The Community Pharmacist’s Role in Diabetes Treatment

By Kimberly Ference, PharmD

Upon completion of this activity, the pharmacist should be able to achieve these directives:
1. Describe the pathophysiology of diabetes and how it relates to medications used to treat diabetes.
2. Explain the diagnostic criteria and screening recommendations related to diabetes.
3. State the goals of therapy for diabetes.
4. Discuss the place in therapy of all antidiabetic agents.
5. Describe general differences between all antidiabetes agents, including types of insulin.
6. List the various diabetes complications and appropriate monitoring for each.
7. Demonstrate how recent updates for diabetes care can be incorporated into everyday practice.

INTRODUCTION

Diabetes is prevalent in the United States, affecting approximately 23.6 million people. Among that number, 2 percent are unaware that they have diabetes. It is also estimated that 57 million Americans have impaired fasting glucose (prediabetes), which increases their risk of developing frank diabetes if not managed properly. Needless to say, the opportunity for community pharmacists to intervene and interact with these patients is substantial. Community pharmacists have direct access to diabetes patients frequently, which directly enables them to provide proper education and recommend appropriate screening for disease and complications. “The Standards of Medical Care in Diabetes—2010,” published by the American Diabetes Association (ADA), provides recommendations relating to diabetes self-management education (DSME), including evidence to support DSME’s importance. ADA specifically mentions the importance of “community health workers” providing DSME.

Diabetes is a complex, multifactorial disease that requires involvement from various members of the health care team, including the patient. A well-informed patient is essential to ensure self-management and awareness. In the U.S. health care system, it is often difficult for primary care providers to find time to educate patients with diabetes and, in some cases, screen for diabetes complications. It is for this reason they call upon on other members of the health care team to provide diabetes education and screening. Community pharmacists possess the knowledge and skills to assess, screen, educate, and answer questions from patients with diabetes, and refer them to appropriate resources when needed.

PATHOPHYSIOLOGY

Diabetes is a chronic metabolic disorder characterized by the presence of hyperglycemia due to a relative or absolute deficiency in insulin production, insulin resistance, or both (diabetes mellitus). It is a disease that affects people of all ages and is the leading cause of death, disability, and economic burden in the United States. Diabetes complicates other diseases and conditions and leads to significant morbidity and mortality. The disease has a significant impact on quality of life, and the economic costs are enormous. The prevalence of diabetes is on the rise, and it is estimated that 9.3% of the U.S. population has diabetes. Diabetes is a disease that requires lifelong management and care.

<table>
<thead>
<tr>
<th>Risk Factors for the Development of Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Family history of diabetes in first-degree relative</td>
</tr>
<tr>
<td>• Overweight or obese</td>
</tr>
<tr>
<td>• Physical inactivity</td>
</tr>
<tr>
<td>• Ethnicity: African American, Latino, Native American, Asian American, Pacific Islander</td>
</tr>
<tr>
<td>• Prediabetes</td>
</tr>
<tr>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Dyslipidemia (HDL&lt;35 mg/dL and triglycerides &gt;250 mg/dL)</td>
</tr>
<tr>
<td>• History of gestational diabetes or delivery of a baby weighing &gt; 9 lbs</td>
</tr>
<tr>
<td>• History of cardiovascular disease (CVD)</td>
</tr>
<tr>
<td>• History of polycystic ovary disease</td>
</tr>
<tr>
<td>• Other conditions with insulin resistance</td>
</tr>
</tbody>
</table>

Risk Factors for the Development of Diabetes

• Family history of diabetes in first-degree relative
• Overweight or obese
• Physical inactivity
• Ethnicity: African American, Latino, Native American, Asian American, Pacific Islander
• Prediabetes
• Hypertension
• Dyslipidemia (HDL<35 mg/dL and triglycerides >250 mg/dL)
• History of gestational diabetes or delivery of a baby weighing > 9 lbs
• History of cardiovascular disease (CVD)
• History of polycystic ovary disease
• Other conditions with insulin resistance
by insulin deficiency. Long-term hyperglycemia has been shown to increase the risk of developing diabetes-related complications. There are four different classifications of diabetes: type 1, type 2, gestational, and secondary (as a result of genetic conditions, medications, and various other causes). A list of risk factors for the development of diabetes can be found in the box on page 29.

Insulin is an endogenous hormone that is released from beta cells located in the pancreas in response to elevated plasma glucose. In patients without diabetes, insulin stimulates carbohydrate metabolism and facilitates transfer of glucose into cardiac and skeletal muscle and adipose tissue, and converts glucose into glycogen (the stored form of blood sugar). An absolute insulin deficiency arising from beta cell destruction is responsible for the adverse changes in glucose control seen in type 1 diabetes (formally known as \textit{juvenile diabetes} or \textit{insulin-dependent diabetes mellitus}). Although the source of beta cell destruction is not fully understood, it is thought to be autoimmune in nature.

Elevated plasma glucose concentrations that occur in type 2 diabetes (formally known as \textit{adult onset diabetes} or \textit{non-insulin-dependent diabetes mellitus}) are caused by a combination of insulin resistance and inadequate compensatory insulin secretion in response to a meal. Insulin resistance predominantly occurs when insulin-mediated glucose uptake by the liver fails. This results in a compensatory overproduction of glucose and therefore increases blood glucose concentration. Impaired insulin secretion occurs when the pancreas continuously produces insulin in an effort to maintain euglycemia (normal amounts of blood glucose), resulting in hyperinsulinemia. It is this elevated amount of insulin in the circulation that negatively affects the function of the pancreatic beta cells by decreasing further insulin secretion. Thus increased insulin concentrations ultimately result in loss of beta-cell mediated compensatory insulin secretion in response to meals, leading to impaired glucose tolerance.

Other mechanisms contribute to maintenance of glycemic control. Under normal physiologic circumstances, glucagon-like peptide 1 (GLP-1), an endogenous incretin hormone, is released by the intestine throughout the day. These levels increase in response to food intake. GLP1 regulates glucose homeostasis by a variety of means, including increasing insulin production and the release from pancreatic beta cells, and slowing of gastric emptying and decreased food intake. Glucagon-like peptide1 also decreases inappropriate pancreatic alpha cell secretion of glucagon, which increases hepatic glucose production in response to low blood glucose. The enzyme dipeptidyl peptidase-4 (DPP-4) rapidly inactivates GLP-1. Diabetes medications developed in recent years have targeted the GLP-1 pathway. These medications act by inhibiting GLP-1 enzymatic inactivation (DPP-4 inhibitors) or augmenting the effects of endogenous incretin (GLP-1 agonists).

**SCREENING AND DIAGNOSIS**

The ADA recommends screening for diabetes starting at age 45 in those without risk factors. If the screening results are normal, the patient should be reassessed every three years, taking into account changing risk factors and health status. Earlier testing should be considered if the patient is overweight as classified by BMI and has additional risk factors as described in Table 1. Diabetes screenings that take place in a community pharmacy can serve as a pre-screening and help to identify patients who otherwise would not have been screened.

There are several different methods used to make a diagnosis of diabetes. Prior to the release of the 2010 Standards of Care, hemoglobin A1C (A1C) was not recommended by the ADA as a diagnostic criterion because of the lack of assay standardization, and therefore questionable accuracy. Since the development of the National Glycohemoglobin Standardization Program (NGSP), the ADA now endorses the use of A1C as a diagnostic option. An A1C of ≥ 6.5 percent is considered diagnostic and should be confirmed by a second test on a subsequent day. Currently, point-of-care (POC) devices should not be used when assigning A1C for diagnosis, as they are not standardized. One advantage to using A1C as a diagnostic marker is that testing does not require fasting.

Other diagnostic methods include a fasting (at least eight hours) plasma glucose of ≥ 126 mg/dL or an oral glucose tolerance test (OGTT) with a two-hour plasma glucose of ≥ 200 mg/
The OGTT includes a 75 g glucose load and should be in compliance with the World Health Organization’s standards. Both of the tests require confirmation by repeat testing on a subsequent date. A random plasma glucose of ≥200 mg/dL occurring in a patient displaying classic symptoms of hyperglycemia (such as polyuria, polyphagia, or polydipsia) would also meet the criteria for a diagnosis of diabetes. This test does not need to be repeated. Subsequently, prediabetes is considered when fasting plasma glucose is 100–125 mg/dL, or a two-hour plasma glucose during an oral glucose tolerance test is 140–199 mg/dL. An A1C of 5.7–6.4 percent is also considered prediabetes.

TREATMENT GOALS OF THERAPY

Overall diabetes treatment goals include reducing risk for development of long-term microvascular and macrovascular complications, decreasing diabetes related morbidity and mortality, prevention of acute complications caused by continued hyperglycemia, prevention of hypoglycemic episodes, and improving/maintaining quality of life. These goals should be incorporated into the care plan and frequently revisited with the patient as a part of regular self-management sessions.

Glycemic control is assessed through the measurement of A1C and capillary plasma glucose, and self-monitoring blood glucose (SMBG) values. Of these tests, SMBG is the least accurate; however, it is more convenient and less invasive than the others. Self-monitoring blood glucose is beneficial as a means to self assess glycemic control and assist in the evaluation and prevention of hypoglycemia. The ADA recommends testing three or more times daily in patients using multiple daily insulin injections and insulin pumps. For patients with diabetes not using insulin, the monitoring frequency is not well defined and evidence of benefit is controversial. Although some studies suggest frequent monitoring leads to lower A1C values and better overall outcomes, there is also evidence that suggests frequent monitoring reduces quality of life without improving glycemic control. Some health care providers question the cost-effectiveness and clinical significance of frequent SMBG in patients not utilizing insulin. Less stringent monitoring may be recommended for these patients, and should be individualized based on patient need. Goals for plasma glucose are illustrated in Table 1.

The ADA and American Association of Clinical Endocrinologists (AACE)/American College of Endocrinologists (ACE) differ slightly in their recommendations for A1C goals. Assessment of A1C should be performed every three months for patients not meeting glycemic goals, and at least twice yearly for those who are controlled. Several clinical trials have demonstrated that tight glycemic control reduces cardiovascular risk and prevents the development of microvascular complications. In contrast, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial demonstrated an increase in mortality in patients receiving intensive glucose lowering. It appears that tight glucose control may increase or decrease risk depending on patient-specific factors and type of therapy administered. Maintaining an A1C of approximately 7 percent is appropriate, based on the conflicting data surrounding risk, and A1C goals should be individualized. The ADA recommends less stringent A1C goals (i.e., ≥ 7 percent) for the following patients: the elderly, those at risk or those with a history of severe hypoglycemia, long-standing difficult-to-control diabetes, several comorbidities, and decreased life expectancy.

The ADA recently endorsed using a new test that is recommended when discussing glucose control with patients. Estimated average glucose (EAG) is used in conjunction with A1C testing, and most laboratories provide an EAG when an A1C is ordered. It is thought to be more understandable when discussing laboratory monitoring with patients, as it correlates with patient SMBG values.

Table 1: Goals for Glycemic Control

<table>
<thead>
<tr>
<th>Test</th>
<th>ADA Goal</th>
<th>ACE and AACE Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>&lt;7%</td>
<td>&lt;6.5%</td>
</tr>
<tr>
<td>Estimated average glucose</td>
<td>&lt;154 mg/dL</td>
<td>&lt;140 mg/dL</td>
</tr>
<tr>
<td>Preprandial plasma glucose</td>
<td>70-130 mg/dL</td>
<td>&lt;110 mg/dL</td>
</tr>
<tr>
<td>Postprandial plasma glucose</td>
<td>&lt;180 mg/dL</td>
<td>&lt;140 mg/dL</td>
</tr>
</tbody>
</table>
Other goals of therapy include a blood pressure of <130/80 mmHg and a low-density lipoprotein level of <100 mg/dL in most (<70 mg/dL in those with a high risk for cardiovascular disease). Prevention and monitoring for macrovascular complications, including hypertension and dyslipidemia, are discussed later in the prevention and monitoring for complications section.

### LIFESTYLE MODIFICATIONS
The National Diabetes Self-Management Education Task Force describes DSME activities as the assessment of the individual’s specific education needs, identification of the individual’s specific diabetes self-management goals, education and behavioral intervention directed

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Staring dose</th>
<th>Maximum Daily Dose</th>
<th>Adjustments for Renal/Hepatic Impairment</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Glucophage Riomet</td>
<td>500 mg once to twice daily or 850 mg once daily</td>
<td>2,550 mg</td>
<td>Renal: Avoid</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Metformin ER</td>
<td>Fortamet Glucophage XR</td>
<td>100−1,000 mg once daily</td>
<td>2,000 mg</td>
<td>Hepatic: Not recommended</td>
<td></td>
</tr>
<tr>
<td>2nd Generation sulfonyleureas</td>
<td>Glyburide (micronized)</td>
<td>Micronase DiaBeta Glynase Glucotrol Glucotrol XL</td>
<td>2.5−5 mg once to twice daily</td>
<td>20 mg</td>
<td>Renal: Not recommended</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Glipizide</td>
<td>Amaryl Glimepiride Glimepiride</td>
<td>1.5 to 3 mg daily</td>
<td>12 mg</td>
<td>Hepatic: Lower doses recommended to avoid hypoglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone Pioglitazone</td>
<td>Avandia Actos</td>
<td>2−4 mg once or twice daily</td>
<td>10 mg</td>
<td>Renal: No Hepatic: No</td>
<td>C</td>
</tr>
<tr>
<td>Alpha-glucosidase Inhibitors</td>
<td>Acarbose M miglitol</td>
<td>Precose Glyset</td>
<td>25 mg with each meal</td>
<td>100 mg</td>
<td>Renal: Not recommended Hepatic: No</td>
<td>B</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide Nateglinide</td>
<td>Prandin Starlix</td>
<td>0.5−1 mg 3 times daily with each meal</td>
<td>16 mg</td>
<td>Renal: Repaglinide: Yes Nateglinide: No Hepatic: No</td>
<td>C</td>
</tr>
<tr>
<td>Dipeptidyl Peptidase-4 inhibitors</td>
<td>Sitagliptin Saxagliptin</td>
<td>Januvia Onglyza</td>
<td>100 mg daily 2.5−5 mg daily</td>
<td>100 mg</td>
<td>Renal: Yes Hepatic: No</td>
<td>B</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Bromocriptine Mesylate</td>
<td>Cycloset</td>
<td>0.8 mg daily</td>
<td>4.8 mg</td>
<td>Renal: No Hepatic: No</td>
<td>B</td>
</tr>
</tbody>
</table>
toward achieving identified goals, and evaluation of the individual’s attainment of identified goals. There is ample evidence suggesting that DSME improves quality of life, disease-oriented outcomes, and cost savings. The ADA recommends that all patients receive DSME at the time of diagnosis and periodically thereafter. It is possible for community pharmacists to acquire advanced training to provide reimbursable DSME services.

Medical nutrition therapy (MNT) is an integral part of diabetes management and is recommended for all patients with diabetes. The ADA suggests that MNT sessions be individualized, ongoing, and performed by a registered dietitian specializing in diabetes. Topics should include, but are not limited to, food planning, portion control, calorie reduction, appropriate fat intake, carbohydrate counting, and understanding glycemic index.

As a cornerstone of nonpharmacologic therapy, physical activity, as tolerated, is recommended in all adults. Patients should be advised to consult with their physician before starting an exercise program. In general, moderate-intensity aerobic exercise should performed for a total of 150 minutes per week. Alternatively, well-conditioned patients may participate in a weekly total of 75 minutes of intense aerobic activity. In type 2 patients, resistance training involving major muscle groups is recommended two to three times per week. For older patients (over 65), these recommendations may not be feasible or safe. For these patients, recommend low-impact activities such as chair exercises or water aerobics or, at a minimum, ask them to maintain an active lifestyle.

Physiological and social problems can adversely affect a patient’s ability to properly care for his or her diabetes. Therefore, patients should undergo psychological and social screening upon diagnosis and periodically thereafter. Screening includes assessing attitudes about having diabetes, expectations of medical management, affect and mood, quality of life, and resources (financial, social, and emotional). Patients displaying potentially troublesome characteristics such as depression with potential for self-harm, anxiety, eating disorders, or cognitive function decline with impaired judgment should be referred to an appropriate mental health consultant specializing in diabetes care. Often, nonadherence to medication therapy may result from one of the above mentioned factors. Community pharmacists should screen for and attempt to identify and address the underlying cause.

**ORAL MEDICATIONS**

**Biguanides**

Metformin is the only available biguanide on the market in the United States. Biguanides lower blood glucose by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. It is the most effective oral agent in terms of providing glycemic control, reducing A1C by 1–2 percent, and it is considered first-line therapy for the treatment of type 2 diabetes. However, greater A1C lowering may be seen in patients with a higher initial A1C. Moreover, metformin has been shown to reduce overall mortality and risk of myocardial infarction in obese or overweight patients with type 2 diabetes, independent of its effects on glycemic control. Another benefit of using metformin is that it is not associated with weight gain, as is the case with most other diabetes medications. Metformin is classified as weight neutral and in some cases has been associated with mild to moderate weight loss.

| Table 3: Available Combination Products |
|------------------------- |------------------------- |
| **Generic Name** | **Brand Name** |
| Metformin/ glipizide | Metaglip* |
| Metformin/ glyburide | Glucovance* |
| Metformin/ pioglitazone | ActoPlus Met ActoPlus Met XR – NEW FORMULATION |
| Metformin/ repaglinide | Prandil Met |
| Metformin/ rosiglitazone | Janumet |
| Metformin/ sitagliptin | Avandamet |
| Pioglitazone / glimepiride | Duetact |
| Rosiglitazone / glimepiride | Avandaryl |

*Available as both brand and generic
Available Products
Metformin is available in both immediate release and extended release formulations (Table 2). There are several metformin combination products available (Table 3). Immediate release metformin is available on the majority of generic savings plans and is affordable for most patients.

Dosing and Dose Adjustments
Starting doses differ based on product used, as listed in Table 4. Generally, a lower starting dose is used with gradual titration to minimize gastrointestinal side effects. Glycemic control is rarely seen with doses <1500 mg daily and clinical maximum dose is 2000 mg daily. Providers may consider dose titration every 1–2 weeks as tolerated.

Adverse Effects
The most common side effects are gastrointestinal symptoms such as diarrhea, nausea, vomiting, flatulence, indigestion, and abdominal discomfort. Most gastrointestinal side effects subside after a few weeks of therapy, and patients should also be instructed to take with food to minimize these effects. Lactic acidosis is an extremely rare yet potentially severe side effect of therapy and caused by metformin accumulation. Hypoglycemia is not a common side effect as metformin does not affect insulin release.

Drug Interactions
Iodinated contrast dye may cause acute renal impairment, which can potentiate metformin-induced lactic acidosis.

Contraindications/Precautions
Metformin is contraindicated in patients with renal impairments, defined as a SCr of ≥1.5 mg/dL in men and ≥1.4 mg/dL in women. Use metformin with caution in patients with conditions that are associated with an increased risk of lactic acidosis, including congestive heart failure requiring medical management, extreme aging, chronic alcohol use, and active liver disease.

Sulfonylureas
Sulfonylureas decrease plasma glucose by stimulating insulin release from the pancreatic beta cells, reducing glucose output from the liver and increasing insulin sensitivity. Similar to metformin, sulfonylureas decrease A1C by 1–2 percent. Sulfonylureas are considered second line for the treatment of type 2 diabetes, and are recommended after failure to achieve glucose control with maximum clinically effective doses of metformin along with lifestyle modifications. Glimepiride and glipizide are the preferred agents within this class, as they produce less hypoglycemia when compared with the other agents. More importantly, first generation agents and glyburide may be associated with increased mortality, which is suspected to be dose related.

Available Products
Sulfonylureas are classified into two categories: first generation (chlorpropamide, tolazamide, tolbutamide) and second generation (glimepiride, glipizide, glyburide). Certain sulfonylureas are available in combination product formulations, listed in Table 3. Several sulfonylureas are available on generic savings plans that are affordable for most patients.

Dosing and Dose Adjustments
Starting doses differ between agents within the class and are listed in Table 4. A low to moderate starting dose is recommended with gradual titration to minimize risk for hypoglycemia. Elderly patients should be started at lower doses. Patients should be instructed to take sulfonylureas 30 minutes before eating, and extensively counseled on the importance of not skipping meals while taking these medications. Clinical efficacy is usually seen with moderate doses. High to maximum dosing does not typically provide greater blood sugar lowering, and increases the risk of hypoglycemia. Providers may consider dose titration every 1–2 weeks as tolerated.

Adverse Effects
The most common side effect is hypoglycemia. Glyburide and chlorpropamide are associated with an increased risk for hypoglycemia compared with other sulfonylureas. Weight gain (one pound on average) is also common.
Patients may also experience headache, dizziness, and gastrointestinal upset.

**Drug Interactions**
The most common drug interactions occur with other medications that potentiate hypoglycemia.

**Contraindications/Precautions**
Use of a sulfonylurea is contraindicated in patients with type 1 diabetes and diabetic ketoacidosis. Precautions should be taken with patients who are susceptible to hypoglycemia and have hepatic or renal insufficiency. Patients with a sulfonamide allergy should be counseled as to the potential for cross-sensitivity, and appropriate precautions should be employed.

**Thiazolidinediones**
Thiazolidinediones (TZDs or glitazones) reduce blood glucose concentrations by enhancing the effects of existing insulin through improved peripheral glucose uptake, decreased hepatic glucose production, and decreased insulin resistance. When used as monotherapy for the treatment of type 2 diabetes, TZDs reduce A1C by 0.5–1.4 percent. Unlike other oral medications, TZDs may take up to 12 weeks to see full benefit. The ADA does not recommend use of rosiglitazone due to the increased risk of myocardial infarction. This risk does not appear to be associated with pioglitazone, and it remains a therapeutic option as an add-on to maximum clinical doses of metformin, along with lifestyle modifications, for patients who have not achieved glycemic control. This combination is not recommended in patients with hypoglycemia, edema, CHF, or bone loss. Pioglitazone also positively affects the lipid profile by increasing high density lipoprotein and decreasing triglycerides. However, it is important to note that pioglitazone has not been shown to improve clinically relevant outcomes such as reduced mortality risk, or reduction of diabetes-related endpoints.

**Available Products**
For the time being, there are two available products in the United States: pioglitazone (Actos) and rosiglitazone (Avandia). The FDA was considering the withdrawal of rosiglitazone for the market, but an advisory committee voted to keep the drug on the market in July 2010. These agents are also available in a combination tablet with metformin and glimepiride. Currently, none of these products are available as a generic, and they are quite costly for patients without prescription insurance.

**Dosing and Dose Adjustments**
Pioglitazone (Actos) is dosed once daily and may be increased in increments as needed to control blood glucose, taking into account that it may take several weeks to reach full therapeutic benefit. Initial dose and maximum dose recommendations can be found in Table 4.

**Adverse Effects**
In clinical trials, TZDs were associated with an increased risk of fluid retention, leading to peripheral edema, weight gain, and increased risk of heart-failure exacerbations and hospitalizations.

**Drug Interactions**
Due to their mechanisms of action, concurrent use with sulfonylureas and insulin increase the risk of hypoglycemia.

**Contraindications/Precautions**
Thiazolidinediones are contraindicated in patients with established New York Heart Association (NYHA) class III or IV heart failure. Concomitant insulin use is associated with greater amounts of fluid retention. Likewise, TZDs should be used with caution in patients with a history of symptomatic edema. An increased risk for development of bone fractures was observed in clinical trials for both agents, and they should be used cautiously in patients with a history of bone loss. These agents should be used with caution in patients with a history of anemia, as volume overload may cause hemodilution, manifested as a decrease in measured hemoglobin and hematocrit. Thiazolidinediones may result in resumption of ovulation. Premenopausal anovulatory women should be counseled about this risk.
Meglitinides
Meglitinides (glitazones or glinides) are short-acting secretagogues, working similarly to their longer-acting sulfonylurea counterparts. When used for the treatment of type 2 diabetes, meglitinides have been shown to reduce A1C by 0.5–1.5 percent, with nateglinide (Starlix) being slightly less effective than repaglinide (Prandin). Neither agent has been shown to reduce clinically relative endpoints. Meglitinides are approved for the treatment of type 2 diabetes, as an adjunct to diet and exercise. The ADA does not recommend meglitinides for routine use in the treatment of type 2 diabetes, as they have not demonstrated clinical or cost-effective superiority compared with routine therapies. Meglitinides may be used as adjunct therapy in patients who are unable to take standard treatment, and may be particularly beneficial in those with elevated postprandial glucose elevations.

Available Products
Nateglinide (Starlix) and repaglinide (Prandin) are the two products available in the United States. Both products are only available as brand name and are costly for patients without prescription insurance.

Dosing and Dose Adjustments
Meglitinides have a shorter onset of action and duration of action when compared with sulfonylureas and therefore require more frequent dosing. Starting and maximum recommended doses differ between the two agents and can be found in Table 2. They should be taken 15 minutes before meals and are titrated weekly. To avoid hypoglycemia, instruct patients to omit their dose if skipping a meal.

Adverse Effects
Common adverse effects include hypoglycemia, upper respiratory infection, and headache. Glinides are associated with less hypoglycemia when compared with sulfonylureas.

Drug Interactions
Combination therapy with sulfonylureas is not recommended, given their similar mechanism of action and risk for hypoglycemia. Repaglinide is contraindicated with use of gemfibrozil and should be used with caution in combination with itraconazoles, as they can potentiate its hypoglycemic effects. These three medications should never be used together.

Contraindications/Precautions
The use of meglitinides is contraindicated in patients with type 1 diabetes or DKA, and those using gemfibrozil. Use caution in patients with liver disease, renal disease, or adrenal or pituitary insufficiency, and those susceptible to hypoglycemia (such as elderly and malnourished persons).

Alpha-Glucosidase Inhibitors
Alpha-glucosidase inhibitors lower postprandial glucose levels by delaying carbohydrate absorption in the brush border of the small intestine. They have been shown to reduce A1C by 0.5–0.8 percent but have not been shown to improve overall or cardiovascular mortality. Alpha-glucosidase inhibitors are recommended as adjunct therapy for the treatment of type 2 diabetes in patients who are unable to achieve glycemic control with diet alone. They are not routinely used due to their limited efficacy and gastrointestinal side effects, and are not recommended for routine use by the ADA. They may be used as adjunct therapy in patients that are unable to tolerate standard treatment or those with difficult to control postprandial blood glucose readings. Acarbose may have a role in treatment of prediabetes based on results of a single trial in patients with impaired glucose tolerance (IGT), in which patients receiving acarbose demonstrated a reduced risk of cardiovascular events.

Available Products
Acarbose (Precose) and miglitol (Glyset) are the two alpha-glucosidase inhibitors available in the United States. Acarbose is available as both brand and generic, whereas miglitol is only available as brand. Cost differs based on product, with acarbose (generic) being the least expensive option.

Dosing and Dosage Adjustments
To decrease gastrointestinal side effects, initiate therapy at low dose three times daily with the first bite of each meal. Starting dose and
maximum recommended dose information can be found in Table 2. Titration should be based on glucose control and tolerance. Patients with high carbohydrate diets may observe a larger decrease in A1C.

**Adverse Effects**
The most common side effects from therapy are gastrointestinal in nature (flatulence, diarrhea, and abdominal pain) and occur in high incidences, leading to poor long-term adherence rates. These adverse effects often preclude the routine use of alpha-glucosidase inhibitors as a treatment option.

**Drug Interactions**
Concurrent use with sulfonylurea may potentiate hypoglycemia and should be avoided. Instruct patients experiencing hypoglycemia to treat symptoms with sucrose, as the alpha-glucosidase inhibitors slow absorption of complex carbohydrates. Digestive enzyme supplements (amilase and pancreatin) and intestinal adsorbents (charcoal) may cause a reduction of glycemic effects, and concomitant use is not recommended.

**Contraindications/Precautions**
Alpha-glucosidase inhibitors are contraindicated in the following situations: SCr >2 mg/dL, cirrhosis, diabetic ketoacidosis, colon ulcerations, conditions that worsen with increased intestinal gas, digestive diseases, inflammatory bowel disease, partial bowel obstruction, and predisposition to bowel obstruction.

**Dipeptidyl Peptidase-4 Inhibitor**
Dipeptidyl peptidase-4 inhibitors block the breakdown of the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), thus potentiating their effects, which are responsible for increasing glucose-mediated insulin secretion and decreasing glucagon secretion. When used as monotherapy for the treatment of type 2 diabetes, DPP-4 inhibitors have been shown to decrease A1C by 0.6–0.9 percent. Dipeptidyl peptidase-4 inhibitors are indicated for use in type 2 diabetics as monotherapy or in combination with other antidiabetic agents to improve blood glucose. They are not recommended for routine use by the ADA due to their limited clinical efficacy when compared with other anti-diabetes agents. These agents have not been shown to reduce cardiovascular or overall mortality. They may be used as adjunct therapy in patients who are unable to tolerate standard treatment and may have some benefit in patients who are overweight, as they are weight neutral.

**Available Products**
Saxagliptin (Onglyza) was approved for use by the FDA in 2009 and was released in 2010. Sitagliptin (Januvia) was the first available DDP-4 inhibitor and is available in combination with metformin (Janumet). Both medications are available only as brand names and are costly for patients without prescription insurance. Two additional agents in this class are under FDA review for approval.

**Dosing and Dose Adjustments**
Both sitagliptin (Januvia) and saxagliptin (Onglyza) are administered once daily without regard to meals. Dosing information is available in Table 2.

**Adverse Effects**
Common side effects include headache, nasopharyngitis, and upper respiratory tract infection. Urinary tract infections were also observed with saxagliptin therapy. The use of sitagliptin alone or in combination with metformin has been associated with the development of acute pancreatitis in 88 cases. Instruct patients to monitor for symptoms of pancreatitis (such as upper abdominal pain, often radiating to the back, and accompanied by nausea, vomiting, and diarrhea) and recommend discontinuation if symptoms occur. The majority of cases were resolved with discontinuation of sitagliptin. Pancreatitis has not been observed with saxagliptin. However, it has not been on the market for a long period of time.

**Drug Interactions**
Use with caution in patients taking medications that are metabolized by the CYP3A4 and CYP3A5 system. Inducers of the above enzyme systems may increase metabolism and may decrease efficacy. Drugs that inhibit these
enzyme systems may interfere with metabolism and potentiate side effects of the drug. The risk of hypoglycemia is increased when DPP-4 inhibitors are used in combination with sulfonylureas.

**Contraindications/Precautions**
Use caution when using sitagliptin in patients with a history of pancreatitis, as safety in this population has not been studied. Patients with renal dysfunction require dose adjustments for both agents.

**Central Acting Dopamine Agonists**
Bromocriptine mesylate is a dopamine receptor agonist, and its exact mechanism for glucose reduction is unknown. It is FDA-indicated as an adjunct to diet and exercise in adults with type 2 diabetes. It should be not be used to treat type 1 diabetes or diabetic ketoacidosis. Limited efficacy data exists for when it is used in combination with thiazolidinediones, and efficacy has not been confirmed in combination with insulin. Reductions in A1C of approximately 0.5 percent have been observed when used as monotherapy and when added to other therapy including sulfonylureas and metformin. This is a new class approved to treat type 2 diabetes and the ADA has not commented on its place in therapy. More clinical evidence is needed to determine place in therapy.

**Available Products**
Bromocriptine mesylate (Cycloset) was approved for use by the FDA in May 2009 and is available as an 0.8 mg tablet.

**Dosing and Dose Adjustments**
Therapy should be initiated with a dose of 0.8 mg daily and increased weekly by 0.8 mg until a maximum tolerated dose of 1.6 to 4.8 mg is achieved. Bromocriptine should be taken within two hours after waking in the morning with food to minimize gastrointestinal side effects. Information about Cycloset dosing is located in Table 2.

**Adverse Effects**
Common side effects seen in clinical trials include nausea, fatigue, dizziness, vomiting, and headache. Hypoglycemia was not commonly observed when bromocriptine was used as monotherapy. Bromocriptine may cause somnolence, and patients should be advised not to operate heavy machinery if experiencing this adverse effect.

**Drug Interactions**
Concomitant use of bromocriptine and dopamine receptor antagonists (such as domperidone) may reduce the effectiveness of bromocriptine. Bromocriptine may increase ergot-related adverse effects and reduce ergot effectiveness. Bromocriptine is extensively metabolized by CYP3A4 and should be used with caution when coadministered with strong inhibitors (such as macrolide antibiotics, azole antifungals, and HIV protease inhibitors), inducers (such as rifampin and dexamethasone), or substrates of CYP3A4.

**Contraindications**
The use of bromocriptine is contraindicated in patients allergic to ergot-related drugs, those with syncopal migraines, and nursing women. Bromocriptine use is associated with hypotension and should be used with caution in patients taking antihypertensive medications. Use with caution in patients with a history of psychosis, as bromocriptine may exacerbate psychotic disorders or reduce the effectiveness of antipsychotics.

**INJECTABLE MEDICATIONS**

**Amylin Agonists**
Amylin is a hormone secreted in conjunction with insulin from the pancreatic beta cells. It reduces postprandial blood glucose by slowing gastric emptying, reducing both glucagon secretion, and induces appetite suppression. Amylin agonists decrease A1C by 0.5–0.7 percent. Amylin agonists are indicated as adjunctive therapy for the treatment of type 1 diabetes in patients using mealtime insulin who have failed to achieve glucose control. They are also indicated for the treatment of type 2 diabetes as an adjunctive agent for patients taking mealtime insulin who have failed to achieve glucose control with optimal insulin therapy (with or without the use of metformin and sulfonylurea). They
Amylin agonists are not recommended for routine use by the ADA due to their limited efficacy and poor tolerability. They may be used as adjunct therapy in patients who are unable to tolerate standard treatment or those with difficult-to-control postprandial blood glucose readings. They could be considered in overweight patients, as they have been proven to decrease weight by 2–3 pounds. Amylin agonists have not been shown to reduce cardiovascular or overall mortality.

**Available Products**
Pramlintide (Symlin) injection is the only amylin agonist available in the United States.

**Dosing and Dose Adjustments**
Dosing recommendations for the use of pramlintide differ based on type of diabetes. Starting doses and maximum doses are listed in Table 4. Pramlintide is administered immediately prior to major meals. Prophylactic insulin dose reduction by 50 percent is recommended upon the initiation of pramlintide to reduce the risk of hypoglycemia. Frequent blood glucose monitoring is recommended during dose initiation and titration.

**Adverse Effects**
The most common side effects observed with pramlintide include headache, hypoglycemia, nausea, vomiting, and anorexia. Nausea occurs in approximately 30 percent of patients and is often the rate-limiting factor for dose titration. Although pramlintide is indicated for use in combination insulin, there is a black box warning for the risk of severe hypoglycemia (usually seen within three hours) when used in combination with insulin.

**Drug Interactions**
Anticholinergics, alpha-glucosidase inhibitors, and other medications that alter gastrointestinal motility are not recommended for use in combination with amylin agonists. Concurrent use with glucose-lowering medications may increase the risk of hypoglycemia, and monitoring is recommended when used in combination.

**Contraindications**
Amylin agonists are contraindicated in patients with a confirmed diagnosis of gastroparesis and hypoglycemia unawareness. Treatment with pramlintide is not recommended in the following patients: those with A1C >9 percent, those who show poor compliance with medication and glucose monitoring or who have severe recurrent episodes of hypoglycemia, and pediatric patients.

**Glucagon-like Peptide-1 Receptor Agonist**
Incretin, or GLP-1, is an endogenous hormone that modulates glycemic response. Glucagon-like receptor agonists enhance glucose-dependent insulin secretion, decrease glucagon secretion, and slow gastric emptying, resulting in lower blood glucose levels. Decreases in A1C of 0.5–1 percent are observed in patients using GLP-1 agonists. This class of medications is indicated for use in patient with

<table>
<thead>
<tr>
<th>Table 4: Non-Insulin Injectable Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Class</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Amylin agonists</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Glucagon-like Peptide-1 agonists</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

www.americaspharmacist.net November 2010 | america's PHARMACIST 39
type 2 diabetes as an adjunct to diet and exercise. Exenatide is also indicated for use as adjunct therapy for patients with type 2 diabetes and inadequate glycemic control with metformin and/or a sulfonylurea, and/or a thiazolidinedione. These agents may improve glycemic control but are associated with more gastrointestinal side effects than other agents. The ADA recommends use of GLP-1 agonists as an adjunct to lifestyle and maximum clinical effective doses of metformin. Exenatide may reduce body weight, but neither agent has been shown to improve patient-oriented outcomes such as cardiovascular or overall mortality.

Available Products
Exenatide (Byetta) and liraglutide (Victoza) are both solutions for subcutaneous injection available in multidose pens for daily use. Liraglutide was approved for use in 2010. A once weekly injection of exenatide is under development. None of these products are available as a generic and they are costly for patients without prescription insurance.

Dosing and Dose Adjustments
Exenatide is administered twice daily within 60 minutes before meals. The initial dose of liraglutide is intended to reduce gastrointestinal symptoms and does not provide effective glycemic control. Liraglutide should be initiated once daily without regard to meals or time of day. Seventy-eight post-marketing reports of altered kidney function in patients taking exenatide have prompted changes to prescribing information. It is not recommended in patients with a creatinine clearance less than 30 mL/min, and it should be used with caution in those with a creatinine clearance of 30–50 mL/min. The prescribing information also says to monitor patients carefully for the development of kidney dysfunction and evaluate the continued need for exenatide if kidney dysfunction is suspected while using the product. Liraglutide has not been extensively studied in the presence of renal dysfunction and should be avoided.

Adverse Effects
In clinical trials, the most commonly reported adverse effects for GLP-1 agonists were dose-related gastrointestinal distress. Overall, in five clinical trials gastrointestinal adverse effects were reported in 41 percent of patients taking liraglutide, compared with 17 percent treated with the sulfonylurea glimepiride. Both drugs have been associated with acute pancreatitis, although this is rare.

Drug Interactions
Patients receiving GLP-1 agonists are at increased risk of hypoglycemia when added to therapy with sulfonylureas, and consideration should be given to reducing the sulfonylurea dose. However, no standard recommendations have been established at this time.

Contraindications
The use of liraglutide is contraindicated in patients with a personal history or family history of medullary thyroid carcinoma, and in patients with multiple endocrine neoplasia syndrome type 2 (MEN2). These risks have not been observed in patients taking exenatide. Exenatide is contraindicated in patients with a hypersensitivity to the active drug or any component of the formulation.

Insulin
Commercially available insulin products mimic the plasma glucose regulatory actions of endogenous insulin by stimulating carbohydrate metabolism, facilitating transfer of glucose into cardiac and skeletal muscle and adipose tissue, and converting glucose into glycogen. Prescription insulin is a life-sustaining medication in those with type 1 diabetes. It is also the treatment of choice for hyperglycemic emergencies such as diabetic ketoacidosis or hyperosmolar hyperglycemic states. Insulin decreases blood sugars, A1C, and the frequency of hyperglycemic symptoms to a greater extent than any other agent, but it has not been shown to improve cardiovascular or overall mortality. When used in adequate doses, insulin can decrease any level of elevated A1C to, or close to, glycemic goals. The ADA recommends adding insulin for type 2 patients receiving the maximum tolerated dose metformin and whose A1C remains >8.5. Newer and more expensive analogues (such as aspart and glargine) have demonstrated marginal, if
any, benefit compared with older, less expensive insulins (such as regular and NPH) in terms of glycemic control or incidence of hypoglycemia.

Available Products
Insulins are characterized by their onset and duration of action. In general, insulins are categorized as bolus (administered prior to meals) or basal (administered one to two times daily) in nature. Bolus and basal insulin may be further categorized as rapid- or short-acting and intermediate- or long-acting, respectively. Premixed insulin preparations are a combination of basal and bolus insulin.

Dosing and Dose Adjustments
In those with type 1 diabetes, administration of a basal/bolus insulin replacement regimen that mimics natural physiologic insulin secretion is initiated using a weight-based approach. In general, endocrinologists or those with an advanced understanding of insulin initiate therapy in these types of patients. For patients with type 2 diabetes, a basal augmentation insulin regimen can be added to metformin at a starting dose of 10 units or 0.2 units/kg administered at night. Certain patients will require the additional bolus insulin to provide glycemic control. This decision is made based on the patient’s self-monitoring of blood glucose values and frequency of hyperglycemic symptoms. Many insulin titration schedules exist. Most patients will achieve glycemic control by titrating an insulin dose by two units every three days until blood glucose values are consistently in the target range or hyperglycemic symptoms resolve. There is no ceiling dose of insulin, but frequent hypoglycemia may limit dose titration. Insulin properties are described in Table 5.

Adverse Effects
Hypoglycemia is the most common adverse effect seen with insulin use. Insulin doses should not be increased in the presence of frequent hypoglycemia, and a dose decrease may be appropriate if an underlying cause cannot be identified and addressed. Upon insulin administration, or dose adjustment, patients should be educated to prevent, recognize and treat hypoglycemia. Insulin is associated with modest weight gain, but the benefits of glycemic control often outweigh the small increase in weight. Lipohyperotrophy may result from reuse of needles or

<table>
<thead>
<tr>
<th>Table 5: Available Insulin Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Name</strong></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Rapid-Acting</td>
</tr>
<tr>
<td>Aspart</td>
</tr>
<tr>
<td>Lispro</td>
</tr>
<tr>
<td>Glulisine</td>
</tr>
<tr>
<td>Short-Acting</td>
</tr>
<tr>
<td>Regular</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Intermediate-Acting</td>
</tr>
<tr>
<td>Neutral Protamine Hagedorn (NPH)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Long-Acting</td>
</tr>
<tr>
<td>Giargine</td>
</tr>
<tr>
<td>Detemir</td>
</tr>
<tr>
<td>Combination Products</td>
</tr>
<tr>
<td>Regular and NPH</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Lispro and neutral protamine lispro</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Aspart and neutral protamine aspart</td>
</tr>
</tbody>
</table>
repeated injections in the same area. Educate patients to rotate injection sites at each administration. Excessive insulin doses may cause hypokalemia. Although not conclusive, some evidence suggests insulin may cause a small increase in cancer risk.

Drug Interactions
Insulin use potentiates the risk of hypoglycemia when combined with medications that increase endogenous insulin secretion or peripheral utilization. Use of insulin and thiazolidinediones result in greater increases of fluid retention compared to either agent alone.

Contraindications
Insulin is contraindicated during an acute episode of hypoglycemia and in those with a hypersensitivity to insulin or any of its components. Hypersensitivity reactions to human recombinant insulin formulations are rare and occur less often than with porcine- and bovine-derived insulin products, which are no longer commercially available. Close monitoring of serum potassium is recommended in those taking insulin who are at high risk for hypokalemia (such as loop diuretic use).

Pregnancy Category
Insulin is safe and effective for the treatment of diabetes during pregnancy and is considered the drug of choice. Most insulins are considered pregnancy category B, with detemir, glargine, glulisine, and Novolog Mix having a rating of category C.

TREATMENT ALGORITHM/DISCUSSION OF TREATMENT PROGRESSION
In 2009, the ADA and the European Association for the Study of Diabetes released a consensus statement with recommendations for the treatment of type 2 diabetes, including an algorithm (Figure 1). The treatment algorithm is broken down into tier 1 (well-validated therapies that represent the best-established and most effective and cost-effective therapeutic strategies) and tier 2 (less well-validated therapies that may be considered in certain clinical situations). Tier 1 recommendations consist of the initiation of metformin and lifestyle modifications on diagnosis,
and sulfonylureas and basil insulin as add-on therapy when further glycemic control is desired. The addition pioglitazone or a GLP-1 agonist is recommended when hypoglycemia is particularly undesirable or in patients who are unable to tolerate or use tier 1 therapies. Alpha-glucosidase inhibitors, meglitinides, DPP-4 inhibitors, and amylin agonists are not listed as tier 1 or 2 agents due to their overall limited efficacy, lack of patient-oriented evidence, and increased cost when compared with other therapies. Cycloset was not commercially available during the publication of the consensus statement.

PREVENTION AND MONITORING FOR COMPLICATIONS
Morbidity and mortality associated with diabetes is not a result of high blood sugars in and of itself. Instead, it is due to the effects hyperglycemia has on other systems of the body. Although many believe glycemic control is the most important aspect of diabetes care, addressing CVD risk factors such as hypertension, dyslipidemia, and smoking provides an overall greater benefit in terms of risk reduction. Diabetes complications are commonly categorized as either macrovascular or microvascular in nature. Dysfunction and damage of large vessels (macrovascular) contribute to the development of atherosclerosis, coronary heart disease, stroke, and peripheral vascular disease. Microvascular complications result from disease of the small blood vessels found in the eyes, nerves, and kidneys. The community pharmacist has the ability to provide education to patients relating to the monitoring and prevention of diabetes complications. Recommendations for complication screening are found in Table 6.

BLOOD PRESSURE
In patients with diabetes, hypertension is associated with an increased risk for the development of macrovascular and microvascular complications. Long-standing, uncontrolled blood pressure in patients with type 1 diabetes is a predisposition for developing nephropathy. Goal blood pressure for all patients with diabetes is <130/80 mmHg and should be measured at every office visit. A diagnosis of hypertension is made by assessing office blood pressure above goal on two separate occasions. Therapeutic lifestyle modifications are recommended for the treatment of hypertension in all patients and may be used first-line for blood pressures of <140/90 mmHg for up to three months. Several antihypertensive regimens (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, and beta blockers) are recommended for treatment and have been shown to reduce short-term effects of major cardiovascular events. Thiazide diuretics or angiotensin-converting enzyme (ACE) inhibitors are the preferred agents for the treatment of stage 1 hypertension (140–159/90–99 mm Hg). A two-drug combination using thiazide diuretic plus ACE inhibitor is recommended when treating stage 2 hypertension (>160/100 mm Hg). Newer evidence calls into question the utility of beta-blockers for the treatment of hypertension in diabetes patients. A recent meta-analysis of eight randomized trials comparing atenolol versus other antihypertensives found either no significant differences or worse outcomes with atenolol for total mortality, stroke, or myocardial infarction. It remains to be seen whether or not these findings hold true for other beta-blockers. For the time being, it is reasonable to reserve beta-blockers for those with a history of myocardial infarction or heart failure and utilize other proven therapies for the treatment of hypertension.

DYSLIPIDEMIA
Lipid abnormalities are common in patients with diabetes. Elevated low-density-lipoprotein cholesterol (LDL-C) is associated with an increased risk for the develop-

Table 6: Recommendations for Complication Screening

<table>
<thead>
<tr>
<th>Screening</th>
<th>Recommended Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>At every visit</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Annually</td>
</tr>
<tr>
<td>Monofilament foot exam</td>
<td>Annually with visual inspection at every visit</td>
</tr>
<tr>
<td>Diabetic eye exam</td>
<td>Annually</td>
</tr>
<tr>
<td>Urine microalbumin</td>
<td>Annually</td>
</tr>
</tbody>
</table>
ment of CVD. Controlling LDL-C is the primary target of therapy unless triglycerides are >500 mg/dL due to the risk of acute pancreatitis. In this case, treatments for elevated triglycerides (such as fibrates, fish oil, and niacin) should be employed. Once triglycerides are below 500 mg/dL, LDL-C becomes the target of therapy. Goal LDL-C for diabetes patients with or without overt CVD is <100 mg/dL. An optional goal of <70 mg/dL may be considered in very high-risk patients, including those with overt CVD and multiple or poorly controlled risk factors (such as metabolic syndrome). Screening is conducted using a fasting lipid profile and should be performed annually for all diabetes patients. Less stringent monitoring may be considered in patients who have achieved their LDL-C goal. Therapeutic lifestyle modifications are recommended in all patients above goal LDL-C. Statins are considered the drug of choice for the treatment of dyslipidemia. In diabetes patients with cardiac risk factors but without a history of CVD, statin therapy reduced the risk of first major cardiovascular events regardless of initial LDL-C. These results helped inform the ADA, which resulted in the latest recommendations that statins be considered independent of baseline lipid levels in those over the age of 40 without CVD and one or more CVD risk factors. In patients under 40 without overt CVD, therapeutic lifestyle changes (TLC) plus a statin are recommended when LDL-C is above goal. In patients with established CVD the recommendations are less ambiguous. In addition to aspirin, a beta-blocker, and an ACE inhibitor, statin therapy is considered the standard of care to prevent a future event and should be offered to all patients without a contraindication.

ANTIPLATELET THERAPY
In previous years, the use of aspirin for primary prevention of CVD was recommended in diabetes patients at increased risk; defined as over 40 years old with additional risk factors (family history of CVD, smoking, hypertension, dyslipidemia, or albuminuria). Newer evidence questions the use of aspirin for primary prevention. Recently published clinical trials failed to demonstrate a reduction in cardiovascular endpoints in diabetes patients using aspirin for primary prevention. Based on the results of these trials, which were included along with other trials in a meta-analysis performed by the ADA, the recommendations regarding aspirin use for primary prevention were revised. Consider recommending aspirin for primary prevention in men over 50 and women over 60 with a 10-year CVD risk of >10 percent and additional risk factors as defined above. The recommended dose of aspirin is 75–162 mg daily. The benefits of aspirin use for secondary prevention are well established, and it should be used in diabetes patients with a history of CVD. Clopidogrel may be used in patients with a history of CVD and an aspirin allergy.

RETINOPATHY
Diabetic retinopathy is defined as damage to the retina caused by long-term hyperglycemia. Retinopathy affects both type 1 and type 2 patients and is usually related to duration of diabetes. In the United States, diabetic retinopathy is the leading cause of blindness in adults between the ages of 20 and 74. The ADA recommends screening for diabetes retinopathy shortly after diagnosis for people with type 2 diabetes, and within five years of diagnosis for type 1 diabetes patients older than 10. A dilated eye examination performed by an ophthalmologist or optometrist is recommended yearly. Control of blood glucose and blood pressure has been shown to reduce the risk of developing retinopathy in type 1 and 2 diabetics.

NEPHROPATHY
Diabetic nephropathy is the most common cause of end-stage renal disease in the United States. Albuminuria (protein in the urine) is used as a marker for nephropathy. Patients with type 1 diabetes in general, and patients with type 2 with microalbuminuria (small amounts of protein in the urine), are at increased risk for disease progression and macroalbuminuria (large amounts of protein in the urine), as well as the development of fulminate kidney disease. Risk factors for diabetic nephropathy include hypertension, poor glucose control, and microalbuminuria. A diagnosis of microalbuminuria may be a marker for increased mortality and future
nephropathy. The preferred method for screening is a urine albumin-to-creatinine ratio via a random spot collection. Degrees of albumin-urea are defined as follows: microalbuminuria 30–299 μg/ml and macroalbuminuria ≥300 μg/ml. Initial screening for type 1 diabetes patients is recommended within five years of diagnosis.

For those with type 2 diabetes, initial screening should occur at diagnosis. Monitoring is recommended yearly thereafter. The primary intervention for prevention and progression of nephropathy is blood pressure and blood glucose control. Treatment strategies to prevent worsening of nephropathy differ based on type of diabetes and degree of albuminuria. Both ACE inhibitors and ARB’s have been shown to slow the progression of albuminuria in type 2 diabetes patients with documented microalbuminuria. Reduction in overall mortality has been seen with the use of ACE inhibitors, whereas there is limited evidence suggesting a reduction in mortality with ARB therapy. According to the ADA, ACE inhibitors or ARBs may be considered for use in type 2 patients with microalbuminuria. The treatment of choice for macroalbuminuria in type 2 diabetes is an ARB, as they have been shown to reduce risk for end-stage renal disease in this population.

The favored agents in those with type 1 diabetes with any degree of albuminuria are ACE inhibitors. The combination of ACE inhibitors and ARBs has been shown to reduce progression to albuminuria in certain patients, but there is no data to support long-term reduction in renal and cardiovascular events. If combination therapy is considered, close monitoring is required due to increased risk of hyperkalemia.

**PERIPHERAL NEUROPATHY**

Nerve damage is a complication of both type 1 and type 2 diabetes mellitus. There are several different types of diabetic neuropathies. The most frequent neuropathy is symmetric distal polyneuropathy (DPN), commonly referred to as peripheral neuropathy. Peripheral neuropathy presents as pain, numbness, and tingling in the extremities, most commonly in the legs, feet, and toes. Incidence is thought to increase with duration of diabetes. Education about proper foot care and assessment of sensation can reduce risk for the development of diabetic foot ulcers. The ADA recommends annual testing for loss of protective sensation (LOPS) using a 10 g monofilament, plus testing any one of the following: vibration using a 128-hertz (Hz) tuning fork, pinprick sensation, ankle reflexes, or vibration perception threshold. Patients should be educated on proper foot care and instructed to examine their feet daily for sores, cuts, and dryness. A comprehensive foot exam should be performed annually by a health care provider, to include assessment of sensation as described above, pedal pulses, and visual inspection. A visual inspection is recommended at every follow-up visit. Achieving glycemic control is considered a first-line preventive measure. Medications may be used to provide symptomatic pain relief. These include amitriptyline, nortriptyline, imipramine, gabapentin, carbamazepine, pregabalin, duloxetine, opioids, nonsteroidal anti inflammatory agents, and capsaicin cream.

**VACCINATIONS**

Patients with diabetes are more susceptible to infections and should be educated about the importance of staying up-to-date with the recommended vaccinations. The ADA and Centers for Disease Control (CDC) specifically recommend that patients with diabetes receive seasonal influenza and pneumococcal vaccinations, as influenza and pneumonia are associated with an increased risk of morbidity and mortality in the elderly and patients with certain comorbidities including diabetes. A yearly seasonal influenza vaccination starting in September is recommended for all diabetes patients age 6 months and older. The pneumococcal vaccination is also recommended for all patients with diabetes age 2 years and older. The pneumococcal vaccination should be administered on diagnosis. A second vaccination is recommended in patients age 65 and older if more than five years have passed since their last vaccination.

**SMOKING CESSATION**

The health risks of cigarette smoking and increased risk of morbidity and mortality for patients who choose to smoke...
are well known. All patients with diabetes should be counseled on the benefits of smoking cessation and advised to quit. There are several therapeutic options available to assist in smoking cessation, including nicotine replacement therapy, bupropion (Zyban SR), and varenicline (Chantix). The effectiveness of these commonly used medications appears similar. The use of medication to assist with smoking cessation, therefore, should be chosen based on individual preferences and potential contraindications to therapy. The benefits of smoking cessation counseling in combination with pharmacologic therapy are greater than either practice alone. Counseling provided by trained community pharmacists has been shown to increase a patient’s likelihood of quitting.

**ACUTE COMPLICATIONS**

Hypoglycemia is a risk for all patients with diabetes taking medications that may predispose them to low blood glucose (such as insulin and sulfonylureas). Clinical diagnosis of hypoglycemia is defined as a blood glucose of <50 mg/dL. However the ADA recommends treatment when blood glucose is <70 mg/dL. Common signs and symptoms of hypoglycemia include fatigue, shakiness, sweating, headache, hunger, and confusion. Patients with elevated blood glucose levels may experience hypoglycemic symptoms without having a blood glucose of <70 mg/dL as their blood glucose is being reduced to near-normal or normal ranges. Patients experiencing hypoglycemic symptoms should be advised to check finger-stick blood glucose and, if it is <70 mg/dL, should consume 15–20 g of glucose or carbohydrate (equal to three glucose tablets or four ounces of orange juice). Patients should be instructed to check finger-stick blood glucose again in 15 minutes to ensure resolution of hypoglycemia. This intervention may be repeated as needed if initial symptoms do not resolve or blood glucose does not rise above 70 mg/dL. Once above blood glucose is >70 mg/dL, suggest eating a small snack to maintain euglycemia. For a conscious patient experiencing a hypoglycemic episodes with a blood glucose of <50 mg/dL, 30 grams of carbohydrate or glucose consumption is recommended. In unconscious patients, a glucagon kit should be utilized and emergency management services activated.

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are potentially fatal conditions that occur in diabetes patients with elevated blood glucose. They are both considered medical emergencies, and patients should receive inpatient treatment. Diabetic ketoacidosis is caused by insulin deficiency and is most common in young type 1 diabetes patients. However, it can occur in adult type 1 patients and type 2 diabetes patients. The most common causes of DKA are alcohol abuse, infection, and noncompliance with treatment. Signs and symptoms of DKA include fruity/acetone breath, nausea, vomiting, dehydration, polydipsia, polyuria, and rapid breathing. Hyperosmolar hyperglycemic states occur primarily in older type 2 patients and result from extremely elevated glucose and dehydration, which increase plasma osmolality and altered mental status. A hyperosmolar hyperglycemic state is usually not associated with ketoacidosis. Signs and symptoms of HHS include weakness, visual disturbance, and leg cramps. Nausea, vomiting, lethargy, confusion, hemiparesis, seizures, and coma are less common symptoms of HHS. Fortunately, patients rarely present with these acute conditions in the community pharmacy. However, it is important for pharmacists to recognize the signs and symptoms of DKA and HHS to

**Table 7: Diabetes Update 2010**

- A1C newly endorsed as a diagnostic test
- Estimated average glucose now recommended in conjunction with A1C monitoring
- New evidence suggests A1C “close to” 7% is acceptable for most patients (ACCORD trial)
- New Antidiabetic Agents
  - a) Onglyza (saxagliptin): New DPP-4 inhibitor
  - b) Cycloset (bromocriptine mesylate): New class (dopamine agonists) for treatment of type 2 diabetes
  - c) Victoza (liraglutide): New GLP-1 agonist
  - d) ActoPlus Met XR: New formulation
- Recommendations for the use of aspirin for primary prevention have been updated

Source: The Standards of Medical Care in Diabetes—2010, published by the American Diabetes Association (ADA).
and in the evening before dinner (220–260 mg/dL).

PMH: Type 2 diabetes
Hypertension (diagnosed two years ago)
Osteoporosis

Medications: Lisinopril 10 mg daily
Risedronate 35 mg once weekly
Os-Cal 500 + Extra D 1 tablet twice daily
Metformin 500 mg daily for seven days, then BID (new with today’s prescription)

Allergies: Sulfa (hives and difficulty breathing)

Family History: Mother (68) has type 2 diabetes
Father (70) has CHF

Social History: Smokes 1 pack per day
Denies alcohol
Caffeine: 1–2 beverages per day

Weight: 180 lbs.
Height: 5’3”

Blood Pressure: at physician’s office today was 120/72

Diet: Has cut out sugar and is watching carbohydrate intake

Exercise: Has started walking three days per week for about 15 minutes

Framingham risk: 9%

What important metformin counseling points would you review her when starting therapy?

Metformin therapy is considered first-line because it provides a significant reduction in blood glucose. More importantly, it has been shown to reduce the risk of premature death and other diabetes-related endpoints in patients such as her. The most common side effects from metformin therapy are gastrointestinal in nature; they usually are seen at the beginning of therapy or after a dose increase, and they subside after a few weeks of therapy. Patients should be instructed to take with food to minimize these effects. Lactic acidosis is an extremely rare yet potentially severe side effect of therapy. Patients should be counseled to self-monitor for symptoms of lactic acidosis (hyperventilation, myalgia, malaise, unusual somnolence) and notify a health care provider if these symptoms occur. Kidney function will be monitored by their physician while on this medication. Patients may begin to see a decrease in their FSBG as soon as two

Continued on page 38
CASE STUDY 1B
JD returns to your pharmacy, three months after her initial visit, with a prescription for motormin 1,000 mg twice daily. Under the direction of her physician, she has been taking metformin 500 mg two tablets twice daily for the past six weeks and has not experienced any side effects. She states that her FSBG “are not quite where they should be” and that her doctor is considering adding insulin to her regimen if the new dose of metformin does not work. She states that she “is not ready for insulin” and asks if you know anything about the two new diabetes medications that she saw on television, Onglyza and Victoza. She wants to know if these medications can be used instead of insulin. Upon further questioning, you uncover that she is opposed to using insulin due to fear and the association with her mother’s worsening diabetes. Her mother was weeks after starting, and they can also tell the medication is working if their symptoms of hyperglycemia decrease in frequency/severity.

At this time, would you recommend aspirin in JD? If so, what dose would you recommend?
This patient does not meet the criteria for aspirin therapy for primary prevention as set by the ADA. She is not more than 60 years old and her Framingham 10-year CHD risk is under 10 percent. However, she does have risk factors such as smoking and hypertension. These risk factors should be addressed as part of a comprehensive care plan. You should consider reassessing the patient’s CHD risk once the patient is over 60 years old and recommend aspirin at that time if appropriate. Doses of 81 mg daily have been shown effective in providing cardioprotection.

What complication education and screening would you recommend at this time?
Blood pressure screening is recommended at every office visit. Patient has hypertension and is at goal blood pressure (according to reading in office today) of under 130/80 mmHg. Recommend continuous assessment to ensure goals are being met and the treatment regimen is appropriate.

Dyslipidemia
The ADA recommends screening with a fasting lipoprotein profile on diagnosis. In this patient, therapy with a statin may be considered independent of baseline lipid levels, as she is over 40 years old without CVD and one or more CVD risk factors (smoking, hypertension).

Retinopathy
The ADA recommends screening for diabetic retinopathy shortly after diagnosis for type 2 diabetes patients. A dilated eye examination is recommended yearly.

Nephropathy
The ADA recommends initial screening for nephropathy shortly after diagnosis for type 2 diabetes patients, using a urine albumin-to-creatinine ratio via a random spot collection. Monitoring is recommended annually thereafter.

Foot Exam
The ADA recommends comprehensive foot exams annually, which include assessment of sensation, pedal pulses, and visual inspection. A visual inspection is recommended at every follow-up visit. Education about proper foot care is also recommended.

Smoking Cessation
JD should be advised about the benefits of smoking cessation and advised to quit. Smoking cessation counseling in combination with pharmacologic therapy may be of benefit in this patient.

Vaccinations
The ADA and CDC recommend offering pneumococcal and seasonal influenza vaccines to all diabetes patients without a contraindication. As it is currently flu season, the patient is due for her annual influenza vaccination. The patient should also be advised to receive a pneumococcal vaccination if it has not been administered in the past.
started on insulin just prior to going on dialysis. The patient has lost 10 pounds and quit smoking after her smoking cessation counseling session at your community pharmacy. Her FSBG are as follows: morning fasting: 160–180 g/dL, and before dinner: 180–200 mg/dL. Recent A1C was 8 percent.

What would you tell JD about her available treatment options?
According to the ADA treatment algorithm, the use of sulfonylureas or basal insulin is recommended as add-on therapy once patients have reached maximum clinical doses of metformin. As JD has a sulfonamide allergy that resulted in difficulty breathing, the physician is considering basal insulin. Given the patient’s fear of insulin, JD would benefit from education about the advantages and disadvantages of insulin therapy, as well as addressing any insulin myths or misconceptions.

If the patient is still opposed, alternative options may be considered. At that time, the patient would benefit from education regarding the benefits and risks of antidiabetes medication options (such as tier 2 less well-validated therapies) that may be considered in her situation. The tier 2 therapies include pioglitazone and GLP-1 agonists. The use of pioglitazone is not recommended in this patient given her history of osteoporosis. Therefore, liraglutide (Victoza) or Exenatide (Byetta) are therapeutic options for this patient. JD may be unaware that GLP-1 agonists are injectables and she may not be interested, given her fear of insulin (an injectable). Use of DPP-4 inhibitors (Onglyza) are not recommended in the ADA’s treatment algorithm due to their overall limited efficacy, lack of patient-oriented evidence, and increased cost when compared with other therapies. Onglyza may be considered in patients who are unable to take standard treatment, which may be the case with this patient.

CONTINUING EDUCATION QUIZ
Select the correct answer.

1. An absolute insulin deficiency arising from beta cell destruction best describes which type of diabetes?
   a. Type 1
   b. Type 2
   c. Gestational
   d. Prediabetes

2. Which of the following patients would benefit most from a diabetes screening?
   a. A 44-year-old woman with no risk factors
   b. An overweight 40-year-old male with no other risk factors
   c. An obese 35-year-old African American female
   d. A 38-year-old female with a history of gestational diabetes and a BMI of 23

3. According to the ADA, which of the following lab values is considered diagnostic for diabetes if confirmed by a second reading on a subsequent day?
   a. Oral glucose tolerance test (two hours postprandial) ≥180 mg/dL
   b. Fasting plasma glucose ≥110 mg/dL
   c. Estimated average glucose ≥126 mg/dL
   d. Hemoglobin A1C ≥6.5 percent

4. The ADA recommends a goal two-hour postprandial plasma glucose of less than:
   a. 130 mg/dL
   b. 140 mg/dL
   c. 180 mg/dL
   d. 200 mg/dL

5. Which of the following tests is recommended in conjunction with A1C monitoring, as it is thought to be more understandable when discussing laboratory monitoring with patients because it correlates with patient SMBG values?
   a. Fasting plasma glucose
   b. Estimated average glucose
   c. Postprandial plasma glucose
   d. Preprandial plasma glucose
6. Which of the following antidiabetic medication class is considered first line for the treatment of type 2 diabetes?
   a. Thiazolidinediones
   b. Sulfonylureas
   c. Biguanides
   d. Dipeptidyl peptidase inhibitors

7. Due to the concern for adverse cardiovascular effects, which of the following medications is no longer recommended for use by the ADA?
   a. Glyburide
   b. Rosiglitazone
   c. Acarbose
   d. Nateglinide

8. According to the ADA treatment algorithm, pioglitazone is recommended for the treatment of type 2 diabetes in which of the following situations?
   a. In combination with metformin as a second-line, well-validated treatment option
   b. In combination with metformin in patients who are unable to use tier 1 agents
   c. In combination with insulin in patients who are unable to use tier 1 agents
   d. In patients with CHF that are unable to use metformin

9. Which of the following medications is associated with hypotension and should be cautiously in patients taking antihypertensives?
   a. Saxagliptin
   b. Liraglutide
   c. Bromocriptine
   d. Rosiglitazone

10. All of the following medications promote weight loss in diabetes patients EXCEPT:
    a. Glipizide
    b. Exenatide
    c. Amylin
    d. Metformin

11. Which of the following statements best describes the primary difference between exenatide (Byetta) and liraglutide dosing?
    a. Liraglutide is dosed twice daily with meals, while exenatide is dosed once daily without regard to meals.
    b. Exenatide is dosed twice daily with meals, while liraglutide is dosed once daily without regard to meals.
    c. There is no difference in dosing and both should be taken with meals.
    d. There is no difference in doing and both can be taken without regard to meals.

12. Which of the following insulins should you instruct patients to administer prior to a meal?
    a. NPH (Humulin N)
    b. Glargine (Lantus)
    c. Detemir (Levemir)
    d. Glulisine (Apidra)

13. All of the following medications have been associated with an increased risk of pancreatitis EXCEPT:
    a. Sitagliptin
    b. Saxagliptin
    c. Exenatide
    d. Liraglutide

14. What is the drug of choice for the treatment of diabetes during pregnancy?
    a. Insulin
    b. Sulfonylureas
    c. Thiazolidinediones
    d. Glucagon-like peptide inhibitors

15. With type 2 diabetes, which of the following aspects of care provides the most benefit in terms of risk reduction?
    a. Smoking cessation
    b. Use of ACE inhibitors
    c. Blood glucose control
    d. Use of aspirin
16. Which of the following is the recommended goal blood pressure for a diabetic patient with hypertension?  
a. <120/80  
b. <130/80  
c. <130/85  
d. 140/90

17. Based on recent evidence, which of the following diabetes patients is most likely to benefit from the use of aspirin to reduce the risk of cardiovascular disease?  
a. A 30-year-old male with hypertension and a 10-year CHD risk of 8 percent  
b. A 40-year-old female with hyperlipidemia and a 10-year CHD risk of 5 percent  
c. A 50-year-old male smoker with a 10-year CHD risk of 11 percent  
d. A 50-year-old female smoker with a 10-year CHD risk of 8 percent

18. Which of the following interventions has NOT been shown to reduce the risk of worsening nephropathy in patients with diabetes?  
a. Use of an ACE inhibitor  
b. Use of a beta-blocker  
c. Control of blood pressure  
d. Control of blood glucose

19. The ADA recommends annual screening for all of the following diabetes complications EXCEPT:  
a. Urine microalbumin  
b. Diabetes eye exam  
c. Monofilament foot exam  
d. Blood pressure

20. Which of the following interventions would you recommend to treat symptoms of hypoglycemia in a conscious patient receiving both glipizide and acarbose with a blood glucose of 65 mg/dL?  
a. Glucagon injection  
b. Humulin R injection  
c. Three glucose tablets  
d. A bowl of ice cream

The Community Pharmacist’s Role in Diabetes Treatment
Nov. 1, 2010 (expires Nov. 1, 2013) • Activity Type: Application-based

FREE ONLINE C.E. Pharmacists now have online access to NCPCA’s C.E. programs through Powered by CECity. By taking this test online—go to the Continuing Education section of the NCPCA Web site (www.npapanel.org) by clicking on “Professional Development” under the Education heading you will receive immediate online test results and certificates of completion at no charge.

To earn continuing education credit: ACPE Program 207-000-10-011-H01-P
A score of 70 percent is required to successfully complete the C.E. quiz. If a passing score is not achieved, one free reexamination is permitted. Statements of credit for mail-in exams will be available online for you to print out approximately three weeks after the date of the program (transcript Web site: www.cec.org). If you do not have access to a computer, check this box and we will make other arrangements to send you a statement of credit: 

Record your quiz answers and the following information on this form.

NCPA Member License
NCPA Member No. ____________________________ State ______ No. __________________
Nonmember License
NCPA Member No. ____________________________ State ______ No. __________________

All fields below are required. Mail this form and $7 for manual processing to:  
NCPCA C.E. Processing Ctr., 405 Glenn Drive, Suite 4; Sterling, VA 20164

Last 4 digits of SSN MM-DD of birth

Name

Phone number (home or work)

Address

City State ZIP

Store e-mail (if avail.) Date quiz taken

Quiz: Shade in your choice

a b c d e  a b c d e  a b c d e  a b c d e
1. 2. 3. 4. 5.  11. 12. 13. 14. 15.
6. 7. 8. 9. 10. 16. 17. 18. 19. 20.

Quiz: Circle your choice

21. Is this program used to meet your mandatory C.E. requirements?  
a. yes  b. no
22. Type of pharmacist:  
a. owner  b. manager  c. employee
23. Age group:  
a. 21–30  b. 31–40  c. 41–50  d. 51–60  e. Over 60
24. Did this article achieve its stated objectives?  
a. yes  b. no
25. How much of this program can you apply in practice?  
a. all  b. some  c. very little  d. none

How long did it take you to complete both the reading and the quiz? ______ minutes

NCPA® is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. NCPCA has assigned two contact hours (0.2 CEU) of continuing education credit to this article. Eligibility to receive continuing education credit for this article expires three years from the month published.