

Optimizing combination therapy for type 2 diabetes in adolescents and adults: A case-based approach

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Diabetes affects 18.2 million people in the United States.⁵ It is a leading cause of morbidity and mortality.⁵ Diabetes is associated with more than \$90 billion in direct medical costs and with an estimated \$40 billion in indirect costs (ie, disability, work loss, and premature mortality).⁵ Type 2 diabetes accounts for 90% to 95% of total cases. It disproportionately affects certain minority populations, and it is increasingly being identified in children and adolescents.^{5,7}

The obesity epidemic has received tremendous media and public attention and has sobering implications for the development of metabolic syndrome, which is often the precursor to diabetes, and cardiovascular disease (CVD).^{8,9} In 1 study, the hazard ratio for development of diabetes was 3.85 for individuals who gained 20 kg or more over approximately 10 years, as compared with individuals whose weight remained relatively stable over the same period.¹⁰ Obesity is associated with elevations in free fatty acid levels and in other compounds which contribute to insulin resistance¹¹—a key underlying defect in metabolic syndrome and type 2 diabetes. Thus, particularly in genetically predisposed individuals, obesity (through elevated fatty acids) may be the factor that drives insulin resistance to

PRACTICE RECOMMENDATIONS

Children and adolescents who are overweight and have additional risk factors (ie, high-risk ethnic group or signs of insulin resistance) should be screened for diabetes every 2 years **(SOR: C)**.

Management of type 2 diabetes in all age groups requires a multifactorial approach that addresses not only glycemic control (A1C <7%) but also other cardiovascular risk factors such as hypertension, dyslipidemia, and obesity **(SOR: A)**.¹

Most patients with type 2 diabetes will eventually require combination therapy with 2 or more agents to attain and maintain glycemic control **(SOR: A)**.^{2,3}

Combining an insulin secretagogue (ie, sulfonylurea or meglitinide) and an insulin sensitizer (ie, metformin or a glitazone) capitalizes on unique mechanisms of action and results in significant A1C lowering **(SOR: C)**.

If a patient is unable to achieve glycemic control on 2 oral agents, insulin therapy is an appropriate consideration and should be added to oral agents (rather than substituted) **(SOR: B)**.⁴

clinical diabetes. In addition, elevated free fatty acid levels also may contribute to the other key underlying defect in type 2 diabetes: progressive pancreatic β -cell loss which results in insulin deficiency.¹² Similar to the trend in adults, childhood obesity has now reached epidemic proportions

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TABLE 1

Screening recommendations for type 2 diabetes in children

Testing for type 2 diabetes is recommended every 2 years at onset of puberty or aged >10 years (whichever comes first) if the child*

- Is overweight[†]
- And has 2 of the following risk factors:
 - Family history of type 2 diabetes in first- or second-degree relative
 - High-risk race or ethnicity (Native American, African American, Hispanic, Asian American, Pacific Islander)
 - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome)

*Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria.

[†]Overweight is defined as BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height.

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and has been associated with the increased prevalence of glucose intolerance, metabolic syndrome, and biomarkers of increased CVD risk in this young population.¹³⁻¹⁵

TYPE 2 DIABETES IN ADOLESCENTS

CASE 1 Suspected new-onset type 2 diabetes

A 16-year-old Hispanic boy presents for treatment of weight loss. He is a defensive tackle on the high school football team and has a strong appetite. His height is 6 ft 1 in and he weighs 250 lb; his body mass index (BMI) is 32 kg/m², and most of the fat is abdominally distributed (waist circumference, 42 in). Both of his parents are obese, and a grandfather and aunt have type 2 diabetes. Further examination reveals a blood pressure (BP) level of 135/87 mm Hg and acanthosis nigricans. A random fingerstick test shows a blood glucose level of 240 mg/dL.

Until recently, type 2 diabetes rarely was observed in children, occurring in only 1% to 2% of children with new-onset diabetes.¹⁶ However, depending on the sampling strategy, race or ethnicity of the population, and the region of the country sampled, it now has been estimated that type 2 diabetes accounts for anywhere from 8% to 45% of all diabetes reported among children and adolescents.^{6,16} Prevalence estimates of pediatric type 2 diabetes in popu-

lation-based studies range from 4.1 per 1,000 in the National Health and Nutrition Survey (NHANES III) to 50.9 per 1,000 among Pima Indians in Arizona.¹⁷ Unlike the trends of increasing incidence and prevalence of type 2 diabetes in the pediatric population, a similar trend in type 1 diabetes has not been observed.⁷

The diagnosis and treatment of type 2 diabetes in pediatric patients can be challenging. Type 2 diabetes is associated with an increased BMI and is more common in adolescents than in younger children.⁶ Puberty is associated with relative insulin resistance and, along with the time-related effects of obesity, resistance may play a role in the subsequent onset of type 2 diabetes in pediatric patients. However, as an increasing number of children become obese at an earlier age, the onset of disease may occur earlier.

Other risk factors for type 2 diabetes in childhood include having a first- or second-degree relative with the disease or non-European ancestry (Americans of African, Hispanic, Asian, Pacific Islander, or Native American descent). In addition, acanthosis nigricans is a skin condition that serves as a specific, though insensitive, marker of insulin resistance. Among adolescent females, polycystic ovary syndrome has been associated with insulin resistance irrespective of excess weight or frank obesity¹⁸ and may be associated with an increased risk of type 2 diabetes.⁶

TABLE 1 provides criteria for screening for type 2 diabetes in children. The adolescent in the case presented has several risk factors for type 2 diabetes, including obesity, a positive family history, Hispanic descent, and acanthosis nigricans. To more definitively diagnose type 2 diabetes, additional laboratory tests are needed, including assessment of blood glucose and insulin production, as well as the presence of autoantibodies.

CASE 1 Laboratory assessment

The patient has a fasting plasma glucose (FPG) level of 215 mg/dL. β -Cell or insulin autoantibodies are not detected. He has a normal-to-high fasting C-peptide level, microalbuminuria, and a serum creatinine level of 0.8 mg/dL. His lipid panel results include: total cholesterol, 234 mg/dL; low-density lipoprotein (LDL) cholesterol, 159 mg/dL; high-density lipoprotein (HDL) cholesterol, 45 mg/dL; and triglycerides, 150 mg/dL.

A comparison of the typical presentation and laboratory findings in pediatric type 1 and type 2 diabetes is listed in TABLE 2. This information underscores that there is significant overlap between the 2 disease classifications.

The laboratory results for this patient confirm a diagnosis of type 2 diabetes. C peptide is a marker of endogenous insulin production and is particularly helpful in the classifica-

tion of diabetes when it is high, which is indicative of type 2 diabetes. However, it should be noted that a finding of low C-peptide levels does not rule out type 2 diabetes since there is a possibility that glucose toxicity is temporarily limiting insulin production. Indeed, in such a case, insulin therapy can be initiated to establish glycemic control and promote endogenous insulin production by reducing glucose toxicity. Similarly, although the absence of pancreatic β -cells and insulin autoantibodies is consistent with a diagnosis of type 2 diabetes, the presence of such antibodies does not completely rule out type 2 diabetes.¹⁹

Like many patients with type 2 diabetes, the current patient exhibits a cluster of CVD risk factors that characterize the metabolic syndrome, including dyslipidemia (elevated total cholesterol, LDL cholesterol, triglyceride levels, and low HDL cholesterol levels), hypertension, glucose intolerance, hyperinsulinemia, and central or abdominal obesity. This is not surprising as an estimated 30% of overweight adolescents, defined as those with BMI at or above the 95th percentile, meet the criteria for metabolic syndrome.¹⁴

CASE 1 Initial therapy

The patient is provided with education on lifestyle modifications to reduce weight and obtain better control of glucose, lipids, and BP. Instructions include ways to improve his eating habits and to increase his physical activity when away from the football field, such as limiting time spent watching TV and playing video games and increasing exercise time and effort. The patient also is instructed on self-monitoring for blood glucose (SMBG) and is given a referral to an ophthalmologist to determine whether there is any baseline retinopathy.

At his 3-month follow-up, the patient's A1C is 8.7%, and his weight has not changed. At this point, lifestyle

TABLE 2

Classification of type 1 and type 2 diabetes in pediatric patients

	TYPE 1 DIABETES	TYPE 2 DIABETES
Age	Throughout childhood	Pubertal
Onset	Acute, severe	Mild to severe, often insidious
Insulin secretion C-peptide level	Very low Absent	Variable Variable
Insulin sensitivity*	Normal	Decreased
Insulin dependence[†]	Permanent	No
Genetics	Polygenic	Polygenic
Race/ethnic distribution	All (low frequency in Asians)	African American, Hispanic, Asian, American Indian, Pacific Islanders
Association		
Obesity	No	Yes, strong
Acanthosis nigricans	No	Yes
Autoimmunity	Yes	No
Presence of autoantibodies	Yes	No [‡]

*Insulin sensitivity is given as a pathogenic factor.

[†]In the absence of acute illness or other stress.

[‡]Although autoimmunity is not a cause of type 2 diabetes, diabetic autoimmune markers can be present at times and should not be used to rule out a diagnosis of type 2 diabetes in children and adolescents.¹⁹

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modifications are reinforced, and pharmacotherapy with extended-release metformin is initiated and titrated to 2,000 mg/d.

Typically, the first approach to managing type 2 diabetes involves dietary changes and instituting an exercise program to reduce weight and to improve insulin sensitivity. This was the approach used in the patient described above. However, as is frequently the case, lifestyle modifications by themselves are insufficient to meet the American Diabetes Association (ADA) or American Association of Clinical Endocrinologists targets for glycemic control (A1C <7% and <6.5%, respectively).^{20,21} It is important to note here that the ADA does recommend less stringent glycemic control guidelines in very young children (ie, those aged less than 13 years).¹⁶ As is the case for adults with diabetes, pharmacologic therapies typically are needed in addition to lifestyle changes to lower elevated blood glucose levels. However, unlike the situation with adults, the list of drugs approved by the Food and Drug Administration for use in pediatric patients is limit-

TABLE 3

Available oral antidiabetic agents

DRUG	DAILY DOSE (MG)	DOSES/DAY	PRIMARY MECHANISM(S)	EXPECTED A1C REDUCTION (%)	COMMON ADVERSE EFFECTS
Sulfonylureas			Augment insulin secretion	1-2	Hypoglycemia, weight gain*
Glimepiride	1-8	1			
Glipizide	2.5-40	1-2			
Glipizide controlled release	2.5-20	1			
Glyburide	2.5-20	1-2			
Glyburide micronized	3-12	1-2			
Meglitinides			Augment insulin secretion	1-2	Hypoglycemia, weight gain
Repaglinide	0.5-16	2-4			
Nateglinide	360	2-4			
Biguanides			Increase sensitivity to insulin, decrease hepatic glucose production	1-2	Gastrointestinal symptoms [†]
Metformin [‡]	Adults: 500-2,550 Children (10-16 yr) 500-2,000	2-3			
Thiazolidinediones			Increase sensitivity to insulin	1-1.5	Fluid retention, weight gain [‡]
Rosiglitazone	2-8	1-2			
Pioglitazone	15-45	1			
α-Glucosidase Inhibitors			Slow digestion of carbohydrates	0.5-1	Flatulence, gastrointestinal discomfort, weight gain
Acarbose	75-300	3			
Miglitol	75-300	3			

*Glimepiride had a neutral effect on weight in clinical studies and was associated with a lower incidence of hypoglycemia than other sulfonylureas.⁴⁹⁻⁵¹
[†]Lactic acidosis has been reported with metformin use, but is extremely rare. The risk may be related to an underlying predisposition to lactic acidosis.
[‡]There have been some reports of liver toxicity with second-generation thiazolidinediones.
Adapted from American Association of Clinical Endocrinologists;²¹ Nathan DM. Clinical practice. Initial Management of glycemia in type 2 diabetes mellitus. *N Engl J Med.* 2002;347:1342-1349.

ed (ie, currently only metformin and insulin preparations are approved for pediatric use).

Metformin was chosen as the initial therapy in this adolescent for several reasons, including demonstrated efficacy and tolerability in pediatric studies, approval for

use in this population, and because it is generally not associated with weight gain. The patient needs a 1.7% reduction in A1C; therefore, metformin was titrated to the maximum daily dosage of 2,000 mg (expected to, on average, reduce A1C by 1% to 2%). In a recent, randomized, dou-

ble-blind, placebo-controlled trial of pediatric patients (aged 10 to 16 years) with type 2 diabetes,²² metformin 1,000 mg bid significantly reduced baseline-adjusted mean A1C values compared with placebo (7.5% vs 8.6%, $P < 0.001$) without negatively affecting body weight or lipid levels. The adverse events profile of metformin in children was similar to that observed in adults, primarily involving gastrointestinal events.

CASE 1 Monotherapy inadequate

After 6 months on metformin therapy, the patient returns for follow-up. His A1C measure has improved to 7.7%, but his weight remains unchanged. At this point, a discussion is initiated about using combination therapy to bring his diabetes under control.

This case study illustrates an important point about the treatment of type 2 diabetes: pharmacologic therapy with a single antidiabetic agent often is insufficient to reach target goals for glycemic control.² Frequently, this reflects the insidious, progressive nature of the disease, which may be present for years before being recognized. As a general rule, combination therapy involves the use of drugs with different mechanisms of action. Clinical trials evaluating combination therapy generally follow this rationale.

Since there are limited pediatric data for the majority of oral agents, the clinical decision regarding which agents to use in combination often is based on the available data in adults. Information regarding efficacy, safety, and tolerability for the different oral antidiabetic drugs used in adults with type 2 diabetes is provided in **TABLE 3**.

Secretagogues (ie, sulfonylureas and meglitinides) have been reported to typically reduce A1C values by 1% to 2% at maximal doses. Generally, the shorter-acting meglitinides have been considered useful for reducing postprandial hyperglycemia and are taken before meals.²³ Unlike traditional sulfonylureas, glimepiride also has demonstrated efficacy in controlling postprandial hyperglycemia.²⁴ All patients starting therapy with a secretagogue should be counseled on recognition of hypoglycemic symptoms and appropriate self-treatment. While severe hypoglycemia is not common in type 2 diabetes, it can occur with any agent that increases insulin secretion.

The glitazones lower A1C levels by an estimated 1% to 1.5%. Although they primarily reduce insulin resistance, they also may have beneficial effects on blood lipids, BP, and inflammatory markers associated with CVD, suggesting a theoretical benefit for reducing macrovascular complications.²⁵ Glitazones, however, have been associated with weight gain and fluid retention, which in adults may unmask or exacerbate congestive heart failure.²⁵ Additionally, although pioglitazone and rosiglitazone do not

appear to carry the same risk of hepatotoxicity as the first member of the class, troglitazone, there have been a few case reports of liver injury or failure in patients treated with pioglitazone²⁶⁻²⁸ or rosiglitazone.²⁹⁻³¹ In the absence of pediatric and long-term data, caution is warranted with use of these agents in this population.

α -Glucosidase inhibitors are helpful in controlling mealtime glycemic excursions and may have utility in patients who require smaller reductions in A1C. Use of these relatively safe agents is limited due to gastrointestinal side effects (ie, diarrhea and flatulence are common),³² which can prevent titration to optimal doses. Since the primary mechanism of action is inhibition of carbohydrate digestion, patients who are using these agents in combination with therapies that can cause hypoglycemia should be counseled to use simple sugars (ie, glucose tablets) rather than complex carbohydrates to self-treat hypoglycemia.

If oral agents cannot achieve adequate glycemic control, addition of insulin is a rational, well-tolerated, and effective option.^{3,4,33} Insulin therapy is often underutilized and delayed in patients with type 2 diabetes who would benefit from earlier introduction of such therapy.³⁴ The pediatric experience with insulin is extensive, but mostly in type 1 diabetes. The potential need for and benefits of insulin therapy may be discussed with patients as early as at the time of diagnosis to help alleviate some of the anxiety patients have regarding this therapy.³⁵

■ TYPE 2 DIABETES IN ADULTS

CASE 2 Woman with chronic diabetes

A 60-year-old woman presents for her annual checkup complaining of weight gain, fatigue, and tingling in her feet. Her recent history includes recurrent urinary tract and yeast infections. When initially diagnosed with type 2 diabetes 5 years ago, she had been counseled to increase activity to reduce weight; however, she had been unable to maintain consistent effort. She is 5 ft 4 in tall and weighs 230 lb (BMI, 39.5 kg/m²) with a waist circumference of 40 in. Her weight has fluctuated, but she has had a net gain of 30 lb over the last 5 years. Education and lifestyle modification efforts were reinitiated 1 year ago. The patient is a smoker and has cut her habit to 5 cigarettes per day. Her A1C and total cholesterol levels 1 year ago were 7.8% and 203 mg/dL, respectively. The patient also had cataract surgery 1 year ago. Her current medications include lisinopril 40 mg/d, furosemide 40 mg bid, and rosiglitazone 4 mg/d. She performs SMBG infrequently.

On examination, her BP is 125/72 mm Hg. A random fingerstick blood glucose test shows 210 mg/dL. She exhibits normal monofilament sensation, vibratory sensa-

TABLE 4

A1C reductions noted in clinical trials and reports of combination therapy for type 2 diabetes

REGIMEN	A1C REDUCTION (%)
Sulfonylurea + metformin ⁵⁸	~1.7
Sulfonylurea + glitazone ^{40,48}	~1.3
Sulfonylurea + α -glucosidase inhibitor ⁵⁹	~0.9
Metformin + meglitinide ⁴⁶	~1.4
Metformin + glitazone ^{40,45}	~1
Insulin + oral agents ⁴	Open to target

tion, and ankle jerks. She also shows signs of mild pedal edema with no foot lesions and normal pedal pulses.

There are a number of signs suggesting this patient's diabetes is inadequately controlled, including her complaints of fatigue and repeated yeast infections. Poorly controlled diabetes also is associated with peripheral neuropathy, which may manifest as a tingling sensation or numbness that begins in the feet and moves upward; however, her physical examination is negative for neuropathy.³⁶ A random blood glucose level is of limited value and should not be relied upon as an indicator of the patient's glycemic status. An A1C measurement is overdue for this patient and will reflect her overall glycemic control in recent months.

A total cholesterol level is rarely adequate for clinical decision making and thus a follow-up lipid profile is warranted. Her BP is well controlled with her current antihypertension regimen. The ADA guidelines recommend adequate treatment of hypertension (target BP, <130/80 mm Hg) in diabetic patients and suggest use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) because, in addition to their antihypertensive effects, these agents may provide renal benefits for patients with albuminuria or renal insufficiency.²⁰ More typically, a thiazide rather than a loop diuretic is used in combination with an ACE inhibitor (or another antihypertensive drug class) as treatment for hypertension but, since the patient's BP is well controlled with her current regimen and she has mild pedal edema, the loop diuretic may be maintained.

Her weight gain and peripheral edema may in part be due to rosiglitazone treatment. Edema that is not caused

by congestive heart failure is not a contraindication for glitazone use but requires close monitoring and should lead to a consideration of alternate therapy.²⁵

CASE 2 Laboratory assessment

The patient's glycemic indices are: FPG, 184 mg/dL; A1C, 9.4%; postprandial glucose (PPG), 311 mg/dL. A random urine sample reveals microalbuminuria (protein/creatinine, 38 μ g/mg). Her serum creatinine is 1.6 mg/dL. Her lipid panel reveals: total cholesterol, 271 mg/dL; LDL cholesterol, 165 mg/dL; HDL cholesterol, 35 mg/dL; and triglycerides, 355 mg/dL. Liver function tests are within normal limits. Further evaluation indicates that she does not have congestive heart failure.

The laboratory results indicate very poor control of overall and postmeal glucose levels. In addition, she now has microalbuminuria. Although poor adherence with therapy should be ruled out, the loss of control with a previously effective therapy is not unusual and underscores the progressive nature of diabetes.

Collectively, this patient's poor glycemic control, dyslipidemia and central obesity, place her at a very high risk for CVD.³⁷

CASE 2 Therapy adjusted

Glimepiride 4 mg/d is added to the rosiglitazone; in addition, atorvastatin 20 mg/d and fenofibrate 160 mg/d are prescribed. Lifestyle modifications (eg, dietary changes, exercise, smoking cessation) are reinforced, and the patient is referred to a certified diabetes educator.

The comprehensive approach taken for this patient is consistent with that advocated by the results in the Steno-2 Study. Gaede et al¹ demonstrated that a targeted, intensified, multifactorial, interventional approach to improving macrovascular and microvascular risk factors in patients with type 2 diabetes reduces the risk of macrovascular and microvascular diabetic complications by about 50% compared with conventional treatment.¹ Specifically, patients receiving intensive therapy had a significantly lower risk of CVD, nephropathy, retinopathy and autonomic neuropathy.¹ Intensive, multifactorial therapy involved dietary interventions; a consistent exercise program; smoking cessation; use of ACE inhibitors (or ARBs for patients intolerant to ACE inhibitors) for renal benefits and combined with diuretics and other agents, if necessary, to treat hypertension; lipid-lowering therapy to treat hyperlipidemia (statins, plus fibrates for isolated cases of hypertriglyceridemia); pharmacotherapy for glucose control; daily vitamin-mineral supplements; and daily aspirin as a secondary measure for the prevention of CVD.

In general, pharmacotherapy of diabetes should be individualized, since not all agents are equally appropriate for all patients. A variety of studies have demonstrated that adding a second antidiabetic agent to a first typically results in additional improvements in glycemic control.³⁸⁻⁴⁷

In the example here, a sulfonylurea was chosen because of its complementary mechanism of action with an insulin sensitizer. Since the patient had an elevated serum creatinine, metformin was not considered to be an appropriate choice. In addition, the combination of a glitazone with sulfonylurea therapy has been reported to achieve reductions in A1C^{40,48} at least comparable to those reported in analyses of the combination of a glitazone with metformin.^{40,45} **TABLE 4** provides reported reductions in A1C that have been observed in clinical trials of various combination regimens in type 2 diabetes. Since these are not head-to-head comparisons of the various regimens, the data simply illustrate the range of A1C reductions that may be achieved with combination therapy. In this patient, glimepiride was chosen because of its weight neutral effect,⁴⁹ potentially lower incidence of hypoglycemia,^{50,51} favorable effect on postprandial glucose (that may ameliorate cardiovascular risk),⁵²⁻⁵⁶ and once-daily dosing.

Given the progressive natural history of type 2 diabetes, and the fact that this patient currently requires a >2% A1C reduction, it is reasonable to anticipate that she will eventually need insulin to attain glycemic control. Recently, Riddle et al⁴ demonstrated that addition of a basal insulin (neutral protamine Hagedorn [NPH] or glargine) to existing oral agents reduced the A1C to <7% in the majority of patients with type 2 diabetes. Insulin glargine was associated with significantly less hypoglycemia than NPH insulin. This is an important consideration since hypoglycemia remains a major barrier to insulin therapy in type 2 diabetes.⁵⁷ Sulfonylurea therapy should be maintained when insulin is initiated, as this combination has been demonstrated to be highly effective in improving glycemic control and is associated with a low incidence of hypoglycemia.^{3,33} In the current patient, the addition of basal insulin glargine would complement her other antidiabetic therapies. Insulin glargine would primarily normalize her FBG, while glimepiride controls PPG and rosiglitazone improves insulin sensitivity. Thus, this regimen would address the 2 most important defects in type 2 diabetes—insulin deficiency and insulin resistance.

Clinical trials have shown that combination therapy with oral agents and insulin, as well as with multiple oral agents, is effective.^{4,38,39} However, more long-term and comparative studies of these multiple-agent combinations are needed. It is important to set expectations with patients that

gaining good control of diabetes frequently requires combination therapy with multiple agents with the ultimate goal of avoiding the onset of new complications or of delaying progression of existing complications.

■ SUMMARY

The increased prevalence of obesity, metabolic syndrome, and type 2 diabetes in adolescents and adults is an ominous sign of more serious disease in the future. A concerted effort on the part of health care professionals to improve the care of patients with type 2 diabetes is needed to bring this burgeoning problem under better control. Diabetes is a recognized coronary risk equivalent; thus, a comprehensive multifactorial approach that rigorously addresses glycemia, as well as elevated BP and lipids, is recommended.

Most patients with type 2 diabetes will eventually require combination therapy with 2 or more agents to attain and maintain glycemic control.^{2,3} In particular, combinations of agents with complementary mechanisms of action (eg, an insulin sensitizer with a secretagogue) demonstrate greater improvements in glycemic control. Based on the progressive nature of diabetes, a principle in the pharmacotherapy of glucose control is that, in absence of untoward effects, if a given agent is secondarily unable to provide adequate glycemic control (ie, there was initial improvement in glucose control and then subsequent deterioration), additional agents—whether oral agents or insulin—should be added rather than substituted.

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