



# Enhancing treatment success with incretin-based therapies: A comprehensive approach to the patient with diabetes <sup>☆</sup>

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Adding glucagon-like peptide-1 (GLP-1) receptor agonists to insulin therapy for patients with type 2 diabetes mellitus (T2DM): why and how patients with T2DM who progress to insulin therapy usually do so by starting with a single injection of a long-acting insulin analog, added to oral anti-diabetic drugs. Long-acting insulin analogs provide basal insulin coverage and address elevated fasting blood glucose levels. Because of the near universal efficacy of insulin, such approaches are almost always successful in lowering blood glucose levels, but may not bring patients to goal because they do not address postprandial hyperglycemia. The approach to postprandial hyperglycemia has typically been to add doses of rapid-acting insulin analogs before meals. However, this may increase the risk of hypoglycemia and weight gain, and may not be acceptable to patients both in terms of patient tolerability and adherence. New approaches include the addition of GLP-1 receptor agonists to insulin in patients with uncontrolled T2DM. This article reviews the data and the clinical context of such action with respect to issues of glycemic efficacy, patient tolerability, and safety.

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## Introduction

Type 2 diabetes mellitus (T2DM) is a complex and increasingly common metabolic disease that is characterized by hyperglycemia and associated with microvascular and macrovascular complications. The current goal of therapy for the patient with diabetes is to improve metabolic control with as few adverse effects as possible.<sup>1,2</sup> Obesity and T2DM are intricately linked, with weight gain, especially visceral adiposity,<sup>3</sup> being a major contributor to the increasing incidence of T2DM.<sup>4</sup> Both conditions are independent risk factors for cardiovascular disease (CVD), which is the cause of death for the majority of patients with

diabetes.<sup>5</sup> Lifestyle interventions and glucose-lowering medications can be prescribed to minimize the state of chronic hyperglycemia and to address the pathophysiological defects associated with T2DM. Other metabolic abnormalities, including dyslipidemia, hypertension, and oxidative stress, must also be addressed to reduce the patient's risk of CVD.<sup>1,6</sup>

Many factors influence the selection of glucose-lowering therapy. First and foremost are well-established factors such as glucose-lowering efficacy (including the use of mechanisms of action that target the core defects of diabetes pathophysiology, of which there are many),<sup>7</sup> safety (tolerability and harm avoidance in the short- and long-term treatment of this chronic disease),<sup>1</sup> and patient factors such as cost and patient acceptance of and adherence to therapy.<sup>2</sup>

## Adherence to diabetes medications

Patient adherence to diabetes regimens is a major barrier to the ideal management of diabetes. Half of patients with

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diabetes stay on their medications for 6 months or less.<sup>8</sup> Understanding patient concerns about diabetes therapy can help physicians make treatment choices with a higher likelihood of patient adherence. Although patients with T2DM believe glucose control is important, medication side effects and risks influence patients' treatment choices. Attempts to understand patient motivations for adherence or nonadherence based on features of effectiveness and side effects of diabetes medication have been undertaken. In 1 study that involved American patients with T2DM, glucose control was the most important medication feature, followed by medication-related CV risk and weight gain, respectively, the latter 2 being negatively associated with patient adherence.<sup>9</sup>

What advantages do glucagon-like peptide-1 receptor agonists (GLP-1 RAs) offer with regard to patient adherence? They successfully lower blood glucose with a low risk of hypoglycemia, without weight gain, and with no known CV adverse effects.<sup>10-16</sup> They appear to be preferred by patients over insulin and sulfonylureas (both of which may result in weight gain and carry a risk of hypoglycemia).<sup>17-19</sup> Treatment satisfaction reported with GLP-1 RAs appears to be independent of their weight loss effects. Patients prefer these agents to dipeptidyl peptidase-4 (DPP-4) inhibitors, perhaps because of the weight effects and also for reasons of perceived efficacy.<sup>16</sup>

### Glucose efficacy

Incretin-based therapies work via increasing insulin secretion and inhibiting glucagon release from the pancreas. DPP-4 inhibitors work by decreasing the breakdown of endogenous levels of GLP-1. GLP-1 RAs work by stimulating the receptors directly. DPP-4 inhibitors thus promote physiological levels of GLP-1, and GLP-1 RAs provide supraphysiological levels; as such the latter are more potent in their glucose-lowering actions.<sup>20</sup> Both agents still work only in the presence of hyperglycemia and are thus unlikely to be associated with hypoglycemia unless used with insulin or sulfonylureas. Short-acting GLP-1 RAs (ie, short-acting exenatide) and DPP-4 inhibitors tend to lower postprandial glucose levels more than fasting glucose levels.<sup>21</sup> The longer-acting GLP-1 RAs (liraglutide and exenatide once weekly) have more profound actions on

fasting plasma glucose levels, as well as actions on postprandial glucose levels, resulting in greater overall A1C reductions than the shorter-acting exenatide or the oral DPP-4 inhibitors.<sup>21-24</sup>

### Hypoglycemia as a barrier

Hypoglycemia remains the primary barrier to achieving glycemic control.<sup>25,26</sup> Hypoglycemia adversely affects patient quality of life.<sup>27</sup> Reducing the likelihood of hypoglycemia, particularly nocturnal hypoglycemia,<sup>28</sup> may facilitate treatment acceptance and adherence. The adverse consequences of hypoglycemia are much more than nuisance side effects—they are a common cause of drug-induced hospitalization.<sup>29</sup> Hypoglycemia increases the morbidity, mortality, and economic costs of diabetes.<sup>30,31</sup> Chronically recurrent hypoglycemia may lead to impairment of the counter-regulatory system, with the potential for the development of hypoglycemia unawareness syndrome, increased severe hypoglycemia-associated hospitalization, and increased mortality.<sup>32</sup> Other data show that hypoglycemia may be either a marker or predictor of later death.<sup>33</sup>

Avoidance of hypoglycemia by treating with appropriate, individualized regimens for patients with T2DM should be a primary focus of physicians.<sup>34-36</sup> Figure 1 shows neurogenic (autonomic) and neuroglycopenic symptoms at different levels of hypoglycemia of which physicians should be aware.<sup>32</sup> Recent data show that almost 20% of patients who received a sulfonylurea experienced at least 1 episode of hypoglycemia (defined as a blood glucose level <70 mg/dL).<sup>37</sup> Utilizing traditional agents (eg, metformin and thiazolidinediones) that do not promote hypoglycemia, in combination with newer agents such as DPP-4 inhibitors and GLP-1 RAs, offers a therapeutic advantage when trying to help patients reach their hemoglobin A1C goal without the added risk of hypoglycemia. GLP-1 RAs and DPP-4 inhibitors work in glucose-dependent fashion and are thus associated with a low risk of hypoglycemia, except when used with a sulfonylurea or with insulin, where the risk of sulfonylurea-related hypoglycemia may be exacerbated. However, their use with insulin has recently been approved, and in studies with basal insulin, the use of GLP-1 RAs may be an alternative to adding prandial insulin when prandial glucose

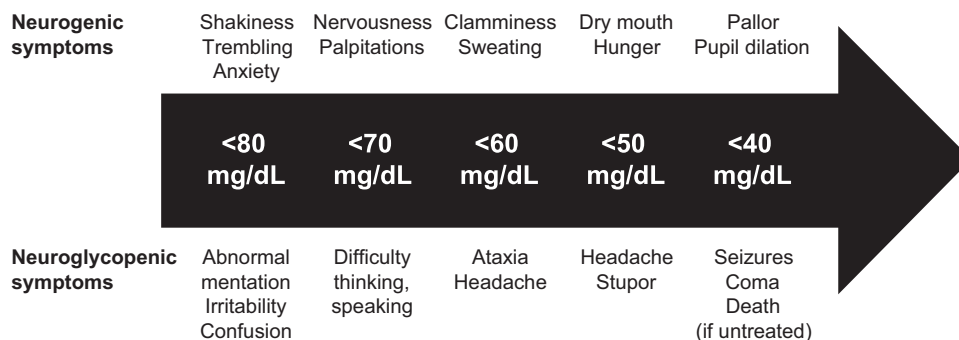


Figure 1 Hypoglycemia: critical point of care in diabetes management.

control becomes necessary, without increasing the risk of hypoglycemia or weight gain.<sup>38</sup>

## Effects of incretin-based therapies on weight

Both the low risk of hypoglycemia and the positive (or in the case of DPP-4 inhibitors, neutral) effects on weight of the GLP-1 RAs are among the reasons that current treatment guidelines highlight the use of this class of agents.<sup>34,39</sup> More than 80% of people with T2DM are obese or overweight.<sup>40</sup> Both T2DM and obesity are independent risk factors for CVD. Weight gain in patients with T2DM can contribute to patient frustration and may negatively impact their compliance with therapeutic regimens. Unfortunately, many therapies aimed at maintaining and improving glucose control are associated with weight gain. Among the older antidiabetes agents, most, including the insulin secretagogues (insulin and sulphonylureas) and sensitizers (thiazolidinediones), can lead to weight gain, except for metformin, which is weight-neutral. Among the newer agents, the DPP-4 inhibitors generally are weight-neutral in addition to lowering glucose, while the GLP-1 RAs lead to weight reduction when used to treat the hyperglycemia of T2DM.

Whereas DPP-4 inhibitors are considered weight-neutral, the GLP-1 RAs slow gastric emptying and promote satiety<sup>41</sup> and are associated with weight loss in some but not all patients.<sup>42</sup>

## CV safety

In part because of the issue with rosiglitazone, all new antidiabetes therapies must undergo testing for CV safety (rosiglitazone was withdrawn from the unrestricted prescribing because of suspected cardiovascular risks of the medicine). Clinical trials are underway assessing the efficacy and safety of GLP-1 RA therapy.<sup>43</sup> We have information from clinical trials demonstrating that when used to treat diabetes, GLP-1 RAs may improve markers of CV risk, including hypertension (notably, reductions in systolic blood pressure), dyslipidemia (notably, improvements in triglycerides), and other markers of inflammation (eg, C-reactive protein).<sup>44</sup> In addition, data are available for the 2 agents that have been on the market for several years, noting that no adverse CV outcomes have been observed with either liraglutide<sup>45</sup> or exenatide twice a day.<sup>46,47</sup> Recent data show that exenatide once weekly improved glycemic control, cardiometabolic risk factors, and a composite index of an A1C <7%, without weight gain or hypoglycemia, over 1 year of treatment.<sup>48</sup>

## Minimizing common adverse effects

DPP-4 inhibitors are generally well tolerated. Because of their greater pharmacologic effects, GLP-1 RAs do have some dose-related adverse effects, primarily related to the gastrointestinal (GI) system (nausea and sometimes vomiting), that diminish with time. These adverse effects may be related to the slowing of gastric emptying that GLP-1 RAs

have, which can result in feelings of fullness. These can be minimized by advising the patient to eat slowly and to stop eating when they feel full (not to overeat). In the case of exenatide given twice a day, doses should be given 0-60 minutes before eating. Taking the medication 60 minutes prior to meals results in maximum satiety; taking it right before eating minimizes GI side effects.<sup>49</sup> Both exenatide twice a day and liraglutide once a day are dose titrated to maximal effect—slowing the titration or reverting to a lower dose until nausea resolves in the case of more troublesome GI side effects—and can help the patient acclimate to the therapy. There is no dose titration with the once-weekly formulation; however, both the longer-acting GLP-1 RAs (liraglutide and exenatide once a week) appear to have lower rates of GI side effects than exenatide twice daily.<sup>50,51</sup> GI symptoms are common but transient, and there appears to be little potential for interaction with other drugs. Generally, patients do not discontinue therapy because of these effects. Nausea, mostly mild and transient, was responsible for a 6% dropout rate in clinical studies of the short-acting exenatide.<sup>52</sup> Clinical experience shows that symptoms generally subsided during the first month of treatment with liraglutide.<sup>53</sup> Making the patient aware of the possibilities and ways to reduce or tolerate these effects is helpful in improving the likelihood of adherence. Dosing suggestions are provided in Table 1.<sup>49,54,55</sup>

## Precautions

All patients with T2DM are at risk for the development of pancreatitis.<sup>34</sup> All incretin-based therapies (DPP-4 inhibitors and GLP-1 RAs) should be used with caution in patients with a history of pancreatitis.<sup>56</sup> Patients should be counseled about the signs and symptoms of pancreatitis (eg, severe abdominal pain, and vomiting). If pancreatitis should occur during treatment, therapy should be discontinued. However, information from claims databases suggests no greater risk of pancreatitis with incretin-based therapies compared to any other class of diabetes drugs.<sup>57</sup>

## Use in renal impairment

Impaired renal function is a common comorbidity (or complication) associated with T2DM.<sup>58</sup> Renal insufficiency may preclude the use of some antihyperglycemic medications and require that the dosages of others be reduced.<sup>59</sup>

Renal impairment (RI) also increases the risk of hypoglycemia in patients with T2DM.<sup>59</sup> Currently, there is limited experience with the use of GLP-1 RAs beyond mild-stage renal disease. In patients with mild-to-moderate RI, it appears appropriate to administer exenatide without dosage adjustment. In patients with moderate renal failure and in those with renal transplantation, exenatide should be used with caution when initiating or escalating dose.<sup>49,54</sup> Poor tolerability and significant changes in pharmacokinetics make the therapeutic doses of 5 and 10 µg exenatide unsuitable in severe RI or end stage renal disease.<sup>60</sup>

**Table 1** Dosing recommendations

Generic (Trade)	Starting dose	Titration	Timing	How available	Metabolism	Drug interactions	Comments
Exenatide (Byetta)	Initiate at 5 µg per dose twice daily	Increase to 10 µg twice daily after 1 mo based on clinical response and tolerability	Inject subcutaneously within 60 min prior to morning and evening meals (or before the 2 main meals of the day, approximately 6 h or more apart)	250 µg/mL exenatide  5 µg per dose, 60 doses, 1.2 mL prefilled pen  10 µg per dose, 60 doses, 2.4 mL prefilled pen	Tissue/renal	May impact absorption of orally administered medications  Postmarketing reports of increased INR sometimes associated with bleeding. Monitor INR frequently until stable upon initiation or alteration of therapy	Patients should be informed that pen needles are not included with the pen and must be purchased separately  Patients should be advised which needle length and gauge should be used
Exenatide extended-release (Bydureon)	2 mg every 7 d	Not applicable	Can be administered at any time of day, independent of meals. Must be injected immediately after powder is suspended	Single-dose tray containing: 1 vial of 2 mg exenatide, 1 vial connector, 1 prefilled diluent syringe, and 2 needles (1 provided as a spare)	Tissue/renal		Glucose-lowering effect may take ~2 wk to be evident; take this into account if switching a patient from another treatment regimen
Liraglutide (Victoza)	0.6 mg once a day for 1 wk. This dose is intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control.	After 1 wk, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg	Can be administered at any time of day, independent of meals	Solution for subcutaneous injection, prefilled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL)	Tissue	May impact absorption of orally administered medications	

Available data suggest that patients with T2DM with RI can use standard treatment regimens of liraglutide,<sup>61,62</sup> but caution is recommended when initiating or escalating doses in patients with RI to ensure that they do not experience GI symptoms that might result in dehydration.<sup>55</sup>

## Contraindications

Both liraglutide and exenatide extended-release carry black box warnings cautioning against use of these agents in patients with personal or family history of medullary thyroid

carcinoma,<sup>55,54</sup> based on findings of high-dose therapy in rodents. This is a very rare type of cancer, not to be confused with some of the more common forms of thyroid cancer. There are vast species differences in thyroid responses to GLP-1 RAs, with rodents having high expression of these receptors in C-cells, compared to monkeys or humans.<sup>56,63</sup> No specific laboratory monitoring is recommended.

## Dosing recommendations

Dosing recommendations are provided in Table 1.<sup>49,54,55</sup> There is an increased risk of hypoglycemia when GLP-1 RAs are used in combination with medications known to cause hypoglycemia (eg, insulin or insulin secretagogue); physicians should consider reducing the dose of insulin or insulin secretagogue when starting a patient on a GLP-1 RA.

Exenatide is available in 5- and 10- $\mu$ g fixed-dose pen devices. Patients should be counseled to take the pen needle off between injections otherwise it may leak.

Patients typically start with a dose of 5  $\mu$ g twice daily, administered before meals. Patients may take their doses before lunch and before the evening meal if they are not breakfast eaters. The dose may then be titrated to 10  $\mu$ g twice a day (BID) as indicated and tolerated. Exenatide should be administered 0-60 minutes before meals, with less nausea noted when it is given closer to the meal, but with maximum satiety when given 1 hour before the meal. If a dose of exenatide is missed, the patient should skip the missed dose and resume the usual dosing schedule with the next scheduled dose. They should not double the dose to “catch up.”<sup>49</sup>

Liraglutide is available as pen sets, with each individual pen delivering doses of 0.6, 1.2, or 1.8 mg. Patients will use 2 pens/mo at the 1.2 mg once daily dosing level and 3 pens/mo at the 1.8 mg once daily dosing level. Patients may inject at any time of day, independent of mealtimes (but preferably at the same time each day). The starting dose is 0.6 mg daily. When tolerated, the dose is increased to 1.2 mg once daily. Some patients may require further dose escalation to 1.8 mg once daily; glucose-lowering and weight effects are dose-related. If a dose of liraglutide is missed and it is <12 hours from when the patient should have taken it, the dose of liraglutide should be taken. However, if a dose of liraglutide is missed and it is >12 hours from when it should have been taken, patients should be counseled to not take an extra dose and not increase the dose on the following day to “make up” for the missed dose.<sup>55</sup>

Exenatide extended-release was approved in January 2012; it is given once weekly. It is available as single-dose trays; each individual tray provides injection of 2 mg of exenatide extended-release, and thus patients receive 4 dose trays/mo. Patients may inject at any time, with or without regard to a mealtime. Healthcare providers should counsel patients to tap the container, if needed, to loosen the powder, and to connect the orange vial connector to the vial and then

to the syringe (twist on). Diluent should then be injected into the vial, which should be shaken until the drug is fully suspended (small bubbles are acceptable). Patients or caregivers should then withdraw suspension into the syringe, attach a 23 gauge 5 by 16 needle, and push the plunger until the top is even with the dotted line on the syringe. The dose may then be injected subcutaneously into the stomach, back of arm, or thigh. Approximately 77% of people feel a bump after injection of medication under the skin, and around 1 in 5 may have a localized reaction from the injection; however, only ~1% of subjects discontinued due to injection site reactions. If patients should miss a dose of exenatide extended-release, they should take it as soon as remembered, provided the next scheduled dose is at least 3 days from the current time. However, if a dose of extended-release exenatide is missed and it is <3 days from when they would take the next dose, they should wait until the next regularly scheduled dose to restart the medication.<sup>49</sup>

As with other protein-based therapies, GLP-1 RAs may induce the formation of antibodies. Low-titer antiexenatide antibodies are relatively common with exenatide treatment (32% exenatide BID, 45% exenatide extended-release patients), but had no apparent effect on efficacy. Higher-titer antibodies were less common (5% exenatide BID, 12% exenatide extended-release); increasing antibody titer was associated with reduced average efficacy that was statistically significant for extended-release exenatide.<sup>64</sup> Liraglutide is less immunogenic than exenatide; the frequency and levels of antiliraglutide antibodies are low and do not impact glycemic efficacy or safety.<sup>65</sup> This may be due to the fact that liraglutide is closer in amino acid sequence to human GLP-1 than is exenatide.

## The importance of patient counseling

Patient counseling about GLP-1 agents is critical with respect to adverse reactions and appropriate expectations. Patient adherence to newly prescribed medications can be influenced by the prescriber's belief in the drug. Patients should be educated about the beneficial effects of good glycemic control in reducing the risk of diabetes-related complications. They should understand that diabetes is a progressive and changing disease, which will require efforts on the part of patients to incorporate lifestyle changes and work with their physician on tailoring and updating treatment regimens over time. With regard to GLP-1 RAs specifically, an accurate patient history, to avoid use in patients with a past history of pancreatitis or personal or family history of the rare forms of thyroid cancer described in the black box warnings, will facilitate appropriate patient selection. Patients should clearly be made aware of the most common adverse effects, those GI side effects (primarily nausea) that can be minimized with slow dose escalation, and, in the case of exenatide twice a day, appropriate timing of meals with respect to dosing. Helping patients understand how drugs work together to control diabetes can facilitate acceptance. The knowledge that GLP-1 RAs are very

effective in lowering blood glucose levels when taken as directed may help improve patient outcomes. Patients are likely to be pleased that these agents do not cause weight gain. They may also be pleased to know that it is possible that they may lose weight, but it should be clear that the primary reason for prescribing these agents is to control blood glucose levels, and that not all patients will lose significant amounts of weight or in fact any weight at all. Asking patients what they know or may have heard about these agents is 1 way to begin a meaningful conversation. Asking patients what may get in the way of adhering to treatment recommendations is extremely important as well. Identifying any barriers to diabetes management is necessary to improve the quality of diabetes care, including the improvement of metabolic control, and diabetes self-management. Continuity of care and consistent contact are also critical.

## Conclusions

Effective management of T2DM requires a multifactorial approach extending beyond glycemic control. Clinical practice guidelines suggest targets for A1C, blood pressure, and lipids, and emphasize weight reduction and avoiding hypoglycemia. GLP-1 RAs are effective in improving glycemic control with a low risk of hypoglycemia, have the potential for weight loss, and show improvements in markers of CV risk. As assessed by a composite outcome of A1C <7% (the American Diabetes Association's treatment goal), no hypoglycemia, and no weight gain, GLP-1 RAs are useful treatment options compared with other commonly used therapies.<sup>10</sup> By reinforcing the role of patients with T2DM in treatment decisions, better compliance and achievement of treatment goals can be met.

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