ABSTRACT

Type 2 diabetes mellitus (DM) has reached epidemic proportions, with approximately 19 to 20 million Americans affected by this disorder. Just from 1990 to 2000, the prevalence of DM has increased by 49%, a rise that appears linked to the increasing rate of obesity. The central defects in type 2 DM are decreased insulin secretion and insulin resistance, with the latter often exacerbating the former. This article provides an extensive review of the pathophysiology and management of type 2 DM, with a focus on recent guideline recommendations from the American Diabetes Association and the European Association for the Study of Diabetes. Significant advances in the treatment of type 2 DM include prevention efforts aimed at delaying progression of glucose intolerance to overt DM and development of new classes of blood glucose–lowering medications to supplement older therapies. Included in this article is a discussion of specific pharmacologic agents, as well as a stepwise approach for initiating and advancing interventions. The major factors in selecting a particular intervention include the agent’s ability to achieve and maintain glycemic goals and patients’ baseline levels of glycemic control. The effects of individual therapies on cardiovascular disease risk factors (eg, hypertension and dyslipidemia) and on the prospects of long-term glycemic control (eg, changes in body mass, insulin resistance, and insulin secretory capacity) are also important. For the majority of patients, more than 1 medication will be necessary over time. In general, antihyperglycemic drugs with different mechanisms of action will have the greatest synergy. An update on the newest drugs (ie, incretin-based therapies and amylin agonist) and formulations available for type 2 DM is also provided.

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Type 2 diabetes mellitus (DM), as recently as 30 years ago, the only pharmacologic options for treating diabetes included pork or bovine insulin and sulfonylureas. Treatments that prevented diabetic complications and tests for assessing patient control of blood glucose levels did not exist. Patients were almost exclusively adults, with children or young adults rarely affected by type 2 diabetes mellitus (DM). As a whole, fewer people developed type 2 DM compared to today’s population, mostly because obesity and physical inactivity were not pervasive.

DIABETES THERAPY: PRESENT AND FUTURE

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know it. Just from 1990 to 2000, the prevalence of DM has increased by 49%, a rise that appears linked to the increasing rate of obesity. Increased diagnosis of type 2 DM in children also is associated with rising rates of obesity. Up to 45% of children with newly diagnosed diabetes have type 2 DM, and most are overweight or obese at diagnosis. This trend is especially alarming because, as younger people develop the disease, the complications, morbidity, and mortality associated with DM are all likely to occur at younger ages. The economic impact of DM is considerable, with the annual direct healthcare costs estimated to be at least 153 billion international dollars worldwide.

The central defects in type 2 DM are decreased insulin secretion and insulin resistance, the latter of which can be overcome by a fully functioning pancreas. The pancreas, in fact, has a remarkable capacity to adapt to conditions of increased insulin demand (in obesity, pregnancy, and cortisol excess) to maintain normoglycemia. However, when β-cell secretion of insulin begins to fail, hyperglycemia supervenes. Mechanisms behind β-cell failure are currently being investigated and may include chronic elevation of glucose and/or fatty acids. Impaired insulin secretion is often exacerbated by insulin resistance, which is characterized by the inability of insulin to decrease plasma glucose levels through suppression of hepatic glucose production and stimulation of glucose use in skeletal muscle and adipose tissue. Insulin resistance develops in several possible ways and is closely linked to abdominal obesity. Eventually, the pancreas fails to meet the demands of insulin resistance and hyperinsulinemia, which leads to glucose intolerance and type 2 DM.

The relative contribution of insulin secretion and insulin resistance to the development of hyperglycemia may differ as a result of heterogeneity of the disease. Under most circumstances, insulin resistance is the earliest detectable defect in individuals with prediabetes, but it is not known whether this is the primary defect or secondary to other abnormalities, such as abdominal obesity with excessive free fatty acid turnover and increased lipid deposits in muscle. Initially, enhanced insulin secretion can compensate for the insulin resistance, but early-phase insulin secretion is impaired. In the transition from normal to impaired and diabetic glucose tolerance, insulin sensitivity deteriorates approximately 40%, whereas insulin secretion deteriorates 3- to 5-fold. In patients with manifest diabetes, chronic hyperglycemia can result in further deterioration of insulin sensitivity and secretion (glucotoxicity), which is aggravated by elevated free fatty acids (lipotoxicity).

One of the most significant efforts aimed at containing type 2 DM involves studies examining prevention strategies, such as the National Institutes of Health-funded Diabetes Prevention Program clinical trial. In this study of more than 3000 overweight adults with impaired glucose tolerance, lifestyle intervention (loss of 5%–7% of body weight and 30 minutes of exercise 5 times/week) reduced the risk of converting to type 2 DM by 58%. In another arm of the study, metformin produced a reduction of 31% in the risk of conversion to DM. Other efforts aimed at improving DM management include tight glucose control standards, a wide array of patient-friendly glucose monitors, and new drug development. Whether used alone or in combination with other blood glucose-lowering interventions, newer agents have provided an increased number of choices for practitioners and patients, but they have also heightened uncertainty regarding the most appropriate means of treating DM. In providing practitioners with a clear pathway to follow in choosing the most appropriate interventions for patients with diabetes, regularly updated guidelines are critical. This next section will focus on recommendations from a consensus statement on management of hyperglycemia in type 2 DM, released by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).

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 and the UK Prospective Diabetes Study (UKPDS), to have a substantial impact on diabetic complications, including retinopathy, nephropathy, and neuropathy. 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; however, the effect on CVD in type 2 DM remains unclear. Correction of comorbidities, such as hypertension and dyslipidemia, has also been shown to improve microvascular and cardiovascular complications. The most recent glycemic goal recommended by the ADA/EASD guidelines is an A1c level less than 7%. Per the ADA/EASD guidelines, “An A1c of ≥7%...
should serve 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 <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 postprandial levels, usually measured 120 minutes after a meal, may be checked. These levels should be less than 180 mg/dL to achieve A1c levels in the target range.

**PRINCIPLES IN SELECTING ANTIHYPERGLYCEMIC INTERVENTIONS**

Glucose lowering effectiveness, extraglycemic effects, safety profiles, and expense are all factors that are taken into consideration when choosing a particular pharmacologic intervention. 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, because the beneficial effects of therapy on long-term complications appear to be derived from the level of glycemic control achieved, rather than on any other attributes of a particular drug. Therefore, the major factors in selecting a particular intervention include the agent’s ability to achieve and maintain glycemic goals (Table) and patients’ baseline levels of glycemic control.9 The ADA/EASD guidelines state, “When levels of glucose 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.9

The effects of individual therapies on CVD risk factors (eg, hypertension and dyslipidemia) and on the prospects of long-term glycemic control (eg, changes in body mass, insulin resistance, and insulin secretory function) are also considered.9

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**Table. Summary of Antidiabetic Interventions as Monotherapy**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Expected Decrease in A1c, %</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Initial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifestyle to decrease weight</td>
<td>1–2</td>
<td>Low cost and many benefits</td>
<td>Fails for most in 1st year</td>
</tr>
<tr>
<td>and increase activity</td>
<td>Metformin</td>
<td>Weight neutral and inexpensive</td>
<td>GI side effects and rare lactic acidosis</td>
</tr>
<tr>
<td>Step 2: Additional therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>1.5–2.5</td>
<td>No dose limit, inexpensive, and improved lipid profile</td>
<td>Injections, monitoring, hypoglycemia, and weight gain</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.5</td>
<td>Inexpensive</td>
<td>Weight gain and hypoglycemia*</td>
</tr>
<tr>
<td>TZDs</td>
<td>0.5–1.4</td>
<td>Improved lipid profile</td>
<td>Fluid retention, weight gain, and expensive</td>
</tr>
<tr>
<td>Other drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>0.5–0.8</td>
<td>Weight neutral</td>
<td>Frequent GI side effects, 3 times/d dosing, and expensive</td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.5–1</td>
<td>Weight loss</td>
<td>Injections, frequent GI side effects, expensive, and little experience</td>
</tr>
<tr>
<td>Glinides</td>
<td>1–1.5†</td>
<td>Short duration</td>
<td>3 times/d dosing and expensive</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>0.5–1</td>
<td>Weight loss</td>
<td>Injections, 3 times/d dosing, frequent GI side effects, expensive, and little experience</td>
</tr>
</tbody>
</table>

*Severe hypoglycemia is relatively infrequent with sulfonylurea therapy. The longer-acting agents (eg, chlorpropamide, glyburide [glibenclamide], and sustained-release glipizide) are more likely to cause hypoglycemia than glipizide, glimepiride, and gliclazide. †Repaglinide is more effective at lowering A1c than nateglinide.

A1c = glycosylated hemoglobin; GI = gastrointestinal; TZD = thiazolidinediones.

capacity) are also important. One critical step that is likely to improve the probability that a patient will have better long-term control of DM is to make the diagnosis early, when the metabolic abnormalities of DM are usually less severe. Lower levels of glycemia at time of initial therapy are associated with lower A1c over time and decreased long-term complications. Also, because type 2 DM is a progressive disease, addition of medications to control worsening glycemia over time tends to be the rule, rather than the exception.

**LIFESTYLE MODIFICATIONS**

Exercise and weight loss almost always improve glycemic levels, as well as other CVD risk factors, such as blood pressure and atherogenic lipid profiles. The benefits of even modest weight loss can be seen relatively rapidly, usually within weeks to months. The biggest limitation of these interventions is long-term adherence, as seen by the high rate of weight regain among patients who are overweight. Consequently, a large majority of patients will require the addition of medications over the course of their DM.

**PHARMACOLOGIC THERAPY**

**METFORMIN**

The only biguanide available in most of the world, metformin lowers glycemia by reducing hepatic glucose output and increasing insulin sensitivity. Considered first-line therapy by the ADA/EASD consensus statement, metformin monotherapy will lower A1c by approximately 1.5 percentage points. Metformin should be titrated to its maximally effective dose, usually considered to be 2000 mg/day, as tolerated; however, the average daily dose has been reported to be less than 1300 mg/day. Metformin is generally well tolerated, with the most common adverse effects being gastrointestinal (GI; eg, nausea, vomiting, or diarrhea). Although metformin monotherapy is usually not accompanied by hypoglycemia and can, therefore, be used in patients with prediabetic hyperglycemia, concomitant use with other hypoglycemic agents (eg, insulin or sulfonylureas) can produce hypoglycemic episodes. Though lactic acidosis is rare, the complication is always a matter of concern because of its potentially fatal outcome. The major nonglycemic effects of metformin include weight stability or modest weight loss and reductions in triglycerides and plasminogen activator inhibitor-1 (a CVD risk factor). Data from the UKPDS have demonstrated that metformin has a beneficial effect on cardiovascular outcomes in patients with type 2 diabetes.

**SULFONYLUREAS**

Sulfonylureas lower glucose by enhancing insulin secretion via β-cell stimulation and appear similar to metformin in lowering A1c levels (1.5% reduction). The major adverse effect is hypoglycemia, with severe episodes (accompanied by coma or seizures) being infrequent but more common and prolonged in elderly patients. Initiation of sulfonylurea therapy is sometimes accompanied by weight gain of approximately 2 kg. However, some newer agents (eg, glimepiride) have been reported to be weight neutral. Sulfonylureas were implicated as a potential cause of increased CVD mortality in the University Group Diabetes Program study, but this outcome has not been substantiated by the UKPDS study.

**GLINIDES**

Similar to sulfonylureas, glinides stimulate insulin secretion. Glinides tend to have a more glucose-dependent effect on insulin secretion as compared to older sulfonylureas, such as glyburide. Earlier generations of sulfonylureas produce a continuous stimulation of insulin secretion. Of the 2 glinides currently available in the United States, repaglinide is considered to be almost as effective as metformin or sulfonylureas in decreasing A1c (1.5% reduction). The glinides have a similar risk of weight gain as the sulfonylureas, but hypoglycemia may be less frequent (at least with nateglinide) than with some sulfonylureas.

**GLUCOSIDASE INHIBITORS**

Glucosidase inhibitors act by slowing digestion of carbohydrates in the small intestine, predominantly lowering postprandial glucose spikes. These agents reduce A1c by 0.5% to 0.8% and are less effective in lowering blood glucose than metformin or sulfonylureas; they generally do not cause hypoglycemia. Because glucosidase inhibitors ultimately result in increased delivery of carbohydrates to the colon, they are commonly associated with increased gas production and GI symptoms. These adverse effects are a cause of discontinuation in 25% to 45% of patients. Recently, however, there has been a growing interest in this class because of a study examining acarbose as a means of preventing development of DM in high-risk patients with impaired glucose tolerance. Results
showed an unexpected reduction in severe CVD outcomes\textsuperscript{16} and a 25% reduction in the progression from impaired glucose tolerance to DM.\textsuperscript{17}

**Thiazolidinediones**

Thiazolidinediones (TZD or glitazones) act by increasing the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin. Because TZDs are mostly used in combination with other agents, data on glycemic effects of monotherapy are limited, with A1c reductions reported in the range of 0.5% to 1.4%.\textsuperscript{9} Weight gain and fluid retention are the most common adverse effects associated with TZDs. The latter complication usually manifests as peripheral edema, although new or worsened heart failure may occur. TZDs may also increase subcutaneous adiposity, with redistribution of fat from visceral deposits shown in some studies. Increased bone fractures in women also have been reported with TZDs.\textsuperscript{18-20} These agents have a beneficial or neutral effect on atherogenic lipid profiles, with pioglitazone having a more beneficial effect than rosiglitazone.\textsuperscript{21,22} In the Prospective Pioglitazone Clinical Trial in Macrovascular Events study, pioglitazone was shown not to have any significant effects on primary CVD outcomes after 3 years of follow-up, but there was a significant reduction in important secondary endpoints, such as death, myocardial infarction, and stroke.\textsuperscript{21} More recently, a meta-analysis of published clinical trials has raised concerns over a potential association between rosiglitazone and an increased risk of myocardial infarction and death from CVD.\textsuperscript{6} The study was limited by lack of access to original source data and findings that were of borderline significance, but nevertheless, clinicians should consider the possibility of cardiovascular adverse effects with this class of drugs.

**Insulin**

Of all the diabetes medications, insulin is the most effective in lowering glycemia. When used in adequate doses, it can decrease any level of elevated A1c to, or close to, the therapeutic goal. But compared to insulin doses used in type 1 DM, relatively large doses (≥1 unit/kg) may be necessary to overcome insulin resistance that is seen in type 2 DM.\textsuperscript{9} When using intermediate- or long-acting insulins, patients may also require prandial therapy with short- or rapid-acting insulins to mimic physiologic control of glycemia (Figure 1).\textsuperscript{9} Although insulin therapy has beneficial effects on triglyceride and high-density lipoprotein 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 type 2 DM versus type 1 DM. Compared with neutral protamine hagedorn and regular insulin, insulin analogs with longer, non-peak pharmacokinetic profiles, as well as analogs with very short durations of action, may decrease the risk of hypoglycemia.

**Initiating Diabetes Therapy and Advancing Interventions**

According to the ADA/EASD guidelines, when initiating therapy, \textsuperscript{*} the measures of glycemia that are targeted on a day-to-day basis are the fasting and preprandial glucose levels. Self-monitoring of blood glucose (SMBG) is an important element in adjusting or adding new

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**Figure 1. Algorithm for the Metabolic Management of Type 2 Diabetes**

![Algorithm](Image)

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\textsuperscript{*} Check A1c every 3 months until <7% and then at least every 6 months. \textsuperscript{1} Although 3 oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense. \textsuperscript{9} See Figure 2 for initiation and adjustment of insulin.

A1c = glycosylated hemoglobin.

Reprinted with permission from Nathan et al. Diabetes Care. 2006;29:1963-1972.\textsuperscript{9}
interventions, and, in particular, in titrating insulin doses. Attempts to achieve target glycemic levels with some regimens, particularly sulfonylureas or insulin, may be associated with modest hypoglycemia, with glucose levels ranging between 55 mg/dL and 70 mg/dL. These episodes are generally treated with oral carbohydrates (glucose tablets or 4–6 oz juice) and may rarely progress to more severe hypoglycemia. Unfortunately, fear of hypoglycemia is a major barrier to good glycemic control, because patients prefer to maintain higher glucose levels to cushion against hypoglycemia.

Figure 1 is an algorithm depicted in the ADA/EASD consensus statement, containing recommendations for initiating and titrating various agents. The guidelines outline the following:

Our consensus is that metformin therapy should be initiated concurrent with lifestyle intervention at diagnosis. Metformin is recommended as the initial pharmacologic therapy, in the absence of specific contraindications, for its effect on glycemia, absence of weight gain or hypoglycemia, generally low level of side effects, high level of acceptance, and relatively low cost. Metformin treatment should be titrated to its maximally effective dose over 1 to 2 months, as tolerated. Rapid addition of other glucose-lowering medications should be considered in the setting of persistent symptomatic hyperglycemia.

The A1c level dictates, in part, which agent is selected next, with consideration given to insulin for patients with A1c greater than 8.5% or with symptoms secondary to hyperglycemia. Insulin can be initiated with a basal (intermediate- or long-acting) agent (Figure 2). When further adjustments are needed, the ADA/EASD guidelines recommend the following:

- If lifestyle, metformin, and a second medication do not result in goal glycemia, the next step should be to start, or intensify, insulin therapy. When A1c is close to goal (<8%), addition of a third agent could be considered; however, this approach is relatively more costly and potentially not as effective in lowering glycemia, compared with adding or intensifying insulin. Intensification of insulin therapy usually consists of additional injections of a short- or rapid-acting insulin, administered before meals to reduce postprandial hyperglycemia. When prandial rapid- or very rapid-acting insulin injections are started, insulin secretagogues (sulfonylurea or glinides) should be tapered and discontinued, because they are not considered synergistic with insulin.

For the majority of patients, more than one medication will be necessary over time. In general, antihyperglycemic drugs with different mechanisms of action

![Figure 2. Initiation and Adjustment of Insulin Regimens](image-url)

Insulin regimens should be designed taking lifestyle and meal schedule into account. The algorithm can only provide basic guidelines for initiation and adjustment of insulin. See Hirsch et al. Clin Diabetes. 2005;23:78-86 for more detailed instructions.

*Premixed insulins are not recommended during adjustment of doses; however, they can be used conveniently, usually before breakfast and/or dinner if proportion of rapid- and intermediate-acting insulins is similar to the fixed proportions available.

A1c = glycosylated hemoglobin; BG = blood glucose; NPH = neutral protamine hagedorn.
will have the greatest synergy. Insulin plus metformin and insulin plus a TZD are particularly effective in lowering glycemia, although the latter combination can cause fluid retention. TZDs and metformin also have been shown to have modest additive effects, because they increase insulin sensitivity via different target organs.

**Introduction to New Drugs and New Formulations**

*Incretin-based Therapies*

Incretins are peptide hormones that are released from the GI tract following food ingestion and mimic glucose-stimulated insulin secretion. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are the 2 major incretin hormones. These incretin hormones stimulate insulin secretion in a glucose-dependent manner, which essentially enhances the synthesis of insulin. In patients with type 2 DM, GLP-1 receptor agonists enhance insulin release and inhibit glucagon secretion. Because both effects are glucose-dependent, the risk of hypoglycemia is low with GLP-1-based therapies. But because of the rapid inactivation by the proteolytic enzyme dipeptidyl peptidase-IV (DPP-IV), the actions of native GLP-1 and GIP in vivo are relatively short. As a result, therapeutic strategies to overcome the effects of DPP-IV, including the development of DPP-IV–resistant GLP-1 analogs (eg, exenatide), agents that inhibit the enzymatic activity of DPP-IV (eg, sitagliptin and vildagliptin), and perhaps other DPP enzymes, such as DPP-VIII and DPP-IX, have become a subject of research.

The only US Food and Drug Administration (FDA)-approved incretin mimetic (GLP-1 agonist), exenatide, is administered twice daily by subcutaneous injection and binds to the GLP-1 receptor on the pancreatic β cell to increase the effectiveness of glucosemediated insulin secretion. Although there are far less published data on this new agent than on other hypoglycemic drugs, exenatide appears to lower A1c by 0.5 to 1 percentage points, mainly by lowering postprandial blood glucose levels. Exenatide also suppresses glucagon secretion and slows gastric motility. The agent is not associated with hypoglycemia, but it has a relatively high frequency of GI side effects, with 30% to 45% of treated patients experiencing one or more episodes of nausea, vomiting, or diarrhea. In open-label studies, exenatide often produced weight loss, which continued for at least 2 years and did not appear to be related to the agent’s GI symptoms.

The 2 lead compounds in the DPP-IV inhibitor class are vildagliptin and sitagliptin with only the latter agent having US FDA approval for use alone or in combination with metformin or a TZD. Administration of sitagliptin leads to increases in levels of endogenous GIP and GLP-1, which subsequently results in A1c reductions of 0.65% and placebo-subtracted A1c reductions of 0.79% to 0.94% when used with metformin and as monotherapy, respectively. Because 2- to 4-fold increases in sitagliptin plasma levels have been observed in patients with moderate-to-severe renal insufficiency, renal function testing and consideration of dosage adjustments should accompany therapy. Most common side effects include upper respiratory tract infection/symptoms and headache. Recent reports of skin rashes with vildagliptin have necessitated further safety analyses with this agent.

**Amylin Agonists (Amylinomimetics)**

Amylin is a neuroendocrine hormone that is co-secreted with insulin from pancreatic β cells in response to meals. Amylin inhibits postprandial glucagon secretion, slows the rate of gastric emptying, enhances satiety, and reduces food intake. Together, these amylin-mediated activities result in the suppression of postprandial glucose excursions. Patients with type 2 DM are known to have a markedly impaired amylin and insulin response to meals. Pramlintide is a synthetic analog of the β cell hormone amylin and is currently approved for use in the United States only as adjunctive therapy with insulin. Pramlintide is administered subcutaneously before meals and decreases postprandial glucose excursions. In clinical studies, A1c has been decreased by 0.5 to 0.7 percentage points. The major clinical side effects of this drug, which is injected before meals, are GI in nature. Approximately 30% of patients in the clinical trials have developed nausea. Similar to exenatide, pramlintide is associated with weight loss.

**New Formulations**

In an effort to improve medication adherence among patients with diabetes, the pharmaceutical industry has introduced a variety of once-daily controlled-release dosage formulations, as well as combi-
nation products. Some recently approved combination products include glyburide/metformin hydrochloride (HCl) combination tablets, pioglitazone/metformin HCl combination tablets, rosiglitazone/metformin HCl combination tablets, rosiglitazone maleate/glimepiride combination tablets, pioglitazone/glimepiride combination, glipizide/metformin HCl combination tablets, and sitagliptin/metformin combination tablets. In regard to controlled-release products, several extended-release formulations of metformin are available for once- or twice-daily administration. Compared to immediate-release metformin, controlled-release products not only have less frequent dosing schedules, but they also appear to be associated with better GI tolerability, which would potentially facilitate titration to maximum effective doses. In one study, 3 different treatment regimens of extended-release metformin (1500 mg/day once daily, 1500 mg/day twice daily, or 2000 mg/day once daily) were found to be comparable to immediate-release metformin (1500 mg/day twice daily) in safety and efficacy.30 Although the overall incidence of adverse events was similar for all treatment groups, fewer patients in the extended-release metformin groups discontinued treatment because of nausea during the initial dosing period compared with the immediate-release metformin group. Also, fewer patients dropped out of the study due to lack of efficacy.30

ROLE OF THE PHARMACIST

The increasing prevalence of DM, the advent of new and improved therapies, and the education required for patients by managed care organizations and insurance companies have created many opportunities for pharmacists to participate in diabetes management. In the community and hospital setting, pharmacists are increasingly involved in screening high-risk individuals for DM, evaluating patients’ medication regimens, and influencing lifestyle modifications.31 Hospital pharmacists often play a critical role in creating protocols for tight glucose control in intensive care units and management of ketoacidosis and hypoglycemic episodes. Pharmacists are often responsible for teaching patients how to use insulin at discharge, and they can be consulted regarding titration of insulin and other hypoglycemic therapy.

Because many patients receive monthly refills of their prescribed medications, patients interact with pharmacists in the community setting more frequent-ly than with any other member of the diabetes team. This contact offers an ideal opportunity for pharmacists to educate patients on glucose goals, use of SMBG, and proper administration of insulin and oral medications. Having access to medication profiles and the patients themselves, community pharmacists are in an ideal position to intervene with physicians on dose titrations, drug interactions, and guideline recommendations. Additionally, community pharmacists can provide patients with positive reinforcement for continuing lifestyle changes and preventive care for their diabetes. The benefits of pharmacist-driven DM care services have been well documented in the literature.

In one community-based pharmaceutical care service targeting patients with DM, community pharmacists provided scheduled consultations, clinical assessment, goal setting, monitoring, and collaborative drug therapy management with physicians.32 In a 5-year assessment of the program, more than 50% of patients experienced sustained improvements in A1C and lipid levels. Moreover, costs shifted from inpatient and outpatient physician services to prescriptions, and direct medical costs and days of employee sick time decreased. Two other pharmacist-managed diabetes care clinics achieved higher screening rates and attained treatment goals more often, compared to national averages.

CONCLUSIONS

Much of the morbidity related to DM can be substantially reduced with interventions that achieve relatively normal glucose levels. 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 pharmacologic armamentarium also has complicated management of the disease. Through education and clinical interventions, pharmacists can help simplify treatment regimens, individualize therapy, and ultimately optimize patient outcomes.

REFERENCES