Therapeutic Options for the Management of Type 2 Diabetes Mellitus

Liza Takiya, PharmD, CDE, BCPS; and Sweta Chawla, PharmD

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

This activity has been planned and produced in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education. The Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of the CME activity.

The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 1.0 hour in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

This CME activity was produced under the supervision of Tabb Moore, MD, Associate Professor, Johns Hopkins University School of Medicine.

Drs Takiya and Chawla have not received financial support for consultation, research, or evaluation and do not have a financial interest relevant to this article. The authors have indicated that this article does not reference unlabelled/unapproved uses of drugs.

Program released November 30, 2002; program expires November 30, 2004.

CONTINUING PHARMACY EDUCATION CREDIT

This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-999-02-209-H-01. This course expires on November 30, 2004.

From the Department of Clinical Pharmacy, University of the Sciences in Philadelphia, Penn (LT); and Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, NY (SC).

Address correspondence to: Liza Takiya, PharmD, CDE, University of the Sciences in Philadelphia, 600 South 43rd Street, Philadelphia, PA 19104. E-mail: l.takiya@usip.edu.

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.

(Am J Manag Care 2002;8:1009-1023)

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 UKPDS[6] 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-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.