

## Type II diabetes: How to use the new oral medications

A TWO-PART INTERVIEW WITH NANCY J.V. BOHANNON, MD, BY DAVID B. JACK, MD



Several new oral drugs have been approved for the management of type II diabetes. Metformin is an "antihyperglycemic agent" that decreases hepatic glucose production and improves insulin sensitivity. It may be used as monotherapy or in combination with a sulfonylurea. Acarbose slows carbohydrate absorption after a meal, giving endogenous or injected insulin more time to respond to ingested glucose. Glimepiride is an insulin-sparing sulfonylurea with a once-daily dosing schedule. How might these medications fit into the primary care of older diabetics? To find out, GERIATRICS reader David B. Jack, MD, interviewed Nancy Bohannon, MD, for this "Ask the Expert" article.

Bohannon, NJV, Jack DB. Type II diabetes: Tips for managing your older patients. *Geriatrics* 1996;51(April):33-37.

Caring for our aging diabetic patients is a constant juggling act, deciding which improvements in diabetic control justify the risk of potential side effects. For the first time in 20 years, several new oral drugs are available for the management of type II diabetes:

- Metformin HCl (Glucophage) and acarbose (Precose) are chemically unrelated to insulin or the sulfonylureas.
- Glimepiride (Amaryl) is an insulin-sparing sulfonylurea with a once-daily dosing schedule.

To find out how these new medications might fit into the primary care practice, I interviewed diabetes and lipids expert Nancy Bohannon, MD. Last month, in part 1 of this interview, we covered tips for managing your older diabetic patients. (1) This month, we discuss how to use these new oral medications as part of your comprehensive approach to the treatment of type II diabetes (see algorithm, page [5]).

**Q.** *I've been switching my obese type II patients from sulfonylureas to metformin, even if they have good hemoglobin (Hgb) A1c levels, because I want to diminish their risk of atherosclerosis and stroke. Should I be doing this?*

Metformin is an "antihyperglycemic agent" that decreases hepatic glucose production and improves insulin sensitivity. It tends to decrease total cholesterol, LDL, and triglycerides, and does not produce hypoglycemia or hyperinsulinemia when given alone. The drug may be used as monotherapy or in combination with a sulfonylurea for a synergistic effect.

For obese type II diabetics, I would consider adding metformin to improve dyslipidemia if they have a lipid problem. And if they are diabetic, they probably do have a lipid problem. Their dyslipidemia may not be high LDL; it is more likely low HDL and/or high triglycerides. If they have any dyslipidemia, I would try to add on the metformin and then titrate down, but I probably would not stop the sulfonylurea.

**Q.** *Would you continue the sulfonylurea even if they were on just a low-dose, such as 5 mg of glipizide?*

The problem becomes compliance and multiplicity of medications. If the patient is well-controlled on one pill a day of glipizide (Glucotrol), I am going to have a hard time telling them to take metformin two or three times a day, especially if they are taking a lot of other drugs.

If their LDLs are bad but their blood sugar is well-controlled, then address their lipids. I would rather add one HMG-CoA reductase

inhibitor dose per day than add on two metformin doses. If they are really well-controlled on the sulfonylurea, I would probably leave well enough alone regarding the diabetes therapy.

A lot of my older diabetics like metformin. Its main side effect in younger patients is diarrhea, but it tends to normalize the stool for the older patient with chronic constipation.

**Q.** *Do you try to keep the Hgb A1c less than 1% above normal?*

That's what I would like it to be. I would allow it to be 2% above normal if I feel that insulin is the next step for a particular patient, or if I am worried about something else. Say their creatinine is 1.7 mg/dL, so I can't use metformin, which is contraindicated in patients with renal insufficiency, and they are already on sulfonylureas and acarbose.

**Q.** *Have you had much success in getting older diabetics off insulin by switching them to metformin?*

I wouldn't be opposed to trying it, but I have had more success with my recently-diagnosed, overweight, middle-aged patients. My older patients often have had diabetes a long time, and they usually are not obese anymore. They need insulin, because they have "pancreatic poop-out." Their pancreas has been struggling all these years to put out maximum amounts of insulin and just can't do it any more.

**Q.** *From a scientific perspective, would you then prefer to have those elderly patients on insulin versus sulfonylureas?*

No, not if I could get equally good control with either one. If patients are responding well to the sulfonylureas, obviously they do have enough insulin secretory capacity.

**Q.** *When you are combining insulin plus an oral agent, does it make more sense to use metformin for some type II diabetics?*

Yes, for type II diabetics who are obese and insulin-resistant. But I probably would have tried a sulfonylurea (and metformin, since it has been available) before using insulin.

If I start an obese, insulin-resistant patient on metformin and it's not working, then I will try adding a sulfonylurea. If the patient is one of the 20% in whom a sulfonylurea doesn't do anything, I would stop the sulfonylurea, keep the metformin going if it's having some effect in lowering blood sugar, and add insulin if cost is not a consideration and side effects are minimal.

Once you are giving any insulin, it is cheaper to give more insulin to attempt to overcome the insulin resistance than to add any oral agent. But metformin may help to decrease the insulin resistance and allow similar control with less insulin or fewer injections.

**Q.** *I understand that the new agent acarbose lowers blood sugar by smoothing out carbohydrate absorption.*

Yes; a nickname for acarbose is a "starch blocker." Normally, all the carbohydrate in a meal may be digested and absorbed in about 1 hour, leading to a high postprandial peak blood sugar. With acarbose, the carbohydrate digestion--and therefore absorption--is slowed to take place over 3 hours, and so blood sugar tends to go up more gradually. This gives endogenous or injected insulin more time to put glucose into the muscle where it belongs, so the postprandial blood sugar level doesn't go so high. That's why acarbose will decrease Hgb A1c values by 0.5 to 1%.

**Q.** *Isn't that what fiber would do?*

Acarbose is a lot easier to take than the 25 grams or more of soluble fiber you would need daily for a similar effect. Most people don't tolerate that much fiber terribly well.

**Q.** *How is acarbose to be taken, and how do you adjust the dose?*

The patient takes acarbose with the first bite of food at each meal. And even though the before-

meal blood sugars might not change, the Hgb Alc improves because you've eliminated a lot of hyperglycemia between meals.

Start with a very low dose (25 mg tid with the first bite of each meal), and increase monthly by 25 to 50 mg at each dose, as tolerated, until adequate postprandial glucose response or the maximum dose of 100 mg tid has been reached (whichever of these comes first).

It takes quite a while for the small intestine to adapt to this therapy. If you rush the titration, the potential for GI side effects increases. The therapeutic effectiveness of acarbose is due to its local GI effect, not to a systemic effect (only about 2% is absorbed).

**Q.** *Is there any risk of hypoglycemia associated with acarbose?*

Not from the acarbose. However, when acarbose is added to sulfonylurea therapy, the sulfonylurea can cause hypoglycemia.

It is extremely important to counsel the patient that if hypoglycemia does occur, he or she must use glucose (dextrose) tablets or gel to treat the low blood sugar. The usual "simple sugars" (such as orange juice, Life Savers, or regular Coke) must be digested before they are absorbed and will not raise the blood sugar rapidly in the presence of acarbose. Acarbose does not interfere with lactase, so milk could be used to treat low blood sugar if the patient is not lactose intolerant.

Because carbohydrate is absorbed over such a long time with acarbose, there is less likelihood of hypoglycemia before the next meal in insulin-treated patients. Regular insulin has a much longer duration of action than might be considered ideal and is often still driving the blood sugar down 3 or 4 hours after a meal. This can contribute to low blood sugar before the next meal. Acarbose makes that meal last longer, so it acts as a buffer for hypoglycemia.

**Q.** *Does acarbose suppress the patient's appetite?*

Acarbose is not an appetite suppressant. Most overweight Americans are overweight not because of hunger but because of overeating and under-exercising due to our culture and sedentary lifestyle.

**Q.** *The third new antidiabetic agent that has been approved is glimepiride. What makes it different from other sulfonylureas?*

Glimepiride (Amaryl) is a third-generation oral sulfonylurea that can be used either as monotherapy or in combination with insulin. Glimepiride seems to directly stimulate glucose use in peripheral tissues independent of its insulin stimulation activity. This results in lower insulin levels with treatment with glimepiride as compared with glipizide or glyburide, the second-generation sulfonylureas.

Glimepiride has a once-daily dosing schedule and has been found to be effective in doses between 1 and 4 mg/day. Occasional patients (with Hgb A1c greater than 8% at baseline) require a dose of 8 mg/day.

**Q.** *My older patients are often taking several different medications. Are there potential drug interactions that I should be aware of when using glimepiride?*

More than 4,200 patients have received glimepiride in clinical trials around the world, including 1,500 who received at least 1 year of exposure. The safety profile of glimepiride was as good as or better than that of glipizide and glyburide. No clinically meaningful drug interactions with glimepiride were detected in the phase II/III trials.

**Q.** *What is the risk of hypoglycemia with glimepiride?*

In controlled clinical trials, glimepiride appeared to cause slightly less hypoglycemia and reduced hyperinsulinemia, due to its extra-pancreatic effects.

## REFERENCE

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## SUGGESTED READING

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# ALGORITHM

## Suggested algorithm for treatment of type II diabetes

