

# Recommendations for Improving Adherence to Type 2 Diabetes Mellitus Therapy—Focus on Optimizing Insulin-Based Therapy

R. Keith Campbell, RPh, MBA, CDE

**W**hile insulin was once regarded as a last resort for the treatment of type 2 diabetes mellitus (T2DM), to be initiated only after the failure of oral therapies, this is no longer the case.

The *Standards of Medical Care in Diabetes—2012*, produced by the American Diabetes Association (ADA), states that insulin should be considered as initial treatment, with or without additional agents, for newly diagnosed patients with T2DM whose blood glucose or glycated hemoglobin (A1C) levels are markedly elevated and/or who are highly symptomatic.<sup>1</sup> Notably, however, initiation of insulin therapy is frequently delayed despite inadequate glycemic control.<sup>2</sup>

Patients and healthcare providers may resist the initiation and intensification of insulin therapy for a variety of reasons. Patient resistance to insulin is premised around several concerns, including anxiety about treatment complications such as hypoglycemia, fear of needles, and inconvenient dosing schedules.<sup>3</sup> These concerns have been addressed in recent years with the development of new formulations and modes of insulin delivery that help lower the risk of complications while alleviating needle fear and improving dosing convenience. However, the existence of these newer options does not, alone, overcome patient resistance, and formal as well as informal patient education is necessary to address patient concerns regarding insulin therapy. For example, educating patients about forms of insulin that reduce the risk of hypoglycemia and that are more easily integrated into their lifestyles can help lessen anxieties. Similarly, patients should be assured that needles are much smaller and less invasive than they once were, and that insulin pens are easy to use, convenient, and not associated with significant pain.

This article will focus on strategies for improving adherence to insulin treatment, and will review available formulations and newer forms of insulin that can help improve treatment adherence, potentially improving outcomes and lowering healthcare costs. The article will also include a discussion of the role of education in improving adherence.

## Resistance to Insulin Therapy and Concerns Regarding Treatment Complications

Patients' concerns about insulin take several forms. For many patients, resistance to insulin is also a result of their perception

### Abstract

Despite its unsurpassed efficacy in the management of diabetes, insulin has been resisted and feared for its risk of side effects (ie, weight gain, hypoglycemia). Many patients and providers have perceived insulin as a last resort therapy given to patients with a poor prognosis, and some patients even as a form of punishment for poor self-management. Also, fear of needles is a constant concern. Fortunately, these challenges to insulin use may be overcome via patient education as well as new developments in insulin therapy. Insulin formulations have been developed that possess pharmacokinetic profiles better adapted to the physiologic needs of patients with type 2 diabetes mellitus (T2DM), including rapid- and long-acting insulin analogues, as well as premixed formulations. Appropriate use of these agents is associated with improved glycemic control, higher levels of adherence to treatment, and lower healthcare costs. A variety of pen delivery systems for insulin delivery are available that allow for easier, more discreet, and more accurately dosed insulin therapy. Patients generally prefer pen delivery systems, and they are associated with greater adherence and better glycemic control as compared with vial and syringe use. In addition to the ever-increasing variety of insulin formulations and delivery systems, educational initiatives are absolutely vital in order to overcome the limited knowledge about diabetes, self-management, and coping skills that can be seen in a large proportion of people with T2DM. Improved adherence to treatment, better outcomes, and reduced costs are contingent upon the appropriate use of, and full access to, appropriate treatment and patient education.

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that insulin is only used for “serious” cases, and that it is socially embarrassing to have to use insulin. Some patients regard the use of insulin as a kind of punishment imposed by the healthcare provider for patients’ inability to properly control their disease, or as a sign of their personal failure, and an indication that their disease has entered a new, more dire stage.<sup>3,4</sup> Patients with T2DM—whether they are taking insulin or are being treated with other kinds of hypoglycemic agents—also express high levels of concern about balancing glycemic control with the need to avoid side effects. Concerns about weight gain as well as heart attack risk due to medication in particular may be associated with poorer adherence.<sup>5</sup>

Needle anxiety is very common among patients who require insulin.<sup>3</sup> A number of recent developments have helped to address some of patients’ concerns regarding needles by making the administration of insulin simpler and more discreet. Needles have become smaller and narrower in design, which helps reduce the fear and pain associated with injections. Studies of patients with diabetes have demonstrated greater satisfaction with and acceptance of smaller diameter needles.<sup>6,7</sup>

The advent of pen devices has also had a large impact on the acceptability of injections in diabetes and on adherence.<sup>8,9</sup> Pen devices incorporate a variety of design elements that make them particularly convenient and discreet to use, while maximizing portability and dosing accuracy as compared with vial and syringe. Pen devices include both disposable prefilled devices and durable devices with prefilled replacement cartridges.<sup>9</sup> Moreover, manufacturers continue to refine the design of pen devices. For example, newer designs that are easier to use for patients with limited dexterity have been developed.<sup>10</sup> The design of pen devices has also been refined to improve the readability of dosing scales.<sup>11</sup>

### Pen Devices for Insulin Delivery

Issues of safety and efficacy obviously precede questions of adherence, and both safety and efficacy have been shown to be comparable for insulin delivery by pen devices versus syringe delivery.<sup>11</sup> At the same time, data from the medical literature largely support the advantages of insulin delivery via pen devices for improving adherence, and in most cases also support a concurrent lowering of healthcare utilization and costs.<sup>12</sup>

Lee et al analyzed claims data from 57 managed care organizations (MCOs) and identified 1156 patients newly initiating the use of a pen device who had previously used syringes for insulin delivery, and who represented a national

cross-section based on demographics and insurance plan type. The claims analysis showed that patients with T2DM who switched to a prefilled insulin analogue pen device exhibited significantly better medication adherence based on medication possession ratio (MPR) (69% vs 62%;  $P < .01$ ); 64% fewer claims for hypoglycemic events ( $P < .05$ ); fewer hypoglycemia-related emergency department (ED) and physician visits (both  $P < .05$ ); and lower overall annual treatment costs ( $P < .01$ ), including lower costs for ED visits, physician visits, hospitalization, and pharmacy expenditures (all  $P < .01$ ).<sup>13</sup>

Baser et al undertook a retrospective claims analysis using data from one of the largest US health plans, and found that over the course of the study period (5 years and 3 months), those who had been using a vial and syringe for insulin delivery and continued to do so ( $n = 532$ ) experienced a 0.13 increase in adherence based on MPR compared with a 0.22 increase in adherence for those who switched from vial and syringe to a pen device ( $n = 532$ ), a difference that was highly statistically significant ( $P = .0011$ ).<sup>14</sup>

Pawaskar et al compared adherence and costs for North Carolina Medicaid patients with T2DM in 2 separate patient cohorts: 1) patients switching from syringe-delivered to pen-delivered insulin versus those remaining on syringe-delivered insulin, and 2) patients initiating syringe-delivered insulin versus those initiating pen-delivered insulin as an add-on to oral antidiabetic drugs (OADs).<sup>15</sup> In the first patient cohort (patients switching from syringe-delivered to pen-delivered insulin versus those remaining on syringe-delivered insulin), diabetes medication adherence based on MPR was lower for those switching to pen devices compared with those who stayed with syringes (45% vs 56%;  $P < .05$ ), although overall medication adherence (ie, adherence to all medications, including diabetes medications) improved among patients using pen delivery (92% vs 90%;  $P < .05$ ). Total healthcare costs were somewhat lower in the pen delivery group, although not significantly so. In the second cohort (patients initiating syringe-delivered insulin versus those initiating pen-delivered insulin as an add-on to OADs), patients receiving insulin via pen were slightly more adherent (53% vs 50%), but not to the point of statistical significance. Overall treatment costs, however, were significantly lower for patients in the pen delivery group ( $P < .05$ ), including lower total diabetes-related costs, as well as lower hospitalization costs, outpatient costs, and insulin prescription costs (all  $P < .05$ ).<sup>15</sup>

A recent study employing data from a large nationwide database, which included information from a wide variety of managed care plans, focused on the relative clinical effects of initiating insulin therapy with disposable pen

**Table 1.** Adherence and Healthcare Cost With Syringe-Delivered Versus Pen-Delivered Insulin<sup>9,13,15-17</sup>

Study	Adherence Measure(s)	Adherence Results	Healthcare Cost Results
Davis et al (2008) <sup>16</sup>	Rate of patient self-administration of insulin while in hospital; postdischarge use of pen versus syringe	Greater percentage of patients administered at least 1 dose with pen device versus syringe while in hospital (77% vs 12.5%; $P = .001$ ); postdischarge, 12 patients (35%) in the pen group continued with pens, and 14 patients (41%) switched to syringes, while 23 patients (58%) in the syringe group continued with syringes, and 4 patients (10%) in the syringe group switched to pens	Higher total insulin costs per patient in the pen group versus the syringe group (\$154.39 vs \$108.04); when costs were adjusted to compare equivalent amounts of insulin dispensed, there was a cost savings of \$36 per patient in the pen group
Pawaskar et al (2007) <sup>15</sup>	MPR	Comparison group 1: overall medication adherence was higher in the pen group compared with the syringe group (92% vs 90%; $P < .05$ ); comparison group 2: no significant difference in adherence between the pen and syringe groups (53% vs 50%)	Comparison group 1: no significant difference in total healthcare costs (excluding drug costs) between the pen and syringe groups (\$11,476.42 vs \$10,755.31); comparison group 2: significantly lower costs (excluding prescription costs) in the pen group versus the syringe group (\$14,857.42 vs \$31,764.78)
Cobden et al (2007) <sup>9</sup>	MPR	Higher MPR in the pen group versus the syringe group (68% vs 59%; $P < .01$ )	All-cause healthcare costs were lower in the pen group versus the syringe group (\$16,004 vs \$14,256; $P < .01$ )
Lee et al (2006) <sup>13</sup>	MPR	Higher MPR in the pen group versus the syringe group (69% vs 62%; $P < .01$ )	All-cause healthcare costs were lower in the pen group versus the syringe group (\$16,359 vs \$14,769; $P < .01$ )
Graff and McClanahan (1998) <sup>17</sup>	Patient-reported adherence	Higher percentage of patients reported not missing a dose in the prefilled syringe group versus the vial/syringe group (85% vs 72%)	Not evaluated

MPR indicates medication possession ratio.

delivery compared with initiating therapy with syringe delivery in 3842 patients with T2DM ( $n = 1921$  for each group).<sup>8</sup> The study period consisted of a 6-month period of baseline data and a 12-month follow-up period starting at the initiation of insulin therapy. With regard to glycemic control, patients using the pen device (whose mean baseline A1C levels were higher than those using a syringe) experienced a significantly greater A1C decrease than those in the syringe group. After 12 months, A1C levels were similar in both groups, as were the numbers of patients achieving an A1C less than 7%. Healthcare utilization and healthcare costs were also similar in both groups, while adherence was significantly better among patients using the pen device.<sup>8</sup>

The clinical utility and impact on adherence of a biphasic insulin pen device was analyzed in 486 patients with T2DM

who had converted from syringe delivery, using data drawn from the PharmaMetrics database.<sup>9</sup> Adherence was significantly improved ( $P < .01$ ) compared with the study subjects' previous experience with syringes, while hypoglycemic events were reduced by 74% ( $P < .05$ ), as were hypoglycemia-related ED and physician visits (both  $P < .05$ ). In addition, all-cause annual costs, hypoglycemia-related costs, and other diabetes-attributable costs were all significantly lower with biphasic pen use (all  $P < .01$ ).<sup>9</sup>

Finally, a literature review identified 5 studies comparing syringe- with pen-delivered insulin for adherence, hypoglycemic events, and costs. While the studies were heterogeneous in design, they overwhelmingly observed improvements in adherence and reductions in both healthcare utilization and costs associated with pen device use (Table 1).<sup>9,12,13,15-17</sup>

### Evolving Varieties and Formulations of Insulin

The development of purified short- and intermediate-acting human insulins has helped address limitations inherent in earlier insulin formulations, and the more recent introduction of various formulations and novel varieties of insulin analogues has helped improve outcomes and adherence while also contributing to lower overall costs.<sup>18-21</sup>

Insulin analogues have been developed with characteristics (ie, onset of effect, peak effect, and duration of effect) that are more suited to the physiologic needs of patients with T2DM. Insulin analogues are available in rapid-acting and long-acting formulations. The rapid-acting insulin analogues reach peak levels more rapidly than human insulin, while long-acting basal analogues are designed to have a relatively flat plasma concentration profile.<sup>22</sup> Premixed formulations combining rapid- and intermediate-acting insulin are also available; these formulations offer some of the advantages of the ideal insulin control seen with basal-bolus administration but with a simpler dosing schedule. This approach offers a middle ground between dosing convenience and optimal control.<sup>23</sup>

A recent study evaluated the clinical impact of long-term treatment with biphasic premixed analogue formulations in 115 patients with T2DM with a mean disease duration of 10 years.<sup>21</sup> Study subjects had previously been on either insulin therapy (31%) or OADs (69%), while 81 (70%) patients received metformin. Their mean baseline A1C was 8.7%. Patients received 1 of 3 different types of biphasic premixed analogue formulations. After a mean treatment duration of approximately 2.9 years, A1C levels were reduced to a mean of 7.3% ( $P < .001$ ) and 36% of patients achieved an A1C of 7% or less. Fasting blood glucose levels also declined, from a baseline mean of 193 mg/dL to 141 mg/dL ( $P < .001$ ). Significant improvements in adherence were observed after the switch to a biphasic premixed analogue formulation ( $P = .001$ ), while no weight or blood pressure changes were observed and no major hypoglycemic events occurred.<sup>21</sup>

The clinical efficacy and impact on treatment costs of long-acting insulin analogues compared with intermediate-acting human insulin (NPH) have been evaluated in a number of studies. Pharmacy and medical claims data from an MCO in the southeastern United States were used to compare a long-acting insulin analogue, glargine, with NPH in 1434 patients with diabetes (5.2% of patients taking glargine and 2.9% taking NPH had type 1 diabetes). The mean treatment duration was 8.6 months.<sup>20</sup> By the end of the treatment period, 4.8% of patients taking glargine and 6.5% of patients taking NPH had experienced a hypoglycemic event. Using

a negative binomial regression model, the estimated rate of hypoglycemic events for a patient with an A1C of 7% was 18.3 per 100 patients in the NPH group versus 7.3 per 100 patients in the glargine group ( $P = .0009$ ). The number needed to treat (glargine versus NPH) in order to avoid a single hypoglycemic event was 9. The mean annual medication costs per patient were \$47 higher for treatment with the insulin analogue versus NPH ( $P = .042$ ).<sup>20</sup> These data are consistent with a retrospective, 36-month, observational study from the United Kingdom, published in 2010, comparing 4 types of medium- and long-acting insulin—NPH, detemir, glargine, and a premixed formulation—in 4337 patients with diabetes who had previously been insulin-naïve. Data were derived from a nationwide primary care database. The study authors observed that NPH was associated with the poorest glycemic control of the 4 treatments, while the premixed formulation, although it caused greater weight gain and required higher dosing, offered the highest rates of treatment adherence. Adherence 12 months after initiation of treatment was 92% for the premixed formulation, 83% for glargine, 78% for detemir, and 75% for NPH. At 36 months, ranking for adherence remained the same, with the premixed formulation achieving statistically significant superiority over glargine and NPH. Thirty-six month data were not available for detemir, as it had not been available in the United Kingdom for long enough to allow for this extended review.<sup>18</sup>

With regard to issues of cost, a 2010 study compared total and medication expenditures in 400 patients with T2DM treated with NPH and 1698 patients treated with insulin glargine, using private insurance claims data. Inclusion criteria included not having used either drug within 6 months of the study index date. Treatment with both agents was associated with increased diabetes-related drug costs, with the glargine group incurring significantly higher costs ( $P < .05$ ). However, total medical costs were lower for both groups at the end of the study period.<sup>19</sup>

Currently available long-acting basal insulin analogues should be administered at approximately the same time each day.<sup>24,25</sup> An ultra-long-acting basal insulin in development (insulin degludec) may allow greater flexibility with regard to timing of administration; this flexibility has the potential to help improve patient adherence to insulin therapy.<sup>25</sup> The efficacy and safety of the ultra-long-acting basal insulin administered once daily versus insulin glargine administered once daily, both in combination with rapid-acting insulin administered at mealtime, have been evaluated in a 1-year clinical trial in which 992 patients were randomized. The ultra-long-acting basal insulin achieved similar glycemic

**Table 2.** Effects of Intensive Diabetes-Related Education Initiative on Patients With a History of Glycemic Control and Psychosocial Challenges<sup>34</sup>

	Baseline <sup>a</sup>	One Year Postintervention <sup>a</sup>
A1C (n = 69)	8.5 ± 1.3 <sup>c</sup>	8.1 ± 1.2
Number of hypoglycemic events <sup>b</sup>	9.3 ± 8.1 <sup>c</sup>	5.7 ± 5.9
One or more severe hypoglycemic events	18%	12%
PAID (n = 56)		
PAID total	38 ± 22 <sup>d</sup>	22 ± 15
Emotional problems	44 ± 26 <sup>d</sup>	25 ± 16
Treatment-related problems	28 ± 22 <sup>d</sup>	20 ± 17
Food-related problems	31 ± 24 <sup>d</sup>	21 ± 19
Social support–related problems	22 ± 26 <sup>c</sup>	12 ± 19

A1C indicates glycated hemoglobin; PAID, Problem Areas in Diabetes questionnaire.  
<sup>a</sup>Means compared with the reference group by independent-samples *t* tests.  
<sup>b</sup>In past 4 weeks.  
<sup>c</sup>*P* < .01.  
<sup>d</sup>*P* < .001.  
 Adapted from Keers JC, Groen H, Sluiter WJ, Bouma J, Links TP. *J Eval Clin Pract*. 2005;11(3):293-303.

control as insulin glargine, with a decreased risk of hypoglycemia.<sup>26</sup>

### Educational Interventions to Improve Adherence

Adherence to treatment among patients with T2DM is strongly influenced by patients' level of knowledge, which includes not only what they know and do not know, but misconceptions as well. A recently published systematic review of the medical literature regarding patient knowledge of diabetes management found that a variety of inaccurate beliefs and assumptions on the part of patients, and a generally poor level of health literacy, contribute to an imbalanced view of diabetes therapy that significantly underestimates the consequences of being nonadherent.<sup>28-30</sup>

It has been demonstrated that when patients receive education regarding glycemic control, they are more adherent to treatment and better at achieving glycemic control. Patients who receive education also incur lower treatment costs.<sup>29-32</sup> The medical literature also suggests that patient education about glycemic control must include not only an initial intervention, but periodic reinforcements, if it is to remain effective.<sup>31,32</sup> A recent study took the results from 2 instruments, the Michigan Diabetes Knowledge Test (MDKT) and the Morisky Medication Adherence Scale (MMAS), given to 505 patients with T2DM, and aligned them with the patients' medical records. The study authors found that adherence was associated with higher levels of knowledge about diabetes, and that higher levels of knowledge and higher levels of adherence were both associated with lower

A1C (both *P* < .01) and with superior glycemic control (A1C ≤ 6.5%) (both *P* < .05).<sup>33</sup>

The cost efficacy of implementing diabetes educational programs has been examined in a variety of ways. A Dutch study evaluated the impact of a “multidisciplinary intensive” diabetes education program on A1C, diabetes-related distress, and treatment costs in 69 patients with long-term difficulties in achieving glycemic control who were also experiencing diabetes-related psychosocial problems. A group of 230 outpatients with T2DM served as a reference group. The educational program involved an initial 10-week period in which patients were educated on a variety of diabetes-related topics including diet, exercise, and self-management, as well as psychosocial issues relevant to living with diabetes and behavioral coping strategies. Two follow-up educational visits were also provided 6 and 12 weeks after the first educational module. One year postintervention, the mean combined direct and indirect costs for the patients in the educational program, though still higher than the reference group, were nearly halved from the period before the intervention (*P* = .001). A1C levels, which had been significantly higher than the reference group before the intervention, declined significantly 1 year later (*P* < .01), at which point they were almost the same as the reference group. Similarly, significant improvements from baseline to 1 year postintervention were seen for all psychosocial issues, including emotional (*P* < .001), treatment-related (*P* < .001), food-related (*P* < .001), and social support–related (*P* < .01) issues (Table 2).<sup>34</sup>

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A recently published analysis of data from the International Diabetes Management Practices Study (IDMPS) included 5692 patients with T2DM receiving a variety of diabetes education interventions in the real world who were compared with an equal number of patients with T2DM receiving no education on diabetes. Diabetes education was found to be associated with significantly improved glycemic control, greater use of insulin, lower rates of several chronic complications, and higher rates of employment. Healthcare resource use was also significantly higher in the group receiving the educational interventions; however, overall medical costs would be expected to be lower considering the reduced rate of chronic complications.<sup>35</sup>

Another recently published study specifically evaluated the impact of accredited diabetes self-management education programs provided by diabetes educators only. Compared with controls, those receiving formal self-management education were likely to have reduced treatment costs, an effect that was increased with multiple education encounters. Improvements in adherence to therapy and to best practice treatment were also seen in patients receiving education.<sup>31</sup>

### Conclusion

The ADA's *Standards of Medical Care in Diabetes—2012* states that insulin should be considered as initial treatment, with or without additional agents, for newly diagnosed patients with T2DM who have elevated blood glucose or A1C levels and/or who are highly symptomatic.<sup>1</sup> Traditional insulin formulations, however, have been associated with significant clinical and adherence-related challenges. The development of novel formulations and means of delivery has made insulin easier to use, helping to improve adherence, glycemic control, and cost-effectiveness. More sophisticated insulin formulations, such as long- and short-acting analogues, and premixed formulations, have improved adherence and glycemic control in patients with T2DM, with little or no impact on costs. Also, pen devices are now widely accepted and are associated with better adherence, superior outcomes, and lower treatment costs compared with vial and syringe use.

Although newer formulations and means of delivering insulin have contributed a great deal to the successful management of diabetes, educational initiatives remain as important as ever, due to knowledge gaps and misconceptions among patients with T2DM. Educational initiatives, particularly accredited programs conducted by diabetes educators, have proved beneficial in terms of outcomes, costs, and adherence. Strategies for improving adherence to insulin-

based therapies within a managed care environment include the implementation of educational initiatives for providers and patients as well as open access to effective and more convenient therapeutic options.

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**Address correspondence to:** R. Keith Campbell, RPh, MBA, CDE, Washington State University, College of Pharmacy, 1505 Stadium Way, Pullman, WA 99164. E-mail: rkcamp@wsu.edu.

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