

Therapeutic Options for the Management of Type 2 Diabetes Mellitus

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AUDIENCE

This activity is designed for primary care physicians, pharmacists, pharmacy directors, managed care organization medical directors and administrators, and payers for health services.

GOAL

To explain the economic and societal impact of type 2 diabetes mellitus on the American population and describe new pharmacologic therapies for type 2 diabetes.

LEARNING OBJECTIVES

1. Describe the economic impact of diabetes mellitus on the US healthcare expenditure.
2. Define the diagnostic criteria for diabetes mellitus.
3. Differentiate diabetes mellitus from impaired fasting glucose and impaired glucose tolerance.
4. Identify the goals of the treatment and the complications of diabetes.
5. Discuss the mechanism of action, contraindications, side effects, and monitoring parameters of rosiglitazone, pioglitazone, metformin, miglitol, nateglinide, insulin glargine, insulin aspart, and inhaled insulin.

CONTINUING MEDICAL EDUCATION CREDIT

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CONTINUING PHARMACY EDUCATION CREDIT

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The incidence of diabetes mellitus is steadily increasing in the United States. Currently the United States spends approximately \$100 billion in healthcare costs annually for the management of diabetes. Most of the costs are attributed to hospitalizations and treatment of diabetes complications. Preventing these complications with tight glycemic control is the key to reducing morbidity, mortality, and healthcare costs secondary to diabetes mellitus. Recently, the American College of Endocrinology also stressed earlier screening for diabetes and endorsed lowering the goal percent of hemoglobin glycosylation to 6.5%. These strategies help identify patients with diabetes at an earlier stage and in turn prevent more complications. Better control of diabetes is now feasible with the recent approval of 8 new antidiabetic products. Pioglitazone and rosiglitazone are agents with a novel mechanism of action. Metformin XR, insulin aspart, and miglitol are agents that are similar to previously marketed products, but have different pharmacokinetic or pharmacodynamic properties. Metformin/glyburide is the first combination product for the treatment of diabetes. Nateglinide represents the first agent in a new class of antidiabetic agents and insulin glargine is a novel insulin preparation. All of the agents have unique characteristics that may render them useful in specific patient populations.

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The term *diabetes mellitus*, from the Latin for "sweet urine," is used to describe a series of metabolic disorders that are characterized by glucose intolerance. Diabetes mellitus (DM) is a chronic disease that affects approximately 16

million Americans, with an estimated 90% diagnosed with type 2 DM.¹ Although DM has no known cure, recently a number of advancements in treatment have been developed. Outcomes from the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study (UKPDS) trials coupled with new drug therapies have provided practitioners with new treatment approaches.

EPIDEMIOLOGY

The Centers of Disease Control (CDC) recently declared diabetes an “emerging epidemic” because of the steady rise in incidence rates. In past years the annual incidence rate was steady at about 2 to 3 per 1000 people; however, in 2000 the incidence rate increased to 6 per 1000 people. This rise is attributed to many causes such as the increase in the life expectancy of Americans, increase in overall population, and the increased incidence of obesity and sedentary lifestyle. Approximately 800 000 new cases of DM are documented yearly, with the highest prevalence rate among patients older than 65 years.¹ The disease has no gender predilection; however, in the United States, African Americans, Latin Americans, and Native Americans have the highest incidence of DM.¹ If left unmanaged, DM results in devastating consequences. It is the number one cause of adult blindness in the United States and the second most common cause of end-stage renal disease.² Diabetes is also associated with other comorbid conditions including hypertension, dyslipidemia, myocardial infarction, ischemic stroke, lower extremity amputations, and peripheral/autonomic neuropathy.

The management of diabetes is associated with approximately \$100 billion in healthcare costs annually, accounting for 13% of total US healthcare expenditures.³ Of the \$100 billion, \$44 billion is spent on direct medical costs: approximately half of the costs are dedicated to treatment of the condition itself and the other half to treatment of the chronic complications.⁴ Not only does the management of diabetes have a significant impact on direct medical costs, it also accounts for significant morbidity and indirect medical costs. In 1997, the American Diabetes Association (ADA) estimated that DM was associated with approximately \$37.1 billion in disability costs and \$16.9 billion secondary to mortality.³ Studies have demonstrated that by using intensive therapy regimens for diabetic patients, the overall cost of healthcare may decrease by reducing the treatment costs of chronic complications.⁴

PATHOPHYSIOLOGY

Of the 16 million people with diabetes in the United States, approximately 90% to 95% have type 2 DM.¹ Type 2 DM is a chronic metabolic disorder of abnormal glucose homeostasis resulting from inadequate insulin action and insulin secretion. Unlike type 1 DM, type 2 DM is believed to stem from a dual effect of (1) insulin resistance and (2) secondary β -cell failure. Insulin resistance is a phenomenon by which insulin receptors found on peripheral muscle cells are unable to bind or recognize serum insulin properly, resulting in a compensatory increase in pancreatic production of insulin. Due to inadequate functioning insulin receptors and insulin activity, intracellular uptake of serum glucose is poor. This continuum results in further hyperglycemia and hyperinsulinemia. This phenomenon varies greatly from type 1 DM in which the primary defect is β -cell production of insulin. Type 1 DM is an autoimmune disorder in which the β cells in the pancreas are destroyed and therefore the pancreas is unable to produce insulin.

DIAGNOSIS

Diabetes may be diagnosed from results of 3 blood tests: fasting blood glucose, random blood glucose, or oral glucose tolerance test (OGTT). The ADA recommends screening all patients over age 45 every 3 years, and younger patients with significant risk factors. The American College of Endocrinology and the American Association of Clinical Endocrinology support these recommendations, and specifically state that all high-risk patients should be screened beginning at age 30. Screening entails acquiring fasting blood glucose levels. The diagnosis of DM can be made with any combination of 2 of the following results: fasting blood glucose concentration of 126 mg/dL or higher, random blood glucose concentration of more than 200 mg/dL with hyperglycemic symptoms, or 2-hour OGTT of more than 200 mg/dL.⁵ Although glycosylated hemoglobin (HbA_{1c}) is recommended as a monitoring parameter for DM, it is not recommended as a diagnostic test because patients with normal HbA_{1c} levels may have abnormal fasting or random blood glucose levels. Therefore, the HbA_{1c} test has limited sensitivity to detect patients with diabetes.

Many patients may not have clinically defined DM, but may have “prediabetes” with either an

Table 1. Diagnostic Criteria for Diabetes Mellitus*

	Fasting Plasma Glucose [†] , mg/dL	Random Plasma Glucose, mg/dL	2 Hour Plasma Glucose Post-OGTT [‡] , mg/dL
Euglycemia	< 110	< 140	< 140
Impaired fasting glucose	110–125	< 140	< 140
Impaired glucose tolerance	< 110	140–199	140–199
Diabetes mellitus	≥ 126	≥ 200 [§]	≥ 200

*Data from Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.⁵

[†]Fasting is defined as no caloric intake for at least 8 hours.

[‡]Oral glucose tolerance test (OGTT) consists of a glucose load of 75 g anhydrous glucose dissolved in water.

[§]Random plasma glucose ≥ 200 mg/dL with patient exhibiting symptoms of hyperglycemia.

impaired fasting glucose or impaired glucose tolerance. Because each of these conditions increases the risk of developing diabetes, prompt lifestyle modifications are indicated for these patients. **Table 1** outlines diagnostic criteria for impaired fasting glucose, impaired glucose tolerance, and DM.

CLINICAL FEATURES

Many patients with type 2 DM may be asymptomatic at the time of diagnosis since because hyperglycemic symptoms do not occur until the blood glucose level is significantly elevated. Patients with type 2 DM tend to be overweight, possibly secondary to the propensity for hyperinsulinemia. Also, traditionally, type 2 DM was thought to occur in patients older than 40 years; recently, however, the incidence of type 2 DM among children has risen, possibly secondary to the increase in sedentary lifestyle and poor dietary habits. Symptoms of uncontrolled blood glucose levels such as fatigue, headache, and polyphagia are mainly a result of lack of cellular energy. Polyuria is a result of osmotic diuresis secondary to glucose spilling in the urine, whereas polydipsia is a result of dehydration secondary to polyuria. Acute changes in vision such as blurred vision are a result of an increase in osmotic pressure in the retinal cavity.

Long-term complications of DM include a variety of macrovascular and microvascular complications. Paresthesias and neuropathy are a result of neuronal damage due to chronic hyperglycemia. Nephropathy and retinopathy are a result of increased pressure in the renal and retinal arteries. Myocardial infarction, ischemic stroke, and peripheral vascular disease are

a result of poor control of dyslipidemias, and changes in endothelial lining. Fortunately, all of the devastating long-term complications may be prevented with good glycemic control. The UKPDS⁶ demonstrated that intensive treatment strategies utilizing insulin, oral sulfonylureas, or metformin can decrease the risk of any diabetes-related end point including angina, myocardial infarction, heart failure, stroke, renal failure, amputation, retinopathy, blindness, or sudden death due to hypoglycemia or hyperglycemia by 12%. This 10-year study also demonstrated that by decreasing HbA_{1c} by 11%, (from 7.9% to 7.0%) the risk of microvascular complications (retinopathy, nephropathy, and neuropathy) decreases by 25%.⁶

TREATMENT APPROACH

Effective management of the disease requires a partnership between the patient and the healthcare professional. The healthcare professional must aggressively treat and educate, and the patient must adhere to appropriate nonpharmacologic, pharmacologic, and self-care measures. Successful treatment of diabetes is achieved by adopting a holistic approach. Diabetes can affect the medical, social, and financial aspects of a person's life, therefore each aspect should be discussed with the patient.

The goal for managing diabetes is to achieve optimal blood glucose control to prevent or minimize complications. Based on the recent update from the American College of Endocrinology and the American Association of Clinical Endocrinologists,⁷ "optimal glycemic control" is defined as HbA_{1c} less than 6.5% with fasting blood glucose levels between

80 and 110 mg/dL and postprandial blood glucose levels less than 140 mg/dL.⁷ Because recent studies have supported the relationship between lowering HbA_{1c} and risk reduction of macrovascular and microvascular complications, these goals are more aggressive than traditional goals. By achieving these goals it has been found that the risk of microvascular and macrovascular complications of DM is reduced by 14% to 25%.⁷ Many other preventive measures such as vaccination for pneumonia and influenza, treatment with aspirin and angiotensin-converting enzyme inhibitors, ophthalmology visits, and podiatry visits, should also be considered in patients with diabetes.

Nonpharmacologic treatments including dietary changes and physical activity are the cornerstones of therapy for DM. However, many patients are unable to achieve optimal glycemic control with nonpharmacologic measures alone. Due to the lack of options and cost, oral sulfonylurea agents were traditionally considered the first-line treatment option for type 2 DM. Monotherapy with sulfonylureas provides fair glycemic control with minimal side effects and at relatively low cost; however, they are also known to cause hyperinsulinemia. Hyperinsulinemia is associated with the "metabolic syndrome," which is characterized by obesity, hypertension, and dyslipidemias resulting in a possible increased risk in cardiovascular deaths. These effects of hyperinsulinemia are independent of the effect of hyperglycemia seen in diabetes. Many of the newer therapeutic options do not induce hyperinsulinemia, and therefore are becoming first-line therapy.

NEW THERAPEUTIC OPTIONS

Since 1999, 8 new products have been available for the treatment of diabetes. Each agent is unique in its pharmacokinetic or pharmacodynamic properties. A brief discussion of each of the new products follows. **Table 2** summarizes the pharmacologic and clinical efficacy of the individual products as well as the cost comparisons of each product.

Thiazolidinediones

The thiazolidinediones, or more commonly called "glitazones," enhance insulin sensitivity at the level of the skeletal muscle, hepatic, and adipose tissue. These agents stimulate peroxisome proliferator-activated receptor- γ (PPAR- γ), which enhances the replication of the glucose transporter, GLUT-4, allowing extracellular glucose to move intracellularly, thereby lowering overall blood glucose levels. Because the

glitazones act at the molecular level, peak glucose-lowering effect is seen 10 to 14 weeks after initiation of therapy. Also, glitazones do not stimulate insulin production, therefore hyperinsulinemia does not result, and when used as monotherapy the risk of hypoglycemia is minimal.

Along with improving glycemic control, glitazones are also currently being studied for their use in polycystic ovarian syndrome (PCOS), because hyperinsulinemia is a characteristic of PCOS. Because these agents stimulate ovulation in premenopausal amenorrheic women, it is important to counsel patients on proper contraception methods.

PPAR- γ is also responsible for lipid metabolism. Consequently, the thiazolidinediones are found to increase low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol levels by 5% to 15%, and decrease triglyceride levels by 5% to 15%.⁹⁻¹¹ In a 26-week study, statistically significant increases in total cholesterol, LDL-C, and HDL-C were found in rosiglitazone treatment groups at 4 mg daily and 8 mg daily when compared with baseline levels and when compared with metformin monotherapy. No significant difference in triglyceride levels was found between or within groups.¹¹ Pioglitazone also showed similar lipid effects when compared with placebo. Overall, pioglitazone was found to significantly increase in HDL-C, LDL-C, and total cholesterol levels, and to decrease triglyceride levels when compared with baseline values.^{9,10,12} These results are clinically relevant because patients with diabetes traditionally have low HDL-C and high triglyceride levels. Therefore the thiazolidinediones may improve the lipid profile of diabetic patients; however, it is important to note that they may also increase LDL-C. Along with the effects on cholesterol levels and insulin sensitivity, PPAR- γ is also found to stimulate adipocyte replication, causing weight gain.¹³ Although the weight gain is minimal (about 5 to 10 pounds), more studies are needed to determine the clinical effect of the weight gain.^{10,13,14} Given the high prevalence of obesity in type 2 DM, even minimal weight gain could be considered a significant adverse effect.

Treatment with these agents as monotherapy or in combination with metformin, sulfonylureas, or insulin has traditionally been well tolerated. Occurrences of adverse events are comparable to placebo with the exception of edema. In fact, thiazolidinediones as metformin have less hypoglycemic effect compared with other antidiabetic agents. Common adverse events include upper respiratory infection and headache. In addition,

Table 2. Comparisons of Selected Antidiabetic Agents*

Drug Product	Mechanism of Action	Absolute Contraindication	Maximum HbA _{1c} Lowering (%) (Monotherapy)	Equivalent Doses	Cost (\$)† (AWP for 30-day supply)
Glyburide (Micronase/ Diabeta)	Stimulates β -cell to enhance insulin secretion from pancreas	Pregnancy, type 1 diabetes, sulfa allergy	1.0-1.5	10 mg twice daily	46.30 (generic)
Metformin (Glucophage/Glucophage XR)	Inhibits hepatic gluconeogenesis and enhances insulin sensitivity	Men SCr > 1.5 mg/dL, women SCr > 1.4 mg/dL; acute/uncompensated heart failure, sepsis, hypoxia	1.0-1.5	1000 mg twice daily	89.53; 78.80 (XR)
Metformin/Glyburide (Glucovance)	Inhibits hepatic gluconeogenesis. Stimulates β -cell to enhance insulin secretion from pancreas	Pregnancy, type 1 diabetes, sulfa allergy, men SCr > 1.5 mg/dL, women SCr > 1.4 mg/dL, acute/uncompensated heart failure, sepsis, hypoxia	1.0-2.0	500/5 mg (2 tablets) twice daily	93.99
Miglitol (Glyset)	Inhibits α -glucosidase enzymes in order to delay carbohydrate metabolism and absorption	Gastrointestinal obstruction, inflammatory bowel disease	0.5-1.0	100 mg 3 times daily	62.81
Nateglinide (Starlix)	Stimulates β -cell to enhance insulin secretion from pancreas	Type 1 diabetes, pregnancy	0.5-1.0	120 mg 3 times daily	86.40
Pioglitazone (Actos)	Stimulates PPAR- γ to enhance synthesis of glucose transporters	Class III/IV heart failure, liver failure	1.0-1.5	45 mg daily	154.29
Rosiglitazone (Avandia)	Stimulates PPAR- γ to enhance synthesis of glucose transporters	Class III/IV heart failure, liver failure	1.0-1.5	8 mg daily	142.40
Aspart (NovoLog)	Insulin analog	No absolute contraindications	Depends on dose	1 vial (1000 units)	45.31
Lispro (Humalog)	Insulin analog	No absolute contraindications	Depends on dose	1 vial (1000 units)	45.11
Insulin NPH (Novolin)	Insulin analog	No absolute contraindications	Depends on dose	1 vial (1000 units)	24.34
Glargine (Lantus)	Insulin analog	No absolute contraindications	Depends on dose	1 vial (1000 units)	43.95

*Data from Cardinale.⁸

†Generic cost of medications are provided when available.

HbA_{1c} indicates hemoglobin A_{1c}; AWP, average wholesale price; SCr, serum creatinine; PPAR- γ , peroxisome proliferator-activated recep-

edema and anemia have been associated with the thiazolidinediones.^{11,14-16} Due to the risk of developing a fluid overload status, these agents are not recommended in patients with New York Heart Association class III or IV heart failure. Recently, exacerbation of congestive heart failure has been an increased concern for patients treated with the thiazolidinediones. Patients should be warned and should be prompted to seek medical attention if they develop edema, shortness of breath, weight gain, fatigue, or weakness. Decreases in hemoglobin and hematocrit levels have also been associated with the first 4 to 8 weeks of therapy and may be related to the increase in fluid volume. The risk of developing anemia is mild; however, hemoglobin levels should be monitored during the initial months of treatment. Present clinical trials have not identified hepatotoxicity as a common adverse effect, however, the glitazones are contraindicated in patients with liver disease. In addition, monitoring liver function at baseline, every other month for the first year, and every 6 months thereafter is required when using these agents. Lastly, like most oral

antidiabetics, the glitazones are not recommended in pregnant patients and are classified as pregnancy category C.¹⁵

Troglitazone was the first member of this class of drugs to be approved; however, in March, 2000 it was withdrawn from the market because it was associated with idiosyncratic hepatotoxicity.¹⁷ Currently 2 thiazolidinediones are on the market: rosiglitazone (Avandia; SmithKline Beecham, Philadelphia, Penn), and pioglitazone (Actos; Takeda Pharmaceuticals America, Inc, Lincolnshire, Ill). Currently, no direct head-to-head trials have compared pioglitazone and rosiglitazone. However, many studies have been conducted to demonstrate the efficacy of both agents within similar cohorts.

Rosiglitazone Maleate (Avandia). Rosiglitazone is the second member of the thiazolidinedione class that was approved by the US Food and Drug Administration (FDA) in 1999 as monotherapy or in combination with metformin in conjunction with diet and exercise to lower blood glucose levels in patients with type 2 DM.¹⁵ Rosiglitazone is available as 2-, 4-, and 8-mg tablets and may be administered

with or without food to a maximum dose of 8 mg/day at once- or twice-daily dosing. The primary route of elimination is through the kidney; however, no dose adjustment is required for patients with renal impairment. Currently no clinically significant drug interactions have been associated with rosiglitazone.¹⁵

Rosiglitazone has been evaluated as monotherapy and in combination with metformin or sulfonylureas in multiple, 26-week-long, trials. Results from these studies have consistently

Table 3. Comparison of Clinical Trials of Currently Marketed Thiazolidinediones

Reference	Patients, No.	Duration, Wk	Drug Regimen and HbA _{1c} Reduction
Phillips et al ¹⁸	959	26	Rosiglitazone 4 mg qd: -0.8%* Rosiglitazone 2 mg bid: -0.9%* Rosiglitazone 8 mg qd: -0.1%* Rosiglitazone 4 mg bid: -1.5%*
Fonesca et al ¹¹	483	26	Met 2.5 g qd/Ros 4 mg qd: -1.0%* Met 2.5 g qd/Ros 8 mg qd: -1.2%*
Wolffenbuttel et al ¹⁹	593	24	Sulfonylurea/Ros 2 mg qd: -0.59%† Sulfonylurea/Ros 4 mg qd: -1.03%†
Aronoff et al ⁹	408	24	Pioglitazone 15 mg qd: -1.0%* Pioglitazone 30 mg qd: -1.0%* Pioglitazone 45 mg qd: -1.6%*
Einhorn et al ¹⁰	249	16	Met/Pioglitazone 30 mg qd: -0.83%‡
Kipnes et al ²⁰	478	16	Sulfonylurea/Pio 15 mg qd: -0.8%§ Sulfonylurea/Pio 30 mg qd: -1.2%§

* $P < .001$ when compared with placebo.

† $P < .05$ when compared with sulfonylurea alone.

‡ $P < .01$ when compared with metformin alone.

§ $P < .05$ when compared with placebo.

HbA_{1c} indicates hemoglobin A_{1c}; qd, every day; bid, twice a day; Met, metformin; Ros, Rosiglitazone; Pio, pioglitazone.

demonstrated that rosiglitazone significantly reduces HbA_{1c} and fasting plasma glucose levels in patients with type 2 DM.^{11,18,19} When used as monotherapy, rosiglitazone has demonstrated a reduction in HbA_{1c} at all dosage ranges (4-8 mg/day). Clinically significant decreases in HbA_{1c} were observed at the maximal dosing of 8 mg/day. Interestingly, the 4 mg twice-daily dose had a greater effect on HbA_{1c} than the 8 mg daily dose. In a 26-week study with 959 patients, rosiglitazone demonstrated a dose-dependent reduction in HbA_{1c} when compared with placebo¹⁸ (Table 3). In addition, combination therapy with rosiglitazone shows similar significant improvements. In a 26-week study 483 patients who were already stabilized on metformin 2.5 g daily were randomized to either continuing metformin 2.5 g daily or receiving metformin 2.5 g daily in combination with rosiglitazone at either 4 or 8 mg daily.¹¹ Results showed a significant drop in HbA_{1c} with either combination (Table 3).

Rosiglitazone in combination with sulfonylureas has an additive effect. During a 24-week, multicenter study, 593 patients were randomized to receive sulfonylurea monotherapy, or a sulfonylurea in combination with rosiglitazone at either 2 or 4 mg daily.²⁰ The sulfonylurea/rosiglitazone combinations were associated with dose-dependent decreases in HbA_{1c} in comparison with sulfonylurea-monotherapy¹⁹ (Table 3).

Pioglitazone Hydrochloride (Actos). Pioglitazone is the newest thiazolidinedione approved by the FDA as monotherapy or in combination with a sulfonylurea, metformin, or insulin for the improvement of glycemic control in patients with type 2 DM when diet and exercise is insufficient. Pioglitazone is available in 15-, 30-, and 45-mg tablets and can be taken without regard to meals. The drug is metabolized primarily hepatically, and to date no clinically significant drug interactions have been documented. However, the cytochrome P450 isoform CYP3A4 is partially responsible for metabolism. Patients on multiple hepatically metabolized drug regimens should be monitored for possible drug interactions.²¹

Pioglitazone is effective as monotherapy or in combination with sulfonylureas, metformin, or insulin.²¹ In a 6-month study, 408 patients were randomized to either placebo, or pioglitazone 7.5, 15, 30, or 45 mg daily.⁹ All doses of pioglitazone reduced HbA_{1c} significantly when compared with placebo; however, higher doses had a greater effect on HbA_{1c} (Table 3). When stratifying patients between those who were naïve to therapy and those who were previously treated with drug therapy, the glucose-lower-

ing effect was dramatically greater in those patients who were naïve to therapy at all doses.⁸ Maximum HbA_{1c} lowering was found 10 to 14 weeks after initiation of therapy.

Similar, statistically significant glycemic lowering has been demonstrated when pioglitazone is used in combination with either metformin or sulfonylureas. In a 16-week, double-blind study, 249 patients were randomized to either metformin alone or metformin plus pioglitazone 30 mg daily.¹⁰ At week 16, the pioglitazone group statistically significantly lowered HbA_{1c} by 0.83%.⁹ (Table 3). In another 16 week trial, placebo or pioglitazone at 15 or 30 mg was used in combination with a stable regimen of a sulfonylurea in 478 patients.²⁰ The most common sulfonylurea used was either glyburide (55%) or glipizide (37%). A statistically significant dose-dependent decrease in HbA_{1c} and fasting plasma glucose concentrations was found between the 2 pioglitazone doses and both statistically significantly decreased HbA_{1c} when compared with placebo (Table 3).

Overall, the data supports the use of rosiglitazone and pioglitazone as monotherapy or in combination with other antidiabetic agents to improve glycemic control. Although no trials have compared rosiglitazone and pioglitazone head to head, neither agent seems to provide a large benefit over the other. As a class, they enhance glycemic parameters by lowering HbA_{1c} by about 1.5 points, and have potential beneficial effects on lipid parameters.

Metformin (Glucophage, Glucophage XR, Glucovance)

Approval of metformin has changed treatment strategies for type 2 DM. Although traditionally sulfonylureas were considered first-line therapy for patients with type 2 DM, metformin is now preferred in certain patient populations. Metformin primarily affects glucose levels by inhibiting hepatic gluconeogenesis; however, it also increases peripheral glucose uptake, and decreases intestinal absorption of glucose.²² Because metformin does not stimulate further insulin production, and therefore does not cause hyperinsulinemia, this agent is now favored over sulfonylureas, especially in the obese populations. The UKPDS 34 study demonstrated the use of metformin in overweight (> 120% ideal body weight) patients over a 10-year period. When compared with sulfonylureas and insulin therapy, metformin had an overall lower incidence of weight gain in obese diabetics patients.²³

Overall, metformin achieves tight glycemic control without weight gain when compared with sul-

fonylureas and significantly reduces HbA_{1c} by 1 to 1.5 percentage points with continued therapy. Also, although minor, metformin beneficially affects the lipid profile by decreasing LDL-C by 1.0% to 1.5% and increasing HDL-C levels by 4% to 5%. However, contraindications to metformin limit its use. Metformin is associated with lactic acidosis. Although the incidence of lactic acidosis is low, it should be used cautiously in patients with conditions that may predispose them to acidosis such as heart failure, pulmonary congestion, and respiratory distress.²³ It should be discontinued in patients with hypoxemia, metabolic acidosis, sepsis, and acute heart failure or class IV heart failure.²³ It is absolutely contraindicated in patients with elevated serum creatinine levels (> 1.5 mg/dL in men, > 1.4 mg/dL in women), and should be used cautiously in patients with impaired renal function. Serum creatinine, therefore, should be monitored periodically.²³ Metformin must also be discontinued for 48 hours after any procedure using iodinated contrast dyes to prevent cases of lactic acidosis.²³

Metformin is currently available in 3 different formulations: immediate-release (Glucophage; Bristol-Myers Squibb, Princeton, NJ), extended-release (Glucophage XR; Bristol-Myers Squibb), and in a combination formulation with glyburide (Glucovance; Bristol-Myers Squibb). All metformin products have similar indications, contraindications, and precautions. Although the immediate-release formulation has been on the market for more than 7 years, the others are new.

Metformin/Glyburide (Glucovance). Glucovance is the first combination oral hypoglycemic product. The combination formulation of metformin and glyburide was approved by the FDA in July 2000. Although combination therapy (> 1 agent) is routinely necessary for adequate glycemic control, no combination products have been available until recently. The UKPDS 28 study²⁴ suggests combination therapy with metformin and a sulfonylurea agent achieves superior, long-term glycemic control over monotherapy with sulfonylureas. Fasting plasma glucose levels were significantly reduced and a greater percentage of patients achieved goal HbA_{1c} levels over the course of 3 years with combination therapy when compared with sulfonylurea monotherapy. (fasting plasma glucose -0.47 vs 0.44, $P < .00001$; percentage of patients achieving (HbA_{1c} goal 32% vs 21%).²⁴

The metformin/glyburide combination product allows for glycemic control by targeting 2 different mechanisms of action. The combination not only

enhances insulin secretion, but also decreases hepatic gluconeogenesis and enhances insulin sensitivity. In a 20-week study, the combination of metformin/glyburide at mean doses of 818 mg/4.1 mg daily provided a statistically greater drop in HbA_{1c} than monotherapy metformin at mean doses of 1317 mg daily (-0.5%, $P < .001$) or with monotherapy glyburide at mean doses of 5.3 mg daily (-0.29%, $P < .005$).²⁵

As with any combination product, the goal is to provide a convenient dosing formulation for the patient to achieve consistent medication adherence. For many patients, the combination product can reduce their daily pill burden by 2 to 3 tablets. As with antihypertensive agents, both dosage frequency and number of tablets affect adherence to diabetic regimens.²⁶ Therefore, with enhanced adherence to the medication regimen, the combination product may provide better glucose control than with the 2 agents used individually in combination.

Metformin XR (Glucophage XR). Glucophage XR is formulated as a dual-gel matrix system that degrades and slowly releases the active ingredient in hydrophilic environments. It has been found to be similar in efficacy to the immediate-release metformin; however, the extended-release formulation may be dosed once a day with less fewer gastrointestinal side effects than the immediate-release product. In a 24-week, double-blind trial with 205 patients, metformin XR 1000 mg daily was similar in efficacy to metformin 500 mg twice daily.²⁷ In a dose-ranging trial, 732 patients were randomized to 6 treatment arms for 16 weeks. Within the trial, when comparing metformin XR 2000 mg daily with metformin XR 1000 mg twice daily, the twice-daily dosing regimen decreased HbA_{1c}, body weight, and fasting plasma glucose greater than the once-daily dosing regimen; however, the results were not statistically significant. As for lipid parameters, metformin XR 1000 mg daily decreased LDL-C (-3.3% vs -1.3%), and increased triglyceride levels (25.3% vs 6.3%) significantly more than metformin 500 mg twice daily; however, the immediate-release metformin increased HDL-C (4.8% vs 1.0%) more than the extended-release formulation.²⁷ Also, unlike the immediate-release formulation, metformin XR is available only in 500-mg tablets.²⁷

Miglitol (Glyset)

Carbohydrate intake and metabolism lead directly to increases in post-prandial glucose levels. The degradation of the carbohydrates from polysaccha-

rides to monosaccharides is dependent on functioning α -glucosidase (sucrase, isomaltase, maltase, glucoamylase, and trehalase), β -galactosidase (lactase), and α -amylase enzymes located in the brush border membrane of the small intestines. Inhibition of these enzymes prevents the metabolism of complex carbohydrates and thus inhibits or delays their absorption, blunting the effect on postprandial glucose levels.

Miglitol (Glyset, Pharmacia and Upjohn, Kalamazoo, Mich) is the second agent in the α -glucosidase inhibitor class. It was approved by the FDA in August 1999 as a dietary adjunct for the treatment of type 2 DM.²⁸ It is a reversible competitive inhibitor of the α -glucosidase enzymes similar to acarbose, although each agent has different affinities to the various α -glucosidase enzymes. Miglitol is structurally similar to glucose, allowing for inhibition of a wider range of α -glucosidase enzymes.²⁹

Miglitol is effective in inhibiting the postprandial glucose surge, by delaying the absorption of carbohydrates. With the administration of miglitol, intact carbohydrates progress from the small intestines to the large intestines where they are metabolized by colonic bacteria and subsequently absorbed. The presence of intact carbohydrates in the large intestines accounts for considerable gastrointestinal discomfort, thereby limiting miglitol's use. Also, miglitol is contraindicated in patients with gastrointestinal obstruction or inflammatory bowel disease. Because miglitol's actions are confined to the gastrointestinal tract, the drug does not incur hyperinsulinemia and use may be feasible in patients with type 1 DM in conjunction with insulin, or during pregnancy. However, these are off-label uses for miglitol.

In clinical trials,³⁰ miglitol modestly reduced HbA_{1c} by 0.5 to 0.8 percentage points. In a dose-ranging study, 192 patients were randomized to placebo, miglitol 50 mg 3 times a day, or miglitol 100 mg 3 times a day. At the end of 14 weeks, HbA_{1c} dropped 0.39 and 0.41 percentage points with miglitol 50 and 100 mg, respectively.³⁰

Comparatively, miglitol has similar glycemic effects as moderate doses of other antidiabetic agents. In a 24-week, randomized, multicenter trial, miglitol 100 mg 3 times daily was compared with glibenclamide 3.5 mg twice daily and placebo.³¹ One hundred nineteen patients were evaluated for body weight and HbA_{1c}, blood glucose, and triglyceride levels. In the miglitol and glibenclamide groups, HbA_{1c} decreased by 0.75 and 1.01 percentage points, respectively, fasting blood glucose decreased by 10

and 14 mg/dL, and postprandial glucose decreased by 31 and 32 mg/dL.³¹

Miglitol does not lower HbA_{1c} levels as robustly as other antidiabetic agents. However, the drug may be an appropriate alternative in patients who do not tolerate or have contraindications to other agents, or patients who have high postprandial glucose levels. Miglitol should also be considered in patients who are at high risk of hypoglycemia because the drug has no effect on insulin secretion.

Nateglinide (Starlix)

Nateglinide (Starlix; Novartis Pharmaceutical Corp, East Hanover, NJ) is the first drug in the new class of antidiabetic agents called the D-phenylalanine agents. It was approved by the FDA in December 2000 for use as monotherapy or in combination with metformin in patients with type 2 DM.³² Although it is considered to be in a different class than the sulfonylureas or meglitinides, nateglinide has a similar mechanism of action. Nateglinide is an insulin secretagogue that binds to the ATP-sensitive potassium channel on the β cell in the pancreas. In contrast to sulfonylureas, nateglinide achieves its peak effect within 20 minutes of administration and has a duration of action of 4 hours.³²

When compared with sulfonylureas, nateglinide 120 mg before meals is found to have a larger effect on mealtime glucose excursion than glyburide 10 mg once daily and also has a limited effect on fasting insulin levels. The data suggest that similar postprandial glycemic control can be achieved with nateglinide as with glyburide without the consequence of hyperinsulinemia.³³ However, in a separate 24-week study comparing glyburide 10 mg daily with nateglinide 60 mg 3 times a day and 120 mg 3 times a day, the nateglinide groups had a significant increase in HbA_{1c} and fasting plasma glucose levels, possibly due to nateglinide's short duration of action.³²

Nateglinide has also demonstrated effectiveness in combination therapy with metformin. In a 24-week study, 701 patients were randomized to nateglinide 120 mg 3 times a day before meals, metformin 500 mg 3 times a day before meals, combination therapy, or placebo.³⁴ Combination therapy with nateglinide and metformin resulted in the largest drop in HbA_{1c} level. Although the percentage drop in HbA_{1c} with metformin was greater than with nateglinide monotherapy, the difference was small (HbA_{1c} -1.2 vs -0.9). The incidence of hypoglycemia, which was most common in the combina-

Table 4. Amino Acid Sequence of Selected Insulin Products

Amino Acid Position	Types of Insulin				
	Human	Beef	Pork	Glargine	Aspart
A8	Threonine	Alanine	Threonine	Threonine	Threonine
A10	Isoleucine	Valine	Isoleucine	Isoleucine	Isoleucine
A21	Asparagine	Asparagine	Asparagine	Glycine	Asparagine
B28	Proline	Proline	Proline	Proline	Aspartic acid
B29	Lysine	Lysine	Lysine	Lysine	Lysine
B30	Threonine	Alanine	Alanine	Threonine	Threonine
B31 and B32	—	—	—	Arginine	—

tion therapy group, was similar in the nateglinide and metformin monotherapy groups (12.8% vs 10.1%).³⁴

Nateglinide is a potent inhibitor of cytochrome p450 2C9 and to a lesser extent the 3A4 isoenzymes, and it is highly protein bound (98%); therefore, the potential for drug interactions is significant. Nateglinide is contraindicated in patients with type 1 diabetes, and in pregnancy. The most common side effects are upper respiratory tract infections, arthropathy, diarrhea, and hypoglycemia.³²

INSULIN PREPARATIONS

Insulin has always been considered the most effective therapy for patients with diabetes; however, it is typically reserved as a last-line agent for patients with type 2 DM due to its invasive nature, and propensity to cause hypoglycemia and hyperinsulinemia. Because of the route of administration, most patients do not prefer insulin and therefore compliance rates with insulin are typically lower than with other antidiabetic agents. New routes of administration of insulin are currently being investigated, including orally inhaled insulin; however, these formulations are still a few years away from the market. Recently, 2 new formulations of insulin emerged into the market: insulin glargine and insulin aspart. **Table 4** depicts the structural differences in the amino acid sequence of selected insulin preparations. **Table 5** shows the pharmacokinetic properties of various insulin preparations.

Insulin Glargine (Lantus)

Insulin glargine (Lantus; Aventis Pharmaceuti-

cals Inc, Kansas City, Mo) is a new formulation of insulin that is marketed as a “peak-less” insulin. It was approved by the FDA in April 2000 for the treatment of adult and pediatric patients with type 1 DM or adults with type 2 DM who require a daily basal insulin dose. Insulin glargine is stable in the vial at an acidic pH of 4. When injected subcutaneously, the solution neutral-

izes and precipitates into microcrystals in the subcutaneous fat, thereby producing a “depot-like” formulation of insulin. It is released slowly from the subcutaneous fat at a consistent rate over 24 hours, thereby providing a linear release rate without a dramatic peak or trough in contrast to other insulins. Unlike other long-acting insulins, glargine it is a clear solution. Lantus is available in 10-mL vials or 3-mL cartridges to be used only with the Optipen delivery system (Aventis Pharmaceuticals Inc). Due to the stability of the insulin, it cannot be mixed with any other type of insulin. Glargine should be refrigerated, but is stable for approximately 28 days at room temperature.³⁵ Rotation of injection site, as with other insulin products, will help in avoiding administration-related pain or irritation.

Insulin glargine has a duration of 24 hours, thereby mimicking normal physiologic basal secretion of insulin. Although insulin glargine may be more useful in patients with type 1 DM because they lack a basal release of insulin, the formulation also benefits patients with type 2 DM who require large doses of insulin. Insulin glargine is an appropriate alternative to the common twice-daily NPH insulin dosing regimen with a lower risk of hypoglycemia. Potency of insulin glargine is comparable to that of human insulin and the initial dose in insulin-naïve patients should be approximately 10 units, followed by dosing adjustments based on glycemic control. When converting a patient from a once-a-day insulin injection with a long-acting or ultra long-acting insulin to insulin glargine, a one-to-one unit conversion may be used. If a patient accidentally injects supratherapeutic doses of insulin glargine, they may experience hypoglycemic symptoms for 24 hours. Therefore, the dose of insulin glargine should be

reduced by 20% when switching from a twice-a-day dosing of NPH insulin to prevent the risk of hypoglycemia, and then slowly titrate the dose upwards. Insulin glargine has not been adequately studied in pregnancy or in patients younger than 6 years. Currently it is classified as pregnancy category C.³⁵

In a 28-week, open-label comparative trial, patients with type 2 DM currently treated with NPH insulin were randomized to receive insulin glargine once daily, NPH once daily, or NPH twice daily.³⁶ Insulin glargine and both NPH insulin groups demonstrated similar statistically significant decreases in HbA_{1c} from baseline; however, there was no statistically significant difference between insulin products. An interesting outcome of the trial was the insulin glargine group had a 25% lower risk of nocturnal hypoglycemia compared with the NPH group.³⁶ Similar results were demonstrated in a 52-week comparative trial conducted in patients with type 2 DM, who were poorly controlled on oral therapy.³⁷ Decrease in nocturnal hypoglycemia is most likely a direct reflection of the peak effect of the bedtime dose of the NPH insulin as opposed to the peakless characteristic of insulin glargine. In addition, insulin glargine demonstrated its 24-hour duration of action by significantly decreasing post-dinner glucose concentrations compared with the NPH-treated groups.³⁷

Insulin glargine is a novel addition to the family of insulins. Its pharmacokinetic properties render it an ideal insulin to use for patients lacking normal physiologic basal insulin or requiring large doses of insulin. Although insulin glargine has some limitations, many can be avoided with proper patient counseling.

Insulin Aspart (NovoLog)

Insulin aspart (NovoLog, Novo Nordisk Pharmaceuticals, Inc, West Princeton, NJ), a new, synthetic, rapid-acting insulin formulation, was approved by the FDA in June 2000. It is an insulin analog whereby the proline amino acid in the 28 position of the β -chain was replaced by aspartic acid.³⁸ (Table 4). Due to this alteration in amino acid sequence, the time-action profile of insulin aspart is quicker than regular insulin. This differs from insulin lispro (Humalog; Eli Lilly and Co, Indianapolis, Ind), another rapid-acting insulin, whereby the proline and lysine in position 28 and 29 of the β -chain are

Table 5. Comparison of Pharmacokinetics of Selected Insulin Products

Drug	Onset, h	Peak, h	Duration, h
Lispro (Humalog)	0.25	0.5-1.5	6-8
Aspart (NovoLog)	0.25	1-3	3-5
Insulin NPH (Humulin/Novolin)	1-1.5	4-12	24
Insulin Ultralente (Humulin/Novolin)	4-8	10-24	> 36
Glargine (Lantus)	1	N/A	24

inverted. Aspartic acid is negatively charged, thereby preventing the normal development of hexamers of the insulin, leading to rapid absorption.³⁹ Once injected, insulin aspart quickly dissociates into a monomeric form due to the negatively charged amino acid and therefore is quickly absorbed (Table 4). The substitution of aspartic acid changes the pharmacokinetics of the insulin; however, it does not alter the pharmacodynamics and biologic action of the insulin.

Normal physiologic insulin is secreted at a basal rate and in response to meals. The pharmacokinetics of insulin aspart mimics the mealtime insulin surge if administered properly. In a phase I trial, 20 healthy subjects were randomized in a crossover fashion to receive either 0.2 U/kg of insulin aspart or regular insulin in the thigh, abdomen, and deltoid with a 1-week washout period in between.⁴⁰ The results revealed T_{max} was significantly shorter and C_{max} was greater with the insulin aspart than regular insulin regardless of the injection site. The mean T_{max} from the abdomen was 94 ± 46 min and 173 ± 62 min for the insulin aspart and regular insulin, respectively.⁴⁰

In regard to blood glucose control, insulin aspart is primarily compared to regular insulin. In a double-blind, double-dummy crossover trial, patients with type 2 DM were randomized to insulin aspart 0.15 U/kg immediately before meals, regular insulin 0.15 U/kg immediately before meals, or regular insulin 0.15 U/kg 30 minutes before meals. Postprandial glucose excursion was significantly less with insulin aspart ($899 \text{ mmol/m} \pm 609$) when compared with regular insulin immediately before meals ($1102 \text{ mmol/m} \pm 497$); $P < .01$); however, no difference was noted between insulin aspart ($899 \text{ mmol/m} \pm 609$) and regular insulin 30 minutes prior to meals (868 ± 374).⁴¹

In another study,⁴² the efficacy of long-term insulin aspart use was demonstrated. Eight hundred

eighty-two patients with type 1 DM were randomized to either insulin aspart or regular insulin for 12 months. The doses of these agents were adjusted during the run-in period to meet fasting and postprandial glycemic targets. All patients were also allowed doses of NPH insulin as their basal insulin, which was also adjusted during the run-in period. The average dose of insulin aspart and regular insulin was approximately 0.42 U/kg. At 12 months, the HbA_{1c} values was slightly, but significantly lower in the insulin aspart group ($7.78\% \pm 0.04\%$ vs $7.91\% \pm 0.06\%$, $P = .0046$). Also at 12 months, the postprandial levels after each meal was significantly lower in the insulin aspart group than the regular insulin group. The incidence of hypoglycemia was similar in both groups.⁴²

Insulin aspart may be left at room temperature for 28 days or refrigerated.³⁸ It has not been adequately studied in pregnancy or the pediatric population (younger than 6 years). Currently it is pregnancy category C. The alteration in amino acid sequence does not limit insulin aspart's use with NPH insulin or in continuous infusion insulin pumps. Studies have shown that it may be used safely when mixed with NPH insulin; however, studies with other insulin formulations have not been performed to date. Also when used in continuous subcutaneous insulin infusion pumps, insulin aspart is just as effective in controlling daily blood glucose levels and maintaining HbA_{1c} as regular buffered insulin.⁴³

Inhaled Insulin

Research to develop inhaled insulin has been under way for years; currently the formulation is in phase II and phase III trials. Many of the issues that prevent the approval of inhaled insulin surround the pharmacokinetic profile. The initial concerns included its absorption from the oral cavity and its quick degradation in peripheral tissues and stomach. Due to these problems, it has been difficult to determine the reproducibility of the onset of effect and duration of effect. Preliminary results from recent studies demonstrate successful treatment of type 1 and type 2 DM with inhaled insulin.

Inhaled insulin has a rapid onset of action. In a phase II study with 18 healthy male volunteers, the kinetics of inhaled insulin was compared with regular insulin and lispro.⁴⁴ Inhaled insulin 6 mg had a similar onset of action to lispro 18 units rather than regular insulin 18 units.⁴⁴ The reproducibility of inhaled insulin's glucose-lowering effect was studied in a randomized, open-labeled study with 16 healthy

volunteers. Patients were given either regular insulin 0.2 U/kg or inhaled insulin 4 to 6 inhalations of 20% formulation 10 minutes preprandially in a crossover fashion. Both regimens decreased postprandial glucose similarly (regular insulin by 43 mg/dL, inhaled insulin by 47 mg/dL) without a statistically significant difference.⁴⁵

Most recently, an open-labeled, parallel-group study randomized 73 patients to either 12 weeks of traditional insulin regimen of 2 to 3 times daily subcutaneous injections or preprandial dry-powder inhaled insulin plus a bedtime subcutaneous injection of ultralente insulin. The mean daily insulin dose was 61.4 units in the inhaled insulin group and 46.9 units in the traditional insulin group. The HbA_{1c} at week 12 decreased similarly in both groups from baseline (7.7% vs 7.9% , inhaled insulin vs traditional therapy, respectively).⁴⁶ Although the study had strict patient selection criteria and was an open-labeled trial, it provides encouraging efficacy data for the use of inhaled insulin.

ECONOMIC IMPLICATIONS

Treatment of diabetes not only consists of lowering blood glucose values, but also treating and preventing related complications. The overall medical care costs associated with DM are a large proportion of the healthcare costs in the United States. An estimated \$10000 is spent yearly on healthcare for each person with diabetes, whereas only \$2700 is spent on each patient without diabetes.³ A study evaluating the cost of medical care of 3017 patients with type 2 DM demonstrated that the cost of medical care increased significantly for patients with HbA_{1c} percentages above 7%. Each 1 percentage point of HbA_{1c} over the value of 6% increased costs by approximately 4%, 10%, 20%, and 30%, indicating patients with poorly controlled diabetes utilize a greater percentage of healthcare dollars than persons with well-controlled disease.^{47,48}

In another study, health-economic benefits and quality of life were studied as they related to glycemic control in diabetic patients. Five hundred sixty-nine patients were randomized to either diet and placebo, or diet and glipizide XL therapy for 12 weeks. Quality of life was assessed by separate visual analog scales (VAS) of perceived physical health, mental and emotional health, symptom distress, general health perceptions, and self-reported cognitive function. Other end points were health-related days missed from work, healthcare use, and restrict-

ed activity days. The VAS for the quality-of-life parameters resulted in statistically significantly greater positive results for all parameters in the active group than the placebo group, except for the mental and emotional health VAS. Also, absenteeism dropped by 0.8% in the active group; however, for the placebo group the absenteeism increased by 8.1%. The number of patients who had restricted activity days dropped in the active group by 0.4%, but increased in the placebo group by 4.4%. The active group also utilized less healthcare (office visits, emergency room visits) than the placebo group (27.7% vs 34%), resulting in an approximate cost savings of \$11 per patient per month.⁴⁹

A managed care organization demonstrated that most healthcare expenditures related to diabetes were attributed to hospitalizations (39%), whereas only 7% were due to primary care visits, and only 9% were related to pharmacy costs.⁵⁰ Better utilization of primary prevention strategies and aggressive management of diabetes may reduce overall expenditures. Based on the UKPDS economic analysis, intensive blood glucose control with insulin, metformin, and/or sulfonylureas decreased overall healthcare costs of patients with type 2 DM by 1.3% when compared with "conventional" (ie, diet) therapy. Although intensive blood glucose control increased pharmacy costs, costs associated with treatment of complications (hospitalizations, referral to specialist, etc) were significantly reduced.⁵¹ Therefore from a total health-system perspective, the overall medical costs decreases with intensive blood glucose control.⁵²

Table 2 outlines the cost of various prescription antidiabetic medications on a monthly basis; however, they are based on the average wholesale price, which may vary from the actual cost to the patient. Dosages used to determine costs represent the dose of the drug necessary to lower the HbA_{1c} by 0.5% to 1%. Agents with the potential to lower HbA_{1c} to a greater extent than others are priced higher than agents that have less effect on the HbA_{1c}, therefore it is important not only to look at the cost of the medication, but also its effectiveness.

In most cases, patients take combination therapy for the treatment of diabetes; therefore, overall costs for treatment for each individual patient may be more than reflected in Table 2. It is important to note that the combination product, Glucovance, is less expensive than using both products independently (metformin and glyburide) at equivalent doses. Pioglitazone and rosiglitazone require frequent liver function test monitoring

throughout the course of therapy; thereby increasing overall medical costs associated to treatment with these agents. However, these agents have the potential to lower HbA_{1c} by a maximum of 1.5% and they do not perpetuate hyperinsulinemia. The insulin preparations are competitively priced, however, it is important to take into account the cost of insulin syringes when prescribing insulin.

CONCLUSIONS

Utilizing drug therapy to achieve tight glycemic control and prevent complications of diabetes is essential in lowering overall medical costs. Unfortunately, a recent study^{53,54} of a random sample of 733 diabetic patients from the National Health and Nutrition Examination Survey database showed 58% of patients had HbA_{1c} > 7%. Diabetes is undertreated in the United States, leading to enormous healthcare costs. With new therapeutic options and aggressive management, the overall healthcare costs attributed to diabetes can significantly decline. Combination therapy using antidiabetic agents with different mechanisms of action is becoming the standard of care to meet glycemic treatment goals. Eight new antidiabetic products including 2 new formulations of insulin have been added to our armamentarium for the treatment of diabetes in the past 2 years. The agents have novel mechanisms of action and unique efficacy and safety data. Because of their unique characteristics, particular agents may be more advantageous in certain populations over others.

Nateglinide, insulin aspart, and miglitol are beneficial in controlling postprandial hyperglycemia and have a low incidence of hypoglycemia due to their short duration of action. Although they are priced competitively compared with the other agents, they may not provide adequate basal control in patients with poorly controlled diabetes if used as monotherapy. Therefore these agents may be reserved for patients who have moderately controlled DM (HbA_{1c} < 8%), or used in combination with other agents. Each one of the agents is similar to agents already on the market (ie, repaglinide, insulin lispro, and acarbose), therefore a cost-benefit analysis may be indicated before approving these agents for formulary status over similar agents that may already have formulary status.

Insulin glargine, rosiglitazone, pioglitazone, and metformin/glyburide all provide significant decreases

in HbA_{1c}; however, due to their specific contraindications and side effect profiles, each needs to be carefully chosen for a given patient. Insulin glargine has most commonly been compared with insulin NPH. Although studies show similar glycemic results with either therapy, insulin glargine has the potential to decrease usage of insulin syringes, alcohol swabs due to its once-daily dosing, and has the potential to decrease emergency room visits due to limited risk of hypoglycemia. With further studies being conducted, insulin glargine should be considered for formulary status. Thiazolidinediones have an impressive effect on the HbA_{1c}; however, liver function tests must be monitored throughout the duration of therapy. With the increased inconvenience and cost of liver function test monitoring, thiazolidinediones should be reserved as add-on, or second-line therapy. However, due to their unique mechanism of action and impact on glycemic control, they should be considered for formulary status. Since there does not seem to be much difference between the 2 thiazolidinedione products (ie, pioglitazone, rosiglitazone) in terms of dosing, side effects, and cost, one or the other may be recommended for formulary status. The metformin/glyburide combination product provides excellent glycemic control and is priced competitively, therefore should be considered for formulary status, whereas the extended-release metformin product does not seem to add any clinical benefit over the immediate-release product.

Treatment options for diabetes are expanding with medications that have novel mechanism of actions, pharmacokinetic parameters, and dosing regimens. Managed care organizations have identified the treatment of diabetes and its complications as one of the leading contributors to the overall expenses of the healthcare budget. By using an aggressive, patient-specific approach to therapy, glycemic control may be achieved, along with limited complications, and an enhanced quality of life.

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