Clinical Medicine

Perspective

Clinical Recommendations to Manage Gastrointestinal Adverse Events in Patients Treated with Glp-1 Receptor Agonists: A Multidisciplinary Expert Consensus

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Abstract: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are indicated in type 2 diabetes and obesity for their high efficacy in controlling glycaemia and inducing body weight loss, respectively. Patients may develop gastrointestinal adverse events (GI AEs), namely nausea, vomiting, diarrhoea and/or constipation. To minimize their severity and duration, healthcare providers (HCPs) and patients must be aware of appropriate measures to follow while undergoing treatment. An expert panel comprising endocrinologists, nephrologists, primary care physicians, cardiologists, internists and diabetes nurse educators convened across virtual meetings to reach a consensus regarding these compelling recommendations. Firstly, specific guidelines are provided about how to reach the maintenance dose and how to proceed if GI AEs develop during dose-escalation. Secondly, specific directions are set about how to avoid/minimize nausea, vomiting, diarrhoea and constipation symptoms. Clinical scenarios representing common situations in daily practice, and infographics useful to guide both HCPs and patients, are included. These recommendations may prevent people with T2D and/or obesity from withdrawing from GLP-1 RAs treatment, thus benefitting from their superior effect on glycaemic control and weight loss.

Keywords: type 2 diabetes; obesity; glucagon-like peptide-1 receptor agonists; gastrointestinal adverse events; guidelines

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1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have represented a paradigm shift in the treatment of type 2 diabetes (T2D) and obesity. The incretin effect induced

by GLP-1 RAs allows for glycaemic control in a glucose-dependent manner more efficiently than other therapeutic classes without increasing the risk of hypoglycaemia [1]. Interestingly, some of them are able to cross the blood–brain barrier and act on the brain to stimulate satiety [2], which leads to food intake reduction and, consequently, body weight loss, which occurs at the expense of fat mass. As a result, the risk of progression to T2D decreases, and improvements in lipid profile, blood pressure or sleep apnoea have been observed [3]. GLP-1 RAs also exert pleiotropic actions with metabolic, hepatic, renal and cardiovascular beneficial effects [4–7]. Of note, a recent meta-analysis encompassing those clinical trials focused on the cardiovascular safety of GLP-1 RAs found significant reductions in MACE3 (a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke), hospitalization for heart failure and progression of chronic kidney disease [8]. The currently commercialized GLP-1 RAs with indications for T2D or obesity are summarized in Supplementary Table S1.

Ample clinical evidence arising from trials and real-world scenarios highlights that the most frequent adverse events (AEs) associated with GLP-1 RA are those of a gastrointestinal (GI) nature, namely nausea, vomiting, diarrhoea and constipation. According to the literature addressing clinical trials, GI AEs usually develop in 40–70% of treated patients, although they have sometimes been reported in up to 85% [9–17].

GI AEs arise irrespective of the half-life (long/short action) or route of administration (subcutaneous/oral) of the chosen GLP-1 RA. They are usually transient, typically starting during the dose-escalation period and generally resolving shortly after the maintenance dose is reached, and, in most cases, they are mild to moderate in severity. A recent report summarizing the results of several trials reported that the majority (99.5%) of documented GI AEs in people with obesity on GLP-1 RA treatment were non-serious [18]. A meaningful body of evidence in real-world settings roughly replicates these observations [19–22]. Nevertheless, it is essential that patients and healthcare professionals (HCPs) are aware of the right procedures to follow to prevent GI AEs from arising or, if they occur, to mitigate their effects and improve adherence and persistence to the treatment.

GI AEs may lead to the temporary or permanent discontinuation of GLP-1 RA treatment. Although interruption has been reported to occur in up to 12% of GLP-1 RA-treated patients (vs. ~2% in those treated with placebo) [9–18], permanent discontinuations range between 1.6–6% of treated patients (vs. <1% with placebo), according to clinical trial programs [9,15,18]. In the real-world setting, persistence with GLP-1 RA therapy has been found to range between 40% and 60% and between 34% and 67% at 180 and 360 days, respectively [23–25]. The results seem to be better with once-weekly administered GLP-1 RAs compared to those requiring once-daily injections [26–28]. The adequate management of GI AEs would potentially improve a patient's experience while undergoing treatment with GLP-1 RA, preventing discontinuations secondary to GI AEs.

The literature addressing the management of GI AEs in clinical practice associated with the use of GLP-1 RA from a multidisciplinary perspective is scarce [29]. For this reason, we formed a multidisciplinary team consisting of HCPs of several specialties and a diabetes nurse educator (DNE) with experience in the management of patients treated with GLP-1 RA in their daily practice. The main goal of this document is to reach a consensus regarding patient education and procedures to minimize the frequency and intensity of GLP-1 RA-associated GI AEs. Hopefully, this multidisciplinary consensus may contribute to expanding our knowledge of the practical use of GLP1-RAs, providing useful tools for physicians to use when managing people with T2D or overweight/obesity with this therapeutic class. More importantly, the better management of GI AEs could potentially have a positive impact on the adherence/persistence, effectiveness of treatment and quality of life (QoL) among GLP-1 RA-treated patients.

2. Methods

A multidisciplinary expert panel comprising three endocrinologists, two nephrologists, two primary care physicians (PCPs), two cardiologists, two internists and one DNE, all of them

with clinical expertise in the management of people with T2D or obesity with GLP-1 RA-based therapies, convened across virtual meetings to reach a consensus. The participants performed a comprehensive literature search using prespecified keys (Supplementary Table S2). The experts agreed that GI AEs should be the main topic to focus on when addressing the optimal medical care of patients treated with GLP-1 RA. The proper management of such occurrences is of paramount importance since it contributes significantly to treatment adherence and persistence and may improve QoL. Hepatobiliopancreatic AEs are also discussed in brief because, although they are extremely infrequent, it is important to exercise caution with those patients with a history of pancreatic and gallbladder disorders. Finally, widely accepted myths and erroneous considerations concerning other AEs and profiles of subjects wrongly considered unfit to receive this medication are also reviewed to ensure that as many patients as possible can benefit from treatment with GLP-1 RA.

3. AEs Most Frequently Associated with GLP-1 RAs

As anticipated, the AEs that were most frequently associated with GLP-1 RAs are those of a GI nature. Table 1 shows a summary of their frequency of occurrence in phase III clinical trials. Among the most common GI side effects, namely nausea, vomiting, diarrhoea and constipation, nausea appears systematically as the most frequent event in all clinical trials. The prevalence of the other GI AEs is lower. Overall, the onset of GI AEs is slightly higher in those trials designed to assess the efficacy and safety of GLP-1 RAs in people with obesity, which may be ascribed to the fact that doses are higher than those used in clinical trials in people with T2D. It is worth mentioning that long-acting agents have been associated with less nausea and vomiting but with more diarrhoea [30], which might be explained by a more sustained effect of these compounds on GLP-1 intestinal receptors [31]. Finally, it is worth mentioning that flatulence may occasionally appear, although studies reporting its frequency are lacking.

Table 1. Frequency of GI AEs in clinical trials with GLP-1 RA in people with obesity or T2D.

GLP-1 RA	Program	Refs	Patient Profile	Dose	Method of Administration	Nausea	Vomiting	Diarrhoea	Constipation
Semaglutide	SUSTAIN	9	T2D	1 mg	s.c. once weekly	15–24	7–15	7–19	4–7
Semaglutide	STEP	10	Obesity *	2.4 mg	s.c. once weekly	14–58	22–27	10–36	12–37
Semaglutide	PIONEER	11	T2D	14 mg	p.o. SID	8–23	6–12	5–15	7–12
Liraglutide	LEAD	12	T2D	1.8 mg	s.c. SID	10–40	4–17	8–19	11
Liraglutide	SCALE	13	Obesity *	3 mg	s.c. SID	27–48	7–23	16–26	12–30
Dulaglutide	AWARD	14	T2D	1.5 mg	s.c. once weekly	15–29	7–17	11–17	n.r.
Exenatide	DURATION	15	T2D	2 mg	s.c. once weekly	5–14	<1–6	5–11	1–8
Exenatide	—	16	T2D	10 µg	s.c. BID	35–59	9–14	4–9	5
Lixisenatide	GETGOAL	17	T2D	20 µg	s.c. SID	16–40	7–18	4–12	5†

Results are expressed as percentages of patients from the treatment cohort who experienced the AE at least once during the period of the study. Values correspond to the minimum and maximum values reported when considering all the studies of the program. * One out of 6 studies recruited people with obesity and T2D as well. † Data reported in one study only. BID, twice a day; GI AEs, gastrointestinal adverse events; GLP-1 RA, GLP-1 receptor agonist; n.r., not reported; p.o., oral; Refs, references; s.c., subcutaneous; SID, once a day; T2D, diabetes mellitus type 2.

4. Practical Guide to Follow When Initiating Treatment with GLP-1 RAs

4.1. Patient Education Prior to GLP-1 RA Start

Patient education in terms of how to take and deal with satiety once GLP-1 RAs are started is crucial for ensuring treatment compliance. It is accepted that persistence improves when weight is adequately managed and safe, straightforward treatments are used [32–34]. GLP-1 RA-based treatments comply with these characteristics. The proper education of patients by HCPs on their expectations when initiating treatment, how to prevent AEs, and how to treat them if they appear is particularly important. Patients have to learn that, although GI AEs may occur, these will be transient and of mild/moderate

severity in the majority of cases and that following specific dietary recommendations will relieve symptoms (Table 2, Figures 1–3).

Table 2. Guidelines for patients.

Recommendations to Minimize Occurrence/Severity of GI AEs when Starting GLP-1 RA Therapy
General recommendations
Observe the guidelines of the data sheet regarding posology and method of administration
Improve eating habits Eat slowly Eat only if you are really hungry Eat smaller portions Avoid lying down after having a meal Stop eating in case of feeling of fullness Increase meal frequency Avoid drinking using a straw Eat without distractions and enjoy savouring the food Try not to be too active after eating Avoid eating too close to bedtime
Adapt food composition to your requirements Choose easy-to-digest food, low fat diets (focus on bland foods) Use oven, cooking griddle or boiling Increase fluid intake, especially clear, fresh drinks (in small sips), but no so much as to make you feel too full Healthy food that contain water (soups, liquid yogurt, gelatin, and others) Avoid sweet meals Avoid dressings, spicy foods, canned food, sauces that are not home-cooked
Get some fresh air and do some light exercise
Keep a food diary, as it may be useful to identify foods or meal timings that make it worse
Additional recommendations for patients with nausea
Provided that 30 min have passed since the last GLP-1 RA dose, eat foods able to ease the symptoms of nausea, such as crackers, apples, mint, ginger root or ginger-based drinks
Avoid strong smells
Additional recommendations for patients with vomiting
Be particularly careful with hydration
Eat smaller amounts of food in more frequent meals
Additional recommendations for patients with diarrhoea
Generous hydration, for example with water, lemon and a teaspoon of bicarbonate
Avoid isotonic drinks intended to be used in the context of sport activities
Avoid dairy products, laxative juices or meals, coffee, alcoholic drinks, soft drinks, very cold or very hot foods, products with sweeteners ending in "ol" (sorbitol, mannitol, xylitol, maltitol), including candy and gum
Avoid (or temporarily reduce your intake of) foods with high fibre content * such as grain and seed products, such as grain cereals, nuts, seeds, rice, barley, whole grain bread or baked goods vegetables such as artichokes, asparagus, beans, cabbage, cauliflower, garlic and garlic salts, lentils, mushrooms, onions, sugar snap, snow peas skinned fruits, apples, apricots, blackberries, cherries, mango, nectarines, pears, plums
Eat chicken broth, rice, carrots, very ripe fruit without skin
Additional recommendations for patients with constipation
Ensure the amount of fibre in your diet is adequate
Increase physical activity
Ensure your diet is healthy and balanced
Drink generous amounts of water (or other sugar-free liquids)
Additional recommendations when GLP-1 RA are unusually severe or/and persistent
In case of persistence of nausea and/or vomiting, avoid drinks during meals, rather have them between 30 and 60 min before and/or after meals
If nausea, vomiting, diarrhoea and/or constipation persist in spite of following all the guidelines depicted above, inform HCP as soon as possible

* Gradually increase the amount of fibre intake once the symptoms improve. HCP, healthcare provider.

Figure 1. Minimizing occurrence/severity of GI AEs: patients general guidelines.

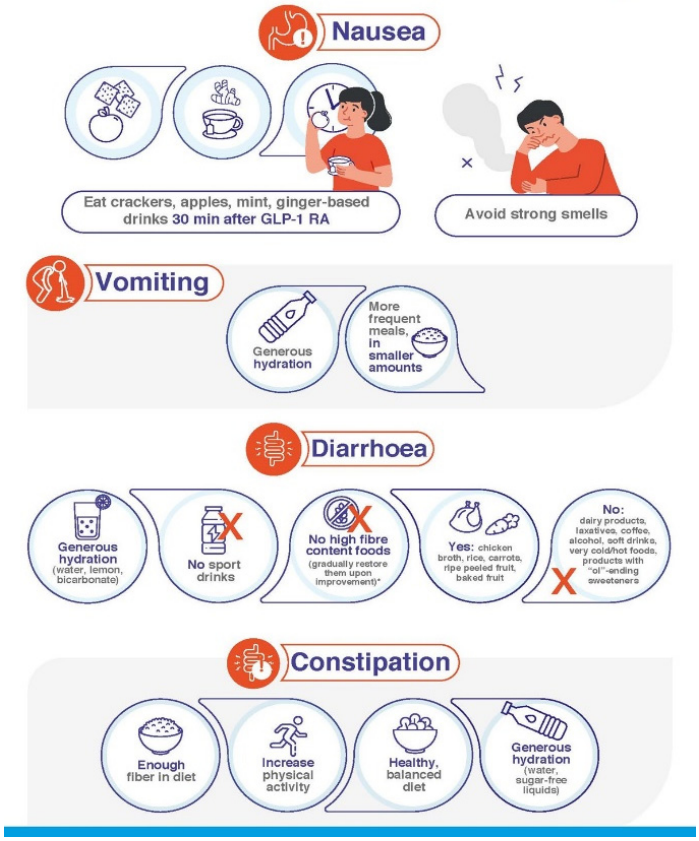

Figure 2. Additional specific guidelines for each separate GI AE.

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