Oral Agents in the Management of Type 2 Diabetes Mellitus

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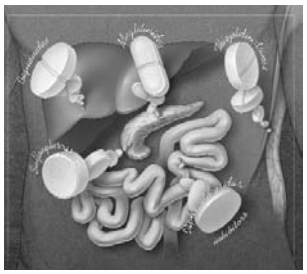
Despite exhaustive efforts to better manage patients with type 2 diabetes mellitus (formerly known as non–insulin-dependent diabetes mellitus), attempts at maintaining near normal blood glucose levels in these patients remains unsatisfactory. This continues to pose a real challenge to physicians as the prevalence of this disease in the United States continues to rise. Type 2 diabetes is defined as a syndrome characterized by insulin deficiency, insulin resistance and increased hepatic glucose output. Medications used to treat type 2 diabetes are designed to correct one or more of these metabolic abnormalities. Currently, there are five distinct classes of hypoglycemic agents available, each class displaying unique pharmacologic properties. These classes are the sulfonylureas, meglitinides, biguanides, thiazolidinediones and alpha-glucosidase inhibitors. In patients for whom diet and exercise do not provide adequate glucose control, therapy with a single oral agent can be tried. When choosing an agent, it is prudent to consider both patient- and drug-specific characteristics. If adequate blood glucose control is not attained using a single oral agent, a combination of agents with different mechanisms of action may have additive therapeutic effects and result in better glycemic control. (Am Fam Physician 2001;63:1747-56,1759-80.)

A patient information handout on type 2 diabetes mellitus, written by the authors of this article, is provided on page 1759.



See editorial on page 1687.

The prevalence of type 2 diabetes mellitus (formerly known as non–insulin-dependent diabetes mellitus) in the United States has increased dramatically over the past two decades and continues to rise.[1] Despite the introduction of new agents to the armamentarium of hypoglycemic agents, efforts for better management of this disease have been disappointing and the control of blood glucose levels remains unsatisfactory.[2] Recently, the results of the United Kingdom Prospective Diabetes Study (UKPDS) were released.[3] This study, the largest and longest study of patients with type 2 diabetes, has reinforced the belief that improved control of blood glucose levels can substantially lower the overall morbidity associated with this disease, underscoring the urgency to obtain better glucose control in these patients. The focus of this review will be the management of patients with type 2 diabetes using one or more of the five available classes of oral hypoglycemic agents: sulfonylureas, meglitinides, biguanides, thiazolidinediones and alpha-glucosidase inhibitors *(Table 1)*. Options for monotherapy and combination therapy, efficacy of specific agents, adverse effects and special populations are some issues addressed in this review.

In patients who have type 2 diabetes, pharmacologic intervention is required if the desired level of glycemic control is not achieved with diet and exercise within a three-month period.

Type 2 diabetes can be described as a syndrome characterized by insulin deficiency, insulin resistance and increased hepatic glucose output.[4,5] With this in mind, therapies used to treat patients with this disease are aimed at correcting one or more of these physiologic abnormalities. Current recommendations of the American Diabetes Association include a trial of diet and exercise as first-line therapy for the treatment of patients with type 2 diabetes.[6] If the desired level

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TABLE 1
Classes of Oral Hypoglycemic Agents

Drug class	*Agent*	*Drug class*	*Agent*
Sulfonylureas	*First generation*	Meglitinides	Repaglinide (Prandin)
	Acetohexamide (Dymelor)		Nateglinide (Starlix)
	Chlorpropamide (Diabinese)	Biguanides	Metformin (Glucophage)
	Tolazamide (Tolinase)	Thiazolidinediones	Pioglitazone (Actos)
	Tolbutamide (Orinase)		Rosiglitazone (Avandia)
	Second generation	Alpha-glucosidase inhibitors	Acarbose (Precose)
	Glyburide (Micronase)		Miglitol (Glycet)
	Glipizide (Glucotrol)		
	Glimepiride (Amaryl)		

of glycemic control is not achieved with diet and exercise within a three-month period, pharmacologic intervention is required.

Criteria for initiation of therapy with an oral agent versus insulin are debated among diabetologists, but the decision should be made jointly by the physician and patient to obtain the best results.[7] (Because of the apparently progressive nature of the beta cell defect in type 2 diabetes, current oral therapies may not prevent an eventual decline in glycemic control, and it is likely that many patients will ultimately require insulin therapy.) Once the decision is made to initiate therapy with an oral agent, it is prudent to consider patient-specific (age, weight, level of glycemic control) and agent-specific characteristics (relative potencies, duration of action, side-effect profiles, cost) to make the most appropriate choice *(Tables 2 and 3[8])*. *Figure 1* illustrates a reasonable stepwise approach for initiating oral therapy in patients with type 2 diabetes and is consistent with the recommendations put forth by several expert committees and diabetes subspecialists.[4-6,9]

TABLE 2
Clinical Efficacy of Oral Hypoglycemic Agents

Class of hypoglycemic agents	*Reduction in HbA_{1c} (%)*	*Reduction in FPG (mg per dL [mmol per L])*
Sulfonylureas	0.8 to 2.0	60 to 70 [3.3 to 3.9]
Meglitinides	0.5 to 2.0	65 to 75 [3.6 to 4.2]
Biguanides	1.5 to 2.0	50 to 70 [2.8 to 3.9]
Thiazolidinediones	0.5 to 1.5	25 to 50 [1.4 to 2.8]
Alpha-glucosidase inhibitors	0.7 to 1.0	35 to 40 [1.9 to 2.2]

HbA_{1c} = glycosylated hemoglobin A_{1c}; FPG = fasting plasma glucose.

Sulfonylureas

Sulfonylureas have remained the mainstay of antidiabetic therapy since the early 1950s. Following the release of the University Group Diabetes Program (UGDP) study,[10] which implicated tolbutamide in increased mortality secondary to cardiovascular events, the use of the first generation sulfonylureas (acetohexamide, chlorpropamide, tolbutamide and tolazamide) quickly fell out of favor.[11] Recent data, as summarized in an earlier review, supporting the benefits of the sulfonylureas as well as the availability of newer generation sulfonylureas with more favorable side-effect profiles (glyburide [Micronase], glipizide [Glucotrol] and glimepiride [Amaryl]), have contributed to their renewed popularity.[3,8]

Sulfonylureas work by stimulating insulin release from the beta cells of the pancreas and may slightly improve insulin resistance in peripheral target tissues (muscle, fat). On average, this class reduces glycosylated hemo-

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TABLE 3
Average Dose and Cost Comparison of Hypoglycemic Agents

Drug class	*Brand name*	*Generic*	*Available strengths*	*Brand name dose range (mg/day) and cost*†*	*Generic name dose range (mg/day) and cost*†*
Sulfonylureas	DiaBeta	Glyburide	1.25, 2.5, 5.0	5 ($21.24) to 20 ($84.96)	5 ($16.06 to 20.40) to 20 ($64.26 to $81.73)
	Micronase	Glyburide	1.25, 2.5, 5.0	5 ($26.49) to 20 ($105.96)	5 ($16.06 to 20.40) to 20 ($64.26 to $81.73)
	Glynase	Glyburide (micronized)	1.5, 3.0, 4.5, 6.0	0.75 ($13.73) to 12 ($73.18)	1.5 ($8.86 to 11.33) to 12 ($50.45 to $60.96)
	Glucotrol	Glipizide	5.0, 10	10 ($24.63) to 40 ($90.46)	10 ($18.21 to 20.82) to 40 ($66.84 to $76.62)
	Glucotrol XL	Glipizide	5.0, 10	5 ($10.65) to 20 ($42.17)	‡
	Amaryl	Glimepiride	1.0, 2.0, 4.0	1 ($7.34) to 8 ($44.86)	‡
Meglitinides	Prandin	Repaglinide	0.5, 1.0, 2.0	1.5 ($51.61) to 16 ($199.20)	‡
	Starlix	Nateglinide	60, 120	180 ($83.00) to 360 ($86.50)	
Biguanides	Glucophage	Metformin	500, 850, 1,000	1,500 ($58.16) to 2,550 ($98.87)	‡
	Glucophage XR	Metformin	500	1,000 ($39.24) to 2,000 ($74.48)	‡
Thiazolidinedione	Actos	Pioglitazone	15, 30, 45	15 ($85.50) to 45 ($148.50)	‡
	Avandia	Rosiglitazone	2.0, 4.0, 8.0	4 ($75.00) to 8 ($136.90)	‡
Alpha-glucosidase inhibitor	Precose	Acarbose	25, 50, 100	150 ($46.54) to 300 ($60.01)	‡
	Glyset	Miglitol	25, 50, 100	150 ($51.75) to 300 ($59.26)	‡
Combination	Glucovance	Glyburide/ Metformin	1.25/250 2.5/500 5.0/500	2.5/500 ($23.50) to 20/2,000 ($94.00)	‡

**—Estimated cost to the pharmacist based on average wholesale prices in Red book, Montvale, NJ; Medical Economics Data, 2000. Cost to the patient will be higher based on prescription filling fee.*

†—Prices are for a 30-day supply.

‡—*Generic formulation not available.*

Information from Luna B, Hughes AT, Feinglos MN. The use of insulin secretagogues in the treatment of type 2 diabetes. Prim Care 1999;26:895-915.

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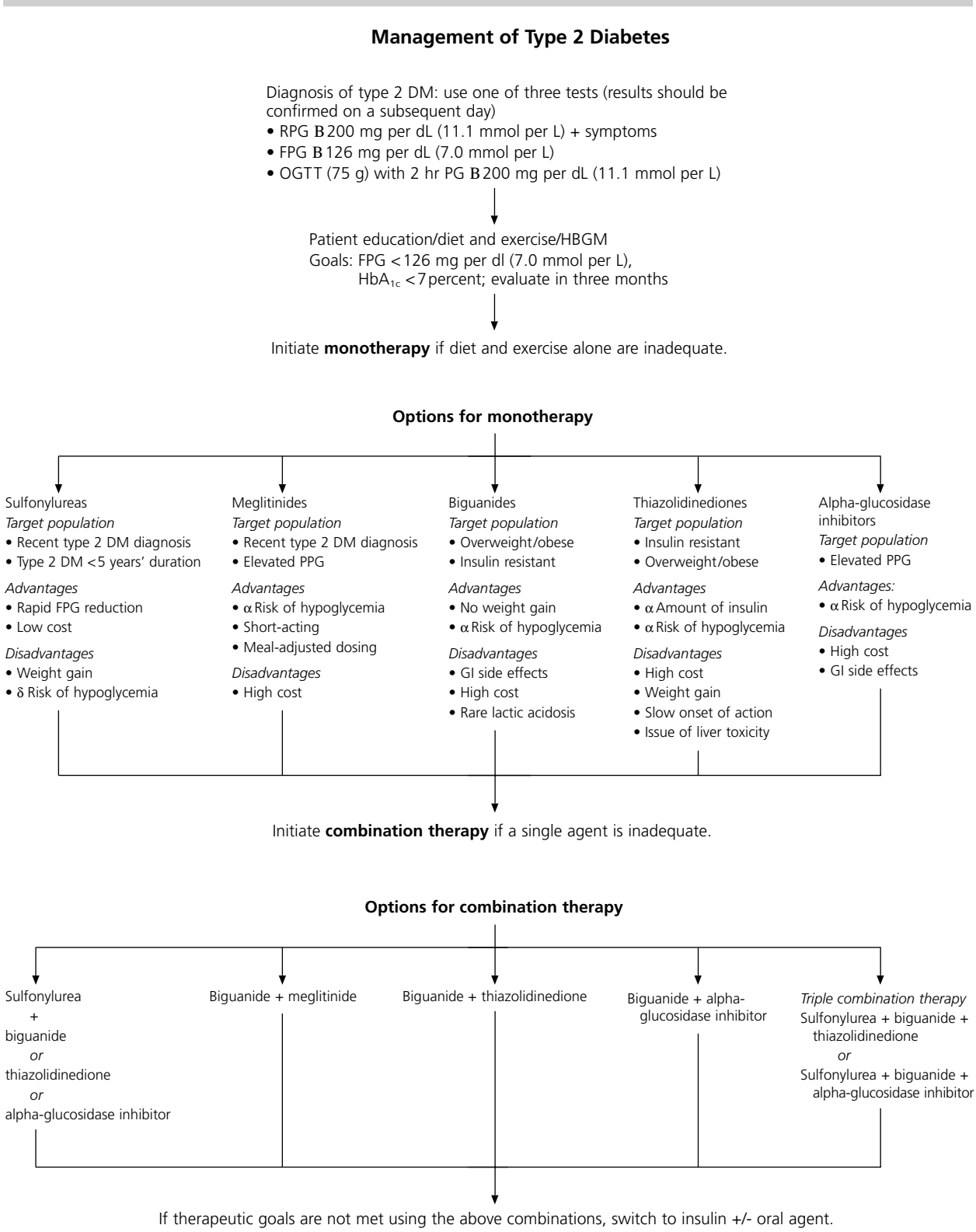

FIGURE 1. Stepwise approach for the management of type 2 diabetes in patients inadequately controlled with diet and exercise. (RPG = random plasma glucose; FPG = fasting plasma glucose; OGTT = oral glucose tolerance test; PG = plasma glucose; HbA1c = glycosylated hemoglobin A1c; HBGM = home blood glucose monitoring; DM = diabetes mellitus; GI = gastrointestinal; PPG = postprandial glucose)

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globin A_{1c} (HbA_{1c}) levels by 0.8 to 2.0 percent and fasting plasma glucose (FPG) concentrations by 60 to 70 mg per dL (3.3 to 3.9 mmol per L), with the greatest reductions observed in patients with the highest FPG concentrations at the initiation of therapy.[4,5,8] Hypoglycemia is the most worrisome side effect of the sulfonylureas. It is of particular concern with agents that are metabolized to an active metabolite with significant renal excretion. These agents include chlorpropamide (Diabinese) and glyburide, both of which should be avoided in the setting of impaired renal function and used with caution in elderly patients. Glipizide and glimepiride are associated with a lower incidence of hypoglycemia. All sulfonylureas have been associated with weight gain and thus, may not be the optimal first choice for obese patients.

Unfortunately, not all patients treated with a sulfonylurea will have an adequate response. Treatment failure with sulfonylurea therapy can be divided into two categories: primary and secondary. Primary failure results when a patient exhibits an initial poor response to sulfonylurea therapy (a decrease in FPG levels of less than 20 mg per dL [1.1 mmol per L]). Approximately 20 to 25 percent of patients with type 2 diabetes will demonstrate primary failure to sulfonylurea therapy.[12] Secondary failure results when the patient responds well to treatment initially (a decrease in FPG of greater than 30 mg per dL [1.7 mmol per L]), but eventually the treatment fails to maintain adequate control. This phenomenon is reported to occur in approximately 5 to 10 percent of patients per year.[12] Despite these drawbacks, sulfonylureas have been shown to be potent and cost-effective glucose-lowering agents.

When initiating sulfonylurea therapy, the lowest effective dose should be used and titrated to the desired effect at one- to two-week intervals. Most of the hypoglycemic effects of the sulfonylureas will be observed at one half of the maximum dose recommended for a specific agent. In patients who are not responding at one half the maximum dose, an alternative agent or combination therapy should be considered.

When most of the hypoglycemic effects are not observed at one half the maximum dose of the sulfonylureas in patients who have type 2 diabetes, an alternative agent or combination therapy should be considered.

Meglitinides

Repaglinide (Prandin) is a new non-sulfonylurea insulin secretagogue agent, the first available from the meglitinide class. Nateglinide (Starlix), the newest member of the class, has recently become available. The mechanism of action of the meglitinides closely resembles that of the sulfonylureas. The meglitinides stimulate the release of insulin from the pancreatic beta cells. However, this action is mediated through a different binding site on the "sulfonylurea receptor" of the beta cell, and the drug has somewhat different characteristics when compared with the sulfonylureas. Unlike the commonly used sulfonylureas, the meglitinides have a very short onset of action and a short half-life. Repaglinide has shown similar effects on HbA_{1c} and FPG levels when compared with glyburide, 0.5 to 2 percent and 65 to 75 mg per dL (3.6 to 4.2 mmol per L), respectively.[8] Some potential advantages of this class of agents include a greater decrease in postprandial glucose and a decreased risk of hypoglycemia.

Because of the short onset of action of the meglitinides (15 to 30 minutes), patients should be instructed to administer a dose immediately before a meal. If a meal is omitted throughout the day, patients should be instructed to skip the corresponding dose to prevent hypoglycemia. Likewise, if an extra meal is added throughout the day, the patient should add a dose to cover that meal. Repaglinide can be titrated to a dosage of 4 mg before each meal (maximum dosage of

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