Glucagon-Like Peptide 1 Receptor Agonists Have the Potential to Revolutionize the Attainment of Target A1C Levels in Type 2 Diabetes—So Why Is Their Uptake So Low?

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A target A1C of <7% is the recommended goal for most people with type 2 diabetes. However, many are not achieving this target with their current treatment. Glucagon-like peptide 1 (GLP-1) receptor agonists are highly efficacious in achieving glycemic control and could aid primary care providers (PCPs) in getting patients to their A1C target. However, despite their potential, use of GLP-1 receptor agonists in the primary care setting is limited. This review provides guidance for PCPs on how to help patients achieve their glycemic target and overcome perceived barriers of GLP-1 receptor agonist use, with the overall goal of improving PCP confidence in prescribing these agents.

KEY POINTS

- The attainment of target A1C levels in people with type 2 diabetes appears to be declining.
- In primary care settings, the use of shared decision-making and motivational interviewing, consideration of cost-effective treatments, the introduction of diabetes-only appointments, and the prescription of therapies with low hypoglycemia risk could improve patients' attainment of glycemic targets.
- Glucagon-like peptide-1 receptor agonists offer highly efficacious A1C reduction, along with weight loss and reduced risk of cardiovascular or microvascular events; however, their use in primary care is low.
- To increase uptake, primary care providers and patients should understand that these agents have a low hypoglycemia risk and a simple titration process and that their side effects can be mitigated.

A strong association between A1C and the development of diabetes complications has been previously shown (1). Diagnosis cutoffs and treatment targets have been devised based on this association. A1C levels between 5.7 and 6.4% are used to diagnose prediabetes, and those >6.4% are used to diagnose diabetes (2). In addition, current treatment guidelines recommend an A1C target <7.0% (<53 mmol/mol) for most people with type 2 diabetes but also recommend that this target should be individualized based on patient requirements. Although this review focuses on A1C levels, it should be noted that the American Diabetes Association (ADA) also recommends other assessments such as the continuous glucose monitoring (CGM)-derived metrics of time in range and glucose management indicator to assess glycemic control (3–5).

Glucagon-like peptide-1 (GLP-1) receptor agonists have been proven an effective approach to managing glycemia in type 2 diabetes (6,7). The ADA's *Standards of Medical Care in Diabetes—2022* (8) recommend prescribing GLP-1 receptor agonists as one of two possible first-line therapies to reach appropriate glycemic targets in people with type 2 diabetes who have or are at high risk for atherosclerotic cardiovascular disease (ASCVD). Additionally, GLP-1 receptor agonists are recommended for patients with type 2 diabetes who do not have and are not at risk for ASCVD as agents of "higher glycemic

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https://doi.org/10.2337/cd22-0027

efficacy" that should be considered when assessing patients' preferences and needs. GLP-1 receptor agonists are also recommended for people with chronic kidney disease (CKD), especially if there is no albuminuria (Table 1) (8). The American Association of Clinical Endocrinologists and American College of Endocrinology have similar guidelines. They recommend the first-line use of long-acting GLP-1 receptor agonists when patients have certain comorbidities (i.e., established or high risk for ASCVD, stage 3 CKD, or heart failure with reduced ejection fraction) and an A1C <7.5%, or in patients with an A1C ≥7.5–9% as part of dual or triple therapy with metformin (5). Other American and European associations recommend the use of GLP-1 receptor agonists before insulin therapy, but only when first-line metformin fails to achieve glycemic targets (9,10). GLP-1 receptor agonists not only have been associated with lowering A1C levels early and keeping those levels low, but some are also associated with weight loss, reduction of major cardiovascular events, and renoprotective effects through their microvascular benefits (8). It is important for primary care providers (PCPs), and indeed all prescribers who treat patients with type 2 diabetes, to be aware of each of these aspects of GLP-1 receptor agonists when they discuss treatment options with their patients.

In this narrative review, we explain the risks associated with poor glycemic management in people with type 2 diabetes and the rationale for and benefits of achieving and maintaining good glycemic control (i.e., an A1C <7%). Guidance for PCPs is provided on how to overcome clinical barriers to help patients achieve their target A1C levels. We then focus on the role of GLP-1 receptor agonists in attaining glycemic control, detailing how perceived barriers to their use can be overcome in clinical practice. The overall goal is to provide practical information to improve PCP confidence in prescribing GLP-1 receptor agonists to achieve glycemic control in people with type 2 diabetes.

Importance of Achieving Target A1C

Hyperglycemia is associated with microvascular complications, including retinopathy, nephropathy, and neuropathy (1,11,12), and is a risk marker for ASCVD (13). Furthermore, data obtained from ACCORD (Action to Control Cardiovascular Risk in Diabetes) and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trials and an Italian multicenter study showed that long-term fluctuations in A1C predict such diabetes complications and increase mortality (14–16).

According to data from multiple randomized controlled trials, the risk of microvascular complications in people with type 2 diabetes can be reduced by intensive glycemic control (17–21). Results from one study provided evidence for A1C thresholds of 6.5% for reducing microvascular complications and 7.0% for macrovascular disease and death (22). Relatedly, increased A1C time in range has been shown to reduce mortality and

TABLE 1 ADA 2022 Guidelines for Prescribing GLP-1 Receptor Agonists (8)

In People With Type 2 Diabetes and . . .	Recommendation
ASCVD or high risk for developing ASCVD	GLP-1 receptor agonists with proven CVD benefit are one of two possible first-line therapies, along with SGLT2 inhibitors.
CKD with albuminuria (e.g., ≥200 mg/g creatinine)	GLP-1 receptor agonists with proven CVD benefit are recommended if first-line SGLT2 inhibitors are not tolerated or are contraindicated.
CKD without albuminuria (e.g., eGFR <60 mL/min/1.73 m^2)	GLP-1 receptor agonists with proven CVD benefit are recommended as one of two first-line therapies, along with SGLT2 inhibitors.
A1C above target	GLP-1 receptor agonists are recommended as agents of "higher glycemic efficacy" and should be considered when assessing patients' preferences and needs, as follows: • When there is a need to minimize hypoglycemia, GLP-1 receptor agonists are recommended because they have no or low inherent risk of hypoglycemia. • When there is a need to minimize weight gain or promote weight loss, GLP-1 receptor agonists with good efficacy for weight loss are recommended.

First-line therapy depends on the comorbidities and patient-centered considerations outlined in this table. Management generally also includes metformin and lifestyle modification. eGFR, estimated glomerular filtration rate.

cardiovascular disease (CVD) risk (23). In a post hoc analysis of people newly diagnosed with type 2 diabetes from the UKPDS (UK Prospective Diabetes Study), historic A1C values had a greater impact than recent A1C values on 10- to 15-year risk of all-cause mortality and myocardial infarction (24). A similar legacy effect of early glycemic control being associated with long-term CVD benefits was also found in two other trials (25,26). Thus, early detection of diabetes and intensive glycemic control from the time of diagnosis are essential to maximize reduction of long-term risks of diabetes-related complications. PCPs should, therefore, have confidence in intervening early and aiming for an A1C <7% as a glycemic target for most people with type 2 diabetes.

Despite these data, a recent analysis found that the rate of attainment of A1C <7% in adults with diabetes fell from 57.4% in 2007–2010 to 50.5% in 2015–2018 (27). Additionally, this attainment rate declined despite expansion in the diabetes therapeutic armamentarium and technology to aid in diabetes management. Barriers to achieving glycemic goals therefore must exist in everyday primary care practice.

Barriers to Achieving Target A1C

Based on our expertise and experience in primary care, we identify below some common barriers faced by PCPs as they work with people with type 2 diabetes to achieve their A1C targets, as well as suggested solutions to overcome these barriers.

Suboptimal Adherence

Recently proposed terminology defined adherence to medication as the process by which patients take their medications as prescribed and is further divided into three quantifiable stages: initiation, implementation, and discontinuation (28). It is well understood that good adherence to antihyperglycemic medication is required to achieve a target A1C of <7%. However, suboptimal adherence is common with type 2 diabetes treatments. For example, one systematic review found that the prevalence of adherence (the percentage of the study population that was classified as adherent) to type 2 diabetes medications ranged from 38.5 to 93.1%; this review concluded that nonadherence is an ongoing problem that urgently needs to be addressed (29).

Contributing factors to suboptimal adherence include diabetes fatigue, lack of motivation, and medication burden, each of which can be eased through PCP intervention. ADA guidelines promote the use of shared decision-making between physicians and patients (8); talking to and understanding patients' preferences can help to motivate them and ensure that they feel involved in the development of their own treatment plan. PCPs should also gain an understanding of the specific barriers their patients face attempting to adhere to their medications, including both real and perceived barriers. This understanding can be achieved through motivational interviewing. In addition, patients' adherence is likely to vary from one drug to another; therefore, PCPs should inquire about their patients' adherence to each of their medications and offer solutions to overcome their reported barriers and improve adherence.

Reducing medication burden can also improve adherence. To reduce medication burden, PCPs could consider the use of once-weekly (QW) subcutaneous (SC) injections, including dulaglutide (30), exenatide extended-release (ER) (31), and semaglutide (32), rather than once-daily (QD) or twice-daily (BID) SC injections. A meta-analysis of seven studies evaluating 75,159 people with type 2 diabetes with follow-up periods ranging from 6 to 12 months showed that patients have better adherence to QW SC GLP-1 receptor agonists than to QD SC agents in that drug class (33). Good adherence to a medication enables glycemic control and may delay the need for further treatment intensification to basal or frequent mealtime insulin injections.

Cost

The high cost of disease management contributes to suboptimal medication adherence in people with type 2 diabetes and is therefore a barrier to achieving glycemic targets (8). In 2017, people with diagnosed diabetes incurred estimated average medical expenditures of ~ $16,750 per year, which was ~2.3 times higher than such costs in people without diabetes (34). Consequently, it has been estimated that one in four of Americans with diabetes who take insulin reduce their dosage or stop taking their medication altogether because they cannot afford to continue it as prescribed (35).

PCPs are aware of cost as a barrier to achieving glycemic targets, but often view it as a barrier that they do not have the ability to overcome. However, we believe that PCPs have the capability to break down the barrier of cost by educating patients and directing them to multiple available cost-reduction options. PCPs can encourage the use of copay cards or manufacturer coupons when appropriate to reduce patients' total out-of-pocket costs. Alternatively, some pharmaceutical

companies sponsor patient assistance programs that give financial aid or free drug products to individuals in low-income groups (36). Other solutions, such as Medicaid, which offers health coverage for low-income patients, and Medicare, which supports individuals ≥65 years of age and younger people with disabilities, can also be mentioned (37). Furthermore, PCPs should discuss cost deductibles with patients before initiating therapy and encourage patients to communicate their cost barriers so providers can help with solutions or select less expensive therapeutic options.

Hypoglycemia Avoidance

Hypoglycemia symptoms can include confusion, shakiness, irritability, hunger, and tachycardia. Severe hypoglycemic episodes can progress to unconsciousness, seizure, coma, or death. Accordingly, hypoglycemia prevention is a crucial component of diabetes management (3).

Some PCPs may have an inaccurate perception that reducing A1C to <7% increases patients' risk of hypoglycemia and therefore may be reluctant to advise this A1C target. This belief is likely based on an interpretation of data from the ACCORD trial, in which A1C reduction was associated with an increased risk of severe hypoglycemia (38). However, recent post hoc analyses of ACCORD data have indicated that lower A1C was not, in fact, associated with an increased risk of hypoglycemia and that people with poor glycemic control had a greater risk of hypoglycemia, irrespective of their treatment group (39). A1C variability, as opposed to reduced A1C levels, appeared to be the driver of hypoglycemia.

Although we appreciate that all PCPs should strive to avoid severe hypoglycemia in patients with type 2 diabetes, and especially those who are older and have CKD or CVD, aiming for A1C <7% does not need to increase hypoglycemia risk. PCPs should consider treatments that have a low hypoglycemic risk to aid patients in reaching their target A1C safely (8).

Therapeutic Inertia

Therapeutic inertia occurs when physicians do not intensify (or de-intensify) patients' treatment when it is appropriate to do so. We focus here on the failure to intensify the treatment of patients with type 2 diabetes, as this lack of intensification can prevent patients from achieving their A1C target. Such therapeutic inertia is highly prevalent; real-world data show that therapeutic responses to poor glycemic control, even when A1C levels far exceed recommended targets, are exceptionally poor (40). Causes of therapeutic inertia are multifactorial and include provider-level factors such as time constraints and inexperience in treating diabetes, patient-level factors such as concerns over side effects or new treatment regimens, and system-level factors such as limited availability of medications or high drug costs (41).

The ADA's Overcoming Therapeutic Inertia (OTI) initiative aims to create fundamental change in the care of people with type 2 diabetes, by providing the latest thought leadership and practical tools for avoiding therapeutic inertia (42). The overall goal of the OTI initiative is to increase the proportion of people who achieve and maintain an A1C <7%. In the primary care setting, it is vital for providers to seek education about diabetes risks and management and stay up-to-date on treatment guidelines (41). Monitoring patients' A1C levels at regular intervals and assessing and modifying their treatment as needed are also crucial steps to avoid therapeutic inertia (8,41).

ADA guidelines suggest that A1C should be measured every 3–6 months: every 6 months when A1C levels are stable and at goal or every 3 months if the target A1C is not being met (3). However, it is our opinion that PCPs should increase the frequency of appointments and A1C testing to every 6–8 weeks for patients whose A1C is >9%. We also suggest the implementation of diabetes-only appointments, to ensure that patients receive focused, in-depth consultations about their diabetes. The ADA's OTI initiative also recommends diabetes-only visits for the opportunities they present to develop treatment plans, set shared treatment goals, and build trust between patients and providers (42). To address PCPs' time constraints or diabetes inexperience, we propose engaging with other members of an interdisciplinary care team to manage diabetes and reduce therapeutic inertia. This interaction could include, for example, making referrals to a certified diabetes care and education specialist and/or a registered dietitian with diabetes expertise.

Reluctance for Polypharmacy

Patients are reluctant to take, and PCPs are reluctant to prescribe, a high number of medications. To minimize polypharmacy, PCPs should consider the therapeutic efficacy of the different available medication classes for the management of type 2 diabetes, which can help to ensure that the target A1C is reached as quickly and with as few medications as possible; attaining the target A1C early should minimize the need for additional medications to maintain glycemic control later in life. In addition, PCPs

should spend adequate time at the outset encouraging and educating patients about their treatment plan, including describing the unique role of each prescribed drug. PCPs should also review and reassure patients about potential drug interactions. This shared decision-making process encourages patients' involvement in their disease management. We also recommend the use of medications that offer multiple therapeutic effects to help streamline therapies or the use of combination medications, where applicable, to reduce treatment burden (8).

Role of GLP-1 Receptor Agonists in Achieving Target A1C

Despite clear guidelines, the recommended target A1C <7% for most people with diabetes is not being met with current intervention methods; in the United States in 2019, the average A1C for people with type 2 diabetes was 7.3% (43), and this value rose to 8.2% for people using intensive insulin therapy (44). However, data from head-to-head trials comparing different GLP-1 receptor agonists provide evidence that agents in this drug class are highly efficacious in achieving glycemic control and could be of help to get patients to their A1C target in the primary care setting. Across these trials, 30–80% of individuals achieved an A1C <7%, with the highest proportions recorded with semaglutide (both SC and oral formulation, 34–80%) and dulaglutide (51–78%) (Table 2). However, caution is required when comparing data across trials because of differences in baseline characteristics and trial designs.

Data comparing GLP-1 receptor agonists with other injectable and oral hypoglycemic agents have differentiated GLP-1 receptor agonists from other agents in several ways. Newer GLP-1 receptor agonists are more efficacious than or have comparable efficacy to that of insulin therapy for A1C reduction in people with type 2 diabetes (45,46) and are associated with superior A1C reduction compared with sodium–glucose cotransporter 2 (SGLT2) inhibitors (47) and dipeptidyl peptidase 4 (DPP-4) inhibitors (48). Meta-analyses have shown that GLP-1 receptor agonists have the greatest A1C-lowering effect as add-on therapy to insulin versus thiazolidinediones, SGLT2 inhibitors, and DPP-4 inhibitors (49) and as add-on therapy to metformin versus SGLT2 inhibitors and DPP-4 inhibitors (50,51). In the primary care setting, patients taking the GLP-1 receptor agonist liraglutide were shown to have adequate glycemic control for longer than those taking oral antidiabetic drugs from other classes, and fewer patients discontinued liraglutide versus the oral drugs (52). Notably, GLP-1 receptor agonists are also more efficacious in terms of reducing body weight than most oral glucose-lowering drugs and insulin formulations and have an overall lower hypoglycemia risk than insulin or sulfonylureas (46). Furthermore, compared with DPP-4 inhibitors, GLP-1 receptor agonists have been associated with greater reductions in weight with no increased risk in hypoglycemia (48).

GLP-1 receptor agonists also have secondary pleiotropic benefits, mainly in terms of reducing CVD risk. There is also evidence for a potential renal protective effect through their microvascular benefits (Table 3). As a result, fewer adjustments in medications may be required in the long term if PCPs maximize the early use of GLP-1 receptor agonists, which can decrease both A1C and body weight and offer positive effects on CVD and possibly CKD. PCPs should be aware of these potential benefits when considering the use of a GLP-1 receptor agonist for the treatment of type 2 diabetes.

Barriers to GLP-1 Receptor Agonist Use in Primary Care

Despite the potential of GLP-1 receptor agonists, their uptake worldwide has been lower than might be expected (53,54). As summarized in Table 4, we identify below some perceived barriers to the use of GLP-1 receptor agonists in the primary care setting and offer suggestions for overcoming them.

Perceived Risk of Hypoglycemia

Similar to one of the previously discussed barriers to achieving the recommended A1C target, there is a perceived risk of hypoglycemia with the use of GLP-1 receptor agonists, particularly when combined with other antihyperglycemic medications. However, data show that independent use of GLP-1 receptor agonists has a minimal hypoglycemia risk (8). These agents reduce blood glucose by increasing glucose-dependent insulin secretion from the pancreas (6). Therefore, their mechanism of action requires a supply of glucose as a substrate; thus, GLP-1 receptor agonists reduce A1C levels from hyperglycemia toward normoglycemia with little potential of causing hypoglycemia (6,7). PCPs should be assured by this glucose-dependent mechanism of action and by trial data that have shown no increased hypoglycemia risk when GLP-1 receptor agonists are used on their own.

In our clinics, we have also found methods to minimize hypoglycemic episodes when GLP-1 receptor agonists are

TABLE 2 Key Efficacy and Safety Outcomes for Within-Class Head-to-Head Trials of GLP-1 Receptor Agonists

Trial	Design	GLP-1 Receptor Agonists Studied	ETD A1C, %	Proportion of Patients Attaining an A1C <7.0%	ETD Body Weight	Most Common Treatment-Emergent Adverse Event
Trials comparing QW with QD/BID GLP-1 receptor agonists						
AWARD-1 (67)*	52-week, randomized, blinded (for dulaglutide), parallel-group, placebo-controlled	Dulaglutide SC 0.75 mg QW	−0.31 (95% CI −0.44 to −0.18)†, *P* <0.001	66%, *P* <0.001	1.27 kg, 2.80 lb‡§, *P* <0.001	Nausea, 16%
		or dulaglutide SC 1.5 mg QW	−0.52 (95% CI −0.66 to −0.39)†, *P* <0.001	78%, *P* <0.001	−0.24 kg‡§, −0.53 lb‡§, *P* = 0.474	28%
		versus exenatide SC 10 μg BID	NA	versus 52%	NA	versus 26%
AWARD-6 (68)	26-week, randomized, open-label	Dulaglutide SC 1.5 mg QW	−0.06 (95% CI −0.19 to 0.07)†, *P*<0.0001 (noninferiority)	68%, *P* NR	0.71 kg (95% CI 0.17–1.26), 1.57 lb (95% CI 0.37–2.78)†, *P* = 0.011	Nausea, 20%
		versus liraglutide SC 1.8 mg QD	NA	versus 68%	NA	versus 18%
DURATION-5 (69)	24-week, randomized, open-label, comparator-controlled	Exenatide ER SC 2 mg QW	−0.7 (95% CI −0.9 to −0.4)‡, *P* <0.01	58%, *P* <0.0001	−0.95 kg (95% CI −1.9 to 0.01), −2.09 lb (95% CI −4.19 to 0.02)†, *P* NR	Nausea, 35%
		versus exenatide SC 10 μg BID	NA	versus 30%	NA	versus 14%
DURATION-6 (70)	26-week, randomized, open-label, parallel-group	Exenatide ER SC 2 mg QW	0.21 (95% CI 0.08–0.33)‡, *P* = 0.0018	53%, *P* = 0.0011	0.90 kg (95% CI 0.39–1.40), 1.98 lb (95% CI 0.86–3.09)‡, *P* = 0.0005	Nausea, 9%
		versus liraglutide SC 1.8 mg QD	NA	versus 60%	NA	versus 21%
SUSTAIN 10 (71)	30-week, randomized, open-label	Semaglutide SC 1 mg QW	−0.69 (95% CI −0.82 to −0.56)†, *P* <0.0001	80%, *P* <0.0001	−3.83 kg (95% CI −4.57 to −3.09), −8.44 lb (95% CI −10.08 to −6.81)†, *P* <0.0001	Nausea, 22%
		versus liraglutide SC 1.2 mg QD	NA	versus 46%	NA	versus 16%
Trials comparing QW with QW GLP-1 receptor agonists						
SUSTAIN 3 (72)	56-week, randomized, open-label, active comparator-controlled, parallel-group	Semaglutide SC 1 mg QW	−0.62 (95% CI −0.80 to −0.44)†, *P* <0.0001	67%, *P* <0.0001	−3.78 kg (95% CI −4.58 to −2.98), −8.33 lb (95% CI −10.10 to −6.57)†, *P* <0.0001	Nausea, 22%
		versus exenatide ER SC 2 mg QW	NA	versus 40%	NA	versus 12%

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TABLE 2 Key Efficacy and Safety Outcomes for Within-Class Head-to-Head Trials of GLP-1 Receptor Agonists (Continued)

Trial	Design	GLP-1 Receptor Agonists Studied	ETD A1C, %	Proportion of Patients Attaining an A1C <7.0%	ETD Body Weight	Most Common Treatment-Emergent Adverse Event
SUSTAIN 7 (73)	40-week, randomized, open-label, active-controlled, parallel-group	Semaglutide SC 0.5 mg QW	−0.40 (95% CI −0.55 to −0.25)†, P <0.0001	68%, P <0.0001	−2.26 kg (95% CI −3.02 to −1.51), −4.98 lb (95% CI −6.66 to −3.33)†, P <0.0001	Nausea, 23%
		versus dulaglutide SC 0.75 mg QW	NA	versus 52%	NA	versus 13%
		Semaglutide SC 1 mg QW	−0.41 (95% CI −0.57 to −0.25)†, P <0.0001	79%, P = 0.0021	−3.55 kg (95% CI −4.32 to −2.78), −7.83 lb (95% CI −9.52 to −6.13)†, P <0.0001	21%
		versus dulaglutide SC 1.5 mg QW	NA	versus 67%	NA	versus 20%
Trials comparing oral semaglutide QD with a QW/QD SC GLP-1 receptor agonist‖						
PIONEER 4 (74)	52-week, randomized, double-blind double-dummy, active-controlled, placebo-controlled	Oral semaglutide 14 mg QD	−0.3 (95% CI −0.5 to −0.1)†, P = 0.0002	61%, P = 0.1193	−1.3 kg (95% CI −2.1 to −0.5), −2.87 lb (95% CI −4.63 to −1.10)†, P = 0.0019	Nausea, 20%
		Liraglutide SC 1.8 mg QD	NA	versus 55%	NA	versus 18%

*Data presented are from the primary end point of 26 weeks. †Mean ETD from baseline. ‡Least squares mean ETD from baseline. §95% CIs not available. ‖Data from PIONEER 9 and PIONEER 10 are not presented because these trials were completed in Japan, and the maximum doses of liraglutide and dulaglutide used were half the approved doses in the United States (75,76). ETD, estimated treatment difference; NA, not applicable; NR, not reported.

added to insulin or sulfonylurea therapy. PCPs can use A1C as a guide. For patients whose A1C is >8%, we recommend not reducing sulfonylurea or insulin doses. Instead, PCPs should discuss blood glucose self-monitoring and hypoglycemia awareness with patients and provide close follow-up for 1–2 months after GLP-1 receptor agonist initiation. For patients whose A1C is <8%, sulfonylurea or insulin doses should be reduced by 25–50% at the time of GLP-1 receptor agonist initiation, and basal insulin should be reduced to no more than 0.5 units/kg.

Another recommendation would be to use patient-driven reverse titration, through which patients monitor their fasting blood glucose levels in the morning, with the aim of achieving a target of <140 mg/dL (7.8 mmol/L). Basal insulin should be reduced by 1 unit if morning fasting glucose is <140 mg/dL. This insulin adjustment, which for glargine should occur daily and for degludec should occur every 3 days, minimizes the risk of hypoglycemia after adding a GLP-1 receptor agonist.

Associated Side Effects

The common occurrence of gastrointestinal (GI) events with GLP-1 receptor agonists—most frequently nausea (Table 2)—may affect PCPs' decisions when considering medications to prescribe. Awareness of GI side effects enables PCPs to educate their patients so these effects do not disrupt or create a barrier to GLP-1 receptor agonist treatment. Patient education should explain that these GI events typically occur early in treatment, are mild to moderate in severity, and are transient in nature (55). Patients should learn to observe satiety cues and

TABLE 3 Cardiovascular and Microvascular Benefits of GLP-1 Receptor Agonists in Type 2 Diabetes Management

Benefit	Details
Reduced risk of cardiovascular complications	• Several GLP-1 receptor agonists have an indication for CVD risk reduction in patients with type 2 diabetes and established CVD (30,32,61). • Diabetes and cardiology guidelines now recommend these agents for individuals with type 2 diabetes who are at elevated CVD risk (8–10,77). • ADA guidelines recommend using GLP-1 receptor agonists for patients with established ASCVD or indicators of high ASCVD risk independent of A1C levels (8).
Reduced risk of microvascular complications	• GLP-1 receptor agonists have been shown to reduce rates of nephropathy in patients with type 2 diabetes (78,79). • GLP-1 receptor agonists have been shown to have no specific effect on retinopathy (79,80).

understand that calorie reduction will not result in emaciation or hypoglycemia.

PCPs can take additional approaches to overcome side effects as a barrier to GLP-1 receptor agonist use. Slow and/or individualized titration with close monitoring or using a lower-than-approved maximum dose can help to mitigate GI side effects (56–58). For example, PCPs could implement a transient dose de-escalation followed by an attempt at re-escalation once symptoms have resolved. Dietary recommendations such as avoiding high-fat foods and consuming small portions can also mitigate GI symptoms (56). Furthermore, PCPs should be mindful that hypovolemic GI side effects may risk acute kidney injury in patients with impaired renal and hepatic function and so should be particularly attentive to these patients (59).

Concerns have been raised about the risk of thyroid cancer associated with GLP-1 receptor agonists. Currently, there is insufficient data to establish or exclude a causal relationship between medullary thyroid carcinoma

TABLE 4 Barriers to GLP-1 Receptor Agonist Use and Suggestions to Overcome Them

Barrier to GLP-1 Receptor Agonist Use	Suggestions to Overcome Barriers

Perceived risk of hypoglycemia	• Understand that the glucose-dependent mechanism of action of GLP-1 receptor agonists means that their use on their own does not increase hypoglycemia risk.
	• If GLP-1 receptor agonists are used in combination with insulin or a sulfonylurea:
	  ○ If A1C is <8%, consider reducing the dose of the concomitant medicine.
	  ○ If A1C is >8%, do not reduce the concomitant medicine but do discuss blood glucose monitoring and hypoglycemia awareness with patients and closely follow-up for 1–2 months after treatment initiation or implement patient-driven reverse titration of insulin.

Associated side effects	• Reassure patients that GI side effects are typically mild to moderate and transient and can be mitigated by observing satiety cues, avoiding high-fat foods, and consuming small portions. • Consider slow and/or individualized titration with monitoring (e.g., implement dose de-escalation followed by an attempt at re-escalation once symptoms have resolved).
Perceived titration complexity	• Follow simple and steady up-titration approach as recommended in prescribing information (30–32,60–63,81).
Concerns about injections	• Discuss and understand how patients feel about injections before making prescription decisions. • A once-daily oral formulation of semaglutide is available and may be appropriate for patients who prefer to avoid injections.
Insurance coverage limitations	• Select a GLP-1 receptor agonist that is preferred on the patient's insurance plan formulary. • Ensure that the medication is requested under the correct *International Classification of Diseases* code. • If needed, introduce patients to Medicare "donut hole" programs or assistance programs for uninsured patients. • Follow up with status of any needed medication pre-authorizations and involve team members in moving the process along. • Document a narrative for each medication, backed by ADA or other professional organization recommendations.

(MTC) and GLP-1 receptor agonist use in humans. Agents in this class are contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2 (32) but not for any other thyroid-related issues.

Perceived Titration Complexity

We believe that GLP-1 receptor agonists are somewhat unnecessarily perceived as complex treatments. When starting a patient on a GLP-1 receptor agonist, an approach of steady up-titration is recommended in most cases (Table 5) (30–32,60–63). This strategy facilitates optimal tolerance to the treatment by limiting side effects at lower doses before patients are exposed to higher doses (58). Although the process may seem complicated, once it is understood that titration happens over the course of a few weeks (Table 5), after which a patient is on a stable dose, PCPs should feel confident in considering the use of these agents.

Perceived Reluctance to Take Injections

People with type 2 diabetes who are seen by endocrinologists are more commonly prescribed GLP-1 receptor agonists than those seen by PCPs (64). From our work, we understand that, because most GLP-1 receptor agonists are received via SC injection, PCPs may mistakenly assume that patients are reluctant to use them and so perceive injection avoidance as a barrier to the use of these agents. However, when surveyed, <10% of patients treated with an injectable therapy reported finding injections painful (65). It is likely, therefore, that injection avoidance is more of a barrier for providers than for their patients.

We have found it helpful to talk to patients about their thoughts on injections before making prescription decisions. PCPs should feel assured that injections are not a barrier to patient uptake in most cases and have confidence in the injection and titration process when considering the use of GLP-1 receptor agonists. When a patient does have concerns about using an injectable therapy, several team-based approaches can be used to overcome these concerns. For example, a pharmacist or diabetes education specialist can assist in demonstrating how to use injection devices, instruct patients on proper injection technique, and allow supervised injections until patients become comfortable (66). However, it also should be noted that, for the GLP-1 receptor agonist semaglutide, a QD oral formulation is now available as an alternative to the QW SC injectable formulation (63).

TABLE 5 Dosing Schedule of Approved GLP-1 Receptor Agonists for Type 2 Diabetes

GLP-1 Receptor Agonist	Approved Dosing Schedule
Dulaglutide	• Initiate at 0.75 mg SC QW. • Increase dose to 1.5 mg QW if additional glycemic control needed. • After 4 weeks at 1.5 mg, increase dose to 3 mg QW if additional glycemic control needed. • After 4 weeks at 3 mg, increase dose to 4.5 mg QW if additional glycemic control needed (30).
Exenatide BID	• Initiate at 5 μg SC BID. • After 1 month at 5 μg, increase dose to 10 μg twice daily (60).
Exenatide ER	• Initiate at 2 mg SC QW with no further titration (31,81).
Liraglutide	• Initiate at 0.6 mg SC QD for 1 week. • After 1 week at 0.6 mg, increase dose to 1.2 mg QD. • Dose can be increased to 1.8 mg QD for additional glycemic control (61).
Lixisenatide	• Initiate at 10 μg SC QD for 14 days. • On day 15, increase dose to 20 μg QD (62).
Semaglutide oral	• Initiate at 3 mg QD for 30 days. • After 30 days at 3 mg, increase dose to 7 mg QD. • Dose may be increased to 14 mg QD if additional glycemic control is needed after at least 30 days at 7 mg (63).
Semaglutide SC	• Initiate at 0.25 mg SC QW. • After 4 weeks at 0.25 mg, increase dose to 0.5 mg QW. • If after at least 4 weeks additional glycemic control is needed, increase to 1 mg QW. • If after at least 4 weeks additional glycemic control is needed, increase to 2 mg QW (32).*

*The U.S. Food and Drug Administration approved semaglutide SC 2.0 mg for the treatment of type 2 diabetes on 28 March 2022 (82).

Insurance Coverage Limitations

Health insurance plans in the United States may limit patients' treatment options. Patients may opt for a high-deductible health plan with low monthly premiums; however, the costly out-of-pocket payments for medications under such plans could deter patients from considering GLP-1 receptor agonist treatment. Limited insurance coverage is therefore a barrier to the uptake of these agents.

PCPs have several roles to plan in helping to overcome this barrier. They should check to determine the preferred GLP-1 receptor agonist on patients' insurance plan formulary and implement or switch to the preferred agent if needed. They should also ensure that the medication is requested under the correct *International Classification of Diseases* code to avoid coverage rejection. In addition, PCPs can introduce their patients to Medicare "donut hole" programs or noninsured patient assistance programs, when applicable.

Delays between treatment decisions and treatment initiation because of denials or delays in insurance coverage are common. We believe that PCPs should be consistent in following up on the status of pre-authorization medications and involve their team members in moving this process along. PCPs should also document a narrative for each medication, backed by recommendations from ADA or other professional organizations, in their chart notes. This narrative can then be accessed readily when following up with pre-authorization requests.

Future Considerations

As previously noted, a target A1C of <7% is currently recommended for most people with type 2 diabetes. However, it is noteworthy that type 2 diabetes is one of the few chronic diseases for which normalization of the disease-affected variable (i.e., normoglycemia as indicated by an A1C <5.7%) is not the target for control. In the future, treatment targets may decrease toward the normoglycemic range. CGM may help to achieve these more stringent targets, and its use in the primary care setting may grow. In the future, routine use of CGM may facilitate patients' understanding of their disease and improve providers' insight regarding adherence.

Conclusion

A target A1C of <7% is recommended for most people with type 2 diabetes; however, many are not achieving this target with their current diabetes treatment plan. GLP-1 receptor agonists are highly efficacious at getting people with type 2 diabetes to target A1C levels safely. Some agents in this drug class also offer secondary benefits including reductions in weight and in risks of CVD and microvascular complications. Despite their potential usefulness for the treatment of type 2 diabetes, GLP-1 receptor agonists remain underused because of several real or perceived barriers. PCPs can help to overcome these barriers with the guidance provided in this review. PCPs should have confidence in the recommended A1C target of <7% and the use of GLP-1 receptor agonists to help patients achieve it.

ACKNOWLEDGMENTS

Editorial support was provided by Molly Clark, BSc, Beverly La Ferla, MRes, and Helen Marshall, BA, of Ashfield MedComms, an Inizio company.

FUNDING

Editorial support for this article was funded by Novo Nordisk, which had a role in reviewing the manuscript for medical accuracy.

DUALITY OF INTEREST

A.K. is an advisor for Mannkind and Novo Nordisk and a speaker for Abbott, Dexcom, Lilly, Mannkind, and Novo Nordisk. E.M.M. has served on advisory boards for Abbott, the American Diabetes Association, Bayer, Boehringer Ingelheim, Diabetes Wise-Stanford University, Lilly, Merck, MicroGenDX, Novo Nordisk, Plenity, and Sanofi and on speakers bureaus for Abbott, Boehringer Ingelheim, Lilly, and Novo Nordisk and has received research support from Abbott and Pendulum. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

The authors contributed equally to this work by providing references to cite, suggesting and organizing the content to be included, critically reviewing each draft, and approving the final draft for submission. E.M.M. is the guarantor of this work and, as such, had full access to all the data in the review, and takes responsibility for the integrity of the data and the accuracy of the content.

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