Obesity Facts

Perspectives

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Ten Top Tips for the Management of GLP-1 Receptor Agonists in Adults within Primary Care

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GLP-1 receptor agonists (GLP-1RAs) like semaglutide and tirzepatide are increasingly used in clinical practice, given their proven efficacy in managing obesity and type 2 diabetes (T2D) [1]. This guide and infographic (Fig. 1; also available as online suppl. material, see https://doi.org/10.1159/000546472) support primary care staff in managing adult patients on these medications.

What Are GLP-1RAs, and How Do They Work?

GLP-1RAs replicate the activity of the endogenous incretin hormone GLP-1, which is secreted by the gut in response to food intake. GLP-1RAs promote weight loss by reducing appetite via slowed gastric emptying and acting on the brain's appetite centres. They enhance insulin secretion in a glucose-dependent manner, reducing the risk of hypoglycaemia and concurrently suppressing glucagon secretion, leading to decreased hepatic glucose production [2]. Gastric inhibitory polypeptide is also a gut hormone, which plays a role in appetite reduction.

Which GLP-1RAs Are Licenced for Obesity?

For obesity treatment, only liraglutide 3.0 mg, semaglutide 2.4 mg, and tirzepatide 5, 10, and 15 mg are licenced in adults. Semaglutide and liraglutide are GLP-1RAs, while tirzepatide is a dual GLP-1/gastric inhibitory polypeptide co-agonist. Dosing schedules are detailed in Figure 2a. Patients may privately obtain these medications, so it's important to enquire non-judgmentally (e.g., "To ensure safe prescribing, are you taking any weight loss medications you buy online?").

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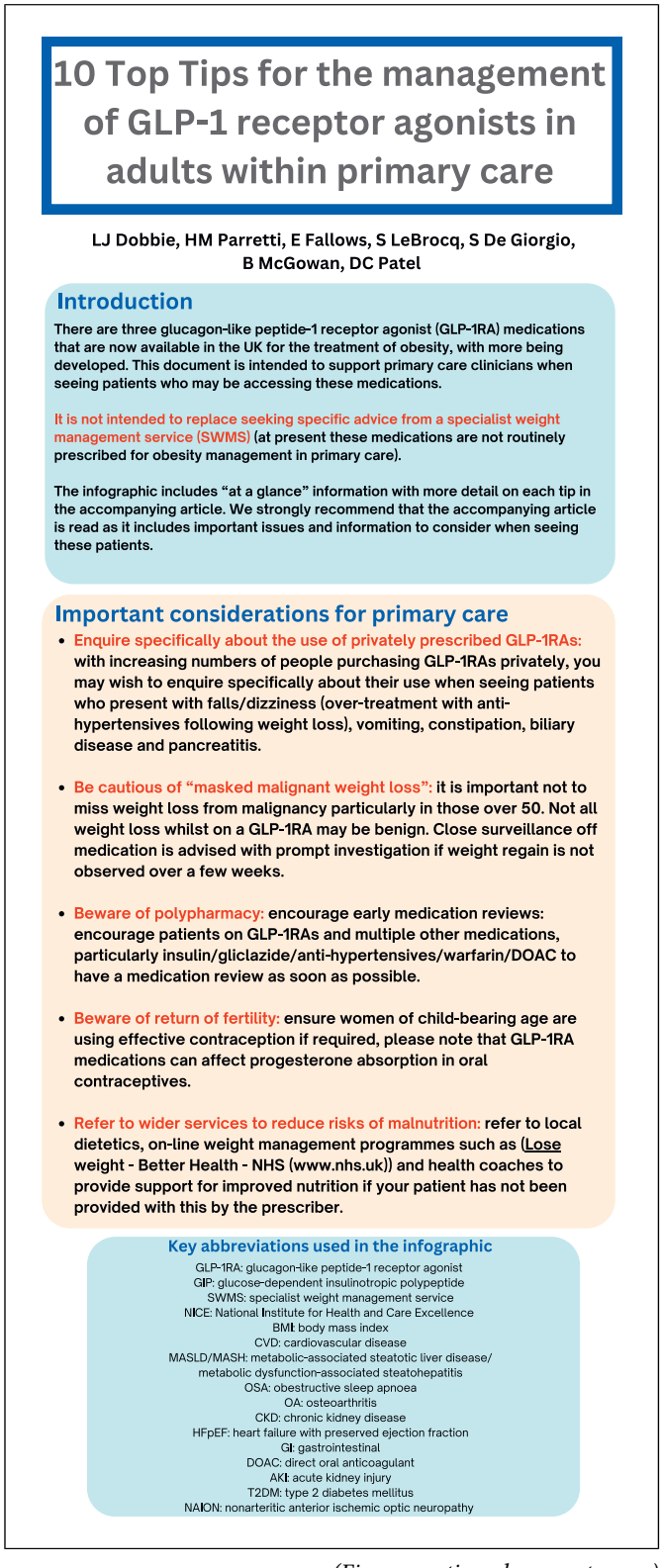

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Who Is Eligible, and What Support Do Patients Need?

Within the UK, National Health Service (NHS) adult patients can be prescribed GLP-1 agents licenced for T2D according to local guidance. However, at present primary care staff cannot prescribe GLP-1 RA for obesity and currently must refer patients to specialist weight management services. There are also National Institute of Clinical Excellence (NICE) approved digital providers of wrap-around care to support prescribing of GLP-1RA [4]. NICE recommends prescribing semaglutide 2.4 mg with dietary and physical activity support for adults with weight-related complications (i.e., cardiovascular disease) and BMI ≥35 kg/m^2 (or exceptionally ≥30) within specialist services [5]. Due to supply and funding constraints, most UK patients cannot access semaglutide 2.4 mg, even in specialist services. Tirzepatide has been evaluated by NICE for obesity management and will have a phased roll-out [6]. NICE recommends that patients receive support from a multidisciplinary team delivering comprehensive weight management programs, emphasizing calorie restriction, increased physical activity, and behavioural interventions for long-term success by trained professionals [7].

Benefits of GLP-1RAs?

GLP-1RAs significantly reduce weight and improve glycaemic control, with emerging benefits for other obesity-related health conditions. Combined with behavioural interventions, semaglutide 2.4 mg achieves an average 15% weight loss at 1 year, while tirzepatide 15 mg reaches 22% at its top dose of 15 mg. Weight loss also occurs at lower doses if higher doses are not tolerated due to side effects. There are emerging/established benefits for cardiovascular disease, heart failure, chronic kidney disease, sleep apnoea, osteoarthritis, and metabolic-associated steatotic liver disease [8].

Excessive Weight Loss and Risk of Malnutrition?

Some patients, termed "super-responders," lose more weight than expected. Additionally, some patients with normal weight may risk underweight by privately purchasing GLP-1 RAs off-licence. While weight loss benefits those with obesity, excessive loss may signal underlying pathology rather than the GLP-1 RA's effect.

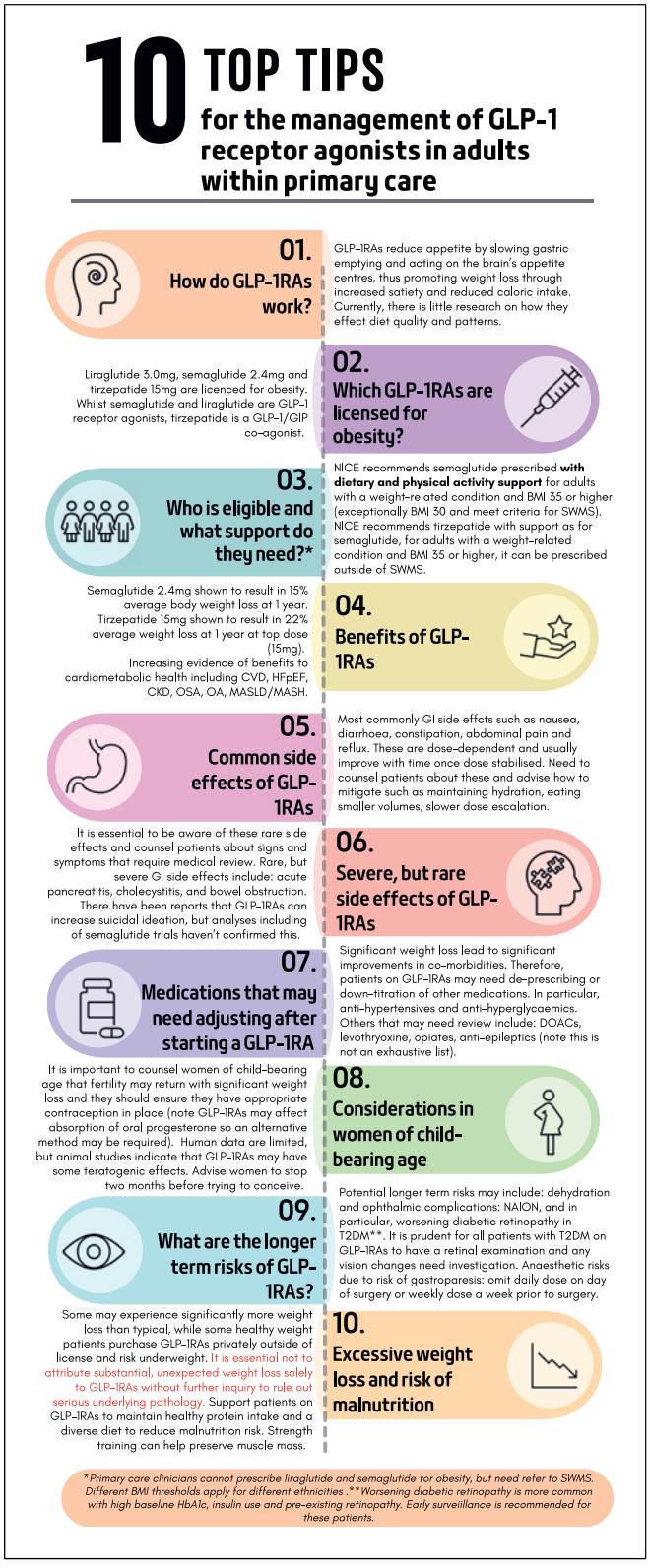


Fig. 1. Ten top tips for GLP-1 RAs in adults within primary care summary infographic.

For example, if a patient maintains stable weight reduction for a year but then loses more weight after 6 months on the same GLP-1RA dose, secondary causes should be investigated, especially due to a higher malignancy risk in patients with obesity.

It is essential not to attribute significant, unexpected weight loss solely to GLP-1 RAs without further enquiry. Excessive weight loss or continued loss after stopping the medication should be investigated as per any unexplained weight loss.

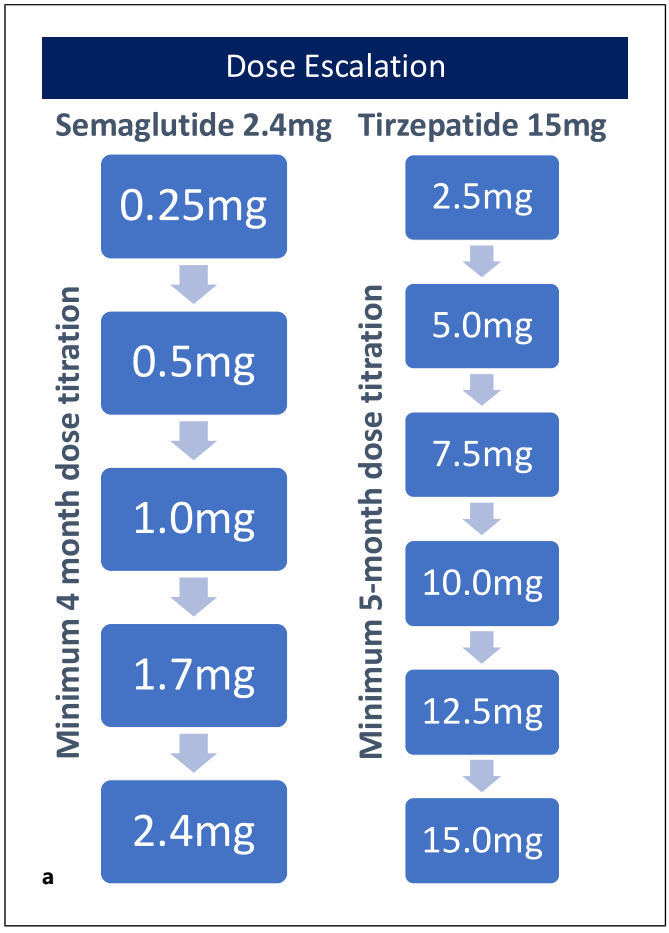
People with obesity often experience malnutrition, a "double burden" [9] that may be exacerbated by GLP-1RA use. Patients using GLP-1RAs should maintain a diet rich in healthy proteins and whole foods while avoiding ultra-processed foods, especially in those with frailty. Strength training can help preserve muscle mass during treatment and prevent weight regain after stopping the medication. Patients should be referred to health coaches, dietitians, physiotherapists, or online weight management programmes for additional support.

Common Side Effects?

GLP-1RAs commonly cause gastrointestinal side effects that are dose-dependent and typically settle once the dose stabilizes. Patients should be educated on gastrointestinal side effects at treatment initiation. Counselling patients on management strategies, such as adequate hydration, smaller meals, reducing alcohol intake, and increasing dietary fibre, is crucial. For moderate-severe side effects, slower dose escalation, temporary dose reductions, or lower target doses may help. Short-term use of adjunct medications like proton pump inhibitors and H2-antagonists for reflux, or cyclizine for nausea, can be beneficial. The requirement for these adjunct medications typically decreases over time and should not be used long term [3].

Rare Severe Side Effects?

GLP-1RAs are generally well tolerated; however ,patients should be counselled to seek urgent medical attention if they experience severe abdominal pain, as this may indicate underlying acute pancreatitis, cholecystitis, or bowel obstruction. Recent studies indicate that semaglutide does not increase suicide risk [10], but caution is still advised for patients with significant mental health conditions.



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Medications Review Requirements during GLP-1RA Treatment?

Significant weight loss can improve obesity-related complications, potentially necessitating the de-prescribing or down-titration of other medications. Key risks include hypoglycaemic agents like insulin and gliclazide, risking potentially life-threatening hypoglycaemia, and inappropriate antihypertensive treatments increasing falls risk. DPP-4 inhibitors (gliptins) should be stopped as not recommended together, as well as antimotility medications like codeine and loperamide. Reduced gastrointestinal motility and altered drug absorption may require dose adjustments of medications including warfarin, direct oral anticoagulants, opioids, and antiepileptic agents. Patients should be counselled that regaining weight after stopping GLP-1 RAs can reverse improvements, potentially requiring medications to be resumed. Patients in disease remission should continue annual chronic disease reviews.

Considerations in Women of Childbearing Age?

GLP-1RAs may enhance fertility and manage polycystic ovary syndrome. While weight loss can improve fertility, GLP-1RAs pose potential teratogenic risks, with animal studies suggesting decreased foetal survival and possible congenital defects [11]. Therefore, GLP-1RAs should be stopped 2 months prior to trying to conceive. In women with polycystic ovary syndrome, weight loss can improve fertility [12]. Therefore, women of childbearing age should be advised that significant weight loss may increase fertility, requiring effective contraception. Alternatives to oral contraception may be required due to absorption changes.

Longer-Term Risks of GLP-1RA?

There is no consistent human evidence that GLP-1RAs increase the risk of thyroid or pancreatic cancer. However, rodent studies suggest a link to medullary thyroid cancer, leading to contraindications for individuals with a personal or family history of MEN2A or medullary thyroid cancer [13].

GLP-1RAs can cause gastroparesis, requiring anaesthesia precautions due to aspiration risk. Guidance advises patients to skip daily doses on the day of surgery or weekly doses 1 week before surgery [14]. As GLP-1RAs can suppress thirst, patients should be counselled to maintain fluid intake to prevent dehydration and acute kidney injury.

GLP-1RAs pose risks of severe eye complications, particularly worsening diabetic retinopathy with rapid and significant HbA1c reduction. There is also concern regarding the potential risk of non-arteritic anterior ischemic optic neuropathy, although the study in question had several limitations [15]. Patients with T2D should undergo retinal exams within a year before starting GLP-1RAs, and any vision changes during treatment should be promptly investigated.

Overall, GLP-1RAs are becoming critical tools in the management of obesity and T2D. For safety and successful outcomes, these treatments must be accompanied by comprehensive wrap-around care which includes dietary, behavioural, and medical support. Primary care staff should stay updated on evolving research and guidelines, as GLP-1RAs are increasingly prescribed and likely to be licenced for more obesity-related health conditions.

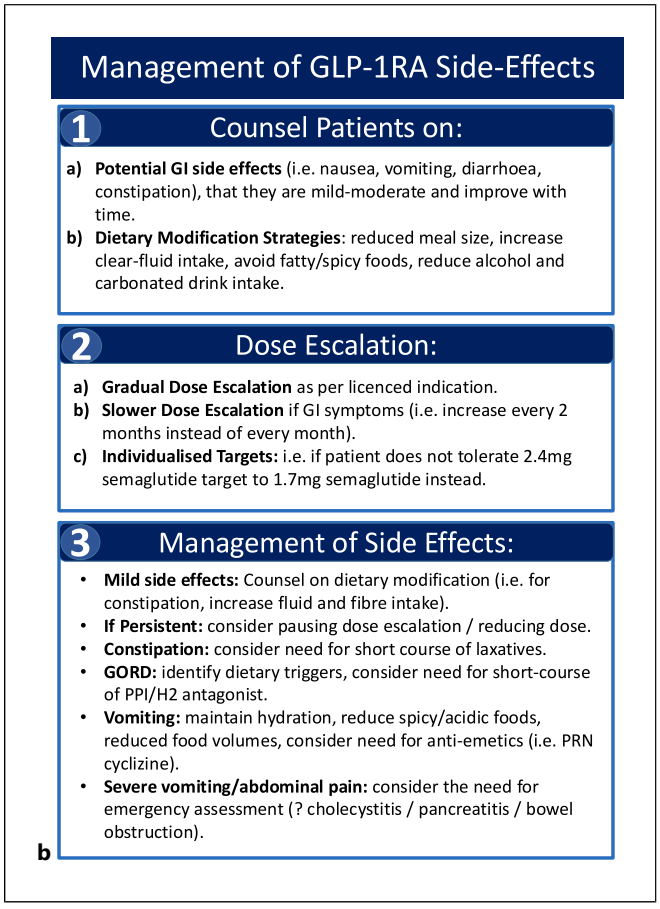

Fig. 2. a Dose escalation for semaglutide and tirzepatide. **b** Management of GLP-1RA side effects. Adapted from Wharton et al. (2022, Postgrad medicine) [3].

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Conflict of Interest Statement

S.L.B. has done consultancy work for second nature, simple online pharmacy, and check-up; has received honorarium for speaking for Novo Nordisk, Eli Lilly, and Boehringer Ingelheim; and is the founder and director of all about obesity and a trustee of ASO. D.C.P. has done advisory work for Astra Zeneca, Boehringer Ingelheim, and Eli Lilly; has done educational work for Eli Lilly and Novo Nordisk; and has shareholdings in Reset Health. B.M. is a shareholder in Reset Health and performs advisory and educational work for Novo Nordisk and advisory work for Lilly, Pfizer, and Johnson and Johnson. S.D.G. has been funded by Novo Nordisk previously to create RCGP educational material and to do teaching for Novo Nordisk's in house staff and is a founder of all about obesity, which has received seed funding from Novo Nordisk. H.M.P. is a British Obesity and Metabolic Surgery Society (BOMSS) council member; has organized educational events supported by Ethicon for BOMSS members (honoraria received for educational events); has developed an algorithm for the management of obesity in primary care with accompanying resources for MGP publishing, which were supported by arm's length sponsorship from Novo Nordisk (honoraria received); is a member of the NICE obesity management clinical guidelines and quality standards committees and was an expert advisor for the NICE Early Value Assessment of digital technologies for delivering specialist weight-management services to manage weight-management medicine; and is a co-author on a paper reporting a secondary analysis of data from the ACTION-IO study (funded by Novo Nordisk) (no payments received). All other authors declare no COI.

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Author Contributions

L.J.D., B.M., and D.C.P. led the conception and design of the work. L.J.D. wrote the initial draft with H.M.P., E.F., S.L.B., S.D.G., B.M., and D.C.P. revising it critically for important intellectual content. L.J.D., H.M.P., E.F., S.L.B., S.D.G., B.M., and D.C.P. gave the final approval of the version to be submitted. L.J.D. takes responsibility for the integrity of the work as a whole, from inception to the final article.

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