Physicians' Corner

Insulin and Type 2 Diabetes Mellitus Treatment Today: Are We at a Tipping Point?

Commentary provided by Charles F. Shaefer, Jr., MD, FACP, FCCP
University Primary Care Physicians, Augusta, Georgia

In the last 10 weeks, I have had the privilege of crisscrossing the country and being in teaching contact with numerous primary care providers—physicians, physician assistants, nurse practitioners, and certified diabetes educators. Clearly, awareness is growing among the primary care community regarding the possible impact of the increasing epidemic of type 2 diabetes mellitus (DM) in our patient population. Also, primary care has an urgent interest in developing strategies to best treat this disease. This bodes well, since it is now almost universally accepted that 90% of all type 2 DM patients will be cared for within the primary care community. One clearly senses that primary care providers are preparing for this epidemic challenge.

In his book *The Tipping Point: How Little Things Can Make a Big Difference*, Gladwell[1] describes the forces that propel an idea or concept into sudden success or acceptance. He identifies a sequence of events that occur before something reaches "the tipping point" of general acceptance. He gives a fascinating example of the introduction of a superior hybrid seed corn to farmers in Greene County, Iowa, in 1928. The acceptance of this breakthrough occurred in very predictable waves. First, the Innovators—the adventurous ones—stuck their necks out and tried the new corn; then the Early Adapters got on board based on the limited experience of the few Innovators. These Early Adapters were respected thought leaders in the community, leaders who had been watching for a few years what those wild Innovators were doing. Then the rank and file followed suit, planting the new corn—the Early Majority and the Late Majority. And finally, even the Laggards, who saw no reason to change what they were doing at all, caught on to the fact that something better was available. This mimics the recent history of insulin use for routine treatment of type 2 DM. The Innovators have been extensively using insulin therapy in type 2 DM, and they have been for awhile. The Early Adapters, our collection of respected thought leaders in primary care, are comfortable with the early use of basal insulin and are beginning to explore how prandial insulin will fit into their practice. It appears that the vast majority of the primary care community now sits at the tipping point, ready to tip to embracing routine insulin use—both basal and prandial—for the treatment of type 2 DM. The recent American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus algorithm, which leads to early basal insulin use, should be a strong factor influencing the majority adoption of insulin therapy.[2]

Given the evidence building in favor of insulin use as a routine part of type 2 DM treatment, one has to ask the question: what are the uncertainties that might keep all physicians from jumping on board—that is, from "tipping"? In my travels, I have discovered a small, but incredibly common, set of questions that arise in the mind of physicians who are contemplating DM treatment strategies. Regardless of what part of the country I was in, the same questions kept coming up over and over. First, how does a provider choose between the 9 different classes of therapeutic agents that are available? Secondly, at what point in the treatment paradigm should insulin be brought into play? Thirdly, when insulin is introduced, what should be done with the oral agents? Finally, after basal insulin is used, how does prandial insulin fit into a primary care practice?

There are a huge number of choices of oral and injectable and even inhalable products to help our patients reach national glycosylated hemoglobin (A1C) goals.[3] This array of choices can be baffling, and the sheer number of them can discourage definitively selecting a specific product. I have recently experienced similar difficulty committing to the purchase of a laptop computer. The many choices and selection options makes deciding on a final purchase extremely difficult (I've been shopping for over 6 months—a cyber version of clinical inertia). Recent National Health and Nutrition Examination Survey data show that although patients are more likely to receive one or more oral antidiabetic drugs (OADs) than they are to receive insulin, we are not reaching A1C goals any better with the wider usage of single and combination oral stategies.[4] Are we actually lost in our maze of choices? Nathan's recent commentary in *The New England Journal of Medicine* suggests so.[3] It is not so much that we are without effective agents, but that perhaps we are lacking the aggressiveness to use these well-established agents (including insulin) early on. The challenge here is to move with resolution, with whatever agents, to achieve the A1C goal in a timely fashion.

The overwhelming number of OAD choices may confuse practitioners about when to bring insulin therapy into play. In the Diabetes Attitudes, Wishes and Needs study,[5] 33% of physicians said that insulin should be used as "the last resort." In fact, if insulin is withheld until all OADs and combinations have been consumed, there will be an interminable time

delay in achieving national goals for A1C control as all the permutations and combinations are played out; simple math dictates this. Such a delay is unacceptable because the burden of a long period of elevated A1C is not a time free of contribution to diabetic complications.[6] Delay in achieving goal A1C is not inevitable; there are several studies which show that basal insulin, when introduced as add-on therapy to 1 or 2 oral agents, can achieve glycemic control within 12 to 16 weeks.[7,8] Thus, insulin should be introduced early on, when 1 or 2 oral agents do not achieve desired control, based on established A1C goals. This precise sense of urgency to achieve national A1C goals is reflected and supported in the ADA/EASD treatment algorithm for type 2 DM.[2]

Many primary care providers are concerned about what to do with oral agents that are being taken at the time basal insulin is introduced. This is an important question, and I have to admit that in the early days of the introduction of basal insulin, I puzzled over this quite a bit. The answer to this question in type 2 DM is found in the United Kingdom Prospective Diabetes Study data,[9] which actually showed that basal insulin plus an oral agent produced better A1C control than basal insulin alone. OADs generally are continued when basal insulin is added, unless the OAD in question is not indicated for use with insulin or there are concerns about undesirable interactions, such as fluid retention with insulin and thiazolidinediones. We are trying to craft a treatment strategy that supplements, enhances, and replicates what the pancreas accomplishes, so it is most logical to simply add on basal insulin to supplement basal coverage without otherwise altering the oral regimen.

Another frequent area of uncertainty among practitioners is how to judge the impact of basal insulin when it is introduced. Wrestling with this concept is how many providers first encounter the larger question of prandial supplementation. Not uncommonly, some use higher and higher doses of basal insulin in an attempt to drive the A1C ever lower without consideration for the impact that mealtime glucose excursion may be having on overall success. Basal insulin should be used to achieve fasting blood sugars (FBS) at target levels of 90 to 130 mg/dL.[10] Normalizing FBS is the purpose and end point of basal insulin therapy, not actual A1C achievement, nor trying to meet the mealtime insulin needs by "over-basaling." Fortunately, in most cases, a single basal insulin injection plus appropriate OAD will achieve nationally targeted A1C levels early on. The Treat-to-Target Trial[7] is an excellent example of this concept. So where does prandial insulin fit in? Prandial insulin is the tool to use when excellent A1C levels cannot be achieved despite FBS in an acceptable range. Monnier et al[11] studied the contribution of fasting and postprandial sugars to A1C determination. His group found that at lower A1C levels (based on quintiles), postprandial control will contribute more to the achievement of lower A1C levels than will further FBS control. At higher A1C levels, the FBS is the major determinant of success; at lower levels of A1C, the postprandial state is the key to further improvement. As I suggested earlier, some providers attempt to control A1C with ever-increasing doses of basal insulin and become frustrated because of unexpected hypoglycemia or poor A1C results. Once the FBS is fixed with basal insulin plus OAD(s), it is then time to consider the addition of prandial therapy.

So, in summary, what have I learned from my 10 weeks on the teaching trail? First, primary care providers are eager to do an excellent job controlling their patients' type 2 DM and are hungry to learn more about how to accomplish this goal. The vast array of choices for therapy can often overwhelm the clinician. Hopefully, an expanding familiarity with the ADA/EASD consensus algorithm[2] will help simplify and encourage introduction of basal insulin as a second or third therapeutic option. Next, we should refresh ourselves regarding the primary utility of basal insulin: it is to fix the FBS. Fortunately, this will often establish A1Cs at the national goal level, especially early on. Finally, primary care providers need to continue to familiarize themselves with the concept of introducing prandial insulin to achieve or maintain excellent A1C results. This often can be done with a single dose of rapid-acting insulin at the largest meal of the day. Such an addition is well within the scope of service that can be comfortably offered in the primary care setting.

The farmers in Greene County, Iowa, learned from their peers about hybrid seed corn, and so primary care providers should be taking notes from the experiences of our peer group. *Insulin* and other academic journals, webcasts, Continuing Medical Education conferences, peer-to-peer meetings, and discussions with trusted colleagues will help us arrive at the best possible treatment strategies for type 2 DM patients in our primary care setting.

REFERENCES

1. Gladwell M. *The Tipping Point: How Little Things Can Make a Big Difference*. New York, NY: Back Bay Books/Little Brown and Company; 2002.
2. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2006;29:1963–1972.
3. Nathan DM. Finding new treatments for diabetes—how many, how fast . . . how good? *N Engl J Med*. 2007;356:437–440.

4. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among US adults diagnosed with type 2 diabetes: A preliminary report. *Diabetes Care*. 2004;27:17–20.
5. Peyrot M, Rubin RR, Siminerio LM. Physician and nurse use of psychosocial strategies in diabetes care: Results of the cross-national Diabetes Attitudes, Wishes and Needs (DAWN) study. *Diabetes Care*. 2006;29:1256–1262.
6. Nathan DM, Davidson MB, DeFronzo RA, et al, for the American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: Implications for care. *Diabetes Care*. 2007;30:753–759.
7. Riddle MC, Rosenstock J, Gerich J, for the Insulin Glargine 4002 Study Investigators. The Treat-to-Target Trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26:3080–3086.
8. Hermansen K, Davies M, Derezinski T, et al. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes [published correction appears in *Diabetes Care*. 2007;30:1035]. *Diabetes Care*. 2006;29:1269–1274.
9. Wright A, Burden AC, Paisey RB, et al, for the UK Prospective Diabetes Study Group. Sulfonylurea inadequacy: Efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS 57) [published correction appears in *Diabetes Care*. 2002;25:1268]. *Diabetes Care*. 2002;25:330–336.
10. American Diabetes Association. Standards of medical care in diabetes—2007. *Diabetes Care*. 2007;30(Suppl 1):S4–S41.
11. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: Variations with increasing levels of HbA(1c). *Diabetes Care*. 2003;26:881–885.