

An Update on Insulin Injection Devices

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ABSTRACT

Background: Over the past 15 years, it has become clear that better glycemic control can lead to a substantial reduction in diabetic complications and that such control often requires the use of insulin therapy. However, a number of barriers exist to starting such therapy in patients with diabetes mellitus (DM). Many of these barriers to treatment are related to the use of a syringe to inject the medication. In the past ~20 years, various “pen” devices have become available that help to reduce the stigma associated with insulin injection, allowing more patients to achieve the glycemic control that they require.

Objectives: This article provides an overview of the various pen devices available in the United States for subcutaneous insulin delivery and discusses the benefits these devices can provide to patients; their disadvantages are also discussed. Third-party reimbursement for these devices is highlighted.

Methods: A MEDLINE search was performed (1980–2007) to identify relevant articles (English-language only) using appropriate key terms, including *insulin pen* and *insulin delivery device*. Technical specifications and availability information for the various pen devices were obtained directly from their manufacturers. Insurance coverage data were provided by major national insurance carriers.

Results: There are a number of excellent pen devices available for administering each of the currently offered basal and bolus insulin analogues as well as neutral protamine Hagedorn and regular insulins. These devices range from disposable pens—which are supplied to the patient prefilled from the pharmacy, used until empty, and then discarded—to refillable digital pens, some of which have the ability to “remember” prior insulin doses. Data from various studies indicate that both patients and their physicians generally prefer insulin pens over the traditional vial and syringe delivery method. These devices are simple to use, allow patients to be more discreet in social situations, can easily be carried in a shirt pocket or purse, do not need to be refrigerated while in use, are associated with a lesser degree of injection anxiety, and may even be more accurate at lower doses. They may also be the preferred delivery system for the visually impaired, given their larger displays and the audible/tactile “click” produced each time the dose is increased by 1 U. Insulin pens lead to increased patient confidence and satisfaction and improved attitude toward insulin therapy. Most major insurance plans provide some coverage for the disposable pens as well as the cartridges for refillable pens, but this is often under tier 2 and some insurers may require prior authorization.

Conclusions: Insulin pens provide DM patients with a number of advantages over a vial and syringe and can often help them overcome major barriers to the initiation of insulin therapy. The use of insulin pens leads to increased patient compliance and potential improvements in glycosylated hemoglobin, but data on glycemic control are not available. The pens should be offered to virtually all patients who require insulin therapy, except in instances in which these pens are financially prohibited. (*Insulin*. 2007;2:173–181) Copyright © 2007 Excerpta Medica, Inc.

Key words: insulin pen, diabetes mellitus, compliance, glycosylated hemoglobin.

INTRODUCTION

Since the discovery of insulin and its subsequent use in the treatment of diabetes mellitus (DM) in 1921–1922, it has traditionally been supplied in a vial.¹ Based on the evidence that has become available over the past 15 years, we now have

ample data to show that glycemic control is imperative in managing both type 1 and type 2 DM to prevent or reduce diabetic complications.^{2–4} As most physicians are aware, to use this medication the patient is required to insert a syringe into the vial, draw up the necessary dose, and inject it subcu-

taneously. However, the use of a syringe carries with it a significant negative association for many patients. For some, it conjures up images of heroin addicts they have seen on television or in the movies. For others, it reminds them of a relative who suffered from blindness or an amputation because of poorly controlled DM. Others find it socially unacceptable to use such a system when dining out. Still others have a phobia of the needles themselves or the act of injection. All of these issues frequently lead to a delay in initiation of insulin therapy, a refusal by the patient to use insulin, and poor compliance with insulin therapy once it is finally started. Because of these concerns, many physicians are often hesitant to begin insulin therapy, fearing the patient's resistance. Thus, to ensure that patients with DM receive the appropriate treatment, a better method of administering insulin is clearly necessary. An incredible amount of time and effort have been put into finding such a method. Technologies such as inhaled insulin or buccal insulin offer the hope of delivering the medication without the need for injection.⁵ But until these methods become more widely available and have a proven safety record, some form of subcutaneous injection is sure to remain the primary method for insulin administration. Despite this, we are no longer limited to the traditional vial and syringe for subcutaneous administration of insulin.

Novo Nordisk Pharmaceuticals Inc. (Princeton, New Jersey; hereinafter referred to as Novo Nordisk) brought the first insulin "pen" to market in 1985, introducing an alternative to the syringe and vial delivery system. Since then, numerous delivery systems have been developed, and ~20 years of patient experience with them are now available for review. These devices are mostly in the form of insulin pens, so named because of their similarity in size and appearance to a pen. They provide the patient with a number of benefits and help to address many of the aforementioned concerns, which will be discussed in detail below.

This article provides an overview of the various pen devices available in the United States for subcutaneous insulin delivery and discusses the benefits these devices can provide to patients; their disadvantages are also discussed. Third-party reimbursement for these devices is highlighted.

MATERIALS AND METHODS

A MEDLINE search was performed (1980–2007) to identify relevant articles (English-language only) using appropriate key terms, including *insulin pen* and *insulin delivery device*. Technical specifications and availability information for the various pen devices were obtained directly from their manufacturers. Insurance coverage data were provided by major national insurance carriers, including CIGNA Corporation; Aetna Inc.; Oxford Health Plans, L.L.C.; United HealthCare Services, Inc.; and Blue Cross and Blue Shield Association.

INSULIN INJECTION DEVICES CURRENTLY AVAILABLE IN THE UNITED STATES

Each of the 3 major insulin-producing pharmaceutical companies has several insulin delivery devices on the market,

most commonly in the form of pens. Disposable pens come from the pharmacy prefilled with insulin (usually 300 U/pen) and are discarded once they are empty. They are generally very easy to use after a short training session: the patient simply attaches a needle to the end, primes the device by ejecting 2 U through that needle, turns a knob to dial the appropriate dose, and finally injects that dose into the subcutaneous tissue. Because there is no cartridge to insert or change, minimal skill is required on the patient's part. Refillable pens are obtained either from the provider's office or the pharmacy (depending on the particular pen) and must be used with insulin-containing cartridges obtained from the pharmacy. Although they are slightly more complex to operate, refillable pens may have more advanced features (such as dose memory) and cause less environmental waste (as they are reusable) than the disposable pens.⁶ The most commonly used pen devices available in the United States will be discussed here and are summarized in **Table I**.

It is important to note first, however, that the majority of insulin pens in use at this time are manufacturer specific. Each of the 3 major insulin-producing companies markets ≥ 1 insulin pen device that can be used only with select insulin products from that company. This is especially true for the disposable pens because they come prefilled from the manufacturer. Although other manufacturers market refillable pen devices, these are not widely used, and the lack of cartridge compatibility has made it difficult to produce a device that can be used with multiple manufacturers' insulins. Therefore, it is essential to review the insulins available from each of the 3 major manufacturers.

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Novo Nordisk has a number of insulins on the market. These include the long-acting analogue insulin detemir (Levemir[®]), the short-acting analogue insulin aspart (NovoLog[®]), regular human insulin (Novolin[®] R), neutral protamine Hagedorn (NPH) insulin (Novolin[®] N), and the premixed insulins NovoLog[®] Mix 70/30 (70% insulin aspart protamine and 30% insulin aspart) and Novolin[®] 70/30 (70% NPH and 30% regular human insulin). Eli Lilly and Company (Indianapolis, Indiana; hereinafter referred to as Lilly) markets the short-acting analogue insulin lispro (Humalog[®]), regular human insulin (Humulin[®] R), NPH insulin (Humulin[®] N), and the premixed insulins Humulin[®] 70/30 or Humulin[®] 50/50 (70% or 50% NPH and 30% or 50% regular) and Humalog[®] Mix75/25[™] or Humalog[®] Mix50/50[™] (75% or 50% insulin lispro protamine and 25% or 50% insulin lispro).

Table 1. Summary of the major insulin pen devices currently available in the United States.

Device Name	Refillable?	Insulin Types	Comments
FlexPen®*	No	Aspart (NovoLog®*) Detemir (Levemir®*) Premixed (NovoLog® Mix 70/30*)	Easy to use and train patients. May be best pen device for the visually impaired. Both basal and bolus insulins available in the same pen (only need to train the patient on 1 pen).
NovoPen® 3*	Yes	Regular (Novolin® R*) NPH (Novolin® N*) Premixed (Novolin® 70/30*)	Analogues not available. May be better for the visually impaired.
Humalog® pen†	No	Lispro (Humalog®†) NPH (Humulin® N†) Premixed (Humalog® Mix75/25™,† Humalog® Mix50/50™,† Humulin® 70/30†)	Easy to use and train patients. The only disposable NPH pen. May be especially useful in pregnant women or other patients in whom NPH is used as the basal insulin (only need to train the patient on 1 pen for both basal and bolus). Safety feature to prevent accidental discharge of insulin.
HumaPen® MEMOIR™†	Yes	Lispro (Humalog®)	Digital. Memory for the last 16 doses given (also includes "priming" doses). Purchase pen at pharmacy (prescription only). Not covered by insurance at this time. Only available with insulin lispro (no basal insulin available).
SoloStar® pen‡	No	Glargine (Lantus®‡)	Easy to use and train patients. Up to 80 U of insulin per injection.
OptiClik® pen‡	Yes	Glargine (Lantus) Glulisine (Apidra®‡)	Digital. Obtain pen from physician's office (free of charge). Can be used with basal and bolus insulin (separate pen should be used for each).

NPH = neutral protamine Hagedorn.

*Novo Nordisk Pharmaceuticals Inc., Princeton, New Jersey.

†Eli Lilly and Company, Indianapolis, Indiana.

‡sanofi-aventis, Bridgewater, New Jersey.

Sanofi-aventis (Bridgewater, New Jersey) markets a long-acting analogue, insulin glargine (Lantus®), and a short-acting analogue, insulin glulisine (Apidra®).

Disposable Pens

As noted earlier, the disposable pens are manufacturer specific and come prefilled with a single type or mixture of insulin. Insulins detemir, aspart, and Novolog Mix 70/30 are available in a disposable pen device known as the FlexPen® (Novo Nordisk), which can deliver up to 60 U at a time. All FlexPens are made of blue plastic but have labels that are color-coded by type of insulin to reduce confusion in patients using >1 insulin. Insulins lispro, Humulin N, Humulin 70/30, Humalog Mix75/25, and Humalog

Mix50/50 are available in a different disposable pen. This pen is white with a grey cover and allows for a maximum dose of 60 U per injection. It also has a safety feature whereby the dial must be pulled out before a dose can be selected, thus preventing accidental discharge of insulin. Regular insulin, NPH, and Novolin 70/30 are available in a delivery device known as the InnoLet® (Novo Nordisk), which is not shaped like the familiar pen. It is a rectangular white device with a large round dial on the front for dose selection and a large button on the top for dose delivery. None of the insulin analogues are currently available with this device, somewhat limiting its utility. Insulin glargine is now available in the recently released SoloStar® Pen (sanofi-aventis). The SoloStar is a grey-colored pen that can deliver

up to 80 U of insulin per injection. Insulin glulisine is not presently available in a disposable pen but will likely be released in the SoloStar pen in the future.

Refillable Pens

Two refillable pens are presently available from Novo Nordisk, the NovoPen[®] 3 for adults and the NovoPen[®] Junior for children. These pens can be filled with regular, NPH, or Novolin 70/30 insulin cartridges. Neither pen can be used with the insulin analogues at this time. Insulin lispro is available in cartridges for the newly released, refillable HumaPen[®] MEMOIR[™] (Lilly). This is a digital pen device that provides memory for the last 16 doses injected (including date and time) and delivers a maximum dose of 60 U. It is slightly larger than the disposable pen devices but remains very portable. Lilly is expected to release several other refillable pens in the near future. Insulins glargine and glulisine are available in cartridge form for a refillable pen device called OptiClik[®] (sanofi-aventis). This is a blue plastic pen with a digital display for the dose to be injected. Each cartridge holds 300 U, and a separate pen should be used for each type of insulin. It currently does not have a dose memory feature.

Information for patients and physicians on the available insulin pen devices is provided on the following manufacturer-specific Web sites: for the OptiClik pen, visit www.opticlik.com; for Novo Nordisk pen devices, visit www.insulindevice.com; for Lilly pen devices, visit www.lillydiabetes.com under the “products” and “insulin pens” tabs; and for the SoloStar pen, visit www.lantus.com/solostar_insulin_pen.aspx.

Pen Needles

No matter which insulin pen device is chosen, a separate prescription for pen needles will be required, but standardization has made this area far less complex than in the past. Becton, Dickinson and Company (hereinafter referred to as BD; Franklin Lakes, New Jersey) and Novo Nordisk are the 2 major pen needle manufacturers in the United States, and each makes needles in several sizes and lengths. BD's line of Ultra-Fine[™] pen needles is compatible with all of the insulin pens discussed in this article, essentially making them the closest to a “universal” pen needle that is currently available. The NovoFine[®] line of pen needles is recommended only for use with any of Novo Nordisk's pen devices but in practice will also fit onto Lilly pens. However, there are many reports (both clinical and anecdotal) of difficulty using the NovoFine needles with the OptiClik pen, so this use should probably be avoided. The pen needles are intended for 1-time use, although there is evidence that they can be used multiple times without significant needle-tip deformity or increased injection-induced pain.⁷

Both BD and Novo Nordisk also make safety needles. Novo Nordisk's device is called the NovoFine[®] Autocover[™] and BD's is the newly released AutoShield[™]. These devices keep the pen needle covered before and after use and prevent reuse of the same needle. They are targeted toward prevention of needlestick injuries in institutions or other

situations in which the patient is not self-administering the injection. However, they may also help to reduce anxiety in children or patients with needle phobia (as the needle remains invisible to the patient).

BENEFITS AND PATIENT PREFERENCES

As discussed earlier, the use of syringes to inject insulin carries a strong negative association with many patients, often leading to a delay or even refusal to initiate insulin therapy. Therefore, as the need for multiple daily injections of insulin continues to rise, it is necessary to develop new and more convenient methods of delivery to make this therapy available to a wider range of patients. The insulin pen is a device that helps accomplish this goal. Many studies⁸⁻¹³ have established both patient and physician preferences for the pen devices over the traditional vial and syringe, and the pen devices have a number of advantages. They are generally more convenient for the patient, allow for more discreet injection in social situations, are associated with considerably less fear of injection, and may be more accurate at lower doses. They also lead to an improved attitude toward the use of insulin therapy.¹⁴

Many studies have established both patient and physician preferences for the pen devices over the traditional vial and syringe, and the pen devices have a number of advantages.

In a randomized, open-label trial of 103 patients comparing the FlexPen with the vial/syringe for delivery of twice-daily Novolog 70/30 insulin,¹¹ 74% of the patients preferred the FlexPen. In addition, 85% felt the FlexPen was “more discreet for use in public,” 74% found it easier to use than the vial/syringe, and 85% found the numbers on the pen easier to read than the syringe. Patients felt the pen provided them with a greater sense of confidence regarding their glycemic control, but there were no significant differences in fasting plasma glucose or fructosamine levels between the groups.

There is further evidence that the pen devices are generally preferred by patients and can reduce fear of injection. In a survey of 242 diabetic patients (99 insulin users and 143 noninsulin users),¹⁰ the majority of patients indicated their preference for pen devices, citing social acceptability and ease of use as the major reasons. In another prospective, randomized, open-label trial of 260 diabetic patients,⁸ the vial/syringe was compared with the InnoLet injection device. Patients using the device reported less “fear of self-injection,” and the majority of patients indicated their preference for the InnoLet device over the vial and syringe.

There is very limited evidence comparing patient preference for one type of pen over another, but Lilly recently released a study involving its new HumaPen MEMOIR.⁶ In this relatively short study, 300 diabetic patients currently

using an insulin pen were converted to the HumaPen MEMOIR for either basal or prandial insulin for 8 weeks. (Although this pen was used to deliver basal insulin in this study, it is currently available for use only with the prandial insulin lispro.) Most of these study patients had been using a pen from sanofi-aventis or other Lilly pens before the trial. By the end of 8 weeks, >80% of the participants indicated a preference for the HumaPen MEMOIR over their prior insulin pen. A few failures of the pen device occurred, which required the patients to obtain a new pen; however, there were no major adverse events related to device failure. Overall, 96% of patients found the device to be easy to use, and 85% of the patients and 100% of the providers found the memory feature to be useful (to confirm that a dose was taken, to confirm the time of the last dose, or to view the amount of insulin taken on prior doses). Providers may also find the memory feature useful when assessing patients' compliance with their insulin regimen (and with priming the device).

Aside from patient preferences, there is also evidence that the pen devices are more accurate than the vial and syringe at lower doses. In one study comparing the NovoPen, Humalog pen, vial and syringe, and an insulin pump,¹⁵ the pens and pump were significantly more accurate ($P < 0.001$ at 1-U dose) than the vial and syringe at doses of 1 to 2 U. The authors noted that the syringe was "dangerously inaccurate" at these low doses. Another study comparing the NovoPen and the vial and syringe demonstrated that the pen was more accurate at 1-, 2-, and 5-U doses.¹⁶ The pen tended to undershoot the desired dose slightly and the syringe to overshoot. These findings are particularly important for children, who may require low doses of insulin. At such doses, even small inaccuracies can be significant, leading to increased episodes of hypoglycemia.

Additionally, there is some evidence that switching patients from vial and syringe insulin delivery to pen insulin delivery can improve compliance with therapy. A recent retrospective study¹⁷ looked at 1156 diabetic patients in a medical and pharmacy claims database who were on insulin therapy delivered by vial and syringe (human or analogue) and were then converted by their physicians to pen delivery systems of insulin analogues. The investigators found that the percentage of patients adherent to their insulin therapy (defined as a medication possession ratio >0.8) rose from 36.1% to 54.6% after conversion to the pen device. They also noted a decrease in the rates of hypoglycemia and hospital utilization after conversion. One confounding variable is that a substantial number of patients were converted from human insulins by vial and syringe to insulin analogues by pen, although this was controlled for in the multivariate analysis.

There is some evidence that switching patients from vial and syringe insulin delivery to pen insulin delivery can improve compliance with therapy.

Furthermore, pen devices may be more useful than the vial and syringe in patients with limited eyesight. These patients are often unable to read the small numbers on the insulin syringe and therefore often depend on others to prefill syringes for them, essentially excluding the possibility of mealtime dose-adjustment based on carbohydrate intake. Insulin pens provide a larger dose display and an audible/tactile "click" each time the dose is increased by 1 U. This allows visually impaired patients the independence of selecting the appropriate insulin dose at the time of the meal, thus reducing their reliance on others. According to a study of 48 nonvisually impaired, diabetic patients who were randomized to either the NovoPen 3, HumaPen[®] Ergo (Lilly), Humalog pen, InnoLet, or FlexPen,¹⁸ the FlexPen and NovoPen 3 provided the most audible/tactile "click" when setting the dose and led to the most patient confidence in dose setting and most reliability in dose setting. Although there are currently no data with these pens in visually impaired patients, such patients are reliant on the audible and/or tactile click of the pen to set the appropriate dose. Therefore, there may be an advantage to the FlexPen in this population.

Because of the many benefits, insulin pen usage has rapidly spread throughout much of Europe. For example, a European study of 1002 patients in 22 centers across 7 countries found that ~80% of diabetic patients on insulin were using a pen for at least 1 type of insulin.¹⁹ In the United Kingdom, pen use is ~3 times more common than in the United States.²⁰ The reason for this difference is multifactorial but includes significant practice differences between the 2 countries. Type 2 DM patients in the United Kingdom are generally referred to specialized nurses when they need to transition to insulin. Because of their specialization, these nurses are very familiar with the available pens and their use. At the time of the initial visit, patients are allowed to choose the pen device they feel is best for them (from any manufacturer), and then the most appropriate insulin regimen available with that device is selected by the provider. This differs from the standard practice in the United States, where the brand of insulin prescribed is often determined by insurance coverage issues or by the physician, and then the patient must use the devices available with that brand. Furthermore, in the United Kingdom, pens and needles are fully covered by the national health care system, removing any cost barriers to their use.²⁰ As in the United States, the majority of patients in the United Kingdom prefer the pen devices to the syringe and vial.

DISADVANTAGES

Despite the many benefits and overall patient preference for insulin pen devices discussed here, there are some disadvantages. First, pens are more costly than the vial and syringe to the health care system and possibly to the patient. A more detailed discussion of this matter can be found in the next section. Another issue is that the design of the pen can make it somewhat difficult to determine when the full dose of insulin has been injected. Because of the mechanics of the

pen device and the fact that insulin has to be forced through a tiny opening in the needle tip, insulin can still be flowing out of the pen for several seconds after the button is fully depressed. The larger the dose of insulin, the longer it will take to inject through the needle. This is a problem because if the needle is prematurely withdrawn from the skin, an underdose error results and the excess insulin is wasted. There is no way to determine how much insulin was actually injected and how much wasted, and hyperglycemia generally results. To avoid this, the injection device must be held in place with the button fully depressed for 5 seconds before withdrawal from the skin. In addition, when using a pen device, there is no way for the patient to actually observe when all of the insulin has been injected, which can be done with a syringe. Although this may be a problem for some patients, with adequate training it should be an avoidable one.

Another potential disadvantage is the introduction of air or biologic materials into the pen during injection. In a study of 120 diabetic patients using older pen devices (BD pen, Novolet® [Novo Nordisk], Novopen 3, or Omnipen [not available in the United States]), the investigators determined that noninert material was found in 62% of the pen cartridges during normal usage.²¹ This material included squamous and epithelial cells. The study also revealed the presence of air bubbles in 45% of the cartridges. Because of these potential problems, pens should not be shared between multiple patients (even with separate needles). In addition, the needle should be removed from the pen immediately after each use to avoid the introduction of air into the insulin reservoir.

Furthermore, because the pen is a mechanical device, the potential exists for malfunction. Rare cases of pen failure were seen in most of the studies discussed in the previous section. It is therefore important to discuss the availability of a backup device with patients who are using the insulin pen. Finally, although the vast majority of patients prefer the pen delivery system, there will always be some who prefer the vial and syringe for various reasons.

REIMBURSEMENT AND COST ISSUES

On a unit-for-unit basis, insulin sold in a pen device or cartridge is more expensive than insulin sold in a vial (**Table II**). Because of this, the use of insulin pens will increase the cost of purchasing insulin to the health care system as a whole. However, when all factors are considered, this may not translate into an increase in diabetic treatment cost. A recent study of managed care claims of 1156 diabetic patients who were converted from human or analogue insulin with vial and syringe to analogue insulin with pen device demonstrated that this conversion reduced the overall cost to the health care system.¹⁷ Conversion to the pen device led to increased patient compliance, decreased hospital admissions for hypoglycemia, and fewer emergency department and office visits. This study was confounded by the fact that in the process of conversion from vial to pen, many patients were also converted from human insulin to analogue insulin, which likely contributed to the reduction in hypoglycemia.

Despite this limitation, it suggests that the conversion to insulin analogue pens may reduce the overall treatment cost of diabetic patients in the managed care setting. However, further studies are clearly necessary before a definitive conclusion can be made.

Many third-party payors have multiple tiers of prescription drug coverage. Tier 1 carries the lowest copayment for the patient (or even no copayment) and is most often reserved for generic medications. Tiers 2 and 3 (and/or 4) carry successively higher copayments and are reserved for brand name preferred (tier 2) or nonpreferred (tier 3 or 4) medications. At least one of the disposable pens (FlexPen or Humalog pen) is generally covered to some extent by each of the major third-party insurers. However, this coverage is often under tier 2 and may therefore increase the out-of-pocket expense to the patient. In addition, a few insurers require prior authorization for insulin pen devices. Disposable pens are dispensed from the pharmacy in packs of 5 (1500 U); therefore, for 1 copayment, the patient will receive 1.5 times the amount of insulin contained in 1 vial (1000 U). This may help to offset any cost differential due to tier 2 coverage and may even represent a cost savings for the patient, although it clearly does not alter the overall cost to the health care system.

The OptiClik pen is provided to the patient for free by the physician (pens can be obtained by physicians directly from sanofi-aventis at no cost). The patient then obtains the insulin-containing cartridges from the pharmacy (also dispensed in a package of five 300-U cartridges at a time). These cartridges are more likely to be covered under tier 3 than the disposable pens and may require prior authorization. The new HumaPen MEMOIR must be purchased by the patient from the pharmacy and is available by prescription only. It is currently not covered by insurance, but discount coupons are available from Lilly (substantially reducing the cost of the pen). The pen is designed to be reused for a period of ~3 years and should not require any maintenance over that time. Once again, insulin-containing cartridges are obtained from the pharmacy.

Because of the large number of prescription drug insurance plans available in this country, each with its own regional differences, it is difficult to provide an accurate estimate of the cost differential to the insured patient between the pen and vial. With some insurers, there may be no difference because insulin analogues dispensed in both the vial and pen are tier 2 medications (as there is no generic available in either case). With others, the insulin analogue vials may be in tier 1 or 2, while the pens are in tier 2 or 3. Furthermore, some insurers place insulin analogues from one manufacturer in tier 3 and analogues from another in tier 2. However, it is uncommon for an insurer to have none of the short-acting insulin analogues available in a pen device in tier 2 or below, although this can occur with the long-acting analogues. The actual difference in copayment between the tiers can range from as little as \$10 to as much as \$40 to \$50, or even higher. Representatives from the 3 major insulin-producing companies are generally very

Table II. Retail price comparison of insulin analogues in the United States.*

Product Name	Package	Units per Package	Retail Price, \$	Price per Unit, \$	Percent Difference in Unit Price (Pen vs Vial)
Novolog ^{®†}					
Vial	1 Vial	1000	88.52	0.089	18.53
FlexPen [®]	1 Box of 5	1500	157.39	0.105	
Novolog [®] Mix 70/30 [†]					
Vial	1 Vial	1000	89.73	0.090	23.62
FlexPen	1 Box of 5	1500	166.38	0.111	
Levemir ^{®†}					
Vial	1 Vial	1000	84.15	0.084	16.45
FlexPen	1 Box of 5	1500	146.99	0.098	
Humalog ^{®‡}					
Vial	1 Vial	1000	78.47	0.078	36.14
Pen	1 Box of 5	1500	160.24	0.107	
Humalog [®] Mix75/25 ^{™‡}					
Vial	1 Vial	1000	84.00	0.084	17.06
Pen	1 Box of 5	1500	147.50	0.098	
Lantus ^{®§}					
Vial	1 Vial	1000	79.79	0.080	31.26
Cartridge	1 Box of 5	1500	157.10	0.105	

*Pricing data are based on the retail price available to consumers at www.drugstore.com as of May 2007.

[†] Novo Nordisk Pharmaceuticals Inc., Princeton, New Jersey.

[‡] Eli Lilly and Company, Indianapolis, Indiana.

[§] sanofi-aventis, Bridgewater, New Jersey.

familiar with local insurance coverage issues, so they may represent a valuable resource for determining coverage in a specific area.

As discussed earlier, all of the pen devices require a separate prescription for pen needles, which are screwed onto the tip of the pen. The BD needles are priced similarly to the BD insulin syringes, and other manufacturers (such as UltiMed Incorporated, St. Paul, Minnesota) have started to produce pen needles that can be used across a wide range of devices with even lower prices. The needles are also covered by most third-party insurers. However, pen needles are presently somewhat more costly than insulin syringes to the health care system as a whole (because of the lack of generic brands).

In addition to insurance coverage, other issues must be addressed. Although pens are more expensive than the vial and syringe on a unit-for-unit basis, these devices can ultimately represent a cost savings (to both the patient and the health care system as a whole) for patients taking small daily doses of insulin. This is because all insulins "expire" a certain number of days after opening the vial (usually 30 days but can be 10–15 days for premixed insulin). Once the expiration date is reached, the remainder of the vial must be discarded, leading to wasted insulin in patients using <1000 U per month. Because the pen devices contain less insulin per pen (usually 300 U) with the same duration of use before expiration, there is generally no waste due to insulin expiration.

Many hospitals are switching to pen delivery systems for inpatients too, and this has made it even easier to teach patients to use these devices before discharge. One of the main reasons for this is a reduction in wasted insulin. Many diabetic patients will not be able to consume an entire vial of insulin during a single hospital stay. Assuming 1 vial (1000 U) of insulin was assigned to each insulin-treated inpatient and not used for other patients, this would lead to a large amount of wasted insulin. Insulin pens are able to reduce this waste because each pen contains only 300 U of insulin. Taking a simple example, a patient on 50 U/day of insulin who stays in the hospital for 3 days will consume 150 U of insulin. This represents a loss of 850 U of insulin if a vial is assigned to that patient, but only 150 U of insulin if a pen is assigned. The use of insulin pens in the hospital also provides an opportunity for introducing patients to and training them in the use of these devices for use at home. In addition, the in-hospital use can provide the patient with many of the advantages of home insulin pen use already discussed.

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Although insulin pen use in the hospital helps to reduce waste in most cases and provides a forum for patient training, there are some disadvantages. From a safety standpoint, there is some evidence that insulin pen use actually increases the number of needlestick injuries to the hospital staff.²² This is likely related to the need to unscrew the needles from the tip of the pen after use. Continued training of the staff in proper technique and the use of safety needles (such as those discussed earlier) should help to reduce this increased risk but may increase costs to the system. In addition, staff members who are accustomed to injecting insulin with a syringe may find the pen devices challenging to use, especially at first. With the pen device, they are unable to see when the entire dose has been injected and may prematurely remove the needle from the skin, leading to an underdose. As with any new device, there may also be a certain degree of resistance to change, and a learning curve should be expected. However, with better training, more experience, and the possible use of safety needles, the potential exists to correct all of these problems.

DISCUSSION

Compared with a vial and syringe, insulin pens are more convenient for patients to carry with them, they allow for discreet injection of premeal insulin in social situations (such as at a restaurant), and they often help reduce needle phobia and the negative stigma associated with a syringe. With the use of a needle-guard device, they can even make the needle completely invisible to the patient, further reducing the fear of injection. They do not require refrigeration while in use and can therefore be stored in the patient's handbag, pocket, or backpack. The pens make it easier for patients to measure the correct insulin dose, and often afford the elderly and

visually impaired a greater degree of independence. They may even improve glycemic control by promoting increased compliance, but outcome data on improvements in glycosylated hemoglobin or fructosamine are not currently available. Overall, insulin pens lead to increased patient confidence and satisfaction and potential improvements in control.

Certain digital pens may provide more advanced features. Although current digital pens are restricted to a memory capacity of only 16 doses, increased memory as well as other features will certainly be added as technology advances. Future pens may incorporate carbohydrate-counting assistants, insulin dose calculators, or even glucometers. They also promise more accurate and reliable dose delivery. For all of these reasons, insulin pen devices are preferred over the traditional vial and syringe by the vast majority of patients. Their use is widespread throughout much of Europe, where ~80% of patients are using pen devices. Aside from cost and training issues, there are few major disadvantages to the use of insulin pens. Also, it remains unclear whether the widespread use of these devices would actually produce an increased cost to the health care system. Therefore, provided it is financially feasible for the patient, there is little reason not to offer these insulin pens to all individuals with DM who require insulin therapy.

CONCLUSIONS

Insulin pens provide DM patients with a number of advantages over a vial and syringe and often can help them overcome major barriers to the initiation of insulin therapy. The pens should be offered to virtually all patients who require insulin therapy, except in instances in which these pens are financially prohibited.

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