Effect of insulin pen devices on the management of diabetes mellitus

JERRY MEECE

The number of people with diabetes mellitus worldwide is expected to more than double from 171 million in 2000 to 366 million in 2030, based on demographic changes alone.[1] Consequently, the estimated cost of diabetes care in the United States is expected to increase from $132 billion in 2002 to $156 billion (in 2002 dollars) by 2010 and $192 billion by 2020.[2] Given the increasing prevalence of obesity and its significance as a risk factor for diabetes, the expected number of cases of diabetes and actual cost in future years could be even higher.

Tight glycemic control is of paramount importance if patients are to minimize the risk of developing the long-term complications of type 2 diabetes mellitus.[3] Nevertheless, the National Health and Nutrition Examination Survey showed a decrease in glycemic control rates (percentage of patients with a glycosylated hemoglobin [HbA_{1c}] level of <7%) from 44.5% in 1988–94 to 35.8% in 1999–2000.[4] More recent data gathered during 2003–04 by the American Association of Clinical Endocrinologists (AACE) showed that two thirds of patients with type 2 diabetes did not have an HbA_{1c} level of ≤6.5%.[5]

Economic studies have confirmed the value of tight glycemic control, with lower HbA_{1c} levels associated with reductions in diabetes-related health care costs and other health economic benefits, such as improved productivity and higher employment.[6-9] It has been estimated that total cost savings of $50 billion and $72 billion could be made over 10 years if HbA_{1c} levels could be maintained at the American Diabetes Association and AACE target levels of <7.0% and ≤6.5%, respectively, in all U.S. patients with uncontrolled type 1 or type 2 diabetes.[10]

Due to the progressive decline in β-cell function and the progression of the disease, the majority of patients with type 2 diabetes ultimately require insulin therapy to achieve or maintain glycemic control.[11] The patient, physician, and other members of the diabetes care team need to work together to ensure that insulin therapy is initiated early and that adherence to insulin therapy is maintained to maximize the likelihood of long-term glycemic control.[12,13] Despite the demonstrated efficacy of insulin therapy in achieving and maintaining glycemic control,[14] there is often reluctance from both physicians and patients to initiate this treatment.[15,16]

Insulin initiation is now becoming easier with the use of insulin analogues with improved pharmacodynamic properties and the availability of pen devices for the administration of insulin. Several different insulin pen devices are available in the United States; some are equipped with replaceable insulin cartridges, whereas others use a prefilled nonreplaceable cartridge that is disposed of after use. With the health care system currently operating at near-capacity and the diabetes epidemic showing signs of worsening, pharmacists must understand what tools are available and most cost-effective for achieving positive outcomes as an integral part of the diabetes care team. As the understanding of the advantages and ease of use of insulin pen devices increases, matching the proper insulin delivery system to an individual patient's needs will be a key responsibility for the pharmacist.

We conducted a literature search in PubMed using the term "insulin pen" and the relevant outcome term (e.g., satisfaction, adherence, cost) to identify studies that assessed the use of pen devices and their effects on patient satisfaction and adherence to therapy, the risk of hypoglycemia, and health care resource utilization and costs.

Ease of use, convenience, and improved accuracy. Studies have

JERRY MEECE, B.S.PHARM., FACA, CDE, is Director of Clinical Services, Plaza Pharmacy and Wellness Center, 411 North Grand Avenue, Gainesville, TX 76240 (jmeece@cooke.net).

shown that insulin pen devices are easy to use, are more convenient than conventional administration with a vial and syringe, and can improve dosing accuracy compared with conventional syringes.[17-20] In a randomized, open-label, crossover study of 121 patients with diabetes (107 with type 2 diabetes), a nonvalidated questionnaire revealed that 74% of patients considered an insulin analogue pen device easier to use than conventional syringes, and 85% indicated that the insulin-dose scale was easier to read.[19] Ease of use could be particularly important for elderly patients who have difficulties with accurate self-dosing using a vial and syringe.[17,21-24] One trial of 79 elderly patients with diabetes (77 with type 2 diabetes) and visual or motor disabilities who had difficulty or required assistance with the vial and syringe found that 53% of patients could independently use a prefilled insulin injection device, compared with only 20% who could independently use the vial and syringe.[23] While the prefilled insulin injection device could be used independently by more patients, there was no indication as to whether patients had difficulty in using it or whether they accurately measured their insulin dose.

In a crossover study that included 60 elderly patients (>60 years old), 54 (90%) found the functioning of a prefilled insulin pen easy to understand and preferred it for future treatment over conventional syringes because it was faster and easier to use.[17] The ease of use and portability of pen devices enable patients to administer insulin where and when it is needed, and the discreet design may reduce the possible embarrassment of needle use in public. Korytkowski et al.[19] found that 85% of patients considered the insulin analogue pen device more discreet for use in public than vials and syringes.

Pen devices have also been shown to improve dose accuracy compared with conventional vials and syringes,

particularly with low insulin doses.[20,25,26] Korytkowski et al.[19] found that 82% of patients indicated more confidence with setting the required dose with the insulin analogue pen than the vial and syringe compared with 11% of patients who felt more confident with the vial and syringe. In a survey of users of prefilled insulin pens, 333 (73%) of 456 patients said that the dosing mechanism was more accurate compared with insulin administration using vials and syringes.[18] While the conclusions of these two studies are limited by the fact that only patient perceptions of dose accuracy were presented with no verification of actual dose accuracy, other studies have indicated improved accuracy of insulin doses with pen devices compared with vials and syringes.[20,25,26] It should be noted, however, that no study has assessed patients' perception of dose accuracy and then verified the actual administered dose.

Taken together, these results indicate improved ease of use, convenience, and dosing accuracy with pen devices compared with vials and syringes, all of which should help improve patient satisfaction, medication adherence, and, ultimately, glycemic control.

Improved patient satisfaction and medication adherence. Adherence to oral antidiabetic therapy has been shown to range from 36% to 93% in 11 retrospective studies of patients with type 2 diabetes who received treatment for 6–24 months, while adherence to insulin therapy was found to be 62% in a large retrospective study of patients with type 2 diabetes.[27] Poor adherence to diabetes medications is inevitably associated with higher HbA_{1c} levels[28,29] and increased mortality rates.[30] Poor adherence to insulin therapy has also been associated with increased hospital admissions as a result of acute diabetes complications.[29]

The use of insulin pen devices may be helpful in overcoming some of the

barriers to effective insulin therapy and improving patient satisfaction, which could lead to increased adherence. A number of studies have shown that patients prefer insulin pen devices over vials and syringes for the administration of insulin.[19,31,32] A statistically significant improvement ($p < 0.05$) in all items of the Diabetes Treatment Satisfaction Questionnaire (DTSQ), including flexibility, ease of treatment, hypoglycemia status, and satisfaction, was found in an observational study that included 1622 insulin-treated patients with type 1 or 2 diabetes who switched from traditional syringe insulin injections to an insulin pen device.[31] In another study, significant improvements ($p < 0.001$) occurred in all measures of patient-reported outcomes, including convenience, flexibility, and overall preference, in 372 patients with type 2 diabetes who switched to a prefilled insulin analogue pen device.[32]

In a randomized, open-label, crossover trial of 121 patients with type 1 or 2 diabetes, 74% preferred a prefilled insulin analogue pen device over vials and syringes.[19] The majority of patients in this study considered the pen device to be more discreet (85% versus 9%), easier to use (74% versus 21%), and easier to read (85% versus 10%) than vials and syringes. One limitation of this study was the use of a nonvalidated questionnaire. The study also assessed treatment satisfaction using the validated DTSQ, which found that overall treatment satisfaction was similar with both insulin devices. Overall, more patients preferred an insulin pen device over vials and syringes in a questionnaire survey that assessed product-attribute expectations in 302 patients with type 1 or 2 diabetes who were current insulin users or nonusers.[33] In this study, ease of use, activity interference, and social acceptability were rated significantly higher for an insulin pen device by both current insulin users and

nonusers. Similarly, in a survey of patients using an insulin pen device, 351 (77%) of 456 patients found it easier to comply with their insulin regimen using the pen device compared with vials and syringes.[18]

A recent analysis of third-party managed care claims data (PharMetrics database from 57 commercial health plans) from 1156 patients with type 2 diabetes found that conversion to a prefilled insulin analogue pen device was associated with increased adherence in patients with type 2 diabetes.[34] In this study, managed care claims data were analyzed for six months before and for at least two years after patients switched treatment from a human insulin or insulin analogue vial and syringe to an insulin analogue pen device containing either insulin aspart or biphasic insulin aspart protamine. The percentage of patients who were considered adherent to therapy (defined as a medication possession ratio of ≥80%) was significantly higher after switching to or adding the pen device compared with the period before switching (54.6% versus 36.1%, $p < 0.01$). A follow-up analysis of the 486 patients who switched to the biphasic insulin aspart 70/30 pen device revealed that adherence significantly increased in this subset of patients ($p < 0.01$).[35]

In all the studies mentioned so far in this section, patients were unlikely to have purchased their pen devices. If patients had to purchase their own pen devices, their opinion of the device may have differed and the adherence rates may have been substantially altered.

A recent study evaluated the effect of pen devices in a low-income Medicaid population.[36] Two analyses were conducted with patients with type 2 diabetes: (1) patients who converted from vials and syringes to a pen device ($n = 560$) versus patients continuing to use vials and syringes ($n = 560$) and (2) patients taking oral antidiabetic drugs who

initiated insulin therapy with a vial and syringe ($n = 1162$) versus those initiating therapy with a pen device ($n = 168$). The diabetes-related medication adherence rate was significantly lower for patients who switched to a pen device compared with those who continued to use a vial and syringe (45% versus 56%, $p < 0.05$). There was no difference in adherence rates between the two delivery methods in patients initiating insulin therapy.

Lower rates of hypoglycemia. Hypoglycemia is one of the primary barriers to achieving tight glycemic control.[37,38] Intensive insulin therapy has been associated with a greater risk of hypoglycemia[3,39,40] and a number of recognized causes of hypoglycemia (i.e., errors in insulin dosing, missed or delayed meals or reduced intake, strenuous unplanned exercise, and the target level of glycemic control). The fear of hypoglycemia has been identified as an important risk factor for reducing health-related quality of life.[41] This fear may also discourage patients from using more intensive insulin therapy and result in reduced medication adherence. If patients are to achieve and maintain tight glycemic control, the fear of hypoglycemia must be addressed so that insulin can be initiated earlier and adherence to therapy improved. The closer insulin supplementation is able to mimic physiological insulin secretion, the lower the risk of hypoglycemia.

A recent analysis of third-party managed care claims data for 1156 patients with type 2 diabetes revealed that switching to or adding a prefilled insulin analogue pen device increased medication adherence and correlated with a significant decrease in hypoglycemic events.[34] After controlling for different lengths of follow-up (six months before and at least two years after switching treatment), the likelihood of experiencing a hypoglycemic event was reduced by half after switching to the insulin analogue pen device (odds ratio

[OR], 0.50; 95% confidence interval [CI], 0.37–0.68; $p < 0.05$). Further, multivariate analysis showed that the occurrence of hypoglycemic events decreased by nearly two thirds in patients considered adherent to therapy (incidence rate ratio, 0.35; 95% CI, 0.11–0.81; $p < 0.05$). The findings of this study were confounded by the fact that 51.5% of patients were originally receiving human insulin and, while converting from vial to pen, also converted from human insulin to an insulin analogue, which may have also contributed to the reduction in hypoglycemic events. However, this was controlled for in a multivariate analysis that showed no significant difference in the rate of hypoglycemia between patients who were initially treated with human insulin and those initially treated with an insulin analogue. In the follow-up subset analysis of the 486 patients who converted to the biphasic insulin aspart 70/30 pen device, previous users of an insulin analogue demonstrated a 63% reduction in the number of hypoglycemic events after switching to the pen device (OR, 0.37; 95% CI, 0.16–0.82; $p < 0.05$) compared with a 57% reduction for those who originally received human insulin (OR, 0.43; 95% CI, 0.19–0.98; $p < 0.05$).[35]

An observational study of 1622 patients receiving insulin injections who switched from a traditional syringe to an insulin pen found that the pen device was associated with a statistically significant improvement ($p < 0.05$) in hypoglycemia or hyperglycemia status and all other items assessed on the DTSQ.[31]

In the aforementioned study by Korytkowski et al.,[19] six major hypoglycemic events were reported with the use of vials and syringes, two of which were serious adverse events. In contrast, no hypoglycemic events occurred during treatment with the insulin pen. Overall, there were no major differences in the safety profiles of the two delivery systems.

Reduced health care costs. *Overall health care costs.* There is indisputable evidence that intensive treatment of diabetes and tight glycemic control significantly reduce the risk of diabetes-associated complications.[3,39] There is also increasing evidence that intensive glycemic control provides economic value to those who pay for health care.[6] Furthermore, increased adherence to antidiabetic medications has been found to be a significant predictor of reduced total annual health care costs.[7-10,42]

Lee et al.[34] found that annual health care costs decreased significantly after switching to or initiating therapy with an insulin analogue pen. The overall annually adjusted mean all-cause health care costs per patient decreased significantly from $16,359 to $14,769 after switching from vials and syringes to an insulin analogue pen device ($p < 0.01$). Approximately 60% of these health care costs were diabetes related.

In the analysis of Medicaid data, total health care costs (excluding prescriptions) in year 2 were comparable for patients switching to a pen device and those continuing to use vials and syringes ($11,476 versus $10,755) but were significantly lower for patients initiating insulin therapy with a pen device ($14,857) compared with a vial and syringe ($31,765) ($p < 0.05$).[36]

Diabetes-related costs. The treatment of hypoglycemia is a costly component of diabetes-related therapy.[43,44] The mean cost per hypoglycemic episode has been estimated at $1186 (ranging from $181 for an office visit to $4924 for a hospital visit) in an analysis of claims data from 2118 patients with type 1 or type 2 diabetes treated with insulin.[44] Another estimate of $1087 per hypoglycemic event ($427 in the outpatient setting) was derived from a retrospective analysis of claims data for 1434 patients who started treatment with isophane insulin human or insulin glargine.[43]

In the study by Lee et al.,[34] annual hypoglycemia-attributable costs (the amounts paid to the health care provider by the third-party payer for claims related to hypoglycemic events) per patient decreased by more than half after switching from vials and syringes to a prefilled insulin analogue pen device (from $1415 to $627) ($p < 0.01$). These significant hypoglycemia-attributable cost savings were largely due to significant annualized mean savings in hospitalization costs of $569, physician-visit costs of $92, pharmacy costs of $78, and emergency department costs of $65. Cost savings in hospitalizations and emergency department visits associated with hypoglycemia were largely driven by decreases in the mean annual hospital length of stay (9.6 days versus 6.4 days, $p < 0.01$) and emergency department visits (7.4 visits versus 5.2 visits, $p < 0.01$). Overall, hypoglycemia-attributable cost savings accounted for 57% of the total savings in diabetes-related health care resource use.

Other diabetes-associated costs (the sum of the amounts paid for claims related to type 2 diabetes, excluding hypoglycemia-attributable costs) in this study also significantly decreased by $600 overall per patient per annum, with savings of $1300 in physician visits, $629 in pharmacy costs, and $115 in associated emergency department visits (driven by the significant annual mean decrease in emergency department visits).[34]

This analysis also assessed the effect of switching to a prefilled insulin analogue pen on health outcomes and associated health care costs and showed that there were significant reductions in hypoglycemia-related health care resource utilization.[34] There were significant decreases in hypoglycemia-related emergency department visits (OR, 0.44; 95% CI, 0.21–0.92; $p < 0.05$) and physician visits (OR, 0.39; 95% CI, 0.24–0.64; $p < 0.05$), whereas hypoglycemia-related hospitalizations (OR, 0.88;

95% CI, 0.47–1.66) and outpatient visits (OR, 0.79; 95% CI, 0.31–2.01) remained similar after switching to or starting therapy with the insulin analogue pen device.

While the study of Medicaid data did not present hypoglycemia-attributable costs, it did show significant reductions in hospital costs ($1,196 versus $4,965 per patient) and outpatient costs ($7,796 versus $13,104) for patients initiating insulin therapy with a pen device versus vials and syringes ($p < 0.05$ for both comparisons).[36]

Pharmacy costs. In 2002, insulin (including delivery systems and supplies) and oral antidiabetic drugs accounted for only 7.6% and 5.4%, respectively, of the total health care expenditures attributable to diabetes (over $91 billion).[2] Thus, up-front spending on drug costs represents only a small proportion of the costs of diabetes, and reductions in the costs of treating the complications of diabetes could more than offset any short-term increases in drug costs.

In the study by Lee et al.,[34] there was a reduction in diabetes-related pharmacy acquisition costs after switching to the insulin analogue pen device. The total cost of insulin remained similar in the overall cohort group and in the subcohorts of patients who had received either human insulin or an insulin analogue pen device, but there were significant decreases in the annual per-patient cost of oral antidiabetic drugs in the overall cohort ($1579 versus $915, $p < 0.01$) and within the subcohorts (previous human insulin: $765 versus $472, $p < 0.01$; previous human insulin analogue: $814 versus $443, $p < 0.01$).

Although published wholesale pharmacy costs for insulin analogue pen devices are higher than those for vials of human insulin or insulin analogues, the maintenance of insulin costs may be due to the fact that improvements in adherence and outcomes may have allowed for

lower daily doses of insulin. Also, with the pen devices, there would be less insulin wastage due to the expiration of open vials. In addition, the reduction in oral antidiabetic drugs could be a reflection of improved self-management and subsequent improved outcomes after switching to the insulin analogue pen device, which may have led physicians to reduce the prescribed number, strength, or daily dose of oral antidiabetic drugs, thereby resulting in the reduced cost of oral antidiabetic drugs.

In the study of Medicaid data, patients who initiated insulin therapy with a pen device had significantly lower insulin prescription costs than those who initiated insulin therapy via a vial and syringe ($6123 versus $7466, $p < 0.05$).[36]

Use of insulin pens in the United States. Although insulin pens are now widely used in Europe, with their use surpassing syringes as the most common insulin delivery device in the United Kingdom, syringes remain the most common choice for insulin delivery in the United States.[45] There may be a number of obstacles to widespread use of pen devices in the United States, including provider factors and cost. In the United States, over 80% of patients with diabetes are cared for by a primary care physician who is less likely to have been exposed to the benefits of pen use in his or her training.[45] In Europe, patients with diabetes are more likely to be cared for by a multidisciplinary team led by an endocrinologist and including a diabetes educator, such as a diabetes nurse specialist, who are more likely to be familiar with pen use, will initiate insulin earlier, and are more likely to use intensive insulin therapy than primary care physicians in the United States. With intensive insulin therapy and more frequent injections of insulin, the greater convenience and ease of use of pen devices are more likely to become apparent. Cost, or the perceived higher costs

of insulin pens, may also be a factor, limiting the widespread use of pen devices in the United States, especially for individuals without health insurance. In Europe, government health care systems reimburse patients for pen purchases; however, in the United States, the cost of insulin pens may be higher than that of vials and syringes for patients who do not have health insurance. This is an important issue and indicates that cost to patients may be a barrier for use of pens, despite increased patient preference for these devices.[19]

In the United States, the level of coverage and reimbursement for the cost of purchasing disposable pen devices and cartridges for refillable pens varies from plan to plan, and some copayment by the patient may be required. Some refillable pens are provided free to the patient from the physician, and others can be purchased with discount coupons available from the manufacturers.[46] But even with insurance coverage, navigating the prescription benefit plan can be daunting for both health care professionals and patients. For patients covered by insurance, the cost of insulin pens versus vials and syringes is small in most cases, depending on the number of units used per month. The copayment may be the same for a box of five prefilled insulin syringes (1500-unit boxes) as it is for 1000 units of the same insulin in a vial, translating to an advantage for the pen user.[45] There may also be less wastage of insulin due to expiration of an open vial, meaning that the overall price differences between vials and syringes and pen devices are not substantial.[46] It is more likely that provider factors, such as unfamiliarity and underestimation of the possible benefits of pen use or perceived higher costs of pen devices, play a larger part in determining the level of insulin pen use than actual costs of pen devices.

The role of the pharmacist in diabetes management. A multi-

disciplinary care team is needed to ensure effective management of patients with diabetes, and pharmacists have a key role to play within this team. From the initiation of insulin therapy, the pharmacist could help patients target glycemic levels faster and with fewer hypoglycemic episodes by making dosage adjustments as necessary. This may be achieved by collaborative practice agreements between pharmacists and physicians, which are becoming increasingly popular in more than 40 states. Pharmacist-adjusted dosages can be further helped by the use of simple algorithms, such as that used in the Treat-To-Target Trial[47] (appendix) or in the large observational PREDICTIVE 303 study.[48]

Pharmacists also have an important task in describing the various insulin delivery methods and their benefits to help patients make informed decisions about the most appropriate delivery method for their lifestyles. Furthermore, becoming familiar with the insurance copayments and formularies concerning insulin pens may allow the pharmacist to add to the services offered to patients with diabetes.

By improving patient access to information and advice, increasing patient education, and giving detailed guidance on the proper use of insulin pens, pharmacists may also contribute to short-term cost savings due to fewer emergency room visits and fewer unplanned physician visits.

Summary. The administration of insulin with a pen device is preferred by patients over administration with a vial and syringe, and the preference is associated with improved adherence to therapy, a decreased incidence of hypoglycemic episodes, and a reduction in associated health care resource utilization and costs. Despite a higher wholesale pharmacy cost for insulin analogue pen devices over vials of insulin, insulin costs may not increase after switching patients

to an insulin analogue pen device, and a reduction in oral antidiabetic drug costs may lead to an overall significant decrease in pharmacy costs. Even if there are short-term increases in pharmacy acquisition costs, there is an enormous potential to curtail the largest portion of diabetes-related resource utilization and cost attributable to hospitalization and to physician, outpatient, and emergency department visits. If higher levels of adherence translate into improved glycemic control, the greatest reductions in overall health care costs from switching from vials and syringes to an insulin analogue pen device may come from a reduction in the long-term complications of diabetes and the considerable associated costs. The use of insulin pen devices in the United States needs to increase if patients and the health care system in this country are to benefit from these advantages.

References

1. Wild S, Roglic G, Green A et al. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. *Diabetes Care.* 2004; 27:1047-53.
2. Hogan P, Dall T, Nikolov P, for the American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care.* 2003; 26:917-32.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998; 352: 837-53.
4. Koro CE, Bowlin SJ, Bourgeois N et al. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. *Diabetes Care.* 2004; 27:17-20.
5. State of Diabetes in America report. www.aace.com/public/awareness/stateofdiabetes/DiabetesAmericaReport.pdf (accessed 2007 Mar 1).
6. Gilmer TP, O'Connor PJ, Manning WG et al. The cost to health plans of poor glycemic control. *Diabetes Care.* 1997; 20:1847-53.
7. Shetty S, Secnik K, Oglesby AK. Relationship of glycemic control to total diabetes-related costs for managed care health plan members with type 2 diabetes. *J Manag Care Pharm.* 2005; 11:559-64.
8. Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus. A randomized, controlled, double-blind trial. *JAMA.* 1998; 280:1490-6.
9. Wagner EH, Sandhu N, Newton KM et al. Effect of improved glycemic control on health care costs and utilization. *JAMA.* 2001; 285:182-9.
10. Minshall ME, Roze S, Palmer AJ et al. Treating diabetes to accepted standards of care: a 10-year projection of the estimated economic and health impact in patients with type 1 and type 2 diabetes mellitus in the United States. *Clin Ther.* 2005; 27:940-50.
11. Hirsch IB, Bergenstal RM, Parkin CG et al. A real-world approach to insulin therapy in primary care practice. *Clin Diabetes.* 2005; 23:78-86.
12. Donnelly LA, Morris AD, Evans JM, for the DARTS/MEMO collaboration. Adherence to insulin and its association with glycaemic control in patients with type 2 diabetes. *QJM.* 2007; 100:345-50.
13. Wright A, Burden AC, Paisey RB et al. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. (UKPDS 57). *Diabetes Care.* 2002; 25:330-6.
14. 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; 29:1963-72.
15. Korytkowski M. When oral agents fail: practical barriers to starting insulin. *Int J Obes.* 2002; 26(suppl 3):S18-24.
16. Ziemer DC, Miller CD, Rhee MK et al. Clinical inertia contributes to poor diabetes control in a primary care setting. *Diabetes Educ.* 2005; 31:564-71.
17. Coscelli C, Lostia S, Lunetta M et al. Safety, efficacy, acceptability of a pre-filled insulin pen in diabetic patients over 60 years old. *Diabetes Res Clin Pract.* 1995; 28:173-7.
18. Graff MR, McClanahan MA. Assessment by patients with diabetes mellitus of two insulin pen delivery systems versus a vial and syringe. *Clin Ther.* 1998; 20:486-96.
19. Korytkowski M, Bell D, Jacobsen C et al. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. *Clin Ther.* 2003; 25:2836-48.
20. Lteif AN, Schwenk WF. Accuracy of pen injectors versus insulin syringes in children with type 1 diabetes. *Diabetes Care.* 1999; 22:137-40.
21. Puxty JA, Hunter DH, Burr WA. Accuracy of insulin injection in elderly patients. *Br Med J.* 1983; 287:1762.
22. Da Costa S. A co-ordinated approach to insulin transfer in the older type 2 patient. *J Diabetes Nurs.* 1997; 1:123-6.
23. Shelmet J, Schwartz S, Cappleman J et al. Preference and resource utilization in elderly patients: InnoLet versus vial/syringe. *Diabetes Res Clin Pract.* 2004; 63:27-35.
24. Kesson CM, Bailie GR. Do diabetic patients inject accurate doses of insulin? *Diabetes Care.* 1981; 4:333. Letter.
25. Gnanalingham MG, Newland P, Smith CP. Accuracy and reproducibility of low dose insulin administration using pen-injectors and syringes. *Arch Dis Child.* 1998; 79:59-62.
26. Keith K, Nicholson D, Rogers D. Accuracy and precision of low-dose insulin administration using syringes, pen injectors, and a pump. *Clin Pediatr.* 2004; 43:69-74.
27. Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care.* 2004; 27:1218-24.
28. Krapek K, King K, Warren SS et al. Medication adherence and associated hemoglobin A1c in type 2 diabetes. *Ann Pharmacother.* 2004; 38:1357-62.
29. Morris AD, Boyle DI, McMahon AD et al. Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. *Lancet.* 1997; 350:1505-10.
30. Kuo YF, Raji MA, Markides KS et al. Inconsistent use of diabetes medications, diabetes complications, and mortality in older Mexican Americans over a 7-year period. Data from the Hispanic established population for the epidemiologic study of the elderly. *Diabetes Care.* 2003; 26:3054-60.
31. Albano S, for the ORBITER Study Group. Assessment of quality of treatment in insulin-treated patients with diabetes using a pre-filled insulin pen. *Acta Biomed.* 2004; 75:34-9.
32. Rubin RR, Peyrot M. Quality of life, treatment satisfaction, and treatment preference associated with use of a pen device delivering a premixed 70/30 insulin aspart suspension (aspart protamine suspension/soluble aspart) versus alternative treatment strategies. *Diabetes Care.* 2004; 27:2495-7.
33. Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. *Clin Ther.* 2004; 26:1498-505.
34. Lee WC, Balu S, Cobden D et al. Medication adherence and the associated health-economic impact among patients with type 2 diabetes mellitus converting to insulin pen therapy: an analysis of third-party managed care claims data. *Clin Ther.* 2006; 28:1712-25.
35. Cobden D, Lee WC, Balu S et al. Health outcomes and economic impact of therapy conversion to a biphasic insulin analog pen among privately insured patients with type 2 diabetes mellitus. *Pharmacotherapy.* 2007; 27:948-62.
36. Pawaskar MD, Camacho FT, Anderson RT et al. Health care costs and medication adherence associated with initiation of insulin pen therapy in Medicaid-enrolled patients with type 2 diabetes: a retrospec-

tive database analysis. *Clin Ther.* 2007; 29:1294-305.

37. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care.* 2003; 26:1902-12.

38. Davis S, Alonso MD. Hypoglycemia as a barrier to glycemic control. *J Diabetes Complications.* 2004; 18:60-8.

39. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993; 329:977-86.

40. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes.* 1997; 46:271-86.

41. Currie CJ, Morgan CL, Poole CD et al. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. *Curr Med Res Opin.* 2006; 22:1523-34.

42. Balkrishnan R, Rajagopalan R, Camacho FT et al. Predictors of medication adherence and associated health care costs in an older population with type 2 diabetes mellitus: a longitudinal cohort study. *Clin Ther.* 2003; 25:2958-71.

43. Bullano MF, Al-Zakwani IS, Fisher MD et al. Differences in hypoglycemia event rates and associated cost-consequence in patients initiated on long-acting and intermediate-acting insulin products. *Curr Med Res Opin.* 2005; 21:291-8.

44. Heaton A, Martin S, Brelje T. The economic effect of hypoglycemia in a health plan. *Manag Care Interface.* 2003; 16:23-7.

45. Da Costa S, Brackenridge B, Hicks D. A comparison of insulin pen use in the United States and the United Kingdom. *Diabetes Educ.* 2002; 28:52-60.

46. Magnotti MA, Rayfield EJ. An update on insulin injection devices. *Insulin.* 2007; 2:173-81.

47. Riddle MC, Rosenstock J, Gerich J et al. The Treat-To-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care.* 2003; 26:3080-6.

48. Meneghini L, Koenen C, Rojas PB et al. Efficacy and safety of insulin detemir in a large cohort of patients with type 2 diabetes using a simplified self-adjusted dosing guideline: results of the PREDICTIVE 303 study. *Diabetes.* 2007; 56:A51. Abstract.

Appendix—Forced insulin weekly titration schedule used in the Treat-To-Target Trial[a]

Start with basal insulin 10 IU/day at bedtime and adjust weekly

Mean Self-Monitored FPG values from Preceding 2 Days	Increase of Insulin Dosage (IU/day)
≥180 mg/dL (≥10 mmol/L)	8
140–180 mg/dL (7.8–10.0 mmol/L)	6
120–140 mg/dL (6.7–7.8 mmol/L)	4
100–120 mg/dL (5.6–6.7 mmol/L)	2

[a]The target fasting plasma glucose was ≤100 mg/dL. Exceptions to the algorithm were: no increase in dosage if plasma-referenced glucose <72 mg/dL was documented at any time in the preceding week, and small insulin dose decreases (2–4 IU/day/adjustment) if severe hypoglycemia (requiring assistance) or plasma-referenced glucose <56 mg/dL were documented in the preceding week. Copyright © 2003, American Diabetes Association. Reprinted, with permission, from reference 47. FPG = fasting plasma glucose.