New and Emerging Injectable Therapies for Type 2 Diabetes for the Internal Medicine Physician: Experts Address Common Questions

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Author Note
Lawrence Blonde,1 Ayotunde Dokun,2 Frank Lavernia3
1  Director, Ochsner Diabetes Clinical Research Unit, Frank Riddick Diabetes Institute, Department of Endocrinology, Ochsner Medical Center, New Orleans, Louisiana
2  Associate Professor of Medicine and Endocrinology, Chief Endocrine Services, Regional One Health, University of Tennessee Health Sciences Center, Memphis, Tennessee
3  Founder, North Broward Diabetes Center, Coconut Creek, Florida
Corresponding address: Dr. Blonde, 1514 Jefferson Hwy, New Orleans, LA 70121
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Target Audience

This activity has been designed to meet the educational needs of general internal medicine physicians, internal medicine subspecialty physicians, and other healthcare professionals involved in the management of patients with type 2 diabetes mellitus (T2DM).

Learning Objectives

1. Describe indications for starting basal insulin therapy in patients with type 2 diabetes mellitus.
2. Use appropriate basal insulin in a physiologic manner and titrate therapy to achieve fasting plasma glucose goals.
3. Acknowledge and address patient barriers to insulin therapy by explaining how new therapies have been designed to mitigate barriers.
4. Intensify therapy in a patient-specific manner using new and emerging options, whether by premixed insulin or other prandial insulin or injectable therapies.

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New and Emerging Injectable Therapies for Type 2 Diabetes for the Internal Medicine Physician: Experts Address Common Questions

Abstract
Exogenous insulin has been in constant evolution since its development in the 1920s. New basal insulin agents have been developed to reduce some of the limitations of existing agents, such as hypoglycemia (particularly nocturnal hypoglycemia), and to provide once-daily dosing. More concentrated formulations of existing insulins have also been produced for patients who are very insulin resistant and require high doses/high volumes of insulin. Additionally, a new premixed insulin with less variability and less hypoglycemia has been approved. For prandial control or treatment intensification when basal insulin does not achieve treatment targets, the addition of some of the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has demonstrated good efficacy. Co-formulations of GLP-1 RAs with basal insulin agents have been developed. This review, which is based on a recent symposium designed specifically for internal medicine physicians, presents information on new and emerging injectable therapies in a question and case-based format. These new treatment options offer internal medicine physicians additional ways to improve glycemic control with the promise of greater tolerability.

Keywords:
Type 2 diabetes mellitus, basal insulin, long-acting, degludec U100, degludec U200, premixed degludec/aspart, glargine U300, intensification, combination, GLP-1 receptor agonists, degludec/liraglutide, glargine/lixisenatide.

Introduction
The number of Americans diagnosed and living with type 2 diabetes mellitus (T2DM) has dramatically increased and represents a major health problem to the US healthcare system.1-3 Diabetes is a major cause of early mortality from atherosclerosis and cardiovascular disease (CVD);4-7 it is also the leading cause of adult blindness, non-traumatic leg amputations, and chronic kidney disease.8,9 Despite national efforts to improve quality in diabetes care, we have reached a plateau in stemming the diabetes crisis.9 Incremental improvements in achieving glycemic and blood pressure targets have been achieved, with a more robust change in reaching lipid goals.9 However 48% of Americans with diabetes still had not achieved A1C goals <7% (Table 1).9

One of the major challenges of T2DM is its progressive and multifactorial pathophysiology.10-12 The natural history of T2DM is characterized by progressive deterioration of pancreatic beta-cell function, leading to worsening glycemia over time. As current antihyperglycemic therapies have not yet been shown to profoundly alter this natural history, many patients eventually will require exogenous insulin therapy to attain or maintain adequate glycemic control. However, insulin can be useful at any point along the disease continuum.11

<table>
<thead>
<tr>
<th>Blood Glucose Targets for Non-Pregnant Adults With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
</tr>
<tr>
<td>Preprandial capillary plasma glucose (PG)</td>
</tr>
<tr>
<td>Peak postprandial capillary PG</td>
</tr>
</tbody>
</table>

More or less stringent targets may be appropriate for individual patients if achieved without significant hypoglycemia or adverse events. Targets may be individualized based on patient characteristics.

<table>
<thead>
<tr>
<th>More stringent (&lt;6.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short diabetes duration</td>
</tr>
<tr>
<td>Long life expectancy</td>
</tr>
<tr>
<td>Type 2 diabetes treated with lifestyle or metformin only</td>
</tr>
<tr>
<td>No significant CVD/vascular complications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Less stringent (&lt;8.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypoglycemia history</td>
</tr>
<tr>
<td>Limited life expectancy</td>
</tr>
<tr>
<td>Advanced microvascular or macrovascular complications</td>
</tr>
<tr>
<td>Extensive comorbidities</td>
</tr>
<tr>
<td>Long-term diabetes in which general A1C targets are difficult to attain</td>
</tr>
</tbody>
</table>

Lowering A1C below or around 7.0% has been shown to reduce microvascular complications

The approach to glycemic management and glycemic targets must be individualized by considering the overall condition of each patient as well as the presence of complications and comorbid conditions, known duration of diabetes, risk for hypoglycemia and/or adverse consequences of hypoglycemia, and the presence of macro- and microvascular complications.13

Insulin is the oldest and most efficacious antihyperglycemic agent for patients with both type 1 diabetes mellitus (T1DM) and T2DM, yet there is still a need for clinician education in order to optimize its use.

Education for internal medicine physicians about how to best treat patients with diabetes has become increasingly important for several reasons: the sheer volume of patients with this chronic condition, the complexity of their treatment,14 and increase in available medication options. To this end, this supplement explores the use of new and emerging insulins and non-insulin injectable agents in treatment regimens for patients with T2DM, using a question and case-based format.
Question 1: What are current indications for initiating insulin therapy?

Case Vignette #1

George is a 56-year-old white male with a 3-year history of T2DM. He is 5’11” tall and weighs 220 lb (BMI = 31 kg/m²). He is taking glimepiride 4 mg daily, metformin 1500 mg daily, and sitagliptin 100 mg once daily. He is unable to tolerate higher doses of metformin because of gastrointestinal side effects of nausea and diarrhea. George’s A1C level is 9.2%. His fasting plasma glucose (FPG) levels have ranged between 200 and 230 mg/dL for the past couple of weeks. George complains of frequent trips to the bathroom at night and of being tired. He has no history of CVD or hypoglycemia and no diabetes-related complications. He has hypertension and dyslipidemia, which are controlled with an angiotensin-converting enzyme inhibitor and a statin.

The Role of Insulin

The discovery of insulin was one of the greatest scientific accomplishments in the last century and changed the prognosis for those diagnosed with type 1 diabetes from a fatal illness to one that could be treated. Almost immediately there was a significant increase in survival rates. To this day, insulin remains essential for patients with T1DM, and important for patients with T2DM, especially in later stages when endogenous insulin secretion can be markedly impaired. Dr. Cefalu and colleagues, in a recent editorial in Diabetes Care compared insulin to be considered the ‘essential black dress’ of diabetes therapy – always there, always useful, and generally appropriate for use in most patient types and with most other treatment options. There have been major improvements in administration methods, purity, antigenicity, pharmacodynamics, pharmacokinetics, and other factors important to patients and healthcare professionals (HCPs) alike.

Patients with diabetes who were treated with animal and human insulins were often unable to achieve glycemic targets because of a high incidence of both hyper- and hypoglycemia. This was partially because animal and human insulins were unable to provide a continuous, low level of basal insulin to mimic the normal basal secretory pattern of the beta cells. In the search for good glycemic control with less risk of hypoglycemia, the first basal insulin analogs have been major improvements in administration methods, purity, antigenicity, pharmacodynamics, pharmacokinetics, and other factors important to patients and healthcare professionals (HCPs) alike.

Indications and Recommendations for the Use of Insulin in T2DM

Across the Treatment Spectrum of T2DM

Insulin is a recommended option across the spectrum of diabetes progression for patients with T2DM. It is indicated as initial pharmacotherapy in patients with “severely” uncontrolled T2DM. Insulin also has the advantage of being effective where other agents may not be and should be considered a part of any combination regimen when hyperglycemia is severe, especially if the patient is symptomatic or if any catabolic signs are present—or, in those with glucose toxicity at diagnosis, where high glucose levels inhibit insulin secretion and insulin activity. Objectively, this might be identified by one or some of the following: a random glucose >300 mg/dL, A1C >10%, ketonuria and weight loss, and where subjectively the patient may experience excessive urinating, excessive thirst, blurry vision, and fatigue.

For the Management of Long-Standing T2DM

In cases of long-standing diabetes, pancreatic insulin secretory capacity is usually significantly reduced. For any patient who does not achieve a target A1C level despite intensive therapy with a combination of non-insulin pharmacotherapies basal insulin should be considered an essential part of the treatment strategy, according to the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) 2015 patient-centered position statement for the management of hyperglycemia in T2DM. Insulin is also useful for patients with advanced hepatic or renal disease.

Treatment Intensification: When Non-insulin Therapy Fails to Achieve A1C Goals

In the American Association of Clinical Endocrinologists (AACE) algorithm, the use of basal insulin should be considered when non-insulin antihyperglycemic therapy fails to achieve target A1C goals or when the patient, whether drug naive or not, has symptomatic hyperglycemia. There are other special considerations for which insulin therapy is especially suited. These include the treatment of hyperglycemia in hospitalized patients, patients treated with high-dose steroids, and pregnant patients. Insulin is the traditional first-choice drug for blood glucose control during pregnancy because it doesn’t cross the placenta, and it is the most effective for fine-tuning blood glucose levels.

Many (if not most) patients with T2DM are likely to use insulin at some point in their lives (assuming reasonable longevity), whether for short-term use to treat acute hyperglycemia, or while hospitalized, or if they have diabetes long enough to result in marked impairment of beta-cell function.

To Manage Acute Hyperglycemia

Insulin therapy also has been used on a short-term basis to manage acute hyperglycemia in patients newly diagnosed with T2DM. The temporary use of short-term intensive insulin therapy (for example, 3 weeks to 6 months of basal-bolus insulin therapy) early in the course of T2DM has been effective and may offer favorable long-term effects on beta-cell function. After receiving this treatment, some patients will often experience sustained euglycemia without requiring antihyperglycemic therapy for up to a year or more. This apparent “remission” of diabetes is likely secondary to improved beta-cell function. Hyperglycemia eventually returns, and patients often go on to receive oral agents.
Question 2: How should insulin therapy be initiated?

Start the Discussion About Insulin Early in the Course of Diabetes

If possible, physicians should begin discussion with their patients about insulin therapy well before its projected time of initiation. Many physicians like to introduce the concept of using insulin as a safe, effective, and relatively painless treatment “option” early in their discussion of treatment choices rather than using it as a “threat” if other treatments or lifestyle modifications are not effective. Patients are more likely to accept insulin if they understand its benefits, the relative lack of pain of injections using newer, narrower-gauge needles, and have received education and had their questions answered. They need to know goals of therapy and be taught insulin self-titration. Self-management education should be provided by Certified Diabetes Educators (CDEs), ideally working in ADA-recognized diabetes education programs that are widely available throughout the United States.

Consider Patient-Specific Factors and Barriers

Beyond any patient misconceptions about insulin treatment, the patient’s general approach to medication can influence whether prescribing insulin will be successful. Questions that HCPs working with patients starting on insulin may want to ask about the patient are:

- What traditionally has been their level of adherence to medications? Perceived physician inattention and lack of engagement has a direct relationship with insulin adherence and glycemic control.
- What is the health literacy of the patient? Health literacy is the ability to obtain, read, understand and use healthcare information to make appropriate health decisions and follow instructions for treatment. Limited health literacy has been shown to be associated with poor glycemic control in insulin-taking T2DM patients, suggesting that additional, patient-specific measures are needed if therapy is to be successful.
- To what extent do their comorbidities put them at greater risk for hypoglycemia or its effects?
- Older adults with diabetes have a higher risk for hypoglycemia due to altered adaptive physiologic responses to low glucose levels.
- What about cost? Does this patient have insurance to pay for the therapy you are prescribing? What will their co-pay be? Are they going to pay out of pocket for their medications? Are they going to get into the Medicare “donut hole” quickly?

These general factors are important to consider and to discuss with any patient prior to starting insulin.

The availability of pen devices has definitely eased the burden of introducing the use of insulin to patients. Patients find this delivery method much more acceptable and less painful, and are more adherent to therapy than with older vial and syringe delivery methods. Pens also allow more accurate insulin dosing by patients. Although the percentage of patients using insulin pen delivery devices in the United States is increasing, it is still low compared with other countries and is a factor that should be considered when trying to address barriers to the introduction of insulin to a patient.

Other common barriers to the use of subcutaneous insulin include fear of hypoglycemia, number of injections, weight gain, and concerns regarding regimen flexibility. Currently available insulins do not address the barriers typically associated with insulin, nor the desired physiologic rapid-on, rapid-off control of prandial hyperglycemia coupled with reduced rates of hypoglycemia. With current prandial insulin options, data show 5.7 days per month of prandial
insulin omission/non-adherence. Studies of patient adherence reveal a need for insulin regimens that are less restrictive and burdensome, and with lower risk of hypoglycemia.

Although basal insulin analogs and neutral protamine Hagedorn (NPH) insulin have been shown to be equally effective in reducing A1C levels in clinical trials, basal insulin analogs are associated with significantly less hypoglycemia. AACE recommendations suggest starting with a basal insulin analog, if possible. Newer longer-acting basal insulin analogs provide some additional benefits compared to the basal insulin analogs that have been available (ie, detemir U100, glargine U100); compares some of the properties of the newest basal insulin preparations with those of the older basal insulin analogs and NPH.

Case Vignette #1, continued

The merits of insulin for replacing a hormone deficiency and reducing glucose “toxicity” with a single daily injection is explained to George. Based on the AACE algorithm, he is prescribed a starting dose of 0.2–0.3 U/kg of a basal insulin analog because his A1C is >8% (Figure 2). The nurse in the office teaches him how to do the subcutaneous injections and has him inject the first dose in the office so that he can (1) demonstrate proper injection technique and (2) confirm that the injection is associated with minimal if any discomfort. George is asked to perform fasting SMBG daily and based on these values titrate his insulin dose every 3 days aiming for an FPG value of < 110 mg/dL. (See the AACE algorithm for self-titration against FBG and goals, Figure 2). Metformin is continued. Glimepiride is reduced to 2 mg daily to lower the risk of hypoglycemia with the concomitant use of insulin. Alternatively it could be discontinued. The nurse provides counseling about hypoglycemia, nutrition, and the possibility of insulin-related weight gain. He has a follow-up appointment in 3 months. In the interim, he will be seen by a CDE.

Case Vignette #2

Caroline is a 62-year-old female who has had T2DM for 8 years. She is currently taking metformin 1000 mg BID, sitagliptin 100 mg QD, and NPH insulin 50 U at bedtime. Her A1C level has been trending up from 6.8% to a current level of 7.3%. She has also noted some hypoglycemic episodes that have awakened her during the night (she has documented these in her blood glucose log; levels ranged from 50 to 65 mg/dL) as well as some pre-breakfast hyperglycemia (fasting) (200–210 mg/dL). She sometimes takes less than the prescribed dose of the NPH insulin because of concern about hypoglycemia.

Caroline is experiencing some nocturnal hypoglycemia. Nocturnal hypoglycemia, even if non-severe, can adversely affect patient’s quality of life, feeling and function, and result in work loss and reduced productivity. Adverse effects may be noted both at the time the hypoglycemia occurs and during recovery, which may take an extended period of time.

A change to this patient’s therapeutic regimen is clearly indicated. She is taking NPH insulin, which has several less-than-desirable properties for an “ideal” insulin. NPH had been the predominant basal insulin in clinical use, until the advent of basal insulin analogs. NPH requires resuspension before injection. The time-action profile (peak activity 4–9 hours after subcutaneous administration) increases the risk for between-meal and especially nocturnal hypoglycemia. Therefore, it acts more as an intermediate-acting insulin, without the flat pharmacodynamic profile that is desired to provide a steady level of insulin action over a 24-hour period. NPH has a duration of action of usually less than 24 hours and may need to be administered twice daily. It often has significant intra- and inter-individual variability.

The basal insulin analogs (such as insulin glargine U100 and insulin detemir U100) have a longer duration of action, a flatter time-action profile with less of a peak, less variability, and less hypoglycemia than NPH insulin. Meta-analyses have provided evidence that existing basal insulin analogs are associated with less nocturnal hypoglycemia than NPH insulin. These would be options for Caroline, as would some newer basal insulin analogs. For example, ultra-long-
acting insulin formulations are being introduced with the potential for more durable antihyperglycemic efficacy of 24 hours or longer, less glycemic variability, and less hypoglycemia than traditional basal insulin analogs and human NPH insulin.21,64

It is important for physicians to understand the newer insulin options and their pharmacokinetics to be able to appropriately select the best insulin for a particular patient. Table 2 compares some of the properties of the newest basal insulin preparations with those of the older basal insulin analogs and NPH;55,65-68 however, some of the data reported are from patients with T1DM rather than T2DM.

Table 2. Select PK/PD parameters of recently approved insulin component agents and their existing comparator counterparts (long-acting)55,65-68

<table>
<thead>
<tr>
<th>Pk/PD Parameter</th>
<th>Degludec U100, U200</th>
<th>Glargine U300</th>
<th>Glargine U100</th>
<th>Detemir U100</th>
<th>NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>30-90 minutes</td>
<td>Develops over 6 hours</td>
<td>2-4 hours</td>
<td>0.8-2 hours</td>
<td>2-4 hours</td>
</tr>
<tr>
<td>Duration of action</td>
<td>42 hours</td>
<td>&gt;30 hours</td>
<td>Up to 24 hours</td>
<td>Up to 24 hours</td>
<td>10-16 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>25 hours</td>
<td>18-19 hours</td>
<td>~12 hours</td>
<td>5-7 hours</td>
<td>6.6 hours</td>
</tr>
<tr>
<td>Time to steady state</td>
<td>3-4 days</td>
<td>3-4 days</td>
<td>2-3 days</td>
<td>24 hours</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Insulin Degludec U200 and U100 vs Insulin Glargine U100

Insulin degludec is another of the new ultra-long-acting basal insulin analogs. It comes in 2 dose formulations: U200 (pen device: maximum dose of 160 units per injection [in 2-unit increments]) and U100 (pen device: maximum dose of 80 units per injection [in 1-unit increments]). It is also approved as part of a new premixed product with insulin aspart (described below) and combination product with a GLP-1 RA (liraglutide). Insulin degludec forms soluble and stable dihexamer with the help of phenol and zinc.24 Immediately following subcutaneous injection of insulin degludec, phenol from the vehicle diffuses rapidly. Insulin degludec hexamers then link via single side-chain contacts, assembling long, multihexamer chains. Zinc diffuses slowly, causing individual hexamers to disassemble and release monomers, which are absorbed from the depot into circulation. The result is protracted activity, caused primarily by the slow release from these long hexamer chains.27 This helps degludec to achieve a steady-state concentrations with a half-life of more than 25 hours and duration of action of up to 42 hours.27 As shown in patients with T1DM, insulin degludec has one-fourth the pharmacodynamic variability of glargine U100.28

The BEGIN clinical trial program for degludec is reportedly the largest insulin development clinical trial program on record.29 It was designed to evaluate this new once-daily basal insulin across a broad spectrum of patients and dosing regimens. The patient populations included insulin-naïve T2DM, insulin-treated T2DM and T1DM, patients, and treatments included basal-bolus therapy, basal plus oral therapy, basal versus oral therapy, and a study assessing use of degludec in an alternating-time dosing regimen.28

A pre-planned meta-analysis of all of the phase 3 T2DM trials confirmed that similar improvements in A1C levels are achievable with insulin degludec when compared with insulin glargine U100.40 Among insulin-naïve T2DM subjects, significantly lower rates of overall confirmed and nocturnal confirmed hypoglycemia were reported with insulin degludec relative to insulin glargine U100 (estimated rate ratio [RR]:0.8 and RR:0.64). In the overall T2DM population, significantly lower rates of overall confirmed and nocturnal confirmed episodes were reported with insulin degludec relative to insulin glargine U100 (RR:0.83 and
Question 4: When do you stop titrating basal insulin?

Case Vignette #3

Gena is a 47-year-old female with a 9-year history of T2DM. She is a busy accountant, especially during tax season. Initially her A1C levels were under control (<6.5%) on metformin 1500 mg daily, glimepiride 4 mg QD, and U100 insulin glargine, 55 U once daily at bedtime, with an average FPG of 120 mg/dL. However, at her last two 3-month checkups, her A1C level had increased to 7.3%. She had initially attributed the increase to some transient poor adherence to lifestyle – medical nutrition therapy and physical activity had suffered during the busy times at the office. However, tax season is now over, and there have been no improvements in her glycemic control. Her current weight is 212 lb and her height is 5’10”, resulting in a calculated BMI of 30.4 kg/m².

Given Gena’s findings, would you increase her dose of insulin glargine? At what unit per kg body weight of basal insulin should you stop up-titrating basal insulin and instead consider adding an agent to address prandial control? (Her current dose of insulin glargine is approximately 0.57 U/kg.)

Both fasting hyperglycemia and increments of glucose after meals contribute to overall glycemic exposure. In general, once FPG levels are well controlled, the contribution of postprandial glucose (PPG) excursions needs to be addressed in patients with A1C levels close to, but not at, goal. Postprandial hyperglycemia accounts for the majority of overall glycemic exposure above normal levels in patients in the lowest range of A1C (<7.3%) in the landmark trial by Monnier. These results were confirmed in a study by Riddle and colleagues in T2DM patients treated with basal insulin.

Continuing to increase basal insulin doses increases the likelihood of hypoglycemia with little chance of successfully lowering total A1C. Gena’s FPG levels are close to target, so increasing the basal insulin dose, which targets fasting hyperglycemia, would be unlikely to achieve target A1C levels without causing hypoglycemia. Data from 15 randomized, treat-to-target trials in patients on insulin glargine, with or without oral antidiabetic drugs (OADs) for 24 or more weeks have shown that continued upward titration of basal insulin glargine to doses greater than 0.5, 0.7, and even >1.0 U/kg did not result in further improvements in glycemic control. The data showed that one can obtain about a 0.5% decrease in A1C level for each 0.1-U/kg/day increment in insulin dose, up to a threshold of 0.5 U/kg. Beyond this dose, improvement in A1C level is often minimal, and there is increased risk for weight gain and hypoglycemia continues. ADA/EASD13,17 and AACE/ACE23 treatment recommendations suggest adding agents that target PPHG when basal insulin doses reach or exceed 0.5 U/kg. Other considerations for stopping titration of basal insulin are when A1C levels are not at goal despite achieving the target FPG with basal insulin; FPG is at target with basal insulin but PPG levels are persistently above goal; when further increases in basal insulin result in hypoglycemia; and when large glucose drops occur overnight or between meals.

Case Vignette #3, continued

Based on these data, you would not continue to increase the dose of insulin glargine. After checking postmeal glucose levels, which were elevated at 180-200 mg/dL, consideration was given to reducing her basal insulin dose and adding an agent that could address postprandial glucose levels.
Question 5: What are some of the new options for intensifying therapy when basal insulin alone has not achieved target glycemia?

Case Vignette #4

Javier is an uncircumcised 64-year-old male with a 9-year history of T2DM. He is 5’10” tall and weighs 190 lb, with a BMI of 28 kg/m². His current diabetes medications include metformin 2000 mg daily, sitagliptin 100 mg/daily, and insulin glargine U100, 55 U at bedtime. His A1C level initially declined but now has increased to 7.5%; FPG averages about 120 mg/dL; PPG levels are elevated, especially after his evening meal (220 mg/dL). His past medical history is significant for recurrent urinary tract infections (balanitis [swelling of the foreskin]). Otherwise, he is a relatively healthy, overweight individual, exercising 4-5 times a week, and following a diet recommended by his CDE who is a registered dietitian. What therapeutic strategies will you discuss with Javier?

His A1C remains elevated despite having achieved a near target FPG with insulin glargine treatment. He therefore needs treatment addressing elevated PPG levels to achieve his A1C goal. Several treatments and strategies are available for internal medicine physicians when intensifying therapy for patients on optimized basal insulin therapy. AACE treatment recommendations suggest that if patients are not at goal on basal insulin, clinicians should consider adding a GLP-1 RA, a dipeptidyl peptidase-4 (DPP-4) inhibitor, or a sodium glucose cotransporter-2 (SGLT-2) inhibitor before prandial insulin in most patients (Figure 3). All of these agents improve glycemic control when combined with basal insulin. They also have a lower risk for weight gain and/or hypoglycemia and so may be preferred to sulfonylureas or thiazolidinediones for combination with insulin.11

Case Vignette #4, continued

Javier is already on a DPP-4 inhibitor. He is probably not a good candidate for a SGLT-2 inhibitor, given his history of urinary tract infections; and genital mycotic infections are an adverse effect reported more commonly in those who have had them before and in uncircumcised men on SGLT-2 inhibitors.55

Figure 3. AACE Algorithm: options for intensifying insulin when glycemic control not at goal 2

Add GLP-1 RA

OR

Add SGLT-2 inhibitor

OR

Add Prandial Insulin
• Basal plus one (adding to largest meal), Basal plus two, Basal plus 3
OR
• Basal bolus


The 2017 ADA/EASD treatment algorithm recommends adding 1 rapid-acting insulin injection before largest meal (basal plus), slowly moving the patient to a basal-bolus regimen, or switching the patient to an alternative insulin regimen.13 These types of regimens are frequently used, but there is still widespread reluctance to intensify insulin treatment due to fear of weight gain and hypoglycemia.93 Intensive insulin treatment can be limited by factors such as the number of injections, mealtime restrictions, complex titration algorithms, and patient adherence.48

Degludec 70 units/Insulin and Aspart 30 units per mL (100 units/mL for the Combination)

There is a new premixed insulin approved for use in the United States and currently available in Europe.94 Insulin degludec with insulin aspart offers physicians and patients with T2DM a simpler regimen than other basal-bolus or premix-based insulin regimens. This combination offers stable daytime basal coverage, a lower rate of hypoglycemia, and some flexibility in injection timing compared with other premixed insulins. The onset of action for the insulin aspart component is 14 minutes; the peak plasma time for aspart is 72 minutes, and that of insulin degludec is 9 hours. Steady state for insulin degludec occurs in 3 to 4 days. The half-life of insulin degludec is approximately 25 hours.147

The initial dose of premixed insulin degludec/aspart is 10 units subcutaneously once a day. When switching from other once- or twice-daily premixed insulin, clinicians should start with the same unit dose and injection schedule as the current original premixed preparation. Short- or rapid-acting insulin may be used for meals not covered by this insulin mix. If the patient is switching or intensifying from once- or twice-daily basal insulin, they should be started at the same unit dose as the basal insulin once a day with the main meal of the day. It is important to monitor blood glucose levels after starting therapy, especially for patients switching from once-daily basal insulin to this insulin mix, due to the rapid-acting insulin component.97 Weight gain can occur with insulin therapy, including the degludec/aspart premixed combination.

Use of GLP-1 RAs in Combination with Basal Insulin and Coformulations Containing Basal Insulin and a GLP-1 RA in the Same Preparation

GLP-1 RAs provide supraphysiologic GLP-1 receptor activation compared with DPP-4 inhibition.99 This results in enhancement of glucose-dependent insulin secretion, a glucose–dependent decrease in excessive glucagon secretion, slowing of gastric emptying, and enhanced satiety, which can be associated with weight reduction.90 GLP-1 RAs by themselves have a low risk for hypoglycemia or weight gain. The main adverse effect associated with their use is are gastrointestinal in nature (nausea, vomiting, and diarrhea).100,101

Several GLP-1 RAs have been used successfully in combination with basal insulin.12 In particular, the shorter-acting GLP-1 RAs that have effects on postprandial hyperglycemia are well suited for this purpose. Many studies reported weight loss and a reduction in insulin use when a GLP-1 RA was added to existing insulin therapy. The most common finding across all types of studies
was that combination therapy improved glycemic control without weight gain or an increased risk of hypoglycemia.\textsuperscript{102} Other GLP-1 RAs that have approval for use with basal insulin include once-weekly albiglutide.

The rationale for the use of the 2 classes of injectable agents together was defined succinctly by Balena and colleagues in 2013.\textsuperscript{103-108} Their line of reasoning was as follows:

- T2DM is a progressive, multifactorial disease.
- However, the more intensively T2DM is treated, the greater is the risk of hypoglycemia and weight gain.
- Achieving treatment intensification while moderating these risks poses a challenge to patient management.
- Basal insulin analogs provide control of FPG; however, their utility in the control of PPHG is limited.
- GLP-1 RAs stimulate glucose-dependent insulin secretion, suppress glucagon secretion, delay gastric emptying, and decrease appetite.
- Use of GLP-1 RAs in combination with basal insulin offers an alternative approach to insulin therapy intensification.
- Prospective interventional trials demonstrate that GLP-1 RAs added to basal insulin decrease PPHG, lower A1C levels, decrease weight, and lower basal insulin requirements without increasing the risk of major hypoglycemic events.

Today, this combination therapy requires more than 1 injection, as each drug class has to be given separately. However, 2 products are in development as fixed-dose combinations that include both a basal insulin and one of the relatively shorter-acting GLP-1 RAs. A number of clinical trials have been published for the fixed-dose combination of insulin degludec/liraglutide,\textsuperscript{100,101,107-112} and for the fixed-dose combination of insulin glargine/lixisenatide.\textsuperscript{113-115} As these fixed-dose combinations become available, more barriers to insulin therapy will be reduced and more opportunities to successfully lower A1C levels with low risks of weight gain and hypoglycemia will be available. In addition, positive cardiovascular outcomes data for liraglutide were reported at last year’s ADA meeting, supporting a macrovascular benefit of this particular GLP-1 RA.\textsuperscript{116}

**Summary and Conclusion**

The majority of patients with T2DM are likely to eventually require insulin to obtain or preserve satisfactory glucose control and to achieve an A1C level <7%. Insulin should be considered for T2DM when non-insulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has very elevated blood glucose levels and is symptomatic. Attention should be paid to both fasting hyperglycemia and PPHG in order to achieve optimal glycemic control. Using medications that are associated with fewer adverse events may improve adherence. New and emerging insulins and insulin combination products are available that can be employed by internal medicine specialists to improve glycemic control.
References


75. sanofi-aventis U.S. L. Toujeo® prescribing information. 2015.


Posttest Questions

New and Emerging Injectable Therapies for Type 2 Diabetes for the Internal Medicine Physician: Experts Address Common Questions

1. Anna is a 65-year-old female with a 5-year history of T2DM treated with dual oral therapy and who had an A1C level of 6.8% until 12 months ago. After retiring from her job as a tour guide, she has settled into a more sedentary lifestyle and has taken several cruises as a benefit of her former job. Anna has been enjoying the large buffets and gained weight during the trips. Recently she has also contracted an upper respiratory tract infection. She presents with complaints of polyuria, nocturia, and polyphagia. A random blood glucose level is 320 mg/dL. Which of the following is a reasonable indication to start insulin therapy in this patient?
   A. Acute hyperglycemia
   B. Long-duration T2DM
   C. When non-insulin therapy is no longer achieving goals
   D. Weight gain

2. According to the ADA, based on the limited history you have on Anna, what are the fasting plasma glucose (FPG) and postprandial glucose (PPG) goals would you discuss with her, knowing her relatively short history of T2DM and assuming a relatively healthy status?
   A. FPG: 70-120 mg/dL, peak PPG: <150 mg/dL
   B. FPG: 80-130 mg/dL, peak PPG: <180 mg/dL
   C. FPG: 100-120 mg/dL, peak PPG: <200 mg/dL
   D. FPG: 140 mg/dL, peak PPG: <220 mg/dL

3. According to the ADA, above which dose should you consider stopping increases in basal insulin doses and consider adding an agent to address PPHG?
   A. >0.3 U/kg/day
   B. >0.5 U/kg/day
   C. >0.7 U/kg/day
   D. >1.0 U/kg/day

4. Which of the following is NOT a reason to stop increasing basal insulin doses past the maximum “optimal” U/kg/day of basal insulin identified in Q3?
   A. No greater efficacy in A1C lowering past recommended maximum basal insulin U/kg/day
   B. Increased risk of hypoglycemia past the recommended maximum basal insulin U/kg/day
   C. Increased risk of injection site reactions past the recommended maximum basal insulin U/kg/day
   D. Increased weight gain past the recommended maximum basal insulin U/kg/day

5. Which of the following is NOT an advantage of newer longer-acting basal insulins that is supported by clinical trial evidence?
   A. Insulin degludec can be administered at any time of day, once daily (as long as 8 hours have elapsed between doses).
   B. Insulin glargine U300 can be administered at a lower dose in the same patient who has used insulin glargine U100 previously.
   C. Both insulin degludec and insulin glargine U300 have lower risks of nocturnal hypoglycemia than insulin glargine U100.
   D. The more concentrated insulins require lower volumes of insulin to be injected and come in prefilled pens that do not require patients or physicians to calculate dose conversions.

6. Which of the following is NOT part of the 2016 AACE/ACE recommendations for adding prandial control once basal insulin has been intensified as much as possible?
   A. Add a dose of prandial insulin before largest meal
   B. Add an oral SGLT-2 inhibitor
   C. Add a GLP-1 RA
   D. Discontinue basal insulin and start a premixed insulin twice daily

7. Which of the following is NOT a common barrier to the use of intensified insulin therapy that may be addressed by emerging fixed-dose combination products (e.g., a basal insulin with a GLP-1 receptor agonist)?
   A. Fear of hypoglycemia
   B. Lack of injections
   C. Number of injections
   D. Weight gain

8. When a GLP-1 RA is used in combination with insulin therapy, the most common findings in clinical trials are (compared to increasing insulin doses alone)
   A. Equivalent glycemic control without weight gain or an increased risk of hypoglycemia
   B. Improved glycemic control without an increased risk of hypoglycemia, but with an increased risk of pancreatitis
   C. Improved glycemic control without weight gain but with an increase in daytime hypoglycemia
   D. Improved glycemic control without weight gain or an increased risk of hypoglycemia

9. Which of the following is NOT a common barrier to the use of intensified insulin therapy that can be addressed by the first approved premixed insulin product in more than a decade?
   A. Concerns regarding regimen flexibility
   B. Fear of hypoglycemia
   C. Number of injections
   D. Weight gain

10. Which of the following is NOT a correct statement about insulin therapy in the modern approach to T2DM treatment?
    A. Insulin continues to be a mainstay of therapy, and most patients will require its use at some point in their lives.
    B. Patient barriers to the use of insulin can be addressed through education, communication, and the selection of new and emerging insulin analogs.
    C. There is a rationale for the use of 2 injectable classes of antidiabetic agents in the treatment of T2DM.
    D. The role of prandial insulin continues to remain important because no other non-insulin therapies can adequately address postprandial hyperglycemia.
New and Emerging Injectable Therapies for Type 2 Diabetes for the Internal Medicine Physician: Experts Address Common Questions

Instructions for Posttest and Evaluation

Two ways to claim credit:

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2) Fax your post-test answers and evaluation (BOTH PAGES) to 609-921-6428. Your certificate will be sent to you within 4 weeks.

Name ___________________________________________________________________________________________________________

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Time spent in the activity/Credits claimed: ________________

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POSTTEST (Please circle the best answer for each question. A score of ≥ 70% is required to receive credit)

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<th>A</th>
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**EVALUATION FORM**

(* = required question)

**Profession***
- [ ] Physician
- [ ] Advanced Practice Nurse
- [ ] Nurse
- [ ] Physician Assistant
- [ ] Pharmacist
- [ ] Other please specify _____________________________

**Specialty***
- [ ] Internal Medicine
- [ ] Endocrinology
- [ ] Family Medicine
- [ ] Other please specify __________________________________________________

**Approximately how many patients do you see per week who may be impacted by this education?***
- [ ] 0 / I do not see patients
- [ ] 1-10
- [ ] 11-20
- [ ] 31-40
- [ ] 41-50
- [ ] >50

**Number of years in practice***
- [ ] <5
- [ ] 6-10
- [ ] 11-15
- [ ] 16-20
- [ ] 21-25
- [ ] >25

**This activity improved my: (check all that apply)***
- [ ] Knowledge
- [ ] Competence/Skills
- [ ] Performance
- [ ] Patient Outcomes
- [ ] None of the above

Please list one new concept you learned in this activity.  ____________________________________________________________________________________

**Please indicate your agreement with the following statements about this activity**

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<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neutral</th>
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<td>The content covered was useful and relevant to my practice.*</td>
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<td>The information learned during this activity will help improve my skills or judgment within the next six months.*</td>
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<td>I am better able to: Describe indications for starting basal insulin therapy in patients with type 2 diabetes mellitus*</td>
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<td>I am better able to: Use appropriate basal insulin in a physiologic manner and titrate therapy to achieve fasting plasma glucose goals*</td>
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<td>I am better able to: Acknowledge and address patient barriers to insulin therapy by explaining how new therapies have been designed to mitigate barriers*</td>
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<td>I am better able to: Intensify therapy in a patient-specific manner using new and emerging options, whether by premixed insulin or other prandial insulin or injectable therapies*</td>
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<td>I would recommend this activity to others.*</td>
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**Comments about the content/learning materials.**

Based on what you learned in this activity, what will you do differently in the care of your patients? (check all that apply)*
- [ ] Implement new information or skill in my practice
- [ ] Create/revise protocols, policies, and/or procedures
- [ ] Seek additional information
- [ ] Activity validated current practice
- [ ] Do nothing differently—The content was not convincing
- [ ] Do nothing differently—System barriers prevent me from changing my practice
- [ ] Not applicable. I have no patient contact.

Please list one change you anticipate making in your practice (if none, please write “N/A”).  _______________________________________________________________

What barrier(s) outside of your control impact your ability to make the practice change(s) you indicated above? (check all that apply)*
- [ ] Institutional
- [ ] Lack of practice guidelines
- [ ] Lack of patient compliance/adherence
- [ ] Patient lack of knowledge regarding disease/treatment
- [ ] Other please specify __________________________________________________
- [ ] Insurance/Financial
- [ ] Time
- [ ] Adverse side-effects of treatment
- [ ] Challenges in communication/collaboration among members of the care team
- [ ] No barriers

What information would you like to see in future activities that may help you address those barriers?  _______________________________________________________________

**Suggestions to improve this activity?**

Thank you for participating. As an added bonus, we will inform you of upcoming opportunities for future CME-certified activities.

If you do not wish to be notified of future CME activities, check here to opt out. [ ]