Review

Anti-obesity drugs for the gastroenterologist

Lisa Sharkey [1,2]

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[1]Institute of Gastroenterology and Hepatology, King's College Hospital Dubai, Dubai, UAE
[2]Gulf Medical University, Ajman, Ajman, UAE

Correspondence to
Dr Lisa Sharkey; lisasharkey@icloud.com

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly used in the management of diabetes mellitus and obesity and have become accessible to many through non-standard prescribing pathways. Studies are demonstrating a plethora of positive effects on cardiovascular health, renal disease and liver disease, which may be directly related to the mitigation of the diabetes or obesity-associated risks of these complications or possibly direct protective effects. However, these agents slow gastrointestinal motility, which can lead to side effects of increased gastro-oesophageal reflux, nausea, vomiting, constipation or paradoxical diarrhoea. More severe adverse effects include cholelithiasis, acute pancreatitis and increased risk of medullary cell thyroid cancer. Gastroenterologists are being increasingly consulted for the side effects, and a discussion around best management of these symptoms is presented. Safety around endoscopic procedures has also been subject to much discussion, and the latest guidance is outlined for endoscopists.

KEY POINTS

- ⇒ Glucagon-like peptide-1 (GLP-1) is an incretin hormone which lowers blood sugar levels and slows gastrointestinal motility.
- ⇒ First developed as treatments for diabetes, GLP-1 receptor agonists are increasing in popularity for weight loss, thanks in part to social media and celebrity endorsements.
- ⇒ Gastrointestinal side effects are common, and many patients will seek help from general practitioners or gastroenterologists. The most common side effects are nausea, vomiting and constipation.
- ⇒ In the future, there may be expanded indications for use, such as dumping syndrome or chronic diarrhoeal conditions.
- ⇒ The management of side effects is discussed based on evidence-based practice and real-world experience.
- ⇒ Recommendations for safe endoscopic practice for patients taking GLP-1RA now focus on an individualised approach, considering the urgency of the procedure, the presence of active symptoms and the indication for the GLP-1RA and adjuncts such as bedside gastric ultrasound.

INTRODUCTION

Diabetes and obesity are major worldwide public health concerns, with an estimated 529 million and 878 million affected, respectively (2021/22 data).[1 2] The global health and economic burden of these conditions is difficult to overestimate. Large-scale pharmaceutical and research investment in these areas has led to the development of a number of effective treatment options, with the glucagon-like peptide-1 (GLP-1) agonists being the most well-known.[3] This is partly due to their effectiveness, but many have been influenced by celebrities and online personalities championing these medications for weight loss. Some of the major non-glycaemia-related actions of GLP-1 receptor agonists (GLP-1RA) are on the gastrointestinal (GI) tract, and gastroenterologists have been increasingly involved in managing the GI side effects of these medications. The balance of reducing side effects without losing therapeutic efficacy can be challenging.

GLUCAGON-LIKE PEPTIDE-1 (GLP-1)

In the late 19th and early 20th century, much work was being done by physicians and physiologists around the role of the pancreas in diabetes, culminating of course with the discovery of insulin in 1922, but even then, it was proposed there was more to the story than just insulin. French physiologist Jean La Barre first used the term 'incretine' in 1932 to describe a substance which lowered glucose levels by augmenting insulin release and actions.[4 5] We now know that

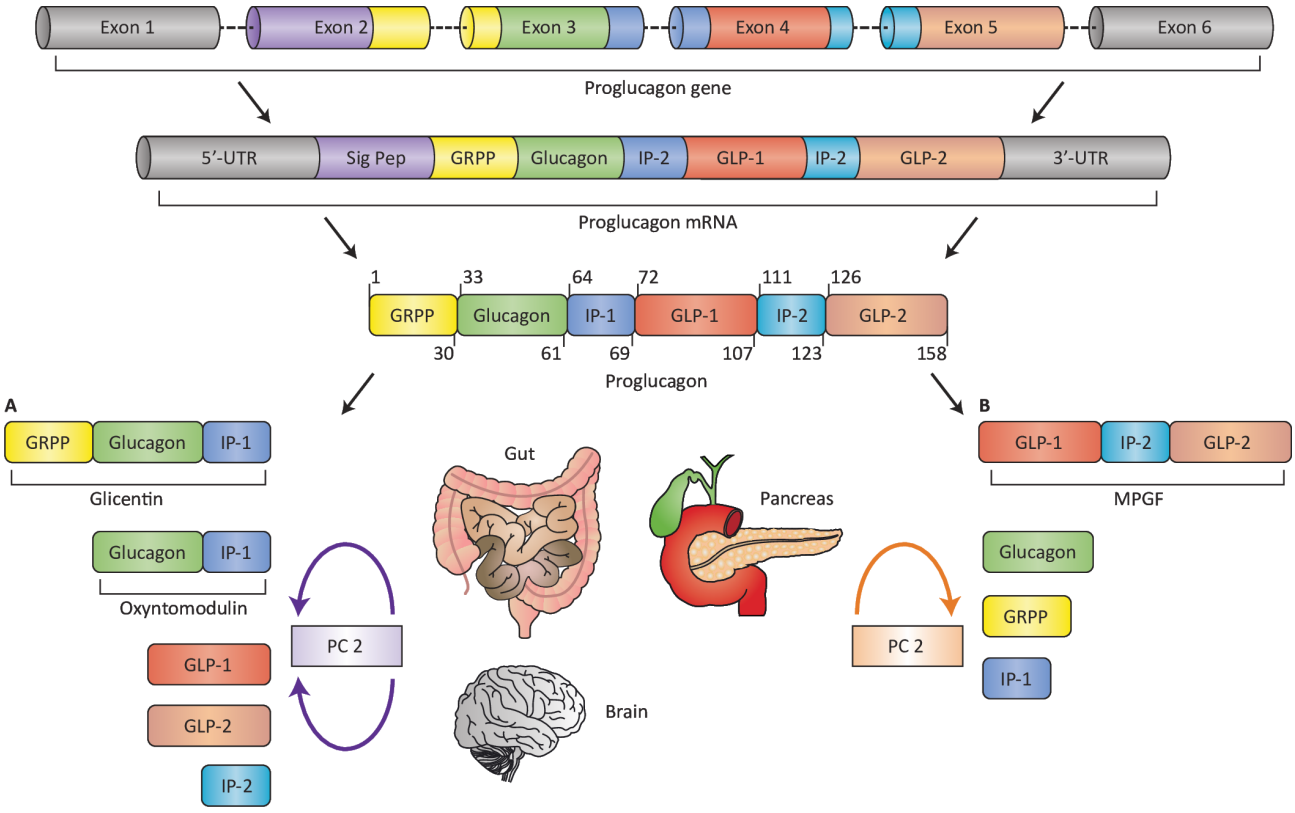

Figure 1 Generation of glucagon-like peptide-1 from proglucagon with differential products in the intestine and brain compared with the pancreas (From Müller TD *et al*[7]). IP, intervening peptide; GRPP, glicentin-related pancreatic polypeptide; GLP-2, glucagon-like peptide-2; MPGF, major proglucagon fragment; PC, prohormone covertase.

GLP-1 and glucose-dependent insulinotropic peptide (GIP) are the two main incretin hormones. They both enhance insulin secretion by the pancreatic islet cells and inhibit glucagon secretion, thereby lowering postprandial blood glucose levels, and have trophic effects on pancreatic β-cell mass.[6]

Endogenous GLP-1 is formed from the cleavage of proglucagon, which is secreted from L cells scattered throughout the intestine but concentrated in the distal ileum. The presence of luminal macronutrients is the main stimulus for GLP-1 secretion. Intestinal cells and neurons contain prohormone convertase (PC) 1, which cleaves proglucagon into glicentin, oxyntomodulin, GLP-1, GLP-2 and IP-2, while the action of PC2 in the pancreas produces glucagon and the major proglucagon fragment[7] (figure 1).

Native GLP-1 has a very short half-life (2 min) due to degradation by dipeptidyl dipeptidase-4 (DPP-4). The available GLP-1RAs have undergone various modifications to extend the half-life and allow once daily or once weekly dosing. Parallel drug developments in DPP-4 inhibitors to enhance the actions of endogenous GLP-1 led to the release of the 'gliptans', the first of which was sitagliptin, which was Food and Drug Administration (FDA) approved in 2006. The actions of GLP-1 are not restricted to the GI tract (see figure 2) and explain some of the neuroprotective, anti-inflammatory and behavioural modifications being reported in studies.[7]

GLUCOSE-DEPENDENT INSULINOTROPIC PEPTIDE

Named for its initial observed effects on lowering gastric acid secretion, the gastric inhibitory peptide was renamed when the incretin and pancreatotrophic effects were described. It also positively affects bone remodelling and regulates appetite and satiety[8] (figure 3). Currently, tirzepatide is the only combined GLP-1RA and GIP inhibitor available, and it has been shown to have more pronounced effects on glycaemic control and weight loss when compared with the pure GLP-1RA. A retrospective analysis of over 41 000 adults receiving semaglutide or tirzepatide published in July 2024, which favoured tirzepatide, has probably contributed to the recent surge in popularity of this drug. The authors showed patients receiving tirzepatide were significantly more likely to achieve weight loss of 5%, 10% and 15% and changes in weight were more marked across 3 month, 6 month and 12 month timepoints.[9]

AVAILABLE GLP-1RAS

The details of the available medications are shown in table 1. The most widely prescribed agents are

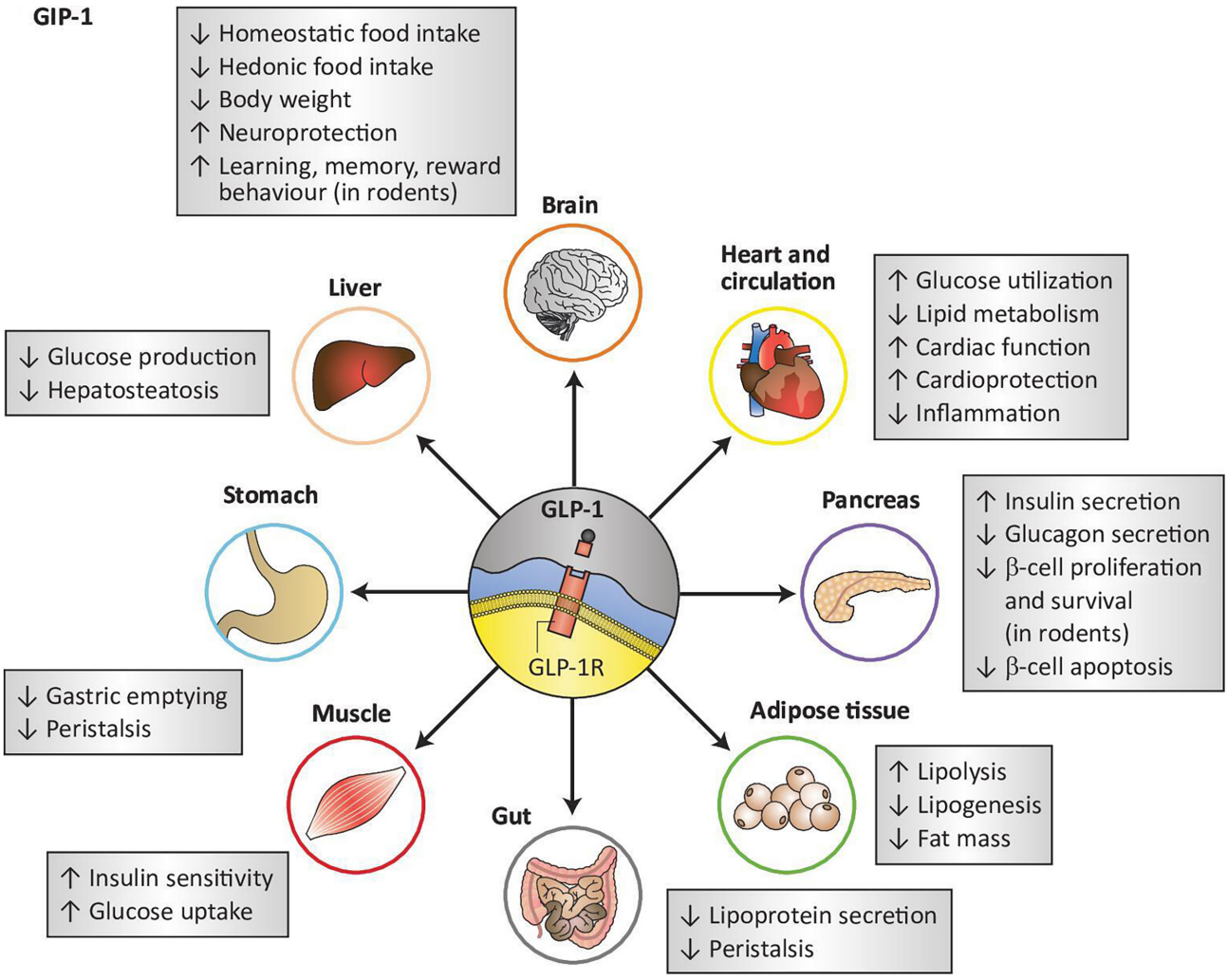

Figure 2 Actions of glucagon-like peptide-1 on the gastrointestinal tract and other organ systems (From Müller TD *et al*[7]).

semaglutide (Ozempic, Wegovy) and tirzepatide (Munjaro). For weight loss, tirzepatide, with dual action on GLP-1 and GIP receptors, has been especially successful. These agents are mainly administered subcutaneously, as they are peptide-based molecules with low bioavailability. However, a version of semaglutide attached to an 'absorption enhancer' (Rysbelsus) is now available.[10] Pharmaceutical companies are investigating the feasibility of inhaled and transdermal versions. For the purpose of this review, the term GLP-1RA is used to refer to all agents, including the combined GLP-1 and GIP agonist tirzepatide.

THERAPEUTIC USES OF GLP-1 AGONISTS BEYOND DIABETES AND WEIGHT LOSS

There are already multiple published beneficial effects to these medications in people with diabetes and those without (almost 1400 clinical trials on PubMed currently). Aside from improved glycaemic control and 'simple' weight loss, significant beneficial effects have been reported in major adverse cardiovascular events including reduced risk of cardiovascular death (RR 0.90, 95% CI 0.83 to 0.91, p=0.004) and reduced risk of non-fatal stroke (RR 0.85, 95% CI 0.77 to 0.94, p=0.001).[11] The vascular endothelium and cardiac myocytes express GLP-1 receptors. Positive chronotropic and inotropic effects in heart failure have been demonstrated with infusions of GLP-1 in animal studies and small short-term studies of patients with acute heart failure post-myocardial infarction and in patients with chronic systolic and diastolic dysfunction.[12] Tirzepatide has demonstrated additional benefits of slowing renal decline when used in conjunction with insulin and reduced all-cause mortality compared with other GLP-1RAs.[13] In patients with type 2 diabetes mellitus (T2DM), reductions in composite renal outcomes and renal failure have been outlined in meta-analyses.[14]

Of great interest for gastroenterologists and hepatologists is the potential for using GLP-1 agonists in metabolic dysfunction-associated steatotic liver disease (MASLD). There are likely to be multiple effects, as weight loss and improved glycaemic control alone are important targets in MASLD, but there may be direct hepatoprotective effects also. A post hoc analysis of patients with T2DM receiving dulaglutide or

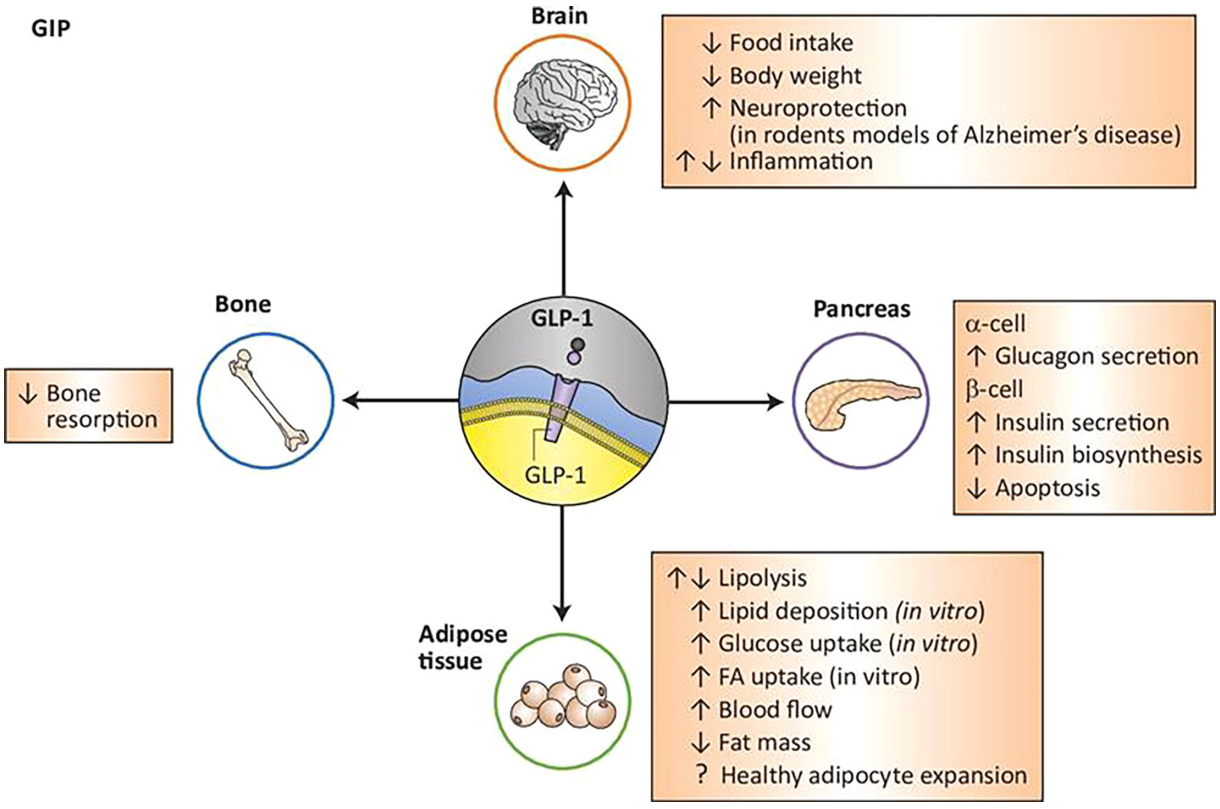

Figure 3 Actions of glucose-dependent insulinotropic polypeptide, formerly known as gastric inhibitory polypeptide (From Müller TD *et al*[7] and Nauck MA *et al*[8]).

tirzepatide showed improved biomarkers of MASLD with levels of cytokeratin-18 M30 fragment and procollagen III significantly reduced in patients treated with higher doses of tirzepatide.[15]

In a retrospective, propensity score matched study from veterans affairs (VA) hospitals in patients with MASLD, treatment with GLP-1RA compared with DPP-4 inhibitors reduced progression to cirrhosis (HR 0.86, 95% CI 0.75 to 0.98), but there was no protective effect in those who had already developed cirrhosis.[16] This suggests the timing of treatment needs to be considered, and we also need studies on changes in liver histology with these agents, as this VA trial used clinical and biochemical diagnoses. The ESSENCE trial[17] will report on patients with steatohepatitis and F2/F3 fibrosis who have received semaglutide 2.4 mg per week and will examine histological and clinical progression.

Considering their mechanism of action, there is a rationale for using GLP-1 agonists in conditions such as dumping syndrome to slow gastric emptying, diarrhoea-dominant IBS, bile acid diarrhoea due to their potentiation of the 'ileal brake' mechanism[18] or even short bowel syndrome and high output stomas.[19] These are currently not licensed indications nor have any trials been undertaken to date. However, the possibilities are interesting. Studies are underway examining a possible role in addiction behaviour and neuroplasticity, and there is the potential for an explosion in the use of these medications. There is clearly still much work to be done on how to mitigate the risks and side effects, how to optimise dosing schedules and combination GLP-1, GIP, glucagon and possible other enterohormone receptor agonism. For the immediate future, gastroenterologists may find themselves increasingly occupied with managing the side effects of these medications.

GASTROINTESTINAL SIDE EFFECTS

Some GI side effects are entirely predictable from the mechanism of action. Slowing GI motility can result in new onset or worsening of pre-existing symptoms related to gastro-oesophageal reflux, constipation and nausea/vomiting.

Prescribing clinicians should be discussing all potential side effects before commencing treatment and agreeing with patients that dosing schedules may need to be adjusted if significant adverse symptoms occur. However, as many vendors are online and perhaps are only performing minimal checks before issuing these mediations, gastroenterologists may be faced with patients who were completely unaware these side effects are expected and are very concerned by their new symptoms.

Of course, clinicians should bear in mind the differential diagnosis of any new conditions and investigate as per standard pathways if there is any suspicion of another underlying diagnosis. This can be difficult

Table 1 Currently available glucagon-like peptide-1 receptor agonists

Generic name	Brand names	Company	UK approval status	EU approval status	US approval status	Dosing information
Exenatide	Byetta	Eli Lilly	Since 2006 for T2DM	Since 2006 for T2DM	2005	5 mcg twice daily. Discontinued March 2024
	Bydureon	AstraZeneca	Since 2011 for adults with T2DM	Since 2011 for T2DM in adults and since 2022 for children/ adolescents	From 2018 for adults and 2021 for children/ adolescents	2 mg once weekly
Liraglutide	Saxenda	Novo Nordisk	For weight loss since 2020 on NHS	From 2015, from 2021 for weight loss in adults and 2023 for weight loss in children	Since 2014 for weight loss in adults, 2020 for children (12 and over)	Starting dose 0.6 mg, titrated up to 3 mg
	Victoza	Novo Nordisk	For T2DM in adults and children	Since 2009 for T2DM	In adults since 2010 and in children since 2019, for T2DM	Starting dose 0.6 mg once daily, titrated up to 1.8 mg daily
Semaglutide	Wegovy	Novo Nordisk	Since September 2023 for weight loss	Since 2022 for weight loss	For weight loss since 2021	Starting dose 0.25 mg once weekly, titrating up to 2.4 mg
	Ozempic	Novo Nordisk	Yes, for T2DM only	Since 2018 for T2DM only	Since 2017 for T2DM	Starting dose 0.25 mg weekly, increasing up to 2 mg
	Rysbelus	Novo Nordisk	From 2020 for T2DM	From 2020 for T2DM	From 2019 for T2DM	Oral dosing, initially 3 mg daily then 7 mg or 14 mg daily
Tirzepatide*	Munjaro	Eli Lilly	Yes, for T2DM only	For T2DM and weight loss	Since 2022 for T2DM	Initial dose 2.5 mg once weekly, progressing up to 15 mg
	Zepound	Eli Lilly	N/A	N/A	FDA approved for weight loss	Initial dose 2.5 mg once weekly, progressing up to 15 mg

T2DM, type 2 diabetes mellitus. Source: company websites, National Institute for Health and Clinical Excellence (www.nice.org.uk, accessed 15 September 2024), European Medicines Agency (www.ema.europa.eu, accessed 15 September 2024), Federal Drug Administration (www.fda.gov, accessed 15 September 2024)
*Dual agonist of GLP-1 and GIP.
FDA, Food and Drug Administration; T2DM, type 2 diabetes mellitus.

as standard alarm/red flag symptoms such as weight loss should of course be present if the treatment is working! Temporary cessation to observe for resolution of symptoms, in addition to a temporal relationship with the onset, can provide reassurance to both the clinician and patient.

With the exception of exenatide, there is an initial dose escalation phase, with clinicians starting treatment at the lowest approved dose and escalating at intervals thereafter, mainly to improve tolerance. For example, tirzepatide (Munjaro) is usually given as 2.5 mg once weekly for 4 weeks, followed by 5 mg once weekly for a further 4 weeks and so on until the maximal effective and tolerated dose is reached (up to 15 mg). In general, symptoms are mild and manageable by temporary discontinuation, dose reduction or a delay in dose escalation.

Gastro-Oesophageal Reflux Disease (GORD)

The prevalence of GORD is high in patients with obesity, as it is associated with up to a threefold increase in symptoms. Weight loss is one of the main lifestyle management strategies advised in various guidelines, as it can significantly improve symptoms.[20 21] However, as impaired gastric emptying is one of the pathophysiological associations of GORD, there is a risk of further delays in gastric emptying induced by GLP-1RAs increasing symptoms of GORD.

For the short-acting GLP-1RAs (exenatide, liraglutide, lixisenatide), a study in Gut[22] showed patients starting these agents had an 11% increased risk of being newly diagnosed with GORD when compared with the control group of patients with diabetes receiving alternative medications. All patients with GORD (new or pre-existing) on these agents had significantly increased risk of developing Barrett's oesophagus or a stricture (oesophageal stricture HR 1.284; 95% CI 1.135 to 1.453; Barrett's without dysplasia HR 1.372; 95% CI 1.217 to 1.546; Barrett's with dysplasia (HR 1.505; 95% CI 1.164 to 1.946). These associations were not seen with the long-acting GLP-1RAs in this study, though were observed from the FDA adverse events database real-world pharmacovigilance study.[23]

There are no specific recommendations regarding the management of reflux and associated complications in patients taking GLP-1RAs, so standard management is advised, along with consideration of dose adjustment or cessation depending on individual circumstances.

Management of nausea and vomiting/gastroparesis

These are the most frequent and bothersome symptoms for many. In trials, nausea affected 15–59% of patients, and vomiting affected 5–20%.[23] The immediate temptation to initiate prokinetics needs to be tempered against the possibility of loss of response. Satiety and loss of appetite are major contributing factors to weight loss, and some patients may prefer to suffer through these symptoms to ensure they achieve their goal of better diabetes control or weight reduction. Non-pharmacological suggestions include avoiding strong smells, having mint or ginger-based drinks (though mint can exacerbate GORD symptoms) and separating fluid intake from meals (at least 30 min before and after). The rationale for advising a gastroparesis style diet[24] is sound and effective in the author's experience.

If prokinetics are required, a short course of domperidone or metoclopramide can be given, but prescribers must bear in mind the contra-indications of their use and that they are recommended for short-term use only (5 days only in the case of metoclopramide, www.bnf.nice.org.uk). Extended use would require a comprehensive dialogue with the patient. Prucalopride, a 5HT-4 receptor agonist, has promotility effects in the stomach and colon, so can be useful for managing the drug-induced nausea and constipation. Lower doses than usual are proposed by some in order to balance the symptom-relieving effect against the risk of lowering efficacy, 0.5–1 mg daily, titrated according to response.

Management of constipation

This affected 4–37% of patients in trials,[23] and the mechanism is mainly related to slower colonic motility, but altered nutrient intake probably also plays a role. The first-line simple advice to ensure adequate fluid and fibre intake should be reiterated, and a fibre supplement given if patients are reluctant or unable to increase dietary fibre. PEG-based laxatives can be used, as per standard management of constipation. Prucalopride can also be used, as above, at the lowest dose needed.

Management of diarrhoea

Although somewhat paradoxical given the mechanism of action of these medications, 5–25% of patients in trials did report diarrhoea,[23] which mainly occurred in the first few weeks of treatment only. Patients should be reminded to avoid artificial sweeteners, which are often contained in low-calorie foods, as these can cause osmotic diarrhoea. Screening for infective causes should be done in anyone with acute diarrhoea plus indicators of infection (fever, systemic symptoms, recent travel or infectious contact).

Acute pancreatitis

Data from animal studies showed the occurrence of acute pancreatitis at higher doses of GLP-1RAs. Early clinical trials also showed some risk, so patients with a history of acute pancreatitis were excluded from subsequent trials, and the FDA issued a warning in respect of pancreatitis risk in 2007. More recent meta-analyses have not shown an increased risk, even in patients with a previous history of pancreatitis.[25 26] However, there are relatively small patient numbers and short follow-up times, so again shared decision-making between patient and clinician should be conducted, especially in patients with a history of pancreatitis.

Small intestinal bacterial overgrowth (SIBO)

Slow enteric motility is a known risk factor for SIBO, and gastroenterologists have seen patients presenting with de novo SIBO following commencement of GLP-1 agonists.[27] It is not yet known how common this will be. After all, diabetes and obesity are themselves associated with increased incidence of SIBO.[28 29]

ENDOSCOPY IN PATIENTS TAKING GLP-1

There are two major considerations in patients taking a GLP-1RA who need to undergo endoscopy—the effectiveness of bowel preparation and the safety of sedation/anaesthesia for patients who may have retained gastric contents (RGC), particularly those undergoing upper GI endoscopy. The safety of anaesthesia for surgical procedures has also been subject to much study and opinion, and gastroenterologists can extrapolate some concepts from this area, particularly for those performing procedures under general anaesthesia or deep sedation. The situation has evolved over the last 12 months, so readers are advised to always check updated guidance.

A 2023 single-centre study of patients taking semaglutide prior to upper GI endoscopy showed a significantly increased risk of RGC in patients taking semaglutide compared with controls, which was associated with the presence of GI symptoms and the duration since the last dose was administered.[30] One case of pulmonary aspiration was described in the semaglutide group. A larger two-centre study in 2024 showed no increased risk of aspiration with GLP-1RA compared with sodium-glucose cotransporter-2 inhibitors, but there were higher rates of abandoned procedures in the GLP-1RA group (OR 1.99, 95% CI 1.56 to 2.53).[31] A prospective observational study in volunteers taking semaglutide and controls performed gastric ultrasound after an 8 hour fast. They were found in 70% of semaglutide participants, but just 10% of control participants had solids present on gastric ultrasound.[32] A meta-analysis by Facciorusso *et al*[33] included 13

studies up to May 2024 of 84 065 patients undergoing upper GI endoscopy. They did find a higher rate of RGC (OR 5.56, 95% CI 3.35 to 9.23) and rates of abandonment of procedures (OR 5.13, 95% CI 3.01 to 8.75). However, there were no significant differences in adverse events and aspiration rates. Rates of incomplete mucosal visualisation were not reported, which is an additional important consideration for the endoscopist and patient.

Society statements and guidelines have been issued and amended. A statement from the American Society of Anaesthesiologists in 2023 recommended GLP-1RA be withheld on the day of surgery (for daily dosing) or the week prior to surgery (for weekly dosing), irrespective of the indication for the GLP-1RA. More recently, a multisociety clinical practice guideline superseded this and offered a more comprehensive framework for shared decision-making between clinician and patient for the perioperative period.[34] This guideline outlines features which are associated with increased risk: patients in the escalation phase of treatment, those on higher doses, those receiving weekly rather than daily GLP-1RA, patients with current GI symptoms and those with another reason for delayed gastric emptying (diabetes, Parkinson's disease, other medications known to slow emptying). A point-of-care gastric ultrasound is recommended if there is clinical concern on the day of surgery regarding the presence of RGCs. A gastric volume of 150 ml or less is considered safe to proceed.

A rapid clinical practice update issued by the American Gastroenterology Association advocated an individualised approach, taking into account the indication and urgency of the endoscopic procedure, the indication for GLP-1RA (diabetes or weight loss) and the presence of symptoms.[35] The option to omit the dose immediately prior to the endoscopy is applicable for some; however, for diabetic patients, this may adversely affect their glycaemic control or mandate alterations in the dosing of other medications, including insulin. For those taking GLP-1RA for weight reduction only, this is less of a consideration, and in the author's experience most are happy to skip a dose under these circumstances. Indeed, this specific advice is featured in the 2024 AGA update. However, some have expressed a concern that having a different approach for some patients may constitute obesity bias. Akin to pre-surgical evaluation as above, bedside ultrasound, if available, is useful for avoiding unnecessary cancellations, and we have found it useful in our unit. If this is not available, units should ensure they are otherwise adhering to the latest guidance in this area.

There is a concern that pre-colonoscopy bowel cleansing regimens will not be as effective due to altered transit. Observational studies provided conflicting results on this, with some showing no difference in the Boston Bowel Preparation Scale between treated patients and controls and some showing lower scores in the GLP-1RA group.[36–38] There is always a risk of publication bias in such scenarios. A systematic review of 23 studies showed no difference in subjective bowel preparation scores in patients taking GLP-1RA vs controls[39]; however, this did include some studies in abstract form only, and subsequent further large cohort studies have continued to show an increased risk of poor bowel preparation.[40] An abstract from the American College of Gastroenterology meeting in 2024 reported longer gastric transit time and higher rates of incomplete small bowel visualisation in patients taking GLP-1RA undergoing video capsule endoscopy (VCE) when compared with a control group. 7% of treated patients demonstrated complete failure to pass the capsule beyond the stomach during the entire recording.[41] The author's preference is to again discuss options with the patient, acknowledging the paucity of clinical data, but many patients do not want to risk an incomplete colonoscopy or VCE and prefer to omit a dose of GLP-1RA.

CONCLUSIONS

There is little doubt about the effectiveness of GLP-1 agonism in relation to improved glycaemic control and weight loss, though the longer-term sustainability of the latter remains to be seen. Research into combining agonism of the GLP-1 receptor with GIP, glucagon and possibly other receptors is ongoing, as well as novel mechanisms of drug delivery, for example, by inhalation. Retatrutide, a triple-hormone agonist, has been shown in Phase 2 trials to be extremely effective in inducing weight loss in a dose-dependent manner.[42] Given the potential extraordinary economic and composite health benefits to the individual and population, it seems likely that the area of Bariatric Pharmacology will continue to expand. Therefore, GPs, endoscopists and gastroenterologists will increasingly be called on to manage the GI side effects of these drugs and possibly the consequences of rapid weight loss and nutritional deficiencies. An increasing number of patients undergoing endoscopic procedures will be taking these agents, and a proactive approach is needed to ensure procedures can reliably and safely proceed. Endoscopy units should ensure there are local protocols in place or that they are following the latest international guidance.

X Lisa Sharkey @lisa_shark

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ORCID iD
Lisa Sharkey http://orcid.org/0000-0002-3106-538X

REFERENCES

1 GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2023;402:203–34.
2 Phelps NH, Singleton RK, Zhou B, *et al*. Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *The Lancet* 2024;403:1027–50.
3 Inzucchi SE, McGuire DK. New drugs for the treatment of diabetes: part II: Incretin-based therapy and beyond. *Circulation* 2008;117:574–84.
4 Ahmed AM. History of diabetes mellitus. *Saudi Med J* 2002;23:373–8.
5 Rehfeld JF. The Origin and Understanding of the Incretin Concept. *Front Endocrinol (Lausanne)* 2018;9:387.
6 Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: Similarities and differences. *J Diabetes Investig* 2010;1:8–23.
7 Müller TD, Finan B, Bloom SR, *et al*. Glucagon-like peptide 1 (GLP-1). *Mol Metab* 2019;30:72–130.
8 Nauck MA, Quast DR, Wefers J, *et al*. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. *Diabetes Obes Metab* 2021;23 Suppl 3:5–29.
9 Rodriguez PJ, Goodwin Cartwright BM, Gratzl S, *et al*. Semaglutide vs Tirzepatide for Weight Loss in Adults With Overweight or Obesity. *JAMA Intern Med* 2024;184:1056–64.
10 Aroda VR, Blonde L, Pratley RE. A new era for oral peptides: SNAC and the development of oral semaglutide for the treatment of type 2 diabetes. *Rev Endocr Metab Disord* 2022;23:979–94.
11 Qin J, Song L. Glucagon-like peptide-1 (GLP-1) receptor agonists and cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of double-blind, randomized, placebo-controlled clinical trials. *BMC Endocr Disord* 2022;22:125.
12 Wong SY, Lee ARYB, Sia AHJ, *et al*. Effects of Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA) on Cardiac Structure and Function: A Systematic Review and Meta-Analysis of Randomized-Controlled Trials. *Cardiovasc Drugs Ther* 2024;38:371–89.
13 Chuang MH, Chen JY, Wang HY, *et al*. Clinical Outcomes of Tirzepatide or GLP-1 Receptor Agonists in Individuals With Type 2 Diabetes. *JAMA Netw Open* 2024;7:e2427258.
14 Badve SV, Bilal A, Lee MMY, *et al*. Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol* 2025;13:15–28.
15 Hartman ML, Sanyal AJ, Loomba R, *et al*. Effects of Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide on Biomarkers of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes. *Diabetes Care* 2020;43:1352–5.
16 Kanwal F, Kramer JR, Li L, *et al*. GLP-1 Receptor Agonists and Risk for Cirrhosis and Related Complications in Patients With Metabolic Dysfunction-Associated Steatotic Liver Disease. *JAMA Intern Med* 2024;184:1314–23.
17 Newsome PN, Sanyal AJ, Engebretsen KA, *et al*. Semaglutide 2.4 mg in Participants With Metabolic Dysfunction-Associated Steatohepatitis: Baseline Characteristics and Design of the Phase 3 ESSENCE Trial. *Aliment Pharmacol Ther* 2024;60:1525–33.
18 Kårhus ML, Brønden A, Røder ME, *et al*. Remission of Bile Acid Malabsorption Symptoms Following Treatment With the Glucagon-Like Peptide 1 Receptor Agonist Liraglutide. *Gastroenterology* 2019;157:569–71.
19 Hvistendahl M, Brandt CF, Tribler S, *et al*. Effect of Liraglutide Treatment on Jejunostomy Output in Patients With Short Bowel Syndrome: An Open-Label Pilot Study. *JPEN J Parenter Enteral Nutr* 2018;42:112–21.
20 Bischoff SC, Barazzoni R, Busetto L, *et al*. European guideline on obesity care in patients with gastrointestinal and liver diseases - Joint European Society for Clinical Nutrition and Metabolism / United European Gastroenterology guideline. *United European Gastroenterol J* 2022;10:663–720.
21 Park S-K, Lee T, Yang H-J, *et al*. Weight loss and waist reduction is associated with improvement in gastroesophageal disease reflux symptoms: A longitudinal study of 15 295 subjects undergoing health checkups. *Neurogastroenterol Motil* 2017;29.
22 Liu BD, Udemba SC, Liang K, *et al*. Shorter-acting glucagon-like peptide-1 receptor agonists are associated with increased development of gastro-oesophageal reflux disease and its complications in patients with type 2 diabetes mellitus: a population-level retrospective matched cohort study. *Gut* 2024;73:246–54.
23 Liu L, Chen J, Wang L, *et al*. Association between different GLP-1 receptor agonists and gastrointestinal adverse reactions: A real-world disproportionality study based on FDA adverse event reporting system database. *Front Endocrinol* 2022;13:1043789.
24 Eseonu D, Su T, Lee K, *et al*. Dietary Interventions for Gastroparesis: A Systematic Review. *Adv Nutr* 2022;13:1715–24.
25 Cao C, Yang S, Zhou Z. GLP-1 receptor agonists and pancreatic safety concerns in type 2 diabetic patients: data from cardiovascular outcome trials. *Endocrine* 2020;68:518–25.
26 Lomeli LD, Kodali AM, Tsushima Y, *et al*. The incidence of acute pancreatitis with GLP-1 receptor agonist therapy in individuals with a known history of pancreatitis. *Diabetes Res Clin Pract* 2024;215:111806.
27 Carris NW, Wallace S, DuCoin CG, *et al*. Discontinuing semaglutide after weight loss: strategy for weight maintenance and a possible new side effect. *Can J Physiol Pharmacol* 2024;102:391–5.
28 Feng X, Li XQ. The prevalence of small intestinal bacterial overgrowth in diabetes mellitus: a systematic review and meta-analysis. *Aging (Albany NY)* 2022;14:975–88.
29 Wijarnpreecha K, Werlang ME, Watthanasuntorn K, *et al*. Obesity and Risk of Small Intestine Bacterial Overgrowth: A Systematic Review and Meta-Analysis. *Dig Dis Sci* 2020;65:1414–22.

30 Silveira SQ, da Silva LM, de Campos Vieira Abib A, *et al*. Relationship between perioperative semaglutide use and residual gastric content: A retrospective analysis of patients undergoing elective upper endoscopy. *J Clin Anesth* 2023;87:111091.
31 Alkabbani W, Suissa K, Gu KD, *et al*. Glucagon-like peptide-1 receptor agonists before upper gastrointestinal endoscopy and risk of pulmonary aspiration or discontinuation of procedure: cohort study. *BMJ* 2024;387:e080340.
32 Sherwin M, Hamburger J, Katz D, *et al*. Influence of semaglutide use on the presence of residual gastric solids on gastric ultrasound: a prospective observational study in volunteers without obesity recently started on semaglutide. *Can J Anaesth* 2023;70:1300–6.
33 Facciorusso A, Ramai D, Dhar J, *et al*. Effects of Glucagon-Like Peptide-1 Receptor Agonists on Upper Gastrointestinal Endoscopy: A Meta-Analysis. *Clin Gastroenterol Hepatol* 2024.
34 Kindel TL, Wang AY, Wadhwa A, *et al*. Multisociety clinical practice guidance for the safe use of glucagon-like peptide-1 receptor agonists in the perioperative period. *Surg Obes Relat Dis* 2024;20:1183–6.
35 Hashash JG, Thompson CC, Wang AY. AGA Rapid Clinical Practice Update on the Management of Patients Taking GLP-1 Receptor Agonists Prior to Endoscopy: Communication. *Clin Gastroenterol Hepatol* 2024;22:705–7.
36 Yao R, Gala KS, Ghusn W, *et al*. Effect of Glucagon-Like Peptide-1 Receptor Agonists on Bowel Preparation for Colonoscopy. *Am J Gastroenterol* 2024;119:1154–7.
37 Abu-Freha N, Yitzhak A, Shirin H, *et al*. Glucagon-like peptide-1 receptor agonists significantly affect the quality of bowel preparation for colonoscopy. *Endoscopy* 2025;57:126–33.
38 Nasser J, Hosseini A, Barlow G, *et al*. Food Retention at Endoscopy Among Adults Using Glucagon-Like Peptide-1 Receptor Agonists. *JAMA Netw Open* 2024;7:e2436783.
39 Singh S, Rahman SH, Khan N, *et al*. Effects of glucagon-like peptide-1 receptor agonists on endoscopy outcomes: systematic review and meta-analysis. *Gastrointest Endosc* 2025;101:343–9.
40 Gala K, Tome J, Krall M, *et al*. Quality of bowel preparation for colonoscopy in patients on glucagon-like peptide-1 receptor agonists. *Gastrointest Endosc* 2024.
41 Odah T, Vattikonda A, Stark M, *et al*. Glucagon-like peptide-1 receptor agonists and capsule endoscopy in patients with diabetes: a matched cohort study. *Gastrointest Endosc* 2025;101:393–401.
42 Jastreboff AM, Kaplan LM, Frías JP, *et al*. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial. *N Engl J Med* 2023;389:514–26.