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Treating patients with type 2 diabetes

What is after lifestyle management and metformin?
A focus on the GLP-1 receptor agonists



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Dr Peterson has disclosed that he has served or currently serves on the advisory boards and speakers bureaus for Amylin Pharmaceuticals, Inc., Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Novartis Corporation, Novo Nordisk Inc., Pfizer Inc, and sanofi-aventis. He currently receives research funding from Eli Lilly and Company, Johnson & Johnson, GlaxoSmithKline, Merck & Co., Inc., Novo Nordisk Inc., and sanofi-aventis; and has common stock ownership in Amylin Pharmaceuticals, Inc., and Novo Nordisk Inc.

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LEARNING OBJECTIVES

After reading the supplement, clinicians should be able to:

- List the reasons clinicians have not aggressively applied the knowledge of the benefits of tight glycemic control into improved performance in clinical practice
- Interpret the physiological and clinical data supporting the role of the small intestine in the control of glucose homeostasis
- Explain the pharmacologic basis for why current therapies are limited by their inability to control hyperglycemia over the long term
- Develop practice patterns that will encourage intensified treatment with the most appropriate medications, allowing patients to reach glycemic goals
- Describe patient case scenarios in which incretin-based therapies may help meet the unmet needs of patients with diabetes

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INTRODUCTION

Treating patients with type 2 diabetes: What is after lifestyle management and metformin? A focus on the glucagon-like peptide-1 receptor agonists

ALTHOUGH THE PREVALENCE of type 2 diabetes mellitus (T2DM) in the United States has increased over the past decade to approximately 24 million¹—an increase that is expected to continue—there is reason for optimism in addressing the challenges presented by this debilitating and costly disease. First, the percentage of patients achieving good glycemic control, defined as a glycosylated hemoglobin (A1C) level <7.0%, has actually increased: As reported in the National Health and Nutrition Examination Survey (NHANES), it has risen from 38.1% in 1999-2000 to 55.0% in 2001-2002, 57.8% in 2003-2004, and 59.1% in 2006.² Although this trend is encouraging, the care for patients with T2DM remains suboptimal. A second reason for optimism is that the array of medications available to manage patients with T2DM continues to grow and offers many important advances over the older medications. Some of the newer medications target pathophysiologic mechanisms of T2DM that have not previously been addressed. For example, medications such as the glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors act on the incretin system, which is integrally involved in glucose homeostasis. In addition to lowering blood glucose levels, incretin-based therapies modestly improve blood pressure³⁻⁵ and lipid levels.^{3,4,6} These therapies also offer benefits with regard to weight as well as a low incidence of hypoglycemia.⁷⁻⁹ Unlike other agents, incretin-based therapies are glucose dependent and stimulate insulin secretion only in the presence of elevated levels of blood glucose. Weight gain and hypoglycemia associated with many of the older antihyperglycemic agents are major barriers to treatment adherence; however, these side effects have not been associated with incretin therapy, suggesting important treatment benefits.

Combine lifestyle management and metformin

Initiating treatment with the combination of lifestyle management and metformin at the time of diagnosis of T2DM, unless contraindicated, is a major recommendation in the 2009 consensus algorithm developed by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).¹⁰ This approach is recommended because of the benefits of lifestyle management on blood glucose, blood pressure, lipid levels, and weight, and the benefits of metformin on blood glucose levels, as well as absence of weight gain or hypoglycemia, a high level of patient acceptance, and relatively low cost.¹⁰ Although metformin generally has a low level of side effects, some patients do not initially tolerate the gastrointestinal effects well. To improve patient adherence to metformin, it is generally recommended that patients start with a lower dosage and advance as tolerated. In addition, metformin should be used only in patients with normal renal function.

Which medications? It depends on the patient

Although the combination of lifestyle management and metformin is initially effective in reducing blood glucose levels, the progressive nature of T2DM often requires that other medications be added over time. The question is, which medications? The answer, of course, must be individualized to the patient.

Recognizing the difficulty in managing patients with T2DM, the ADA/EASD developed a simplified algorithm “to help guide healthcare providers in choosing the most appropriate interventions for their [nonpregnant adult] patients with type 2 diabetes.”¹⁰ This consensus algorithm integrates the results of recent clinical trials, product labeling changes, and newly approved medications with the clinical experience of the panel. Because the panel considered all antihyperglycemic drugs currently available, the consensus algorithm compares the full array of treatment options, thereby giving clinicians the greatest opportunity to implement and modify treatment to meet the needs of each patient over the course of the disease.

To be sure, the treatment of patients with T2DM is challenging and many barriers remain. Managing the spectrum of diseases associated with T2DM, such as cardiovascular disease, is another crucial part of a comprehensive treatment plan. In addition, the goal of attaining acceptable glycemic control must be balanced with patient safety. Furthermore, patients’ needs, concerns, capabilities, and support systems, as well as the benefits offered by their health plans, are important factors in selecting and modifying treatment.

As a continuum of education for the primary care physician, this supplement builds on the basic and clinical information presented in *The Journal of Family*

Practice September 2008 supplement, “The Role of Incretin Therapy for Type 2 Diabetes in Family Medicine” (www.jfponline.com/supplements.asp?id=6690). The present supplement addresses the management of patients who do not achieve glycemic control with lifestyle management and metformin.

Primary care physicians encounter the challenge of managing a progressive disease that requires modification and intensification of therapy¹⁰ for the majority of their patients with T2DM. The first article by Dr Peterson provides a checklist of issues to consider in selecting the optimal add-on therapy for each patient. Dr McGill then discusses the advantages and limitations of the tier 1 (insulin, sulfonylurea) and tier 2 (thiazolidinediones, GLP-1 receptor agonists) treatment options considered the preferred therapies by the ADA/EASD for managing patients who do not achieve glycemic control with lifestyle management and metformin. In the third article, Dr Shomali illustrates these concepts using a patient-centered approach by discussing the accumulating clinical efficacy and safety evidence with the GLP-1 receptor agonists in combination with metformin and other antihyperglycemic agents. In the fourth article, Dr Haines continues the case study, addressing the patient education issues specific to the use of GLP-1 receptor agonists. The third and fourth articles focus on the GLP-1 receptor agonists, because they are 1 of the 4 preferred treatments recommended as add-on therapy by the ADA/EASD panel; of these preferred treatments, they are also the least familiar to family physicians. Treatment approaches for optimizing glycemic control in consideration of patient characteristics are also suggested. Not discussed are the alpha-glucosidase inhibitors, the glinides, or pramlintide, which were not included in the 2 tiers of preferred therapies by the ADA/EASD panel. ■

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A checklist approach to selecting the optimal treatment regimen for a patient with type 2 diabetes

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THE MANAGEMENT OF PATIENTS with type 2 diabetes mellitus (T2DM) requires thoughtful consideration of the available treatment options, which must then be tailored to the individual patient in order to achieve and maintain therapeutic goals. This process, which begins at the time of diagnosis and continues for the remainder of the patient's life, can be aided through the use of a treatment checklist, along with the 2009 treatment consensus algorithm jointly developed by the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD).¹

A checklist of attributes or key features of the ideal treatment regimen, along with goals for each patient with T2DM who requires add-on therapy to lifestyle management and metformin, must be developed with a clear objective and monitoring plan in mind. Although the primary focus of this checklist is antihyperglycemic medications and glycemic control, treatment goals for blood pressure and lipids should also be established and treated to goals.

According to the ADA/EASD consensus panel,¹ an overarching treatment principle is to quickly attain glycemic control without causing hypoglycemia or weight gain, and then maintain glycemic control over the patient's life span. Implicit in this treat-to-success approach is the need to modify treatment based on glycemic measures and to match disease progression over the continuum of diabetes care while minimizing potential harm and individualizing treatment. This approach most often requires combination therapy. Also included is the need to manage diabetes in the context of the whole patient and minimize the risk of development or progression of comorbidities such as cardiovascular disease, retinopathy, neuropathy, and nephropathy. This is a challenging set of objectives, but with careful consideration and an individualized approach, it is increasingly possible to achieve these objectives with the greater array of treatment options available.

In this article, I review the treatment checklist, discussing the factors to consider in selecting the ideal diabetes treatment regimen—either monotherapy or combination therapy—for a specific theoretical patient over the continuum of diabetes care. We then apply this checklist in the next 2 articles in this supplement. Undoubtedly, you already consider many of the factors in the checklist as you manage your patients with T2DM, making it a useful means to confirm and enhance your practice patterns. Because the checklist embraces a team approach to patient management, it also provides an opportunity to consider the potential roles for office staff and other health care professionals.

The treatment checklist

Many factors must be considered in developing a treatment plan for patients with T2DM (TABLE). In addition to being useful at the time of diagnosis, the

TABLE

Factors to consider in selecting an antihyperglycemic treatment for a patient with type 2 diabetes

✓ Effective in lowering blood glucose Baseline glycosylated hemoglobin (A1C) Fasting plasma glucose Postprandial glucose
✓ Time to lower blood glucose
✓ Long-term ability to maintain glycemic control
✓ Effect on the pathogenesis of type 2 diabetes mellitus Insulin resistance Pancreatic β -cell dysfunction Altered glucagon secretion
✓ Extraglycemic effects Body weight Blood pressure Lipids Other
✓ Safety and tolerability Hypoglycemia Weight gain Other
✓ Ease of use Route of administration Simple dosing regimen Self-monitoring of blood glucose Likely adherence
✓ Cost Insurance and formulary coverage Copayments

treatment checklist can also be helpful when the treatment plan must be modified to ensure that it is optimally effective. Involving nursing staff, certified diabetes educators, and other health care professionals can be especially helpful in this process.

The following sections focus on the selection and use of antihyperglycemic treatment to manage hyperglycemia. Good nutrition and physical activity should be encouraged, along with monitoring of not only glycemic factors but also blood pressure and lipids, as well as any other risk factors or comorbid conditions. Although some antihyperglycemic agents may have extraglycemic benefits, many patients will be using other agents for comorbid conditions such as hypertension and dyslipidemia. These medications should also be adjusted when blood pressure or lipid goals are not being met.

✓ EFFECTIVE IN LOWERING BLOOD GLUCOSE

The ability of a treatment regimen to effectively lower blood glucose and sustain glycemic control is of major importance, as demonstrated in both the Diabetes

Control and Complications Trial² and the United Kingdom Prospective Diabetes Study (UKPDS),³ which found a strong, direct correlation between reductions in mean glycosylated hemoglobin (A1C) over time and reductions in the progression of retinopathy and nephropathy. These results provide compelling evidence of the need for treatment efficacy to reach an A1C <7% in most patients; however, these and other available data are insufficient to determine whether any particular treatment is superior to another regarding effects on chronic complications.¹

All agents approved by the US Food and Drug Administration as either monotherapy or combination therapy for the treatment of patients with T2DM reduce blood glucose levels, albeit to varying degrees. Insulin reduces blood glucose in a dose-dependent manner, limited only by hypoglycemia. Metformin, sulfonylureas, thiazolidinediones, glinides, and glucagon-like peptide-1 (GLP-1) receptor agonists significantly reduce blood glucose levels.⁴ Combination therapy using agents with complementary mechanisms of action is often needed to achieve glycemic targets [www.jfponline.com/supplements.asp?id=6690].

The efficacy of a treatment in lowering blood glucose is dependent on several factors, including the duration of T2DM as a consequence of declining pancreatic β -cell function, as well as baseline blood glucose and A1C levels. Because fasting plasma glucose (FPG) is a greater contributor to A1C when it is $\geq 8.4\%$, treatments that target FPG reduction may initially be preferred.⁵ However, as the A1C level drops to <8.4% with therapy, the use of treatments that also lower postprandial glucose (PPG) is essential for achieving the target A1C level of <7.0%.⁵ Additional factors include body weight, because of the greater likelihood of insulin resistance with increasing body weight, and previous therapy.

✓ TIME TO LOWER BLOOD GLUCOSE

Medications with a greater and more rapid ability to lower blood glucose are preferable when the A1C level is high or when symptoms of severe or persistent hyperglycemia are present.¹ When the A1C is >8.5%, initiating and carefully titrating basal insulin therapy may be necessary.¹ However, the addition of other glucose-lowering medications should also be considered after 2 to 3 months of treatment with inadequate response or whenever the A1C level is not being achieved.¹ However, the risk of hypoglycemia should be carefully considered, particularly when using aggressive therapy. Before initiating intense regimens, age and other factors should be considered and may be cause for consultation with an endocrinologist.

✓ LONG-TERM ABILITY TO MAINTAIN GLYCEMIC CONTROL

Because T2DM is a progressive disease associated with worsening hyperglycemia and the development of micro- and macrovascular complications, the use of medications that provide long-term glycemic control would be optimal. However, no single medication or combination of medications has been shown to maintain the A1C level at <7.0% over the course of the disease. Therefore, for the vast majority of patients with T2DM, treatment must be intensified or changed over the course of the disease based on blood glucose levels and symptoms. This can involve adding agents or replacing certain agents with those that have greater glucose-lowering efficacy. Because of the need to frequently modify treatment over time, it is essential that the patient take an active role in self-management.^{1,6,7}

✓ EFFECT ON THE PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

The effect of a treatment on one or more underlying pathogenic causes of T2DM is becoming an increasingly substantial consideration. In general, hepatic and peripheral insulin resistance and progressive insulin deficiency caused by β -cell failure are the hallmarks of T2DM. More recently, defects in the incretin response and altered glucagon secretion have also been identified.⁸

When adding a second agent to the initial treatment of lifestyle management and metformin, a medication with a mechanism of action that does not involve increasing hepatic insulin sensitivity, as with metformin, should be chosen. The reduction in the blood glucose level is usually greater when medications that act on different causes of T2DM are used together.¹ With the development of incretin-based therapies, it now appears possible to correct some of the underlying causes of T2DM that are not addressed by most conventional agents, such as β -cell dysfunction⁹⁻¹² and altered glucagon secretion.^{13,14} If confirmed in large clinical trials, the ability to address these pathogenic causes has significant implications for the treatment of patients with T2DM.

✓ EXTRAGLYCEMIC EFFECTS

Similarly, in selecting an antihyperglycemic agent, its effects on parameters and risk factors other than blood glucose level are important considerations. Because obesity is a major risk factor for T2DM, and its prevalence worldwide is increasing dramatically, the effect of treatment on body weight must be considered. This is a particular concern because many of the medications used to treat T2DM promote weight gain. Indeed, the actual and perceived weight

gain associated with the use of many antihyperglycemic medications, including insulin, can be a substantial barrier to treatment.¹⁵ Conversely, weight loss in patients with T2DM is associated with improved control of blood glucose, blood pressure, and blood lipids.¹⁶

T2DM carries substantial risk for cardiovascular disease, with numerous studies showing that treatment of T2DM lowers certain markers of cardiovascular risk.^{2,3,17} Using a variety of antihypertensive medications, the UKPDS demonstrated that for each 10 mm Hg decrease in systolic blood pressure, the average reduction in diabetes-related mortality was 15%, the reduction in microvascular complications was 13%, and the reduction in myocardial infarction was 11%.¹⁸ Although not appropriate as primary therapy for cardiovascular disease, it is a significant factor that diabetes treatments can act synergistically with other treatments to lower cardiovascular risk. For example, the ability of insulin, thiazolidinediones, and GLP-1 receptor agonists to improve the lipid profile may be especially valuable for patients with T2DM and hyperlipidemia. Most patients will be using antihypertensive and lipid-lowering agents to achieve blood pressure and lipid goals. The potential for drug-drug interactions should be checked when changing therapy.

✓ SAFETY AND TOLERABILITY

The safety and tolerability of medications can be substantial barriers to treatment. They are especially significant considerations in the care of patients with T2DM because of the generally silent nature of T2DM until late in the disease. *Safety*, or protection from severe or life-threatening harm, is a central treatment goal. Selection and modification of therapies should be based on concomitant medications and the patient's underlying comorbid conditions. Although safety and efficacy of medications are the primary focus of clinical trials, physicians are encouraged to monitor and report concerns if they arise during postmarketing use. The practice of monitoring how patients take their medications helps to minimize potential contraindications and drug interactions. *Tolerability* relates to the degree to which a patient is willing to accept the adverse effects of a drug. Adverse effects are a common reason cited by patients for not adhering to prescribed diabetes medications.¹⁹ Hypoglycemia is a common fear among patients with diabetes, especially those treated with insulin¹⁵ or long-acting sulfonylureas.^{20,21} Similarly, the potential for treatment-related weight gain can be a substantial barrier for these patients. Some drugs may be associated with transient nausea or other tolerance issues among patients.

✓ EASE OF USE

When selecting treatment options, ease of use is not often at the forefront but should be considered, given the polypharmacy often required by patients who are managing their T2DM and other conditions. Adding 1, 2, or more diabetes medications to what may already be a long list of medications for comorbid conditions may be overwhelming for the patient. The same can be said of lifestyle management, with recommended changes that often challenge lifelong dietary and exercise habits. In the latter case, the involvement of a skilled clinician, such as a diabetes educator, who is experienced in providing care to patients with T2DM, can be helpful in developing a plan that patients may be more likely to follow.

A simplified treatment option, provided that glycemic control is not compromised, improves adherence. Selecting medications that match the patient's lifestyle, are administered on the same schedule as concomitant medications, or involve a similar level of self-monitoring of blood glucose (SMBG) are possible approaches. Insulin is well recognized as a diabetes treatment with numerous barriers to its use.^{15,22} The perceived complexity associated with insulin, including the use of needles, multiple daily dosing, and the need to adjust the dose based on SMBG, can be mitigated in many ways. For example, while the patient is in your office, having him or her self-inject a saline solution using an insulin pen usually demonstrates the simplicity and lack of discomfort. The predictability of long- and short-acting analog insulin simplifies initiation of insulin therapy. Once-daily insulin dosing is widely accepted by physicians and patients because it is relatively simple to use and is associated with a low risk of hypoglycemia.

The same principle applies to SMBG. Although there is no consensus regarding the role and frequency of SMBG,²³ patients may be instructed to self-monitor their blood glucose level at the same time that they take other medications or with a recurring daily event. SMBG should be part of an

educational process to enhance the patient's understanding of diabetes and can be instrumental in empowering the patient to take an active role in self-management.

It is essential to discuss the complex issues that are priorities to the patient, such as difficulty opening the medication bottle or not wanting to take a medication at work. Based on this discussion, the most appropriate treatment regimen can be chosen. The key points to remember are (1) to keep the treatment as simple as possible to achieve the treatment goals, and (2) to frequently discuss with the patient any concerns or difficulties in using the treatment(s).

✓ COST

Given the current trend toward reduced health care benefits and increased copayments and other out-of-pocket expenses, the medication cost to a patient has never been a more prominent treatment consideration. This cost can vary widely based on insurance coverage, formulary availability, and copayments. Similarly, differences in the cost of a medication among pharmacies can be substantial. Consequently, the cost of medications should be discussed with the patient frequently, especially when a change to his or her health plan is being contemplated. In addition, office staff should be instructed to alert the physician when a patient does change his or her health plan so that concerns about medication costs or availability can be addressed and resolved quickly.

Summary

T2DM is a multifaceted disease that requires careful selection of treatment, which must be frequently modified over the continuum of care to attain successful long-term management. A checklist of factors to be considered can be helpful in individualizing treatment for optimal effectiveness based on each patient's needs, concerns, and capabilities. ■

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Selecting among ADA/EASD tier 1 and tier 2 treatment options

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Disclosure

Dr McGill has disclosed that she is on the advisory boards and speakers bureaus for Merck & Co., Inc., and Novo Nordisk Inc. and is on the speakers bureau for AstraZeneca.

USING THE CHECKLIST outlined in the previous article, along with the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) algorithm, let's begin to answer the question, "Which medication should be added when the combination of lifestyle management and metformin therapy no longer achieves the desired glycemic control?" First, in addition to continuing metformin, unless it is contraindicated or not tolerated, lifestyle management must be continued and reinforced at each visit. (See *"Practical applications of therapy with a glucagon-like peptide-1 receptor agonist"* on page S35.) Although the primary role of lifestyle management counseling can be referred to a dietitian or certified diabetes educator, ongoing reinforcement and encouragement by the physician is important for long-term patient adherence and treatment success. By simply prescribing and regularly following up on a lifestyle management plan, adherence can improve more than 5-fold.¹

Among the treatments available for patients with type 2 diabetes mellitus (T2DM) who do not achieve or maintain glycemic control with the combination of lifestyle management and metformin (ie, tier 1/step 1 therapy), 4 other classes of medications are considered preferred therapies by the ADA/EASD consensus panel.² These medications are divided into 2 groups: the tier 1/step 2 therapies, insulin and sulfonylureas, and the tier 2 therapies, the thiazolidinediones (TZDs) and the glucagon-like peptide-1 (GLP-1) receptor agonists. Among these therapies, sulfonylureas are the most cost-effective, whereas insulin is considered the most effective in achieving glycemic goals. However, even the newer formulations of sulfonylureas and insulin are associated with a substantial risk of hypoglycemia and weight gain. Tier 2 therapies are less well validated by clinical research than are tier 1 therapies. The TZDs and GLP-1 receptor agonists minimize the risk of hypoglycemia, and the TZDs cause weight gain, whereas the GLP-1 receptor agonists are associated with weight loss.

This article focuses on the tier 1/step 2 and tier 2 therapies for T2DM, as these are the preferred therapies recommended by the ADA/EASD panel and are, therefore, more likely to be widely used in the primary care management of patients with T2DM. Although the dipeptidyl peptidase-4 (DPP-4) inhibitors are considered by the ADA/EASD panel to be one of the "other" therapies and not a preferred therapy, the DPP-4 inhibitors have been included in this discussion because they also act on the incretin system.

Tier 1/step 2 medications

When metformin and lifestyle management no longer achieve the desired glycemic goals, the ADA/EASD consensus panel recommended adding either basal insulin or a sulfonylurea. If the combination of lifestyle management, metformin, and a sulfonylurea or basal insulin does not provide the desired glycemic control, the panel advised that insulin therapy should be started or intensified.²

TABLE

Comparison of selected antihyperglycemic agents

Agent/class	Insulin	Sulfonylurea	Thiazolidinedione	Glucagon-like peptide-1 receptor agonist	Dipeptidyl peptidase-4 inhibitor
ACTION					
↑ Insulin secretion		x		x	x
↓ Glucagon secretion	x	x	x	x	x
↑ Glucose uptake	x	x	x	x	x
↓ Food intake				x	
↓ Gastric emptying				x	
↑ β-cell function			x	x ^a	x ^a
GLUCOSE-LOWERING EFFECTS					
Fasting	x	x	x	x	x
Postprandial	x	x	x	x	x
Expected decrease in A1C (monotherapy)	1.5% - 3.5%	1.0% - 2.0%	0.5% - 1.4%	0.5% - 1.5%	0.5% - 0.8%
EXTRAGLYCEMIC EFFECTS					
Weight	↑	↑	↑	↓	↔
Blood pressure	↔	↔	↓	↓ (systolic)	↓ (systolic)
Lipids	Improve	↔	Improve (P)	Improve	Improve
Safety/tolerability	Hypoglycemia	Hypoglycemia	Fluid retention; CHF; fractures; risk of MI: ↑ (R), ↓ (P)	Nausea; diarrhea; low incidence of mild/moderate hypoglycemia; acute pancreatitis (E)	Low incidence of mild/moderate hypoglycemia; severe allergic and hypersensitivity reactions (S)
EASE OF USE					
Route	Injection	Oral	Oral	Injection	Oral
Dosing frequency	1 to 4/d	1 to 2/d	1 to 2/d	2/d (E), 1/d (L)	1/d
Comments	Rapidly effective; no dose limit; multiple daily dosing; SMBG needed; inexpensive	Rapidly effective; inexpensive	Monitor hepatic function	Not for use if CrCl <30 mL/min; lower SU dose when used in combination	Lower dose if CrCl <50 mL/min; lower SU dose when used in combination

A1C, glycosylated hemoglobin; CHF, congestive heart failure; CrCl, creatinine clearance; E, exenatide; L, liraglutide; MI, myocardial infarction; P, pioglitazone; R, rosiglitazone; S, sitagliptin; SMBG, self-monitoring of blood glucose; SU, sulfonylurea.

^aPreliminary data only.

Sources: Nathan DM, et al. *Diabetes Care*. 2009;32:193-203; National Institutes of Health. www.ndep.nih.gov/media/Drug_tables_supplement.pdf; accessed March 4, 2009; Rodbard HW, et al. *Endocr Pract*. 2007;13(suppl 1):3-68; Byetta [prescribing information]. San Diego, CA: Amylin Pharmaceuticals, Inc.; 2008; Januvia [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; 2007.

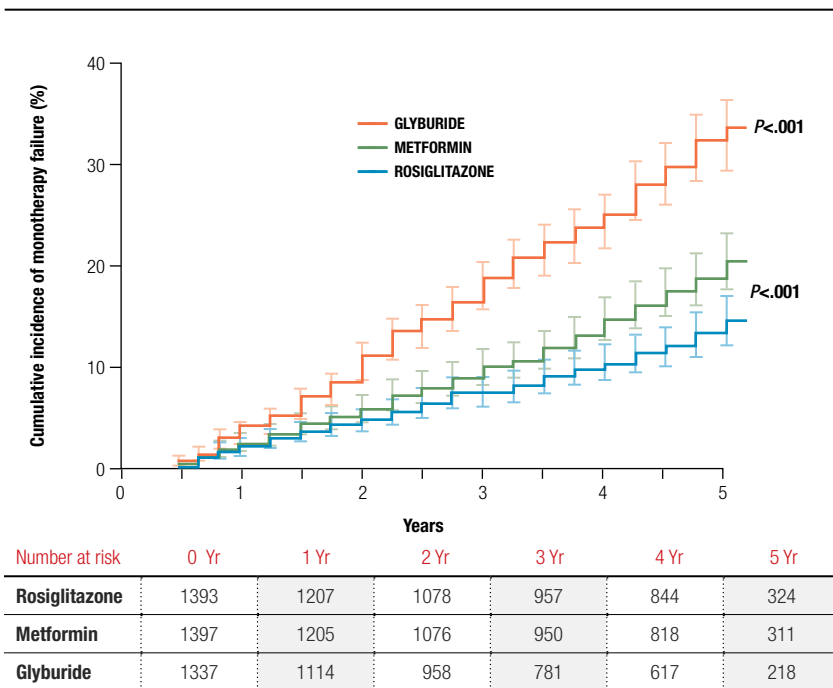
INSULIN

Insulin is the most effective treatment option available to lower blood glucose, and it does so in a dose-dependent manner (TABLE).²⁻⁶ Several generations of insulin formulations have been developed over the past 2 to 3 decades, with the insulin analogs being the most recent. Compared with other insulins— including human insulin—insulin analogs more closely mimic the basal or prandial patterns of endogenous insulin secretion in healthy people than do the older insulin formulations.⁷⁻¹⁰

The use of insulin therapy has generally been limited by concerns regarding weight gain and hypoglycemia.¹¹

However, weight gain and hypoglycemia generally appear to be less common with basal insulin analogs (eg, detemir and glargine) than with neutral protamine Hagedorn (NPH) insulin, while providing similar glycemic control.¹²⁻¹⁷ A significant difference in weight gain of 1.2 kg and 2.8 kg ($P<.001$) has been reported following 24 weeks of treatment with insulin detemir and NPH insulin, respectively, and 1.0 and 1.8 kg ($P=.017$) following 26 weeks of treatment.^{12,13} Similarly, a 24-week study of 756 overweight adults found that the addition of bedtime glargine or once-daily NPH to 1 or 2 oral antihyperglycemic agents resulted in similar glycemic

FIGURE
Kaplan-Meier estimates of the cumulative incidence of monotherapy failure at 5 years with glyburide, metformin, and rosiglitazone



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control. However, symptomatic hypoglycemia was significantly less common with glargine than with NPH (13.9 vs 17.7 events/patient-year respectively; $P<.02$). Weight gain of approximately 3 kg was observed in both groups.¹⁷

The increasingly important role of insulin in the treatment of advanced T2DM or in patients with poor control, as recommended by the ADA/EASD panel² and previously by the American Association of Clinical Endocrinologists,⁴ makes it essential that weight gain, hypoglycemia, and other concerns regarding the use of insulin be addressed through ongoing patient education, beginning at the time of diagnosis. After β -cell failure reaches a critical threshold, some form of insulin therapy will be required. Therefore, patients should be educated about this and not “threatened” with insulin therapy if glycemic control is not achieved with other regimens.

SULFONYLUREAS

The glucose-lowering efficacy of the sulfonylureas (eg, glimepiride, glipizide, chlorpropamide, and glyburide)

as monotherapy—a reduction in glycosylated hemoglobin (A1C) of about 1% to 2%—is similar to that of metformin (TABLE).^{2,4,18-20} Insight into the efficacy and safety of glyburide was recently shown in a randomized, double-blind trial over 4 years that included 4360 patients with newly diagnosed T2DM.¹⁹ Compared with metformin and rosiglitazone, treatment with glyburide resulted in a faster onset of glucose-lowering activity, with the maximum reduction in A1C achieved in approximately 4 months for glyburide vs 12 months for metformin and rosiglitazone. However, the durability of glycemic control achieved was shortest with glyburide. Glycemic control (A1C <7.0%) was maintained for an average of 33 months with glyburide compared with 45 months for metformin and 57 months for rosiglitazone. At 5 years, maximum-dose monotherapy failed in 34% of patients treated with glyburide compared with 21% for metformin and 15% for rosiglitazone (FIGURE). A lack

of improvement in insulin sensitivity over the 4 years and a more rapid decline in pancreatic β -cell function after 6 months likely contributed to the poorer durability of glycemic control with glyburide.

Weight gain is often greatest during the first year of sulfonylurea monotherapy, averaging about 2 kg, after which it stabilizes.^{2,19} Hypoglycemia, including severe hypoglycemia, is more common in patients being treated with glyburide than with metformin or rosiglitazone, with about 40% of patients taking glyburide self-reporting an episode of hypoglycemia.¹⁹ This is likely a result of the non-glucose-dependent action of sulfonylureas to stimulate insulin release at lower glucose concentrations than normal,²⁰ thereby increasing the risk of hypoglycemia. Hypoglycemia is less common with glimepiride and glipizide than with chlorpropamide and glyburide.^{21,22} In fact, glyburide is associated with an 83% greater risk of hypoglycemia than are other sulfonylureas.²² Consequently, glimepiride and glipizide are the preferred choices over chlorpropamide and glyburide.²

Tier 2 medications

THIAZOLIDINEDIONES

Clinical studies of pioglitazone and rosiglitazone monotherapy have generally shown A1C reductions of 0.5% to 1.4% (TABLE).^{2,4,19,20,23} As discussed above, the durability of glycemic control with rosiglitazone is longer than that with glyburide and metformin, with a 5-year monotherapy failure rate of 15%, representing a risk reduction of 63% with rosiglitazone vs glyburide and 32% vs metformin ($P<.001$ for both comparisons).¹⁹

Unlike most other medications used to treat T2DM, the TZDs have been shown to improve various markers of pancreatic β -cell function.^{24,25} During 4 to 6 months of therapy in drug-naïve, sulfonylurea-treated, sulfonylurea-withdrawn, and diet-treated patients with T2DM, treatment with rosiglitazone or pioglitazone markedly increased β -cell function, as assessed by the insulin secretion/insulin disposition index.^{24,25} However, this appears to be a short-term effect. Beyond 6 months of treatment with rosiglitazone, β -cell function, as measured by the homeostasis model of assessment for β -cell function (HOMA-B), declined at an annual rate of 2.0%.¹⁹

Despite their benefits, the TZDs are not without limitations. Weight gain and edema are common with the use of these agents.¹⁹ For example, Kahn et al observed an average weight gain of 4.8 kg over 5 years in patients treated with rosiglitazone, with edema observed in 14% of patients.¹⁹

It is, however, the cardiovascular risks associated with the TZDs that have recently been the subject of several analyses. Recent studies have found a 1.2-fold to a >2-fold increased risk of heart failure with a TZD than with placebo, metformin, glyburide, or various combinations of antihyperglycemic treatments.^{19,26-28} Heart failure appears more likely to occur after a median 24 weeks of therapy and is equally likely with higher or lower doses. Furthermore, the occurrence of heart failure is not limited to older adults.²⁷ Both pioglitazone and rosiglitazone carry a black box warning in the approved product labeling concerning heart failure, and rosiglitazone also carries a black box warning concerning myocardial ischemic events.

Two meta-analyses have suggested that there is an approximately 40% increase in the relative risk for myocardial infarction with the use of rosiglitazone, although in one study no increased risk of cardiovascular mortality was observed.^{29,30} At the same time, pioglitazone has been shown to have a beneficial effect on cardiovascular risk.^{28,31} The reason for the difference in observed cardiovascular risk between the TZDs may be that pioglitazone

improves the atherogenic lipid profile, whereas the overall effect of rosiglitazone on the lipid profile is negative. Treatment with rosiglitazone results in an increase in levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides and in the ratio of total cholesterol to high-density lipoprotein cholesterol (HDL-C),³² with significantly higher levels of LDL-C than are found with metformin or glyburide ($P<.001$ and $P=.008$, respectively).¹⁹

Another newly identified concern associated with the TZDs is an increased risk of fractures, especially of the hip and wrist. The risk of fracture is >2-fold after 12 to 18 months of TZD use compared with nonuse. The risk appears to be similar for patients <70 years and those ≥ 70 years, with pioglitazone and rosiglitazone, and with higher or lower doses, whereas the risk for women is the same or somewhat higher than that for men.^{19,33,34}

As a consequence of the adverse cardiovascular events associated with rosiglitazone and the availability of other treatment options, including pioglitazone, rosiglitazone is not recommended by the ADA/EASD panel for the treatment of T2DM.²

INCRETIN-BASED THERAPIES

The gastrointestinal (GI) system plays an important role in glucose homeostasis and is briefly discussed here. A detailed review of the role of the GI system in glucose homeostasis was published as a supplement to *The Journal of Family Practice* in September 2008 (www.jfponline.com/supplements.asp?id=6690).

The importance of the GI system in regulating glucose homeostasis was first observed when the administration of oral nutrients stimulated a substantially greater insulinotropic response than did intravenous administration of isoglycemic glucose.³⁵ Among the gut peptides identified as being responsible for the greater insulinotropic action with oral nutrients, the most important are the incretin hormones—glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. In patients with T2DM, the secretion of GIP in response to a meal is only slightly impaired ($P=.047$ vs healthy controls), whereas the secretion of GLP-1 is significantly impaired ($P<.001$). Secretion of these peptides varies directly with the degree of insulin resistance such that the greater the insulin resistance, the lower the rise in mealtime secretion of GLP-1 and GIP.³⁶⁻³⁹ Parenteral administration of GLP-1, but not GIP, was found to augment insulin secretion in a dose-dependent manner and to reduce glucagon secretion,³⁸ resulting in decreased concentrations of fasting plasma glucose (FPG) and postprandial glucose (PPG).^{40,41} GLP-1 is rapidly degraded by the

enzyme DPP-4,⁴² which has prompted the development of GLP-1 receptor agonists that mimic and extend the duration of activity of endogenous GLP-1 by resisting DPP-4. The development of DPP-4 inhibitors is another approach being used to extend the duration of activity of endogenous GLP-1.

GLP-1 receptor agonists and DPP-4 inhibitors. GLP-1 receptor agonists regulate secretion of insulin and glucagon in a glucose-dependent manner by acting directly on GLP-1 receptors located in pancreatic α - and β -cells.⁴³ Glucagon secretion is inhibited during hyperglycemia, but it is stimulated as blood glucose levels begin to fall below normal.⁴³⁻⁴⁶ Administration of a GLP-1 receptor agonist results in supraphysiologic levels of GLP-1, thereby causing the physiologic actions of GLP-1 (eg, glucose lowering, decreased glucagon secretion, weight loss, early satiety, and delayed gastric emptying) to be increased.^{37,38,41} DPP-4 inhibitors indirectly increase the level of endogenous GLP-1 by inhibiting the action of DPP-4.⁴⁷ Consequently, the effects of DPP-4 inhibitors are limited by the levels of endogenous GLP-1 and GIP.

The GLP-1 receptor agonist exenatide and the DPP-4 inhibitor sitagliptin are the only agents in their respective classes currently available in the United States. Saxagliptin was recently approved by the US Food and Drug Administration (FDA). New drug applications for the GLP-1 receptor agonist liraglutide and a long-acting form of exenatide, as well as the DPP-4 inhibitor alogliptin, are currently being reviewed by the FDA. Liraglutide was recently approved in the European Union.

Efficacy as monotherapy. Although exenatide is not approved as monotherapy in the United States, the GLP-1 receptor agonists and DPP-4 inhibitors have been studied as monotherapy in patients naive to drug treatment and in those who have not achieved acceptable glycemic control with their current antihyperglycemic treatment.⁴⁸⁻⁵⁵ A summary of the glycemic effects observed in these clinical trials (APPENDIX) may be found on page S34. (Additional detailed information, including the use of GLP-1 receptor agonists in combination with other antihyperglycemic agents, appears in the article, "Practical applications of therapy with a glucagon-like peptide-1 receptor agonist" on page S35 of this supplement.)

Based on clinical trials comparing monotherapy with GLP-1 receptor agonists or DPP-4 inhibitors with other glucose-lowering agents, A1C levels are generally reduced by 0.5% to 1.5% with the GLP-1 receptor agonists and by

0.5% to 0.8% with the DPP-4 inhibitors (TABLE). GLP-1 receptor agonists and DPP-4 inhibitors reduce both FPG and PPG levels.^{48-52,54,56} The glucose-lowering effect of both GLP-1 receptor agonists and DPP-4 inhibitors is greater when the baseline A1C is higher, generally $\geq 9\%$. For example, after 24 weeks of monotherapy with sitagliptin, 100 mg once daily, the placebo-subtracted reductions in A1C were 0.6%, 0.8%, and 1.5% for a baseline A1C level of $< 8.0\%$, 8.0% to $< 9.0\%$, and $\geq 9.0\%$, respectively.⁵¹ Similar results have been observed in trials with alogliptin.⁵⁷

Previous antihyperglycemic treatment has also been shown to affect glycemic response to incretin therapy. In a study by Garber et al,⁴⁹ patients with recently diagnosed T2DM (N=746) were randomized to once-daily treatment with liraglutide, 1.2 or 1.8 mg, or glimepiride, 8 mg, for 52 weeks. In the patients treated with liraglutide, 1.2 mg once daily, A1C was reduced by 1.2% in those previously treated with diet and exercise alone compared with 0.5% for those previously treated with oral antihyperglycemic monotherapy. The respective A1C reductions in those treated with liraglutide, 1.8 mg once daily, were 1.6% and 0.7%.

Safety and tolerability. Because of the potential consequences and frequent occurrence of hypoglycemia with sulfonylureas, glinides, and insulin, the incidence at which the GLP-1 receptor agonists and DPP-4 inhibitors cause hypoglycemia is an important factor when considering their use. In monotherapy studies of GLP-1 receptor agonists, severe hypoglycemia has not been reported.^{48,49} Mild to moderate hypoglycemia has been reported to occur in 5% to 9% of patients treated with exenatide monotherapy⁴⁸ and in 8% to 12% of patients treated with liraglutide monotherapy, the latter in comparison to a 24% incidence of mild to moderate hypoglycemia with glimepiride monotherapy.⁴⁹

Among the DPP-4 inhibitors, hypoglycemia is also generally mild to moderate and appears to be less common, occurring in 0% to 4% of patients treated with sitagliptin compared with 0% to 2% for placebo and 21% for glipizide.⁵⁰⁻⁵² Hypoglycemia appears to be similarly infrequent with alogliptin^{53,54} and saxagliptin.⁵⁵

GI disturbances are the most common adverse events observed with these agents, particularly with the GLP-1 receptor agonists. Nausea, generally mild to moderate in intensity, is the most common GI disturbance, although vomiting and diarrhea may also occur. In early clinical trials without using a dose-escalation strategy, which is now the standard approach, nausea was observed in 57% of patients treated with exenatide, 10 mcg twice daily, vs 4% in those receiving placebo, and vomiting occurred in 22% and

4% of patients, respectively.⁴⁸ Using a dose-escalation strategy, nausea was observed in 28% to 29% of patients treated with liraglutide, 1.2 or 1.8 mg once daily, compared with 9% of those treated with glimepiride ($P < .0001$ for both comparisons). By week 4 of therapy, <10% of patients treated with liraglutide, 1.8 mg, experienced nausea. The dropout rate due to an adverse GI event (eg, nausea, vomiting, diarrhea) was 2% to 4% in patients treated with liraglutide.⁴⁹ In patients treated with the DPP-4 inhibitor sitagliptin, an adverse GI event occurred in 9% to 16% of patients, compared with 6% to 14% for placebo.⁵⁰⁻⁵²

Of potentially greater concern is the issue of acute pancreatitis with exenatide.⁵ Through August 2008, 36 postmarketing cases of acute pancreatitis involving exenatide have been reported.⁵⁸ The relationship of exenatide with pancreatitis is unclear because of the occurrence of pancreatitis in patients with T2DM. A recent epidemiologic study found that patients with T2DM were at 2.8 times greater risk of pancreatitis compared with nondiabetic subjects.⁵⁹ Two cases of acute pancreatitis have also been observed in clinical trials with liraglutide.⁴⁹ One case occurred after 197 days of treatment with liraglutide, 1.2 mg, and the other after 333 days of treatment with liraglutide, 1.8 mg. Both patients recovered, and the patient taking liraglutide, 1.2 mg, continued in the study.

Among patients treated with sitagliptin, there have been postmarketing reports of serious hypersensitivity reactions (eg, anaphylaxis, angioedema, and exfoliative dermatitis) occurring within 3 months of initiating sitagliptin therapy. These reactions sometimes occur after the first dose. While other potential causes are investigated, sitagliptin should be discontinued.⁶

In clinical trials with alogliptin, headache, dizziness, and constipation have been the most commonly reported adverse events, occurring in slightly more patients treated with alogliptin than in those receiving placebo.^{53,54} Skin-related adverse events, mostly pruritus, have also been reported to occur slightly more frequently with alogliptin than with placebo.⁵³

Headache is the most common adverse event observed with saxagliptin, occurring in up to 16% of patients. Other adverse events occurring in 5% to 12% or more of patients include respiratory tract infection, urinary tract infection, nasopharyngitis, arthralgia, nausea, and cough.⁵⁵

Extraglycemic effects. Weight. Because overweight and obesity are important risk factors for T2DM and the potential for weight gain influences patient adherence to treatment, the effect of a treatment for T2DM on weight is an

important consideration. Patient engagement in self-management is the most important factor, and using anti-hyperglycemic agents that are consistent with the overall goal of weight loss offer valuable new advantages. Treatment with insulin, sulfonylureas, and TZDs has been shown to promote weight gain, whereas GLP-1 receptor agonists promote weight loss, generally in the range of 1 to 4 kg.^{48,49} This weight loss appears to result from a mechanism other than nausea, as the mean change in body weight from baseline was found to be similar in patients who experienced liraglutide-associated nausea for >7 days, ≤7 days, or not at all.⁴⁹ The DPP-4 inhibitors are generally considered to be weight neutral, with slight increases to slight decreases in body weight observed in clinical trials.⁵⁰⁻⁵⁵ The difference in the effect on weight between the GLP-1 receptor agonists and the DPP-4 inhibitors may be due to the ability of the GLP-1 receptor agonists to promote early satiety and reduce caloric intake⁴⁰; this is a consequence of the higher pharmacologic levels of GLP-1 achieved with the GLP-1 receptor agonists^{37,38,41} compared with those achieved with DPP-4 inhibitors.⁴⁷

Blood pressure and lipids. The association of T2DM with increased cardiovascular disease emphasizes the importance of modifying risk factors such as blood pressure and blood lipids.⁶⁰ Although most evidence demonstrating improvements in blood pressure and the lipid profile has been found when a GLP-1 receptor agonist or DPP-4 inhibitor has been used in combination with other antihyperglycemic agents,^{50,61-64} similar improvements have been observed in monotherapy trials. For example, liraglutide has been shown to reduce systolic blood pressure by 2.1 and 3.6 mm Hg in once-daily doses of 1.2 and 1.8 mg, respectively, compared with 0.7 mm Hg with glimepiride, 8 mg once daily. Diastolic blood pressure was not significantly changed.⁴⁹

Sitagliptin in daily doses of 50 to 100 mg is associated with a slight increase in triglyceride and total cholesterol levels from baseline, although the increase in triglyceride levels seen with sitagliptin was significantly smaller than that observed with placebo ($P < .05$).⁵⁰ Treatment with alogliptin, 12.5 to 25 mg once daily, reduced total cholesterol levels by 1 to 4 mg/dL after 26 weeks compared with an increase of 10 mg/dL with placebo ($P < .001$); no significant changes in LDL-C or HDL-C levels were observed. Triglyceride levels were significantly reduced with the alogliptin 25 mg dose (-18 mg/dL; $P = .015$) but not with the 12.5 mg dose (-6 mg/dL; $P = .074$) vs placebo.⁵³

These improvements in systolic blood pressure and

lipid profile are beneficial in patients with T2DM who are at high risk for cardiovascular disease; however, these relatively modest effects preclude the use of antihyperglycemic agents as primary therapy for these comorbidities.

Pancreatic β -cell function. The central role of the pancreatic β -cell in the pathogenesis of T2DM makes it a logical focus of treatment. Evolving data suggest that GLP-1 receptor agonists and DPP-4 inhibitors may have a beneficial effect on β -cell function. In monotherapy studies, treatment with sitagliptin, 50 mg twice daily for 12 weeks, has been shown to increase β -cell function by 17% over baseline, compared with a 25% increase for a daily dose of glipizide, 5 mg.⁵⁰ An 11% to 13% increase has been observed with sitagliptin, 100 mg once daily for 18 to 24 weeks, as assessed by HOMA-B.^{51,52} Improvements in β -cell cell function have also been observed with saxagliptin⁵⁵ but not with alogliptin.⁵³ However, while encouraging, these data should be viewed as preliminary until long-term data are available.

Ease of use and cost. The factors contributing to clinical inertia remind us that issues concerning ease of use and cost must also be considered. GLP-1 receptor agonists require subcutaneous administration, whereas DPP-4 inhibitors are taken orally. As is the case with many insulin preparations, the use of self-injecting pens and fine-gauge needles makes the injection of GLP-1 receptor agonists relatively painless and fairly simple. As with most antihyperglycemic medications, GLP-1 receptor agonists and DPP-4 inhibi-

tors use a fixed-dose regimen. The usefulness of self-monitoring of blood glucose for the GLP-1 receptor agonists and DPP-4 inhibitors and other non-insulin therapies is unclear.⁶⁵ The cost of GLP-1 receptor agonists and DPP-4 inhibitors is greater than that for insulin, metformin, or pioglitazone, ranging from about \$9 a day for exenatide to \$6.50 a day for sitagliptin (www.drugstore.com as of July 27, 2009). The actual cost to individual patients will, of course, depend on their insurance coverage and copayments.

Summary

Each of the 4 groups of medications considered preferred therapies for treatment of T2DM by the ADA/EASD panel—insulin, sulfonylureas, TZDs, and incretin-based therapies (GLP-1 receptor agonists)—possesses significant advantages and disadvantages to be considered when individualizing treatment. Insulin and the sulfonylureas are the most researched therapies available, as well as the most cost-effective and the most effective in achieving glycemic goals. The TZDs have been shown to improve various markers of pancreatic β -cell function; however, there is a risk of edema and heart failure with the TZDs; rosiglitazone has been associated with an increase in cardiovascular events. GLP-1 receptor agonists and DPP-4 inhibitors address different pathophysiologic causes than do other diabetes medications and offer the benefit of a low incidence of hypoglycemia. Moreover, GLP-1 receptor agonists promote weight loss, whereas DPP-4 inhibitors are generally weight neutral. ■

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APPENDIX
Selected incretin monotherapy trials

Agent/clinical trial	Previous glucose-lowering medication(s) ^a / Study duration	Baseline			Treatment end			Change ^b		
		A1C, %	FPG, mg/dL	PPG, mg/dL	A1C, %	FPG, mg/dL	PPG, mg/dL	A1C, %	FPG, mg/dL	PPG, mg/dL
EXENATIDE (E)										
Nelson, 2007	Yes/28 d	—	—	—	—	—	—	—	—	—
E, 10 mcg once daily		8.0	191	—	—	—	—	-0.4	-36	-48
E, 10 mcg twice daily		7.9	179	—	—	—	—	+0.2	+11	+11
Placebo										
LIRAGLUTIDE (L)										
Garber, 2009	Yes/52 wk	8.3	167	203	7.5	156	—	-0.8	-11	-31
L, 1.2 mg once daily		8.3	171	205	7.2	149	—	-1.1	-22	-37
L, 1.8 mg twice daily		8.4	171	205	7.9	167	—	-0.5	-4	-25
Glimepiride, 8 mg once daily										
SITAGLIPTIN (Si)										
Scott, 2007	Yes/12 wk	7.9	173	—	7.5	160	—	-0.4	-13	—
Si, 25 mg twice daily		7.8	169	—	7.3	153	—	-0.5	-16	—
Si, 50 mg twice daily		7.9	171	—	7.1	147	—	-0.8	-24	—
Glipizide, 5 mg once daily		7.9	173	—	8.1	180	—	+0.2	+7	—
Placebo										
Aschner, 2006	Yes/24 wk	8.0	171	—	7.4	158	—	-0.6	-13	—
Si, 100 mg once daily		8.0	176	—	8.2	180	—	+0.2	+5	—
Placebo										
Raz, 2006	No/18 wk	8.0	180	263	7.6	167	225	-0.5	-13	-41
Si, 100 mg once daily		8.1	184	265	8.2	191	272	+0.1	+7	+5
Placebo										
ALOGLIPTIN (A)										
DeFronzo, 2008	No/26 wk	7.9	—	—	—	—	—	-0.6	—	—
A, 12.5 mg once daily		7.9	—	—	—	—	—	-0.6	—	—
A, 25 mg once daily								0		
Placebo										
Covington, 2008	No/14 d	7.9	—	236	—	—	—	-0.2	—	-33
A, 25 mg once daily		7.7	—	231	—	—	—	+0.1	—	+8
Placebo										
SAXAGLIPTIN (Sa)										
Rosenstock, 2008	No/12 wk	7.7	156	—	—	—	—	-0.7	-11	-24
Sa, 2.5 mg once daily		7.9	169	—	—	—	—	-0.9	-22	-35
Sa, 5 mg once daily		8.0	169	—	—	—	—	-0.8	-16	-41
Sa, 10 mg once daily		8.0	165	—	—	—	—	-0.3	+3	-1
Placebo										

A1C, glycosylated hemoglobin; FPG, fasting plasma glucose; PPG, postprandial glucose.

^aImmediately prior to study entry.

^bAs reported in the trial (may not equal baseline-treatment end due to rounding).

Sources: Nelson P, et al. *Diabetes Technol Ther.* 2007;9:317-326; Garber A, et al. *Lancet.* 2009;373:473-481; Scott R, et al. *Int J Clin Pract.* 2007;61:171-180; Aschner P, et al. *Diabetes Care.* 2006;29:2632-2637; Raz I, et al. *Diabetologia.* 2006;49:2564-2571; DeFronzo RA, et al. *Diabetes Care.* 2008;31:2315-2317; Covington P, et al., *Clin Ther.* 2008;30:499-512; Rosenstock J, et al. *Diabetes Obes Metab.* 2008;10:376-386.

Practical applications of therapy with a glucagon-like peptide-1 receptor agonist

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Disclosure

Dr Shomali has disclosed that he is on the advisory board for Novo Nordisk Inc. and is on the speakers bureaus for Amylin Pharmaceuticals, Inc., Eli Lilly and Company, and sanofi-aventis.

TYPE 2 DIABETES MELLITUS (T2DM) is a heterogeneous disorder with a complex pathophysiology associated with insulin resistance and altered secretion of insulin and glucagon, resulting in hyperglycemia. Other abnormalities include altered gastric emptying and impaired satiety. Diverse groups of drugs have been developed to lower fasting plasma glucose (FPG) and/or postprandial glucose (PPG) levels by addressing one or more of these pathophysiological mechanisms. Although each group of drugs is variably effective in lowering blood glucose levels, the use of each drug is limited by unwanted consequences, such as weight gain and/or hypoglycemia. Even insulin, the most effective medication available for lowering blood glucose, is not without these unwanted consequences. Because matching the dose of insulin to patient needs based on dietary intake, activity levels, and other variables can be difficult, the use of insulin often requires frequent dose adjustments, variable dosing, and more frequent blood glucose monitoring than is required for other antihyperglycemic agents.¹

Adverse consequences such as weight gain and hypoglycemia serve as barriers to treatment adherence. In fact, adherence to diabetes treatment is among the lowest of many chronic diseases.² One systematic review found that adherence to treatment with oral antihyperglycemic agents over 6 to 24 months ranged from 36% to 93%, with insulin adherence at 62% to 64%.³ Poor adherence can blunt the glucose-lowering effects of medications. In fact, one study showed that a 10% increase in nonadherence to metformin was associated with an increase in glycosylated hemoglobin (A1C) of 0.14%.⁴ Switching to a different form of a medication can improve patient tolerability. For example, switching from immediate-release to extended-release metformin reduced the incidence of an adverse gastrointestinal (GI) event by more than half.⁵

Clearly, none of the options available to treat patients with T2DM is without limitations or is uniformly effective for all patients. As a consequence, the treatment of each individual patient requires an evaluation of the scientific evidence, combined with clinical experience and consideration of the needs, concerns, and capabilities of that patient. Despite the recommendation of the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) panel to initiate therapy with the combination of lifestyle management and metformin for most patients newly diagnosed with T2DM,⁶ the one-size-fits-all approach may lead to suboptimal results. Further, metformin is contraindicated in patients with renal disease or dysfunction.

In addition to the challenges of educating patients about the importance of modifying their eating and exercise patterns with the goal of optimizing long-term benefits, metformin requires titration. Except in patients with a contraindication to metformin, such as those with renal impairment, the initial dose is 500 mg once or twice daily, depending on the formulation. The dose should be titrated over a few weeks, based on patient response and tolerability, to its maximally effective dose of 850 to 1000 mg twice daily (TABLE 1).⁶ During the titration phase, frequent follow-up is needed to monitor glycemic response, identify

TABLE 1

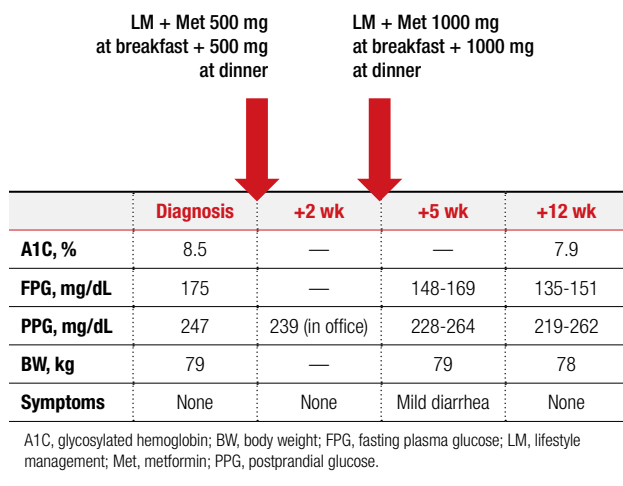
Titration of metformin

1. Begin with low-dose metformin (500 mg) taken once daily (extended-release formulation) or twice daily before breakfast and/or dinner; alternatively, begin with 850 mg once daily.
2. After 5 to 7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg or two 500 mg tablets twice daily before breakfast and/or dinner.
3. If gastrointestinal side effects occur as the dose is advanced, return to the previous lower dose and try again to advance the dose at a later time.
4. The maximum effective dose can be up to 1000 mg twice daily, but is often 850 mg twice daily. Modestly greater effectiveness has been observed with doses up to about 2500 mg/d. Gastrointestinal side effects may limit the dose that can be used.
5. Based on cost considerations, generic metformin is the first choice of therapy. A longer-acting formulation is available in some countries and can be given once daily.

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FIGURE 1

Case study: Early management



adverse events, promote adherence, provide education, and address barriers. Although the optimal frequency of self-monitoring of blood glucose (SMBG) has not been established, SMBG can assist the patient and physician in assessing changes in FPG and PPG levels.¹

■ CASE STUDY

ML is a 53-year-old, African American female diagnosed with T2DM 5 months ago. At diagnosis, her FPG and PPG levels were significantly elevated, as was her A1C level, at 8.5%. She is asymptomatic, with no evidence of polyuria or polydipsia. There is no evidence of cardiovascular disease. ML is overweight. Treatment with metformin (500 mg twice

daily with breakfast and dinner) is initiated. She is instructed to increase the dose to 850 mg twice daily if tolerated. She is referred to a dietitian for lifestyle management counseling. Patient education is initiated, including information about common adverse events associated with metformin therapy. At a follow-up visit 2 weeks later, her in-office blood glucose level is observed to have decreased only slightly. Consequently, the metformin dose is increased to 1000 mg twice daily, with breakfast and dinner. She is instructed on how to self-monitor her blood glucose levels. At her 5-week follow-up visit, her FPG level has decreased by about 10%, but there has been little change in her PPG level. Her A1C level is not measured at this time, because it is still too early to see a change that would reflect the treatment with lifestyle management and metformin.

Question:

If ML's FPG levels remain at >130 mg/dL, and her A1C level does not decrease to <7.0%, how should the treatment plan be modified? Should the dose of metformin be increased? Should another medication be added? If so, when?

There are 3 key points to consider when deciding how to modify the treatment plan. First, doses of metformin >2000 mg/day (up to 2500 mg/day) are not significantly more effective, and gastric tolerability may be a problem.⁶⁻⁹ Second, the target glycemic goal (A1C <7.0%) should be achieved within 2 to 3 months after the initiation of lifestyle management and titration of metformin therapy. If the goal is not achieved, another medication should be added to the treatment regimen.^{6,10} (See "Selecting among ADA/EASD tier 1 and tier 2 treatment options" on page S26 of this supplement.) Third, therapy should be individualized, not only to meet treatment goals but also in consideration of a patient's needs, concerns, and capabilities.

■ CASE STUDY

Because ML had expressed several times that her life had become more complicated since being diagnosed with T2DM, her physician wanted to keep her treatment plan simple. However, after 12 weeks of lifestyle management and metformin, ML's FPG and PPG remain elevated. Her A1C was measured and found to be 7.9%. She has lost 1 kg since diagnosis (FIGURE 1). ML has not experienced a hypoglycemic episode.

Question:

Since ML is not at the target glycemic goal of A1C <7.0% despite lifestyle management and an appropriate dose of metformin, what medication should be added?

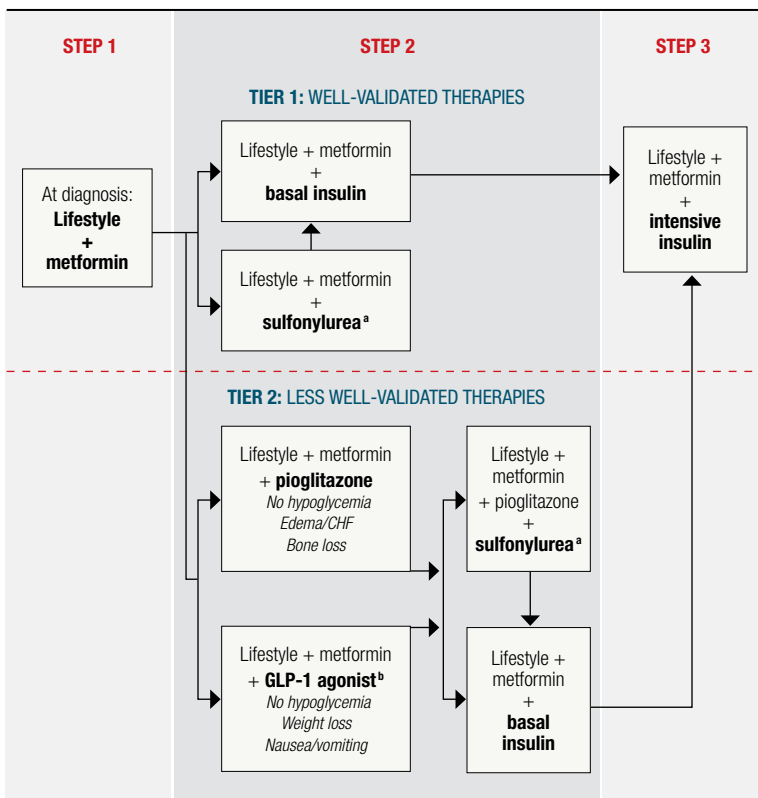
According to the ADA/EASD algorithm, the preferred options are the tier 1/step 2 therapies (insulin or a sulfonylurea) or the tier 2 therapies (a thiazolidinedione [TZD] or a glucagon-like peptide-1 [GLP-1] receptor agonist) (FIGURE 2).⁶ (See “Selecting among ADA/EASD tier 1 and tier 2 treatment options” on page S26 of this supplement.) It should be noted that insulin, a sulfonylurea, or a TZD can be considered for initial therapy if metformin is contraindicated; exenatide is not currently indicated as monotherapy. When adding a second medication, the synergy of the combination, as well as possible interactions among the treatments, should be considered. As discussed in the other articles in this supplement, it is preferable to use medications with different mechanisms of action.⁶

Other medications, such as α -glucosidase inhibitors, glinides, or dipeptidyl peptidase-4 (DPP-4) inhibitors, are available but are not included as preferred options by the ADA/EASD consensus panel.⁶ Reasons for exclusion are that these agents: (1) have fairly modest effects on glucose lowering (α -glucosidase and DPP-4 inhibitors), (2) are poorly tolerated (α -glucosidase inhibitors), (3) require multiple daily dosing (glinides), (4) have limited clinical data, and (5) are high in cost.⁶ However they may be appropriate for some individuals.⁶ In addition, 2 other medications, bromocriptine¹¹ and colesevelam,¹² were recently approved by the US Food and Drug Administration (FDA) for the management of patients with T2DM and, thus, were not included in the ADA/EASD consensus algorithm. The utility of these newer agents is yet to be determined, as clinical experience regarding their use for the treatment of diabetes is limited.

Insulins

Among the preferred therapies, basal insulin is recommended if the A1C level is >8.5% or if the patient has symptoms secondary to hyperglycemia. Although neither is the case

FIGURE 2
Algorithm for the medical management of patients with T2DM: ADA and EASD treatment recommendations



A1C, glycosylated hemoglobin; ADA, American Diabetes Association; CHF, congestive heart failure; EASD, European Association for the Study of Diabetes; GLP-1, glucagon-like peptide-1; T2DM, type 2 diabetes mellitus.

Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C is <7%, and then at least every 6 months. The interventions should be changed if A1C is $\geq 7\%$.

^aSulfonylureas other than glibenclamide (glyburide) or chlorpropamide.

^bInsufficient clinical use to be confident regarding safety.

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with ML, let's briefly review how insulin might have been initiated and titrated. Insulin therapy is typically initiated with basal insulin, ie, intermediate-acting neutral protamine Hagedorn (NPH) insulin or a long-acting analog (detemir or glargine) insulin, at bedtime. A typical starting dose is 0.15 to 0.2 units/kg/day¹³ or 10 units/day.¹⁴

However, in the Treat-to-Target trial, which included oral antihyperglycemic therapy, the average patient required 0.48 units/kg/day of glargine and 0.42 units/kg/day of NPH.¹⁴ Various approaches have been used to titrate the insulin dose based on SMBG.¹⁵ In the Treat-to-Target trial, the dose was increased by 2 units for every 20 mg/dL above an FPG level of 100 mg/dL, to a maximum of 8 units/day.¹⁴ Because the predominant effect of

■ **SIDEBAR 1**

Actions of GLP-1 receptor agonists in regulating glucose homeostasis

- Insulin secretion is stimulated in a glucose-dependent manner, ie, when the blood glucose is high, but not when it is low, thus minimizing the potential for hypoglycemia.
- Gastric emptying is normalized, so that postprandial glucose absorption is slowed.
- Glucagon secretion and hepatic glucose production are suppressed, further reducing the blood glucose level.
- Satiety is enhanced, thus promoting a reduction in food intake and weight loss.

GLP-1, glucagon-like peptide.

Sources: Holst JJ, et al. *Am J Physiol Endocrinol Metab.* 2004;287:E199-E206; Drucker DJ. *Cell Metab.* 2006;3:153-165; Drucker DJ, et al. *Lancet.* 2006;368:1696-1705.

basal insulin is to lower FPG, it is often necessary to also implement bolus insulin, ie, rapid-acting insulin (aspart, glulisine, or lispro) or short-acting (regular human) insulin, to lower PPG. Multiple daily SMBG measurements are needed to guide insulin therapy.¹

Sulfonylureas

The second tier 1/step 2 option, a sulfonylurea, is also a reasonable option because of its primary effect of stimulating insulin secretion. If used as recommended by the ADA/EASD panel, a sulfonylurea would be initiated within months of diagnosis for patients who have not achieved adequate glycemic control with the combination of lifestyle management and metformin. In this setting, a sulfonylurea should be effective in further lowering blood glucose levels, since an estimated 20% to 50% of β -cell function still remains at the time of diagnosis.^{16,17} At the same time, however, the glucose-lowering effects of a sulfonylurea are less durable than some of the other antihyperglycemic agents.¹⁸ One study found that the time to failure of glycemic control with monotherapy averaged 33 months for glyburide compared with 45 months for metformin and 57 months for rosiglitazone.¹⁹ Other limitations of sulfonylurea therapy include a high incidence of hypoglycemia¹⁹ and an average weight gain of about 2 kg.⁶ Since glimepiride and glipizide are less likely to cause hypoglycemia than are chlorpropamide and glyburide,^{20,21} they are the preferred choices when selecting a sulfonylurea.⁶

When hypoglycemia is particularly undesirable, such as in those who perform manual labor, drive for a living, or operate heavy or dangerous machinery, either a TZD or a GLP-1 receptor agonist should be considered. Similarly, if promotion of weight loss is an important goal and the A1C level is <8%, the addition of a GLP-1 receptor agonist to lifestyle management and metformin is appropriate.⁶

Thiazolidinediones

A TZD—specifically, pioglitazone—is a good option for use in combination with metformin because of the varying effects of each agent on glucose homeostasis. Rosiglitazone is not recommended by the ADA/EASD panel because of its potential cardiovascular risk and the availability of other treatment options, including pioglitazone.⁶ After the publication of the ADA/EASD guidelines, data from prospective studies such as Action to Control Cardiovascular Risk in Diabetes (ACCORD),²² Veterans Affairs Diabetes Trial (VADT),²³ and Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD)²⁴ have affirmed the safety of rosiglitazone. Nevertheless, since most patients with diabetes and insulin resistance die of cardiovascular disease, it is disappointing that significant reductions in cardiovascular events and mortality have not been consistently demonstrated with the TZD class. Compared with metformin or a sulfonylurea, TZD monotherapy has a more durable effect on glucose lowering.¹⁹ This effect may be due to the short-term improvement in β -cell function that results from TZD therapy.²⁵

A concern relating to the TZDs is an increased risk of fractures, particularly of the hip and wrist. After 12 to 18 months of TZD use, the risk of fracture is >2-fold compared with nonuse.¹⁹⁻²⁶ A recent meta-analysis showed the risk to be increased in women but not in men with T2DM.²⁷ Because of this increased risk of fractures, a bone density scan may be appropriate, especially for postmenopausal women.

The remainder of this article focuses on the accumulating clinical efficacy and safety evidence on the GLP-1 receptor agonists in combination with metformin and other antihyperglycemic agents.

Question:

What observations have been made in clinical trials in which a GLP-1 receptor agonist has been added to metformin therapy?

The novel GLP-1 receptor agonist class improves T2DM via a number of mechanisms that are complementary to

TABLE 2

Selected clinical trials of GLP-1 receptor agonists as add-on therapy to metformin

Agent/clinical trial	Study design	Baseline				Change from baseline			
		A1C, %	FPG, mg/dL	PPG, mg/dL	BW, kg	A1C, %	FPG, mg/dL	PPG, mg/dL	BW, kg
EXENATIDE (E)									
DeFronzo, 2005	R, TB, 30 wk								
E, 5 mcg twice daily		8.3	176	—	100	-0.4	-7.2	—	-1.6
E, 10 mcg twice daily		8.2	168	—	101	-0.8	-10.1	—	-2.8
Placebo		8.2	170	—	100	+0.1	+14.4	—	-0.3
Barnett, 2007	R, O, C, NI, 32 wk ^a								
E, 5 mcg twice daily x 4 wk, then 10 mcg twice daily		9.0	—	—	—	-1.4	-52	—	-1.6
Glargine		9.0	—	—	—	-1.4	-74	—	+0.6
Kim, 2007	R, IB, 15 wk								
E LAR, 0.8 mg once weekly		8.6	185	—	107	-1.4	-43	—	0
E LAR, 2 mg once weekly		8.3	167	—	110	-1.7	-40	—	-3.8
Placebo		8.6	184	—	101	+0.4	+18	—	0
LIRAGLUTIDE (L)									
Nauck, 2009	R, DB, 26 wk								
L, 0.6 mg once daily		8.4	184	—	—	-0.7	-20	-31	-1.8
L, 1.2 mg once daily		8.3	178	—	—	-1.0	-29	-41	-2.6
L, 1.8 mg once daily		8.4	182	—	—	-1.0	-31	-47	-2.8
Glimepiride, 4 mg once daily		8.4	180	—	—	-1.0	-23	-45	+1.0
Placebo		8.4	180	—	—	+0.1	+7	-11	-1.5

A1C, glycosylated hemoglobin; BW, body weight; C, crossover; DB, double-blind; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; IB, investigator-blinded; LAR, long-acting release; NI, noninferiority; O, open-label; PPG, postprandial glucose; R, randomized; TB, triple-blind.

^aAdded to metformin or a sulfonylurea.

Sources: DeFronzo RA, et al. Diabetes Care. 2005;28:1092-1100; Barnett AH, et al. Clin Ther. 2007;29:2333-2348; Kim D, et al. Diabetes Care. 2007;30:1487-1493; Nauck M, et al. Diabetes Care. 2009;32:84-90.

metformin (SIDEBAR 1).²⁸⁻³⁰ Currently, only exenatide is approved in the United States, whereas liraglutide is in late-stage review with the FDA, after its recent approval in the European Union. All of these mechanisms have a favorable effect on glucose lowering, making the GLP-1 receptor agonist class of medications a desirable add-on therapy, particularly in obese individuals and patients prone to hypoglycemia.

The efficacy and safety profiles of the GLP-1 receptor agonists—when used in combination with metformin—are similar to those with their use as monotherapy (TABLE 2).³¹⁻³⁴ After 30 weeks of treatment with the GLP-1 receptor agonist exenatide, 5 or 10 mcg twice daily as add-on therapy to metformin, the A1C level was reduced by 0.4% and 0.8%, respectively, compared with an increase of 0.1% with the addition of placebo to metformin ($P < .002$ vs placebo). Furthermore, body weight decreased by 1.6 and 2.8 kg, respectively, at 30 weeks compared with baseline ($P < .001$ vs placebo).³¹ The durability of these benefits was demonstrated in a 52-week open-label extension.³⁵ In this study, the exenatide/metformin group demonstrated a sustained reduction of 1.3% in A1C during the 82-week period ($P < .05$ vs baseline), and body weight decreased by 5.3 kg ($P < .05$ vs baseline).

The addition of liraglutide to metformin therapy further reduces blood glucose levels compared with metformin monotherapy, with results similar to those obtained with the addition of glimepiride to metformin (TABLE 2). Twenty-six weeks of treatment with liraglutide at various doses, once daily as add-on therapy to metformin, reduced the A1C level by 0.7% in the liraglutide 0.6 mg group and by 1.0% in each of the liraglutide 1.2 and 1.8 mg and glimepiride 4 mg once-daily groups.³⁴ Reductions in FPG were 20 mg/dL with liraglutide 0.6 mg, 29 mg/dL with liraglutide 1.2 mg, 31 mg/dL with liraglutide 1.8 mg, and 23 mg/dL with glimepiride. Reductions in PPG were 31 mg/dL with liraglutide 0.6 mg, 41 mg/dL with liraglutide 1.2 mg, 47 mg/dL with liraglutide 1.8 mg, and 45 mg/dL with glimepiride. Body weight decreased by 1.8 kg with liraglutide 0.6 mg, 2.6 kg with liraglutide 1.2 mg, and 2.8 kg with liraglutide 1.8 mg, but increased by 1.0 kg in the glimepiride group ($P < .0001$). Analysis of this and 2 other trials involving the combination of liraglutide with oral antihyperglycemic agents showed that the higher the baseline A1C level, the greater the reduction in A1C levels.³⁶ Patients in the upper quartile (mean baseline A1C level, 9.5% to 9.8%) experienced a reduction

FIGURE 3

Case study: Further management

	Diagnosis	+12 wk	+20 wk	+24 wk
A1C, %	8.5	7.9	—	7.5
FPG, mg/dL	175	135-151	108-137	85-126
PPG, mg/dL	247	219-262	203 (in office)	196 (in office)
BW, kg	79	78	78.5	80.5
Symptoms	None	None	None	Bloating, leg swelling

LM + Met 1000 mg at breakfast + 1000 mg at dinner
Add pioglitazone 30 mg at breakfast
Add GLP-1 receptor agonist

A1C, glycosylated hemoglobin; BW, body weight; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; LM, lifestyle management; Met, metformin; PPG, postprandial glucose.

of 1.3% to 1.8% compared with 0.5% to 0.9% for those in the lowest quartile (mean baseline A1C, 7.2% to 7.3%).

There were no cases of severe hypoglycemia in these studies, and the overall incidence of mild to moderate hypoglycemia with exenatide and liraglutide was similar to placebo.^{31,34} The incidence of minor hypoglycemia observed with the addition of liraglutide was significantly less than that seen with the addition of glimepiride (3% vs 17%, *P*<.001). Adverse GI events (nausea, vomiting, diarrhea) were the most frequently reported events, occurring in 35% to 44% of patients in the liraglutide groups and 17% of patients in the glimepiride and placebo groups.³⁴ Nausea was reported by 36% to 45% of exenatide patients compared with 23% of placebo patients³¹ and 11% to 19% of liraglutide patients.³⁴

■ CASE STUDY

To help select a second medication to add to lifestyle management and metformin, the physician discusses the goals of therapy with ML, as well as her needs, concerns, and capabilities. This discussion reveals that ML is concerned about the long-term complications of diabetes. In addition, she is frustrated by her difficulty losing weight. She is also very busy at work, and although she eats breakfast every morning, she has a somewhat erratic eating pattern the rest of the day. ML reports that she has a supportive family, but she wants to keep her treatment simple, preferring to avoid injections and increase the frequency of daily SMBG if possible.

Recognizing that the addition of any of the 4 treatment options to metformin should provide ML with the desired glucose control, the physician considers each option in light of their discussion:

Insulin: Weight gain; hypoglycemia; injections; need for more frequent SMBG; need for frequent dose titration; potential need for addition of meal-time insulin; ADA/EASD panel recommendation, especially if the A1C level is >8.5%.

Sulfonylurea: Weight gain; hypoglycemia; lack of durability seen in A Diabetes Outcome Progression Trial (ADOPT) and the United Kingdom Progressive Diabetes Study (UKPDS); low cost; oral formulation.

TZD (pioglitazone): Weight gain; fluid retention; osteoporotic fractures; oral formulation; potential decrease in risk for myocardial infarction; improved pancreatic β -cell function.

GLP-1 receptor agonist: Injections; GI effects (primarily short-term nausea); promotion of weight loss; low incidence of hypoglycemia; improved pancreatic β -cell function.

The physician concludes that adding pioglitazone would be the best fit for ML at this time (week 12) because of the beneficial β -cell effects, its relatively durable glycemic control, and oral formulation. Although a GLP-1 receptor agonist also would have been a good choice, patient factors led to the selection of a TZD. The physician assures ML that her treatment will be modified if needed. He recommends that ML take pioglitazone, 30 mg, with breakfast, and she agrees.

ML's physician discusses the risk of weight gain and edema. He also schedules ML for a follow-up visit with the dietitian a few days later with the goal of improving her eating habits and food choices.

Over the next 8 weeks (weeks 12-20) (FIGURE 3), ML's FPG and PPG levels improve but are still not within the target goals. At the follow-up visit 4 weeks later (after 12 weeks of TZD therapy), ML has gained 2 kg.

The physician talks with ML about initiating a GLP-1 receptor agonist. She is apprehensive about

TABLE 3

Selected clinical trials of GLP-1 receptor agonists in combination with metformin and another antihyperglycemic agent

Agent/clinical trial	Previous glucose-lowering medication(s)/Study design	Baseline			Change from baseline		
		A1C, %	FPG, mg/dL	BW, kg	A1C, %	FPG, mg/dL	BW, kg
EXENATIDE (E)							
Kendall, 2005	Met + SU/R, DB, 30 wk						
E, 5 mcg twice daily		8.5	182	97	-0.6	-9	-1.6
E, 10 mcg twice daily		8.5	178	98	-0.8	-11	-1.6
Placebo		8.5	180	99	+0.2	+14	-0.9
Blonde, 2006	Met + SU/R, DB, PI, 30 wk; O, 52 wk						
E, 5 mcg twice daily		8.3	173	99	-1.1	-16	-4.4
E, 10 mcg twice daily		8.3	173	99	-1.1	-16	-4.4
Nauck, 2007	Met + SU/R, O, NI, 52 wk						
E, 10 mcg twice daily		8.6	198	86	-1.0	-32	-2.5
Premix aspart 70/30, twice daily		8.6	203	83	-0.9	-31	+2.9
Heine, 2005	Met + SU/R, O, 26 wk						
E, 10 mcg twice daily		8.2	182	88	-1.1	-26	-2.3
Glargine, once daily		8.3	187	88	-1.1	-52	+1.8
Zinman, 2007	TZD ± Met/R, DB, 16 wk						
E, 10 mcg twice daily		7.9	164	98	-0.9	-29	-2.2
Placebo		7.9	159	97	+0.1	+2	+0.1
LIRAGLUTIDE (L)							
Russell-Jones, 2008	Met + glimepiride/R, O, 26 wk						
L, 1.8 mg once daily		8.3	164	85.5	-1.3	-28	-1.8
Glargine		8.2	164	85.0	-1.1	-32	+1.6
Placebo		8.3	169	85.7	-0.2	+10	-0.4
Zinman, 2009	Met + rosiglitazone/R, DB, 26 wk						
L, 1.2 mg once daily		8.5	182	—	-1.5	-43	-1.0
L, 1.8 mg once daily		8.6	185	—	-1.5	-48	-2.0
Placebo		8.4	180	—	-0.5	-9	+0.6

A1C, glycosylated hemoglobin; BW, body weight; DB, double-blind; FPG, fasting plasma glucose; Met, metformin; NI, noninferiority; O, open-label; PI, placebo-controlled; R, randomized; SU, sulfonylurea.

Sources: Kendall DM, et al. *Diabetes Care*. 2005;28:1083-1091; Blonde L, et al. *Diabetes Obes Metab*. 2006;8:436-447; Nauck MA, et al. *Diabetologia*. 2007;50:259-267; Heine RJ, et al. *Ann Intern Med*. 2005;143:559-569; Zinman B, et al. *Ann Intern Med*. 2007;146:477-485; Russell-Jones D, et al. *Diabetologia*. In press; Zinman B, et al. *Diabetes Care*. 2009;32:1224-1230.

injections but is happy to learn that she wouldn't have to monitor her blood glucose more frequently than she does now. After self-administering a saline injection in the office, ML realizes it is virtually painless and easier than she imagined. She likes the prospect of losing some weight and the low risk of hypoglycemia.

Question:

What data support the use of a GLP-1 receptor agonist with 2 other antihyperglycemic agents?

There is considerable evidence concerning the use of a GLP-1 receptor agonist in combination with other antihyperglycemic medications. When necessary to achieve and maintain glycemic control, a GLP-1 receptor agonist can be used as part of a 3-medication regimen that includes a

sulfonylurea or TZD, usually in addition to lifestyle management and metformin.

In general, the addition of a GLP-1 receptor agonist to lifestyle management and metformin plus a sulfonylurea or a TZD results in reductions in blood glucose and body weight similar to those seen with monotherapy with a GLP-1 receptor agonist (TABLE 3).³⁷⁻⁴³ Furthermore, the reduction in blood glucose levels observed with a GLP-1 receptor agonist is comparable to that seen with insulin when each is part of a 3-drug antihyperglycemic regimen.^{39,40,42}

The contribution of GLP-1 receptor agonist therapy to hypoglycemia is difficult to determine when used in combination with 2 other antihyperglycemic agents. Most studies have involved the addition of the GLP-1 receptor agonist to either metformin or a sulfonylurea or a combination of both metformin and a sulfonylurea. In the placebo-

■ **SIDEBAR 2**

Comparison of exenatide with liraglutide in patients inadequately controlled with metformin ± sulfonylurea

Methods

- Randomized, open-label, parallel-group, 26-week trial (N=464)
- Exenatide 5 mcg twice daily for 4 weeks, then 10 mcg twice daily; or liraglutide 0.6 mg once daily for 1 week, then 1.2 mg once daily for 1 week, then 1.8 mg once daily

Results

	Exenatide 10 mcg twice daily	Liraglutide 1.8 mg once daily	P value
Diabetes duration, y	7.9	8.5	—
BMI, kg/m ²	32.9	32.9	—
Baseline A1C, %	8.1	8.2	—
Δ A1C, %	-0.8	-1.1	<.0001
% with A1C <7.0%	43	54	.0015
Δ Fasting plasma glucose, mg/dL	-11	-29	<.0001
Δ Weight, kg	-2.9	-3.2	.2235
Adverse events			
Nausea, %	28	25.5	—
Minor hypoglycemia, events/patient/year	2.6	1.9	.0131
Δ HOMA-B	3	32	<.0001

A1C, glycosylated hemoglobin; BMI, body mass index; HOMA-B, homeostasis model of assessment for β-cell function.

Source: Buse JB, et al. *Lancet*. 2009;374:39-47.

controlled studies, the incidence of hypoglycemia attributed to exenatide ranged from 6% to 15% higher than placebo³⁷ and 11% higher for liraglutide.⁴² In comparison, with insulin glargine or biphasic insulin aspart, the incidence of hypoglycemia was similar to exenatide^{39,40} or liraglutide.⁴² When a GLP-1 receptor agonist is used in combination with a sulfonylurea, reducing the sulfonylurea dose has been observed to reduce the incidence of minor hypoglycemia by more than 4-fold (26.9 vs 6.1 events/patient/year). One study that involved patients treated with metformin and rosiglitazone found that the incidence of hypoglycemia resulting from the addition of liraglutide was 8% to 9%, compared with 5% for the addition of placebo.⁴³

Recently, the results of a clinical trial comparing exenatide and liraglutide in patients inadequately controlled with metformin and/or a sulfonylurea (N=464) were pub-

lished (SIDEBAR 2).⁴⁴ Patients with a baseline A1C of 8.1% to 8.2% were randomized to receive exenatide, 10 mcg twice daily, or liraglutide, 1.8 mg once daily, as add-on therapy. After 26 weeks, patients receiving liraglutide experienced a significantly greater reduction in A1C level than did patients receiving exenatide (-1.1% vs -0.8%, respectively; *P*<.0001). Furthermore, patients treated with liraglutide experienced less frequent minor hypoglycemia than did patients receiving exenatide (1.9 vs 2.6 events/patient/year; *P*=.0131); 2 cases of major hypoglycemia occurred with the addition of exenatide but none with the addition of liraglutide. The amount of weight lost (-3.2 kg vs -2.9 kg) and the incidence of nausea (25.5% vs 28%) were similar for patients receiving liraglutide or exenatide, respectively, although nausea was less persistent with liraglutide.

■ **CASE STUDY**

The physician recommends that ML add a GLP-1 receptor agonist to her regimen of lifestyle management, metformin, and pioglitazone; she agrees. The physician also plans to begin a more comprehensive patient education program for ML. (See “Patient education and monitoring recommendations for the use of GLP-1 receptor agonists” on page S44 of this supplement.)

As part of this program, the physician believes that it would be helpful to refer ML to a certified diabetes educator from the local community. To make the referral, he uses the Diabetes Services Order Form, which can be found online at www.diabeteseducator.org/export/sites/aade/_resources/pdf/DiabetesServicesOrderFormFINAL.pdf. If the physician had not known of a certified diabetes educator within the local community, he could have located one online at http://professional.diabetes.org/erp_zip_search.aspx, or at www.diabeteseducator.org/DiabetesEducation/Find.html. Similarly, if the physician had been unfamiliar with Medicare requirements, he could have learned about them online at www.diabeteseducator.org/export/sites/aade/_resources/pdf/DSOF_educ_piece.pdf.

Summary

Patients such as ML represent a common challenge in the primary care management of patients with T2DM. After some response to initial therapy with lifestyle management and metformin, the A1C goal of <7.0% after

2 to 3 months was not achieved, necessitating the initiation of combination therapy.

The 4 groups of medications recommended by the ADA/EASD panel as the preferred therapies are basal insulin, the sulfonylureas, the TZD pioglitazone, and GLP-1 receptor agonists.

In addition to considering efficacy, safety, cost, and other medication-related factors, the treatment plan must

take into account the patient's individual needs, concerns, and capabilities. These additional considerations help to foster increased patient self-management and greater treatment adherence. To achieve these objectives, comprehensive patient education is essential.

The unique mechanism of action of the GLP-1 receptor agonist class of medications makes these agents a desirable choice as add-on therapy to metformin. ■

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Patient education and monitoring recommendations for the use of glucagon-like peptide-1 receptor agonists

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UNLIKE MOST DISEASES, diabetes requires extensive patient self-management. Educating patients with type 2 diabetes mellitus (T2DM) about self-management skills is essential to improving health outcomes.¹ To achieve the greatest benefit and efficiently use resources, self-management education should be specific and relevant to each patient's needs. Beginning at the time of diagnosis, individualizing patient education is accomplished through an assessment process that identifies the needs, concerns, and capabilities of the patient, including barriers to learning. Since the patient's educational needs will change over time, this assessment process should be done at regular intervals, ideally with each visit. (See "A checklist approach to selecting the optimal treatment regimen for a patient with type 2 diabetes" on page S21 of this supplement.)

An education program that includes behavioral and psychological strategies that are both culturally sensitive and age-appropriate should be developed.¹ Because T2DM is often asymptomatic in its early stages, patients often feel that lifestyle recommendations and treatments have a negative impact on their quality of life. For these reasons, having an honest discussion about the benefits and risks of various treatment options and involving the patient in the therapeutic decision-making process can improve treatment adherence. It is equally important to ask patients to establish short-term goals and priorities and to congratulate themselves when they have met their goals.

Establishing glycemic goals at the outset is important for patient self-management and acceptance of treatment modifications when necessary. To guide management, the American Diabetes Association (ADA) recommends self-monitoring of blood glucose (SMBG) based on the particular needs and goals of the patient. The ADA, however, acknowledges that the optimal timing and frequency of SMBG for patients with T2DM on non-insulin therapy is unclear.²

The primary care provider can use the results of patient SMBG to enhance treatment adherence and goal attainment. For example, having the patient occasionally monitor postprandial glucose (PPG) levels and reflect on what he or she has recently eaten, how much he or she has exercised, and the medication(s) taken can provide an important link between behavior and results.

The primary care provider should ask patients about their home glucose monitoring results at every visit, encourage them to formulate personal strategies they can adopt to improve glycemic control, and affirm their appropriate behaviors and decisions. Regular encouragement and feedback from health care providers about self-monitoring activities is a strong motivator and an essential ingredient to success.

There are several key patient education issues specific to the use of the glucagon-like peptide-1 (GLP-1) receptor agonists (eg, exenatide and liraglutide) in the treatment of T2DM. Let's examine these issues more closely by continuing

the case study from “*Practical applications of therapy with a glucagon-like peptide-1 receptor agonist*” that begins on page S35 of this supplement.

■ CASE STUDY

ML is a 53-year-old African American female diagnosed with T2DM 6 months ago. Her glycosylated hemoglobin (A1C) level has decreased from 8.5% at baseline to 7.5% as a result of treatment with lifestyle management and metformin, 1000 mg twice daily. Pioglitazone was added 3 months ago but was discontinued at this (24 week) visit because of a weight gain of 2.5 kg. After a discussion of her needs, concerns, and capabilities, as well as the clinical evidence supporting the use of GLP-1 receptor agonists, ML and her physician agree to add exenatide, 5 mcg twice daily, to her present regimen of lifestyle management and metformin and increase the dose of exenatide to 10 mcg twice daily 1 month later.

Although exenatide was selected in this case because it is currently the only approved GLP-1 receptor agonist, the concepts that should be discussed with the patient during an initial education session would be similar for any GLP-1 receptor agonist. Liraglutide is a once-daily GLP-1 receptor agonist that has recently been approved in the European Union and is in late-stage review with the US Food and Drug Administration (FDA). When initiating therapy with any antihyperglycemic agent, including a GLP-1 receptor agonist, it is important to address the 3 P's: purpose, potential side effects, and proper use.

Purpose

Question:

What are the potential benefits of taking a GLP-1 receptor agonist?

In order to make an informed decision about using a GLP-1 receptor agonist, patients should have a basic understanding about how this class of medications works. Using terminology the patient can understand, the health care provider should explain that most people with T2DM do not produce enough insulin immediately after eating food and release too much glucagon. GLP-1 receptor agonists improve blood glucose control primarily by restoring a proper balance of these 2 hormones. Health care providers should be careful not to make claims

about the long-term benefits of GLP-1 receptor agonists, because long-term studies on the impact of these agents on microvascular and macrovascular outcomes have not been completed. However, early research with animals, as well as patients with T2DM, indicates that these drugs have promising effects on β -cell function which, in turn, may have long-term health benefits. When coupled with healthy eating habits and regular physical activity, many people lose weight when taking a GLP-1 receptor agonist. For patients who are overweight, it is important to clearly state that weight loss has several health benefits, including improved control of blood glucose, blood pressure, and blood lipids and, for many patients, an increased sense of self-worth and well-being.

Potential side effects

Question:

What are the potential risks of taking a GLP-1 receptor agonist?

Noting that all drugs have potential side effects, the health care provider should clearly state to patients that the most common side effect from a GLP-1 receptor agonist is nausea. This symptom is sometimes described as a bloated feeling after eating, and it is generally mild and transient. Vomiting and more severe symptoms also may occur. These symptoms are most common during the first few weeks of treatment and generally go away with continued use. Some patients have loose stools or diarrhea. These adverse gastrointestinal (GI) effects are similar to those experienced by some patients when initiating metformin.

Because of the glucose-dependent action of GLP-1 receptor agonists, hypoglycemia is uncommon when a GLP-1 receptor agonist is used as monotherapy (not currently indicated) or in combination with metformin. However, when added to a sulfonylurea or any therapy that increases insulin concentration, the frequency and severity of hypoglycemia may increase, thereby necessitating a reduction in the dose of the sulfonylurea. Health care providers should encourage patients to monitor blood glucose and to report hypoglycemic symptoms and episodes confirmed by SMBG so that appropriate dose adjustments can be made in a timely manner.

Acute pancreatitis is a serious problem that has been reported in a very small number of people who have taken exenatide. It is not yet known whether exenatide is the cause of this rare problem or whether it is coincidental.³ However, it is known that patients with diabetes do have

an increased background risk for developing pancreatitis, as compared with a healthy population.⁴ If the patient has risk factors such as excessive alcohol use and/or gallstones, he or she should be monitored carefully; if persistent abdominal pain continues, instruct the patient to seek immediate medical attention for careful evaluation. Should this or any other unexpected adverse event occur with an incretin-based therapy, it is important for physicians to file a report with the FDA via the MedWatch program (www.fda.gov/medwatch/report/hcp.htm).

Proper use

Question:

How is treatment with a GLP-1 receptor agonist initiated?

Both exenatide and liraglutide are started at a low dose, which is increased over a period of a few weeks to reduce the likelihood and severity of nausea.

Exenatide. Start at 5 mcg twice a day for 1 month, then increase to 10 mcg twice a day. The 5 mcg twice-daily dose is the minimum effective dose. Based on fasting plasma glucose (FPG) and/or PPG levels, the dose is generally increased to the maximum dose of 10 mcg twice a day as tolerated.⁵ Exenatide is administered twice daily within 60 minutes before the 2 main meals of the day (generally breakfast and dinner) and at least 6 hours apart.⁵

Liraglutide. In clinical trials, liraglutide was started at 0.6 mg once daily for 1 week, then increased to 1.2 mg once daily for 1 week, and finally increased to 1.8 mg once daily as tolerated. This regimen is under review by the FDA and has been approved by the European authorities.⁶ The 1.2 mg dose appears to be the minimum effective dose. Based on FPG and/or PPG levels, the dose is generally increased to the maximum dose of 1.8 mg once daily as tolerated. In clinical trials, liraglutide was administered once daily at approximately the same time each day without regard to meals.⁶⁻¹⁰

Question:

How are exenatide and liraglutide administered?

GLP-1 receptor agonists are administered subcutaneously in the abdominal fat, upper thigh, or arm. Although many patients will readily agree to administer an injectable medication that will help them lose weight, some patients will express reluctance or fear. It's important to explore the patient's feelings.

Many patients have had a previous negative experience with an injectable medication or vaccination given intramuscularly and requiring a large-gauge needle. Many assume that all injections are painful. Some patients believe that injectable therapies are only used as a last resort and are reserved for patients who have a severe or fatal illness. Many patients lack the self-confidence to administer injectable medications, worry about making errors, or believe that it requires years of training. Many patients associate injectable medication with drug dependency and addiction.

These misconceptions are often reinforced or promulgated through depictions of people using injections on television and in movies. The health care provider should avoid making assumptions but, rather, explore the patient's fears by asking open-ended questions and addressing any misconceptions in an empathetic manner. The vast majority of patients are able to self-administer these medications after they've had an opportunity to handle the injection device and self-administer the medication with supervision. The health care provider should explain that pen delivery devices and fine-gauge needles make injection therapy relatively simple and painless.

Question:

What can be done to reduce the incidence and severity of nausea?

Although adverse GI events (ie, nausea, vomiting, and/or diarrhea) are the most common side effects with GLP-1 receptor agonist therapy, these symptoms are generally mild and subside within several weeks. These adverse events are probably related to reduced gastric emptying. Only 7% of patients treated with exenatide (vs 3% with placebo)⁵ and 4% of patients who took liraglutide as monotherapy discontinued treatment due to these side effects.⁶ When used in combination with metformin—another drug that can cause GI side effects—only 8% stopped taking liraglutide.¹¹ In patients treated with the combination of exenatide and metformin, only 1.8% of patients stopped taking exenatide due to GI side effects.¹²

Two strategies can reduce the likelihood and severity of nausea and vomiting. The first approach, as described above, is to start therapy with a low dose and increase the dose over a few weeks. Should nausea or vomiting occur after the maximum daily dose is given, the dose can be reduced, or in the case of exenatide, a 5 mcg dose can be given prior to one meal and a 10 mcg dose can be given prior to another meal for a few weeks.

Adverse GI events, including nausea, peak in the

first 4 weeks with liraglutide,^{6,11} and within 8 weeks with exenatide.¹² If a patient is initially unable to tolerate the maximum dose, a second attempt to increase the dose should be made if the patient tolerates the lower dose for 4 to 8 weeks. Another strategy that may reduce the likelihood and severity of nausea is to administer the agent immediately before or during, but not after, a meal. However, the effectiveness of exenatide may be diminished if this strategy is used.¹³ Therefore, after 4 to 8 weeks, the patient should attempt to administer the dose 10 to 15 minutes before a meal and then, if tolerated, 30 to 45 minutes prior to a meal.

■ CASE STUDY

At a follow-up visit 5 weeks after initiating treatment with exenatide (29 weeks after diagnosis), ML's physician notes that her blood glucose levels and body weight have improved and her leg swelling has resolved. ML reports no symptoms of hypoglycemia, but states that she experienced mild nausea for a few days after increasing her dose to 10 mcg twice a day. The report from the certified diabetes educator to whom the physician referred ML notes that ML has improved her eating habits but skips lunch 1 or 2 times a week.

Question:

What if the patient doesn't eat as planned or forgets to take the dose?

If a patient takes exenatide but the meal is delayed more than 1 hour after the injection, the patient has a small risk of experiencing hypoglycemia.^{13,14} Consequently, it is prudent to advise the patient to be vigilant for symptoms of hypoglycemia if he or she does not eat when planned and to avoid driving or performing other dangerous tasks until after eating.

On the other hand, if the patient eats and realizes he or she forgot to take exenatide before that meal, that dose should be skipped and the next dose should be taken at the scheduled time. The patient should be advised *not* to double the dose, because this will increase the risk for GI side effects and will not lower blood glucose any better than a standard dose.^{5,14}

Liraglutide can be administered at any time of day without regard to meals, but it should be taken at the same time each day. In clinical trials, liraglutide was administered once daily in the morning or the evening with no apparent difference in blood glucose response.⁷⁻⁹ If a patient forgets to eat a meal or a meal is delayed, the patient

should be advised to eat as soon as he or she remembers and to watch for symptoms of hypoglycemia. The patient should not drive or perform other dangerous tasks until he or she eats.

Question:

Are there any clinically important drug interactions with GLP-1 receptor agonists?

The combined use of a GLP-1 receptor agonist and a sulfonylurea increases the risk for hypoglycemia. As a consequence, it is recommended that the sulfonylurea dose be reduced when the 2 drugs are used in combination.⁵ Exenatide is cleared by glomerular filtration (and is thus contraindicated in patients with severe renal disease), whereas liraglutide is metabolized by endopeptidases and undergoes hepatic or renal metabolism.

GLP-1 receptor agonists slow gastric emptying and may slow or reduce the absorption of orally administered medications. Studies evaluating the potential interactions between exenatide and acetaminophen, lovastatin, and oral contraceptives found that the absorption of these drugs was reduced or delayed and the time to peak concentration was delayed significantly.⁵

The clinical significance of these findings is unclear, but they suggest that the effectiveness of these medications may be reduced. For example, pain relief with acetaminophen may be reduced or delayed if a dose is taken soon after taking exenatide. Until more is known about the clinical significance of these interactions with GLP-1 receptor agonists, the most prudent strategy is to advise the patient to administer acetaminophen, lovastatin, or oral contraceptives 1 hour before or 4 hours after administering exenatide whenever possible.⁵

However, these gastric effects do not uniformly impair the oral absorption of all medications. Studies evaluating the potential for drug-drug interactions between exenatide and digoxin or lisinopril did not demonstrate any clinically significant effect on pharmacokinetic and pharmacodynamic parameters.⁵ Although the concurrent use of exenatide and warfarin did not significantly alter the pharmacokinetics of warfarin in prospective studies, there have been case reports of an increase in the international normalization ratio (INR) and bleeding.⁵

Numerous theoretical pharmacodynamic interactions may occur between GLP-1 receptor agonists and other medications that impact blood glucose, blood pressure, and lipids. Since exenatide and liraglutide lower blood pressure and some blood lipids, appropriate monitoring should be performed when either of these drugs

is initiated. Similarly, medications or nutritional supplements that alter glucose levels (eg, steroids, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, protease inhibitors, atypical antipsychotics, cinnamon) may alter the response to GLP-1 agonists.

At each office visit, it is important to inquire about the patient's use of prescription and nonprescription drugs, as well as nutritional supplements and alternative healing practices, because of the possibility of drug interactions. It is also prudent to encourage the patient to use the same pharmacy for all of his or her medication needs.

■ CASE STUDY

At her 33-week follow-up visit, ML's physician congratulates her on achieving the target A1C goal of <7.0%. ML seems pleased but confides that her life has changed quite a bit since she was diagnosed. ML felt fine before diagnosis, and although she follows a routine of taking her medications, eating better, exercising regularly, and monitoring her blood glucose level every day, she just isn't sure all the effort is worth it. The physician empathizes with ML. He acknowledges that she has made significant changes in her lifestyle

behaviors, but that she may be having difficulty with motivation. He reminds ML of the long-term health benefits of controlling her diabetes and engaging in healthy lifestyle behaviors. He also points out that she:

- Lost 3 kg since diagnosis.
- No longer needs to monitor her blood glucose daily and recommends that she do so only 2 or 3 times a week and whenever she's not feeling well.
- Has had positive changes in blood pressure and lipids that will reduce her risk of heart disease. ML appreciates her physician's support and reaffirms her commitment to improve her diabetes self-management.

Summary

Ongoing patient education and feedback is critical to successful self-management for patients with T2DM. The patient's individualized program is based on an ongoing needs assessment, involves an interprofessional approach with a team of qualified health care professionals, and supports the patient by using positive feedback and motivational strategies at each visit. ■

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