Introduction

Nearly 24 million adults in the United States have diabetes. Of those, most—approximately 90% to 95%—have type 2 diabetes. Both environmental and genetic factors are believed to contribute to the pathogenesis of type 2 diabetes.

Type 2 diabetes is associated with substantial morbidity and mortality. Poorly controlled diabetes often leads to serious long-term complications that include both microvascular disease (e.g., retinopathy, neuropathy, nephropathy) and macrovascular disease (e.g., coronary artery disease, cerebrovascular disease, and peripheral arterial disease). In the United States, diabetes is the most frequent cause of new cases of blindness among adults 20 to 74 years of age, as well as the leading cause of end-stage renal disease. More than 60% of nontraumatic lower-limb amputations are performed in people with diabetes. Atherosclerosis occurs at an earlier age and with greater frequency among people with diabetes, such that diabetes is counted as a coronary heart disease risk equivalent. Two out of three patients with diabetes die from some form of cardiovascular disease (CVD). Overall, the risk for death among people with diabetes is approximately twice that of people without diabetes of similar age.

The long-term complications of type 2 diabetes contribute to exceptionally high disease-related costs. In 2007 (the latest year for which data are available), the direct medical costs and indirect costs (e.g., disability, work loss, premature mortality) associated with diagnosed diabetes in the United States totaled $174 billion. Nearly one in five hospitalizations in 2008 was related to diabetes, representing more than 7.7 million stays and $83 billion in hospital costs—23% of the total hospital costs in the United States. Average medical expenditures among people with diagnosed diabetes are estimated to be 2.3 times higher than what expenditures would be in the absence of diabetes.

Because pharmacists have frequent contact with patients with type 2 diabetes, they are ideally positioned to make substantial contributions to diabetes care. This monograph employs case vignettes to explore common clinical scenarios and emerging problems encountered by pharmacists. As is true in practice, the vignettes may not have a clear resolution. When firm recommendations cannot be made, summaries of the latest thinking about each situation are provided.
Learning Objectives

At the completion of this activity, the pharmacist will be able to:

1. State key statistics regarding the impact of type 2 diabetes in the United States.
2. Summarize the latest thinking about the pathogenesis of type 2 diabetes.
3. Recall treatment goals and options for patients with type 2 diabetes.
5. Identify effective strategies for addressing patient concerns about initiating insulin therapy.
6. Explain the appropriate use of U-500 insulin.
7. Discuss nonglycemic goals in comprehensive type 2 diabetes management.

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Mini-Review: Pathogenesis of Type 2 Diabetes

Type 2 diabetes is characterized by the dual defects of insulin resistance (i.e., diminished liver, muscle, and adipose sensitivity to insulin) and impaired pancreatic β-cell secretory function (i.e., impaired insulin secretion). Insulin resistance is associated with a decrease in the uptake and utilization of glucose by insulin-sensitive tissues (primarily muscle and adipose tissue) as well as ineffective suppression of hepatic glucose production. β-Cells are able to compensate for the decrease in insulin action (and resulting hyperglycemia) by increasing their production of insulin. However, as the fasting plasma glucose concentration continues to rise, the β-cells become less and less able to sustain the necessary levels of insulin secretion. A cycle of diminished insulin secretion and worsening insulin resistance ensues; the β-cells eventually fail altogether.

Because not everyone with insulin resistance goes on to develop type 2 diabetes, there is growing speculation that β-cell deterioration—reflecting both intrinsic secretion failure and reductions in β-cell mass—may actually precede insulin resistance and even contribute to its development. β-Cell dysfunction is now known to occur much earlier in the natural history of type 2 diabetes than originally thought; the landmark United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that approximately 50% of β-cell function already has been lost by the time type 2 diabetes is diagnosed, and some experts posit that as much as 80% of function was lost. Data from the Belfast Diet Study show that β-cell deterioration proceeds relatively slowly at first—at a rate of 1.7% per year for as long as 15 to 17 years—then accelerates abruptly to more than 18% per year between 3 and 5 years after diagnosis. β-Cell failure currently is considered to be more important than insulin resistance in the natural history of type 2 diabetes.

There also is growing appreciation of the role of etiologic mechanisms beyond β-cell dysfunction and insulin resistance. Diabetes expert Ralph DeFronzo, MD, refers to the multiple pathogenic mechanisms of type 2 diabetes as the “ominous octet” (Figure 1). In addition to decreased insulin secretion and decreased uptake of glucose, these mechanisms include increased hepatic glucose production, accelerated lipolysis in adipocytes (elevated plasma free fatty acid levels), diminished incretin effect, hypersecretion of glucagon by pancreatic α-cells, enhanced renal glucose reabsorption, and central nervous system insulin resistance resulting from neurotransmitter dysfunction.

Mini-Review: Approach to Treatment

Abundant conclusive evidence from long-term, randomized clinical trials shows that maintaining hemoglobin A1C levels close to the normal range reduces the incidence and progression of microvascular complications of type 2 diabetes. In general, every percentage point drop in A1C (e.g., from 8.0% to 7.0%) decreases the risk of microvascular complications by 40%. Early intervention to reduce A1C levels also appears to contribute to a long-term reduction in the risk of macrovascular disease.

Accordingly, A1C has become the primary target for glycemic control. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes recommend an A1C goal of <7%. The American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) recommend a more stringent A1C goal of ≤6.5%. All of these organizations recognize that more or less stringent A1C goals may be appropriate for certain patients, depending on the risk for hypoglycemia, comorbid conditions that limit life expectancy, and factors that may limit the safety of attempting aggressive glucose control.

A range of noninsulin oral and injectable antihyperglycemic agents (Table 1) and insulins are used in the treatment of type 2 diabetes. All agents (other than insulin) are limited in their ability to lower A1C. In one recent systematic review and meta-analysis of 61 double-blind, randomized controlled trials that met predefined methodologic criteria, most oral antihyperglycemic agents were found to decrease A1C levels by 0.5% to 1.25% (thiazolidinediones and sulfonylureas lowered A1C by approximately 1.0% to 1.25%). An increase in dose yielded a further decrease in A1C initially, with most of the treatment effect evident by 3 to 6 months. Higher baseline A1C levels were associated with greater declines in A1C; every 1% higher pretreatment A1C level predicted a 0.5% greater fall of A1C levels after 6 months of therapy. Disease duration had no clear effect on treatment response.

Because of the progressive loss of β-cell function in patients with type 2 diabetes, most available antihyperglycemic therapies are unable to maintain glycemic control over time, and the majority of patients eventually require combination therapy. The response to antihyperglycemic agents (other than insulin) usually is more pronounced in patients who are treatment naïve than in those who already are receiving therapy. This was demonstrated in a recent mixed-treatment comparison meta-analysis by Phung and colleagues. The analysis evaluated the efficacy of antihyperglycemic agents used as second-line therapy in patients experiencing an inadequate response to maximized and stable metformin therapy (24 weeks at ≥2,500 mg daily, or the maximally tolerated dose); it included 27 randomized clinical trials that enrolled more than 11,000 participants. The additional reductions in A1C provided by the different classes of drugs ranged from 0.64% to 0.97%.

Eventually, β-cell function deteriorates to such a degree that the secretory capacity of the cells is exceeded and exogenous insu-
lin replacement is required. Insulin remains the most potent glucose-lowering agent available; when used in adequate doses, insulin is able to decrease any level of elevated A1C to, or close to, the therapeutic goal. Most patients experience a 1% to 2% decrease in A1C after insulin therapy is initiated.

Glucagon-like peptide-1 (GLP-1) agonists (incretin mimetics)
- Liraglutide (Victoza)
- Exenatide (Byetta)
- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Pioglitazone (Actos)
- Rosiglitazone (Avandia)
- Thiazolidinediones ("gliptazones")
- Metformin (Glucophage)
- Acarbose (Precose)
- Miglitol (Glyset)
- Amaryl (Glimepiride)
- Glucophage (Metformin)
- Glucotrol (Glipizide)
- Micronase (Glyburide)
- Amaryl (Glimepiride)
- Micronase (Glyburide)
- Acarbose (Precose)
- Dymelor (Acetohexamide)
- Orinase (Tolbutamide)
- Diabinese (Tolazamide)
- Amaryl (Glimepiride)
- Actos (Pioglitazone)
- Byetta (Exenatide)
- Victoza (Liraglutide)
- Januvia (Sitagliptin)
- Onglyza (Saxagliptin)

Other Agents
- Bromocriptine mesylate (Cycloset)
- Colesevelam (Welchol)
- Carboxysalicylic acid sequestrants
- L-carnitine
- L-carnitine-8

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The surprising results of several recent large, long-term clinical trials—which showed no significant reduction in cardiovascular events with intensive glycemic control in patients with type 2 diabetes—reinforced the importance of also controlling nonglycemic risk factors, especially hypertension and dyslipidemias. According to estimates based on data from the Household Component of the Medical Expenditure Panel Survey, approximately two thirds (64.8%) of patients with diabetes have coexisting hypertension, and more than half (52.8%) have coexisting hyperlipidemia. Aggressive control of blood pressure and lipid levels in addition to glycemic control yields multiple benefits:

- Treating blood pressure to specified targets reduces the risk of CVD among patients with diabetes by 33% to 50% and the risk of microvascular complications by approximately 33%.
- In general, for every 10 mm Hg reduction in systolic blood pressure, the risk for any diabetes-related complication decreases by 12%.
- Improved control of low-density lipoprotein (LDL) cholesterol can reduce cardiovascular complications by 20% to 50%.

Case 1: Initiating Therapy in a Newly Diagnosed Patient

Dawn Jones is a 53-year-old white woman who stopped by your diabetes screening station at a recent health fair. She had eaten lunch 1 hour previously; her blood glucose reading was 275 mg/dL. You encouraged Dawn to visit her primary care provider for follow-up. The primary care provider diagnosed type 2 diabetes.

Dawn is 5’ 5” tall and weighs 202 lb (body mass index [BMI] ~34). Her A1C level at diagnosis was 8.7%.

Dawn visits the pharmacy today with prescriptions for metformin 500 mg once daily (to be titrated to 500 mg twice daily) and a glucose monitor. She explains with some pride that she won’t be needing the medication. “I finally joined Weight Watchers yesterday,” she tells you. “I just need to lose some of this weight. Then everything should be just fine.’’

Lifestyle interventions that include medical nutrition therapy and regular exercise (at least 150 minutes/week of moderate-intensity aerobic physical activity) are considered to be the cornerstone of management for type 2 diabetes. Given that approximately two thirds of patients with type 2 diabetes are obese (BMI £30), with a mean BMI of 34.2— and one out of five patients is morbidly obese (BMI £40)— weight loss is a principal focus of lifestyle interventions. Weight loss has a beneficial effect on glycemic control: in the ongoing Look AHEAD (Action for Health in Diabetes) study, overweight and obese patients with type 2 diabetes randomized to an intensive lifestyle intervention lost an average of 8.6% of their initial weight during the first 12 months, with an associated increase from 46% to 73% in the percentage of participants who achieved an A1C <7%.

Weight loss also helps to reduce blood pressure and improve the lipid profile in patients with type 2 diabetes.

Although there is widespread agreement that lifestyle interventions should be included as part of a comprehensive diabetes man-
management strategy, implementing and maintaining these changes poses an exceedingly high hurdle for many patients.\textsuperscript{3,5,13} It is now generally accepted that most patients with type 2 diabetes require pharmacologic therapy superimposed on lifestyle interventions to achieve desired glycemic targets.\textsuperscript{24,31,33}

A consensus algorithm (Figure 2) developed jointly by the ADA and the European Association for the Study of Diabetes (EASD) calls for metformin to be initiated concurrently with lifestyle interventions at the time of diagnosis and titrated to its maximally effective dose over a period of 1 to 2 months, as tolerated.\textsuperscript{4,33} Factors supporting this recommendation include the following:\textsuperscript{33}

- Metformin usually does not cause either hypoglycemia or weight gain.
- Metformin is associated with a generally low level of adverse effects (primarily gastrointestinal).
- The availability of generic versions of metformin contributes to a generally low cost of therapy.

Metformin therapy is recommended for all newly diagnosed patients unless specific contraindications (e.g., renal impairment, hepatic dysfunction, heart failure) are present.\textsuperscript{26,33}

A growing number of primary care providers are aware of the ADA/EASD algorithm, so it is becoming increasingly common to see newly diagnosed patients present with a prescription for metformin. Clinicians may not be aware that the algorithm has been the subject of much controversy; they also may not know that the algorithm reflects the expert opinion of the authors rather than official ADA position.\textsuperscript{13,17,42} Thus, it is not considered a “universal guideline” for diabetes management.\textsuperscript{17}

Other algorithms based on expert opinion are available. Notably, the AACE and ACE collaborated on “Diabetes Road Maps” and a glycemic control algorithm that incorporate all major classes of currently available antihyperglycemic therapies.\textsuperscript{22,23} The treatment pathways in these documents are stratified by A1C level as well as whether the patient is drug naïve or already receiving treatment.\textsuperscript{31} The stated concerns in prioritizing choices of medications include:\textsuperscript{23}

- Minimizing the risk and severity of hypoglycemia.
- Minimizing the risk and magnitude of weight gain.
- Consideration of both fasting and postprandial glucose levels as end points.
- Anticipated degree of patient adherence.

The algorithm (Figure 3) emphasizes the appropriate use of dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists because of their effectiveness in reducing A1C levels, lower risk of hypoglycemia, and beneficial effects on weight (weight neutrality with DPP-4 inhibitors, weight loss with GLP-1 agonists). Sulfonylureas and meglitinides are assigned a lower priority in the algorithm because they cause hypoglycemia and weight gain and provide only short-term beneficial effects on glycemic control.

Although medication costs also were considered when prioritizing choices of medications in the AACE/ACE algorithm, safety and efficacy were viewed as higher priorities than cost.\textsuperscript{23} The authors reasoned that the cost of medications represents only a very small portion (approximately 10%) of the total cost of care for patients with diabetes; the majority of total cost is related to the treatment of diabetes.

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**Figure 2. American Diabetes Association/European Association for the Study of Diabetes Algorithm for the Treatment of Type 2 Diabetes**

![Diagram](https://example.com/diagram.png)

- **Tier 1: Well-validated core therapies**
  - At diagnosis
    - Lifestyle + Metformin + Basal insulin
  - Step 1
    - Lifestyle + Metformin + Sulfonylurea\textsuperscript{a}
  - Step 2
    - Lifestyle + Metformin + Pioglitazone
      - No hypoglycemia
      - Do not use if edema or CHF
      - May cause bone loss
  - Step 3
    - Lifestyle + Metformin + GLP-1 agonist\textsuperscript{b}
      - No hypoglycemia
      - Promotes weight loss
      - May cause nausea/vomiting

- **Tier 2: Less well-validated therapies**
  - Lifestyle + Metformin + Sulfonylurea\textsuperscript{a}
  - Lifestyle + Metformin + Basal insulin

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\textsuperscript{a}Sulfonylureas other than glyburide or chlorpropamide
\textsuperscript{b}Insufficient clinical use to be confident regarding safety.

CHF = congestive heart failure; GLP-1 = glucagon-like peptide-1.

diabetes-associated complications and hospitalizations. Accordingly, it would be “counterproductive” to base treatment decisions primarily on cost if those therapies might result in increased (and more costly) complications, emergency department visits, and hospitalizations.

As shown in Figure 3, monotherapy is recommended only for patients with an A1C level of 6.5% to 7.5%. Metformin is recognized as the most appropriate initial choice for many patients in this range, but DPP-4 inhibitors, GLP-1 agonists, thiazolidinediones, and α-glucosidase inhibitors also are possibilities, especially in the specific situations described in the footnotes to the algorithm. For example, DPP-4 inhibitors are suggested for patients who have elevations in both fasting and postprandial glucose levels; GLP-1 inhibitors are suggested for patients who have greatly elevated postprandial glucose levels.

Combination therapy is recommended for all patients with an A1C level ≥7.6% because no single agent is likely to produce the degree of A1C lowering needed to achieve the target goal. Dual therapy is recommended for patients with an A1C of 7.6% to 9.0%; the preferred combination is metformin with either a GLP-1 agonist, a DPP-4 inhibitor, or a thiazolidinedione, in that order of preference. GLP-1 agonists are given the highest priority because of their somewhat greater effect on reducing postprandial glucose excursions and their potential for inducing weight loss.

Dual or triple drug therapy is recommended for asymptomatic, drug-naïve patients with an A1C level >9.0%. Symptomatic patients and patients already receiving treatment are candidates for insulin therapy, because even triple therapy is unlikely to achieve the target A1C goal.

Although the ADA/EASD algorithm and the AACE/ACE algorithm take different approaches, both focus on lowering the A1C level. Some diabetes experts have called for a radical rethinking of this focus, arguing that therapy for type 2 diabetes should be designed to target the multiple pathogenic abnormalities known to promote β-cell failure. Both DeFronzo and Unger and Parkin have advocated triple pharmacologic therapy consisting of metformin, a thiazolidinedione, and a GLP-1 agonist (in addition to lifestyle interventions), initiated as early as possible during the course of type 2 diabetes. The complementary mechanisms of action of these drugs would preserve β-cell function (and may maintain β-cell mass), increase insulin sensitivity in muscle and hepatic tissue, reduce hepatic gluconeogenesis, inhibit lipolysis, and decrease plasma free fatty acids.
acid levels, as well as provide antiatherogenic effects and support weight loss.\textsuperscript{12,13,17} Importantly, this combination would not cause hypoglycemia.\textsuperscript{12,17} According to DeFronzo, this triple combination approach offers the greatest likelihood of providing durable glucose control through a blunting of disease progression.\textsuperscript{16} DPP-4 inhibitors could be an alternative to GLP-1 agonists in the combination if they are shown to preserve β-cell function on a long-term basis.\textsuperscript{12} (Pharmacists should note that the efficacy and safety of this strategy have not been confirmed; a randomized clinical trial is planned.\textsuperscript{18})

As the treatment options for type 2 diabetes expand, the question of which medication or medications represents the best option for initial therapy in a given patient increasingly will lack a clear, evidence-based solution. The approach recommended to prescribers in the absence of evidence is to inform patients of all treatment options, explain the benefits and risks of each, and engage patients in the decision-making process.\textsuperscript{19} Initiating aggressive combination therapy would be of little benefit if, for example, a patient chose to fill only the least expensive prescription, thereby defaulting to an approach that would fail to fulfill the treatment plan.\textsuperscript{19}

**Case 2: When to Adjust Therapy**

Leroy Thomas is a 58-year-old African American man who was diagnosed with type 2 diabetes approximately 3 years ago. He visits the pharmacy today with a prescription for metformin extended-release 2,000 mg daily. Leroy is not new to your practice; dispensing records for the past 2 years show periodic prescriptions for the same dosage of metformin. Based on transfer notations and a brief discussion with Leroy about adherence, you suspect that he has been “coupon chasing”—visiting other pharmacies to take advantage of the latest promotion. You also are aware that Leroy receives most of his care from a busy group practice and rarely sees the same provider twice in a row.

Leroy is 5’ 10” tall and weighs 218 lb (BMI ~31). You collect the following additional information during today’s visit:
- **A1C:** 8.9%.
- **Blood pressure:** 128/78 mm Hg.

In addition to metformin, Leroy Thomas’s other current medications include:
- Hydrochlorothiazide 25 mg daily.
- Lisinopril 20 mg daily.
- Simvastatin 20 mg daily.
- Aspirin 81 mg daily.

**Test Your Knowledge: At what point should Leroy Thomas’s antihyperglycemic regimen ideally have been adjusted?**

For decades, the paradigm for long-term management of type 2 diabetes involved a stepwise “treat to failure” approach.\textsuperscript{10,12,13,17} Therapy was initiated with lifestyle modifications alone; medications were added slowly and sequentially only when a trial of diet and exercise proved to be inadequate for achieving glycemic control.\textsuperscript{12,13} A single oral agent was titrated to its maximal recommended dose, followed by a second oral agent added and titrated to its maximal dose, and so on.\textsuperscript{12,13}

As a result, prescribers often failed to adjust antihyperglycemic therapy in a timely manner—a problem referred to as clinical inertia.\textsuperscript{12,13,45} Long delays were incurred between treatment steps, leaving patients with uncontrolled hyperglycemia for extended periods.\textsuperscript{46,47} For example, in a study published in 2004, Brown and colleagues found that patients remained on sulfonylurea monotherapy (the usual initial treatment at the time of the study) for a mean of 35.1 ± 17.8 months before a new or additional treatment was started.\textsuperscript{48} During that interval, the patients’ A1C level exceeded 8.0% (the recommended “action threshold” at the time of the study) for a mean of 20.5 ± 18.0 months. Patients who followed the usual treatment progression—lifestyle intervention first, then oral monotherapy, then oral combination therapy, and finally insulin—would have spent approximately 10 years with an A1C level >7% and nearly 5 years with an A1C level >8%.

The current treatment paradigm calls for patients to be evaluated frequently to monitor response to treatment, and for therapy to be intensified rapidly if glycemic goals are not achieved.\textsuperscript{10,12,13} Yet clinical inertia persists in today’s practice environment.\textsuperscript{19} This may be attributed in part to the lack of direct evidence regarding the ideal frequency of physician visits for patients with type 2 diabetes.\textsuperscript{10} The 2010 ADA Standards of Medical Care in Diabetes call for routine A1C testing in all patients with diabetes, at the following recommended intervals:\textsuperscript{23}
- **At least twice yearly in patients who are meeting treatment goals and have stable glycemic control (A1C <7%).**
- **Quarterly in patients whose therapy has changed or who are not meeting glycemic goals.**

Some clinicians schedule follow-up visits to coincide with these testing intervals (i.e., two to four visits per year). Anecdotal evidence suggests that many patients are seen far less frequently, and that A1C testing does not occur as recommended.\textsuperscript{19} The fault does not necessarily lie entirely with health care providers; in some cases, patients may receive inadequate follow-up because they fail to return for routine visits.\textsuperscript{25}

Both the ADA/EASD and AACE/ACE algorithms challenge clinicians to monitor therapy closely and adjust the treatment plan every 2 to 3 months as needed until the goal for A1C has been achieved.\textsuperscript{10,33} Because the response from dose escalation usually is limited, adjusting the treatment plan generally means adding another agent.\textsuperscript{25}

Pharmacists can help to combat clinical inertia by offering point-of-care A1C testing and intervening with prescribers as appropriate. Several devices appropriate for use in pharmacies (e.g., Bayer A1C Now+) have been granted waived status under the Clinical Laboratory Improvement Amendments. However, pharmacists should be aware that the results obtained with these devices may be less sensitive and specific than laboratory testing.\textsuperscript{25}

**Case 3: How to Adjust Therapy**

Martina Hernandez is a 48-year-old Hispanic woman of Mexican descent who was diagnosed with type 2 diabetes approximately 2 years ago. Therapy was initiated with metformin 500 mg twice daily and titrated to the current dose of metformin 1,000 mg twice daily.

Martina is 5’ 1” tall and weighs 180 lb (BMI 34). Although she has successfully lost weight (as much as 25 lb) on various diets in the past, she regained all of the lost weight each time. She is better able to adhere to her goal of taking a 30-minute walk on at least 5 days each week.
When Martina visited her primary care provider earlier this week, her measured A1C level was 8.1%. She comes to the pharmacy today with a prescription for glipizide 10 mg once daily in addition to a metformin refill. She asks the pharmacy technician to make sure that glipizide is on the list of medications that cost $4.

Test Your Knowledge: What constitutes appropriate intensification of antihyperglycemic therapy for Martina Hernandez?

The care of patients with type 2 diabetes whose A1C level remains above target despite metformin therapy and lifestyle modifications is another area of clinical controversy. The ADA/EASD and AACE/AACE algorithms provide strikingly different advice about escalating antihyperglycemic therapy.

The ADA/EASD algorithm calls for a second agent to be added to metformin monotherapy within 2 to 3 months if the maximum tolerated dose of metformin fails to achieve or sustain the glycemic goals (Figure 2). The preferred options for the second agent are a sulfonylurea or insulin, with insulin therapy (basal therapy with an intermediate- or long-acting formulation) recommended for patients with an A1C level >8.5% or symptoms secondary to hyperglycemia.

The ADA/EASD algorithm also offers two “tier 2” options for the second agent: pioglitazone and a GLP-1 agonist. (“Tier 2” represents less well-validated therapies.) Either agent may be considered when the risk of hypoglycemia is especially undesirable (e.g., in patients who have hazardous jobs); a GLP-1 agonist may be considered if weight loss is a major goal of therapy and the patient’s A1C level is <8.0%.

As illustrated in Figure 2, the options for further escalation of therapy depend on which second agent was added. Ultimately, a combination of metformin and intensive insulin therapy (i.e., basal therapy plus bolus injections of a short- or rapid-acting insulin before selected meals to reduce postprandial glucose excursions) is recommended for all patients.

It is noteworthy that none of the other available antihyperglycemic agents—amylin agonists, α-glucosidase inhibitors, meglitinides, or DPP-4 inhibitors—are included in the algorithm. The authors state that these agents were omitted for one or more of the following reasons:

• They have lower or equivalent overall glucose-lowering effectiveness compared with the recommended agents.
• Limited clinical data regarding their use are available.
• They are relatively expensive compared with the recommended agents.

The authors do note that these agents may be appropriate choices in selected patients.

In clinical practice, the choice of a sulfonylurea for second-line therapy is reinforced by the pricing policies of a growing number of pharmacies, which offer select diabetes medications—typically generic versions of metformin and sulfonylureas—to patients at low (e.g., $4) or no cost. Combination therapy with metformin and a sulfonylurea thus becomes the least expensive option by far. A key criticism of the ADA/EASD algorithm is that neither metformin nor the sulfonylureas have been shown to preserve β-cell function.

Sulfonylureas also are associated with a substantial risk of hypoglycemia and weight gain.

In the AACE/AACE algorithm (Figure 3), metformin remains the foundation of combination therapy for most patients because of its safety and mechanism of action as an insulin sensitizer. For patients with an A1C level of 6.5% to 7.5%, the recommended second component of dual therapy is a GLP-1 agonist, a DPP-4 inhibitor, a thiazolidinedione, or a meglitinide or sulfonylurea, in that order of preference. Again, GLP-1 agonists are given the highest priority because of their somewhat greater effectiveness in reducing postprandial glucose excursions relative and their potential for inducing weight loss. When triple therapy is indicated for patients with an A1C level of 6.5% to 7.5%, six combinations are possible, based on the addition of a thiazolidinedione, meglitinide, or sulfonylurea:

1. Metformin + GLP-1 agonist + thiazolidinedione.
2. Metformin + GLP-1 agonist + meglitinide.
3. Metformin + GLP-1 agonist + sulfonylurea.
4. Metformin + DPP-4 inhibitor + thiazolidinedione.
5. Metformin + DPP-4 inhibitor + meglitinide.
6. Metformin + DPP-4 inhibitor + sulfonylurea.

A thiazolidinedione is preferred to minimize the risk of hypoglycemia. Patients with an A1C level of 7.6% to 9.0% would have been started on dual therapy (Figure 3). The preferred strategy for triple therapy is to add a thiazolidinedione to the combination of either metformin plus a GLP-1 agonist or metformin plus a DPP-4 inhibitor. The least preferred combination is metformin, a thiazolidinedione, and a sulfonylurea because of the high risk of weight gain and hypoglycemia. Meglitinides and α-glucosidase inhibitors do not have sufficient A1C-lowering potential to be considered for triple therapy.

The one place in the AACE/AACE algorithm where sulfonylureas are preferred is in triple therapy for asymptomatic patients with an A1C level >9.0% who were started on dual therapy. The recommendation is based on the somewhat greater efficacy and more rapid onset of action of the sulfonylurea compared with a thiazolidinedione.

Nauck and colleagues recently speculated on the most likely future roles of the various incretin-based therapies in the treatment of type 2 diabetes. One of the authors suggested that DPP-4 inhibitors eventually will be ranked before GLP-1 agonists in treatment algorithms because of the greater acceptability of oral administration. Ultimately, DPP-4 inhibitors may replace existing oral antihyperglycemic agents, while the GLP-1 agonists (which are administered by subcutaneous injection) may be viewed as competitors for insulin treatment.

As is the case when therapy for type 2 diabetes is initiated, prescribers seeking to intensify a patient’s treatment regimen are advised to inform the patients of all options available, explain the benefits and risks of each, and include the patient in the decision-making process.

Initiating Insulin Therapy

It is 4 years later. Martina Hernandez is now 52 years old. Her current medication regimen includes:

• Metformin 1,000 mg/sitagliptin 50 mg (administered as a combination product).
• Glipizide 10 mg once daily.

Martina visited her primary care provider earlier this week to assess the current level of glycemic control after 11 months on this regi-
Men. Her measured A1C was 9.2%.

Martina comes to the pharmacy today with a prescription for insulin glargine. As the pharmacy technician readsies the product and associated supplies for dispensing, you sit down with Martina to teach her how to use and inject insulin. She begins to cry. “I knew this would happen,” Martina says. “It’s all my fault because I couldn’t lose weight. My mother had to use insulin when I was a little girl—I’ll never forget what she went through, how painful it was.”

All current treatment algorithms for type 2 diabetes culminate in the initiation of insulin therapy.23,33 Because most patients will require insulin therapy at some point during the course of treatment—and because insulin is considered to have a greater potential than other agents for preserving β-cell function—early initiation of insulin is becoming more widely accepted.23,33 There is growing consensus that insulin no longer should be considered a “treatment of last resort” after other therapies have failed.51

Unfortunately, many patients who could benefit from insulin therapy do not receive it in a timely manner, or may not receive it at all.51 A retrospective cohort analysis by Rubino and colleagues involving more than 2,500 patients with type 2 diabetes illustrates this point.51 In fully half of the patients, insulin initiation was delayed for almost 5 years after combination therapy with oral agents failed to maintain glycemic control, even in the presence of diabetes-related complications.

Both patients and clinicians may be reluctant to initiate insulin therapy—a phenomenon known as “psychological insulin resistance.”23,26,54-59 TABLE 2 provides examples of patient beliefs that may present barriers to insulin therapy as well as possible pharmacist responses that address those issues.23 Some key concerns are discussed in greater detail below.

Many patients cite anxiety about needles and the possibility of pain on injection as the reason for avoiding insulin therapy.54,56,57 This anxiety may be a cover for other concerns—for example, that insulin therapy will be disruptive and inconvenient, leading to a loss of personal freedom and control.54,56 The use of insulin pens can help to allay all of these fears and make patients feel more comfortable with insulin therapy in general.54,56 Pen delivery devices are discreet, easy to use, and accurate

<table>
<thead>
<tr>
<th>Table 2. Pharmacist Responses to Patient Concerns About Initiating Insulin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Belief</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Insulins are not effective</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Insulin causes hypoglycemia</td>
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<tr>
<td></td>
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<tr>
<td>Insulin causes weight gain</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Insulin regimens are complex</td>
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<td></td>
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</tbody>
</table>

Source: Reprinted from reference 51.

Test Your Knowledge: Diabetes

- Health care providers should never use insulin as a threat or punishment for not adhering to lifestyle modifications or medication therapy.
- For each patient, health care providers should strive to identify and address the specific attitudes and beliefs that underlie reluctance to use insulin therapy.

The importance of the latter point was reinforced in a study by Nakar and colleagues comparing the attitudes and beliefs of 92 patients who were hesitant to start insulin therapy with those of 101 patients who recently had begun insulin treatment.69 Prescribers interviewed for the study assumed that the hesitant patients were primarily afraid of the actual injections. In fact, the hesitant patients were far more likely to perceive their illness as not very serious, have a fear of becoming “addicted” to insulin, or be worried about weight gain or hypoglycemia.
Pharmacists can help to overcome psychological insulin resistance by discussing insulin therapy with patients from the time they are first diagnosed with type 2 diabetes. Patients need to understand both the progressive nature of their condition—and the concomitant decrease in insulin production—and the very real possibility that insulin “replacement” will be needed at some point, through no fault of their own. Pharmacists should explain that insulin is an effective means of improving glycemic control at any time during the course of type 2 diabetes; it should not be perceived as a last resort. Insulin pens should be considered for all appropriate patients.

**Case 4: Insulin Therapy in Severe Insulin Resistance**

James Smith is a 67-year-old white man who was diagnosed with type 2 diabetes 10 years ago. He is 5’8” tall and weighs 308 lb (BMI ~47). His current daily insulin regimen—180 units of NPH insulin in the morning, 120 units of NPH insulin in the evening, and 25 units of regular insulin before each meal—provides a total of 375 units. Despite this regimen, James’s A1C has not dropped below 8.9%. You know that he has struggled to inject the appropriate volume each day because of the associated discomfort. He assumes that he is likely to die soon because he “needs to use so much insulin.”

James visits the pharmacy today with a prescription that reads: U-500 insulin regular. Inject “30 units” SQ bid.

James Smith’s other current medications include:
- Lisinopril 20 mg daily.
- Simvastatin 20 mg daily.
- Gabapentin 300 mg three times daily.
- Omeprazole 20 mg daily.
- Paroxetine 20 mg daily.

**Test Your Knowledge: Is the prescription for U-500 insulin a valid and appropriate intervention for James Smith? What potential problems (if any) are associated with the use of U-500 insulin?**

The typical patient with type 2 diabetes who uses insulin requires a total daily dose of approximately 80 units. One of the consequences of the high prevalence of obesity among patients with type 2 diabetes is a growing number of patients with “severe insulin resistance” who require insulin doses in excess of 200 units per day to achieve glycemic control.

The treatment of patients with such large daily insulin requirements can be problematic. Injecting large volumes of insulin (e.g., 2 mL with a dose of 200 units of U-100 insulin) may cause considerable injection site discomfort. The volume of U-100 insulin needed often exceeds the capacity of the delivery device (1 mL maximum for U-100 syringes; 60 to 80 units maximum for insulin pens), necessitating multiple injections to deliver a single dose. Adherence inevitably suffers, resulting in poor glycemic control.

U-500 insulin—a highly concentrated form of human regular insulin containing 500 units per milliliter (i.e., five times more concentrated than U-100 insulin)—represents an attractive alternative for patients with severe insulin resistance. It enables large doses of insulin to be administered in small volumes (e.g., 0.4 mL for a dose of 200 units). Although the cost per vial is considerably higher than the cost for U-100 insulin, the cost per unit ends up being substantially lower because of the smaller volumes required, the possibility of fewer injections per day, use of fewer syringes and supplies, and other savings. Patients who are switched from standard insulin to U-500 typically experience reductions in A1C of about 2% without significant hypoglycemia; the improvement in glycemic control is attributed to increased patient satisfaction and adherence.

Diabetes expert Irl Hirsch, MD, has called U-500 insulin “perhaps the most important underused tool for the type 2 diabetes population.” The underuse he refers to appears to be changing: use of U-500 insulin increased by 137% from June 2007 to June 2009. Pharmacists who are not already seeing prescriptions for U-500 should anticipate encountering them.

Although U-500 insulin is nonmodified regular insulin, its onset, peak, and duration of action are similar to NPH insulin. The dosing thus is similar to NPH, with up to four injections per day (including a bedtime dose when needed). The actual dose of U-500 insulin may be determined by adding up the total daily dose of U-100 insulin and dividing by 5; an initial dose reduction of 10% to 20% has been recommended by some experts, especially for patients with an A1C level <8%.

The dosing instructions can be verified using a dose-equivalence chart such as the one presented in Table 3.

As implied in the preceding paragraph, syringes are another possible source of confusion and error. Standard insulin syringes are marked for U-100 insulin, so the dose of U-500 insulin does not correspond to the unit markings on the syringe. U-500 insulin is not available in insulin pens.) Most published guidance advises using 0.3-mL, 0.5-mL, or tuberculin syringes instead of a 1-mL syringe. However, tuberculin syringes may not be readily available, and some insurers may not provide reimbursement for them (tuberculin syringes may not be viewed as diabetes supplies). If a U-100 syringe must be used, the pharmacist should take special care to explain the amount to be taken in both dose and volume terms, and preferably mark the appropriate level on the syringe. Pharmacists should teach all patients how to draw up the exact dose required by first demonstrating the amount to be measured and then having the patient practice drawing up the correct volume.

The need for caution when using a highly concentrated insulin product should be apparent to pharmacists, especially if there is...
any potential for patients to confuse it with U-100 regular insulin. Pharmacists should ensure that the patient, the patient’s family members, and any caregivers are aware that U-500 insulin is five times more concentrated than U-100 insulins. Patients should be warned that small changes in a dose of U-500 insulin have the potential to cause both greater shifts in blood glucose readings and prolonged, severe hypoglycemia. Doses of U-500 insulin should be adjusted only with the approval of the prescriber.

U-500 insulin is provided in 20-mL vials with the word “concentrated” marked on them. To avoid the possibility of drug administration errors, U-500 insulin should be stored separately from U-100 insulin.

Case 5: Controlling Nonglycemic Risk Factors

Gail Burton is a 53-year-old African American woman who was diagnosed with type 2 diabetes 3 years ago. Her A1C level is controlled to 6.7% on a combination of metformin 1,000 mg twice daily and exenatide 10 μg twice daily.

Through dedicated adherence to lifestyle modifications (and likely with assistance from the GLP-1 agonist), Gail has managed to reduce her weight from 211 lb to 182 lb and maintain it at that level. She is 5’7” tall (BMI ~29).

Gail visits the pharmacy to take advantage of a cholesterol and blood pressure screening event you are offering in conjunction with National Cholesterol Education Month. Results show her blood pressure to be 172/100 mm Hg and the following lipid levels:

- Total cholesterol: 280 mg/dL.
- Low-density lipoprotein cholesterol: 200 mg/dL.
- High-density lipoprotein cholesterol: 35 mg/dL.
- Triglycerides: 225 mg/dL.

Gail is surprised by these results. “I feel really good, I’ve lost weight, I don’t smoke, and I’ve worked hard to get my diabetes under control,” she says with frustration. “Why am I having these other problems?” As you talk with Gail, you discover that her primary care provider had prescribed both simvastatin and lisinopril at her last visit approximately 10 months ago. Gail elected not to fill these prescriptions because, as she explains, “I’m not a really sick person—I don’t need to be taking all these medications.” You question Gail about other aspects of care and find out that she has never been vaccinated against either influenza or pneumococcal pneumonia.

Test Your Knowledge: Diabetes

Patients such as Gail Burton must appreciate that the management of type 2 diabetes involves much more than controlling hyperglycemia. Many pharmacists already are familiar with the “ABCs” of diabetes, which correspond to goals for A1C, blood pressure (<130/80 mm Hg), and LDL cholesterol (<100 mg/dL). An extended alphabet mnemonic (Table 4) can help pharmacists recall additional elements of comprehensive diabetes management.

Attainment of nonglycemic goals for diabetes management remains disappointingly low. Using National Health and Nutrition Examination Survey data from 1999 to 2006, Cheung and colleagues found that only 57.1% of participants with diagnosed diabetes had achieved the target A1C level (<7%), 45.5% had achieved the target blood pressure, and 46.5% had achieved the target LDL cholesterol level. Only 12.2% of participants—one in eight—had attained all three targets. In a recent analysis of Medical Expenditure Panel Survey data from 2005, more than 40% of the study population (2,003 adults with diagnosed diabetes) had not received a flu shot within the previous year.

Effective long-term blood pressure control may be the most important intervention for preventing complications in patients with diabetes. The ADA Standards of Medical Care in Diabetes call for blood pressure to be measured at every routine diabetes visit. When hypertension is present, the treatment regimen should include either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) in addition to lifestyle modifica-

### Table 3. Dosing Conversion Table and Formulas for Dose and Syringe Markings

<table>
<thead>
<tr>
<th>U-500 Insulin Dose (Actual Units)</th>
<th>U-100 Syringe (Unit Markings)</th>
<th>Volume for Tuberculin Syringe (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>0.10</td>
</tr>
<tr>
<td>75</td>
<td>15</td>
<td>0.15</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>0.20</td>
</tr>
<tr>
<td>125</td>
<td>25</td>
<td>0.25</td>
</tr>
<tr>
<td>150</td>
<td>30</td>
<td>0.30</td>
</tr>
<tr>
<td>175</td>
<td>35</td>
<td>0.35</td>
</tr>
<tr>
<td>200</td>
<td>40</td>
<td>0.40</td>
</tr>
<tr>
<td>225</td>
<td>45</td>
<td>0.45</td>
</tr>
<tr>
<td>250</td>
<td>50</td>
<td>0.50</td>
</tr>
<tr>
<td>275</td>
<td>55</td>
<td>0.55</td>
</tr>
<tr>
<td>300</td>
<td>60</td>
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<tr>
<td>325</td>
<td>65</td>
<td>0.65</td>
</tr>
<tr>
<td>350</td>
<td>70</td>
<td>0.70</td>
</tr>
<tr>
<td>375</td>
<td>75</td>
<td>0.75</td>
</tr>
<tr>
<td>400</td>
<td>80</td>
<td>0.80</td>
</tr>
<tr>
<td>425</td>
<td>85</td>
<td>0.85</td>
</tr>
<tr>
<td>450</td>
<td>90</td>
<td>0.90</td>
</tr>
<tr>
<td>475</td>
<td>95</td>
<td>0.95</td>
</tr>
<tr>
<td>500</td>
<td>100</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*The following dosing formulas also may be used: dose (actual units) x 0.02 = dose (actual units) x 0.2 = unit markings in a U-100 insulin syringe; dose (actual units) x 0.002 = volume (mL) in a tuberculin syringe.

tions. If one class is not tolerated, the other should be substituted. Combination therapy with at least two and possibly three or more agents usually is required to achieve the target blood pressure goal; the ADA standards recommend addition of a thiazide or loop diuretic (depending on the patient’s renal status) when a second agent is needed.

Treating hypertension in patients with type 2 diabetes also is important for reducing the risk and slowing the progression of nephropathy, which occurs in 20% to 40% of patients and is the single leading cause of end-stage renal disease. Microalbuminuria is both a marker for the development of nephropathy in patients with type 2 diabetes and a well-established marker of increased CVD risk. ACE inhibitors and ARBs are more effective than other antihypertensive agents in delaying the progression from microalbuminuria to mac- roalbuminuria and reducing the associated decline in glomerular filtration rate. ACE inhibitors and ARBs also independently reduce the loss of kidney function in patients with nephropathy, above and beyond the effect attributable to a reduction in systemic blood pressure. The ongoing Veterans Affairs Nephropathy in Diabetes Study (VA NEPHRON-D) is examining whether combination therapy with an ACE inhibitor and an ARB (lisinopril plus losartan) is superior to ARB monotherapy (losartan alone) for slowing the progression of diabetic nephropathy in 1,850 patients with overt proteinuria.

For most patients with type 2 diabetes, the primary goal of lipid management is to lower LDL cholesterol. Statin therapy is indicated for all patients with overt CVD, as well as all patients older than 40 years of age who have one or more cardiovascular risk factors (other than diabetes). Niacin, fenofibrate, ezetimibe, or a bile acid sequestrant (e.g., colesevelam) may be added if needed to reach the LDL goal.

Although aspirin therapy is recommended as a secondary prevention strategy for all patients with diabetes who have a history of CVD, the role of aspirin for primary prevention in patients with diabetes is controversial. In the past, aspirin therapy was recommended for primary prevention in all patients older than 40 years of age. An updated expert consensus statement issued jointly by the ADA, American Heart Association, and American College of Cardiology Foundation in June 2010 recommends low-dose (75–162 mg/day) aspirin use only for patients who are at increased CVD risk (10-year risk of CVD events >10%) and who are not at increased risk for bleed-

### Table 4. Elements of Comprehensive Diabetes Care

<table>
<thead>
<tr>
<th>Letter</th>
<th>Element of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A1C</td>
</tr>
<tr>
<td>B</td>
<td>Blood pressure/microalbumin</td>
</tr>
<tr>
<td>C</td>
<td>Cholesterol/aspirin</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes education</td>
</tr>
<tr>
<td>E</td>
<td>Eye examinations</td>
</tr>
<tr>
<td>F</td>
<td>Foot examinations</td>
</tr>
<tr>
<td>G</td>
<td>Glucose monitoring</td>
</tr>
<tr>
<td>H</td>
<td>Health maintenance (i.e., immunizations)</td>
</tr>
<tr>
<td>I</td>
<td>Indications for specialty care (i.e., referrals)</td>
</tr>
</tbody>
</table>

Source: Reference 67.

### Conclusion

Type 2 diabetes is a chronic, progressive disease that typically requires a combination of antihyperglycemic therapies—including insulin—to achieve glycemic control and forestall long-term complications. A host of nonglycemic risk factors also must be addressed. Pharmacists are uniquely positioned to identify and address gaps in the care of patients with diabetes and improve therapeutic outcomes for every patient they see.


74. McMurry CA, Gadkari AS. Individual patients hold different beliefs to prescription medications to which they persist vs nonpersist and persist vs nonfulfill. Patient Prefer Adherence. 2010;4:187–95.

Instructions: The assessment questions printed below allow you to preview the online CPE exam. Please review all of your answers to be sure you have marked the proper letter on the online CPE exam. There is only one correct answer to each question.

1. Approximately what percentage of adults in the United States with diabetes has type 2 diabetes?
   a. 30%.
   b. 50%.
   c. 70%.
   d. 90%.

2. Cardiovascular disease is the cause of death in what percentage of patients with type 2 diabetes?
   a. 33%.
   b. 50%.
   c. 66%.
   d. 75%.

3. Which of the following are considered to be the dual defects that characterize type 2 diabetes?
   a. Impaired β-cell function and insulin resistance.
   b. Glucagon hypersecretion and reduced incretin secretion.
   c. Peripheral and central insulin resistance.
   d. Increased lipolysis and impaired β-cell function.

4. What percentage of β-cell function is lost by the time type 2 diabetes is diagnosed?
   a. 10%.
   b. 18%.
   c. 35%.
   d. 50%.

5. The American Diabetes Association (ADA) recommends an A1C goal of _____%, while the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) recommend an A1C goal of _____%.
   a. <8.0; ≤7.0.
   b. <7.0; ≤6.5.
   c. <6.5; ≤7.0.
   d. <6.0; ≤6.5.

6. In general, most oral antihyperglycemic agents are able to decrease A1C levels by an average maximum of:
   a. 0.5%.
   b. 1.0%.
   c. 1.25%.
   d. 2.0%.

7. Which of the following statements is true?
   a. Patients with type 2 diabetes are unlikely to require insulin therapy if they are adherent to oral antihyperglycemic therapy.
   b. Intensive glycemic control is an effective intervention for reducing the risk of cardiovascular events.
   c. Sulfonylureas are the most potent glucose-lowering agents available.
   d. Aggressive treatment of hypertension and dyslipidemias is an important aspect of type 2 diabetes management.

8. In the ADA/European Association for the Study of Diabetes (EASD) algorithm, what is the preferred initial therapy for newly diagnosed patients with type 2 diabetes?
   a. Lifestyle interventions alone.
   b. Lifestyle interventions + metformin.
   c. Lifestyle interventions + a sulfonylurea.
   d. Lifestyle interventions + basal insulin.

9. In the AACE/ACE algorithm, which of the following agents is not recommended for initial antihyperglycemic therapy in a patient with an A1C level of 7.2%?
   a. Metformin.
   b. A sulfonylurea.
   c. A dipeptidyl peptidase-4 (DPP-4) inhibitor.
   d. A thiazolidinedione.

10. In the AACE/ACE algorithm, which of the following regimens would be preferred for initial therapy in a patient with an A1C level of 8.9%?
    a. Metformin monotherapy.
    b. Metformin + a sulfonylurea.
    c. Metformin + a glucagon-like peptide-1 (GLP-1) agonist.
    d. Insulin alone or with other agents.

11. Which of the following triple medication regimens is advocated by DeFronzo for early treatment of the pathogenic abnormalities of type 2 diabetes?
    a. Metformin, a thiazolidinedione, and a GLP-1 agonist.
    b. Metformin, a thiazolidinedione, and a DPP-4 inhibitor.
    c. Metformin, a sulfonylurea, and a thiazolidinedione.
    d. Metformin, a sulfonylurea, and a GLP-1 agonist.

12. According to the ADA/EASD and AACE/ACE algorithms, how frequently should the therapeutic regimen for patients with type 2 diabetes be evaluated?
    a. Every 2 to 3 months.
    b. Every 6 months.
    c. Annually.
    d. Whenever the patient experiences symptoms of hyperglycemia.
13. In the ADA/EASD algorithm, which of the following options is recommended when therapy needs to be intensified in a patient with an A1C level >8.5%?
   a. Increase the dose of metformin.
   b. Add basal insulin to lifestyle interventions + metformin.
   c. Add a GLP-1 agonist to lifestyle interventions + metformin.
   d. Add a sulfonylurea to lifestyle interventions + metformin.

14. A patient with type 2 diabetes has an A1C level of 7.4% despite therapy consisting of lifestyle modifications and metformin. In the AACE/ACE algorithm, what is the preferred second component of dual pharmacotherapy for this patient?
   a. A GLP-1 agonist.
   b. A meglitinide.
   c. A sulfonylurea.
   d. A thiazolidinedione.

15. A man with type 2 diabetes needs to have insulin added to the treatment regimen to improve glycemic control. With some embarrassment, he admits that he is afraid of needles. Which of the following interventions is most likely to address his concern effectively?
   a. Ask him if a family member or friend could assist him in administering the injections.
   b. Assure him that insulin will improve his symptoms and make him feel better.
   c. Recommend a long-acting insulin that only needs to be administered at bedtime.
   d. Suggest that he try using an insulin pen device.

16. Pharmacists might help patients to overcome "psychological insulin resistance" by:
   a. Empowering patients—explaining that they are unlikely to need insulin if they make all of the recommended lifestyle modifications.
   b. Introducing the possibility of insulin use when patients are first diagnosed with type 2 diabetes.
   c. Reassuring patients that insulin therapy is introduced only as a last resort and therefore would not be a concern for many years.
   d. Referring patients to a mental health professional.

17. Tom Rogers has a current total daily insulin dose of 250 units. His most recent A1C level was 7.8%. Tom’s primary care provider wants to switch him to U-500 insulin and calculates an initial total dose of 200 units. If twice daily dosing is desired, which U-100 syringe marking should Tom use to measure each dose?
   a. 20.
   b. 25.
   c. 40.
   d. 50.

18. Approximately what percentage of adults with type 2 diabetes currently achieves the recommended goals for A1C, blood pressure, and cholesterol?
   a. 12%.
   b. 21%.
   c. 33%.
   d. 45%.

19. A patient with type 2 diabetes has a blood pressure reading of 137/85 mm Hg. Which of the following options represents a recommended course of action?
   a. Do nothing—this reading is below the goal of 140/90 mm Hg.
   b. Initiate antihypertensive therapy with a thiazide diuretic.
   c. Initiate antihypertensive therapy with an angiotensin-converting enzyme inhibitor.
   d. Initiate antihypertensive therapy with a calcium-channel blocker.

20. In addition to an annual influenza vaccine, which of the following vaccines is recommended for all patients with type 2 diabetes?
   a. Hepatitis B.
   b. Human papillomavirus.
   c. Meningococcal.
   d. Pneumococcal.

CPE Instructions
Completing a posttest at www.pharmacist.com/education is as easy as 1-2-3...
1. Go to Online CPE Quick List and click on the title of this activity.
2. Log in. APhA members enter your user name and password. Not an APhA member? Just click “Create one now” to open an account. No fee is required to register.
3. Successfully complete the CPE exam and evaluation form to gain immediate access to your Statement of Credit.
Live step-by-step assistance is available Monday through Friday, 8:30 am to 5:00 pm ET from APhA Member Services at 800-237-APhA (2742) or e-mail InfoCenter@pharmacist.com.