



Switching Between Glucagon-Like Peptide-1 Receptor Agonists: Rationale and Practical Guidance

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Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of incretin-based therapies for the management of hyperglycemia and, in some cases, cardiovascular risk in people with type 2 diabetes. These agents act on multiple physiological pathways involved in type 2 diabetes with the effect of increasing insulin secretion and decreasing glucagon to control glucose levels (1,2). They also transiently slow gastric emptying, reduce appetite, and facilitate weight loss and other metabolic improvements (3).

Consensus recommendations from the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) and American Association of Clinical Endocrinologists/American College of Endocrinology advocate that GLP-1 receptor agonists, among other therapies, should be considered as a second-line treatment option in people with type 2 diabetes when glucose levels are not well controlled on metformin (4–6). Additionally, in patients with type 2 diabetes and atherosclerotic cardiovascular disease or chronic kidney disease, a GLP-1 receptor agonist or sodium–glucose cotransporter 2 (SGLT2) inhibitor with proven cardiovascular benefit is recommended as a first-line therapy for the reduction of cardiovascular risk (4–6). GLP-1 receptor agonists may also be used as a first-line treatment in those who cannot use metformin or when reduced renal function precludes metformin use (human-based GLP-1 receptor agonists only) (4–6). In particular, the recommendations favor

GLP-1 receptor agonists and SGLT2 inhibitors because they have a low risk of hypoglycemia and promote weight loss (5).

Several GLP-1 receptor agonists are available in the United States and worldwide, some of which are analogs of human GLP-1 (dulaglutide, liraglutide, and semaglutide), whereas others are exendin-based (exenatide and lixisenatide) (7–13). The GLP-1 receptor agonist albiglutide was also approved, but has been withdrawn for commercial reasons. Until recently, all GLP-1 receptor agonists were administered by subcutaneous injection, although a once-daily oral formulation of semaglutide has now been approved for use in the United States (7). Among the subcutaneous GLP-1 receptor agonists, some are dosed once daily (liraglutide and lixisenatide) or twice daily (exenatide), whereas others are given once weekly (dulaglutide, semaglutide, and exenatide extended release) (8–13).

Several studies and reviews have explored the comparative efficacy and safety profiles of the different GLP-1 receptor agonists (14–19). Pharmacy data suggest that up to one-fourth of patients switch from their initial GLP-1 receptor agonist to another glucose-lowering agent after the first year of treatment (20,21). Some of these patients may be switching to a different GLP-1 receptor agonist, which may occur for several reasons, but practical guidance on how to safely and effectively manage such a transition is scarce. This article summarizes reasons why health care providers (HCPs) may consider switching their patients between different GLP-1 receptor agonists and provides real-world guidance on achieving a smooth transition. We supplement the available data with our clinical experience to provide practical suggestions for switching.

Literature Search Methods

The PubMed database was searched using the terms: 1) GLP-1 AND (switch OR switching OR switched); and 2) GLP-1 AND (once-daily OR “once daily”) AND (once-weekly OR “once weekly”). These searches yielded 161 and 97 results, respectively. Abstracts of the retrieved publications were manually reviewed to identify relevant

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TABLE 1 Key Features of Currently Available GLP-1 Receptor Agonists (7–13)

Generic Name	Derivation	Molecular Weight, kDa	Half-Life	Route of Administration	Dose	Frequency	Dosing Conditions
Lixisenatide	Animal	4.86	~3 hours	Subcutaneous	Adults: 10 µg for 14 days, then 20 µg from day 15	Once daily	At the same time each day, ≤1 hour before the first meal of the day
Exenatide	Animal	4.19	2.4 hours	Subcutaneous	Adults: 5 µg per dose; increase to 10 µg after 1 month based on clinical response	Twice daily	≤1 hour before morning and evening meals (or the two main meals of the day, ≥6 hours apart)
Exenatide extended release	Animal	4.19	7–14 days	Subcutaneous	Adults: 2 mg	Once weekly	Can be taken at any time of day with or without food
Liraglutide	Human	3.75	~13 hours	Subcutaneous	Adults: 0.6 mg for 1 week, then 1.2 mg; if required, increase dose to 1.8 mg after a further week Children ≥10 years: 0.6 mg for ≥1 week; only increase the dose to 1.2 mg or 1.8 mg if required	Once daily	Can be taken at any time of day
Dulaglutide	Human	~63	~5 days	Subcutaneous	Adults: 0.75 mg, increased to 1.5 mg, if needed	Once weekly	Can be taken at any time of day with or without food
Semaglutide	Human	4.11	~7 days	Subcutaneous	Adults: 0.25 mg, increasing to 0.5 mg after 4 weeks. If required, increase to 1 mg after a further 4 weeks	Once weekly	Can be taken at any time of day with or without food
Oral semaglutide	Human	4.11	~7 days*	Oral	Adults: 3 mg for 30 days, then 7 mg, escalated to 14 mg after a further 30 days, if required	Once daily	Must be taken on an empty stomach with no more than 4 fl oz (120 mL) of plain water and at least 30 minutes before the first food, beverage, or other oral medication of the day

*After subcutaneous administration.

articles that included any information related to switching between different GLP-1 receptor agonists.

Characteristics of Available Injectable GLP-1 Receptor Agonists

Although they belong to a single medication class, the approved GLP-1 receptor agonists differ in many ways, including in structure, molecular size, pharmacology, efficacy, and safety (Table 1) (7–13). Native GLP-1 remains in the bloodstream for only a few minutes, so alterations to the molecule (amino acid changes or side chain additions) are required to make it resistant to the effect of dipeptidyl peptidase-4 (1,2). Even then, most of the older GLP-1 receptor agonists require frequent administration (Table 1) (8–10). Newer GLP-1 receptor

agonists that permit once-weekly dosing have been achieved either by attaching heavy chain fragments that slow their degradation (dulaglutide and subcutaneous semaglutide) (11,12) or formulating an extended-release preparation in the case of exenatide (Table 1) (13).

There are other differences among the various injectable GLP-1 receptor agonists that may influence treatment choice (Table 1) (7–13). Once-daily liraglutide and the once-weekly agents can be taken at any time of day, whereas twice-daily exenatide and once-daily lixisenatide must be taken within 1 hour before eating (7–13). Liraglutide is the only GLP-1 receptor agonist indicated for use in children (≥10 years of age) with type 2 diabetes (10). Lixisenatide is available as a fixed-ratio combination with insulin glargine 100 units/mL (22); liraglutide 3.6

PRACTICAL POINTERS

TABLE 2 Summary of Safety and Efficacy Results From Global Phase 3 Head-to-Head Studies of GLP-1 Receptor Agonists Approved for Use in the United States*

Trial Name	Active Comparators	Background Regimen	Time Point for Primary Efficacy Analysis, weeks	Relative A1C Reduction, % (ETD [95% CI], P)	Relative Weight Loss, kg (ETD [95% CI], P)	Safety and Tolerability Observations†
Once daily vs. once/twice daily						
PIONEER 4 (64)	Oral semaglutide 14 mg once daily vs. liraglutide 1.8 mg once daily	Metformin ± SGLT2 inhibitor	26	Similar (-0.1 [-0.3 to 0.0], <0.0001 for noninferiority‡)	Significantly greater with oral semaglutide than liraglutide (-1.2 [-1.9 to -0.6], 0.0003‡)	Nausea: 20 vs. 18% Diarrhea: 15 vs. 11% Vomiting: 9 vs. 5%
LIRA-LIXI (65)	Liraglutide 1.8 mg once daily vs. lixisenatide 20 µg once daily	Metformin	26	Significantly greater with liraglutide than lixisenatide (-0.6 [-0.8 to -0.4], <0.0001)	Similar (-0.6 kg [-1.6 to 0.4], 0.23)	Nausea: 22 vs. 22% Diarrhea: 12 vs. 10% Vomiting: 7 vs. 9%
LEAD-6 (66)	Liraglutide 1.8 mg once daily vs. exenatide 10 µg twice daily	Metformin, SU, or both	26	Significantly greater with liraglutide than exenatide (-0.33 [-0.47 to -0.18], <0.0001)	Similar (-0.38 [-0.99 to 0.23], 0.2235)	Nausea: 26 vs. 28% Diarrhea: 12 vs. 12% Vomiting: 6 vs. 10%
GetGoal-X (67)	Lixisenatide 20 µg once daily vs. exenatide 10 µg twice daily	Metformin	24	Similar based on noninferiority margin of 0.4% for upper CI (0.17 [0.03-0.30], N/R)	Significantly less with lixisenatide than exenatide (1.02 [0.46-1.58], N/R)	Nausea: 25 vs. 35% Diarrhea: 10 vs. 13% Vomiting: 10 vs. 13%
Once weekly vs. once/twice daily						
SUSTAIN-10 (34)	Subcutaneous semaglutide 1.0 mg once weekly vs. liraglutide 1.2 mg once daily	Metformin, SU, or SGLT2 inhibitor, or any combination thereof	30	Significantly greater with semaglutide than liraglutide (-0.69 [-0.82 to -0.56], <0.0001)	Significantly greater with semaglutide than liraglutide (-3.83 [-4.57 to -3.09], <0.0001)	Nausea: 22 vs. 16% Diarrhea: 16 vs. 12% Vomiting: 10 vs. 8%
AWARD-6 (37)	Dulaglutide 1.5 mg once weekly vs. liraglutide 1.8 mg once daily	Metformin	26	Similar (-0.06 [-0.19 to 0.07], <0.0001 for noninferiority)	Significantly less with dulaglutide than liraglutide (0.71 [0.17-1.26], 0.011)	Nausea: 20 vs. 18% Diarrhea: 12 vs. 12% Vomiting: 7 vs. 8%
AWARD-1 (68)	Dulaglutide 0.75/1.5 mg once weekly vs. exenatide 10 µg twice daily	Metformin + pioglitazone	26	Significantly greater with dulaglutide than exenatide (1.5 mg: -0.52 [-0.66 to -0.39], <0.001; 0.75 mg: -0.31 [-0.44 to -0.18], <0.001)	Similar for dulaglutide 1.5 mg and exenatide (-0.24 [N/R], 0.474) Significantly less with dulaglutide 0.75 mg than exenatide (1.27 [N/R], <0.001)	Nausea: 29/17% (1.5 mg/0.75 mg) vs. 28% Diarrhea: 13/9% vs. 8% Vomiting: 17/6% vs. 12%
DURATION-6 (38)	Exenatide 2 mg once weekly vs. liraglutide 1.8 mg once daily	Metformin and/or SU, or metformin ± pioglitazone	26	Significantly less with exenatide than liraglutide (0.21 [0.08-0.33], 0.0018)	Significantly less with exenatide than liraglutide (0.90 [0.39-1.40], 0.0005)	Nausea: 9 vs. 21% Diarrhea: 6 vs. 13% Vomiting: 4 vs. 11%

Continued on p. 393 »

« Continued from p. 392

TABLE 2 Summary of Safety and Efficacy Results From Global Phase 3 Head-to-Head Studies of GLP-1 Receptor Agonists Approved for Use in the United States* (continued)

Trial Name	Active Comparators	Background Regimen	Time Point for Primary Efficacy Analysis, weeks	Relative A1C Reduction, % (ETD [95% CI], P)	Relative Weight Loss, kg (ETD [95% CI], P)	Safety and Tolerability Observations†
DURATION-5 (69)	Exenatide 2 mg once weekly vs. exenatide 10 µg twice daily	Metformin, SU, and TZD, alone or in combination	24	Significantly greater with exenatide once weekly than exenatide twice daily (-0.7 [-0.9 to -0.4], <0.0001)	Similar (-0.95 [-1.9 to 0.01], <0.05)	Nausea: 14 vs. 35% Diarrhea: 9 vs. 4% Vomiting: 5 vs. 9%
DURATION-1 (70)	Exenatide 2 mg once weekly vs. exenatide 10 µg twice daily	Metformin, SU, TZD, or a combination of two	30	Significantly greater with exenatide once weekly than exenatide twice daily (-0.33 [-0.54 to -0.12], 0.0023)	Similar (N/R [-1.3 to 1.1], 0.89)	Nausea: 26 vs. 34% Diarrhea: 14 vs. 13% Vomiting: 11 vs. 19%
Once weekly vs. once weekly						
SUSTAIN-3 (35)	Subcutaneous semaglutide 1 mg once weekly vs. exenatide 2 mg once weekly	1-2 OADs (metformin, SU, TZD)	56	Significantly greater with semaglutide than exenatide (-0.62 [-0.80 to -0.44], <0.0001)	Significantly greater with semaglutide than exenatide (-3.78 [-4.58 to -2.98], <0.0001)	Nausea: 22 vs. 12% Diarrhea: 11 vs. 8% Vomiting: 7 vs. 6%
SUSTAIN-7 (36)	Subcutaneous semaglutide 0.5/1 mg once weekly vs. dulaglutide 0.75/1.5 mg once weekly	Metformin	40	Significantly greater with semaglutide than dulaglutide (0.5 vs. 0.75 mg: -0.40 [-0.55 to -0.25]; 1 vs. 1.5 mg: -0.41 [-0.57 to -0.25]; <0.0001 for both)	Significantly greater with semaglutide than dulaglutide (0.5 vs. 0.75 mg: -2.26 [-3.02 to -1.51]; 1 vs. 1.5 mg: -3.55 [-4.32 to -2.78], <0.0001 for both)	Nausea: 23/21 (0.5/1.0 mg) vs. 13/20% (0.75/1.5 mg) Diarrhea: 14/14 vs. 8/18% Vomiting: 10/10 vs. 4/10%

*The HARMONY 7 trial of albiglutide versus liraglutide (71) has been omitted because albiglutide is no longer available commercially in the United States. †Percentages are proportions of patients reporting the events described. ‡Treatment policy estimand (regardless of trial product discontinuation or rescue medication use in all randomized patients). AE, adverse event; ETD, estimated treatment difference; N/R, not reported; OAD, oral antidiabetic drug; SU, sulfonylurea; TZD, thiazolidinedione.

mg/mL plus insulin degludec 100 units/mL can also be given as a single injection (23). These combinations can be used in patients who need intensification of glucose-lowering therapies and are already on either a basal insulin or a GLP-1 receptor agonist alone (4–6).

In randomized phase 3 trials, GLP-1 receptor agonists have shown better or similar efficacy for glycemic control and weight loss in patients with type 2 diabetes when compared with placebo and other classes of antidiabetic medications (Table 2). Several GLP-1 receptor agonists have also demonstrated cardiovascular benefits in patients at high risk, although this is not a universal finding, as described later (24–30). The main adverse events associated with GLP-1 receptor agonists are gastrointestinal

(GI) in nature, primarily nausea, vomiting, and diarrhea (Table 2). GI side effects usually occur early in the course of treatment. In the clinical experience of the authors, such effects tend to be variable in terms of severity and usually resolve with continuous use. These observations are supported by trial data. Lowering the dose of GLP-1 receptor agonist or using a slower titration regimen may help to mitigate these effects.

Why Switch Between GLP-1 Receptor Agonists?

In clinical practice, unique factors often drive therapeutic decisions that are made by patients, HCPs, or both. The following are potential reasons for switching between GLP-1 receptor agonists.

Need for Improved Glycemic or Weight Control

Several head-to-head studies have compared the clinical efficacy of various GLP-1 receptor agonists and have identified differences in potency for glycemic control and weight loss between agents (Table 2). It should be noted that only liraglutide currently has an indication for weight loss (at a higher dose of 3 mg once daily) (31). These differences may be a factor in clinical decisions for both the initial selection of a GLP-1 receptor agonist and potential switching between GLP-1 receptor agonists.

In general, data suggest that long-acting GLP-1 receptor agonists have greater effects on A1C, fasting plasma glucose, and body weight than those that are short-acting (32,33). Although many analyses do not yet integrate data with semaglutide, several head-to-head clinical trials report that subcutaneous semaglutide 1.0 mg once weekly provided superior A1C and weight reductions compared with liraglutide 1.2 mg once daily (34), as well as both exenatide 2 mg once weekly (35) and dulaglutide 1.5 mg once weekly (Table 2) (36). On the other hand, liraglutide 1.8 mg once daily was similar to dulaglutide 1.5 mg once weekly (37) and better than exenatide 2 mg once weekly (38) in terms of A1C and weight reduction; this finding suggests that dosing frequency is not the only factor that determines glycemic efficacy (Table 2). It is important to note that these head-to-head studies varied in many ways, including in the dosages studied and in the prior and background therapies permitted.

Requirement for Cardioprotection

For patients with elevated cardiovascular risk, there is an evidence-based rationale for switching to a GLP-1 receptor agonist with proven cardiovascular benefit, regardless of the patient's A1C, and for continuing a GLP-1 receptor agonist in patients who are already receiving one but may require additional medications for glycemic control (5).

Liraglutide once daily, dulaglutide once weekly, and subcutaneous semaglutide once weekly have all demonstrated superior cardiovascular outcomes compared with placebo when added to standard-of-care treatment in patients with type 2 diabetes who had a history of cardiovascular disease or are at high cardiovascular risk (24–26). Albiglutide once weekly also showed a cardiovascular benefit but is no longer marketed, as mentioned previously (27). In contrast, no significant improvements in cardiovascular outcomes were observed with lixisenatide once daily in patients who had had a recent acute coronary event (28) or with exenatide once

weekly among patients with or without established cardiovascular disease (29). Oral semaglutide has proven to be noninferior to placebo in high-risk patients in a pre-approval study (30), and a larger trial to evaluate the long-term cardiovascular benefit of oral semaglutide is ongoing (NCT03914326). The differences in cardiovascular outcomes observed between trials of GLP-1 receptor agonists may relate to variations in the design and populations of the trials, but could also be the result of the different characteristics of the GLP-1 receptor agonists themselves (39,40).

Need for Improved Safety and Tolerability

All GLP-1 receptor agonists have the potential to cause GI adverse effects, but it has been suggested that nausea attenuates more rapidly with long-acting GLP-1 receptor agonists than short-acting agents because of their less pronounced effects on gastric emptying (16). There may be differences between GLP-1 receptor agonists in the nature, onset, and duration of GI adverse events (16), and it should also be noted that metformin can contribute to their occurrence (41). Trial data generally support a lower incidence of GI effects with the longer-acting agents (Table 2), and the authors' clinical experience suggests fewer such events when using lower doses.

Injection-site reactions may be a consideration for switching from one GLP-1 receptor agonist to another. Injection frequency appears to be a factor; for example, there were fewer injection-site reactions with once-weekly compared with twice-daily exenatide (42). However, formulation may also play a role; there were fewer injection-site reactions with dulaglutide and subcutaneous semaglutide once weekly (35,43), and also with liraglutide once daily (38), compared with exenatide once weekly.

Avoidance of hypoglycemia is also a potential consideration for switching treatments, but there are no head-to-head data indicating any advantage of one GLP-1 receptor agonist over any other in terms of the incidence of hypoglycemia. In general, the risk of hypoglycemia is low with all GLP-1 receptor agonists (17).

People with type 2 diabetes often have risk factors for acute pancreatitis (e.g., gallstones or hypertriglyceridemia) (44). Data from clinical trials indicate that GLP-1 receptor agonists do not increase the risk of developing pancreatitis (45). However, caution should be exercised in patients with a history of pancreatitis, and GLP-1 receptor agonist therapy should be discontinued if pancreatitis develops (6–13).

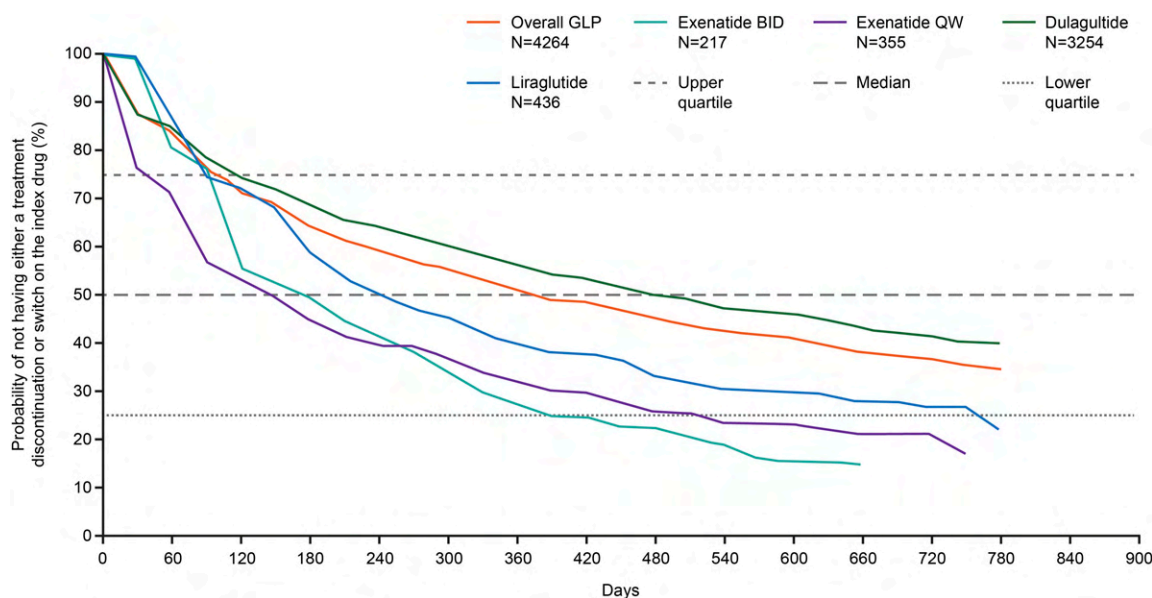


FIGURE 1 Kaplan-Meier analysis of persistence among patients switching from a previous GLP-1 receptor agonist to dulaglutide once weekly, exenatide twice daily or once weekly, or liraglutide once daily. Patients were switched from dulaglutide (5.0%), exenatide twice daily (28.1%), exenatide once weekly (17.4%), or liraglutide (49.5%). Data are from a retrospective analysis of a German prescription database using data from 1 February 2014 to 31 March 2017. Reprinted with permission from Otto et al. (57). BID, twice daily; QW, once weekly.

Patient Preference and Adherence Concerns

Patients' perceptions of their current treatment may drive them to request a change. For example, they may have read or heard about a newer treatment or may have a preference for one delivery device or route over another. It is important to emphasize to patients that glycemic efficacy and weight loss are not necessarily mutually exclusive. Although they may not be losing weight, their treatment may be controlling their blood glucose levels. However, treatment choice should be aligned with the goals of both the HCP and patient.

Across published trials, better adherence to injectable medications was generally found to be associated with improved glycemic control (46). However, in a contemporary, large, real-world study, 39% of patients receiving GLP-1 receptor agonists did not meet efficacy goals; it was suggested that lack of adherence (as well as a greater number of comorbidities) compared with trial populations may have contributed (47). Indeed, U.S. claims data indicate that poor adherence accounts for approximately 75% of the difference in A1C reduction observed with GLP-1 receptor agonists in clinical practice versus in randomized controlled trials (48). ADA/EASD guidelines recommend that a lack of notable response to any noninsulin therapies should be a trigger to review adherence (4).

Dissatisfaction with treatment frequency may be a reason for patients not to adhere fully to their prescribed regimen

and may be ameliorated by a switch from a once- or twice-daily to a once-weekly GLP-1 receptor agonist. Several patient surveys indicate a preference for less frequent dosing with GLP-1 receptor agonists, specifically for once-weekly over once-daily dosing, in both injection-naïve and injection-experienced patients (49,50). Patient-reported outcomes data from clinical trials in Japanese patients indicated that patients considered less frequent injections more convenient and flexible (51) and that their use led to an improvement in quality of life, without compromising glycemic control (52).

Retrospective database studies suggest that adherence and persistence rates with once-weekly injectable GLP-1 receptor agonists are better than those achieved with more frequently dosed treatments (53–56). Real-world prescription data from Germany indicated that, among those switching between GLP-1 receptor agonists (exenatide twice daily, exenatide once weekly, dulaglutide once weekly, or liraglutide once daily), post-switch persistence rates were greater among those receiving dulaglutide once weekly compared with liraglutide once daily and exenatide twice daily (Figure 1) (57).

Dosing frequency is not the sole driver of adherence and persistence, supporting the need to consider the overall profile of each once-weekly GLP-1 receptor agonist when deliberating a switch. For example, in the above studies, persistence rates were greater with dulaglutide once weekly

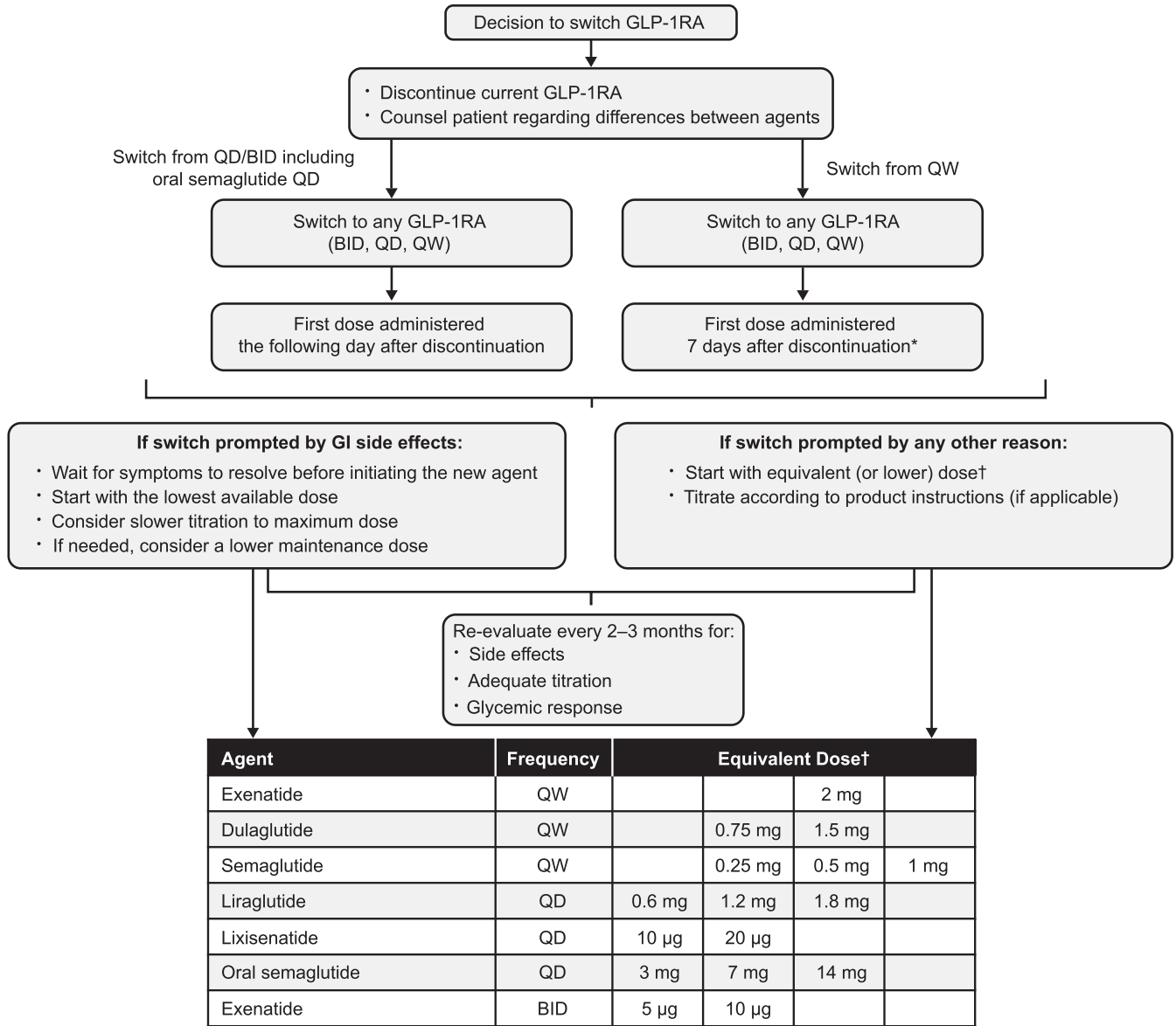


FIGURE 2 Practical algorithm for switching between once-daily and once-weekly GLP-1 receptor agonist therapies. *First dose of 7 or 14 mg to be administered 1–7 days after last injection (based on limited advice in the prescribing information, which specifies only when switching from semaglutide 0.5 mg subcutaneous). †Assessment of equivalent dose is entirely based on authors’ opinion, which in turn is based on head-to-head clinical trials when available and/or clinical experience. Other reasons for switching could include patient preference, concern about drug interactions, and cost/insurance issues. Exenatide once weekly is not available at a lower dose but could be tried if this is an insurance-preferred GLP-1 receptor agonist. BID, twice daily; GLP-1RA, GLP-1 receptor agonist; QD, once daily; QW, once weekly.

compared with exenatide once weekly and liraglutide once daily (53–57). When determining an appropriate strategy to increase adherence with injectable therapies, it is also important to consider the convenience of the dosing device. Ready-to-use formulations and easy-to-use delivery systems such as single-dose prefilled pens and hidden, pre-attached needles may encourage patient acceptance (58).

Other Considerations

Generally, interactions with other medications are not a major concern when switching between GLP-1 receptor

agonists. However, increased bleeding risk has been noted when exenatide was co-administered with warfarin (8,13). All GLP-1 receptor agonists delay gastric emptying, which may affect the absorption of other oral medications (7–13). Although this is not considered clinically relevant in most cases, caution should be exercised when co-administering medications with narrow therapeutic windows (such as levothyroxine and warfarin) (7–13).

Cost is also a potential consideration for HCPs and patients. In situations in which patients cover the cost of

treatment, or when insurance coverage is available only for select therapies, financial considerations may influence the selection of GLP-1 receptor agonist therapy or trigger the need for a switch. In a meta-analysis of 34 published trials, higher diabetes-related pharmacy and total health care costs for patients who were more adherent and persistent were offset by lower diabetes-related and all-cause medical costs (45). In a U.S. database study, diabetes-related total costs were not significantly different between dulaglutide once weekly and liraglutide once daily, but dulaglutide once weekly was associated with higher costs than exenatide once weekly (59).

Because cardiovascular events are a major driver of health care costs in patients with diabetes, previously mentioned reductions in the incidence of major cardiovascular events associated with several GLP-1 receptor agonists have the potential to translate into health economic benefits (39). However, the financial impact of the reported decrease in cardiovascular events has not yet been established (39).

All manufacturers of GLP-1 receptor agonists offer eligible patients copay cards and have patient assistance programs. The details of such incentives depend on the manufacturer, region, and other factors. Practitioners should try to become knowledgeable about formulary coverage and the relevant pre-authorization processes in their area to ensure that patients who need these medications can obtain them as part of their health insurance benefits.

Practical Advice on Switching Between GLP-1 Receptor Agonists

The recommendations discussed here are largely based on the clinical experience of the authors and are summarized in Figure 2.

Considerations for Switching Between Once-Daily and Once-Weekly GLP-1 Receptor Agonists

When switching a patient between two GLP-1 receptor agonists, it is important to ensure that the patient remains a suitable candidate for GLP-1 receptor agonist therapy, with no relevant comorbidities or contraindications either for the class as a whole or for the agent selected. This process includes checking for a personal or family history of multiple endocrine neoplasia syndrome type 2 or medullary thyroid carcinoma.

We recommend assessing patients for GI symptoms attributable to GLP-1 receptor agonists, such as nausea, vomiting, dyspepsia, or changes in bowel habit. Other medications used for diabetes management (e.g.,

metformin or acarbose) may exacerbate these symptoms and intolerance for GLP-1 receptor agonists (60). For patients who have experienced GI adverse events, consider withholding medications in a stepwise manner to determine the causative agent or facilitate tolerance of the GLP-1 receptor agonist. Before switching because of GI intolerance, we recommend ensuring that all reasonable mitigating actions have been implemented, including: 1) verifying that the patient is taking the prescribed dose of the current GLP-1 receptor agonist because dose reduction can often minimize or resolve GI symptoms; 2) ensuring adherence to the provided dietary recommendations (consuming smaller portions and avoiding high-fat foods can decrease symptoms); and 3) trying other mitigating measures without success (e.g., use of natural anti-nausea supplements such as ginger or peppermint, implementation of a short-course liquid diet, or temporarily holding metformin if appropriate). The authors do not recommend pharmacotherapy to alleviate nausea.

When switching from one GLP-1 receptor agonist to another, the authors would typically suggest adherence to the recommended posology described within the label for each agent, including the need for gradual dose titration, when applicable. For the once-weekly GLP-1 receptor agonists subcutaneous semaglutide and dulaglutide, gradual escalation to the recommended therapeutic dose is recommended (11,12). Patients changing from a once-daily GLP-1 receptor agonist because of GI adverse effects may be better suited to a once-weekly medication with adjustable doses so they can start at a lower dose increment, given that GI adverse effects are often dose-dependent. Whereas dulaglutide is initiated at 0.75 mg and increased to 1.5 mg if needed, subcutaneous semaglutide can be started at a “quarter dose” of 0.25 mg; this is increased to 0.5 mg once weekly after 4 weeks and, if needed, to 1 mg after a further 4 weeks (11,12). Slower up-titration might be helpful to further minimize the risk of GI symptoms.

For patients who are tolerating the maximal therapeutic dose of a once-daily or twice-daily GLP-1 receptor agonist (exenatide 10 µg twice daily, liraglutide 1.8 mg once daily, or lixisenatide 20 mg once daily) but who are changing to a once-weekly GLP-1 receptor agonist, we recommend starting dulaglutide once weekly or exenatide once weekly at the maximal therapeutic dose (dulaglutide 1.5 mg, exenatide 2 mg). For subcutaneous semaglutide, we suggest starting at the intermediary 0.5 mg once-weekly dose for 4 weeks before transitioning to the maximal therapeutic dose of 1 mg once weekly to help avoid adverse GI effects (Figure 2).

PRACTICAL POINTERS

Switching from a short-acting to a long-acting GLP-1 receptor agonist could lead to small transient increases in FPG, as shown in the DURATION-1 trial (61). Additional published clinical evidence for this is lacking. However, an exposure-response modeling analysis suggested that an initial deterioration in A1C may be seen when switching from dulaglutide 1.5 mg once weekly or liraglutide 1.2/1.8 mg once daily to the initial recommended 0.25 mg once-weekly dose of subcutaneous semaglutide (62). However, after this initial rebound, switching to subcutaneous semaglutide would be expected to result in additional reductions in A1C and weight compared with the other GLP-1 receptor agonists (60). In our experience, transient increases in glucose levels seen with changing from a once-daily to a once-weekly GLP-1 receptor agonist are not clinically significant. Nevertheless, the starting dose of the new GLP-1 receptor agonist can be adjusted to minimize the potential for such increases (Figure 2). Patients, particularly those who actively self-monitor their glucose levels, should be made aware of this possibility so they can inform their care team as necessary. If glucose levels rise above patient-specific goals, consideration can be given to temporarily adjusting existing diabetes medications or adding in other medications if needed. Explaining this to patients also serves as an educational opportunity to highlight the relationship between dietary patterns and blood glucose levels.

It is important to consider the timing of a switch between treatments. Patients tolerating once-daily GLP-1 receptor agonist therapy at the maximal therapeutic dose should start a once-weekly GLP-1 receptor agonist the day after their last dose of once-daily medication. Those who are not tolerating the maximal dose, or are switching to a once-weekly GLP-1 receptor agonist because of GI adverse effects, should stop the once-daily medication and wait until their symptoms have resolved before starting the lowest dose of the chosen weekly GLP-1 receptor agonist.

Before, during, and after switching treatments, patient communication and reinforcement of educational messages are vital to ensure a smooth transition. Given that different GLP-1 receptor agonists have different dosing recommendations (Table 1), it is important that patients switching between such agents are counseled on any applicable changes to their previous regimen. The usual recommendations and guidance that would be given for initiation of a once-weekly GLP-1 receptor agonist should be provided (e.g., direction to take the medication once weekly, information on how to manage missed doses, device-specific instructions, mealtime considerations, appropriate timing for oral medications, storage

instructions, and availability of programs supporting adherence) (63).

Patients should be advised of the potential for experiencing GI adverse effects after switching to a different GLP-1 receptor agonist and that (as with the initiation of the prior GLP-1 receptor agonist) they should expect these effects to improve over time. They should seek medical advice if such adverse effects are severe, or occur for an extended period, so that their provider may consider dose adjustment (when applicable), discontinuation, or alternative therapies (63).

More generally, patients should be reminded that it might take several weeks for the full efficacy of a GLP-1 receptor agonist to emerge. Providers should use the opportunity of GLP-1 receptor agonist switching to re-educate patients about the mechanisms of action and set patient expectations, especially with respect to the effects of delayed gastric emptying. This information may decrease the risk of discontinuation because of nausea and may help patients to use the medication as a tool for weight loss by eating less.

In keeping with current guidelines, it is recommended that patients are reassessed within 2–3 months of switching to assess the adequacy of dose titration, side effects, need for adjustment of other medications, and achievement of therapeutic goals (4). It should be noted that it may take 3 months to titrate subcutaneous semaglutide to a 1-mg dose, and therefore the maximum glycemic benefit of that agent may not be evident for up to 6 months after the switch. In our experience, weight loss usually continues for 9–12 months. Because of differences in medication adherence and persistence, patients may achieve significant improvements in blood glucose levels that require adjustment of other diabetes medications, such as insulin. Changes in body weight may also require adjustment of antihypertensive medications, thyroid hormone replacement, and other medications.

Additional Considerations When Switching Between Once-Weekly Treatments

In the case of switching between two once-weekly GLP-1 receptor agonists, a practical approach is to stop the current GLP-1 receptor agonist and then begin the new GLP-1 receptor agonist 1 week later, on the same day of the week. Patients tolerating a once-weekly GLP-1 receptor agonist at the maximal therapeutic dose should start the alternative once-weekly agent 1 week after the last dose of the current treatment. The maximal dose of exenatide 2 mg once weekly or dulaglutide 1.5 mg once weekly may be started if switching to one of these agents. For subcutaneous semaglutide, we recommend starting 0.5 mg

once weekly for 4 weeks before advancing to 1 mg once weekly, depending on tolerability and clinical necessity. In our experience, transitioning directly to subcutaneous semaglutide 1 mg once weekly from another GLP-1 receptor agonist can be associated with nausea or GI disturbance.

Patients who are not tolerating the maximal dose of a once-weekly GLP-1 receptor agonist, or those who are switching once-weekly GLP-1 receptor agonists due to GI adverse effects, should delay the initiation of the new GLP-1 receptor agonist therapy until symptoms have resolved. They should then start the lowest dose of the alternative once-weekly GLP-1 receptor agonist and consider a lower maintenance dose.

Once-daily GLP-1 receptor agonist therapies are also available in fixed-ratio combination formulations with long-acting insulins (insulin glargine with lixisenatide [22] and insulin degludec with liraglutide [23]). When switching patients from a once-daily fixed-ratio combination to a once-weekly GLP-1 receptor agonist and separate long-acting insulin, dose equivalency (Figure 2) and insulin dose adjustment must be considered.

Future Perspectives and Conclusion

Until recently, GLP-1 receptor agonists have only been available as subcutaneous injections. However, oral semaglutide once daily provided similar glycemic control, produced greater weight loss, and had similar tolerability to liraglutide once daily (64) (Table 2). Oral semaglutide has now been approved in the United States for use in patients with type 2 diabetes whose A1C is insufficiently controlled with diet, exercise, and metformin (7).

Switching from an injectable GLP-1 receptor agonist to an oral formulation is a distinctly different proposition from switching between injectable formulations, and additional practical guidance will be required on this topic once sufficient clinical experience has been gained. However, the product label contains some relevant information based on the protocols used in clinical trials. If a patient receiving subcutaneous semaglutide 0.5 mg once weekly is to be switched to once-daily oral semaglutide, they should initiate a 7-mg or 14-mg dose up to 1–7 days after their last injection (7). In reverse, patients receiving oral semaglutide 14 mg once daily can transition to subcutaneous semaglutide 0.5 mg once weekly the day after their last oral dose (7).

Switching between GLP-1 receptor agonists can be considered in many clinical scenarios, as explored above, and may be increasingly common given the availability of

newer agents in the class. Although numerous studies have compared the available GLP-1 receptor agonists, few have directly explored the effects of switching between these agents, highlighting a need for further research. Herein, we have aimed to provide practical advice for HCPs considering a switch between GLP-1 receptor agonists, based on our clinical experience. Overall, we favor the use of longer-acting over shorter-acting GLP-1 receptor agonists, but the choice should take into account individual clinical factors, patient preferences, risks, and benefits. The availability of an oral agent in this class provides further options.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to the development of this review article. Medical writing assistance, undertaken at the direction of the authors, comprised literature searches, drafting of the manuscript, editing of the manuscript, preparation of figures and tables, and contributions to the interpretation of the literature in the discussion. All authors are joint guarantors of this work and, as such, had full access to all of the literature search results and references cited and take responsibility for the integrity of the data cited and the accuracy of the analyses provided.

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