

DR. BERNSTEIN'S

DIABETES SOLUTION

A COMPLETE GUIDE TO ACHIEVING NORMAL BLOOD SUGARS

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Chapter 14: Oral Hypoglycemic Agents

If diet and exercise are not adequate to bring your blood sugar readings under control, the next level of treatment to consider is blood sugar-lowering pills, known as oral hypoglycemic agents (OHAs). For people who still have sufficient insulin-producing capacity, OHAs alone may provide the extra help they need to reach their blood sugar target. Some insulin-resistant individuals who produce little or no insulin on their own may find two particular OHAs useful in reducing their doses of injected insulin.

Although there are several OHAs currently on the market, at this writing I routinely prescribe only one of them. By the time you read this, however, a new agent, troglitazone, will be available.* I expect to prescribe it at least as much as I do.

Metformin and Troglitazone—The OHAs of Choice

The great advantage of metformin and troglitazone over all other OHAs is that they help to reduce blood sugar by making the body's tissues more sensitive to insulin, whether it's the body's own or injected. This is a benefit that can't be underestimated. Not only is it a boon to those trying to get their blood sugars under control, but it's also quite useful to those who are obese and simultaneously trying to get their weight under control. By helping to reduce the amount of insulin in the bloodstream at any given time, these two drugs can help in controlling the powerful fat-building properties of insulin. I have many patients who are not diabetic but have come to me for treatment of their obesity. Metformin has been a real plus to the weight-loss efforts of some because of its ability to curtail insulin resistance. I expect the same benefits from troglitazone. Some obese diabetic patients come to me who are injecting very large doses of insulin because their obesity makes them highly insulin-resistant. These high doses of insulin cause a lot of fat-building to take place, and weight loss becomes proportionately more difficult. Metformin and troglitazone make these patients more sensitive to the insulin they're injecting. In one case I had a patient taking 27 units of insulin at bedtime, even though he was on our low-carbohydrate diet. After he started on metformin, he was able to cut the dose to about 20 units. This is still a very high dose, but the metformin facilitated the reduction.

Both OHAs have also been shown to improve a number of measurable cardiac risk factors, including lipid profile, serum fibrinogen, blood pressure, and even abnormal thickening of the heart muscle itself. In addition, metformin has been found to inhibit the destructive binding of glucose to proteins throughout the body—independent of its effect upon blood sugar.

Most of the other OHA drugs on the market, the old sulfonylureas, only work if you are still producing some insulin on your own. They operate by stimulating the pancreas to produce more insulin, which can directly cause your remaining pancreatic beta cells to break down over a period of years. The higher their doses, the more likely will be beta cell burnout. They do not decrease the body's requirements for—or increase its sensitivity to—insulin. They also stimulate insulin production whether the body needs it or not, so there's the constant risk of hypoglycemia. Therefore, the only case in which I still prescribe a sulfonylurea is if a patient's blood sugars cannot be controlled by diet alone and for some reason he's likely to live less than five years—and he is terrified of insulin injections. Otherwise, the harm that sulfonylureas can do simply outweighs any benefit. There's a new sulfonylurea OHA being marketed in the United States which the manufacturer and several published studies claim lowers insulin resistance and serum insulin levels. This product, glimepiride (Amaryl, Parke-Davis), also stimulates beta cells to produce insulin. It is therefore the only sulfonylurea I will prescribe for special situations. At present, I only have one patient who is a "special situation." Thus far, when given the choice, all my other patients have chosen insulin or insulin in combination with metformin.

Who is a Likely Candidate for Metformin or Troglitazone?

Generally speaking, these OHAs are natural choices for a Type II diabetic who despite a low-carbohydrate diet cannot get his weight down or his blood sugars into normal ranges. The blood sugar elevation may be limited to a particular time of the day, it may be during the night, or it may entail a slight elevation all day. We base our prescription on the individual's blood sugar profiles. If even on our diet, blood sugar exceeds 300 mg/dl at any time of the day, I'll immediately prescribe insulin and won't even attempt to use these agents, except to eventually reduce doses of injected insulin. If your blood sugar is higher upon arising than at bedtime, we'd give you metformin or troglitazone at bedtime. If your blood sugar goes up after a particular meal, we'd give you the OHA about 2 hours before that meal. Since food enhances the absorption of troglitazone, we might give this drug with the meal.

Getting Started: some typical OHA Protocols

Let's say you're a Type II diabetic and through weight loss, exercise, and diet, you pretty much have your blood sugars within your target range. Still, your blood sugar profiles show a regular elevation in the mornings after a low-carbohydrate breakfast, probably due to the dawn phenomenon.

In order to get your blood sugars into normal ranges, we'd start you out on a progressive dose. Overall, metformin has a very low side-effects profile, with the exception of gastrointestinal distress—queasiness, nausea, diarrhea, or a slight bellyache—in as many as a third of the people who try it. Most people who experience such distress, however, find that their discomfort diminishes as they become accustomed to the medication. Only a very few patients can't tolerate

it at all. (Some patients, particularly obese patients who are anxious to achieve weight loss that metformin can facilitate, will ignore any initial gastrointestinal distress and use an antacid drug such as Pepcid or Tagamet for relief. Others, who may only experience relatively mild discomfort, are willing to tolerate it for a few weeks just to get things rolling.) Gastrointestinal side effects have not been reported for troglitazone.

In any case, metformin takes about 2 hours to start working. Although the literature says that it peaks 2 hours after that, we find that it literally lasts all night if you take it at bedtime. It comes in two dosage strengths—500 mg and 850 mg unscored tablets. It's my practice always to start patients on the lowest possible dose—so in the above case we'd set you up with a pill cutter and have you take half a 500 mg tablet immediately after breakfast. Studies show that troglitazone starts working after 30 minutes, peaks in about 2–3 hours, and stops working after about 48 hours. Because it remains in the blood for so long, after dosing for a few days it will reduce insulin resistance all day long. It is supplied as 200 mg and 400 mg unscored, coated tablets that probably should not be broken with a pill cutter. The maximum recommended dose is 600 mg per day.

Note that even though it takes 2 hours for metformin to begin working, and your blood sugar elevation is after breakfast, we'd still start you off by having you take the medication immediately after breakfast. We do this in order to reduce the likelihood of gastrointestinal discomfort. Many people don't have any discomfort when they take metformin on a full stomach. Troglitazone, on the other hand, can be taken before meals from the start, without distress, but it may not be fully absorbed without food.

We'd then have you check your blood sugars before lunch. If your blood sugar was lower but still elevated, after a few days, we'd gradually increase the dosage by half a pill (if metformin) until we got your prelunch blood sugars into your target range. To do this, we could go as high as five 500 mg metformin tablets. (Metformin ceases having any cumulative effect after 2,500 mg.) If you were to experience gastrointestinal discomfort at any dose, we'd revert back to the prior dose for three or four weeks and then increase it more slowly.

Once we determined what dose of metformin got your blood sugar normalized, we'd start to shift the dose to before breakfast—immediately upon arising. In shifting doses, we'd again work in small increments. Let's say we had found that it took three 500 mg tablets to get your blood sugars to within your target range. You'd shift the dose by starting to take half a tablet immediately upon arising, and the other 2H tablets immediately after eating. After a week, provided you didn't experience any intestinal distress, we'd shift another half a pill to immediately upon arising, and so on until you were taking all 3 when you got up.

If, after moving a portion of your dose—say, 1 1/2 tablets—you started experiencing gastrointestinal distress, we'd shift half a tablet back to after breakfast. Some people can take several weeks to acclimate to metformin, so we'd let the regimen stand for a few days before we'd try moving it again. We've done this with numerous patients, and it works for most (though not all) without any undue discomfort. This cautious tapering up of dose is not necessary for troglitazone, which is unlikely to cause gastrointestinal side effects.

This is how we'd get your postbreakfast blood sugar elevation under control. Let's look at some other instances where these drugs can be useful.

Let's say you wake up in the morning with a higher blood sugar than when you went to sleep—not an especially elevated blood sugar, just higher than when you went to bed. This would tell me that you need some kind of help overnight. I have many patients whose blood sugars don't go up after meals but do go up overnight. The cause of the rise in blood sugars may be slow digestion of dinner while you're asleep, or may be due to the dawn phenomenon. Whatever the case, you'd still need something to help. Here we'd have you take metformin or troglitazone at bedtime. I'd prefer the troglitazone because it appears to be longer-acting. Again, it takes 2 hours for metformin to start working, 30 minutes for troglitazone, but both drugs appear to work for most of the night.

There's a good chance that your stomach will be empty at bedtime, so you stand a higher risk of developing gastrointestinal distress from metformin. As before, we'd start you with a low dose and bring it up slowly if you showed gastrointestinal distress, or rapidly if you didn't. Over time, as we discovered the proper dose, your blood sugar profiles would, we hope, show that your fasting blood sugar in the morning was the same as at bedtime because of the metformin or troglitazone.

Another instance when we'd start you on these drugs would be if you showed an elevated blood sugar at bedtime. This would reflect the effects of dinner, and to get that under control, we'd want you on one of them before dinner. Again, with metformin, we'd start you out on the smallest possible dose immediately after dinner and eventually shift the dose to precede the meal. If you were also showing overnight blood sugar rises, we'd first work on the dinner dose. Of course, the same protocol can be applied to lunch if blood sugars are routinely elevated before dinner. Many of my patients take metformin before each meal and at bedtime.

Certainly if metformin were to cause gastrointestinal distress, we now have the option of switching to troglitazone. It is very possible that for some individuals we'd use both medications—perhaps metformin before meals and troglitazone at bedtime, or vice versa.

Will These Medications Cause Hypoglycemia?

Some OHAs—specifically the sulfonylureas—carry the very real possibility of causing dangerously low blood sugars, but this is only remotely likely with troglitazone or metformin. This is because their mode of action is to increase your sensitivity to insulin. Neither agent interferes with the self-regulating system of a pancreas that can still make its own insulin. If your blood sugar drops too low, your body will just stop making insulin automatically. Sulfonylureas, on the other hand, because they stimulate insulin production whether the body needs it or not, can cause hypoglycemia.

Although the manufacturer and the scientific literature claim that metformin does not cause hypoglycemia, I did have a single patient who experienced hypoglycemia. She was very obese but only very mildly diabetic, and I was giving her metformin to reduce insulin resistance and facilitate weight loss. When I put her on metformin, her blood sugars went too low—down into

the 60s. While it's possible for any drug to have nearly any effect on a given individual, this was the only case I've seen of hypoglycemia with metformin, and I was using it in a patient who was only mildly diabetic. Her insulin resistance was causing her to make a lot of insulin, but why the metformin brought her down so low I can't explain.

So there may be some very slight risk of hypoglycemia with troglitazone or metformin, but this is not at all comparable to the great risk with the sulfonylureas. One warning, however. The body cannot turn off injected insulin, so if you are taking insulin plus either of these agents, hypoglycemia is possible.

What If These Agents Don't Bring Blood Sugars into Line?

If neither of these drugs is adequate to normalize blood sugars completely, chances are there is something awry in the diet or exercise portion of your treatment program. The most likely culprit for continued elevated blood sugars is that the carbohydrate portion of your diet is somehow not properly controlled. So the first step is to examine your diet again to see if that's where the problem lies. With many patients, this is a matter of carbohydrate craving, patients eating restricted foods. If this is the case, if your carbohydrate craving is so overwhelming, I'd recommend that you look at appetite-suppressing medication as a way of getting uncontrollable craving into line. If diet is not the culprit, then the next thing—no matter how obese or resistant to exercise you might be—would be to try to get you started on a strenuous exercise program. If even this doesn't do the trick, we'll certainly use injected insulin. Another far-out possibility (I say far-out because I haven't tried it yet) would be to use both metformin and troglitazone together.