SUPPLEMENT TO
MANAGED
Care

The Rationale for Early, Aggressive Treatment of Type 2 Diabetes: The Cost Ramifications of Improved Health Outcomes

HIGHLIGHTS

- Overview of the Pathophysiology of Type 2 Diabetes
- Treatment Modalities and Expected Outcomes for Patients
- Costs Associated With the Disease
- The Role of Modeling in Performing Economic Analyses
- Cost-effective Treatment Measures
- AMCP Format for Standardizing Formulary Submissions
- Employer's Perspective on the Disease

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ABOUT THIS PUBLICATION

The mission of this advisory group was to explore the perspectives of many health care professionals concerned with treatment options and outcomes for patients with type 2 diabetes. A diverse group of advisers — which included managed care medical and pharmacy directors, physicians who treat a significant number of patients with diabetes, an academician, and a pharmacist/employee benefit consultant — was assembled. Two-day, face-to-face meetings were designed to provide an environment in which these professionals could learn from each other, challenge each other, and take what they learned back to their organizations.

Clinical practice regarding current treatment modalities and expected outcomes for patients with type 2 diabetes was the initial focus of discussion. Through an examination of the core defects of the disease — insulin resistance and beta-cell dysfunction — the intent was to understand better how to design optimal treatment plans for prevention, or at least mitigation, of the progression of type 2 diabetes.

After the clinical issues, discussion and presentations focused on the management of the disease, with an examination of the profound economic consequences facing our national health care system as well as government payers and employers. The merits of modeling, as a means of forecasting costs and outcomes, were debated. The economic message that early, aggressive treatment of the disease forestalls complications and associated costs generated strong consensus, and the design of optimal treatment plans that maintain blood glucose at near-normal levels was examined from a number of perspectives and with regard to market realities.

Discussion repeatedly returned to the perspective of the payer, the employer in particular. It was mentioned that data currently available on the economic burden of diabetes are not framed in a manner that employers can appreciate or apply to their workplace environment. It is essential to communicate adequately with this important sector of the health care system to persuade payers and employers to take a more proactive approach to the treatment of type 2 diabetes. Outcomes studies that are under way should fill in knowledge gaps and should more clearly define optimal treatment regimens that will ensure improved clinical outcomes within realistic, cost-effective parameters.

Production of this publication was accomplished through a MEDLINE search of germane clinical and management terms. In addition, key points were derived from transcripts of the faculty presentations and discussions at the Avandia Advisors' Group meetings. The content of this supplement was prepared by Susan Keller, Senior Associate, The Zitter Group.

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INTRODUCTORY MESSAGE

Addressing the High Costs of the Diabetes Epidemic in the U.S. Population

PATRICIA WOLFANGEL
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The epidemic of diabetes (affecting 18.2 million individuals, or 6.3 percent of the U.S. population in 2002) is exacting an enormous toll in terms of quality of life, productivity, and cost. Diabetes is the fifth leading cause of death by disease in the United States and the causative factor in excessive morbidity (cardiovascular disease [CVD], blindness, kidney failure, and lower extremity amputation). According to the American Diabetes Association, in 2003, people with diabetes were twice as likely to have CVD as those without, and this serious complication remains the leading cause of death among diabetic patients

In nearly one third of persons with diabetes, the disease is undiagnosed and, by default, untreated. Of those who receive treatment, 63 percent are not at the ADA goal of A_{1c}* level of less than 7 percent (Saydah 2004). To add to the urgent need for more aggressive and effective treatment, the American College of Endocrinology has recommended lowering the A_{1c} goal to 6.5 percent, which would reduce even further the number of Americans at glycemic goal (Takiya 2002).

Direct and indirect costs attributable to diabetes in 2002 were $132 billion (indirect costs doubled from 1998); hospitalization and treatment of complications were significant cost drivers. Direct medical expenses equaled $92 billion, and indirect expenses, such as lost workdays, restricted activity days, permanent disability, and mortality, totaled $40 billion. Per capita medical expenses equaled $13,243 for individuals with diabetes, in comparison with $2,560 for those without the disease (ADA 2003). The situation does not appear to be getting any better; quite the contrary.

From statistical forecasts for disease trends, the prevalence of type 2 diabetes is expected to double within the next 2 decades, with probable and significant increases in the incidence of CVD. High-risk groups include anyone with a cardiovascular risk factor; elderly people; black persons, Hispanics, and Native Americans; relatives of people with diabetes; overweight people; and children and adolescents. The sedentary American lifestyle, along with obesity, are known contributors to the development of the disease (Marso 2002).

Although the literature is equivocal with regard to the cost savings of intensive blood glucose control, there is consensus that tight glycemic control substantially reduces the occurrence and cost of treating diabetic complications. How best to achieve this control continues as a matter of discussion and debate, some of which follows in this supplement.

What cannot be disputed is that diabetes diagnosis and treatment to achievement of glycemic goals must be a priority for health care providers, payers, policy makers, educators, and employers today and in the coming decades.

The content of this publication begins with an overview of the pathophysiology of the disease, wherein the critical role of insulin resistance and beta-cell function in the development and progression of type 2 diabetes is reviewed. The primary treatment modalities currently available are then outlined, and expected outcomes are discussed. The economics of diabetes are framed within the context of cost of care, as well as how modeling can be useful for health care providers and policy makers in projecting comorbidity and associated expenses in relation to various treatment regimens.

Last, two faculty presentations are synthesized. Diana Brixner, PhD, RPh, describes the Academy of Managed Care Pharmacy (AMCP) and Foundation for Managed Care Pharmacy (FMCP) development of a standardized format with which MCOs can accurately and comprehensively evaluate the potential effect that formulary adoption of a new product has on the pharmacy budget and the health plan as a whole. The publication concludes with synthesis of a presentation by Michael Jacobs, RPh, in which the employer perspective is explored vis-à-vis diabetes in the workplace.

In view of the growing epidemic of diabetes, all stakeholders must be involved in assessment of new treatment paradigms. From the literature, as well as from the experience of our board of economic advisers, it appears that early and aggressive treatment of this debilitating disease is a model that all health care providers would be prudent to consider seriously.

* A_{1c} refers to a chemical fraction of glycosylated hemoglobin, a measure of glycemic control over the prior 3 months.

LITERATURE REVIEW

The Rationale for Early, Aggressive Treatment of Type 2 Diabetes: The Cost Ramifications of Improved Health Outcomes

Executive summary

From national statistics regarding the percentage of individuals with type 2 diabetes who are out of glycemic control, it is safe to say that, at best, our current approach to treatment is not working. This approach can be characterized as one that *reacts* to the progressive nature of this disease and then treats the serious complications of hyperglycemia that result from microvascular and macrovascular damage. In view of the growing epidemic, this reactive paradigm must be questioned, and a more proactive, interventional approach that emphasizes preservation of critical beta-cell function and reduction of insulin resistance must be considered.

Changing the clinical treatment paradigm also has economic consequences, inasmuch as health plans and payers may need to consider forestalling or preventing complications as the true goal of therapy. A more proactive approach will probably necessitate an earlier and possibly larger investment in well-documented disease management interventions, repeated lifestyle behavior modification, and more aggressive pharmacotherapy.

Change is never easy, but with the majority of diabetic individuals not maintaining glycemic control and facing near-certain complications, we must critically examine our methods of treatment. Type 2 diabetes could become pandemic in the 21st century, and steps need to be taken immediately to prevent such an occurrence. A clear treatment path for health care providers, payers, and policy makers must be mapped out quickly if we are to stem the rising tide of this devastating disease.

OVERVIEW OF THE PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Insulin resistance and interrelated beta-cell dysfunction and failure are the core pathologic defects in type 2 diabetes. Early in the course of the disease, insulin levels are elevated in an attempt to compensate for the increased insulin resistance of muscle/fat and hepatic tissues. As the disease progresses, insulin levels drop as the beta cells decline in function (DeFronzo 1992).

The natural course of the disease results in hyperglycemia, which, if left untreated, leads to serious complications involving many major organ systems. By the time hyperglycemia is identified, disruption of the normal relationship between beta-cell function and insulin sensitivity is well established. The landmark United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that type 2 diabetes is a progressive disease that stems from declining beta-cell function (Kahn 2000, UKPDS 33).

The continuum ranges from normal glucose tolerance to impaired fasting glucose and impaired glucose tolerance to overt type 2 diabetes. Decreasing glucose tolerance is associated with increasing insulin resistance and decreasing beta-cell function. Abnormal glucose tolerance is particularly common in first-degree relatives of persons with type 2 diabetes (Jensen 2002).

The insulin resistance syndrome

The insulin resistance syndrome (also referred to as syndrome X or the metabolic syndrome) is a collection of potentially lethal metabolic abnormalities, including the following:

- Glucose intolerance
- Central obesity (an especially dangerous risk factor in the development of heart disease)
- Hypertension
- Dyslipidemia
- Hyperinsulinemia
- Hypertriglyceridemia
- Hypertension

In clinical practice, no single test diagnoses the condition. A formal definition of the insulin resistance syndrome, however, was established by the Adult Treatment Panel III of the National Cholesterol Education Panel (NCEP) in 2001. The syndrome can be diagnosed if any three of the following criteria are present:

- Abdominal obesity, defined as waist circumference of more than 102 cm (40 inches) in men and more than 88 cm (35 inches) in women
- Triglyceride levels of 150 mg/dL (1.7 mmol/L) or higher
- High-density lipoprotein (HDL) cholesterol level lower than 40 mg/dL (1 mmol/L) in men and lower than 50 mg/dL (1.3 mmol/L) in women
- Blood pressure of 130/85 mm Hg or higher
- Fasting glucose level of 110 mg/dL (6.1 mmol/dL) or higher

Acceptance of these diagnostic criteria was followed in 2002 with establishment of an ICD-9 code for insulin resistance syndrome: 277.7.

As much as 25 percent of Western populations (or 47 million persons in the United States) meet the criteria to make the diagnosis for metabolic syndrome, which leads to CVD — the major cause of morbidity and mortality in many countries (Kohler 2002, Scott 2003). Insulin resistance, resulting from an interplay of genetic and environmental variables, contributes to the development of

type 2 diabetes. For example, diabetes is believed to develop in insulin-resistant persons with concomitant inherited secretory and glucose-sensing defects in beta cells (Stolar 2002).

More complete recognition in the population at risk and more aggressive treatment of metabolic syndrome is imperative if patients are to be spared the development of type 2 diabetes, coronary artery disease, and stroke. Treatment is multifactorial and includes diet and exercise as well as pharmacotherapy (Davis 1999, Scott 2003).

TREATMENT MODALITIES FOR PATIENTS WITH TYPE 2 DIABETES AND EXPECTED OUTCOMES

The main goal of all treatment modalities for type 2 diabetes is to prevent — or at least delay or mitigate — the complications of the disease. Complications fall into two main categories: *microvascular* (retinopathy, neuropathy, and nephropathy) and *macrovascular* (ischemic heart disease, stroke, and peripheral vascular disease). Even at diagnosis, complications are generally present (Figure 1) (Holman 1997).

In the UKPDS, results of which were first published in 1998, intensive glycemic control was compared with conventional control. UKPDS randomized 3,867 newly diagnosed patients to a conventional blood glucose control policy (fasting plasma glucose <15 mmol/L) and an intensive glucose control policy with sulfonylurea or insulin; the goal was a fasting plasma glucose level of less than 6 mmol/L. The study showed marked deterioration of glycemia with time, as a result of progressive decrease in beta-cell function. Conventional therapy consisted initially of diet and exercise alone; if marked hyperglycemic symptoms or a fasting plasma glucose level exceeding 15 mmol/L developed, however, subjects received nonintensive pharmacologic therapy.

The primary objective of the study was to determine whether improved glycemic control reduced the incidence of diabetic complications, especially CVD, the major source of complications (Turner 1998). The UKPDS demonstrated clearly that diabetes is a progressive disease; the study also documented that intensive blood glucose control reduces the microvascular damage associated with the disease. Substudies of the UKPDS in which all-cause diabetes mortality was examined also determined that improved blood pressure control "substantially reduced the cost of complications, increased the interval without complications and survival, and had a cost-effectiveness ratio that compares favourably with many accepted healthcare programmes" (Gray 2000, UKPDS 34, UKPDS 40, White 2002). With tight control (mean, 144/82 mm Hg) versus conventional control (154/87 mm Hg), heart failure was reduced by 56 percent; strokes by 44 percent; and combined myocardial infarction (MI), sudden death, stroke, and peripheral vascular disease by 34 percent. The ADA currently recommends a blood pressure goal of less than 130/80 mm Hg.

Another well-known study examining intensive versus conventional therapy is from the Steno Diabetes Center in Denmark. The Steno study implemented a stepwise progression of behavior modification (diet, exercise, and smoking cessation) and pharmacologic therapy (metformin, a sulfonylurea, and/or insulin) for treatment of hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with aspirin for secondary prevention of CVD. A total of 160 patients with type 2 diabetes and microalbuminuria participated in the study: 80 in the conventionally treated cohort and 80 in the intensively treated group. The primary end point was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, revascularization, and stroke. After a mean follow-up of 7.8 years, study authors found that the risk of cardiovascular and microvascular complications was decreased by approximately 50 percent in the intensively treated group (Gaede 2003).

Seminal studies such as the two just described clearly illustrate the link between hyperglycemia and diabetic

Diabetes and cardiovascular disease

The presence of diabetes more than doubles the risk of developing CVD. The following factors have been identified as further magnifying the risk (Watkins 2003):

- Smoking
- Hypertension
- Insulin resistance associated with obesity
- Asian ethnicity
- Microalbuminuria
- Diabetic nephropathy (macroalbuminuria)
- Poor glycemic control
- Hyperlipidemia

FIGURE 1 Prevalence of complications at diagnosis: UKPDS

Complication	Prevalence (%)*
Any complication	50
Retinopathy	21
Abnormal ECG	18
Absent foot pulses (≥2) and/or ischemic feet	14

ECG=electrocardiogram; UKPDS=United Kingdom Prospective Diabetes Study.
*Some patients had more than one complication at diagnosis.

ADAPTED FROM HOLMAN 1997, UKPDS 33

complications, and these results are duplicated in other published literature. For example, in another substudy of the UKPDS (Stratton 2000), each percentage point reduction in A_{1c} was linked with the following risk reductions:

- 37 percent for microvascular complications
- 21 percent for any diabetes-related end point
- 21 percent for deaths related to diabetes
- 14 percent for MI

No threshold of risk was identified for any diabetic outcome; therefore, any reduction in A_{1c} level was associated with a reduction in complications, and the lowest risk was observed in patients with A_{1c} levels lower than 6.0 percent (Stratton 2000). The ADA stresses that *any* A_{1c} level above 7 percent is potentially harmful (ADA 2004).

Despite numerous published studies and widely disseminated, scientifically robust clinical practice guidelines, standards of care for most persons with diabetes in the United States still do not meet national recommendations. As mentioned previously, 63 percent of patients with type 2 diabetes receiving drug therapy are not at the A_{1c} goal of less than 7.0 percent (Saydah 2004). The reasons for this are both varied and complex. Diabetes is a multisystem disorder that necessitates multidisciplinary team care. Effective management of the disease must include patient and provider education, lifestyle modification, as well as behavior modification to achieve glycemic goals (Nicollerat 2000). An informed, involved patient is the key to the success of any diabetes treatment program. Because most patients with diabetes eventually require more than one oral antidiabetic drug (OAD) to control glycemic levels, patient preference is also a valid consideration in choosing a pharmacologic regimen (Holmboe 2002).

Review of the options

An initial therapeutic approach of diet and exercise is followed by a progression of monotherapy with OADs, combination or fixed-dose combination therapy, and OADs in conjunction with insulin to control blood glucose levels (Reasner 2002). This progression of therapies generally follows a step-wise approach. Managed care has supported this step-wise approach through the use of prior authorizations or step edits to control utilization. Step edits, however, entail a period of time when the patient lacks glycemic control before advancing to the next level of treatment. For example, in a step-edit approach, a patient might need to have an A_{1c} of greater than 8.0 percent before being authorized to step up therapy from mono to oral combination therapy or oral therapy and insulin. During the time when A_{1c} is greater than 7 percent, macrovascular and microvascular damage are occurring; the goal of optimal diabetes therapy, however, is maintenance of tight control. Therefore, step edits may be an outmoded and counterproductive management strategy, resulting in excessive cost and undue suffering. To ensure optimal glycemic and clinical control, each patient requires a tailored regimen; to reach these goals, physicians need access to all pharmacologic agents (Avandia Advisors' Group 2002, 2003; Seifert 2003).

Overall, the cost of pharmaceutical agents to treat diabetes is a small percentage of the total cost of care. Table 1 on page 8 shows this from a study of a diabetic managed care population wherein pharmaceutical costs were measured in relation to total health care costs as a function of A_{1c} values (Melikian 2002).

The medications to treat diabetes

In addition to injectable insulin, there are five classes of oral medications to treat diabetes; these are differentiated from each other through a variety of mechanisms of action:

- *Sulfonylureas* are insulin secretagogues
- *Metformin,* a biguanide, reduces hepatic glucose output
- *Thiazolidinediones* (TZDs) are insulin sensitizers that improve glucose uptake in adipose tissues and skeletal muscles

Government initiatives to treat diabetes

For an inventory of programs, conferences, fact sheets, and other educational materials, see the Web site «www.cdc.gov/diabetes/index.htm». Also of note is the Better Diabetes Care Program, developed by the National Diabetes Education Program to help address the system changes needed to improve the quality of diabetes care in the United States. The Better Diabetes Care Program is designed to help health care professionals assess needs, plan strategies, implement actions, and evaluate results. Models, links, resources, and tools are available at «www.betterdiabetescare.org/». The Centers for Disease Control and Prevention (CDC) and the National Institutes of Health jointly sponsor the National Diabetes Education Program. The site «www.cdc.gov/diabetes/ndep/more.htm» has links to detailed information about the program. At the Diabetes at Work site, «http://diabetesatwork.org», an assessment tool is available to help managers become aware of the prevalence and costs of diabetes in their workplace and what they may be able to do about it. A fact sheet, hosted by the Washington Business Group on Health, is also available at: «http:www.cdc.gov/diabetes/index.htm».

- *Meglitinides* are rapid-acting insulin secretagogues and target postprandial glucose excursions
- *Alpha-glucosidase inhibitors* delay the absorption of polysaccharides and also act to attenuate postprandial glucose excursions

Insulin therapy should be initiated in patients who cannot maintain an A_{1c} level of less than 7.0 percent with other therapies. Physicians might consider continued use of insulin sensitizers during insulin therapy in order to reduce insulin resistance and treat metabolic syndrome (Bohannon 2002, Brown 1999, Holmboe 2002, Loh 2002).

In 2001, 91.8 million prescriptions were written for OADs in the United States. Of these, sulfonylureas accounted for 36 percent; metformin captured approximately 33 percent of the market; the TZDs accounted for about 17 percent; and other, less frequently prescribed OADs, including combination glyburide-metformin, acarbose, miglitol, repaglinide, and nateglinide, constituted the remaining 14 percent (Wysowski 2003).

Combination therapy

Type 2 diabetes is a progressive disease in which hyperglycemia escalates despite treatment with OADs. Three years after initiation of pharmaceutical treatment, 50 percent of patients require a second drug to control blood glucose levels; after 9 years; 75 percent of patients require additional pharmaceuticals (Seifert 2003, Turner 1999). Because OADs have differing mechanisms of action, they are frequently prescribed in tandem for patients who cannot reach glycemic goals with monotherapy. As a result, combination and the newer fixed-dose combination therapies are becoming more prevalent (Figure 2). The increase in the use of the fixed-dose combination OADs may have occurred partly due to improved patient compliance and the reduced cost of taking only one medication instead of two.

In a study of 6,502 patients with recent diagnoses of type 2 diabetes and enrolled in a managed care plan, there were no initial differences in adherence rates among patients receiving monotherapy, combination therapy, or fixed-dose combination therapy. Among 1,815 patients in whom monotherapy failed and who required a second medication, however, adherence rates fell significantly in comparison with patients receiving initial monotherapy who then switched to fixed-dose combination therapy. Finally, patients who received combination therapy exhibited greater adherence to their medication regimen when they were switched to a fixed-dose medication (Melikian 2002).

TABLE 1 Cost of prescription medications in diabetes treatment

A_{1c} value	Rx costs ($)	Medical costs ($)	Total costs ($)	Rx as a % of total
<7.0	388	8,356	9,940	3.9
7.0–7.9	473	7,318	9,252	5.1
8.0–9.5	618	6,069	7,958	7.8
>9.0	500	6,038	8,086	6.2

SOURCE: MELIKIAN 2002

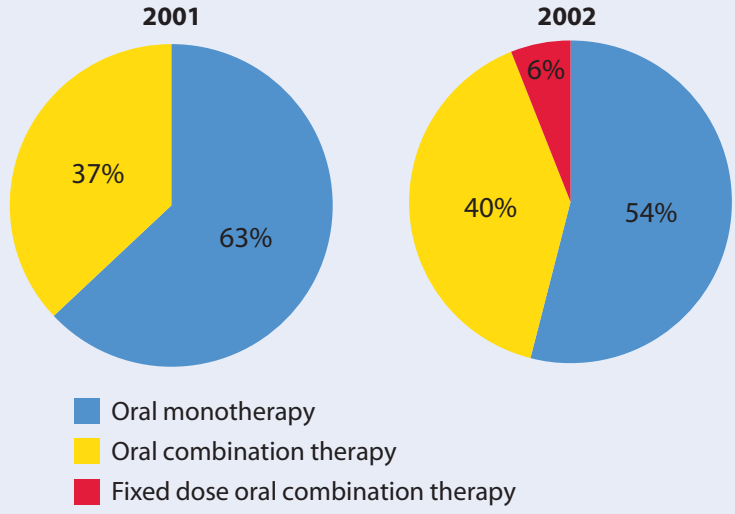
Combination therapy can target the many defects in type 2 diabetes. Sulfonylureas only increase insulin secretion; TZDs reduce insulin resistance and provide a decrease in cardiovascular risk factors. Metformin primarily reduces hepatic glucose production. The TZDs are insulin-sensitizing agents that improve insulin resistance by combining with an intranuclear hormone receptor (see the box on the biochemistry of TZDs on page 9). TZDs reduce circulating free fatty acids and suppress adipose-derived cytokines that increase insulin resistance. Additionally, TZDs improve endothelial function, and they may prevent or delay the onset of type 2 diabetes (Stolar 2002). For example, TZDs used in combination with sulfonylureas or metformin effectively treat hyperglycemia and improve the lipid profile. In obese patients with inadequately controlled type 2 diabetes, adding a TZD to a metformin regimen improves glycemia, insulin sensitivity, and beta-cell function to a clinically significant extent (Ballary 2003, Jones 2003). The addition of a TZD to sulfonylurea therapy also improves insulin sensitivity and establishes glycemic control in some patients in whom monotherapy has failed (Barnett 2002, Yang 2003).

THE CASE FOR EARLY USE OF TZDs

Although each of the major classes of OADs has its strengths, it is prudent to note that limitations of sulfonylureas and metformin — as well as insulin — are beginning to emerge in terms of their inability to protect the beta cell and thus provide long-term glycemic control (Wyne 2003a, 2003b). Proposed diabetic treatment algorithms guide clinicians in the earlier use of TZDs to potentially preserve beta-cell function, prevent or reverse metabolic syndrome, maintain better glycemic control, and reduce diabetic complications (Mayerson 2002).

TZDs act to improve insulin resistance directly, and their "early use may provide substantial benefits to patients with type 2 diabetes" (Miller 2003). TZDs reduce hyperglycemia, hyperinsulinemia, and systolic and diastolic blood pressure and modify dyslipidemia in patients with type 2 diabetes mellitus. Additionally, they have an anti-inflammatory effect on the vascular endothelium (Garg 2003, Lebovitz 2002, Raptis 2001, Viberti 2003). Also, by decreasing insulin resistance, TZDs have beneficial effects on the beta cell that allow the provision of more durable glycemic control and may reduce macro-

FIGURE 2 Trends in oral antidiabetic therapy: the growth of combination therapy



SOURCE: GSK 2001

vascular complications commonly seen in patients with type 2 diabetes (Pathak 2002, Reasner 2002).

There is a great deal of accumulating evidence that early use of pharmacologic agents that target the core defects of type 2 diabetes may prevent or slow the progression of the disease and associated comorbid conditions, especially CVD (Bell 2003, Caballero 2003, Collins 2002, Goldstein 2002, Huerta 2002, Reasner 2002, Weissman 2002, Zangeneh 2003, Zimmet 2002).

Metformin versus TZDs and cardiovascular risk

Patients with poor glycemic control (A_{1c} level >8.5 percent) taking glyburide were randomly assigned to receive metformin or troglitazone for 16 weeks. Primary study end points were glycemic control, insulin resistance, and measures of traditional and novel cardiovascular risk factors such as blood pressure and levels of lipids, plasminogen activator inhibitor-1, C-reactive protein, fibrinogen, and small dense low density lipoprotein (LDL) cholesterol. After treatment, both study groups had similar reductions in fasting plasma glucose, as well as in A_{1c}. The decrease in insulin resistance was, however, 2 times greater in the troglitazone-treated subjects than in those taking metformin. Significant cohort differences also were found when cardiovascular risk factors were measured. For example, TZD therapy was significantly associated with increases in LDL size and elevated levels of HDL cholesterol; triglycerides and C-reactive protein levels declined. The study authors concluded that the addition of a TZD for patients in whom sulfonylurea therapy had failed pro-

The biochemistry of TZDs: how they work

The TZDs are potent peroxisome proliferator-activated receptor gamma agonists with anti-inflammatory properties. TZDs improve peripheral insulin sensitivity by reducing circulating free fatty acids as well as by suppressing adipocytokines, compounds known to increase insulin resistance.

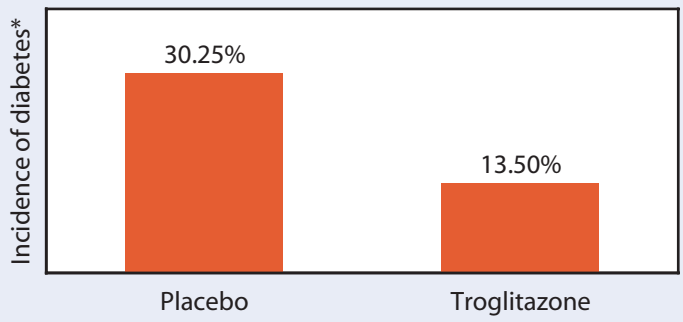
Insulin stimulates nitric oxide release by the endothelium. Like nitric oxide, insulin is a vasodilator, has antiplatelet activity, and is anti-inflammatory. The similar anti-inflammatory properties of TZDs suggest that they too have antiatherogenic effects and improve endothelial function. This is important because the two fundamental states of insulin resistance — obesity and type 2 diabetes — are associated with a significant increase in atherosclerosis, coronary heart disease, and stroke (Braunstein 2003, Dandona 2002). In addition, arteriosclerotic lesions in persons with diabetes are less stable than those lesions in nondiabetic persons. In a study comparing the effects of rosiglitazone with placebo in diabetic and nondiabetic patients with coronary heart disease, those receiving rosiglitazone treatment had significantly reduced levels of metalloproteinase (a marker for the development of unstable plaques). The authors concluded that their data "support the anti-inflammatory and potential antiatherogenic effects of thiazolidinediones" (Marx 2003).

By improving insulin sensitivity, TZDs also ameliorate the dyslipidemia of type 2 diabetes, by significantly raising HDL and improving the buoyancy of the LDL particles.

Lipid abnormalities associated with type 2 diabetes and insulin resistance include low levels of HDL cholesterol and elevated triglyceride levels. Reducing LDL cholesterol while increasing HDL cholesterol reduces the incidence of major coronary events and significantly improves the prognosis for diabetic patients. TZDs increase insulin sensitivity, widen the intima-media thickness of the carotid artery, and appear to inhibit the progression of atherosclerotic plaques (Drexler 2003).

FIGURE 3 Preventing or delaying onset of type 2 diabetes

Diabetes rates at month 30 of trial



*Rates at month 30 of trial based on average annual incidence rates of 5.4 percent for troglitazone and 12.1 percent for placebo during blinded treatment.

SOURCE: BUCHANAN 2002

vided not only good glycemic control (as measured by a fasting plasma glucose level <120 mg/dL) but also apparent benefit for both novel and traditional cardiovascular risk factors. "These data suggest that medications that more effectively address this [insulin resistance] underlying metabolic defect may be more beneficial in reducing cardiovascular risk in type 2 diabetes" (Chu 2002).

Special populations

The development of overt type 2 diabetes is preceded by a clinical condition known as prediabetes that is characterized by impaired glucose tolerance and/or elevated levels of fasting plasma glucose. In both diabetic and prediabetic persons, treatment with TZDs redistributes adipose tissue stores in the body and reduces circulating free fatty acids, which improves tissue response to insulin and tends to "spare" the beta cell and, in fact, may prolong its normal function while improving glycemia and preventing or delaying the onset of microvascular and macrovascular complications. Populations that may benefit most profoundly from early use of TZDs therefore include persons with any known cardiovascular risk factors: hypertension, hyperlipidemia, hypercholesterolemia, and the presence of other novel cardiovascular risk markers (Kudzma 2002).

Another group of potentially appropriate candidates for TZD therapy include women at high risk for type 2 diabetes. Researchers analyzed the effect of amelioration of chronic insulin resistance among 236 women with previous gestational diabetes. Primary end points were preservation of beta-cell function and prevention of progression to type 2 diabetes. Study subjects were randomly assigned to receive a TZD (n=133) or placebo (n=133) in a double-blind manner. Over the course of 30 months of follow-up, placebo recipients progressed to type 2 diabetes at more than double the rate of the TZD-treated women: 12.1 percent versus 5.4 percent, average annual incidence rate, respectively. Figure 3 illustrates incidence rates among the 236 women who returned for at least 1 follow-up visit.

The authors concluded that TZD treatment "delayed or prevented the onset of type 2 diabetes in high-risk Hispanic women. The protective effect was associated with the preservation of pancreatic beta-cell function and appeared to be mediated by a reduction in the secretory demands placed on beta cells by chronic insulin resistance" (Buchanan 2002).

Indicators for progression to type 2 disease

The Insulin Resistance Atherosclerosis Study was a prospective, epidemiologic study of insulin sensitivity and associated risk of the development of diabetes and concomitant CVD. Participants included 903 nondiabetic, multiethnic subjects who were monitored for 5 years. Of those, 148 (16.4 percent) developed type 2 diabetes. Researchers determined that those at greatest risk for development of the disease had low insulin response and high levels of proinsulin. Study authors stated that determining insulin resistance from frequently sampled intravenous glucose tolerance tests can help accurately identify persons with prediabetes who would benefit from intensive pharmacologic intervention to prevent the serious cardiovascular complications of the disease. Insulin resistance, rather than decreased insulin secretion, was determined to be a more reliable indicator of progression to overt type 2 disease (Festa 2003, Hanley 2002).

In the Women's Health Study, researchers found that high levels of C-reactive protein are predictive of type 2 diabetes. TZDs have been shown repeatedly to reduce this nontraditional cardiovascular risk factor; specifically, rosiglitazone decreases C-reactive protein levels (as well as plasminogen activator inhibitor-1 levels, another novel risk factor for CVD). The authors stated: "Some of the adverse cardiovascular effects seen in patients with type 2 diabetes may be reversed by insulin-sensitizing agents" (Haffner 2003).

Potential long-term adverse effects of TZDs appear minor but warrant further consideration. Weight gain and peripheral edema that appears in the ankles and is not considered a risk factor for heart disease have been observed; current long-term data, however, are insufficient for a conclusive statement. The hepatotoxicity as-

FIGURE 4 Outcomes trials in progress

The outcomes studies described herein are under way; results have yet to be published. Noteworthy, though, is that primary or secondary end points in these studies are CV events. For example, in the BARI 2D study, researchers will determine whether treatment that improves insulin resistance can retard progression of CAD compared with glycemic control achieved with an insulin secretagogue (Sobel 2003). In the DREAM trial, the efficacy of ramipril and rosiglitazone will be examined against placebo as a means to prevent diabetes in nondiabetic patients at high risk (Gerstein 2002). ADOPT will provide data on the effect of insulin sensitizers vs. an insulin secretagogue on glycemic control, beta-cell function, and risk factors for macrovascular disease (Viberti 2002). Publication of these studies will enable clinicians, plan administrators, researchers, and policy makers to understand the optimal role of thiazolidinediones (TZDs) in the treatment of type 2 diabetes and its sequelae of comorbid conditions, particularly macrovascular end points.

Study	Main objective	Treatments	Primary end point(s)	Secondary end point(s)
ADOPT A Diabetes Outcome and Progression Trial	To evaluate long-term outcomes of TZD monotherapy	RSG Metformin Glyburide	Time to monotherapy failure	Beta-cell function, IS, microalbuminuria, CV surrogates, LT safety, QoL, PE
DREAM Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications	To evaluate TZD and ACE inhibitor use in preventing progression of IGT to T2DM	RSG + placebo RSG + ramipril Ramipril + placebo	Development of diabetes or death from any cause	• Adjudicated CV end points • Microvascular end points
RECORD Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes	To evaluate glycemic control prevention of CV end points in T2DM	Combination therapy: • Placebo • Rosiglitazone + metformin • Rosiglitazone + SU • SU + metformin	Time to reach the combined CV endpoint	Numerous CV and glycemic end points
BARI 2D* Bypass Angioplasty Revascularization Investigation T2DM	• To compare revascularization+medical therapy vs. medical therapy alone • To compare the glycemic and CV benefits of insulin-sparing (RSG or metformin) vs. insulin-providing (SU or insulin) agents	RSG +/– metformin vs. SU +/– insulin	Rates of MI, ischemic events, angina, QoL	• Pharmacoeconomics of therapy strategy • Evaluation of progression and mechanism of vasculopathy
ACCORD* Action to Control Cardiovascular Risk in Diabetes	To evaluate if a therapeutic strategy targeting intensive glycemic control reduces the rate of CVD • To evaluate whether a strategy to raise HDL and lower TG while maintaining desirable total LDL and acceptable glycemic control reduces the rate of CVD • To determine if a strategy to target SBP<120 reduces CV events	Intensive therapy vs. conventional therapy for hyperglycemia, lipids, and BP	First occurence of major CV event	Other CV outcomes, all-cause mortality, microvascular outcomes, QoL, PE
VADT Veterans Affairs Diabetes Trial — Glycemic Control and Complications in Type 2 Diabetes	• To evaluate whether reduction in major CV events is observed with intensive glycemic control	Intensive glycemic control vs. standard control with step-up therapy including metformin or glimepiride, RSG, and/or insulin	Occurrence of major macrovascular event	Includes angina, claudication, retinopathy, nephropathy, neuropathy, cognitive function, QoL, cost-effectiveness

* Rosiglitazone provided; pioglitazone optional.

ACE=angiotensin-converting enzyme; BP=blood pressure; CAD=coronary artery disease; CV=cardiovascular; IGT=impaired glucose tolerance; IS=insulin secretion; LT=long-term; MI=myocardial infarction; PE=pulmonary embolism; QoL=quality of life; RSG=rosiglitazone; SBP=systolic blood pressure; SU=sulfonylurea; T2DM=type 2 diabetes mellitus; TG=triglycerides.

SOURCES: ABRAIRA 2001, ACCORD, CDA, DREAM STUDY, GREENE 2000, GSK 2001, HOME 2002, NIH «HTTP://WWW.CLINICAL TRIALS.GOV/CT/ACTION/GETSTUDY», VIBERTI 2002

sociated with troglitazone, withdrawn from the market several years ago, appears not to be mediated by peroxisome proliferator-activated receptor gamma and so has not been seen with rosiglitazone or pioglitazone (Fuchtenbusch 2000, Stumvoll 2002). Recently, the FDA has reduced the suggested frequency of liver-test monitoring with pioglitazone.

Although prevention of type 2 diabetes is not the primary goal of TZD therapy, it is quite feasible that early and aggressive treatment with these agents not only prevents or delays the serious complications of the disease but also forestalls the need for insulin injections, frequent blood glucose monitoring, and the associated effects on quality of life.

In lieu of outcomes studies: assessing the effect of diabetes within an MCO

When outcomes studies are not available, health services researchers can work with MCOs that have access to pharmacy, cost, medical (e.g., record of weight change, presence of edema), and laboratory data to determine the utilization of resources associated with diabetes within that plan. Ideally, amputation rates and data on dialysis also would be available. Then the prevalence of adverse events and/or significant differences in outcomes among cohorts of patients taking a variety of medication regimens could be analyzed. Caveat: these analyses would not be a substitute for robust, long-term outcomes studies conducted in real-world environments that can take 8 to 10 years to complete and disseminate results through the published literature (Avandia Advisors' Group 2002, 2003).

LITERATURE REVIEW

The Economics of Diabetes and the Role of Modeling in Performing Economic Analyses

Because diabetes is a progressive disease, its long-term outcomes frequently are associated with significant morbidity and mortality. Nevertheless, the microvascular and macrovascular sequelae of the disease can be mitigated or delayed with good glycemic control. Without adequate control, morbidity — with its negative effect on quality of life and its significant costs — is almost a given, especially among patients with comorbid heart disease, hypertension, or both (White 2002). For example, at one large HMO, treatment of macrovascular complications of type 2 diabetes accounted for 62 to 89 percent of all inpatient costs (Brown 2001).

In considering short-term complications, the message is the same: Better glycemic control means fewer hospitalizations. Using a retrospective design, researchers analyzed databases to identify adult diabetic members of an MCO who could be categorized into three cohorts by A_{1c} measurement: good control (<8 percent), fair control (8 to 10 percent), and poor control (>10 percent). Short-term complications were defined as certain infections, hyperglycemia, hypoglycemia, and electrolyte disturbances. Inpatient (hospital or skilled nursing home) admissions and associated medical charges were calculated for the three cohorts over a 3-year period. Inpatient admissions were 13 per 100 for patients with good control; 16 per 100 for those with fair control; and 31 per 100 for those with poor control. Mean adjusted charges were $970, $1,380, and $3,040, respectively. The authors conclude that better control leads to reductions in medical expenditures and resource utilization. "The potential short-term economic benefits are important to consider when making decisions regarding the adoption and use of new interventions for the management of diabetes" (Menzin 2001).

In summary, "…unless diabetes is properly managed and glucose levels monitored, some component of an integrated health system [hospital versus pharmacy] necessarily bears financial risk. An understanding of the underlying cost distribution for a chronic disease could help in targeting interventions, integrating disease management services, and managing the formal structure of the health plan being considered" (Bhattacharyya 1999).

Fortunately, increasing numbers of studies are documenting the link between aggressive pharmacologic management of type 2 diabetes and the overall cost-effectiveness (Killilea 2002, Pathak 2002). The following is an overview of just a few cost-effective measures and programs that have improved health and economic outcomes for diabetic patients in a managed care environment within the first few years of implementation.

Cost-effective measures to treat the disease

The Diabetes Treatment Centers of America developed a disease management program that focused on optimal screening frequency for diabetic complications and monitoring of glycemic control. The program entailed use of a computerized system that enabled nurse case managers to track patients by degree of comorbidity and outcomes. It provided both patients and practitioners with support tools and materials. In the first year of the program, a retrospective analysis calculated a 12.3 percent (or $660) reduction in costs of care per diabetic member. Even more significant cost savings were realized after implementation of a diabetes disease management program at the Group Health Cooperative of Puget Sound and the University of Washington. Within this program, better glycemic control was associated with savings of $685 to $950 per patient per year. Descriptions of other cost-effective or even cost-saving disease management programs can be found readily in the literature.

Overall, retinopathy screening has been determined to

be clearly cost-saving; improved glycemic control and nephropathy screening and prevention have been shown to be clearly cost-effective; and self-management training and neuropathy screening and prevention have been shown to be possibly cost-effective (Clouse 2002).

Proactive diabetes disease management is highly cost-effective in the short term; the following intervention documented a 4.34:1 return on investment in year 1. In a community-based MCO, 127 members with diabetes were recruited into a disease management program and monitored for 1 year. Resource utilization, as well as clinical indicators such as frequency of A_{1c} testing, symptoms of hyperglycemia, daily glucose meter use, foot and eye examinations, diet, weight, and blood pressure, were measured. The intervention entailed aggressive monitoring and education of diabetic members about glycemic control and microvascular and macrovascular risks, including lipid management, aspirin and beta blocker use when appropriate, blood pressure monitoring, and preventive testing. The intervention relied heavily on a telephone-based, registered nurse-delivered approach. Study authors found that participants better self-managed their disease, which resulted in a substantial reduction in health care utilization and a net decrease in medical costs (Berg 2002).

The role of models in performing economic analyses

Cost models can be useful to physicians, administrators, policy makers, and payers in determining the value of two (or more) equally efficacious medications, allowing them to incorporate actual data about their individual organizations and patient populations with a variety of cost implications and assumptions (Goetzl 2002). In essence, models estimate long-term costs and benefits of new therapies and health care interventions within a given population, allowing a number of assumptions to be tested.

Optimally, models serve these purposes:

- They provide the latest data germane to the disease and therapeutic category
- They are reflective of a managed care health plan's population
- They demonstrate the economic effect of a given therapy on the pharmacy budget
- They demonstrate potential for savings in other areas of the health care environment
- They illustrate the effect on members' premiums
- They calculate when additional system costs might occur

To be reliable, however, models must encompass certain basic principles; these include clinical relevance, transparency, and analytical ability (Coyle 2002a). When specifically looking at diabetes, pharmacy and therapeutics committee members need models that can compare treatments for the disease and its complications in order to make informed formulary decisions. To do this, the model should include calculations on the long-term benefits of reductions in all diabetic complications, be flexible enough to account for changes in drug utilization patterns, and provide data on the effect of a variety of therapies on the existing drug budget. End users of models should be aware of the sources of the data that went into populating the model; these data should be able to be generalized to the patient population at that managed care plan. The medical literature provides managed care professionals with guidance on how to make informed decisions regarding the use of models. To do so requires considerable sophistication to fully grasp the complexities and nuances of modeling. For professionals at MCOs to appropriately evaluate models, joint educational programs between managed care, academia, and the pharmaceutical industry should be implemented (Veenstra 2002).

Overview of a diabetes model

A potential design for a type 2 diabetes model might be expected to utilize standard U.S. population data such as those collected by the federal government in the National Health and Nutrition Examination Survey. As such, it would contain probabilities of microvascular and macrovascular complications that are based on epidemiologic and interventional studies, such as the Diabetes Control and Complications Trial, UKPDS, and Framingham Heart Study. Lastly, it might logically apply estimates of effectiveness of various therapies, given changes in diabetic parameters such as A_{1c} and insulin resistance, and then calculate costs and results of various therapeutic regimens.

A diabetes model could begin with the assumption that defined population groups such as black, Hispanic, white, or other racial populations have either no diabetic comorbidities or stage 1 microvascular or macrovascular disease. The model would then be powered by observations from widely published epidemiologic data that a certain percentage of patients proceed to the next stage of diabetic complications within 12 months. This type of model assumes a certain time frame in years after diagnosis of type 2 diabetes; it includes demographic assumptions as well as clinical assumptions, such as a starting A_{1c} level, for all patients.

The effect of numerous therapies on A_{1c} or insulin resistance reduction could be evaluated in such a model. These might include no pharmaceutical therapy (diet and exercise) and a variety of OAD regimens at differing dosages. Costs for screening and treatment of complications can be built into the model. Measures of effectiveness are based on randomized controlled trial results. Due to significant complexity, model pathways for de-

A Markov model at work

The objective of this study was to assess, from the perspective of a payer, the cost-effectiveness of pioglitazone as a first-line therapy for patients with type 2 diabetes. Utilizing a Markov model, researchers determined the health and economic outcomes of using the TZD in the treatment of diabetic complications, including hypoglycemia, acute MI, stroke, the necessity of lower extremity amputation, nephropathy, and retinopathy. Treatment with pioglitazone was compared with that with metformin, glibenclamide, and diet and exercise. In comparison with other strategies, "a pioglitazone-based strategy was estimated to reduce the cumulative incidence of severe clinical events and long-term complications by between 23 and 36 percent and to increase discounted life expectancy by between 0.13 and 0.35 years." Within certain patient subpopulations, the use of the TZD as a first-line therapy was determined through model calculations to be a cost-effective strategy (Coyle 2002b).

velopment of comorbidities are generally independent and unrelated. This type of assumption probably underestimates true rates of complications and actual costs incurred. Once patients are categorized by type of treatment, a cost analysis then determines the number of diabetic patients surviving after 5 years in each treatment cohort, the cumulative total medical and pharmacy costs they incurred, and the weighted cost per patient year.

Realistically, formulary decisions can and must be made in the absence of such data. When they are available, however, these data can aid in decisions regarding the addition of new products to the managed care formulary, define a product's role for a given population, and assist in creating benchmarks for the product's future performance.

The managed care marketplace is driven by cost and quality considerations in achieving optimal patient outcomes. Currently, the increasing cost shifting to patients and cost concerns of the purchaser seem to dominate the clinical outcomes discussion. Some patients are choosing which drugs they take on the basis of copayment levels. Earlier detection and treatment may or may not save costs in the long or short term. The focus, however, should be on reducing the incidence of diabetic complications, not on cost savings, which may be challenging to realize in this progressive disease state.

Health care professionals should be aware that cost-effectiveness does not equal cost savings. As was illustrated in the diabetes disease management programs outlined previously, what might be a cost center today may well be an area of improved quality of life for patients, reduced diabetic complications, and diminished resource utilization tomorrow (Avandia Advisors' Group 2002, 2003).

FACULTY PRESENTATIONS

Standardizing Managed Care Formulary Submissions: The AMCP Format

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In the following synthesis of Professor Brixner's presentation, the primary components of the Academy of Managed Care Pharmacy (AMCP) format are explored, the evolution of the format is examined, and who is using it and for what purpose are described.

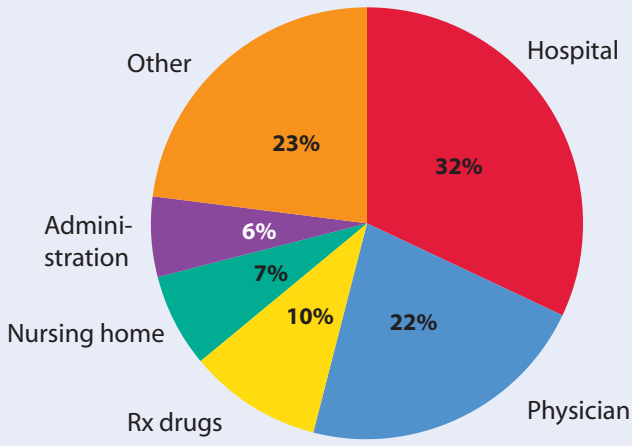
The health care environment

The current environment in health care includes a sharp increase in pharmacy spending as an annual percentage of total health care expenditures. Despite this rapid increase, it must be remembered that the cost of pharmaceuticals still represented only 12.4 percent of all health care spending in 2001, exactly the same percentage that it was in 1970 (OECD 2003). For costs in 2002, see Figure 5.

The reasons for the steady climb in overall expenses of pharmaceuticals are transparent and fall into two basic categories: (1) the influence of employers and managed care and (2) greater utilization of drugs by the aging population. With regard to the first category, because employers and managed care plans now cover millions of lives, prescriptions are generally affordable for millions of Americans. To illustrate: In 1965, 44 percent of prescriptions were paid for out of pocket by individuals. In contrast, by 2001, only 14 percent of prescriptions were paid for out of pocket by individuals; insurance companies, employers, and public payers paid the remainder (CMS 2003).

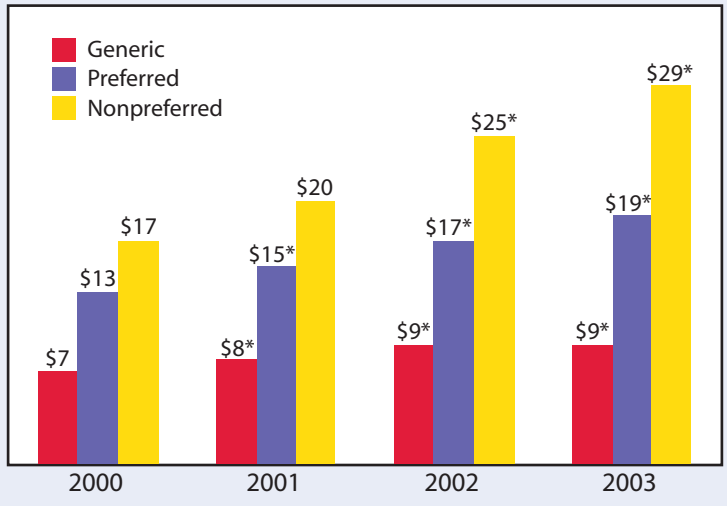
Although these statistics sound like a boon to consumers, it must be remembered that the insured patient's cost share is, in many cases, also on the rise. For example, in an attempt to shift costs back to the consumer, increasing numbers of managed care plans have embraced a three-tier drug coverage plan. In 1998, approximately 35 percent of plans offered a three-tier coverage plan, but by 2000, 80 percent of plans had instituted the three-tier structure to their drug benefit coverage (Cowan 2001). In a three-tier plan, drugs in the first tier are the least expensive, whereas drugs in the third tier are the most costly. Patients being prescribed drugs in the higher tiers may opt not to fill the prescription because of the expense but can potentially need to go to the hos-

FIGURE 5 Health care costs in 2002



SOURCE: FOUNDATION FOR MANAGED CARE PHARMACY 2003

FIGURE 6 Average copayments for generic, preferred, and nonpreferred drugs (2000 to 2003)



*Estimate is statistically different from the previous year shown by drug tier.
NOTE: Figures are rounded to nerest whole dollar.

SOURCE: KAISER/HRET SURVEY OF EMPLOYER-SPONSORED HEALTH BENEFITS: 2000, 2001, 2002, 2003

pital or the emergency room with critical conditions that might have been avoided had their medication been more affordable for them. Thus, the savings of resources in one area (the pharmacy budget) is frequently utilized in other areas of the health care system (Figure 6).

Managed care's focus on prevention — in particular, treatment of high blood pressure, measurement of cholesterol, and earlier detection of cancer — inherently involves pharmaceutical therapy. Last, increased emphasis on evidence-based medicine often involves early and aggressive treatment of chronic disease, which increases utilization of numerous classes of drugs. Overall, more Americans are living longer, and as they age, they require more and more medications.

The role of pharmacoeconomics

In view of accelerating utilization and increasing proportion of cost, employers and payers are asking, "Where is the value of pharmaceuticals?" Pharmacoeconomics, in which the costs and outcomes of using pharmaceutical products as treatment alternatives are identified, measured, and compared, is an attempt to answer this important question. A key objective of pharmacoeconomics is to validate or prove the economic value of a particular pharmaceutical product to treat an identified disease within the managed care environment. Thus, increasing numbers of decision makers within managed care plans are relying on pharmacoeconomic analyses to make informed formulary decisions.

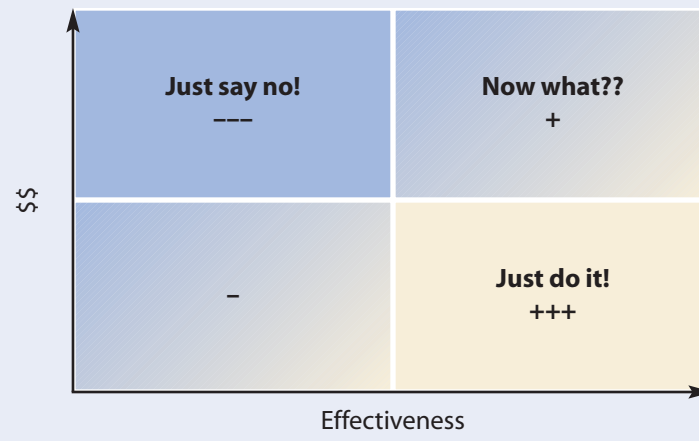
By measuring the effectiveness of a particular product in relation to that product's cost, a grid can be generated (Figure 7, on page 16). Nonetheless, however straightforward this grid appears, it is not a simple task to find the reliable data with which to complete it. In fact, there is no consistent way in which MCOs evaluate the value of the medications they purchase and prescribe. Often, these decisions are based entirely on acquisition cost or the amount of the rebate offered by the manufacturer.

As Figure 7 illustrates, there are two dimensions in considering a new drug for formulary: change in cost or change in efficacy, in comparison with current treatment. If standard therapy is assumed to be at the center of the grid, evaluations of new therapies move the cost-versus-effectiveness ratio into one of the four quadrants. When an option's costs go up but its efficacy stays the same or worsens, this option would most probably be rejected. When costs go down and efficacy increases, this would pose a desirable situation that is only infrequently encountered in the marketplace. In the remaining two scenarios, the use of

pharmacoeconomics to define value comes into play: both cost and efficacy either increase or decrease.

Therefore, the problem, at least until recently, was twofold: First, most MCOs and employers did not have staff with the expertise to evaluate pharmacoeconomic models and/or outcomes data; second, much of the same data were lacking or difficult to obtain. For example, safety and efficacy data and/or evidence-based assessments have been difficult to locate or even nonexistent. Off-label use data and unpublished studies were unavailable. Finally, quality-of-life, functional status, and cost-effectiveness data were provided rarely. Nonetheless, it is just these types of data — as well as the expertise necessary to understand them — that will enable plan and MCO administrators, employers, and payers to accurately and comprehensively determine the value of any class or individual drug being considered for inclusion on their formularies.

FIGURE 7 Pharmacoeconomics: why use it?



SOURCE: FOUNDATION FOR MANAGED CARE PHARMACY 2003

The AMCP steps in

To ameliorate the problem, the AMCP, in conjunction with the Foundation for Managed Care Pharmacy, developed a robust, scientifically sound process with which to evaluate any drug or class of drugs for potential formulary inclusion. When complete, this process, the AMCP Format for Formulary Submissions, produces a dossier. This dossier includes data on efficacy, safety, effectiveness, and economics. Safety and efficacy data are derived primarily from randomized controlled trials, which do not necessarily reflect a real-world scenario: that is, patient selection is rigorously defined. Effectiveness data, in contrast, provide an understanding of the real-world value of a drug. In the economics section of the dossier, it is possible to build models that demonstrate the effect that a particular pharmaceutical agent will have within a defined population.

To synthesize, the AMCP format is a consistent and direct means for the manufacturer to supply information directly to the health plan or the pharmacy benefit management company. The dossier meets FDA requirements for an *unsolicited* request. Because of its unsolicited status and the fact that the dossier can include unpublished studies, a scientific liaison and not an account manager must present it. In addition, the AMCP format establishes a standardized process of evaluation that is based on sound scientific evidence.

The AMCP format is not:

- A sales and/or marketing tool
- A means to confuse
- A formulary kit
- A simple pharmacoeconomic evaluation tool
- An evaluation process to lower the cost of prescription drugs

In fact, the AMCP format might indicate that an increase in drug expenditures could be a sound, long-term investment and result in greater cost-effectiveness systemwide.

Structure of the AMCP format

The AMCP format includes the following five sections: (1) product information (essentially from the package insert); (2) clinical and economic information in a summary spreadsheet format, including reference materials, tables, off-label data, quality-of-life data, and incidence and prevalence statistics; (3) the modeling section with cost-effectiveness models, budget-effect forecasts, assumptions, adjustments, and results; (4) the product value and overall cost section; and (5) supporting information. The section on product value and overall cost is the core of the document and presents key data on the use of a product within various populations and can support early and/or aggressive use of a product to avoid later, long-term costs and comorbidity. Productivity statistics can be included in the values section of the dossier, but absenteeism is much easier to measure.

Adoption of the AMCP format has been increasing. For example, more than 50 MCOs, pharmacy benefit managers, hospitals, and public entities such as the Department of Defense and several state Medicaid departments (covering in total more than 100 million lives) now utilize the format (Neumann 2004).

In conclusion, the AMCP format identifies the evidence that is necessary for making informed formulary decisions, and it standardizes the presentation of this information. Overall, it provides a comprehensive data set with which to begin the decision-making process. It does not, however, provide precise answers for every drug, class, MCO, or patient population. It does not define the decision-making process or guarantee better decisions; those are up to the users of the dossier. Finally, it cannot ensure reduced health care expenditures. By fully recognizing the strengths and limitations of the AMCP format, its users should be able to make well-informed decisions about the inclusion of a particular product within the therapies for their own patient populations.

FACULTY PRESENTATION

The Employer's Perspectives On Type 2 Diabetes

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A slowing economy and a demand for increased work force performance in the presence of reduced staffing levels have led to significant challenges for business today. Added to those challenges is high medical inflation (a 2003 Mercer survey indicates inflation rates of 10.5 percent for medical expenditures and 16.1 percent for pharmaceuticals), making profitability for some employers a daunting goal. Steep rises in medical costs are rooted in a number of factors, not the least of which are an entitlement mentality and the consumer demand for life-enhancing services, new technologies, and emerging drug therapies. Another factor contributing to medical inflation is the rising average age of the labor force: the baby boomer generation is experiencing accelerating rates of health risks such as stress, obesity, high blood pressure, and even poor self-care.

The effect of these factors on the cost of health care is measurable. For example, the average per-member-per-year (PMPY) cost of prescription drugs for employees in their 20s is just over $100; in contrast, PMPY pharmacy costs are $442 for employees in their 40s and $992 for employees in their 60s (Figure 8).

Employers' attitudes and beliefs

Employers are focusing closely on the cost ramifications of an aging work force and the increasing use of pharmaceuticals. Employers continue to view pharmacy as a potential cost-cutting target, and the media blames pharmacy for spikes in health care expenditures. Among employers, there is a heightened promotion of new generic drugs as well as scrutiny of drug utilization, particularly with regard to new biotechnological drugs.

The following are commonly held perceptions among employers:

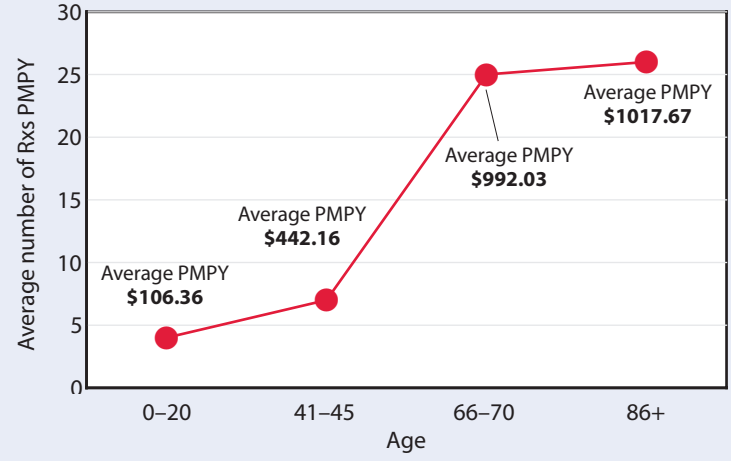
- Pharmacy benefit costs are skyrocketing as a result of price increases.
- Increases in pharmacy benefit costs are the primary driver of health plan cost increases.
- Direct-to-consumer (DTC) advertising is driving pharmacy benefit costs.
- New drugs are overpriced and overutilized; benefits are often exaggerated.

The data and evidence, however, do not support these perceptions. Yet, in the employers' defense, most available information is not presented in terms that they can easily apply. Much clinical information is available, but information translated into business terms will enable employers to see the value of pharmaceuticals. In addition, there is a dearth of studies on pharmaceutical use and work force health. This lack of relevant information also must be seen in the context of the fact that employer card programs still pay for the majority of all prescriptions filled in the United States.

Quantifying the rising cost trend

Mercer Human Resource Consulting conducts one of the largest comprehensive annual health benefit surveys in the United States. The *Mercer National Survey of*

FIGURE 8 The aging work force and per member per year prescription drug costs



PMPY=per member per year cost of prescription drugs.
SOURCE: ADVANCEPCS BENEFITS BAROMETER 2002

Employer-Sponsored Health Plans examines trends focused on cost trends for pharmacy and medical benefits.

Of greatest concern to employers are rising pharmacy expenditures and medical expenditures. To confound the issue further, the two cost centers are still in silos, or separated within many organizations; therefore, it can be difficult for providers or insurers to demonstrate medical savings with increased pharmaceutical expenditure. It also must be remembered that pharmaceuticals represent a relatively small percentage (<20 percent) of the total cost of medical care; the majority of costs are related to hospitalizations and treatment of disease complications (Takiya 2002).

Benefit consultants, coalitions, business leaders, and business groups play a key external role in helping employers develop strategy; in addition, they provide education on health care trends. For example, there is an emerging trend for midsized employers to purchase pharmacy benefit services as a group. Last year, at least three such collectives were developed solely to examine pharmacy purchasing. The question is: As these collectives become larger and more numerous, will they have influence over formulary and health management decisions?

Employer actions to manage the pharmacy budget

Employers are acting on several fronts to aggressively control their pharmacy benefit costs. Management tools designed to deliver prescription drug benefits while controlling costs include:

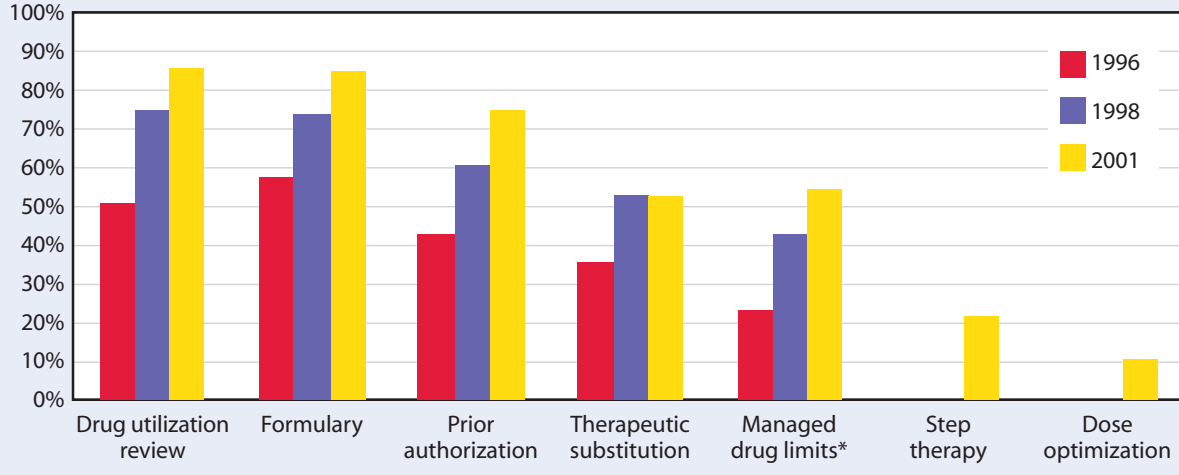
- Disease management
- Utilization management (i.e., quantity limitations and prior authorization)
- Drug utilization review
- Formulary management (i.e., open and closed)
- Delivery systems (i.e., retail and mail order)
- Mechanisms for implementing employee/consumer cost sharing (i.e., generic incentives, multitiered copayments, and coinsurance)

The effects of these practices on utilization, expenditures, and health outcomes are understood only partially. Thorough investigations of any potential unintended consequences of these practices are, for the most part, lacking (Olson 2003). Member cost-sharing has been the primary area in which employers have focused in the past few years. Copayments are the most common form of cost sharing, and the majority of growth has been in the three-tier copayment plan design.

Most important, three-tier copayments now represent much more than half of employer-sponsored plans, and four- and five-tier copayments will arise soon. A five-tier copayment could include generics, brand preferred, brand nonpreferred, specialty drugs, and drugs needed for symptomatic relief rather than lifesaving medications. In brief, employers are promoting use of generic drugs because generics appear to lower costs in the pharmacy budget. Is that a long-term solution? No, but widespread promotion of generics will continue until data demonstrate superior outcomes, improved quality of life, and/or an overall cost-effectiveness vis-à-vis the entire health care system when branded pharmaceuticals are used in place of generics.

FIGURE 9 Employer actions to manage the prescription benefit

Enhanced clinical management



* Managed drug limits is gaining in acceptance.
SOURCE: LILLY TAKEDA BENEFIT SURVEY 2002

As opposed to the copayment design, in which the employee pays a fixed-dollar amount for a prescription, the new dialogue is focused on coinsurance, where the employee pays a percentage — generally around 20 to 30 percent — of the prescription cost. Employers who want employees to have more at stake are slowly changing lower cost copayment plans into coinsurance designs.

Figure 9 illustrates the various employer initiatives to clinically manage the pharmacy benefit and their relative prevalence.

Control of pharmaceutical access is yet another strategy employers utilize to manage the pharmacy benefit. There are several major ways in which this happens:

- Exclusions of predefined, discretionary drugs or classes
- Approval of drugs for only certain indications
- High copayments, delayed coverage, and/or therapeutic class management

Utilization of any of these strategies does not mean that employers are making formulary decisions, but there are a number that make policy decisions. Particularly within the three-tier benefit, large organizations are starting to ask questions such as "Does a drug or therapeutic class fit into the second or the third tier, and what effect might that placement have on my workforce?" These are the types of questions on which clinical benefit consultants advise and assist benefit managers in thinking through the issues from a workplace perspective. This type of interaction is new and emergent and is being reinforced, particularly as new pharmaceuticals are being launched.

Finally, implementing fair and equitable levels of employee cost sharing is necessary if employers, health plans, and other payers are to continue to offer a prescription drug benefit. It must be recognized, however, that quality health care should not be sacrificed for the sake of short-term cost savings (Olson 2003).

DTC advertising

A group of researchers from the Harvard School of Public Health sought to determine whether DTC advertising was driving up utilization of prescription drugs inappropriately, which was thus resulting in higher and unnecessary costs of care. As they reported in the *New England Journal of Medicine*, in the 5 years between 1996 and 2000, there was an approximate tripling of annual spending on DTC advertising. DTC advertising, however, still accounts for only 15 percent of all money spent on drug promotion. The remainder of the promotional budget is targeted to physicians as well as advertisements in medical journals and the distribution of drug samples. Overall, promotion as a percentage of sales has remained fairly constant since the early 1990s.

Although the increased use of television advertisements for pharmaceutical products that are directed to consumers is, and must continue to be, monitored by the U.S. Food and Drug Administration, the study authors reported no measurable effect in terms of patients' requesting and being prescribed medications for which they did not have clinical symptoms. Thus, although DTC advertising may be highly visible, its effect in terms of driving utilization of medications remains negligible (Rosenthal 2002).

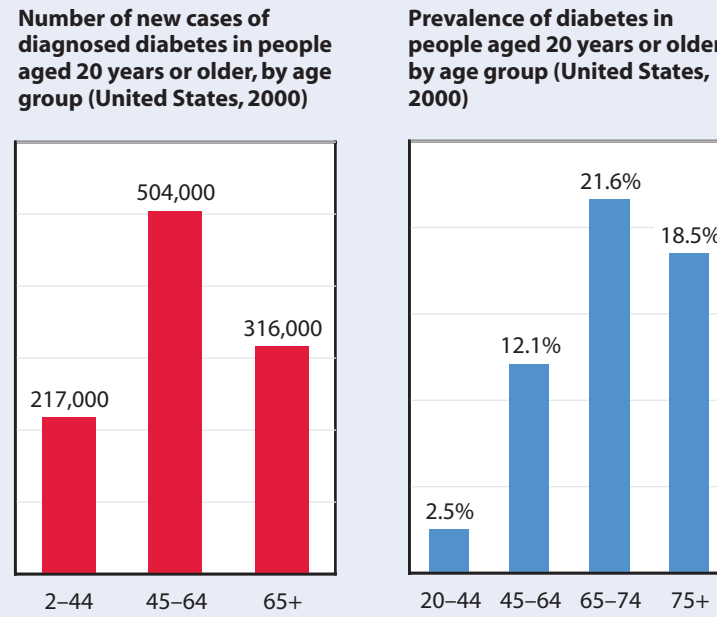
Diabetes diagnosis and prevalence

Figure 10 illustrates the incidence and prevalence of new cases of diabetes per age group. The increasing incidence of diabetes in the baby boomer generation has significant consequences for human suffering as well as future cost burdens to individuals, employers, and society.

The economic burden of diabetes

The economic burden of diabetes on employers is enormous, inasmuch as diabetes is the third most costly health condition for large companies nationwide (Goetzel 2003). Costs to employers stem primarily from direct

FIGURE 10 Disease incidence and prevalence

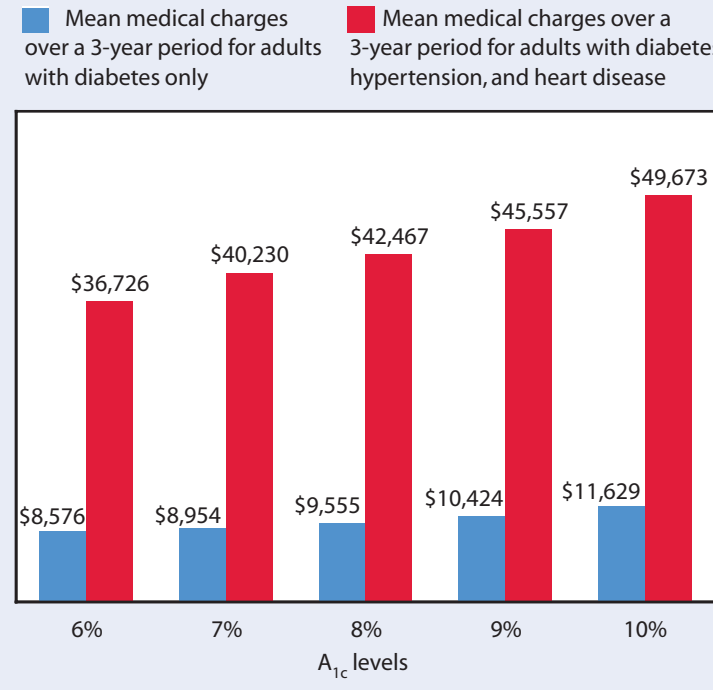


SOURCE: CDC: DIABETES PREVALENCE AND DIAGNOSIS

medical expenditures, loss of productivity, and absenteeism. Utilizing claims data, researchers determined employers' mean annual per capita costs for diabetic beneficiaries in comparison with nondiabetic beneficiaries: $7,778 versus $3,367, respectively, or an incremental cost differential of $4,411 associated with diabetes (Ramsey 2002). Although dramatic, this difference may even be underestimated, because the cost of diminished productivity to employers and society is very difficult to measure. We do know, however, that people with diabetes lose about 8 workdays per year, in contrast to people without diabetes, who are absent on average 1.7 days (CDC: Business and Diabetes 2002).

In addition to medical costs and productivity losses, persons with diabetes are far more likely to have physical disabilities than are those without the disease; these disabilities also translate into costs for employers. Because the prevalence of diabetes is expected to increase dramatically in the next few decades, interventions that will halt or delay the progression from impairment to physical limitation and from limitation to outright disability are urgently needed (Ryerson 2003).

FIGURE 11 Medical costs for 3 years associated with various A_{1c} levels



SOURCE: GILMER 1997

Diabetes disease management: still not a priority

Diabetes — which, along with hypertension and mood disorders, is among the three most costly diseases for employers — is only infrequently addressed through a disease management program. For example, of employers with 1,000 to 20,000 employees, 61 percent do not offer a disease management program to their employees with diabetes; 30 percent of employers offer such a program through a health plan; and 3 percent offer it as a carve-out through an independent vendor (Mercer 2002).

This lack of disease management is a concern because effective programs provide excellent patient-management opportunities, education, follow-up, and integrated information that can be acted on to improve clinical and economic outcomes. Passive support tools for self-management are not enough. To have a measurable effect, a

Diabetes at work

The federal government and private industry have teamed up to offer an approach to deal with the burgeoning diabetes epidemic that threatens the nation's health, productivity, and prosperity. In late 2002, the Department of Health and Human Services launched a Web site aimed entirely at reducing the burden of diabetes in the workplace: «http://diabetesatwork.org».

The Web site provides a resource kit that offers evidence-based disease management interventions, work site wellness strategies, and a variety of other interactive tools for on-the-job diabetes management. "Diabetes care goes far beyond what happens during a doctor's office visit, so it makes good business sense for employers to ensure that the workplace environment provides opportunities for diabetes care support and information about control and prevention," says Health and Human Services Secretary Tommy G. Thompson.

The Diabetes at Work project was developed by the National Diabetes Education Program. For further information, contact the CDC's Diabetes Public Inquiry Line at 1-877-CDC-DIAB, or e-mail them to: diabetes@cdc.gov, or call the National Diabetes Education Program at 1-800-438-5383.

disease management program must be proactive and involve outreach several times a year, including activities at the work site that encourage required lifestyle changes and behavior modification over the long term. Active health promotion produces tangible economic benefit. Improvements in glycemic control reduce hospitalizations, absenteeism, and total medical expenditures. The converse is also true: as the A_{1c} level rises, so do costs. For example, at the target A_{1c} level of 7 percent, the person with diabetes incurs nearly $9,000 annually in medical charges. If the A_{1c} level rises to 10 percent, associated costs rise to well over $11,000 (Gilmer 1997) (Figure 11).

Also contributing to employers' lackluster approach to diabetes disease management is the fact that they do not view diabetes as constituting an emergency. Because of this, the practice of step edits makes economic sense to them. Employers must be educated about the value statement of pharmaceuticals, and the complications of diabetes must be put into terms to which they can relate and understand (Avandia Advisors' Group 2002, 2003).

Because of the high costs associated with diabetes, as well as the sequelae of comorbidity, disability, and mortality, employers should consider selecting health plans that provide enhanced benefits to persons with diabetes, including easy access to both medical and pharmacy services, in addition to aggressive, evidence-based diabetes disease management programs.

CONCLUSION

Diabetes is a multisystem disease that necessitates a multifaceted team approach. For optimal management, the patient must be an informed and engaged partner. Improving the quality of diabetes care in the United States involves individuals and organizations outside the physician's office. These are entities such as the National Committee for Quality Assurance, the developing organization for measures such as Health Plan Employer Data and Information Set (HEDIS), designed to accurately measure the quality of care for patients with diabetes. Process measures such as those included in HEDIS, however, can gauge only how well (or poorly) clinicians are doing in providing care to patients with diabetes. These measures capture what is being done but do not instruct providers and plans on how to optimize care.

To improve the situation, several important steps remain to be taken: Awareness must be raised among members of the health care system, insurers, employers, and the public about the:

- Health and cost ramifications of the epidemic of diabetes
- Need to reduce obesity nationwide, especially among children
- Effectiveness of certain disease management strategies
- Rationale for early, aggressive treatment, entailing both lifestyle modification and pharmacologic approaches

It is unrealistic, in this era of cost containment, to expect large-scale screening for identification of persons with type 2 diabetes or even aggressive pharmaceutical treatment of individuals with prediabetes or impaired glucose tolerance. Nevertheless, assumptions regarding treatment of patients in whom the disease already is diagnosed must be examined. The preceding sections have documented the cost-effectiveness of early, aggressive treatment to maintain near-normal levels of blood glucose and thereby delay or prevent the occurrence of the costly, painful, and even fatal complications of diabetes.

Achieving a new paradigm in diabetes treatment means breaking down the silos that continue to flourish in managed care. Attempting to ratchet down the pharmacy budget without closely examining the effect that action might have on other sectors of the health plan could be a costly exercise overall — one that compromises patient health outcomes.

Aggressive pharmacologic treatment of type 2 diabetes is cost-effective. It is hoped that the publication and dissemination of additional studies supporting this statement, coupled with new and comprehensive tools such as the AMCP format, will begin enabling thought leaders as well as clinicians to reassess their approach to this growing epidemic and improve the quality of life for all patients with this devastating disease.

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