

New oral treatment options and outcome measures may help patients with type 2 diabetes to achieve better results while reducing associated costs.

Improving Oral Pharmacologic Treatment And Management of Type 2 Diabetes

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ABSTRACT

Type 2 diabetes and its associated complications impose a substantial burden on those affected by the disease and have a significant economic impact on the national health care system. Recent estimates indicate a substantial increase in diabetes prevalence in the United States in the past decade, with the largest increases occurring in minority populations. Although diet and exercise are important treatment components, they ultimately fail to control hyperglycemia in many patients. Most patients initially require oral pharmacologic therapy, and many will need multiple agents to stabilize and maintain glycemic control over time. Simplifying oral treatment regimens and reducing pill burden could improve patients' adherence to treatment substantially. Implementation of early and aggressive glycemic control along with appropriate monitoring can reduce the incidence of complications

associated with diabetes, thereby improving patients' outcomes and ultimately decreasing health care costs. Toward these goals, the Diabetes Quality Improvement Project (now the National Quality Improvement Alliance) has developed measures designed to improve the care of patients with type 2 diabetes. These measures, along with new oral treatment options, may allow patients and their health care providers to achieve better glycemic control, improve adherence, and reduce the costs associated with this progressive and chronic disease.

Key terms: type 2 diabetes, oral therapy, management, glycemic, adherence, health care, cost

INTRODUCTION

Type 2 diabetes is a complex, progressive, and chronic disorder that is associated with significant morbidity and mortality in the United States. The Centers for Disease Control and Prevention estimates that 6.2 percent of the U.S. population (17 million Americans) has diabetes (CDC 1998). Of this population, 11.1 million are diagnosed with the disease; the vast majority (90 to 95 percent) has type 2 diabetes. The remaining 5.9 million individuals may have the disease but are undiagnosed on the basis of the revised American Diabetes Association (ADA) criteria of fasting plasma glucose (FPG ≥ 126 mg/dL) (ADA 2002; CDC 1998). Another 16 million adult Americans (ages 40 to 74) have impaired fasting

glucose ($\geq 100 - < 126$ mg/dL) or impaired glucose tolerance (postchallenge glucose 140 – 199 mg/dL) that clearly predisposes them to overt diabetes (ADA 2002, 2004; CDC 1998).

The widespread increase in the prevalence of type 2 diabetes in the United States has been associated with factors such as decreased physical activity, increased prevalence of obesity, and poor dietary habits. Data from the Behavioral Risk Factor Surveillance System showed increases in the prevalence of diabetes across many demographic measures, including sex, age, ethnicity, and concomitant medical conditions (Figure 1) (Mokdad 2000). Recent studies have shown that among certain racial groups, the increase has occurred disproportionately (Burrows 2000; CDC 2003; Mokdad 2000).

The prevalence of type 2 diabetes has increased dramatically during the past decade (1990 – 1998) in Latinos (from 5.6 to 7.7 percent), and to a lesser extent in blacks (from 7 to 8.9 percent) and whites (from 4.6 to 5.9 percent) (Mokdad 2000). This underscores the ongoing need for effective interventions to address the substantial and growing burden of diabetes in both pediatric and adult populations.

Improved nutrition and increased physical activity remain first-line therapies for patients with type 2 diabetes (ADA 2001). For those unable to control their glucose levels with diet and exercise, however, early and aggressive oral pharmacotherapy is essential. These interventions, with

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This paper has undergone peer review by appropriate members of MANAGED CARE'S Editorial Advisory Board.

continuous patient education, can provide long-term health benefits and may reduce overall health care costs.

This article reviews the pathophysiology of type 2 diabetes and the rationale for aggressive glycemic control, describes the financial costs and societal implications of diabetes, outlines a rational oral pharmacologic approach to achieve and maintain glycemic control, describes the importance of patients' treatment adherence to the attainment of improved outcomes, and identifies related pitfalls.

Pathophysiology and rationale for glycemic control

Normal glycemic control is maintained through three interrelated events: insulin-mediated suppression of hepatic glucose production, stim-

ulation of glucose uptake by the peripheral tissues in response to insulin secretion, and secretion of insulin in response to increased plasma glucose concentration (DeFronzo 1999). Defects in any of these metabolic events result in hyperglycemia; over a period of years, insulin resistance and impaired glucose tolerance progress to overt diabetes.

At the time of diagnosis, almost all patients with type 2 diabetes have defects in both insulin action (i.e., insulin resistance) and insulin secretion (Edelman 1998; Nolan 1999). As seen in the United Kingdom Prospective Diabetes Study (UKPDS), the clinical complications associated with diabetes often develop before diagnosis and produce considerable morbidity (Turner 1999). These complications are the primary cause of death in most patients with type 2 diabetes

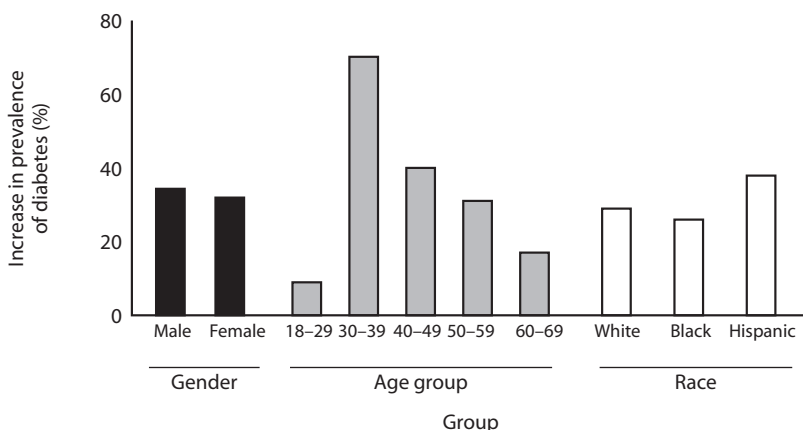
(Table 1) (CDC 1998).

In patients with established type 2 diabetes, the rate of hepatic glucose production is increased despite increased plasma insulin concentrations (DeFronzo 1999). This suggests the presence of hepatic insulin resistance and impaired ability of insulin to suppress hepatic glucose production. The increased rate of hepatic glucose production closely correlates with an increase in the FPG level. Oral antihyperglycemic agents that reduce the basal rate of hepatic glucose production (e.g., biguanides) and enhance glucose uptake in skeletal muscle (e.g., thiazolidinediones [TZDs]) should improve glycemic control (Figure 2) (DeFronzo 1997; DeFronzo 1999; Groop 1989).

The ability of endogenous insulin to increase glucose uptake in the muscles is therefore markedly reduced, further contributing to hyperglycemia, especially prandial glucose levels following a meal. Antihyperglycemic agents (e.g., biguanides, TZDs) that stimulate muscle uptake of glucose help to restore normal glucose homeostasis. Impaired insulin secretion has a major role in pathogenesis, even at the earliest recognizable stages of type 2 diabetes. Insulin secretagogues — agents that stimulate insulin secretion by the pancreatic β -cells — are used to correct this defect of glucose metabolism (Figure 2).

Most patients have impaired insulin secretion as well as increased insulin resistance at diagnosis. Therefore, treatment targeting both defects in glucose metabolism should be particularly effective in attaining glycemic control, especially once FPG is elevated. Combination therapy manages diabetes from a physiologic approach, as it addresses the multiple and progressive metabolic defects of this disease. Overall, continuous and aggressive maintenance of glycemic control within clinical practice guidelines should maximize therapy benefits, reduce the potential for

FIGURE 1 Increasing prevalence of diabetes, 1990 to 1998



SOURCE: MOKDAD 2000

TABLE 1 Complications of diabetes

- Cardiovascular disease — the leading cause of death
- Stroke — 2 to 4 times greater risk
- Renal disease — the leading cause of end-stage renal disease in the United States
- Nerve damage — occurs in approximately 60 to 70 percent of patients
- Foot ulcerations — leading to lower-extremity amputation
- Blindness — responsible for 12,000 to 24,000 new cases each year
- Acute complications — resulting in substantial morbidity or premature death

SOURCE: CDC 1998

macrovascular and microvascular complications, and help lower health care costs.

Economic consequences

The financial burden of diabetes in the United States is massive and steadily growing. Patients with type 2 diabetes are responsible for a disproportionately high percentage of total health care expenditures, with annual treatment costs approaching \$100 billion nationally; direct medical expenses account for approximately \$44 billion, including nearly \$8 billion for diabetes and acute glycemic care, and nearly \$12 billion for related chronic complications. The remaining \$54 billion was spent on indirect costs related to disability (\$37 billion) or premature mortality (\$17 billion) (ADA 1998; CDC 1998).

Recent research suggests that aggressive maintenance of glycemic control (i.e., achieving optimal serum HbA_{1c} levels) is associated with savings in health care costs for adults with diabetes (Gilmer 1997; Wagner 2001). Gilmer and colleagues reported that medical care costs increased significantly for every 1 per-

cent increase above the ADA recommended target HbA_{1c} level of 6 percent (Gilmer 1997) (Figure 3). This trend was observed for patients with or without diabetic complications (Wagner 2001). Wagner and associates compared the health care costs between two cohorts of patients with type 2 diabetes (improved vs. unimproved HbA_{1c} levels) for a 5-year period. For patients with an improved HbA_{1c} level, a significant reduction (\$685 to \$950 per year) in health care expenditures was shown.

Short-term improvements in glycemic control also are associated with substantial health economic benefits and improved quality of life. In a randomized, double-blind, placebo-controlled trial of glipizide vs. placebo, 12 weeks of treatment with the antihyperglycemic agent produced a significant decrease in HbA_{1c} and FPG levels (*P*<.001) (Testa 1998). The associated socioeconomic benefits included higher retained employment, greater productive capacity, reduced absenteeism, fewer bed-days, and fewer days of restricted activity (Testa 1998).

Similarly, Wagner and associates

showed reductions in hospital admissions, emergency room use, specialty care visits, and primary care visits in a cohort of patients with improved HbA_{1c} levels (Wagner 2001).

Management of type 2 diabetes

To help reduce the incidence of diabetes-related complications, the ADA has established acceptable and ideal goals for the treatment of type 2 diabetes; the recommendations include target levels for FPG (80 – 120 mg/dL), bedtime plasma glucose (100 – 140 mg/dL), and HbA_{1c} (<7 percent) (ADA 2002). Although there was no evidence of a glycemic threshold for the development of diabetes-related complications in either the Diabetes Control and Complications Trial or the UKPDS (Stratton 2000; DCCT 1996), it may be beneficial to maintain HbA_{1c} as close to normal levels as possible (i.e., <6 percent). The American Association of Clinical Endocrinologists suggests a target goal of <6.5 percent (AAACE 2000).

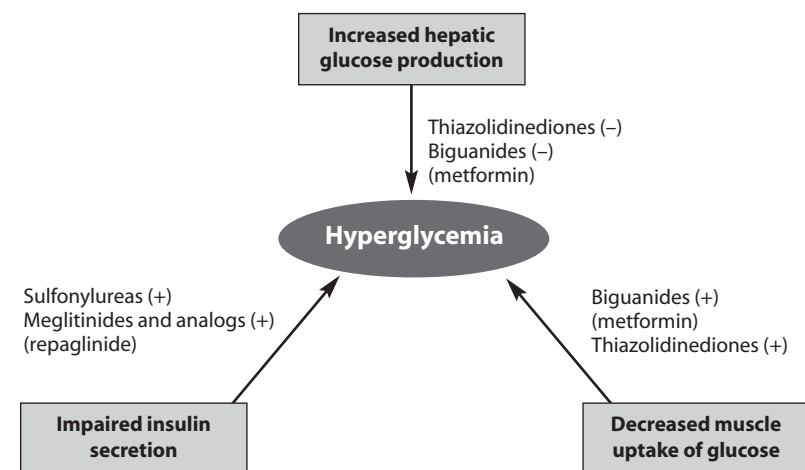
Current standards of care

In recent years, preventive care measures for patients with diabetes have improved substantially. Brown and colleagues (Brown 2000) reviewed changes in preventive practices, risk factors, and clinical outcomes within a large HMO, Kaiser Permanente Northwest Division. From 1987 to 1996, the annual percentage of patients screened for HbA_{1c} increased 4-fold (from 22 to 83 percent), with the majority of patients (56 percent) achieving a serum HbA_{1c} of <8 percent. Screening rates also improved for nephropathy (from 1 to 43 percent), lipid abnormalities (from 37 to 56 percent), and retinopathy (from 50 to 68 percent).

The number of emergency room visits and the number of days spent in acute care declined from 2.5 to 1.8 visits per year and from 3.6 to 2.5 days per year, respectively. Annual mortality rates also improved from 4.8 to 3.8 percent during the surveil-

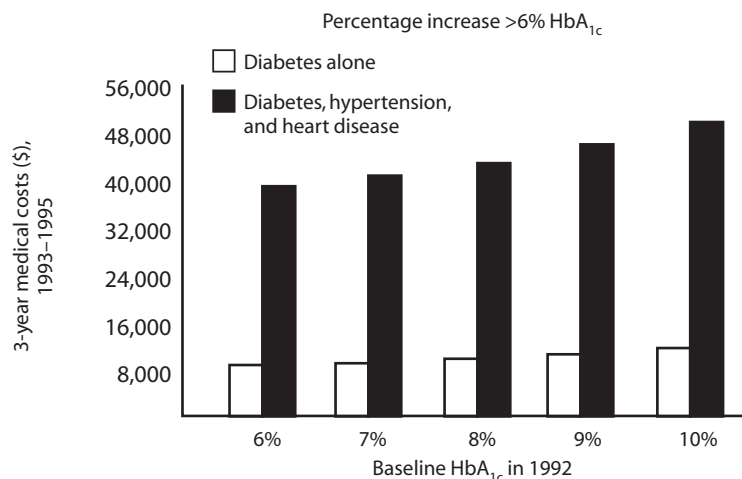
FIGURE 2 The pathogenesis of type 2 diabetes

The pathogenesis of this disease includes hepatic and muscle resistance to insulin and impaired insulin secretion.



The sites of action of oral antihyperglycemic agents are indicated: (-) indicates inhibition; (+) indicates stimulation.

FIGURE 3 Medical charges increase with increasing HbA_{1c} greater than 6 percent



SOURCE: GILMER 1997

lance period. Although the decrease in annual mortality was not significant within the group of patients with diabetes, there was a significant relative improvement in mortality ($P=.01$) when compared with non-diabetic members.

Despite recent improvements in monitoring techniques and morbidity and mortality rates, at least one study suggested that many patients with type 2 diabetes continue to have inadequate glycemic control (Harris 1999). In the Third National Health and Nutrition Examination Survey, slightly more than half of patients surveyed had unacceptable levels of glycemic control (HbA_{1c} >7.0 percent) according to ADA recommendations, and more than one third had HbA_{1c} >8.0 percent (Harris 1999).

Furthermore, more than two thirds of patients receiving oral anti-hyperglycemic agents had an FPG >140 mg/dL, the point at which the ADA recommends additional therapeutic intervention. The development of a system that would standardize treatment of type 2 diabetes would improve patients' outcomes.

Development of outcome measures

The inability to compare care received by patients with diabetes from

different health care providers has given rise to the perception that the health care system should be held accountable for the treatment provided and the outcomes achieved. This accountability has resulted in the development of so-called *performance* and *outcome measures*, administered through a report-card system.

Unfortunately, the multiplicity of

report-card systems, each with their own measures, has created unnecessary work and confusion. The consensus among health care professionals, scientists, providers, accrediting bodies, and purchasers is that a single set of measures would provide a powerful tool for evaluating key components of care as a basis for quality improvement and also would allow valid care comparisons within and across health care settings.

Accordingly, the Diabetes Quality Improvement Project (DQIP) — now the National Diabetes Quality Improvement Alliance — developed a set of disease-specific performance and outcome measures that could be used both as a tool for comparison of care among providers and as a plan for the diabetes population (Table 2) (NCQA 2003).

The Alliance recommends annual HbA_{1c} testing. Patients with serum HbA_{1c} >9.5 percent are identified as having poor glycemic control. Those with high-risk HbA_{1c} levels were identified as patients who might prompt the development of more cost-effective treatment strategies.

TABLE 2 Diabetes Quality Improvement Project measures

Accountability set

- HbA_{1c} testing
- Percentage of patients at highest-risk HbA_{1c} level (>9.5 percent)
- Diabetic nephropathy monitoring
- Lipid profile evaluated within past 2 years
- Percentage of patients with LDL cholesterol concentration <130 mg/dL
- Percentage of patients with blood pressure <140/90 mm Hg
- Eye examination

Quality improvement set

- Distribution of HbA_{1c} values
- Distribution of lipid control (LDL cholesterol)
- Blood pressure distribution
- Documented comprehensive foot exam

Patient-reported measures (in field testing)

- Self-management education, including nutrition education
- Interpersonal care from provider
- Satisfaction with and access to care
- Health status
- Foot examination
- Smoking-cessation counseling

SOURCE: NCQA 2003

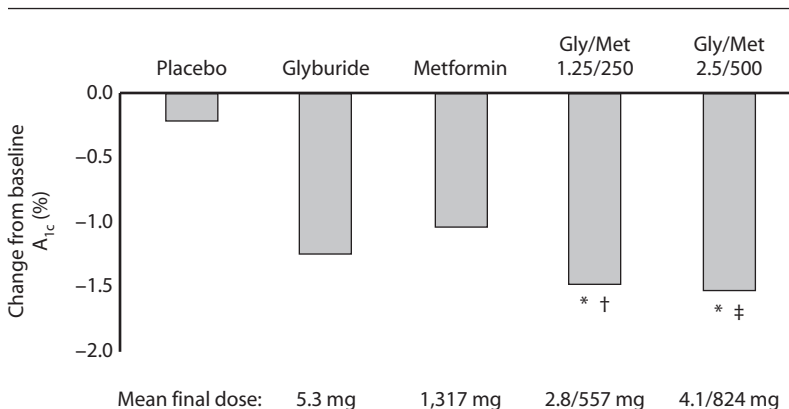
The Alliance measures also recommend monitoring for diabetic nephropathy with microalbuminuria screening tests at least every 2 years. Eye examinations to monitor for diabetic retinopathy are recommended every 1 to 2 years; monitoring of lipid profiles, serum LDL cholesterol concentrations, and blood pressure is also advised (NCQA 2003).

The Alliance also includes measures for quality improvement (Table 2) (NCQA 2003). These measures are used to gain information about the levels of glycemic control within the patient population served. Currently, the Alliance measures are used by an increasing number of health care and related organizations (e.g., the Health Care Financing Administration and NCQA) (Pawlson 2000). The NCQA, which accredits MCOs, has developed a measurement set to assess performance and outcomes. The Health Plan Employer Data and Information Set now includes the Alliance measures (Beed 1999; Pawlson 2000).

Oral pharmacotherapeutic options

Initial treatment for type 2 diabetes should include dietary modification, weight loss, and regular exercise, which should be continued throughout the management of the disease (DeFronzo 1999). Yet diet and exercise alone frequently fail to achieve or sustain the recommended target HbA_{1c} and FPG goals; thus, pharmacotherapy becomes necessary

FIGURE 4 Mean reductions in HbA_{1c} levels with glyburide-metformin as first-line therapy



*P<.001 compared with placebo or metformin.

†P<.016 compared with glyburide.

‡P<.004 compared with glyburide.

Change from baseline HbA_{1c} (mean = 8.2 percent). Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes.

SOURCE: ADAPTED FROM GARBER 2002

to ameliorate hyperglycemia. Several classes of oral antihyperglycemic agents with different mechanisms of action are available (Table 3). Table 4 indicates the efficacy of these agents when administered as monotherapy.

Initially, all these agents are effective as monotherapy. Nevertheless, due to the progressive nature of type 2 diabetes, most patients eventually require multiple agents to achieve and maintain adequate glycemic control. Inadequate glycemic control following monotherapy may be due, in part, to a lack of adherence to therapy.

Accordingly, some older but effective antihyperglycemic agents (e.g., metformin and sulfonylureas) have been reformulated for extended-release delivery. A combination of two insulin sensitizers (metformin plus rosiglitazone) also has been introduced. These novel formulations may enhance patients' adherence with oral therapy and improve long-term glycemic control, insulin sensitivity, and β-cell function more effectively than conventional single-agent formulations (Fonseca 2000).

The combination of various anti-

TABLE 3 Mechanism of action of various antihyperglycemic agents

Classification	Mechanism of action	Specific agents
Insulin secretagogues: sulfonylureas, meglitinides, and analogs	<ul style="list-style-type: none"> • Increase insulin secretion • Stimulate insulin secretion by the pancreatic β-cells 	<ul style="list-style-type: none"> • Glyburide, glimepiride, glipizide • Nateglinide, repaglinide
Biguanides	<ul style="list-style-type: none"> • Decrease hepatic glucose production and increase sensitivity to insulin; • increase peripheral glucose uptake; • decrease intestinal absorption 	<ul style="list-style-type: none"> • Metformin (immediate- and extended-release formulations)
α-Glucosidase inhibitors	<ul style="list-style-type: none"> • Delay digestion of carbohydrates 	<ul style="list-style-type: none"> • Acarbose, miglitol
Thiazolidinediones	<ul style="list-style-type: none"> • Enhance insulin sensitivity 	<ul style="list-style-type: none"> • Pioglitazone, rosiglitazone

hyperglycemic agents with complementary mechanisms of action allows greater glycemic control with lower doses of either agent. Clinical combinations commonly used to treat patients with type 2 diabetes include metformin plus sulfonylurea (DeFronzo 1995; Garber 1997), metformin plus repaglinide (Moses 1999), metformin plus pioglitazone or rosiglitazone (Egan 1999; Einhorn 2000; Fonseca 1999), sulfonylurea plus pioglitazone (Kipnes 2001; Schneider 1999), metformin plus acarbose (Halimi 2000; Rosenstock 1998), and sulfonylurea plus acarbose (Bayraktar 1996; Willms 1999).

The most frequently used combination is metformin plus a sulfonylurea (DeFronzo 1999). Several studies have shown that this combination provides greater glycemic control than either agent alone, with no increase in adverse events (Erle 1999; Hermann 1994; UKPDS 1998a; UKPDS 1998b). The single-tablet formulation of a sulfonylurea (glyburide) plus metformin has been approved by the Food and Drug Administration and is likely to simplify treatment of type 2 diabetes. The glyburide/metformin tablet was developed using a formulation of glyburide of controlled particle size that delivers twice as much of the agent during the first 3 hours of dosing than does glyburide coadministered with metformin. Recently, a combination of metformin plus glipizide was introduced (Donahue 2002).

The use of single-tablet glyburide/metformin was evaluated in a large, 32-week, double-blind, placebo-controlled clinical trial of pa-

tients who failed to achieve glycemic control with diet or exercise alone (Garber 2002). First-line treatment with glyburide/metformin 1.25/250 mg and 2.5/250 mg resulted in significantly better glycemic control at lower doses and with fewer adverse events than glyburide or metformin monotherapy. At Week 20 (primary end point), significant reductions in mean HbA_{1c} (about 1.5 percent) for both glyburide/metformin dosage groups were observed compared with the group administered glyburide (1.24 percent) or metformin monotherapy (1.03 percent) (Figure 4). FPG reduction also was significantly greater in both glyburide/metformin treatment groups than in the placebo and metformin groups ($P < .001$ compared with placebo or metformin). Of clinical relevance, the majority of patients who received glyburide/metformin achieved HbA_{1c} of < 7 percent after 20 weeks of treatment (72 percent for 2.5/500 mg; 66 percent for 1.25/250 mg).

The metformin/repaglinide combination also has proved more effective than either monotherapy in treating patients with inadequate glycemic control (Moses 1999). A greater reduction from the baseline mean HbA_{1c} was observed in the combination treatment group (1.4 percent, $P = .0016$) than in either metformin or repaglinide monotherapy group (0.4 percent and 0.3 percent decreases, respectively).

TZDs (rosiglitazone, pioglitazone) represent a newer class of antihyperglycemic compounds. These agents act as agonists to the peroxisome proliferator activating receptor in in-

sulin-sensitive tissues (i.e., adipose, skeletal muscle, and liver) to enhance the actions of insulin. The principal mechanism of action of metformin appears to be to enhance insulin action at the liver to reduce hepatic glucose output. Thus, the mechanism of action of TZDs is complementary to metformin and insulin secretagogues.

The FDA has approved the combination formulation of metformin plus rosiglitazone, the effects of which were evaluated in patients who had inadequate control with metformin monotherapy (HbA_{1c} > 8 percent) (Fonseca 2000). Metformin plus rosiglitazone for 26 weeks significantly improved HbA_{1c} and FPG levels in a dose-dependent manner. HbA_{1c} decreased by 1.0 percent and 1.25 percent in the metformin 2,500 mg/day plus rosiglitazone 4 mg/day group or 8 mg/day group, respectively ($P < .001$ vs. placebo group for both). Moreover, 28 percent of patients receiving the higher dose of rosiglitazone achieved HbA_{1c} < 7.0 percent. TZDs are known to cause certain adverse effects (e.g., edema and weight gain) (DeFronzo 1999).

Several clinical studies have shown that the addition of acarbose to metformin or to sulfonylurea therapy has an additive effect. The FDA has approved the use of such combinations in patients with type 2 diabetes (Bayraktar 1996; Rosenstock 1998; Willms 1999). In patients with extremely poor glycemic control (mean HbA_{1c} approximately 10 percent at baseline), combination therapy with acarbose plus a sulfonylurea resulted in a mean 2.2 percent reduction in HbA_{1c}. In a placebo-controlled study,

TABLE 4 Relative efficacy of monotherapy with oral antihyperglycemic agents

	Sulfonylureas or repaglinide*	Metformin [†]	Nateglinide	Acarbose	Rosiglitazone or pioglitazone
FPG (mg/dL)	60–70	59–78	9–21	20–30	59–80
HbA _{1c} (%)	1.5–2.0	0.9–2.0	0.5–0.8	0.5–1.0	1.4–2.6

FPG=fasting plasma glucose.

*Varies with agent.

[†]Immediate or extended-release formulation.

SOURCE: 2002 package inserts for drugs listed; Chiasson 1994; Lee 1996

mean HbA_{1c} (0.65 percent) decreased significantly (0.65 percent) in patients receiving metformin plus acarbose, whereas mean HbA_{1c} rose slightly in those receiving metformin plus placebo (Bayraktar 1996).

Patient involvement

Optimal control of diabetes necessitates the patient's full and continuous involvement, characterized by a commitment to lifestyle changes and long-term treatment adherence. MCOs, national societies, and governmental agencies have sponsored educational programs that encourage patients to actively manage their diabetes (Blonde 2000). Controlling glycemia is associated with improved quality of life for patients and their families (Blonde 2000; Turner 1999), including better general health perceptions, better cognitive function, and lower symptom-related distress.

At the workplace, employment retention and production capacity are increased; restricted activity days and absenteeism are decreased. Not surprisingly, deteriorating quality of life is often associated with disease progression and complications, as demonstrated in the UKPDS (Turner 1999). Despite evidence from multiple intervention studies that better glycemic control can improve health outcomes and quality of life, many patients fail to achieve and maintain adequate glycemic control (Beed 1999; Blonde 2000; Turner 1999). This finding may be due in part to patients' poor adherence to their prescribed treatment regimen (Brown 1999).

Perseverance with treatment is critical to achieving optimal glycemic control. The term *compliance* has been used to describe the extent to which a person's behavior coincided with medical or health advice (Lutfey 1999). Yet this term has a connotation that implies obedience rather than participation. Many clinicians now use the term *adherence* to describe treatment perseverance, as it implies

that the patients are active, autonomous, independent, and capable of active involvement in maintaining their health (Lutfey 1999).

Nonadherence to therapy represents a significant yet often overlooked problem in clinical practice. Many factors contribute to nonadherence, including inability to understand the disease and treatment regimen, adverse events associated with treatment, financial barriers, complex treatment regimens, poor communication between caregivers and physicians, and patient avoidance of the health care system (Dezii 2000).

Of these factors, the effect of increasing treatment complexity is the easiest to quantify. Morris and colleagues examined adherence using prescription claims data from more than 2,900 persons with type 2 diabetes (Morris 2000). Treatment adherence was similar in subjects receiving either sulfonylurea or metformin monotherapy (31 vs. 34 percent), but decreased in patients receiving sulfonylurea-metformin combination therapy (13 percent).

Although overall adherence was poor, once-daily dosing and/or fewer tablets taken per day were strongly associated with better adherence rates. Additionally, each increase in frequency of daily dose corresponded with a 22 percent decrease in adherence. Thus, simplification of treatment regimens and reduction of medications taken can improve adherence substantially. New treatment options that simplify doses and combine effective medications may improve adherence and help patients achieve better glycemic control (Melikian 2002).

CONCLUSION

Diabetes is a major health care burden for both patients and society. Intensive glycemic control reduces microvascular and macrovascular complications associated with type 2 diabetes, improves patients' out-

comes, and ultimately decreases health care costs. Improvements in diet and exercise are important in diabetes treatment but are inadequate for controlling glucose levels in most patients. Most patients will require pharmacologic intervention with multiple agents as their disease progresses.

The importance of maintaining aggressive glycemic control in patients with type 2 diabetes has become increasingly evident, yet clinical practices have not matched the understanding of the disease process. Physicians and health management plans must promote regular screening for diabetes-related complications and must target oral pharmacologic treatment aggressively to those with increased HbA_{1c} levels.

Implementation of optimal therapy should lower the rate of complications associated with the disease and enable health care organizations to reduce the associated cost burden.

Control of type 2 diabetes necessitates full involvement of patients, including commitment to lifestyle changes and long-term adherence to treatment. Oral pharmacologic agents that address the dual defects of type 2 diabetes have proven effective for treating these patients.

REFERENCES

- Actos (pioglitazone HCl) package insert. Osaka, Japan: Takeda Chemical Industries, Ltd; July 2002. Available at: «<http://www.actos.com>». Accessed August 6, 2003.
- ADA. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2004;27: S5-S10.
- Amaryl (glimepiride tablets) package insert. Kansas City, Mo.: Aventis Pharmaceuticals Inc; July 2001. Available at: «http://www.aventispharm-us.com/Pis/amaryl_TXT.html». Accessed August 6, 2003.
- AACE. American College of Endocrinology. The American Association of Clinical Endocrinologists Medical Guidelines for the Management of Diabetes Mellitus: The AACE System of Intensive Diabetes Self-Manage-

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- ment: 2000 Update. *Endocrine Pract.* 2000;6:42–84.
- ADA. American Diabetes Association. Economic consequences of diabetes mellitus in the U.S. in 1997. *Diabetes Care.* 1998;21:296–309.
- ADA. Standards of medical care for patients with diabetes mellitus. *Diabetes Care.* 2001;24:S33–S43.
- ADA. Standards of medical care for patients with diabetes mellitus. *Diabetes Care.* 2002;25:213–229.
- Avandia (rosiglitazone maleate tablets) package insert. Research Triangle Park, N.C.: GlaxoSmithKline; May 2002.
- Bayraktar M, Van Thiel DH, Adalar N. A comparison of acarbose versus metformin as an adjuvant therapy in sulfonylurea-treated NIDDM patients. *Diabetes Care.* 1996;19:252–254.
- Beed G. Managing diabetes in a managed care environment: Part II. *Manag Care Interface Suppl.* 1999;32–35.
- Blonde L. Introduction: Removing polytherapy as a barrier to adherence. *Manag Care Interface.* 2000; (Sept., Special Suppl):Introduction.
- Brown JB, Nichols GA, Glauber HS. Case-control study of 10 years of comprehensive diabetes care. *West J Med.* 2000;172:85–90.
- Brown JB, Nichols GA, Glauber HS, et al. Ten-year follow-up of antidiabetic drug use, nonadherence, and mortality in a defined population with type 2 diabetes mellitus. *Clin Ther.* 1999;21:1045–1057.
- Burrows NR, Geiss LS, Engelgau MM, et al. Prevalence of diabetes among Native Americans and Alaska Natives, 1990–1997: an increasing burden. *Diabetes Care.* 2000;23:1786–1790.
- CDC. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National estimates and general information on diabetes in the United States. 1998:1–8.
- CDC. Centers for Disease Control and Prevention. Diabetes: disabling, deadly and on the rise: at a glance 2003. Diabetes Public Health Resource 2003. Atlanta, Ga.: Centers for Disease Control and Prevention; 2003. Available at: http://www.cdc.gov/nccdphp/aag/aag_dtd.htm. Accessed Oct. 6, 2003.
- Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. *Ann Intern Med.* 1994;121:928–935.
- DeFronzo R. Pathogenesis of type 2 diabetes: metabolic and molecular implications for identifying diabetes genes. *Diabetes Reviews.* 1997;5:177–269.
- DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med.* 1999;131:281–303.
- DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med.* 1995;333:541–549.
- Dezii CM. Medication noncompliance: what is the problem? *Manag Care.* 2000;9:7–12.
- DCCT. Diabetes Control and Complications Trial Research Group. The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes.* 1996;45:1289–1298.
- Donahue SR, Turner KC, Patel S. Pharmacokinetics and pharmacodynamics of a combination glyburide/metformin (Glucovance) tablet versus equivalent doses of glyburide and metformin in patients with type 2 diabetes. *Clin Pharmacokinet.* 2002;41:1301–1309.
- Edelman SV. Type II diabetes mellitus. *Adv Intern Med.* 1998;43:449–500.
- Egan J, Rubin C, Mathisen A. Combination therapy with pioglitazone and metformin in patients with type 2 diabetes. *Diabetes.* 1999;48:A117.
- Einhorn D, Rendell M, Rosenzweig J, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. *Clin Ther.* 2000;22:1395–1409.
- Erle G, Lovise S, Stocchiero C, et al. A comparison of preconstituted, fixed combinations of low-dose glyburide plus metformin versus high-dose glyburide alone in the treatment of type 2 diabetic patients. *Acta Diabetol.* 1999;36:61–65.
- Fonseca V, Biswas N, Salzman A. Once-daily rosiglitazone (RSG) in combination with metformin (MET) effectively reduces hyperglycemia in patients with type 2 diabetes. *Diabetes.* 1999;48(Suppl 1):A100.
- Fonseca V, Rosenstock J, Patwardhan R, et al. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA.* 2000;283:1695–1702.
- Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med.* 1997;103:491–497.
- Garber AJ, Larsen J, Piper BA, et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. *Diabetes Obes Metab.* 2002;4:201–208.
- Gilmer TP, O'Connor PJ, Manning WG, Rush WA. The cost to health plans of poor glycemic control. *Diabetes Care.* 1997;20:1847–1853.
- Glucophage (metformin hydrochloride tablets) prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; July 2002. Available at: <http://www.glucophage.com>. Accessed Oct. 24, 2003.
- Groop LC, Bonadonna RC, DelPrato S, et al. Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. Evidence for multiple sites of insulin resistance. *J Clin Invest.* 1989;84:205–213.
- Halimi S, Le Berre MA, Grange VV. Efficacy and safety of acarbose add-on therapy in the treatment of overweight patients with Type 2 diabetes inadequately controlled with metformin: a double-blind, placebo-controlled study. *Diabetes Res Clin Pract.* 2000;50:49–56.
- Harris MI, Eastman RC, Cowie CC, et al. Racial and ethnic differences in glycemic control of adults with type 2 diabetes. *Diabetes Care.* 1999;22:403–408.
- Hermann LS, Schersten B, Bitzen PO, et al. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations: a double-blind controlled study. *Diabetes Care.* 1994;17:1100–1109.
- Kipnes MS, Krosnick A, Rendell MS, et al. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med.* 2001;111:10–17.
- Lee AJ. Metformin in noninsulin-dependent diabetes mellitus. *Pharmacotherapy.* 1996;16:327–351.
- Lutfey KE, Wishner WJ. Beyond compliance is adherence. Improving the prospect of diabetes care. *Diabetes Care.* 1999;22:635–639.
- Melikian C, White TJ, Vanderplas A, et al. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. *Clin Ther.* 2002;24:460–467.
- Mokdad AH, Ford ES, Bowman BA, et al. Diabetes trends in the U.S.: 1990–1998. *Diabetes Care.*

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- 2000;23:1278–1283.
- Morris AD, Brennan GM, MacDonald TM, et al. Population-based adherence to prescribed medication in type 2 diabetes: A cause for concern. *Diabetes*. 2000;49(Suppl 1):A76.
- Moses R, Slobodniuk R, Boyages S, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 1999;22:119–124.
- NCQA. National Committee for Quality Assurance. Diabetes Quality Improvement Project: Initial Measure Set (Final Version [2003]). Washington, D.C. Available at: <http://www.ncqa.org/DPRP/dqip2.htm>. Accessed Oct. 24, 2003.
- Nolan J. Promising new approaches to the management of type 2 diabetes. *Postgrad Med*. 1999;18–24.
- Pawson G. Comprehensive HEDIS measures for diabetic patients. *Manag Care*. 2000;9:5–10.
- Prandin (repaglinide tablets) package insert. Princeton, N.J.: Novo Nordisk Pharmaceuticals, Inc; Oct. 2002.
- Precose (acarbose tablets) package insert. West Haven, Conn.: Bayer Corporation; April 2001. Available at: <http://www.univgraph.com/bayer/inserts/precose.pdf>. Accessed October 24, 2003.
- Rosenstock J, Brown A, Fischer J, et al. Efficacy and safety of acarbose in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 1998;21:2050–2055.
- Schneider R, Eagan J, Houser V. Combination therapy with pioglitazone and sulfonylurea in patients with type 2 diabetes. *Diabetes*. 1999;48:A106.
- Starlix (nateglinide tablets) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2002.
- Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405–412.
- Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA*. 1998;280:1490–1496.
- Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA*. 1999;281:2005–2012.
- UKPDS. United Kingdom Prospective Diabetes Study Group. UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. *Diabetes Care*. 1998a;21:87–92.
- UKPDS. United Kingdom Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998b;352:854–865.
- Wagner EH, Sandhu N, Newton KM, McCulloch DK, Ramsey SD, Grothaus LC. Effect of improved glycemic control on health care costs and utilization. *JAMA*. 2001;285:182–189.
- Willms B, Ruge D. Comparison of acarbose and metformin in patients with Type 2 diabetes mellitus insufficiently controlled with diet and sulphonylureas: a randomized, placebo-controlled study. *Diabet Med*. 1999;16:755–761.