

Sulfonylureas are cost-effective and also may be the only oral agents that inhibit processes inducing hyperglycemia by improving insulin secretion and insulin resistance. New long-acting agents hold even greater promise.

Cost-effective Management of Hyperglycemia in Patients With Type 2 Diabetes Using Oral Agents

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ABSTRACT

Diabetes exacts an enormous toll on health care resources, with extremely high costs attributable to care of diabetes patients in proportion to the afflicted population. Though individual treatment strategies are required for each patient, newer long-acting sulfonylureas may be the initial drugs of choice, as they may be the only oral agents that inhibit the processes inducing hyperglycemia — hepatic glucose production and glucose utilization by the tissues — by improving insulin secretion and insulin resistance. Sulfonylureas also represent the most cost-effective therapeutic option, alone or in combination with other oral agents or insulin. The newer long-acting agents, glimepiride and glipizide GITS, may be more attractive among sulfonylureas, due to their greater insulin-sparing property, fewer hypoglycemic events,

weight neutrality, and once-daily dosing. Glimpepiride may be preferred due to its safety profile, especially for the elderly and those with hepatic and /or renal dysfunction.

INTRODUCTION

Diabetes is a chronic illness that affects all ethnic groups across social and economic levels. An estimated 18 million Americans have the disease, with anticipated epidemic proportions throughout the world (Wild 2004). Most patients have type 2 diabetes, induced by impaired insulin secretion and insulin resistance, causing excessive hepatic glucose production and decreased glucose uptake by the tissues (Gerich 1997, DeFronzo 1988).

Over half of diabetics have poor glycemic control, with HbA_{1c} levels >9.5 percent; the upper limit of normal is 6.0 percent. Complications associated with chronic hyperglycemia — retinopathy, neuropathy, nephropathy, as well as cardiovascular (CV) events — present a major threat to public health and exact huge social and economic tolls (Helseth 1999, Shaw 2000). Fortunately, desirable glycemic control (HbA_{1c} ≤7.0 percent), recommended by the American Diabetes Association, can be achieved with appropriate medical interventions and can delay onset or retard progression of complications, providing significant clinical and economic benefits (ADA 2003, Gray 2000, Testa 1998, Gilmer 1997). Even short-term glycemic control can improve quality of life (QOL) and save health care resources (Testa 1998).

Oral antidiabetic medications

The availability of new therapies has increased the complexity of treatment paradigms and knowledge needed to make informed decisions about optimal cost-effective care. Diabetes is a progressive disease (Turner 1999), and treatment progression is stepwise: diet and exercise, oral monotherapy, oral combination therapy, combination oral agent/insulin therapy, and insulin monotherapy, respectively (White 1999). Though glycemic control with therapeutic lifestyle changes is important, a program of diet and exercise rarely achieves and sustains desirable glycemic levels (White 1999, Helseth 1999, Gilmer 1997). Therefore, oral monotherapy is prescribed for most patients after diagnosis, as there is no evidence regarding short- or long-term benefits with initial combination therapy of drugs including insulin. Extreme hyperglycemia (≥300mg/dL) may necessitate initial transient insulin therapy for achieving prompt glycemic control, followed by use of an oral agent with gradual insulin withdrawal. Oral medications include:

α-glucosidase inhibitors (acarbose, miglitol) — These agents inhibit complex-carbohydrate digestion, with reduction in glucose absorption by the small intestine, leading to lower postprandial glycemia (Holman 1999).

Biguanide (metformin) — This agent's major effect is to reduce hepatic glucose production, with minor stimulation of insulin-mediated glucose transport in skeletal muscle

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(Gunton 2002, DeFronzo 1995).

Meglitinides (repaglinide, nateglinide) — These are rapidly metabolized short-acting agents administered orally before meals to stimulate β -cells to produce post-meal early insulin secretion, to lower postprandial glycemia (Goldberg 1998, Horton 2000).

Sulfonylureas (glimepiride, glyburide, or glibenclamide; chlorpropamide; acetohexamide; glipizide; tolazamide; tolbutamide) — These agents sensitize tissues to glucose by enhancing glucose transporters, thereby stimulating insulin release by β -cells and facilitating glucose uptake (Yu 1999, Sato 1993).

Thiazolidinediones (pioglitazone, rosiglitazone) — These agents promote glucose utilization by activation of PPAR γ receptors, mainly in adipose tissue; they may also inhibit hepatic glucose production (Phillips 2001, Aronoff 2000).

Efficacy comparisons for oral antidiabetic medications are problematic, due to a dearth of head-to-head trials. Moreover, comparisons are hampered by the varying methods used by drug manufacturers for assessment and reporting of drug effects. Significant demographic differences between study populations, duration of diabetes and level of glycemia at entry, are among the factors affecting outcomes. In clinical practice, drug efficacy is determined as improvement from pretreatment glycemia, whereas most clinical trials report the efficacy in comparison to placebo, without frequently providing improvements from pretreatment levels. This method shows a drug in the best light, as hyperglycemia worsens with placebo in most patients.¹

For example, a report comparing the effects of acarbose with placebo added to existing diabetes therapy concluded “acarbose significantly improved glycemic control over 3 years,” even though glycemic control in the acarbose group progressively worsened throughout the study duration (Holman 1999).

To eliminate confounding factors, head-to-head trials are the only way to compare antidiabetic drugs accurately, similar to trials assessing the efficacy of various statins. Moreover, such trials allow apples-to-apples efficacy comparisons, by minimizing variability between patient populations. Finally, even in trials reporting pretreatment glycemic indices (i.e., glucose and HbA_{1c} levels), the efficacy of various drugs cannot be compared because of widely variable pretreatment values; it is necessary to consider that the higher the pretreatment levels, the greater are the declines following treatment. Therefore, comparisons showing percentage lowering from baseline values, as noted in studies with statins, are likely to be more accurate, reliable, and appropriate (Huninghake 1998, Jones 1998). Nevertheless, these data are scarce. Short-term studies indicate sulfonylureas to be at least as effective as or more effective than other agents (Table 1), with reductions in HbA_{1c} levels usually highest in drug-naïve subjects.¹

This finding also is supported by studies comparing the efficacy of troglitazone or metformin monotherapy with troglitazone and metformin combination therapy, and a trial assessing the efficacy of pioglitazone (Aronoff 2000, Inzucchi 1998). HbA_{1c} values before the washout period, while patients were using a sulfonylurea and/or diet and exercise, were lower than those achieved after either metformin or troglitazone prior to using them in combination (Inzucchi 1998). Similarly, mean HbA_{1c} concentration (–1.5 percent) prior to withdrawal of either sulfonylurea or metformin at the beginning of the washout period was distinctly lower than that noted following treatment with pioglitazone.

¹ Aronoff 2000, DeFronzo 1995, Draeger 1995, Goldberg 1998, Gunton 2002, Holman 1999, Horton 2000, Phillips 2001, Raptis 1999, Schade 1998, Simonson 1997, Testa 1998

zone for 24 weeks (–0.6 percent) (Aronoff 2000). Finally, accumulating data suggest that newer long-acting sulfonylureas, especially glimepiride, may offer advantages over other drugs showing the maximum lowering of HbA_{1c} and greater insulin-sparing properties,² and therefore may be an initial drug of choice in subjects with recent disease onset. Yet, in a subject with extreme hyperglycemia (≥ 300 mg/dL) and HbA_{1c} levels of at least 13 percent at diagnosis — combination therapy based on the drug’s individual efficacy assessed by a percentage decline from baseline HbA_{1c} concentration (Table 1) is likely to achieve the desirable glycemic control promptly, as none of the drugs alone lowers HbA_{1c} more than the 40 percent needed in this setting. Alternatively, in subjects manifesting extreme symptoms of hyperglycemia, hyperglycemic hyperosmolar state or, occasionally, ketosis or ketoacidosis due to an accompanying stressful disorder, prompt administration of insulin is the therapy of choice. Yet, once the acute insult or extreme hyperglycemia is ameliorated and the diagnosis of type 2 diabetes mellitus is confirmed by presence of insulin secretion in the absence of islet cell or glutamic acid decarboxylase (GAD) antibodies, euglycemia can be maintained following gradual withdrawal of insulin and initiation of diet or/and an oral agent in most subjects.

This method of assessing efficacy, expressed as a percentage lowering from pretreatment level, may help in determining the initial drug as well as an adjunctive drug during the disease course. For example, glitazone lowers HbA_{1c} levels by about 20 percent from pretreatment concentrations (Table 1). Thus, the desirable HbA_{1c} level of <7.0 percent could be attained by glitazone monotherapy or after addition to other oral drugs

² Draeger 1995, Kabadi 2003, Massi-Benedetti 1996, Sato 1993, Raptis 1999

TABLE 1 Changes in HbA_{1c} observed with oral antihyperglycemic therapy in subjects with type 2 diabetes mellitus*

Drug	Maximum daily dose (mg/day)	Monthly average cost [†] \$	Percent reduction in HbA _{1c} from baseline [‡]
Glipizide GITS	20	45	10–25
Glimepiride	8	52	15–40
Metformin	2550	105	10–25
Rosiglitazone	8	154	6–20
Pioglitazone	45	160	6–20
α-Glucosidase inhibitors	300	70	7–14
Repaglinide	12	167	7–16
Nateglinide	360	90	7–12

*See AWP 2002

† Average wholesale price.

‡ Relatively greater reductions are noted in "drug naïve" subjects.

SOURCES: ARONOFF 2000, DEFRONZO 1995, DRAEGER 1995, GOLDBERG 1998, GUNTON 2002, HOLMAN 1999, HORTON 2000, KABADI 2001, PHILLIPS 2001, RAPTIS 1999, SCHADE 1998, SIMONSON 1997, TESTA 1998

in most patients with baseline HbA_{1c} levels ≤8.5 percent. Yet, if a patient's HbA_{1c} levels are >8.5 to 9 percent while receiving both sulfonylurea and metformin at maximum daily dosages, adding insulin rather than glitazone may be a more cost-effective therapeutic option, because combining these agents with a glitazone is unlikely to lead to attaining HbA_{1c} levels of ≥7 percent (Yale 2001).

The United Kingdom Prospective Diabetes Study is the only long-term and the largest study conducted in subjects with newly diagnosed type 2 diabetes (Stratton 2000; Turner 1998, 1999; UKPDS 1995, 1998). This study confirmed the impact of achieving and maintaining desirable glycemic control by any form of intensive therapy in delaying the onset and progression of chronic micro- and macro-angiopathic complications in type 2 diabetes (UKPDS 1998, Turner 1998, Stratton 2000). A closer look at UKPDS data provides useful information about the comparative efficacy and safety between different therapeutic options (Kabadi 2002). In this study, desirable glycemic targets (HbA_{1c} ≤7 percent or fasting plasma glucose ≤7.8 mmol/L) were maintained in significantly higher numbers of overweight patients re-

ceiving insulin or sulfonylurea monotherapy (28 percent and 24 percent, respectively) compared to those using diet (11 percent) or metformin (13 percent) at 9 years (Turner 1999). Furthermore, secondary failure (HbA_{1c} >7 percent) with sulfonylurea (chlorpropamide) occurred at approximately 7 years versus 5 years with metformin (UKPDS 1998). These observations may be attributable to a greater preservation of β-cell function at 6 and 9 years with sulfonylurea when compared to metformin treatment (Stratton 2000; UKPDS 1995, 1998).

It is apparent that improved glycemic control with any drug circumvents the progressive deterioration of the β-cell function associated with chronic hyperglycemia (glucose toxicity) (Gerich 1998). Nevertheless, a greater preservation of β-cell function by sulfonylureas rather than metformin is counterintuitive, as they are considered to be insulin-secreto- gogues while metformin is deemed to be an insulin sensitizer. This finding may be explained, however, by their extrapancreatic effect of improving insulin sensitivity. This is documented by fasting plasma insulin and its product with fasting glucose — both indices of insulin sensitivity —

without the loss of improved glycemic control following long-term treatment with sulfonylurea in patients with type 2 diabetes, enhancement of sensitivity of exogenous insulin by glyburide in type 1 diabetes as well as *in vitro* studies using isolated or cultured muscle or fat cells, monocytes, or erythrocytes.³

Although sulfonylureas effectively reduce blood glucose levels and are economically advantageous (Table 1), some clinicians are reluctant to use a sulfonylurea as first-line monotherapy for type 2 diabetes due to concerns about hypoglycemia, weight gain, and adverse CV effects all being attributed to hyperinsulinemia. Yet these concerns appear unfounded or exaggerated.

Severe hypoglycemia is extremely uncommon in type 2 diabetes (Bell 1997). In UKPDS, lasting nearly 20 years, major hypoglycemia with a sulfonylurea (chlorpropamide or glyburide) occurred in only 0.4 to 0.6 percent of patients per year and hypoglycemia caused death in two subjects, one receiving insulin and the other receiving metformin (UKPDS 1998). Among sulfonylureas, glimepiride or glipizide GITS are associated with a lower incidence of hypoglycemia as compared to the other sulfonylureas (Holstien 2001).

Weight gain is considered a significant drawback of sulfonylurea therapy, especially when metformin is thought to induce weight loss. In the UKPDS, however, gradual weight gain was noted in *all* patient groups, irrespective of therapeutic option, with the magnitude of weight gain being related to the degree of glycemic control (UKPDS 1998). Nevertheless, attempts must be made to curtail weight gain while achieving glycemic control to further decrease the incidence of diabetes-related endpoints, especially macrovascular in-

³ Beck-Nielsen 1998; Clarke 2003, Garrel 1987; Kabadi 1995, 2001; Muller 1995; Sato 1993, Simonson 1997; Yu 1999.

sults. Also, in recent studies using glimepiride or glipizide GITS, either a lack of weight gain or slight but significant weight loss was achieved and maintained while attaining and sustaining desirable glycemic control (Bugos 2000, Feinglos 2001, Gonzalez 1999, Lechleitner 1999).

CV disease is the leading cause of morbidity and mortality in people with type 2 diabetes (Laakso 1999, Sowers 1999, Stratton 2000, UKPDS 1998). Epidemiology studies suggest that endogenous hyperinsulinemia may be a risk factor for atherosclerosis (Ferrannini 1997). Yet, hyperinsulinemia may be a marker of atherogenic risk rather than a causative factor, as a definitive documentation regarding its role in causing atherosclerosis is lacking (Boyer 1999, Stern 1996). In several studies, including UKPDS, exogenous insulin did not raise the risk of myocardial infarction, stroke, or peripheral vascular disease. Nor was sulfonylurea treatment associated with an elevated risk of any CV outcomes (Boyer 1999, Ohkubo 1995, Stratton 2000, UKPDS 1998). Moreover, in overweight subjects, CV outcomes were not significantly different among groups using intensive therapy consisting of different individual drug regimens (UKPDS 1998). Therefore, hyperinsulinemia induced by exogenous insulin or sulfonylurea did not exacerbate CV outcomes in this study.

Other atherogenic contributors include abdominal obesity, hypertension, and dyslipidemia (Stern 1996). In the absence of insulin (or presence of insulin resistance), uninhibited lipolysis ensues, with enhanced release of free fatty acids leading to increased triglyceride synthesis. Moreover, insulin deficiency or insulin resistance blunts VLDL conversion to LDL via inhibition of hormone-sensitive lipase and promoting accumulation of VLDL, a triglyceride-rich lipoprotein with a decrease in HDL cholesterol, a characteristic dyslipidemia of diabetes (Beck-Nielsen

1998, Gilmer 1997). Finally, chronic hyperglycemia itself may induce macrovascular disease by promoting atherosclerosis and thromboembolism via impaired vasodilatation due to structural and functional alterations in the endothelium, hyperviscosity, and dehydration (Makimattila 1996, Ohkubo 1995, Yki-Jarvinen 1998). Therefore appropriate diabetes treatment is likely to lower the risk of macrovascular events by reducing hyperglycemia, improving dyslipidemia, and a prompt intervention in hypertension. Lipid profiles consistently improve with better glycemic control irrespective of antidiabetic therapy with a 7 to 12 percent decline in serum triglycerides and a 7 to 15 percent rise in HDL cholesterol for each point reduction in HbA_{1c}.⁴ Total cholesterol and LDL-C levels decline following treatment with sulfonylureas and metformin, whereas both rise with the glitazones (Aronoff 2000, DeFronzo 1995, Kabadi 2001, Phillips 2001). In UKPDS, desirable glycemic control (HbA_{1c} ≤7.0 percent) achieved with a sulfonylurea (chlorpropamide or glyburide) or insulin was associated with a 16 percent reduced risk of myocardial infarction (*P*=.052) compared with conventional therapy (UKPDS 1998). Furthermore, a 1.0 percent reduction in HbA_{1c} was associated with a 15 to 20 percent reduction in all diabetes-related endpoints, including macrovascular disease (Stratton 2000).

Finally, CV activity, documented by the effects on K_{ATP} channels in the myocardium vary among different sulfonylureas (Dukes 1996, El-Reyani 1999, Klepzig 1999, Lee 2003, Mocanu 2001). Glimepiride, has shown little effect on K_{ATP} channels in tissues other than the β-cell including myocardium in animals and humans (Dukes 1996). Moreover, the relative

CV activity of sulfonylureas does not correlate with their ability to lower blood glucose. At doses necessary for equivalent blood glucose lowering, glimepiride is more potent than glyburide in preventing reperfusion-induced cardiac arrhythmias in rats (Klepzig 1999), and maintenance of myocardial preconditioning in humans undergoing percutaneous transluminal coronary angioplasty (El-Reyani 1999). This finding may not be of crucial importance in the clinical setting, however, because coronary events, i.e., fatal or nonfatal myocardial infarctions or hospitalizations required for angina pectoris declined in subjects receiving glyburide or chlorpropamide with improvement in glycemic control (Stratton 2000, UKPDS 1998). Glimepiride, however, may offer other advantages over other sulfonylureas (e.g., glyburide), such as a more rapid onset, a longer duration of action, lower fasting circulating insulin levels with enhancement of both the first- and second-phase insulin secretion following a meal (Kabadi 2004) and extrapancreatic mechanisms, documented by its efficacy in greater glucose lowering with lesser circulating insulin in comparison to other sulfonylureas (Muller 1995, Sato 1993), a significantly greater reduction in daily insulin dose (40 percent) in comparison to other sulfonylureas (28 to 30 percent) noted while achieving glycemic control (HbA_{1c} ≤7.0 percent) in patients with type 2 diabetes with secondary failure to these drugs (Kabadi 2003) as well as reaching lower insulin and c-peptide levels in comparison to glyburide during exercise in patients with equivalent glycemic control (Massi-Benedetti 1996). Therefore, with its distinctly better CV profile, glimepiride may be the safest and most effective sulfonylurea. Finally, glimepiride may be a better choice than metformin or glitazones in most subjects, with type 2 diabetes, but especially in patients with, renal insuffi-

⁴Aronoff 2000, DeFronzo 1995, Draeger 1995, Kabadi 2001, Phillips 2001, Testa 1998

ciency, liver dysfunction or heart disease because of its being partially metabolized by both the liver and the kidney and no adverse CV effects (Draeger 1995).

Combination therapy

Because of the progressive nature of Type 2 diabetes in most subjects, oral monotherapy fails to control blood glucose levels in the long term. In the UKPDS, only 50 percent of patients maintained desirable glycemic targets with monotherapy at 3 years and at 9 years, the number declined to only 25 percent (Turner 1999, UKPDS 1998). Therefore, when monotherapy fails, typically, an addition of an oral agent with a different and complementary mode of action improves glycemic control (Step 3) (DeFronzo 1995, Horton 2000, Inzucchi 1998, Turner 1999, UKPDS 1998). Yet, a curious finding of increased diabetes-related mortality was noted with addition of metformin to sulfonylurea (Fisman 1999, UKPDS 1998). This finding may not be attributed to drugs themselves because, individually, they did not increase diabetes related mortality in UKPDS if the desirable glycemic control was attained. Instead, other factors known to increase mortality in diabetes, i.e., older age of the participants, longer duration of diabetes, progressive decomposition of metabolic control may have contributed to the increase in diabetes related mortality. Finally, even the combination of oral agents fails to sustain desirable glycemic control because of declining circulating insulin levels secondary to progressive β -cell dysfunction. At this stage of the disease, initiation of insulin is required, — either as monotherapy or as an adjunct to oral agents to attain and maintain glycemic control.

Insulin monotherapy is usually reserved for stress situations (e.g., myocardial infarction, stroke, infections), as oral agents fail to maintain glycemic control because of a marked

rise in counter regulatory hormones (e.g., catecholamines, cortisol, human growth hormone, glucagon). Moreover, insulin is the lone therapeutic option during pregnancy as well as for children and adolescents with type 2 diabetes mellitus, due to the lack of approval of oral agents. In the absence of stress, however, combining insulin with one or more oral agents is recommended. Subcutaneous injection of insulin NPH or Lente at bedtime, Ultralente in the morning, or 70NPH/30 Regular before dinner induce insulin peaks during the night and blunts nocturnal hepatic glucose overproduction, alleviating fasting hyperglycemia. Oral agents administered during the day then maintain diurnal glycemia by enhancing meal-stimulated insulin secretion and/or facilitating glucose utilization. Sulfonylurea or metformin in combination with insulin lowers daily insulin dose while improving glycemic control, with fewer hypoglycemic episodes and better lipid profiles in comparison to insulin monotherapy.⁵ Moreover, glimepiride lowered the daily insulin requirement more than other sulfonylureas, to the amounts secreted during 24 hours by normal subjects, indicating restoration of normal insulin sensitivity. Yet, insulin dose was not significantly decreased with glitazones when used in combination with insulin (Raskin 2001, Rosenstock 2002). Moreover, a recent documentation of rising prevalence of edema and CHF with the newer glitazones i.e., rosiglitazone 4mg/day and pioglitazone 30 mg/day may preclude use of these agents in combination with insulin (Delea 2003).

Finally, on addition of insulin for patients receiving both glimepiride and metformin in their maximum daily dose and manifesting lapse of glycemic control, daily insulin dose declined almost 75 percent in comparison to insulin monotherapy (Kabadi 2002). Furthermore, this combination regimen reduced hypoglycemic episodes even more with

still a lesser weight gain, in comparison to insulin monotherapy as well as insulin with either glimepiride or metformin. Alternatively, administration of the new insulin analogue, the basal insulin (insulin glargine) may promote more uniform glycemic control with less hypoglycemia in comparison to other intermediate or long-acting insulin (Yki-Jarvinen 2000). Finally, even patients receiving insulin monotherapy may obtain several benefits by reinitiating oral agents including smaller daily insulin dose, fewer injections, less weight gain, and a reduced incidence of hypoglycemic events with discontinuation of insulin in many subjects, to avoid hypoglycemia (Johnson 1996, White 1999, Yki-Jarvinen 2000, Orr 2000). Use of either pioglitazone or rosiglitazone in combination with insulin and either sulfonylurea or metformin is not reported, however.

Cost considerations

The costs of pharmacologic management of type 2 diabetes are offset by the significant reduction in costs associated with diabetic complications (Gilmer 1997, Gray 2000). Nevertheless, some interventions are more cost effective than others. The monthly costs of using the maximum daily dose of glipizide GITS 20 mg or glimepiride 8 mg are markedly lower compared to other oral drugs (Table 1) (AWP 2002). Cost may vary further, due to the required monitoring for side effects such as renal function for metformin and liver function for the glitazones and α -glucosidase inhibitors, as well as treatment for potential adverse effects, mainly hypoglycemia. Sulfonylurea induces hypoglycemia more frequently than other agents. Yet most hypoglycemic events do not require outside intervention and are significantly reduced with glimepiride compared with

⁵ Holman 1987, Johnson 1996; Kabadi 1991; Riddle 1996, 1998; Yki-Jarvinen 1999, Wright 2002

other sulfonylureas (Bell 1997, Holstien 2001). While comparing the cost of oral antidiabetic drugs, it is more important to compare relative efficacy in lowering HbA_{1c}. Thus, for equal lowering of HbA_{1c} (10 percent) from pretreatment levels, therapy with sulfonylureas and especially glimepiride is the most cost effective,

either as monotherapy or in combination with other oral agents or insulin (Tables 2, 3, and 4).

Patient satisfaction

Finally, quality of life can be significantly compromised due to the costs of management and the psychological and physical impact of the

disease. In a 12 week study in subjects with mild to moderate type 2 diabetes, improvements in glycemic control with glipizide GITS was associated with improved overall health perceptions — including emotional well being and vitality — as well as greater productivity, reduced absenteeism at work, and fewer restricted activity days. Also, QOL improvements were not accompanied by measurable increases in hypoglycemia, the most serious side effect of sulfonylurea therapy (Testa 1998). Though metformin, α-glucosidase inhibitors, and the glitazones are infrequently associated with hypoglycemia, their side effect profiles — gastrointestinal distress, anemia, edema, and congestive heart failure — may explain better patient adherence with a sulfonylurea than with the other drugs (White 1999).

TABLE 2 Relative costs of monotherapy with oral drugs for equal (10 percent) lowering of HbA_{1c} from pretreatment levels*

Drug	Average monthly cost (\$)	Relative cost*
Sulfonylurea†	13–20	+
Metformin	35–45	++
Glitazones	75–85	++++
α-glucosidase inhibitors†	40–50	++
Meglitinide†	75–100	++++

*Based on the percentage reductions shown in Table 1 (number of plus signs shows proportionate measure).

†\$17 for glimepiride, \$22.50 for glipizide GITS.

SOURCE: AWP 2002

TABLE 3 Relative cost of combination therapy with oral agents in their maximum daily dose*

Combination therapy	Relative cost†
Sulfonylurea + metformin	+
Sulfonylurea + glitazone	++
Metformin + glitazone	+++
Sulfonylurea + acarbose	+++
Meglitinide + metformin	+++
Sulfonylurea + metformin + glitazone	+++++

*See Table 1 for average monthly cost.

†Number of plus signs shows proportionate measure.

SOURCE: AWP 2002

TABLE 4 Relative costs of combination therapy with insulin and oral agents in their maximum daily dose

Combination therapy*	Relative cost†
Insulin + sulfonylurea + metformin†	+
Insulin + sulfonylurea	+
Insulin + metformin	++
Insulin + glitazone	+++
Insulin + sulfonylurea + glitazone‡	++++
Insulin + metformin + glitazone‡	+++++
Insulin + sulfonylurea + metformin + glitazone‡	+++++

*Insulin combinations with either α- glucosidase inhibitors or meglitinide are not approved.

†Based on Table 1 average monthly cost, (Number of plus signs shows proportionate measure)

‡Glitazone may be used only with close monitoring for possible occurrence of congestive heart failure.

SOURCES: AWP 2002, DELEA 2003

SUMMARY

Diabetes exacts a huge toll on health care resources, with a disproportionately high number of health care dollars spent for patients with diabetes. Though each patient requires individual treatment strategies, the most cost-effective interventions for type 2 diabetes tend to be sulfonylurea-based. Sulfonylureas may be the only oral agents inhibiting processes contributing to hyperglycemia — glucose production and glucose utilization — by ameliorating both defects of insulin secretion and insulin resistance. Among sulfonylureas, glimepiride has the most extrapancreatic activity — resulting in the lowest incidence of hypoglycemia, even following exercise and the least daily insulin dose while used as adjunctive therapy. Thus, glimepiride may be the most cost-effective therapeutic option, as monotherapy or in combination with other oral hypoglycemic agents or insulin.

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