Understanding Clinical Research

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With the explosion of new oral drugs and insulins to treat diabetes, a recent correspondence to the journal *Diabetes Care* from David S.H. Bell, MD, was thought-provoking.[1] His argument was that placebo-controlled trials to assess new oral therapies are unethical because we now have proven and safe therapies. Dr. Bell reasons that because existing therapies have proven risk-to-benefit ratios, a more appropriate course would be to compare the investigational agent against an existing drug—in other words, an "active placebo."

He argues further that by using inactive placebos, we are exposing study subjects to unnecessary hyperglycemia, even if for relatively short periods of time. Currently, pivotal trials for Food and Drug Administration (FDA) approval of diabetes agents last 6 months. Does 6 months of hyperglycemia using an inactive placebo contribute to an adverse effect on quality of life and microvascular complications, as Dr. Bell argues?

This topic has concerned me for a long time. Part of the problem is the types of end points we measure. For FDA approval, end points include fasting plasma glucose and HbA_{1c} levels. As an aside, there has been much controversy and confusion about how to best express these data. Measuring the difference from baseline can be very different from measuring the difference versus placebo, depending on the direction of movement of the placebo group. For example, if drug X lowers HbA_{1c} concentration by 1% from baseline over the past 6 months, but placebo Y results in a 0.5% HbA_{1c} increase, the improvement of HbA_{1c} *compared with placebo* is 1.5%. On the other hand, if there is a similar

reduction in HbA_{1c} with drug X, but placebo Y results in a 0.5% *decrease* in HbA_{1c}, there is only a 0.5% decrease in HbA_{1c} compared with placebo. Therefore, I prefer to know both results: the difference from baseline and the difference versus placebo.

It is critical to point out in these placebo-controlled trials that it is not appropriate to compare drugs by using two different placebo-controlled trials. For example, let us look at registration study data from the package inserts of two relatively new drugs for the treatment of diabetes. Pioglitazone (Actos), when used at 45 mg daily, lowered HbA_{1c} compared with placebo by 1.6%.[2] Nateglinide (Starlix), when used at 120 mg three times a day, lowered HbA_{1c} compared with placebo by 0.7%.[3] Does this mean that pioglitazone is a more powerful drug than nateglinide?

The correct answer to this question is that one cannot tell from the information provided. As shown in Table 1, two very different populations of patients were studied for these two trials.

On first glance, one might say that pioglitazone lowers HbA_{1c} more effectively than does nateglinide. After all, HbA_{1c} was lowered 1.6% more than placebo with pioglitazone and only 0.7% more than placebo with nateglinide. But this is really not a fair comparison because the populations were different. The group receiving pioglitazone had, on average, a baseline HbA_{1c} level 2.2 percentage points higher than the group receiving nateglinide. For HbA_{1c}, as opposed to cholesterol reduction, we usually focus on *absolute* reduction of HbA_{1c} as opposed to *percent* reduction of HbA_{1c}. In this example, the pioglitazone reduced HbA_{1c} by 15.5%, while the nateglinide resulted in a 8.6% reduction. So obviously, no matter how we look at this, pioglitazone is stronger than nateglinide. Right?

Wrong. The higher the HbA_{1c} concentration, the greater the drop with treatment. This is an important concept, which is especially important to understand when comparing drug efficacy.

Table 1. Summary of FDA Studies for Pioglitazone and Nateglinide

	Pioglitazone 45 mg daily	Nateglinide 120 mg three times a day
N	76	168
Baseline HbA_{1c}	10.3%	8.1%
Change from baseline	–0.9%	–0.5%
Change from placebo	–1.6%	–0.7%

Just as importantly, these trials included subjects who were naive to therapy. Patients without previous pharmacotherapy will have greater reductions in blood glucose with treatment. For pioglitazone, 31% (24 subjects) were naive to diabetes therapy, whereas for nateglinide, 78% (131 subjects) were previously untreated with oral anti-diabetes drugs.

Is this enough information to make conclusions about differences in efficacy of two drugs? What about other aspects that would have made the populations from these two studies different? Sex, body mass index, ethnicity, duration of diabetes, and age are all important factors when comparing two drugs. Since these studies come from two different populations, how can we reliably compare these drugs?

The answer is that, from the data presented in Table 1, one really cannot make any conclusions. To be fair, one needs a head-to-head, randomized, double-blind study. With or without a placebo arm, the study population needs to come from the same group of patients so that baseline demographics will most likely be similar between the groups.

If, in our earlier example, drug X was better than drug Z, which was better than placebo Y, we could make valid conclusions about these agents. The point is, these types of studies are not performed for FDA registration, and one should not compare different drugs studied in different populations.

For patients with type 2 diabetes, measurements of blood glucose and HbA_{1c} might not be the best end points, yet those are the ones used to bring agents to market. Since the publication of the U.K. Prospective Diabetes Study (UKPDS), in which sulfonylureas, metformin, and insulin were shown to reduce the frequency of diabetes-related complications, we have entered a new era in diabetes treatment.[4,5] Before the UKPDS, many health care professionals felt that giving insulin to people with type 2 diabetes was actually dangerous because of issues pertaining to weight gain and the potential to increase atherosclerosis and macrovascular end points. The UKPDS invalidated those concerns. However, can we be sure that these types of concerns do not need to be considered when using new classes of oral agents?

It would not be reasonable to have UKPDS-like studies for every new agent or new class of drugs introduced to treat type 2 diabetes. Still, I believe that long-term trials examining microvascular and macrovascular end points should be considered for all new classes of medications to treat type 2 diabetes.

Because we now have indisputable proof that our older drug classes, while reducing blood glucose, also improve the more important end points of heart disease, stroke, retinopathy, nephropathy, and neuropathy, I tend to use agents from the older classes as first-line therapy while we await the more important long-term trials for newer agents and classes. This topic will become even more critical as more new classes of agents are introduced during the next few years.

I know that many of my colleagues, both in primary care and in endocrinology, do not agree with my opinion. There is no consensus about which agents for

type 2 diabetes should be used as first- or second-line therapy, although I agree with the continuing enthusiasm for earlier initiation of combination therapy.[6]

I encourage discussion of these issues, debates about the studies, and dialogue with patients about advantages and disadvantages of the different options. What I neither appreciate nor respect are decisions about which drug to use based on the inventory in the sample cabinet or on which pharmaceutical company was responsible for bagels greeting the office staff when they arrived in the morning. I am concerned that all too often Dr. A chooses drug Y not based on a placebo-controlled trial, but rather because of issues having nothing to do with medicine.

As physicians, we are obligated to understand clinical investigations, including those that are placebo-controlled. By knowing the strengths and weaknesses of these types of studies, we should be better able to make informed recommendations to our patients regarding which medications are best suited for them.

REFERENCES

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