

# Review of Current and Emerging Therapies in Type 2 Diabetes Mellitus

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**T**he prevalence of type 2 diabetes mellitus (T2DM) is approaching epidemic proportions, and diabetes mellitus (DM) affects people of all ages. There has been a dramatic increase in the prevalence of DM over the past 30 years, while previously, far fewer adults (and rarely children) were affected by this condition, mostly because obesity and physical inactivity were not as pervasive. On the other hand, treatments that prevented diabetes-related complications and tests for assessing patient control of blood glucose levels did not exist, and the only marketed drugs included pork or bovine insulin and sulfonylureas.

Fortunately, today's available pharmacologic options include agents that not only target  $\beta$ -cell dysfunction or supplement insulin, but also act at various other recognized landmarks along the pathologic cascade of glucose deregulation. While the core pathophysiologic defects in T2DM still include insulin resistance and  $\beta$ -cell failure, researchers are increasingly recognizing other contributing factors such as accelerated lipolysis in adipocytes, incretin deficiency/resistance in the gastrointestinal tract, hyperglucagonemia in  $\alpha$ -cells, and increased glucose reabsorption in the kidneys.<sup>1,2</sup> As such, new and emerging drugs aim to address some of these important defects that contribute to the clinical profile of T2DM. Also, while the management of hyperglycemia, the hallmark metabolic abnormality associated with T2DM, has traditionally taken center stage, therapies directed at associated comorbidities (eg, dyslipidemia, hypertension, obesity, hypercoagulability) have become an additional focus of current management. This article focuses on current and emerging therapies for T2DM.

## Glycemic Goals of Therapy

Maintaining glycemic levels as close to the nondiabetic range as possible has been demonstrated in landmark trials such as the Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) to have a substantial impact on diabetes-related complications, including retinopathy, nephropathy, and neuropathy.<sup>3-5</sup> Achieving lower glycosylated hemoglobin (A1C) levels with intensive therapy has also been shown to have a beneficial effect on cardiovascular disease (CVD) complications in type 1 DM (T1DM); however, its effect on CVD in T2DM has historically been unclear. A recently published study (the Action

## Abstract

Significant advances in the treatment of type 2 diabetes mellitus (T2DM) include the implementation of prevention efforts aimed at delaying progression of glucose intolerance to overt diabetes mellitus (DM) and the development of new classes of blood glucose-lowering medications to supplement existing therapies. While the current management approach for T2DM continues to encompass traditional drugs that focus on  $\beta$ -cell failure and/or insulin resistance, newer agents that target other defects (eg, incretin deficiency/resistance) are increasingly incorporated. Furthermore, the effect of therapies on associated comorbidities (eg, dyslipidemia, hypertension, obesity, hypercoagulability) has become an additional therapeutic focus. This article provides a discussion of specific pharmacologic agents, based on guidelines from the American Diabetes Association/European Association for the Study of Diabetes and relevant clinical studies. An extensive update on the newest drugs (eg, incretin-based therapies, amylin agonists) and managed care aspects of diabetes care is also included.

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in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation [ADVANCE] trial) offers more perspective on the effects of tight glucose control in T2DM. As with previous research, the ADVANCE trial also failed to show a significant effect of intensive glucose control on the risk of major macrovascular events.<sup>6</sup> ADVANCE evaluated progression to major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy) in 11,140 patients with T2DM randomly assigned to undergo standard or intensive glucose control (glycated hemoglobin [A1C]  $\leq 6.5\%$ ). After a median of 5 years of follow-up, intensive control reduced the incidence of combined major macrovascular and microvascular events (18.1%, vs 20.0% with standard control), as well as that of major microvascular events (9.4% vs 10.9%). However, the combined risk reduction was observed primarily because of a reduction in the incidence of nephropathy (4.1% vs 5.2%), with no significant effect on retinopathy. The type of glucose control had no effect on major macrovascular events or death from cardiovascular or any cause. As expected, the incidence of severe hypoglycemia was higher in the intensive control group (2.7% vs 1.5%). Beyond intense glucose control, much attention has also been given to correction of comorbidities (eg, hypertension, dyslipidemia), which has been shown to improve microvascular and cardiovascular complications of DM.<sup>6</sup>

The most recent glycemic goal recommended by the American Diabetes Association (ADA) is, in general, an A1C level of less than 7%.<sup>7,8</sup> More stringent A1C levels of 6.5% or less have been proposed by earlier guidelines<sup>9</sup>; however, recent studies have found these lower glycemic targets to be associated with either excess CVD mortality (at A1C  $<6\%$ ) or to have no benefit on primary CVD outcomes.<sup>6,10</sup> Clinical judgment should be used in evaluating vulnerable or unstable patients (eg, those with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbid conditions), for whom less stringent A1C goals may be appropriate.<sup>8</sup> An A1C of 7% or greater serves as a call to action to initiate or change therapy, with the goal of achieving an A1C level as close to the nondiabetic range as possible or, at a minimum, decreasing the A1C to less than 7%. The target fasting and preprandial levels of plasma or capillary glucose are between 70 mg/dL and 130 mg/dL. If these levels are not consistently achieved, or A1C remains above the desired target, then postprandial levels, usually measured 120 minutes after a meal, may be checked. These levels should be less than 180 mg/dL in order to achieve A1C levels in the target range.<sup>9</sup>

## Principles in Selecting Antihyperglycemic Interventions

The development of new classes of glucose-lowering medications to supplement older drugs (insulin, sulfonylureas, metformin) has certainly broadened the palette of available treatments and possible combinations; however, it has also highlighted the uncertainty that accompanies the selection of appropriate therapeutic regimens for the heterogeneous population of patients with diabetes. According to a consensus algorithm (released by the ADA and the European Association for the Study of Diabetes) on initiation and adjustment of therapy for T2DM, the choice of specific antihyperglycemic agents is based on several considerations: their effectiveness in lowering glucose levels, extraglycemic effects that may reduce long-term complications, safety profiles, ease of use, and expense.<sup>9</sup> In regard to reducing long-term complications, the consensus statement refrains from recommending one class of glucose-lowering agents (or one combination of medications) over others, since the beneficial effects of therapy on long-term complications appear to be derived from the level of glycemic control achieved, rather than from any other attributes of a particular drug.<sup>9</sup> The effects of individual therapies on CVD risk factors (eg, hypertension, dyslipidemia), as well as on other factors influencing long-term glycemic control (eg, body mass, insulin resistance, insulin secretory capacity), are also important. Another critical aspect of optimal long-term control of T2DM is early diagnosis, when DM-associated metabolic abnormalities are usually less severe. Lower levels of glycemia at time of initial therapy are correlated with lower A1C over time and decreased long-term complications.<sup>11</sup>

With regard to lifestyle modifications, overnutrition and a sedentary lifestyle (both contributing to obesity) are the major environmental factors that increase the risk of T2DM. Not surprisingly, exercise and weight loss almost always improve glycemic levels, as well as other CVD risk factors (eg, blood pressure, atherogenic lipid profiles). The benefits of these lifestyle modifications are usually seen rapidly (within weeks to months), and often before substantial weight loss occurs.<sup>12,13</sup> Long-term adherence remains a major limitation of diet and exercise, as seen by the high rate of weight regain among overweight patients. While bariatric surgery has generated impressive data on the elimination of T2DM with sustained weight loss of 20 kg or more, medication management remains the primary long-term intervention for the majority of patients.<sup>9</sup>

## Pharmacologic Therapy

The characteristics of currently available glucose-lowering interventions, when used as monotherapy, are summarized

in the [Table](#).<sup>7</sup> A major factor in selecting initial therapy or in changing therapy is the level of glycemic control. When levels of glycemia are high (eg, A1C >8.5%), classes with greater and more rapid glucose-lowering effectiveness, or potentially earlier initiation of combination therapy, are recommended. Likewise, when glycemic levels are closer to target goals (eg, A1C <7.5%), medications with lower hypoglycemic potential and/or a slower onset of action may be considered.<sup>9</sup> Since T2DM is a progressive disease, the addition of medications to control worsening glycemia over time tends to be the rule rather than the exception. The following sections provide an overview of traditional and newer/emerging agents used in T2DM.

### **Metformin**

The only biguanide available in most of the world, metformin lowers glycemia by reducing hepatic glucose output and increasing insulin sensitivity. Metformin monotherapy will lower A1C by approximately 1.5 percentage points and it is generally well tolerated, with the most common adverse effects being gastrointestinal in nature.<sup>9</sup> While metformin monotherapy is usually not accompanied by hypoglycemia and has been used safely in patients with prediabetic hyperglycemia, concomitant use with other agents (eg, insulin, sulfonylureas) may result in hypoglycemic episodes. Although lactic acidosis is rarely reported, this complication has a potentially fatal outcome.<sup>9</sup> Renal dysfunction (defined as a serum creatinine  $\geq 1.5$  mg/dL in males or  $\geq 1.4$  mg/dL in females) is considered a contraindication to the use of metformin, since renal dysfunction predisposes patients to lactic acidosis. The major nonglycemic effect of metformin remains either weight stability or modest weight loss. The UKPDS demonstrated a beneficial effect of metformin therapy on CVD outcomes; however, these results need to be confirmed in other studies.<sup>14</sup>

### **Sulfonylureas**

Sulfonylureas lower glucose levels by enhancing insulin secretion and appear similar to metformin in efficacy at lowering A1C levels (1.5% reduction).<sup>9</sup> Metformin, however, is associated with better long-term maintenance of glycemic targets.<sup>15</sup> The major adverse effect associated with sulfonylureas is hypoglycemia, with severe episodes (accompanied by coma or seizures) being infrequent and more common in elderly patients. Longer-acting agents (eg, chlorpropamide, glyburide, glibenclamide, sustained-release glipizide) are considered more likely to cause hypoglycemia than second-generation agents (eg, glipizide, glimepiride). The initiation of sulfonylurea therapy may be accompanied by weight

gain of approximately 2 kg; however, several newer agents (eg, glimepiride) have been reported to be weight neutral. Sulfonylureas have historically been implicated as a potential cause of increased CVD mortality (eg, in the University Group Diabetes Program study); however, this has not been substantiated by the UKPDS or the more recent ADVANCE study.<sup>6,16</sup>

### **Glinides**

Similar to sulfonylureas, glinides (ie, repaglinide, nateglinide) stimulate insulin secretion; however, glinides bind to a different site within the sulfonylurea receptor and have a shorter circulating half-life, necessitating more frequent administration. Of the 2 currently available glinides, repaglinide is considered to be most similar in efficacy to metformin or sulfonylureas in decreasing A1C (1.5% reduction).<sup>9</sup> The glinides have a risk of weight gain similar to the sulfonylureas. Hypoglycemia may be less frequent (at least with nateglinide) than with some sulfonylureas.<sup>17</sup>

### **$\alpha$ -Glucosidase Inhibitors**

$\alpha$ -Glucosidase inhibitors (eg, acarbose) reduce the rate of digestion of polysaccharides in the proximal small intestine, thus primarily lowering postprandial glucose levels without causing hypoglycemia. Compared with metformin and sulfonylureas, these agents are less effective in lowering glucose, and reduce A1C by 0.5% to 0.8%.<sup>9</sup> Because  $\alpha$ -glucosidase inhibitors ultimately result in increased delivery of carbohydrates to the colon, they are commonly associated with increased gas production and other gastrointestinal symptoms, causing discontinuation in 25% to 45% of patients.<sup>9</sup> However, interest in this class has remained due to a study examining acarbose as a means of preventing the development of DM in high-risk patients with impaired glucose tolerance. The study results showed an unexpected reduction in severe CVD outcomes and a 25% reduction in the progression from impaired glucose tolerance to DM.<sup>18</sup>

### **Thiazolidinediones (TZDs or Glitazones)**

TZDs (ie, pioglitazone, rosiglitazone) act by increasing the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin. Because TZDs are mostly used as part of combination therapy, data on glycemic effects of monotherapy are limited, with A1C reductions reported in the range of 0.5% to 1.4%.<sup>9</sup> The most common adverse effects associated with TZDs include weight gain and fluid retention. The latter complication usually manifests as peripheral edema, although new or worsened heart failure may occur. TZDs may also increase subcutaneous adiposity, with some

■ **Table.** Summary of Glucose-Lowering Interventions<sup>7</sup>

Intervention	Expected Decrease in A1C With Monotherapy (%)	Advantages	Disadvantages
<b>Tier 1: Well-Validated Core</b>			
<b>Step 1: Initial Therapy</b>			
Lifestyle to decrease weight and increase activity	1.0-2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0-2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
<b>Step 2: Additional Therapy</b>			
Insulin	1.5-3.5	No dose limit, rapidly effective, improved lipid profile	One to 4 injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea	1.0-2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
<b>Tier 2: Less Well Validated</b>			
<b>TZDs</b>	0.5-1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
<b>GLP-1 agonist</b>	0.5-1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive
<b>Other Therapy</b>			
<b>α-Glucosidase inhibitor</b>	0.5-0.8	Weight neutral	Frequent GI side effects, 3 times/day dosing, expensive
<b>Glinide</b>	0.5-1.5 <sup>a</sup>	Rapidly effective	Weight gain, 3 times/day dosing, hypoglycemia, expensive
<b>Pramlintide</b>	0.5-1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
<b>DPP-4 inhibitor</b>	0.5-0.8	Weight neutral	Long-term safety not established, expensive
<sup>a</sup> Repaglinide more effective in lowering A1C than nateglinide. A1C indicates glycated hemoglobin; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; MI, myocardial infarction; TZD, thiazolidinedione. Reprinted with permission from Nathan DM, Buse JB, Davidson MB, et al. <i>Diabetes Care</i> . 2009;32:193-203.			

studies showing redistribution of fat from visceral deposits.<sup>9</sup> This class has been surrounded by controversy since troglitazone, the first TZD, was removed from the market due to its potential to cause liver failure. While the currently available TZDs have not had the same deleterious hepatic effects as troglitazone, rosiglitazone (but not pioglitazone) has been associated with a 30% to 40% relative increase in the risk of myocardial infarction, according to several meta-analyses.<sup>19,20</sup> TZDs have also been shown to be associated with a 3- to 6-fold increased risk for diabetic macular edema (DME) in a retrospective analysis of more than 100,000 patients in England and Wales. The increased risk of DME, which may damage the retina and cause blindness, was observed after 1

year of exposure and continued to accrue over the 10-year follow-up of the study.<sup>21</sup>

**Insulin**

Of all the diabetes medications, insulin is the most effective in lowering glycemia, and will reduce any level of elevated A1C to, or close to, the therapeutic goal. However, compared with insulin doses used in T1DM, relatively large doses (≥1 unit/kg) may be necessary to overcome the insulin resistance that is seen in T2DM.<sup>9</sup> While initially, patients with T2DM may only require a daily dose of an intermediate- or long-acting insulin (eg, “bedtime insulin”), as the disease progresses, they may eventually also need prandial

therapy with short- or rapid-acting insulins to mimic physiologic control of glycemia. Although insulin therapy has beneficial effects on triglyceride and HDL-cholesterol levels, it is known to cause weight gain of approximately 2 to 4 kg, probably in proportion to the correction of glycemia. Insulin therapy is also associated with hypoglycemia, which occurs less frequently in T2DM versus T1DM. Compared with NPH and regular insulin, insulin analogues with longer, non-peaking pharmacokinetic profiles (eg, insulin glargine), as well as analogues with very short durations of action (eg, insulin lispro), may decrease the risk of hypoglycemia.<sup>9</sup>

## New and Emerging Therapies

### *Incretin-Based Therapies: Glucagon-Like Peptide-1*

#### *Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors*

Incretin hormones, the major ones being glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are involved in the regulation of blood glucose, and to a lesser extent, insulin and glucagon secretion.<sup>22,23</sup> Both GLP-1 and GIP are considered glucose-dependent hormones, meaning that they are secreted when glucose levels rise above fasting levels and that they indirectly stimulate insulin secretion. Normally, these incretin hormones are released from endocrine cells in the small intestine in response to oral nutrient ingestion and, by activating G protein-coupled receptors on pancreatic  $\beta$ -cells, they aid in stimulation of insulin secretion. GLP-1 also reduces the secretion of glucagon, a hormone produced by the pancreas that stimulates the liver to convert glycogen to glucose. Additionally, GLP-1 is known to have central effects, including a reduction in gastric emptying and appetite, and an increased sensation of satiety. In contrast, GIP has a direct stimulatory effect on glucagon secretion and no effect on gastric emptying or satiety.<sup>24</sup>

In T2DM, incretin function (essentially the ability of orally ingested nutrients to further augment glucose-induced insulin secretion) is impaired, potentially as a result of GLP-1 secretory defects and GIP resistance. Among individuals with T2DM, therapeutic GLP-1 receptor agonists have been shown to enhance insulin release and inhibit glucagon secretion. Because these effects are glucose-dependent, the risk of hypoglycemia appears to be low with GLP-1-based therapies.<sup>25,26</sup> Unfortunately, the actions of native GLP-1 and GIP in vivo are short-lived, due to rapid inactivation by the proteolytic enzyme dipeptidyl peptidase-4 (DPP-4). This shortcoming has prompted the development of therapeutic strategies to circumvent effects of DPP-4 and maintain incretin action. These strategies include development of DPP-4-resistant GLP-1 analogues (eg, exenatide, liraglutide), as

well as agents that inhibit the enzymatic activity of DPP-4 (sitagliptin, vildagliptin, saxagliptin), and perhaps other DPP enzymes such as DPP-8 and DPP-9.<sup>25,26</sup>

Exenatide, a twice-daily subcutaneous injection approved in 2005, is a synthetic form of the naturally occurring exendin-4, a peptide similar to human GLP-1 (but with a longer half-life and slower elimination) that binds avidly to the GLP-1 receptor on pancreatic  $\beta$ -cells and augments glucose-mediated insulin secretion.<sup>27</sup> The agent, which is used as an adjunct to other treatments (eg, sulfonylureas, metformin, TZDs), appears to lower A1C levels by 0.5% to 1%, primarily by lowering postprandial blood glucose levels. Exenatide also suppresses glucagon secretion and slows gastric motility, leading to weight loss of 2 to 3 kg over 6 months. The agent is rarely associated with hypoglycemia, and only in patients treated with sulfonylureas, postprandial regulators, or insulin. Exenatide is known to cause a relatively high frequency (30%-45%) of gastrointestinal disturbances (eg, nausea, vomiting, diarrhea), which may subside over time.<sup>9,27</sup>

Liraglutide, approved more recently, is a longer-acting, once-daily human GLP-1 analogue that, like exenatide, is resistant to DPP-4 degradation. Liraglutide's efficacy and safety profile is similar to that of exenatide, but head-to-head studies have indicated that longer-acting GLP-1 analogues generally appear to have better efficacy and fewer gastrointestinal side effects. Data comparing weekly (not yet approved) versus daily exenatide favor weekly exenatide, and data comparing once-daily liraglutide versus twice-daily exenatide favor liraglutide, specifically in regard to gastrointestinal tolerance, incidence of minor hypoglycemia, and glycemic control.<sup>24,28</sup> The preference for long-acting GLP-1 agonists has led researchers to develop several investigational compounds (eg, modified dosage form exenatide, albiglutide, taspoglutide), all of which have longer half-lives, allowing weekly dosing.

While the safety profile of GLP-1 agonists was not concerning after their initial introduction, the Food and Drug Administration (FDA) did issue a warning in 2007 following reports of pancreatitis in some patients taking exenatide. Since then, additional cases have been reported, including instances of hemorrhagic or necrotizing pancreatitis, and 6 deaths associated with pancreatitis.<sup>24</sup> Postmarketing surveillance has also identified isolated cases of pancreatitis in patients taking sitagliptin. In an analysis of a US health-care database, the rates of pancreatitis with exenatide or sitagliptin were no different from those associated with metformin or glyburide, so while a definitive causal relationship between GLP-1 agonists and pancreatitis has not been established, a possible association remains.<sup>24</sup> As such, the FDA

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urges physicians to observe patients initiating or undergoing dose increases of GLP-1 agonists for signs and symptoms of pancreatitis (persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting).

More recently, the FDA also issued a warning regarding the ability of liraglutide to cause dose-dependent and treatment-duration-dependent thyroid C-cell tumors in rats and mice. Since liraglutide's potential to cause thyroid C-cell tumors (including medullary thyroid carcinoma) in humans is unknown, the FDA recommends that patients with thyroid nodules (noted on physical exam or neck imaging) be referred to an endocrinologist for further evaluation. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2).<sup>29</sup>

DPP-4 inhibitors, also called incretin enhancers, exert glucose regulatory actions by prolonging the effects of GLP-1 and GIP, ultimately increasing glucose-mediated insulin secretion and suppressing glucagon secretion. Three DPP-4 inhibitors (sitagliptin, linagliptin, saxagliptin) are currently approved in the United States for the treatment of T2DM, and a number of other DPP-4 inhibitors are in late-stage development.<sup>24</sup> As a class, these agents are considered small molecules that are rapidly absorbed following oral dosing, resulting in over 80% inhibition of DPP-4 and a 2- to 3-fold increase in peripheral plasma concentrations of GLP-1 and GIP. In clinical studies, DPP-4 inhibitors have been shown to lower A1C levels by 0.6% to 0.9%, and have shown neutral effects on weight as well as the potential for the preservation or enhancement of  $\beta$ -cell function.<sup>9,24</sup> The most compelling indication for the use of DPP-4 inhibitors appears to be in combination with metformin in patients with early T2DM who require their first combination therapy. The complementary pharmacology of DPP-4 inhibition and biguanide action may lead to increased glucose-dependent insulin secretion, suppression of hepatic gluconeogenesis, and improvement in insulin sensitivity. Based on clinical evidence suggesting that a substantial proportion of patients receiving a combination of saxagliptin and metformin achieved statistically significant improvements in glycemic control (compared with either treatment alone), a fixed-dose metformin-saxagliptin product was recently approved for T2DM.<sup>30</sup>

Similar to GLP-1 analogues, DPP-4 inhibitors are unlikely to cause hypoglycemia when used as monotherapy; however, combination therapy is the more common approach in T2DM and may require monitoring for hypoglycemia. Because DPP-4 is expressed in many tissues, including

immune cells, this class of compounds has the potential to influence immune function, as evidenced by an increased incidence of infection.<sup>31</sup>

Both DPP-4 inhibitors and GLP-1 analogues appear to have beneficial effects on classic cardiac risk factors by reducing blood pressure, weight, triglycerides, and low-density lipoprotein cholesterol, and increasing high-density lipoprotein cholesterol.<sup>24</sup> It is still unknown whether these surrogate outcomes will yield a clinical benefit, although human GLP-1 infusion has shown positive effects in the settings of acute myocardial ischemia, chronic heart failure, and postmyocardial infarction. Several large cardiovascular outcome trials are currently under way to determine the impact of incretin-based therapies on macrovascular risk.

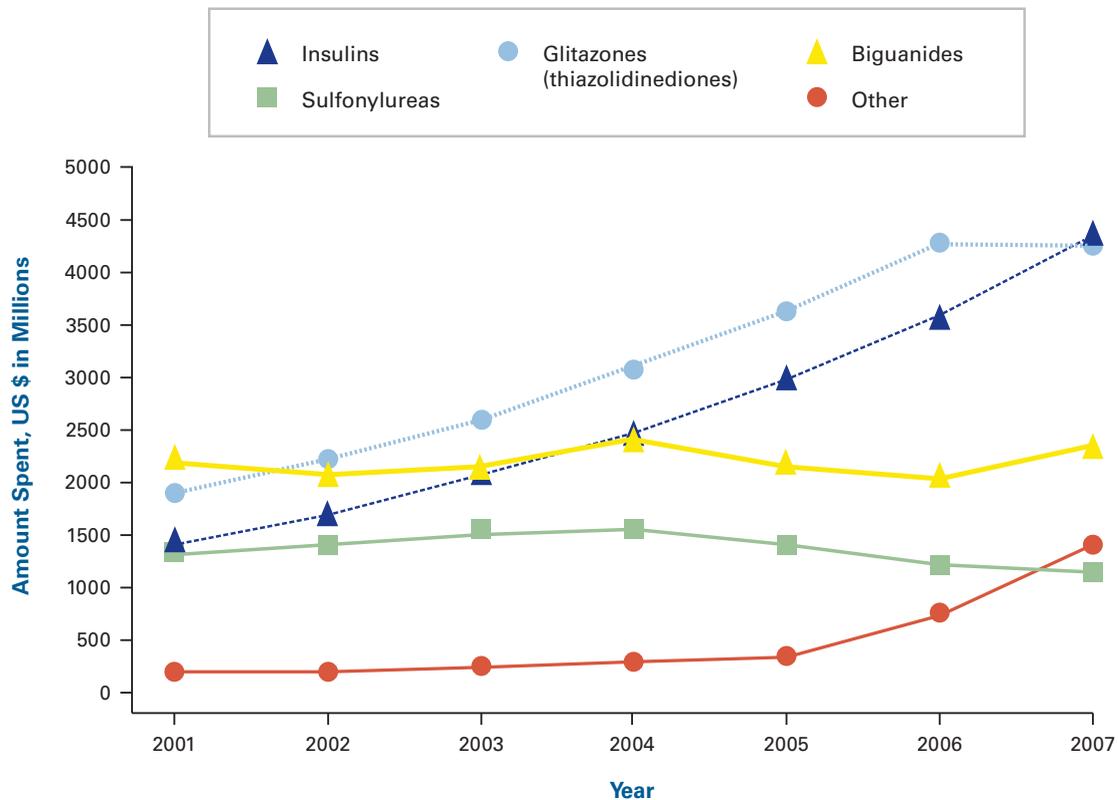
### **Amylin Agonists (Amylinomimetics)**

Amylin, a neuroendocrine hormone cosecreted with insulin in response to meals, is known to inhibit postprandial glucagon secretion, slow the rate of gastric emptying, enhance satiety, and reduce food intake. Amylin-mediated activity normally results in suppression of postprandial glucose excursions; however, in T2DM, amylin and insulin response is markedly impaired.<sup>9</sup> Pramlintide is a synthetic analogue of the  $\beta$ -cell hormone amylin and is currently approved only as adjunctive therapy with insulin. Administered subcutaneously before meals, pramlintide is known to slow gastric emptying and inhibit glucagon production in a glucose-dependent fashion; pramlintide predominantly decreases postprandial glucose excursions.<sup>9</sup> Pramlintide produces A1C reductions of 0.5% to 0.7% and is associated with a relatively high rate of gastrointestinal side effects (30% of patients develop nausea) and weight loss of 1 to 1.5 kg over 6 months. Pramlintide is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with T1DM. To reduce this risk, appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical.<sup>32</sup>

### **New Diabetes Indication for Established Drugs**

An alternative to finding new agents is to examine existing drugs for their potential utility in the management of T2DM. Colesevelam and bromocriptine, which were previously approved by the FDA for other indications, have recently been granted indications for treatment of T2DM.<sup>33</sup> Colesevelam, a bile acid sequestrant traditionally used for the treatment of hyperlipidemia, is thought to delay or alter absorption of glucose from the intestines.<sup>33</sup> In a 16-week trial of patients with baseline A1C levels of 7.5% to 9.5% who were treated with insulin (alone or in combination with oral

■ **Figure.** National Trends in the Amount Spent Per Year on Diabetes Drugs, 2001 to 2007<sup>41</sup>



"Other" includes secretagogues (eg, nateglinide),  $\alpha$ -glucosidase inhibitors (eg, acarbose), dipeptidyl-peptidase-4 inhibitors (ie, sitagliptin phosphate), and incretins (ie, exenatide).

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antidiabetic therapy), colesevelam was shown to provide an A1C reduction of 0.41% and an LDL reduction of 12.8%.<sup>34</sup> The main associated side effects are of gastrointestinal origin (constipation, dyspepsia, nausea) as well as increased triglyceride levels.<sup>35</sup>

Bromocriptine, a dopamine-2 receptor agonist, was shown in a 1-year study to reduce A1C level by approximately 0.6% as monotherapy and 1.2% in combination with insulin or a sulfonylurea.<sup>33</sup> The agent also lowered plasma triglycerides and free fatty acids by approximately 30%, and was associated with fewer cardiovascular events.<sup>33,36</sup> The main associated side effects include nausea, vomiting, fatigue, dizziness, and hypotension.<sup>37</sup>

#### Sodium-Glucose Transporter 2 Blockers

The sodium-glucose transporter 2 (SGLT2) transporter protein is located exclusively in the proximal tubule of the kidney, where 90% of glucose reabsorption takes place.<sup>33</sup> Agents targeting SGLT2 prevent renal glucose reabsorption and lower serum glucose by increasing urinary excretion of

glucose. The resultant glucosuria leads to reduction of plasma glucose, glucotoxicity, and body weight; however, effects may be less pronounced in patients with renal impairment.<sup>38</sup> Dapagliflozin, one of the emerging agents in this class, has been shown to lower A1C by 0.58% to 0.89% in phase 2 trials; however, an FDA advisory committee voted against approval in light of safety concerns regarding its association with bladder and breast cancer, as well as hepatotoxicity.<sup>39,40</sup>

#### Managed Care Aspects of Diabetes Treatment

Along with the rising prevalence and economic burden of T2DM, actual spending on drugs has increased by 87% between 1994 and 2007 (from \$6.7 billion to \$12.5 billion; **Figure**).<sup>41</sup> Researchers examining national trends in T2DM reported significant shifts in treatment since 1994, including: (1) increased use of oral therapies until the early 2000s, followed by a subsequent shift back toward the use of insulin with the advent of ultra short-acting and long-acting preparations, (2) rapid growth of metformin and TZDs in the late 1990s, (3) rapid early growth of incretins and DPP-4 inhibi-

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tors in the past 2 years, (4) a continuous decrease in sulfonylurea use, (5) increasing use of both combination products and multiple products per patient, and (6) substantially increased aggregate drug expenditures and price per prescription. In 2007, the most frequently used therapies included metformin, sulfonylureas, glitazones, insulin, sitagliptin, and exenatide. Newer therapies (ie, GLP-1 agonists, DPP-4 inhibitors) have shown rapid early adoption into practice, although the use of other relatively new therapeutic classes (ie, alpha glucosidase inhibitors, meglitinides) decreased.<sup>41</sup>

As of 2007, major contributors to the increase in aggregate drug expenditures included increased utilization of TZDs, combination products, ultra short-acting insulins and their combinations, and long-acting insulins.<sup>41</sup> During this same period, decreases were seen in metformin and sulfonylurea expenditures. The mean price of a diabetes prescription increased from \$56 in 2001 to \$76 in 2007, due to increasing use of and increasing prescription prices for TZDs (\$119 in 2001 to \$160 in 2007), as well as increased use of more costly newer drugs, including ultra short-acting insulins (\$156 in 2007), long-acting insulins (\$123 in 2007), exenatide (\$202 in 2007), and sitagliptin (\$160 in 2007). The cost of metformin (\$63 to \$29) and sulfonylurea (\$27 to \$20) prescriptions decreased during this same period.<sup>41</sup>

In more closely examining some of the trends that contribute to higher medication costs in T2DM, one study compared healthcare costs among patients with T2DM who added a new oral antidiabetes drug (OAD) to an initial OAD regimen with those who up-titrated their initial OAD.<sup>42</sup> While addition of another OAD to the initial OAD regimen was associated with 9% higher medication costs, combination treatment also resulted in 14% lower inpatient costs and slightly lower (but not statistically significant) total risk-adjusted healthcare costs.<sup>42</sup> Another report debating the merits of newer agents pointed out that compared with older drugs, newer therapies produce modest A1C-lowering effects, are considerably higher in cost, and are not available in generic formulations.<sup>43</sup> Therefore, it has been suggested that newer agents should be reserved for patients who are not adequately managed by traditional therapies with known long-term efficacy and safety profiles.

However, in patients who do require aggressive combination treatment (potentially incorporating older and newer agents) to reach glycemic goals, an increasing body of pharmaco-economic evidence appears to support the additional associated costs, since reductions in A1C have been shown to decrease medical costs and healthcare utilization. In one related study, researchers found that among patients with diabetes in a large managed care organization (MCO), those who achieved a

target A1C of 7% or less incurred 32% lower costs after 1 year of follow-up than those who did not reach the target (\$1171 vs \$1540).<sup>44</sup> Another study followed individuals enrolled in a Minnesota health plan to determine the effect of baseline A1C, CVD, and depression in predicting subsequent health-care costs among those with diabetes.<sup>45</sup> In their 3-year analysis, researchers found that for every 1% rise in A1C levels, there was an associated increase in costs, which were, as expected, higher in those with higher A1C levels and concomitant heart disease, hypertension, and depression.<sup>45</sup> Researchers also found that once the A1C fell to less than 7.5%, A1C ceased to be a predictor of increased costs. Therefore, it is suggested that once glycemic control is achieved, it may be more cost-effective to focus efforts on prevention of cardiovascular events.<sup>45</sup> A more recent study that examined the timing of cost savings in relation to A1C reductions found that a sustained decrease in A1C level is associated with significant cost savings, specifically within 1 to 2 years of A1C improvement (reduction of  $\geq 1\%$ ).<sup>46</sup> Mean total healthcare costs were \$685 to \$950 less each year in the cohort with improved A1C levels; however, these cost savings were statistically significant only among those with the highest baseline A1C levels ( $\geq 10\%$ ) and appeared to be unaffected by the presence of complications at baseline.<sup>46</sup>

Despite the clear benefits of achieving and maintaining glycemic goals and the availability of newer and potentially more effective drugs for the management of T2DM, the number of patients with poor glycemic control has not substantially decreased over the past 10 years. According to the 2007 *State of Health Care* report from the National Committee for Quality Assurance (NCQA), 30% of patients with diabetes enrolled in MCOs (27% in Medicare, 49% in Medicaid) had poor glycemic control (A1C  $> 9\%$ ).<sup>47</sup> In a study of modestly controlled patients (A1C levels 7.9%-8.8%) who were managed with a sulfonylurea and/or metformin, patients spent an average of 14.5 to 25.6 months with A1C values greater than 8% before a therapeutic change was made. Less than 50% of patients treated with sulfonylurea and/or metformin monotherapy were switched to a new regimen as soon as, or before, the A1C exceeded 8%.<sup>47</sup> Furthermore, only 18.6% of patients treated with a combination of these agents were switched upon reaching this threshold. These results indicate that patients with relatively uncontrolled hyperglycemia are not managed promptly with more aggressive therapy, and that perhaps newer therapeutic options are being underutilized or prescribed too late in the disease process.<sup>47</sup>

## Summary

Much of the morbidity related to T2DM may be substantially reduced with interventions that achieve relatively

normal glucose levels and perhaps have beneficial effects on CVD risk factors (eg, hypertension, dyslipidemia) and other factors influencing long-term glycemic control (eg, body mass, insulin resistance, insulin secretory capacity). The increasing availability of numerous classes of medications has given clinicians and patients more therapeutic choices, and perhaps better chances of achieving glycemic goals. However, this rapidly expanding pharmacologic menu has also complicated management of the disease. Ongoing education on new and emerging therapies for T2DM is critical to simplifying treatment regimens, individualizing therapy, and ultimately, optimizing patient outcomes.

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