

Diabetes management in cancer patients

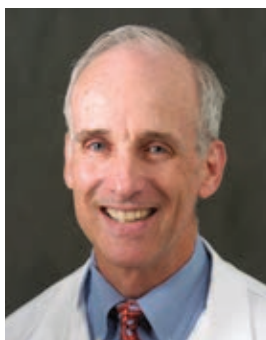
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DR HENRY (DH)

My name is Dr David Henry, I am vice-chair of the Department of Medicine and Clinical Professor of Medicine at Pennsylvania Hospital, in Philadelphia. I will be speaking with Dr Todd Brown, Associate Professor of Medicine and Epidemiology in the Division of Endocrinology, Diabetes, and Metabolism at the Johns Hopkins University in Baltimore, Maryland. Todd, I would like you to review the several different classes of the hyperglycemic management drugs—besides insulin—maybe touch on how they work, and then I'll have you put it together as I ask you about a couple of patient scenarios.



DR BROWN (TB)

Sure. The management of diabetes has changed and become more complicated as new drugs have come on the scene. I'll go through class by class and talk about pros and cons as well as some of the cost issues, which are also important. Besides metformin, which is a drug that's been around for a while and that's pretty much universally loved (with the exception of those people who developed gastrointestinal [GI] side effects), there are a bunch of others.



I'll begin with sulfonylureas. These drugs have [also] been around for a long time. They still have an

important place in our armamentarium. They cause insulin release from the pancreas, no matter what the blood sugar is. That leads to their biggest problem, which is hypoglycemia. On the benefit side, they are very inexpensive and have a long track record. There's also some lingering concern about their cardiovascular risk, long-term. Certainly, compared to metformin, they probably have an increased cardiovascular risk, but it's unclear whether or not that's because metformin-exposed people have lower cardiovascular risk, or it's an additional effect of a sulfonylurea. They still are quite an important part of the armamentarium.

DH Was there any renal or liver function abnormality with sulfonylureas?

TB Yes. People who have liver and renal disease are more prone to get hypoglycemia, and are less likely to be able to defend against hypoglycemia. I'm always a little bit concerned about using a sulfonylurea in patients with later stage renal or liver disease. For more mild impairments these drugs can be used with caution.

Regarding the next class of medications—about which there's been a lot of controversy—are the thiazolidinedione (TZD) class. These are peroxisome proliferator-activated receptor gamma (PPAR- γ) agonists. There have been three drugs in this class. The first was troglitazone, which was taken off the market because of hepatic toxicity. That left two glitazones standing—rosiglitazone and pioglitazone.

Now, rosiglitazone, in a meta-analysis from 2007,¹ was found to be associated with increased cardiovascular events. That led to its near-removal from the market. Since that time, the meta-analysis has been redone.² The drug has been sort of exonerated, but there are some lingering concerns that exist.

The drug in this class that people use is piogli-

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tazone. It is a good drug, but not without its problems. It has a good A1C-lowering effect. It has some interesting off-target effects. It can decrease inflammation, independent of its glucose control. It probably has an independent effect on liver fat, which is interesting for our nonalcoholic fatty liver disease patients. It may have an independent effect on cardiovascular disease and atherosclerosis progression. There was a recent study in the *New England Journal of Medicine* that emphasized that fact, looking at patients who have had a stroke and have insulin resistance.³ Pioglitazone-treated patients versus placebo had a lower risk of a recurrent event—either stroke or myocardial infarction.

The downsides to pioglitazone are the costs. It's still not generic, and the costs are relatively high. It's associated with some weight gain, some of which is related to fat, and some of which is related to fluid. This drug causes adipocyte differentiation and proliferation, so you get an expansion of the subcutaneous fat. It also causes fluid retention. The big problem related to this is congestive heart failure—not only in patients with systolic dysfunction, but also in patients with diastolic dysfunction.

A couple of other problems have relatively recently been uncovered—one is the risk of fracture. Pioglitazone is associated with about a two-fold increased risk in fracture. That's thought to be due to the fact that this drug works on PPAR- γ , as I mentioned, which is an important switch in differentiating mesenchymal stem cells into either an osteoblast or adipocyte pathway. You get increased adipocytes, but fewer osteoblasts. That is thought to be one of the major mechanisms underlying this fracture risk.

DH Very interesting. I have an interest in the research into bone metabolism. Before I forget, [in regard to] pioglitazone's mechanism of action, is insulin sensitivity increased? **[Clarify?]**

TB Yes. This drug is thought to mainly work at the level of the adipocyte. It acts on PPAR- γ , which is a transcription factor that's expressed in many tissues. This drug decreases free fatty acids. Free fatty acids are thought to be a major mediator between the adipose tissue and insulin-sensitive organs—say, skeletal muscle, the beta cell, the liver and obviously the fat itself. Increased free fatty acids lead to skeletal muscle insulin resistance, hepatic insulin resistance, decreased beta cell function, and all those things are problems in type 2 diabetes.

Now, the other issue with glitazones—and probably pioglitazone in particular—is the risk of bladder cancer. This has been seen in a bunch of different studies, and hasn't been seen in others, so there's a lot of controversy now.⁴⁻⁷ In patients who do have bladder cancer, who have a family history of bladder cancer, pioglitazone is not recommended. The mechanism there is unclear.

The other thing that's sort of interesting with pioglitazone is that, of the agents that we have to treat diabetes—or the agents that we have to prevent the progression from prediabetes to diabetes—glitazones are probably the best and the most durable agents. If you look to see who needs an additional agent after being randomized to either a glitazone, sulfonylurea, or metformin, the glitazone is the big winner.⁸ The issues are, of course, the risks and the cost, which may not be worth the benefit if you're talking about prediabetes and preventing people from going on to diabetes, so it is not a recommended agent for that at this point.

Now we get to other drugs that came out in the last 10 years. The first two classes sort of work at different ends of the same pathway, called the incretin pathway. About 30 years ago, the hormone GLP-1 was discovered. It's been long known that the insulin spike that you get after an oral glucose load is much higher than that which you get from an intravenous glucose load.

The question was, what is going on in the gut to tell the pancreas to secrete more insulin? It was hypothesized that there were these incretin hormones that were released and caused augmentation of insulin release with an oral glucose load.

Lo and behold, there are a several incretins, and two that are probably most important. One is called GLP-1, and the other is GIP. Neuroendocrine cells in mostly the large bowel produce GLP-1. They're called L cells. The endogenous GLP-1 has a bunch of different functions. It causes insulin release from beta cells, but only when the blood glucose is elevated. This is important because drugs that work through GLP-1 are less likely to cause hypoglycemia, in contrast to the sulfonylureas, which will release insulin from the beta cell no matter what the ambient glucose levels are.

In addition to glucose-dependent insulin secretion, there is also an effect on glucagon, which normally antagonizes insulin. GLP-1 decreases glucagon, amplifying the effect of the secreted insulin. GLP-1 also slows gastric motility and has a central effect in the hypothalamus on satiety, which is probably responsible for the weight loss associated with this class of drugs.

The way that we tweak the pathway in clinic is one of two ways. The first class I'll talk about is GLP-1 analogs, (otherwise known as GLP-1 receptor agonists). There are a bunch of these drugs. The two that came out first were exenatide and liraglutide. These drugs are like GLP-1, but are modified so they're not broken down quickly. Typically, normal endogenous GLP-1 is broken down in about two minutes or less by an enzyme called DPP-4, which I'll talk about later.

With the modifications with these GLP-1 analogs, they're not broken down. The half-life is long, and they can stick around. The half-life is so long in some of the preparations—by additional pharmacologic modifications—they

can be dosed weekly. All drugs in this class require subcutaneous injection.

The advantage of this class of drugs, in addition to the effect on A1C—which is about a 1% effect, which is quite good—[is that] it's associated with weight loss. In fact, the United States Food and Drug Administration (FDA) approved liraglutide at a higher dose—3 milligrams instead of 1.8 milligrams—for the treatment of obesity in patients who do not have diabetes. It has this weight-loss effect, probably from this central mechanism that we talked about.

It probably has independent effects on decreasing inflammation. It may have a cardiovascular benefit. One interesting thing is that these GLP-1 receptors aren't only in the pancreas, but are found all over the vasculature and the heart. Initially, there was a lot of enthusiasm about the potential beneficial effects of GLP-1 analogs on heart outcomes. That hasn't been shown. In the middle of June at the American Diabetes Association meeting, a study, called LEADER, will be presented which apparently shows a benefit of the GLP-1 analogue, liraglutide, on cardiovascular outcomes. It'll be interesting to see that study when it's presented. Right now, there's only been in press release about it.

The downsides to it are nausea. In about 10% or 15%, the nausea is treatment limiting. It also has some pancreas issues, these are controversial data as well. One is pancreatitis and the other is pancreatic cancer. Typically—in my practice—I don't prescribe this drug to patients who have had a history of pancreatitis, and I don't prescribe it to people who have a history of pancreatic cancer. The pancreatic cancer data, in my opinion, are a little softer and not very convincing. I think the pancreatitis data are somewhat stronger, and I've seen it personally. Safety concerns are always reinforced when you have actual patients who have experienced the adverse outcome.

DH No predictor there of kidney or liver function or dose effect?

TB No, it appears to be relatively idiopathic, as far as who's going to develop pancreatitis and who's not. That is a little bit frustrating, because you don't know who is going to develop a problem. You can't risk stratify people.

The other downside, of course—and this is true of all these new drugs that are not generic—is the cost. This is a big issue in diabetes care in general, that we have drugs that are extremely cheap—like metformin and sulfonylureas—and then we have new drugs that are quite expensive. When you're weighing the risks and the benefits, the costs also have to play a role in that calculation.

DH Agree.

TB The other way to tweak this incretin pathway is to

block the enzyme that breaks down endogenous GLP-1. That's with a DPP-4 inhibitor. These are a class of medications—the suffix that's used is the gliptin class. The first drug in this class was sitagliptin. These are oral medications that block DPP-4 and allow for endogenous levels of GLP-1 and GIP to increase.

They have pretty much the same effects as GLP-1 analog, except the effect is a little bit milder. The A1C-lowering effect is about a 0.7% decrease in A1C, rather than 1%-1.5% with a GLP-1 analog. With that decrease in efficacy, there's also an increase in tolerability. Some people still don't tolerate it because of GI side effects, but much fewer than those people who get GI side effects with GLP-1 analogs.

They have a smaller effect on inflammation, though this is something that's being actively investigated. In the studies that have been done today looking at heart cardiovascular outcomes, there hasn't been a benefit of these drugs on cardiovascular events.⁹⁻¹¹

Cost, of course, is an issue. There have been reports of the pancreas problems that the GLP-1 analogs have. The other downside is for some if these drugs—including saxagliptin and alogliptin—there's an increased risk of heart failure in the clinical trials.^{9,10} It's thought to be that that this is a drug-specific rather than a class-specific effect, but it's something that providers need to understand.

The other benefit of this drug is that, similar to the GLP-1 analogs, they only increase insulin secretion when the glucose is high, so they're much less likely to cause hypoglycemia. This is particularly useful when you have a patient who needs glucose control and who becomes hypoglycemic on a sulfonylurea, but when you take them off, they become hyperglycemic. This seems to be a good class of drugs for those kinds of patients.

The last drug class that I'll talk about works by a completely novel mechanism that's independent of what's going on in the pancreas or even the liver. These are the SGLT2 inhibitors. Glucose is freely filtered by the glomerulus, and it's resorbed in the proximal tubule of the kidney. It's resorbed by two transporters—SGLT1 and SGLT2. This drug blocks SGLT2 so the glucose can be filtered by the glomerulus, but not taken up in the proximal tubule, so the glucose is urinated out.

As you can imagine, if you're urinating glucose, the main side effects are polyuria and also urinary tract infections and fungal infections, as microbes like the high glucose environment. Those, indeed, are the main side effects of these drugs.

On the plus side, they're associated with a decrease in blood pressure, a decrease in weight by a little bit. On the downside, there is an increase of diabetic ketoacidosis, which is true in both type 1 and type 2 patients. It's been used as an adjunctive therapy in type 1 patients because of the insulin-independent mechanism—with decent effects

from an A1C standpoint and a glucose stability standpoint—but there is an increased risk of diabetic ketoacidosis. This has also been seen in type 2 patients. The mechanism really is not clear in type 2 patients.

There's a risk of fractures with this class of drugs. These data are just now beginning to emerge. On the benefit side, there's one study with one of these drugs—empagliflozin—that showed a benefit in terms of cardiovascular mortality.¹²

Now, I should mention that with all these new drugs, after they're approved by the FDA—based on their glucose-lowering properties and hemoglobin A1C is used as a surrogate—the FDA requires a post-approval cardiovascular study to be sure that the drug is not associated with increased cardiovascular events. Since the problems surfaced with rosiglitazone that we had talked about earlier, that has been the standard for the FDA—to require a large study, usually between 5,000 and 10,000 people, to be sure that the drug is not associated with increased events. The empagliflozin study came out at the end of 2015, which showed a benefit—empagliflozin versus placebo—for cardiovascular events.¹²

The choices and the sequencing of diabetes medications really are not clear. Unlike in other disease states—say, in human immunodeficiency virus—where we have a lot of head-to-head comparisons between regimens and specific drugs, we really don't have those kinds of comparisons. There's an ongoing study to see which drug is best in patients who are not controlled on metformin. That study will be very informative, but it'll be several years before we have those data.

The choice of a second agent for people who need an additional agent after metformin really is unclear, and is based on judging the risks and benefits and cost in the patient who is in front of you.

DH That gets me to the practical question—this is “how I treat” from the oncologist perspective. We'll see in the office a 55-year-old, overweight, type-2 diabetic already on metformin who's maybe there for a coagulation issue or cancer treatment and says, “My doctor is out of town, and I need to bring my sugars down. My sugar's 235.” How would you start out treating a patient like that?

TB A1C is similarly in the 8s or something like that?

DH Yes, let's say it's 8.

TB I think that I go through the options with the patients. My typical thing is I would either start a sulfonylurea, or if the patient says, “I don't want anything that could lead to weight gain,” then I would do a GLP-1 analog. If they said, “I've tried a sulfonylurea but my sugars dropped low,” then I would think about a DPP-4 inhibitor.

As far as the other classes go, the SGLT2 inhibitors—the gliflozin class—I've added on sort of as a third-line agent. We're all sort of getting experience with where to place this class of drugs. My general thing is a sulfonylurea or a GLP-1 analog, possibly a gliptin. I don't use a lot of TZDs, mostly because of the risks. They do, in a certain patient population, seem to have very profound effects on blood sugar—more than the average of 1% decrease in hemoglobin A1C. There are significant downsides, too—just the fracture risk alone in a chronic drug in an older person is concerning. I don't use a lot of TZDs. Endocrinologists and diabetologists in general are either very pro-TZD or anti-TZD. There's not really a good consensus. They are quite durable drugs.

DH Let me add this twist. The same patient—55, the same sugar issues, A1C, who now has curable lymphoma—is going to get our typical regimen, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Prednisone is 100 milligrams a day, five days in a row, every three weeks. Usually, it makes glucose crazy. Would you change your regimen in such a patient with that story?

TB Generally, in patients who require steroids for chemotherapy, insulin is always a good option. Sometimes I have patients on insulin on the days that they're getting their chemotherapy, and within a day or two days on either side. Sometimes that's a useful strategy.

It's sometimes tricky for patients who are getting steroids as part of an antiemetic protocol. Oftentimes, trying to lower the dose of dexamethasone is very useful—particularly if the dexamethasone is being given as a preventative measure. I have some patients who are just on insulin for those four days that they get their chemotherapy and a big dose of dexamethasone.

DH That's really helpful. If you take that same patient and either add some impaired liver function—liver metastases is the most common scenario—or a senior who might have come to us with a mild renal impairment or we make it worse with our platinum derivatives, how might you choose a regimen with mild liver or renal insufficiency?

TB With renal disease, the concern with metformin is the risk of lactic acidosis. This drug really is sort of guilty by association, more than anything. Its cousin, phenformin, was taken off the market years ago because of the risk of lactic acidosis. There have been cases of lactic acidosis with patients on metformin, but there are a lot of data—since there's so much experience with metformin—that perhaps the metformin association is a) not very common and b) may not exist at all.¹³⁻¹⁵

The concern about giving people with any degree of renal impairment metformin has dissipated a little bit most recently. In the package insert, the creatinine cut-offs were

1.4 mg/dL in women and 1.5 mg/dL in men. Now, there has been recently some guidance that says that you can go down to a creatinine clearance of 45 cc/min for metformin. You can use it down to a creatinine clearance of 30 cc/min at a lower dose. That increases the people who are eligible for metformin quite a bit.

I'll finish with people with kidney disease. I generally wouldn't do an SGLT2 inhibitor in someone with kidney disease. You need intact kidneys.

DH OK.

TB The gliptin class is quite good in people with kidney disease. At least some of the drugs are renally cleared, which is helpful in that you can dose-adjust. With sita-

gliptin, you can use a lower dose and get a similar effect in patients with renal insufficiency.

From a liver perspective, there's a big cut-off in my mind for people who have mild liver disease vs people who have decompensated cirrhosis or evidence of synthetic dysfunction. In the latter group, I tend to avoid almost all oral medications and stick with insulin in that group, because they're quite tenuous and prone to side effects of drugs.

I think that metformin is a fine drug in the patient who has maybe a liver metastasis, but whose synthetic function is fine.

DH This is really terrific, Todd. I've just been taking some notes and learning a lot as you go through. This is very practical—just the kind of thing we're looking for!

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