

Chapter

8

ORAL MONOTHERAPY AND
COMBINATION THERAPY

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While lifestyle intervention consisting of changes in diet and physical activity can delay the onset of type 2 diabetes, it is far less successful in restoring glycemic control to targets once diabetes has been diagnosed. Oral antihyperglycemic therapy is generally prescribed after the diagnosis has been made. Fortunately, a variety of oral agents are now available, as reviewed in Chapter 6. Several basic principles apply to decisions about the use of these agents, as illustrated in Table 8-1.

TREAT TO TARGETS

Epidemiologic and interventional studies show that better glycemic control is associated with better medical outcomes from high levels to within the normal range of A1C, which is 4% to

Table 8-1 Principles for Using Oral
Antihyperglycemic Therapies

Treat to targets: progressive treatment for a progressive disorder
↓
Standard treatments first
↓
Combinations for multiple physiologic defects
↓
Individualize when standard combination treatments fail

6%.¹⁻⁴ These studies suggest that there is no “threshold” level for A1C, meaning that the benefits of improved control may continue with each further improvement of A1C. The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) have proposed <7% and <6.5 %, respectively, as targets for glycemic control of diabetes.^{5,6} As described in Chapter 4, CADRE proposes targets that are compatible with these, but better suited to a therapeutic plan of action. Control should be as close to normal as safety from hypoglycemia permits, with levels >7% indicating the need to intensify therapy. Depending on the physiology of individual patients, this A1C level corresponds to fasting and preprandial glucose in the 90 to 130 mg/dL (5 to 7.2 mmol/L) range.⁵ These are the usual targets for glucose control with oral agents. The patient should test glucose at home with a plasma-referenced system, and office measurements of A1C should be done regularly (at least twice a year) to confirm maintenance of target control.^{5,6}

PROGRESSIVE TREATMENT FOR A PROGRESSIVE DISORDER

Data from the United Kingdom Prospective Diabetes Study (UKPDS) showing the use of single oral agents from the time of diagnosis of type 2 diabetes illustrate the natural history of oral monotherapy, as depicted in Figure 8-1. Glycemic control gradually worsened as β -cell function declined over time, independent of whether the treatment was diet alone, a sulfonylurea, metformin, or insulin.^{1,2} It may be that thiazolidinediones (TZDs; also known as glitazones), and other future therapies, can protect against the decline of β -cell function but, until this is convincingly demonstrated, we should expect a typical patient's A1C to increase annually by 0.2% to 0.3% during treatment with a single agent.⁷ Therefore, a patient who has 6.5% A1C on maximal lifestyle treatment is likely to see this value rise to 7.0% in about 2 years, and to 7.5% by 3 to 5 years. If control is restored to 6.5% with the addition of an oral agent, this rate of increase is likely to continue. When a change of therapy is indicated, switching to a second oral

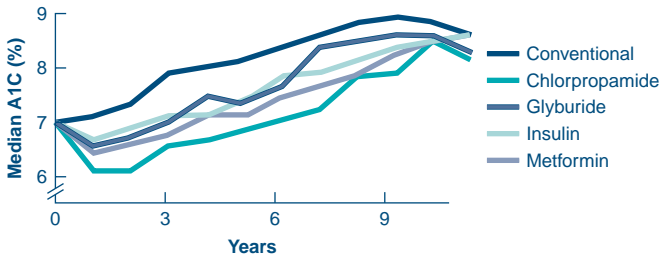


FIGURE 8-1. Natural history of oral monotherapy: glycemic response in UKPDS obese substudy.²

agent is unlikely to be effective, while adding the second agent to the first probably will succeed in restoring control.

STANDARD TREATMENTS FIRST

Several choices for initial therapy are available, and when two or more agents are used in combination, many more options exist. Some of these choices have been more extensively tested and are preferable for other reasons. These have come to be used as standard treatments that should be tried first in most cases. These evidence-based choices will be described later in this chapter.

COMBINATIONS FOR MULTIPLE PHYSIOLOGIC DEFECTS

Soon after diagnosis, especially when the initial A1C is less than 8%, almost any available antihyperglycemic treatment will be effective. Later, as endogenous insulin reserve declines, more than one agent will be necessary. Fortunately, the differing actions of the several classes of oral agents allow their therapeutic effects to be additive, while their side effects are generally not additive, especially if lower doses are used. Table 8-2 charts the different mechanisms of action of the oral agent classes.

As summarized in Table 8-2, a sulfonylurea combines well with metformin, which improves hepatic insulin sensitivity, or with a gli-

Table 8-2 Available Classes and Modes of Action of Oral Antihyperglycemic Agents. Agents with different modes of action (shaded areas in different columns) can be combined for greater effect on glycemic levels.

	Mode of Action*			
	Stimulate Insulin Secretion	Improve Hepatic Response to Insulin	Improve Insulin Action in Muscle/Fat	Delay Gastro-Intestinal Glucose Absorption
Sulfonylureas and Secretagogues				
Metformin				
Glitazones				
α -Glucosidase Inhibitors				

*Darker shading indicates primary mode of action; lighter shading indicates secondary mode of action.

tazone, which improves sensitivity in muscle and fat. In addition, agents that limit postprandial hyperglycemia combine well with those that control overnight (basal) glucose. Thus, an α -glucosidase inhibitor, which limits increments of glucose after meals, is appropriately combined with metformin or a sulfonylurea, which improve

mainly basal glycemia. However, combining a sulfonylurea with a rapid-acting secretagogue provides no added benefit, because the mechanisms of actions of these two classes of agents are so similar.

INDIVIDUALIZE TREATMENTS WHEN STANDARD TREATMENTS FAIL

Although a strong case can be made for a few standard treatments as initial choices, patients and circumstances differ widely, so individualization is often necessary. The choice of treatment should be based on the following considerations:

- ▲ Contraindications to an agent
- ▲ Synergy of mechanisms of action
- ▲ Lack of the expected therapeutic response
- ▲ Occurrence of side effects
- ▲ Hypoglycemia
- ▲ Weight gain
- ▲ Fluid retention
- ▲ Problems with cost
- ▲ Convenience and adherence

INITIAL THERAPY WHEN CONTROL IS VERY POOR

Latent Autoimmune Diabetes in Adulthood (LADA)

Recently diagnosed patients with random glucose values of >300 mg/dL and A1C values of >10% present an immediate therapeutic challenge. Some, despite having onset of diabetes in adulthood, will be found to have late-onset type 1 diabetes, which is also known as latent autoimmune diabetes in adulthood (LADA).^{8,9} LADA is suggested by the following features:

- ▲ Rapid onset of symptoms of diabetes
- ▲ Age <50 years

- ▲ Not overweight
- ▲ No family history of type 2 diabetes
- ▲ Family (or personal) history of autoimmune disorders
- ▲ A positive laboratory test for anti-glutamic acid decarboxylase (GAD) autoantibodies confirms the LADA diagnosis and calls for immediate insulin therapy.

Type 2 Diabetes With A1C >10%

Immediate use of insulin may also be the best choice for patients lacking the features of LADA and likely to have type 2 diabetes, but who have fasting hyperglycemia >250-300 mg/dL and A1C >10% with prominent symptoms such as urinary frequency, weight loss, fatigue, or painful neuropathy. Insulin will quickly improve control and reduce symptoms, and may allow partial recovery of insulin sensitivity and β -cell reserve and function by reducing the effects of glucotoxicity (the detrimental effects of high levels of glucose) and lipotoxicity (detrimental effects of high levels of lipids).^{10,11} Many patients whose control is improved by insulin treatment may be able to discontinue insulin and switch to oral agents successfully or remain on a lower but effective insulin dose in combination with insulin sensitizers.

If glycemic control is very poor but symptoms are lacking, treatment may be started with oral agents. In this setting, the best initial choice is a sulfonylurea, because these agents are as effective as any other, are unlikely to cause side effects even when started at full dosage, and have onset of action within a few days.¹² Typical rates of improvement of fasting plasma glucose (FPG) after starting a sulfonylurea, metformin, or a glitazone are presented in Figure 8-2. The delay in onset of effect from metformin and glitazones, and the relatively lower efficacy of α -glucosidase inhibitors and rapid-acting secretagogues (especially nateglinide), make these agents less suited to initial treatment of poorly controlled diabetes.^{13,16-19} While a few patients will have excellent responses from a sulfonylurea alone, with A1C declining close to

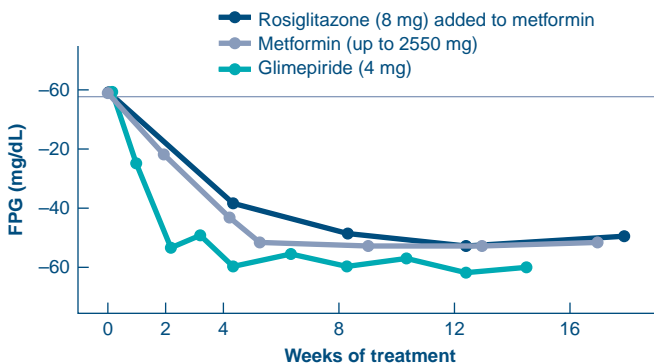


FIGURE 8-2. Temporal onset of glycemic improvement with three classes of oral therapies.¹³⁻¹⁵

7%, most will not. Therefore, a second agent will prove necessary for most patients to achieve the >3% decline needed to restore control to the <7% target level. The preferred second agent will in most cases be metformin, but a glitazone can also be considered, as discussed below.

INITIAL ORAL THERAPY UNDER USUAL CONDITIONS

Most patients beginning oral therapy for diabetes have an A1C between 7% and 10%, and for them considerable evidence is available to guide treatment.^{20,21} Figure 8-3 compares the efficacy of various agents in typical studies. In general, the sulfonylureas and metformin reduce A1C by 1.5% to 2%, with greater therapeutic effects when initial A1C is higher. This is because the reduction of glucotoxicity and lipotoxicity contributes to overall efficacy.^{14,22,23} Studies of glitazones in unselected populations have slightly less efficacy, with some patients showing very little effect and others quite strong effects, especially when the initial A1C is high.^{17,24} Agents that have more effect on postprandial than on basal glucose, namely the α -glucosidase inhibitors and the rapid-acting secretagogue nateglinide, generally reduce A1C by 0.5% to 1.0% in unselected populations.^{18,19}

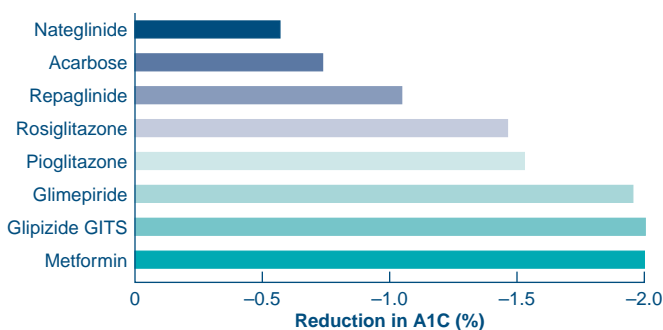


FIGURE 8-3. Relative efficacy of various oral agents used as monotherapy.^{13,16-21}

Standard Therapies: Sulfonylureas and Metformin

Because of their consistently strong glucose-lowering effects, as well as evidence from randomized, controlled trials (notably the UKPDS) proving their ability to reduce medical consequences of diabetes, sulfonylureas and metformin have become the standard initial oral therapies.^{12,25} Other factors favoring these agents include low cost and a long history of use that has thoroughly defined their adverse effects—chiefly hypoglycemia in the case of sulfonylureas, and gastrointestinal symptoms and the risk of lactic acidosis when renal clearance is limited in the case of metformin. Table 8-3 summarizes patient types for whom these medications may be most effective when used alone, but see Chapter 6 for specific dosages, adverse effects, and more complete lists of contraindications.

The debate about which of these two choices is preferable has subsided, as either will be safe and effective for most patients. Furthermore, it seems irrelevant which agent is chosen first, because soon thereafter a second agent will likely need to be added to sustain a target A1C of <7% or lower if tolerated. In general, patients who are more obese (>body mass index [BMI] 30 kg/m²) and who have lower A1C values (<8%) are better candidates for metformin, because of its additional weight-control effect and limited tendency to cause hypoglycemia. In contrast, patients starting with

Table 8-3 Patient Types Most Suited for Initial Therapy With Different Oral Antihyperglycemic Medications

	Typical Patient	Major Contraindication
Sulfonylureas	A1C >9% at diagnosis BMI <30 kg/m ²	Renal failure
Rapid-Acting Secretagogues	Irregular meal patterns Prominent postprandial hyperglycemia	Renal failure
Metformin	A1C <9% at diagnosis BMI > 30 kg/m ²	Impaired renal function
Glitazones	A1C <8% at diagnosis Highly insulin resistant Metformin-intolerant	CHF
α -Glucosidase Inhibitors	A1C <8% at diagnosis Prominent postprandial hyperglycemia	

*BMI, body mass index; CHF, congestive heart failure.

See Chapter 6 for complete characteristics, including contraindications, of each class.

higher A1C values (>8%) may have a more rapid clinical response to a sulfonylurea because, unlike metformin, these agents do not require slow titration to minimize side effects other than hypoglycemia.

A remaining question regarding sulfonylureas is whether they are all interchangeable. Several are available in conventional formulations at very low generic prices (notably glyburide and glipizide). In some formularies, other sulfonylureas are excluded, including long-acting agents that can be taken once daily (e.g., extended-release glipizide and glimepiride). However, beyond the

issue of convenience lie several concerns about the safety of glyburide relative to other agents. Glyburide is currently the most widely used sulfonylurea, but this agent is more likely to cause hypoglycemia than glipizide, chlorpropamide, or glimepiride.^{1,26} Also, recent reports suggest that glyburide—but not glimepiride—has an adverse effect on myocardial preconditioning, that is, the ability of ischemia to protect against the effects of later, more severe ischemia.^{27,28} For many patients, the longer-acting agents may be preferred to simplify administration, limit hypoglycemia, and set aside the lingering concern that glyburide may increase cardiovascular risk.

Individualized Options: Glitazones, α -Glucosidase Inhibitors, and Rapid-Acting Secretagogues

Although most patients begin treatment with a sulfonylurea or metformin, individualized alternatives are appropriate for a substantial minority. Metformin is contraindicated when renal function is impaired (serum creatinine >1.4 mg/dL in women or 1.5 mg/dL in men), and when the drug causes intolerable nausea or diarrhea (in 5% to 10% of patients) even when renal function is normal.^{13,23,29} For such patients, a glitazone is more appropriate, and an α -glucosidase inhibitor is a third alternative. The α -glucosidase inhibitors and nateglinide may also be considered for patients with relatively low A1C and primarily postprandial glucose elevations. Patients with very irregular meal patterns and prominent postprandial hyperglycemia may be good candidates for the rapid-acting secretagogues (repaglinide and nateglinide), which can be taken just before meals and thus may reduce the risk of the between-meal hypoglycemia that may occur with sulfonylureas.

The glitazones require further comment because of important issues that have not yet been resolved by adequate medical outcome trials. In the case of the glitazones, several nonglycemic effects with unknown long-term outcomes have been described. The most widely discussed effects are those on vascular tissues, markers of systemic inflammation, and β -cells, all of which appear to be favorable but the long-term benefits of which remain to be

demonstrated.³⁰⁻³² Fluid retention, anemia, and weight gain frequently occur, and the magnitude of risks posed by these effects is still unknown. Glitazones frequently reduce triglycerides but increase low-density lipoprotein levels, with a net effect that remains uncertain. Glitazones also alter expression of growth factors, and whether these pose risks of neoplasia is unknown. Until the results of long-term trials are available, the use of glitazones remains justified only for their glyceemic effects.

ADVANCING TO COMBINATION THERAPY

By 5 years after diagnosis, most patients will need more therapy than lifestyle efforts plus a single oral antihyperglycemic agent to keep A1C <7%. In fact, most who begin pharmacotherapy only when A1C has become very elevated, >9% or 10%, will have an inadequate response to monotherapy immediately, and require a second agent very soon to reach glyceemic targets. When combination therapy is needed, it should not be delayed.³³

Sulfonylurea + Metformin

The best-tested oral combination is a sulfonylurea plus metformin. Adding one of these agents to the other at full dosage can reduce A1C by 1.5% to 2%.¹³ However, there is a strong rationale to begin using this combination in some cases before titrating to full dosage of the first agent. Figure 8-4 shows that the glyceemic effects of both agents are not proportional to dosage. That is, more than half the benefit of each is achieved with half-maximal dosage.^{23,34,35} At the same time, the side effects increase progressively with dosage, especially for metformin, which causes gastrointestinal discomfort for 20% to 25% of patients at 2,000 mg/day.^{13,35} Adding the second agent in low dosage to the first at half-maximal dosage should minimize costs as well as side effects relative to the glyceemic benefit. For example, adding 5-10 mg extended-release glipizide or 2-4 mg of glimepiride once daily to 500-1,000 mg metformin with evening meal should reduce A1C more than increasing metformin to 1,000 mg twice daily, without risk of gastrointestinal distress. Table 6-1 in Chapter 6 indicates the maximal dosages for oral agents.

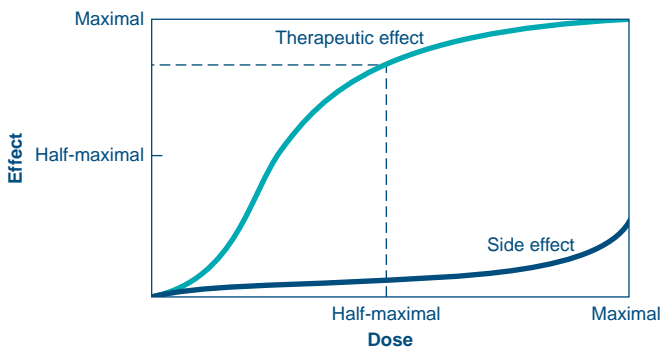


FIGURE 8-4. Dose-effect relationship for antihyperglycemic monotherapy. Graphic representation of theoretical dose-effect relationship for many oral antihyperglycemic drugs. Half-maximal dosages yield far more than one-half the maximal therapeutic effect, while side effects rise sharply as dosage nears maximum.³⁴

Glitazone + Sulfonylurea or Metformin

Almost as well established as the sulfonylurea-metformin combination are a sulfonylurea plus a glitazone, and metformin plus a glitazone. These may also be regarded as standard versions of combination therapy. In each case, 1% to 1.5% reduction of A1C is usually seen, but there are differences in other areas.^{15,36} With a sulfonylurea plus a glitazone, the glycemic benefit may be somewhat greater, but there is usually some weight gain, sometimes clinically noticeable fluid retention, and occasionally hypoglycemia. With metformin plus a glitazone, the glycemic benefit may be more modest, but weight gain is less, and fluid retention and hypoglycemia rarely occur.

As with monotherapy consisting of metformin or a glitazone, the contraindications and safety concerns with these agents should be kept in mind when they are used in combination with other agents. That is, metformin should not be used by patients with impaired renal function, nor should it be used by patients with

elevated liver enzymes (with or without documented liver disease) or congestive heart failure.

Other Combinations

Individualized combinations are also possible. Notably, a rapid-acting secretagogue can be substituted for a sulfonylurea when meal patterns are erratic, when unpredictable hypoglycemia has proved a problem, or when postprandial hyperglycemia is judged especially important to control.³⁷ Similarly, an α -glucosidase inhibitor can be substituted for either metformin or a glitazone in these combinations when one or both is contraindicated or not tolerated.³⁸ The combination of an α -glucosidase inhibitor and a rapid-acting secretagogue is not logical, because both target postprandial glycemia and have little effect on basal glucose control.

Single-Pill Combinations

Recently single-pill combinations of agents have been introduced, although their roles are not yet well defined. These are Glucovance (glyburide plus metformin), Metaglip (glipizide plus metformin), and Avandamet (rosiglitazone plus metformin).³⁹⁻⁴¹ These fixed-dose combination formulations are suggested to be simpler to take and therefore to encourage higher adherence, but this has not been proven. In fact, the number of pills with fixed-dose combination therapy is usually not less than with separate pill combinations. For example, full-dose sulfonylurea plus metformin can be taken as 4 mg glimepiride once daily plus 1,000 mg metformin twice daily (three pills). This compares with two Glucovance 0.5/500-mg tablets twice daily (four pills) for the same effect. Further, it seems unlikely that fixed-dose combinations will be less expensive in the long run. Finally, dose titration designed to minimize side effects (notably those of metformin and glitazones) is likely to be more difficult with fixed-dose combinations. Future combinations of lower doses of glitazones with metformin, and potentially with long-acting sulfonylureas, have the potential for simpler once-daily combination therapy options in early type 2 diabetes. For the present, these combinations cannot be assigned standard treatment status, but they may be appropriate for individualized use by some patients.

TRIPLE ORAL AGENT THERAPY

For many reasons, including patient reluctance to use insulin, increased risk of hypoglycemia, and misperceptions about negative cardiovascular effects of insulin, combination therapy with three or more oral agents is sometimes used when glycemic control is unacceptable with two oral agents. A few short-term studies have verified that this tactic can improve glycemic control in some cases, but long-term clinical studies are lacking.⁴²⁻⁴⁴ In addition, the cost and complexity of some triple therapy regimens may pose problems in some cases. Thus, in general, CADRE recommends adding insulin as the standard tactic when two oral agents are insufficient to reach glycemic targets. Triple oral therapy is an appropriate individualized option for some patients as long as target A1C <7% is achieved. When glycemic control cannot be maintained on two oral agents in combination, insulin should be introduced into the therapeutic plan, as described in Chapter 9.

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