with obesity, and the only one with long-lasting benefits on obesity-related conditions, metabolic health and life expectancy (Sjostrom, 2013). However, metabolic/bariatric surgery is at present accessed by less than 1% of eligible people in the UK (Welbourn et al., 2016). Additionally, not everyone wishes to undergo surgery, meaning other effective treatments are needed.

The study of gastrointestinal hormones has dominated drug discovery over the last 20 years, seeking to mimic the changes seen after metabolic/bariatric surgery, with most of the interest being on GLP-1 (Drucker, 2022) with this incretin hormone increasing insulin secretion and reducing blood glucose (Nauck et al., 1986). Although gut hormone analogues were initially developed for the treatment of type 2 diabetes mellitus (T2DM), the added consequence of these analogues was also clinically significant weight loss resulting in these drugs being considered as medications for obesity, independent of a diagnosis of T2DM.

The first analogue approved specifically for the management of obesity was liraglutide 3 mg daily, based on the results of the *SCALE* trial (Pi-Sunyer

et al., 2015). Liraglutide resulted in a mean ~8% weight loss at 1 year, with this reducing to a mean ~6% weight loss after 3 years of treatment (le Roux et al., 2017).

This was followed by multiple RCTs of novel gut hormone analogues with greater potency for weight loss, resolution of obesity-related conditions and reduced injection frequency. Three series of studies have changed the current landscape significantly, namely *STEP-1*, *SURMOUNT* and the *SELECT* trials. The *STEP-1* RCT demonstrated the efficacy and safety of Semaglutide 2.4 mg, a once-weekly GLP-1 RA (Wilding, Batterham, Calanna, Davies, et al., 2021), with a mean weight loss of 15% for up to 2 years (Garvey et al., 2022). Importantly, 86% lost ≥5% and 32% lost ≥20% bodyweight (Wilding, Batterham, Calanna, Davies, et al., 2021). The subsequent *SURMOUNT* RCT demonstrated that the dual GLP-1/GIP (Glucose-dependent insulinotropic polypeptide) RA, Tirzepatide, showed greater efficacy with participants losing 22.5% at 72 weeks, with 36% of people losing ≥25% bodyweight (Jastreboff et al., 2022). Finally, the *SELECT* trial recruited people with obesity and established cardiovascular disease and showed participants using Semaglutide 2.4 mg had a 20% reduction in major adverse cardiovascular events at 4 years follow-up (Lincoff et al., 2023).

The question is where do we go now and are we going to see weight loss akin to bariatric surgery? With the gut being the largest endocrine organ (Ahlman & Nilsson, 2001), producing dozens of hormones that regulate appetite and metabolism there is great potential for future drugs. Several gut hormone combinations are currently under investigation, including amylin (Frias et al., 2023) and glucagon (Jastreboff et al., 2023). Despite the major opportunities, it is key that clinicians continue to be mindful of unknown side effects and use these medications only for people living with the disease of obesity, combining them with dietary, behavioural and surgical treatments and ensuring services are appropriately set up to aid increased access to care.

In terms of side effects, GLP-1 RAs show a favourable safety profile allowing their wide-scale use, however common side effects, often transient, have been reported. The most common are gastrointestinal, though there have also been reports of hair loss and fatigue within clinical practice. Of importance is that ~90%–95% of participants are still able to tolerate the medications despite these common side effects (Jastreboff et al., 2022; Le Roux et al., 2017; Wilding, Batterham, Calanna, Davies, et al., 2021). To alleviate concerns, the risk of pancreatitis and cholecystitis are low (<1%) and there is no evidence of an increase in any form of cancer, including thyroid cancer (European Medicine Agency, 2013).

Despite many people achieving clinically significant weight loss, there is substantial heterogeneity of weight loss response (Jastreboff et al., 2022; Wilding, Batterham, Calanna, Davies, et al., 2021). It is therefore recommended that discussions are had with patients prior to commencing treatment and realistic weight loss targets are agreed. Focus should also be placed on non-weight-related goals and improvements in health, avoiding a solely weight-centric focus.

GLP-1 RAs provide scalability and reach which is currently not feasible with metabolic/bariatric surgery. At present, within certain healthcare systems (e.g. the NHS in the UK), access to these medications is limited by supply and local commissioning approvals in many regions of the UK. Despite their apparent ease of use, practical challenges need to be considered, for example who gets access to the medication. This requires careful consideration in terms of prioritising patients related to clinical need, the timing, preparation and also what aftercare people have access to across primary and secondary healthcare settings.

In individuals with less urgent clinical needs (i.e. without life-limiting conditions), a longer-term treatment plan should be carefully considered prior to initiating treatment. The concerns surrounding weight regain (Wilding et al., 2022) following treatment discontinuation remain paramount in this decision-making process, particularly while the duration of access to treatment remains limited in some countries (e.g. currently 2 years in England; NICE, 2023). It is therefore recommended that on commencing GLP-1 RA therapy, planning for a patient's management beyond drug discontinuation should already have been discussed. Emerging data suggests that withdrawal of treatment utilising a gradual dose-reduction approach prior to full discontinuation may have better weight-maintenance outcomes compared to simply stopping from the full dose (Seier, Larsen, et al., 2024; Seier, Pedersen, et al., 2024).

However, there remains a need to consider alternative treatments such as metabolic/bariatric surgery or alternative strategies to help maximise long-term health, particularly for those with more complex forms of obesity. Therefore, adequate patient preparation and optimisation in terms of ensuring physical fitness, maintenance of muscle mass, good quality nutrition and mental health are needed prior to initiating therapy with GLP-1 RAs, since they are likely to have significant impacts on the longer-term benefits.

SUPPORTING INDIVIDUALS AND BEHAVIOUR CHANGE – THE PSYCHOLOGIST'S VIEW

From a psychological perspective, the advent of effective medications for obesity is hugely exciting and has the potential to open doors to both physical and mental health improvements that may otherwise have not been achieved for some individuals. There is a hope that the

appetite-reducing effect of GLP-1 RAs will improve psychological well-being by two main mechanisms. First, by reducing the negative effects, stress and weight stigma associated with weight difficulties that often form part of an individual's unhealthy relationship with food and their body. Second, by providing the individual with reflective space to examine their previous use of food and develop alternative coping mechanisms, a compassionate relationship with their body and a focus on healthy living.

However, there are also many valid concerns being expressed within the psychology networks working in obesity. Psychologists approach their clinical practice using a biopsychosocial model and there remain unanswered and unresearched areas in the 'psychosocial' part of the picture.

It has been clearly demonstrated that people seeking obesity management treatment have higher levels of psychiatric conditions, psychological distress, and disordered eating patterns. With GLP1 RAs reducing the rewarding value of high-energy dense foods, individuals may seek rewards or pleasure elsewhere and possibly from unhealthy sources, as seen in people following metabolic/bariatric surgery (Conason et al., 2013) If reward centres are significantly deactivated, this could lead to depression, increasing the risk of self-harm and suicide. In addition, with excess weight at times providing a sense of protection for some individuals, a reduction of this may leave an individual vulnerable or with increased psychological distress unless appropriately addressed. There is likely to be a need for mental health teams to be informed at the initiation of GLP1 RA therapy, given its far-reaching implications. However, the current provision is desperately lacking clear guidance about how to adequately address the psychological care needs of those using GLP-1 RAs.

There is also a significant risk that any use of GLP1 RAs without adequate multi-disciplinary support perpetuates the medicalisation of obesity. This has the potential to unhelpfully endorse a single external, 'bio', locus of control thereby reducing an individual's self-efficacy in managing their weight and maintaining a sense of helplessness. Services should also be designed in a manner not to "leave people behind", for example if the 'drugs don't work' or cannot be tolerated. Resource needs to consider how it will support individuals who experience this disappointment, compounding often years or decades of perceived failure at their weight management.

These are only some issues and concerns being raised by psychologists working in obesity services. In order to harness and embed the potential wider benefits of using a GLP1 RA, we need to actively encourage appropriately resourced and equitably available psychological support within the care pathways, while also collecting real-world data to optimise treatment.

WHERE THIS FITS WITH FOOD AND NUTRITION – THE DIETITIAN'S VIEW

Currently approvals for the use of GLP-1 RAs, alongside the published literature (Jastreboff et al., 2022; Wilding, Batterham, Calanna, Davies, et al., 2021), recommend that GLP-1 RAs are an adjunct to diet and exercise. It is therefore important that when considering using GLP-1 RAs that diet, exercise and drugs should be considered equal partners. In reality, how true this is, has yet to be considered. However, for those currently taking a GLP-1 RA for weight loss, the drug appears to be the key component that allows them to follow the dietary advice by addressing the underlying biology related to hunger and satiety. Furthermore, data show alterations in eating behaviour with less preference for high-fat and non-sweet foods alongside reductions in emotional eating (Blundell et al., 2017; Friedrichsen et al., 2021; Nicolau et al., 2022).

During the initial periods, those who respond to GLP-1 RAs appear to require less lifestyle support, since the drug is doing its job of switching hunger "off" and keeping people "full", and this apparent "honeymoon period" can last until weight maintenance. The question should therefore be, is this the right time to focus on behavioural and lifestyle change or should we instead be focussing on other key aspects, particularly ensuring nutritional adequacy. Interestingly, the addition of intensive behavioural therapy, alongside lifestyle change and Semaglutide 2.4 mg did not contribute to significant additional weight loss (*STEP 3*) (Wadden et al., 2021), perhaps suggesting that the timing of the behavioural intervention may not have been optimally placed. Therefore, a more individualised approach appears to be needed.

Despite dietary advice with GLP-1 RAs being centred around an energy-restricted deficit diet (600 kcal deficit) using estimated total energy equations (Wilding, Batterham, Calanna, Davies, et al., 2021), in reality, the amount of food consumed is significantly less, and at times is similar to those who have undergone bariatric surgery. Furthermore, gastrointestinal side effects such as nausea and sickness alongside changes in bowel habits are common (Jastreboff et al., 2022; Wilding, Batterham, Calanna, Davies, et al., 2021), and this can result in individuals struggling to follow a balanced diet including consuming sufficient protein and micronutrient-rich foods. Concerns have therefore been expressed about the potential for nutritional deficiencies including both macronutrients (i.e. protein) and micronutrients (Almandoz et al., 2024). Individuals who have lower intakes (≤1200 calories), should consider taking complete vitamin and mineral supplements. In addition, prior to starting a GLP-1 RA, people should be checked for any existing nutritional deficiencies and these rechecked if people are having low energy

intakes or poor diet quality and then treated appropriately. At present there are no available data on nutritional deficiencies following GLP-1 RAs and therefore a precautionary approach should be taken to consider this.

The impact of GLP-1 RAs on eating behaviour is well described. The reduction in appetite and weight is undoubtedly beneficial for metabolic health but can also have unwanted consequences on eating behaviour. Specialist dietary input alongside psychological support is required to ensure appropriate food choices to provide adequate nutrient intake. Concerns have also emerged about disordered eating and decompensation of underlying mental health conditions in individuals with emotion-driven eating behaviours and food-related coping strategies. These possible adverse effects illustrate the potential for clinical harm in the absence of careful patient evaluation and follow-up prior to or during treatment.

As people lose weight, they lose not only body fat but also muscle mass. In general, data suggests that the expected loss ratio of fat to muscle is approximately 75:25 (Beavers et al., 2011) respectively, with muscle loss rates over this presenting concern. The available data on body composition changes following GLP-1 RAs are limited but show that body composition appears to improve, with less percentage body fat and an increased proportion of muscle mass (Wilding, Batterham, Calanna, Van Gaal, et al., 2021). However, the issue is that the composition of actual weight lost was not assessed i.e. how much of the weight lost was muscle and how much was fat. When we look at this, we see a markedly different picture. Available body composition data shows an excessive degree of lean tissue loss. Within the *STEP 1* and *SUSTAIN 8* trials there was 38.9% and 39.6% lean tissue loss of total weight loss, respectively (McCrimmon et al., 2020; Wilding, Batterham, Calanna, Davies, et al., 2021). Interestingly, the *SURMOUNT* trial showed lower lean tissue loss (14.3%), via Bod Pod analysis, instead of DEXA, which may, in part, have accounted for the difference. A recent review has suggested that this loss of muscle may not influence physical function (Conte et al., 2024); however, in patients following bariatric surgery, decreases in fat-free mass increase patients' fracture risk and affect muscle strength and functional capacities (Reinmann et al., 2021). Until comprehensive physical function data are available for those on GLP-1 RAs, data from bariatric surgery may be the relevant data available and therefore concerns are still warranted. Furthermore, with an aging population, clinicians should be mindful of sarcopenic obesity (Shimizu et al., 2023) and ensuring that weight loss using GLP-1 RAs does not compound further muscle loss. Therefore, interventions are needed to minimise this loss including optimising protein intake and engaging in adequate physical activity.

It also needs to be considered whether these medications could be used in a different way, such that instead of using them as weight loss medications, they could be used as weight maintenance treatments to address the counter-regulatory effects of diet-induced weight loss on appetite (Iepsen et al., 2016; Sumithran et al., 2011). In a study looking at using Liraglutide and/or exercise following weight loss using a low-energy TDR, it was found that the combination of exercise and liraglutide produced greater weight maintenance and, in fact, weight loss following the diet ceasing (Iepsen et al., 2016, Lundgren et al., 2021).

AN ADJUNCT TO METABOLIC SURGERY? THE METABOLIC/BARIATRIC SURGEON'S VIEW

As our understanding of obesity has improved, and the complexity of the condition has been recognised, this has been reflected in the proposed treatment algorithms. In addition, the heterogeneity of the response to different treatment options means that often more than one modality is needed to achieve the appropriate therapeutic outcome for the individual (Istfan et al., 2020). The concept of multimodal treatment including pharmacotherapy and minimally invasive gastrointestinal surgery known as bariatric and metabolic surgery was introduced first in T2D and was subsequently expanded to obesity (Miras et al., 2019; Pournaras & Le Roux, 2015). In the GLP-1 *Receptor Agonist Intervention for Poor Responders After Bariatric Surgery* (*GRAVITAS*) randomised double-blind, placebo-controlled trial, the use of adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after Roux-en-Y gastric bypass or sleeve gastrectomy metabolic surgery was superior to placebo for glycaemic control and weight loss (Miras et al., 2019). The evaluation of Liraglutide 3.0 mg in patients with poor weight loss and a suboptimal GLP-1 Response (*BARI-OPTIMISE*) randomised placebo-controlled trial included patients at least 1 year after metabolic surgery who had experienced 20% or less bodyweight loss and a suboptimal nutrient-stimulated GLP-1 response. The study reported that 3.0 mg liraglutide once daily results in a significantly greater reduction in bodyweight compared to placebo. Lifestyle intervention, pharmacotherapy, endoscopic treatments and minimally invasive surgery should be offered sequentially or in combination as part of comprehensive obesity care (Mok et al., 2023). This approach is used for other complex conditions such as cancer. The treatment algorithms for these conditions do not include a single modality and therefore comparative trials do not compare chemotherapy with radiotherapy for example. Appropriate escalation of treatment and cessation of modalities that are not effective are the standard of

care. The therapeutic intent needs to be clearly set and this can be neoadjuvant (when pre-bariatric surgery weight loss may enable safe bariatric surgery), rescue (when the effect of an endoscopic or surgical treatment has not achieved the desired therapeutic outcome) and adjuvant (when modalities are combined from the start).

Furthermore, the biological basis of the variable response is well understood in other diseases and obesity is no exception. Just as multimodal care should become the standard of care for obesity, the quality of care improves further when the weight stigma associated with obesity is addressed. More research is needed to define the therapeutic targets at population and individual patient levels. It is clear that weight loss maintenance over 15% is needed to achieve a higher impact (Lingvay et al., 2022). Personalised targets are likely to be required again as is the case for multiple chronic conditions balancing treatment acceptability, tolerance, safety and effectiveness in a shared decision model with patients and carers. As the effect of treatments fatigues with time, the overall health, function and objectives of the treated individual also change requiring adjustments and modifications in care.

CONCLUSION

GLP1 RAs have the potential to permanently change the management of obesity and enable more individuals to achieve their health goals. Despite these clear benefits, the current provision is desperately lacking clear guidance about how to adequately address the multidisciplinary care needs of this complex patient group and their long-term care, given our understanding of obesity as a chronic relapsing disease. Furthermore, we must not forget the long-neglected area of shame and weight stigma (Brown et al., 2022). Post and Persky (2024) demonstrated the risk of negative judgement, as seen with bariatric surgery, extends to GLP1 RAs for the use of a "shortcut" to weight loss (Post & Persky, 2024). Therefore, clinical services need to consider this sensitively as part of how they support people living with overweight and obesity.

While there remains uncertainty about how best to operationally deliver optimal MDT services to support the effective use of GLP-1 RAs, the perspectives discussed through this editorial provide a blueprint of how this should be done in order to develop business cases with service commissioners. Additionally, these insights into the safety of the use of GLP-1 RAs in practice will ultimately support greater numbers of individuals living with overweight and obesity to improve their health and well-being.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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