



# Diabetes Dispatch

## What to add next?

Most would agree and consensus statements support that initial therapy for patients with type 2 diabetes is lifestyle intervention and metformin, for those who are candidates for metformin therapy. But what should be added when goals are not met with metformin and lifestyle interventions?

Recommending specific antihyperglycemic agents should be based on their effectiveness in lowering glucose, other effects that may reduce long-term complications, safety profiles, tolerability, and expense. The glucose lowering effect of individual medications and combinations demonstrated in clinical trials is predicated not only on the mechanism of action of the medication, but also on the patients' baseline blood glucose, duration of diabetes, and previous therapies utilized. Table 1 (see page 3) summarizes the characteristics of currently available monotherapy treatments for diabetes. A major factor in selecting a class of drugs or specific medication is the patients' current level of glycemic control. When blood glucose is high (for example A1C > 8.5%), classes with greater and more rapid glucose lowering effectiveness, or earlier initiation of combination therapy are recommended. Conversely, when blood

glucose is closer to goal, A1C < 7.5%, medications with lesser potential to lower glucose or a slower onset of action may be considered.

What to add next is not a question of if you have to add an additional agent, but when. Type 2 diabetes is a progressive disease with worsening glucose control over time. Therefore, addition of medications is the rule not the exception, if treatment goals are to be met over time. Therapies to consider initially after metformin include sulfonylureas, insulin, and TZDs. Further medication considerations include meglitinides, alpha-glucosidase inhibitors, exenatide, DPP-4 inhibitors, and pramlintide.

**Sulfonylureas.** Sulfonylureas increase insulin release from the pancreas, thereby lowering blood glucose. Examples of sulfonylurease include glyburide, glipizide, and glimeperide. The A1C lowering effect of sulfonylureas is similar to metformin, lowering A1C by about 1.5 percentage points. Sulfonylureas are a reasonable and the least expensive choice to add to metformin. Disadvantages to consider with a sulfonylurea include hypoglycemia and weight gain. Weight gain of about 2 kilograms is common with the initiation of sulfonylurea therapy.

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### Goal.

- *The goal of the Diabetes Dispatch is to increase the reader's knowledge of diabetes treatments and technologies and to provide the most current information on new drugs, therapies, and devices.*
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## What to add next?, continued.

(continued on page 3)

**Insulin.** Insulin is the oldest medication for the treatment of diabetes and has the most clinical experience. It is the most effective of the diabetes medications at lowering blood glucose, there is no maximum dose of insulin. Insulin therapy has beneficial effects on triglyceride and HDL cholesterol levels. Disadvantages to consider include weight gain of about 2-4 kg. This is most likely proportional to the correction of blood glucose and owing predominantly to the reduction of glucose in the urine. This is a reasonable choice to add to metformin therapy particularly if the A1C is >8.5%, or the patient is having symptoms of high blood glucose.

**Thiazolidinediones (TZDs).** TZDs are PPAR-gamma modulators, which essentially increases the sensitivity of muscle, fat, and liver cells to the body's insulin. Examples of TZDs include rosiglitazone and pioglitazone. TZDs, when used as monotherapy, have demonstrated a 0.5-1.4% decrease in A1C. TZDs may be a reasonable choice to add to metformin. TZD combined with metformin have an extremely low risk of hypoglycemia. Disadvantages to consider with TZDs include weight gain and fluid retention. Fluid retention generally occurs as peripheral edema, but new or worsening heart failure can occur.

**Alpha-Glucosidase inhibitors.** Alpha-glucosidase inhibitors reduce the rate of carbohydrate absorption in the small intestine, primarily lowering post-prandial blood glucose levels without causing hypoglycemia. They are less effective at lowering blood glucose when compared to metformin or sulfonylureas, reducing A1C by 0.5-0.8 per-

centage points. Disadvantages to consider with alpha-glucosidase inhibitors include gastrointestinal side effects. In clinical trials 25-45% of participants discontinued the medication due to gastrointestinal side effects.

**Meglitinides.** Like the sulfonylureas, meglitinides increase insulin release from the pancreas, but bind to a different site within the sulfonylurea receptor. This results in a shorter half-life than the sulfonylureas and an increased frequency of dosing. Examples of meglitinides include repaglinide and nateglinide. Me-

glitinides lower A1C by 1-1.5 percentage points. Disadvantages to consider with meglitinides include weight gain, hypoglycemia can still occur, but is less frequent than with sulfonylureas. Meglitinides require multiple daily doses and have increased cost compared to sulfonylureas.

**Glucagon-like peptide 1 agonists (exenatide).** Glucagon-like peptide 1 agonists (GLP-1) mimic a naturally occurring peptide that stimulates insulin secretion. GLP-1 agonist not only increases insulin secretion in response to glucose, but also decreases glucagon release and slows gastric motility. There is currently one GLP-1 agonist available on the market, exenatide. There are far fewer published data on exenatide than other blood glucose-lowering medications, but it does appear to lower A1C by 0.5-2 percentage points, mainly by lowering postprandial blood glucose levels. In published trials, exenatide is as-

sociated with about a 2 to 3 kg weight loss over 6 months. Disadvantages to consider with exenatide include its subcutaneous administration gastrointestinal side effects. In clinical trials 30-45% of participants experienced one or more episodes of nausea, vomiting, or diarrhea.

**DPP-4 inhibitors.** DPP-4 inhibitors block the breakdown of the body's GLP-1, thereby increasing the circulating GLP-1. GLP-1 increases insulin secretion in response to glucose, decreases glucagon release which in turn decreases the glucose secreted by the liver, and slows gastric motility. The one DPP-4

*"There is no strong consensus regarding the second medication to add after metformin other than to choose among insulin, sulfonylurea, or a TZD"*

inhibitor on the market is sitagliptin. Like exenatide, there are far fewer published studies on sitagliptin than other blood glucose-lowering medications. Sitagliptin when used as monotherapy has demonstrated a 0.5-1.1% decrease in A1C and is weight neutral.

**Amylin agonist (pramlintide).** Pramlintide is a synthetic analog of the beta cell hormone amylin. It is only approved to be used with insulin. Pramlintide is administered subcutaneously before each meal. Pramlintide, like amylin, slows gastric emptying, inhibits glucagon production and decreases postprandial glucose levels. Pramlintide has demonstrated an A1C reduction of 0.5-0.7 percentage points. Disadvantages to consider include gastrointestinal side effects. In clinical trials 30% of participants have developed nausea. Weight loss associated with this medication is 1-1.5 kg over 6 months.

Table 1. Summary of treatments of diabetes

Intervention	Expected decrease in A1C (%)	Advantages	Disadvantages
<b>Step 1:</b> Lifestyle changes and metformin			
Decrease weight and increase activity	1-2	Low cost, many benefits	Fails for most in 1 year
Metformin	1.5	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
<b>Step 2:</b> Additional Therapy			
Sulfonylureas	1.5	Inexpensive	Weight gain, hypoglycemia
Insulin	>2.5	No dose limit, inexpensive, improved lipid profile	Injections, monitoring, hypoglycemia, weight gain
TZDs	0.5-1.4	Improved lipid profile	Fluid retention, weight gain, expensive
Alpha-glucosidase inhibitors	0.5-0.8	Weight neutral	Frequent GI side effects, three times a day dosing, expensive
Exenatide	0.5-2.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Meglitinides	1-1.5	Short duration	Three times a day dosing, expensive
DPP-4 inhibitors	0.5-1.1	Weight neutral	Expensive, little experience
Pramlintide	0.5-1.0	Weight loss	Injections, three times a day, frequent GI side effects, expensive, little experience

**Summary.** If lifestyle, metformin, and a second medication do not result in goal blood glucose, the next step should be to start or intensify insulin. When the A1C is close to goal, <8%, addition of a third oral agent could be considered. However, this approach is relatively

more costly and potentially not as effective in lowering blood glucose when compared to insulin therapy. Guidelines and treatment algorithm emphasize-achievement and maintenance of normal blood glucose, initial therapy with lifestyle intervention and metformin, rapid addition

of medications when target blood glucose is not achieved, and early addition of insulin therapy in patients who do not achieve target blood glucose.

Sources:  
 DIABETES CARE 2006, 29(8): 1963-1972.  
 Januvia Package Insert  
 PHARMACOTHERAPY 2008, 28(4): 506-521.

# Number of People with Diabetes Increases to 24 Million

A press release from the Centers for Disease Control and Prevention (CDC) in June of this year states diabetes now affects nearly 24 million people in the United States, an increase of more than 3 million in approximately two years, according to new 2007 prevalence data estimates. **This means that nearly 8 percent of the U.S. population has diabetes.**

In addition to the 24 million with diabetes, another 57 million people are estimated to have pre-diabetes. Among people with diabetes, those who do not know they have the disease decreased from 30 percent to 25 percent over a two-year period.

“These new estimates have both good news and bad news,” said Dr. Ann Albright, director of the CDC Division of Diabetes Translation. “It is concerning to know that we have more people developing diabetes, and these data are a reminder of the importance of increasing awareness of this condition, especially among people who are at high risk. On the other hand, it is good to see that more people are aware that they have diabetes. That is an indication that our efforts to increase awareness are working, and more importantly, that more people are better prepared to manage this disease and its complications.” Diabetes is the seventh leading cause of death in the country and can cause serious health complications including heart disease, blindness, kidney failure, and lower-extremity amputations.

Among adults, diabetes increased in both men and women and in all age groups, but still disproportionately affects the elderly. Almost 25 percent of the population 60 years and older had diabetes in 2007. And, as in previous years, disparities exist among ethnic groups and minority populations including Native Americans, African Americans and Hispanics. After adjusting for population age differences between the groups, the rate of diagnosed diabetes was highest among Native Americans and Alaska Natives (16.5 percent). This was followed by blacks (11.8 percent) and Hispanics (10.4 percent), which includes rates for Puerto Ricans (12.6 percent), Mexican Americans (11.9 percent), and Cubans (8.2 percent). By comparison, the rate for Asian Americans was 7.5 percent with whites at 6.6 percent.

The data are an update of diabetes prevalence estimates last reported two years ago and now published in the 2007 National Diabetes Fact Sheet developed by CDC in collaboration with multiple agencies under the U.S. Department of Health and Human Services and other federal agencies.

CDC, through its Division of Diabetes Translation, funds diabetes prevention and control programs in all 50 states, as well as the District of Columbia and eight U.S. territories and island jurisdictions. The National Diabetes Education Program, co-sponsored by CDC and the National Institutes of Health (NIH), provides diabetes education to improve the treatment and outcomes for people with diabetes, promote early diagnosis, and prevent or delay the onset of diabetes.

For more information on diabetes, please visit <http://www.cdc.gov/diabetes/>.

## Objectives.

1. *Become familiar with agents added to lifestyle and metformin for the treatment of type 2 diabetes.*
2. *Recognize the A1C lowering ability of common therapies for the treatment of type 2 diabetes.*
3. *Review 2007 prevalence data estimates for diabetes.*



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## Continuing Education Quiz

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1. What is the recommended initial therapy for most patients with type 2 diabetes?
  - a. Insulin
  - b. Lifestyle intervention and metformin
  - c. Pioglitazone
  - d. Exenatide
  
2. Therapies to consider initially after metformin include?
  - a. Sulfonylureas
  - b. Insulin
  - c. TZDs
  - d. All of the above
  
3. Expected decrease in A1C % by metformin?
  - a. >2.5%
  - b. 1.5%
  - c. 0.5%
  - d. 0.8%
  
4. Expected decrease in A1C % by insulin?
  - a. >2.5%
  - b. 1.5%
  - c. 0.5%
  - d. 0.8%
  
5. Which medications for the treatment of diabetes work with the GLP-1 system?
  - a. TZDs
  - b. Exenatide
  - c. Sitagliptin
  - d. Both B and C

6. One disadvantage of lifestyle interventions?
  - a. Fails for most in 1 year
  - b. Weight gain
  - c. Low cost
  - d. Hypoglycemia

7. According to the Center for Disease Control and Prevention how many people in the United States are now affected by diabetes?

- a. 21 Million
- b. 2 Million
- c. 24 Million

8. According to the Center for Disease Control and Prevention what is the rate of diagnosed diabetes for Native Americans and Alaska Natives

- a. 6.6%
- b. 16.5%
- c. 11.8%
- d. 12.6%



### LESSON EVALUATIONS

To obtain C.E. credit for this lesson you must answer the questions on the quiz (70% correct required) and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. In May and November of each year we will mail a statement of credit, unless otherwise arranged with the AkPhA office.

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