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SYMPOSIUM

Evolution of Diabetes Insulin Delivery Devices

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Abstract

The first manufactured insulin pump was introduced in the 1970s and the first insulin pens in 1985; since then, many improvements have been made to both devices. The advantages of pens over syringes have been confirmed in numerous studies and include greater accuracy, ease of use, patient satisfaction, quality of life, and adherence. United States claims database analyses indicate that the improved adherence made possible by use of an insulin pen has the potential to reduce diabetes care costs when compared with using a vial and syringe. Features of certain advanced pump models include the ability to connect wirelessly to a blood glucose meter or to a subcutaneous interstitial glucose sensor for semicontinuous glucose-driven insulin rate adjustment. A new trend in the design of insulin pumps is the tubing-free patch pump that adheres directly to the skin. The low rate of insulin pen usage in the United States compared with European countries and the fact that many patients report that they are not offered the option of an insulin pen by their physician suggest that there is a need to increase patient and provider awareness of the currently available devices for insulin administration.

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Introduction

The publication of the results of the landmark Diabetes Control and Complications Trial (DCCT) in 1993 clearly demonstrated the need for intensified methods of blood glucose (BG) control in type 1 diabetes to prevent complications such as retinopathy, nephropathy, and neuropathy.[1] Five years later, the importance of intensive glycemic control to prevent microvascular complications in type 2 diabetes was shown by the United Kingdom Prospective Diabetes Study (UKPDS).[2] However, the need for more convenient, safer, and more effective methods of insulin administration had been apparent long before the DCCT and UKPDS results were published.[3] When insulin was first discovered in the early 1920s, the method of delivery used large glass syringes and reusable needles, both of which needed sterilization by boiling after each use. Needles were sharpened with a pumice stone so they could be reused. For over 50 years, vial and syringe remained the only delivery option available for routine clinical use. The first manufactured insulin pump was introduced in the 1970s, while the first manufactured insulin pen, the NovoPen® (Novo Nordisk), was introduced in 1985.[4]

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Abbreviations: (A1C) glycated hemoglobin, (BG) blood glucose, (CI) confidence interval, (CSII) continuous subcutaneous insulin infusion, (DCCT) Diabetes Control and Complications Trial, (DKA) diabetic ketoacidosis, (FDA) Food and Drug Administration, (MDI) multiple daily injections, (MPR) medication possession ratio, (OR) odds ratio, (QALY) quality-adjusted life year, (RCT) randomized controlled trial, (UKPDS) United Kingdom Prospective Diabetes Study

Keywords: continuous subcutaneous insulin infusion, diabetes, insulin delivery, insulin pen, insulin pump

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Since then, many improvements and innovations have been made to both insulin pumps and pen devices. Furthermore, insulin analogs have become available that enable both continuous subcutaneous insulin infusion (CSII) using an insulin pump and insulin therapy using multiple daily injections (MDI) to more closely match physiologic insulin patterns.[5–8]

For various reasons that are unrelated to the scientific evidence base, the rate of adoption of insulin pens and pumps has differed greatly between the United States and Europe. Insulin pumps are more widely used on the American side of the Atlantic than on the European side, whereas insulin pens are used as an alternative to syringes by the majority of diabetes patients in Europe but by only approximately 15% of diabetes patients in the United States.[9,10] The faster development of insulin pumps in the United States may be due to the fact that the United States was the country where the first manufactured insulin pump was invented.[10] Additionally, the publication of the DCCT results greatly contributed to the rapid growth of CSII use in the United States, because almost half of the DCCT patients in the intensive treatment arm had been treated with CSII. As initial instruction for use of CSII takes considerably longer than that for an insulin pen, the use of CSII in the United States may also be facilitated by the availability of certified diabetes educators, who have the time and expertise to educate patients in the correct use of this technology.

Both insulin pens and insulin pumps can offer benefits to patients, including the potential for improved clinical outcomes. However, in a survey of 600 patients using insulin for the treatment of type 2 diabetes in the United States, many patients reported that they had not been offered the option of an insulin pen by their physician.[11] Together with the low rate of insulin pen use in the United States compared with European countries, this suggests that there is a need to increase provider awareness of the benefits and limitations of the currently available devices for insulin administration in type 2 diabetes so that patients are informed of the range of options available and are thus able to choose the device that best suits their individual circumstances. Therefore, this article reviews the benefits and limitations of insulin pens and pumps in the treatment of diabetes.

Methods

This review is based on a literature search of the PubMed database using the following search strategy: "(diabetes *or* insulin *or* insulins) *and* (pen *or* pens *or* pump *or* pumps *or* CSII *or* continuous subcutaneous insulin infusion)". Health economic papers were identified by adding the search term "cost *or* economic." Searches were limited to articles published in English between January 1, 1985, and September 29, 2009. Priority was given to meta-analyses, systematic reviews, practice guidelines, and controlled clinical trials. Additional articles were identified from the reference lists of review articles.

Benefits and Limitations of Insulin Pens Versus Vial and Syringe

Insulin injection using vial and syringe delivery has the potential for several problems, including the inconvenience of carrying several materials and preparing the syringe, the adverse psychological and social impact of using a syringe (because syringes are associated with sickness and drug abuse), use of the incorrect insulin product, and failure to administer accurate doses. The development of insulin pens has therefore focused on ways to counter such problems. Several disposable and reusable pen devices have been developed that provide options for delivering rapid- and long-acting insulins and insulin premixes. **Table 1** lists the pen devices that are currently available in the United States. The advantages of insulin pens over syringes have been confirmed in numerous studies.[12–22]

Table 1.
Insulin Pen Delivery Devices Available in the United States[a]

Refillable pens (manufacturer)	Prefilled disposable pens (manufacturer)
Autopen® 24 (Owen Mumford)	FlexPen (Novo Nordisk)
Autopen Classic AN3800 (Owen Mumford)	Humalog® KwikPen™ (Eli Lilly)
Autopen Classic AN3810 (Owen Mumford)	Humalog Pen (Eli Lilly)
HumaPen LUXURA HD (Eli Lilly)	SoloSTAR® (sanofi-aventis)
HumaPen MEMOIR (Eli Lilly)	
NovoPen 3 (Novo Nordisk)	
NovoPen 4 (Novo Nordisk)	
NovoPen Junior (Novo Nordisk)	
OptiClik® (sanofi-aventis)	

[a] Compatible insulin analogs for pen devices: Novo Nordisk = insulin detemir, insulin aspart, and biphasic insulin aspart 70/30; Eli Lilly = insulin lispro, insulin lispro mix 75/25, and insulin lispro mix 50/50; and sanofi-aventis = insulin glargine, insulin glulisine. The Autopen Classic takes Eli Lilly insulin cartridges, and the Autopen 24 takes sanofi-aventis insulin cartridges. The NovoPen models use 3 ml PenFill® cartridges.

These advantages, which include greater accuracy, convenience, patient preference, and adherence, are discussed here.

Accuracy, Ease of Use, and Patient Preference

In a study of syringes and pens used by children with type 1 diabetes, pens were more accurate than syringes in measuring out insulin at low insulin doses (<5 U).[20] At doses above 5 U, pens and syringes had similar accuracies. In another study, pens were found to be more accurate than syringes at doses of 1 and 2 U.[16] In a survey of 507 insulin users, 89% of 479 respondents (not all patients answered all survey questions) considered an insulin pen to be more socially acceptable than a vial and syringe; 86% of 475 respondents indicated that a pen was easier to use; and 86% of 488 respondents said that it took less time to prepare and administer injections with a pen.[14] Similar responses were found in a survey of nurses in a community hospital after implementation of insulin pen devices.[22] The majority of nurses stated that insulin pens were more convenient than vials/syringes. In addition, implementation of insulin pen devices did not increase the nurses' time spent to teach patients to self-inject insulin and did not increase insulin-related needle stick injuries.

Korytkowski and colleagues[17] assessed patient preference for an insulin pen versus vial and syringe in a randomized, open-label, crossover study in 121 adults with type 1 or type 2 diabetes. Patients were randomized to use either a prefilled pen or vial/syringe to administer an insulin analog premix regimen for four weeks, followed by four weeks' use of the other injection device. In summary, 74% of patients indicated a preference for the pen over the vial/syringe (compared with 20% who preferred the vial/syringe), 85% considered the pen more discreet for use in public (compared with 9% for the vial/syringe), 74% considered it easier to use overall (compared with 21% for the vial/syringe), and 85% found the insulin dose scale on the pen easier to read (compared with 10% for the vial/syringe). The quality-of-life benefits of insulin pens compared with syringes have also been confirmed in other studies using generic quality-of-life scales.[18,21]

Adherence

Adherence to the appropriate insulin therapy is a major element of good glycemic control, and there is evidence that insulin pens can improve patient adherence compared with vial and syringe delivery.[12,19] Lee and associates[19] analyzed U.S. managed care claims data for 1156 subjects with type 2 diabetes. This study found that medication adherence (measured by the medication possession ratio [MPR]) significantly improved from 62% to 69% ($p < .01$) after conversion from regular human or analog insulin injection using a vial and syringe to a prefilled insulin analog pen (containing either insulin aspart or biphasic insulin aspart 70/30). In a similar study by Cobden and coworkers[12] of 486 subjects who switched from vial and syringe to an insulin pen prefilled with biphasic insulin aspart 70/30, the MPR increased from 59% to 68% ($p < .01$). However, it should be noted that, although the MPR is a well-established measure of adherence, it is not possible to confirm with claims data that patients are correctly or accurately administering their drugs, and it is also not possible to include factors such as drug sharing or wastage.

Health Economics of Insulin Pens

Insulin analogs supplied in cartridges or prefilled pens have a higher per unit of insulin cost than do insulin analogs supplied in vials. For example, one vial (1000 U) of insulin glulisine costs $105.95, which equates to a cost of 10.6 cents per unit of insulin. Five prefilled insulin pens containing insulin glulisine (total of 1500 U) have a total cost of $201.01, equating to a cost of 13.4 cents per unit of insulin (26% more than the cost of insulin glulisine supplied in a vial). (Prices are the retail prices available to consumers at www.drugstore.com as of March 18, 2010. These prices are without health insurance coverage. Co-pays for pens and vials are similar for most health insurance plans.) However, most pen devices now have good formulary coverage, so cost should not be a limitation to the patient or physician. Data from the two studies that analyzed U.S. managed care claims data indicate that the improved adherence made possible by use of an insulin pen has the potential to reduce diabetes care costs (not including the cost of insulin) when compared with vial/syringe delivery, despite higher prescription costs for pen delivery.[12,19]

In the study by Lee and colleagues,[19] in addition to improved medication adherence in patients who converted from vial/syringe therapy to a prefilled insulin analog pen, the likelihood of experiencing a hypoglycemic event significantly decreased after conversion (odds ratio [OR] = 0.50; 95% confidence interval [CI], 0.37–0.68; $p < .05$). There were also significant decreases in hypoglycemia-attributable emergency department visits (OR = 0.44; 95% CI, 0.21–0.92; $p < .05$) and physician visits (OR = 0.39; 95% CI, 0.24–0.64; $p < .05$). Total mean all-cause annual treatment costs were reduced by $1590 per patient (from $16,359 to $14,769; $p < .01$). Annual hypoglycemia-attributable costs were reduced by $788 per patient (from $1415 to $627; $p < .01$), predominantly as a result of decreased hospitalization costs (from $857 to $288; $p < .01$). Annual diabetes-attributable costs were reduced by $600 per patient (from $8827 to $8227; $p < .01$). There were similar findings in the study by Cobden and associates,[12] with significant decreases observed in the likelihood of hypoglycemic events and in treatment costs after conversion to a prefilled pen containing an insulin analog premix.

Another study assessed patients with type 2 diabetes enrolled in the North Carolina Medicaid program and found that initiating insulin therapy with an insulin pen was associated with significant reductions in health care resource utilization and associated costs compared with starting insulin therapy using a vial and syringe.[23] In this study, diabetes-related medication adherence was comparable with the two delivery methods, with an adherence rate of 53% for patients initiating insulin with a pen compared with a rate of 50% in patients using a syringe. However, total annualized health care costs were significantly lower for patients using an insulin pen than for those using a syringe ($14,857.42 versus $31,764.78; $p < .05$). Cost reductions with pen therapy compared with vial/syringe use were seen in hospital costs ($1195.93 versus $4965.31; $p < .05$), diabetes-related costs ($7324.37 versus $13,762.21; $p < .05$), and outpatient costs ($7795.98 versus $13,103.51; $p < .05$).

Glycated Hemoglobin

Although two studies have reported that switching from vial/syringes to prefilled insulin analog pens improved adherence as measured by the MPR, no rigorous, controlled studies to date have shown that insulin pen use is associated with greater reductions in glycated hemoglobin (A1C) as compared with vial and syringe use. One small study in 23 homeless patients found that switching from vial and syringe to a reusable insulin pen improved glycemic control at 3 and 6 months.[24] In a study in 72 patients with type 1 diabetes who switched from vial and syringe injections to four or five injections per day with an insulin pen, glycemic control improved at follow-up (9–13 months after the switch) only in those patients who has previously been receiving one or two injections per day.[25] When these patients were followed up for a further five years, metabolic control was found to deteriorate over time.[26] However, the lack of a control group in these studies means that the effects of the natural history of the disease and of regression to the mean cannot be excluded.

As mentioned earlier (in the *Accuracy, Ease of Use*, and *Patient Preference* section), in the randomized, open-label, crossover study conducted by Korytkowski *et al.*,[17] patients with type 1 or type 2 diabetes were randomized to use either a prefilled pen or vial/syringe to administer biphasic insulin aspart 70/30 for four weeks, followed by four weeks' use of the other injection device. No statistically significant differences were found between the two devices in mean fasting plasma glucose, serum fructosamine, or four-point glucose profile.

Other Refinements

Over the past 20 years, insulin pens have been constantly refined, with certain newer models offering advantages over older ones. For example, the latest improved FlexPen® (Novo Nordisk) requires a lower injection force while maintaining dose accuracy when compared with the older, original FlexPen.[27] Another example is the inclusion of a memory function in the HumaPen® MEMOIR™ device (Eli Lilly), which records the date, time, and amount of the previous 16 doses (including priming doses), so that patients and healthcare providers can see exactly how much insulin the patient last took and when. Finer needles and safety needles that are associated with reduced pain perception have also been developed for use with insulin pens.[28,29] Disposable prefilled pens (which many patients find more convenient than the reusable cartridge-type pens) are now available for all insulin analogs. Many current insulin pen models also allow backward dialing to correct misdialed doses without wasting insulin. Two models allow the dose to be adjusted in half-unit increments (HumaPen LUXURA™ HD [Eli Lilly] and NovoPen Junior [Novo Nordisk]).

Limitations Versus Vial and Syringe

Apart from their higher prescription cost, the main limitation of pens compared with syringes is the inability for patients to mix their own insulin formulations (i.e., neutral protamine Hagedorn insulin mixed with regular insulin). However, three different premixed biphasic insulin analogs are available for use in prefilled and reusable pens. Furthermore, the mixing of insulin preparations is known to be highly inaccurate when performed by elderly patients.[30]

Benefits and Limitations of Insulin Pumps

Improvements in insulin pump technology are also having an impact in providing an alternative option for insulin delivery in patients failing to achieve glycemic control using a MDI regimen and in other selected patients. The brick-sized devices of decades past have been replaced by small pumps no bigger than a pager. Modern external insulin pumps weigh less than 4 oz and consist of an insulin reservoir, a small battery-operated pump, and a computerized control mechanism. Pumps deliver a continuous infusion of insulin (usually a rapid-acting insulin analog) via a cannula that is placed subcutaneously. Pumps are programmed to deliver both basal and bolus doses. Premeal or snack bolus doses can be selected to cover the user's estimated carbohydrate intake at mealtime and to correct for out-of-range BG readings. All pumps have occlusion and near-empty alarms. Pumps are also supplied with multiple basal delivery profiles that allow the patient to select different basal infusion rates based on differences in daily or weekly schedules. For example, a patient might require a different basal pattern on weekdays compared with weekends, or a schoolchild might need to adjust if the school day involves sporting activities.

Table 2 provides an overview of the features of currently available insulin pumps. Many advanced models (e.g., OneTouch® Ping™, OmniPod®, and MiniMed Paradigm®) can connect wirelessly to BG meters. The MiniMed Paradigm can also connect wirelessly to a disposable subcutaneous interstitial-glucose sensor for semicontinuous glucose-driven insulin rate adjustment; this system is currently the only integrated pump and continuous glucose monitoring system available. Currently available continuous interstitial glucose monitoring systems are not as accurate as current home glucose meters but are useful for providing patients with the ability to monitor changes in glucose levels between finger stick readings.

A new trend in the design of insulin pumps is the tubing-free "patch" pump. The only currently available patch pump is the OmniPod. The OmniPod pump/reservoir unit adheres directly to the skin and contains an integrated infusion set and automated inserter. The pump/reservoir unit communicates wirelessly with a separate controller that includes an integrated BG meter. Benefits of this patch pump design that have been reported by patients include the ability to wear the pump in the shower and the greater convenience of a tubing-free system. In one small study, 90% of patients (18 of 20) preferred using the OmniPod's automated cannula insertion system versus inserting with their current infusion sets.[31] Use of a patch pump may be particularly beneficial in adolescents, as 52% of 48 adolescents in one study reported that they disconnected their (conventional design) pump for exercise.[32]

Like the OmniPod, the OneTouch Ping also comes with a separate wireless controller that includes an integrated BG meter and integrated food database for bolus calculations. The OneTouch Ping, which uses a conventional (i.e., nonpatch) pump design, can be controlled from both the pump itself as well as from the wireless controller.

It is expected that more patch pumps will come onto the market in the future. The Solo™ MicroPump (Medingo, Ltd.) is a patch pump that has already received U.S. Food and Drug Administration (FDA) approval but, as of the time of this writing, is not yet available for sale. Another likely future advance in the development of CSII technology is the development of more accurate continuous glucose monitoring systems for use in combination with insulin pumps.

Continuous Subcutaneous Insulin Infusion in Type 1 Diabetes

Among patients with type 1 diabetes, the principal indications for CSII include patients who are unable to achieve acceptable glycemic control using MDI, patients with histories of frequent or severe hypoglycemia, and patients who need more intensive management because of microvascular complications.[33,34] Since the introduction of long-acting insulin analogs, the "dawn phenomenon" has become a less frequent indication for CSII.[34] However, pump therapy is not only costly, but requires a high level of motivation and commitment to diabetes self-management, with frequent checks of BG levels throughout the day, a responsibility that not all patients with diabetes are willing or able to undertake. In addition, some patients, particularly adolescents, may be self-conscious about being attached to a foreign object.[35]

When used in CSII, rapid-acting insulin analogs have been shown to produce a modest but significantly greater reduction in A1C compared with regular human insulin and are preferred by patients.[5] **Table 3** provides an overview of the insulins approved for pump therapy, including the maximum time allowed in the insulin reservoir.

Table 2.
Key Features of Insulin Pumps Available in the United States[a]

Insulin pump model	Accu-Chek® Spirit	OneTouch Ping	MiniMed Paradigm 522/722	DANA Diabecare IIS	OmniPod Insulin Management System	Nipro Amigo®
Manufacturer	Disetronic Medical Systems AG	Animas Corporation	Medtronics, Inc.	Sooil Development	Insulet	Nipro Diabetes Systems
Basal programs	Five profiles with 24-hourly basal rates each; temporary basal rate in 10% increments from 0% to 200%, and 15 min increments from 15 min to 24 h	12 basal rates in four personalized programs; temporary rate from 30 min to 24 h in 30 min intervals or 10% increments	Three profiles with up to 48 rates each	Four profiles with 24 rates per profile; temporary basal rate in 25% increments ±100%	Seven profiles with 24 rates each	Four profiles with 48 rates available per profile; temporary basal rate in 10% increments from 10% to 200% or 15 min increments from 15 min to 24 h
Basal range	0.1–25 U/h in 0.1 U increments	0.025–25 U/h in 0.025 U increments	0.05–35 U/h	0.00–16 U/h	0.05–30 U/h in 0.05 U increments	0–30 U/h in 0.05 U increments
Smallest bolus	0.1 U	0.05 U	0.05 U	0.1 U	0.05 U	0.05 U
Overdelivery alarm	No	Yes	Yes, self-tests and safeguards help prevent overdelivery	Yes, internal cross checks	No, safety systems monitor delivery and perform safety checks on pod and PDM	Yes, internal processors continually monitor pump function to prevent overinfusion and underinfusion
Reservoir size	315 U	200 U	176 or 300 U	300 U	200 U	300 U
Display features	Reversible display; backlit display	Color screen	Backlight	Backlight; energy-saving sleep mode	Color screen on PDM controller	Backlight
Connection	Standard luer-lock	Standard luer-lock	Proprietary	Proprietary	Integrated infusion set with no tubing required	Standard luer-lock
Waterproof	IPX8 (60 min at 2.5 m)	Waterproof (up to 12 ft for 24 h)	Splash resistant	IPX8	IPX8 (30 min at 8 ft)	IPX8 (35 min at 1 m)
Additional features	Standard, advanced, or custom selectable user menus; side-mounted tactile buttons; audible or vibrating bolus confirmation and alerts; supports infrared wireless data transfer	Includes a meter/remote that works wirelessly with the pump; audible or vibrating pump alerts; integrated food database	Interacts wirelessly with continuous glucose monitor as part of the MiniMed Paradigm REAL-Time System; optional remote control at additional cost; audible or vibrating alerts	Icon-based interface	Tube-free, disposable system device applied directly to body with adhesive; uses wireless PDM for managing insulin delivery; integrated food database; built-in BG meter in PDM	Pump casing is shatter resistant; audible or vibrating alerts and button feedback

[a] The Solo MicroPump (Medingo, Ltd.) has received FDA approval but, as of the time of this writing, is not yet available for sale. PDM, personal diabetes manager

The benefits of providing continuous delivery of a rapid-acting insulin analog may be substantial for selected patients.[36] Compared with MDI, the potential advantages of insulin pump therapy in type 1 diabetes include a lower A1C, a reduced total daily insulin dose, a reduced risk of hypoglycemia, lower BG variability, elimination of the need for daily injections, and increased flexibility in meal timing and size.[8,37–39] A meta-analysis of 11 randomized controlled trials (RCTs) comparing CSII (using rapid-acting insulin analogs) with MDI in type 1 diabetes found that CSII was associated with a significantly lower A1C compared with MDI (standardized difference in mean: 0.3 percentage points in favor of CSII; 95% CI, 0.1–0.4; $p < .001$).[40] No significant difference was observed in the rate of severe hypoglycemia. All 11 RCTs included in this meta-analysis enrolled patients failing on MDI who were randomized to continue with the same MDI regimen or switch to CSII. The results of this meta-analysis therefore support the principal indication of CSII as being patients unable to achieve acceptable glycemic control using MDI.

Another meta-analysis included three RCTs that compared CSII and optimized MDI therapy using rapid-acting analogs in adults with type 1 diabetes.[41] The pooled estimated A1C reduction with CSII compared with MDI was 0.35 percentage points in favor of CSII (95% CI, −0.10 to 0.80; $p = .08$). There was no significant difference between CSII and MDI in the rate of hypoglycemic events. Importantly, a greater relative benefit of CSII was observed in patients with higher baseline A1C, suggesting that CSII may be particularly beneficial in patients with the poorest initial glycemic control.[42]

Continuous Subcutaneous Insulin Infusion in Type 2 Diabetes

Another meta-analysis assessed CSII versus MDI in type 2 diabetes. This meta-analysis included four RCTs that were of at least 12 weeks' duration and found that CSII did not produce any significant improvement of A1C compared with MDI (standardized difference in mean: 0.09 percentage points; 95% CI, −0.08 to 0.26; $p = .31$).[43] Current evidence thus shows no clear benefits of CSII over MDI in the general type 2 diabetes population. Further research is required to investigate whether CSII may be useful in specific groups of type 2 diabetes patients, such as patients with marked insulin resistance; after failure of other intensified insulin regimens; during preconception, pregnancy, and lactation; following transplantation; and in cases of insulin allergy.[44]

Complications of Insulin Pump Therapy

Insulin pumps may undermedicate or overmedicate if they malfunction or are used improperly. Device problems that have been reported to the FDA include alarm problems, loosening and/or occlusion of the catheters, bent cannula, and screen display problems.[45] Potential complications of CSII therapy therefore include diabetic ketoacidosis (DKA) and hypoglycemia.[46] However, more reliable pumps and improved patient education have greatly reduced these risks. As with MDI therapy, DKA should be preventable through the use of published DKA prevention guidelines that recommend frequent monitoring of urine or serum ketones and BG, with appropriate intervention when ill.[47]

Table 3.
Types of Insulin Used in Pump Therapy

Insulin	U.S. brand name (manufacturer)	Approved age groups in the United States	Maximum time allowed in reservoir
Rapid-acting insulin analogs			
Insulin aspart	NovoLog® (Novo Nordisk)	Children and adults	Six days
Insulin glulisine	Apidra® (sanofi-aventis)	Children and adults	48 h
Insulin lispro	Humalog (Eli Lilly)	Children and adults	48 h
Regular human insulin	Humulin® R (Eli Lilly) Novolin® R (Novo Nordisk)	Children and adults Children and adults	48 h 48 h

While infusion-site infections are uncommon, irritation or inflammation at the infusion site are common complications of using an insulin pump,[48] though their incidence has been reduced by the introduction of more modern infusion sets (for example, sets that use a Teflon cannula) and by better patient education. Adherence with the advised infusion site preparation and cannula insertion techniques, and with the recommended site duration and site rotation schedule, may minimize dermatologic complications.[49]

Health Economics of Continuous Subcutaneous Insulin Infusion

To date, only one cost-effectiveness analysis comparing CSII with MDI in patients with diabetes in the United States has been published.[50] A previously validated health economic model (the CORE Diabetes Model) was used to determine the incremental cost-effectiveness ratio of CSII compared with MDI using published clinical and cost data. The primary input variable was change in A1C and was assumed to be an improvement of −0.9% in children/young adults and −1.2% in adults for CSII compared with MDI. A series of Markov constructs simulated the progression of diabetes-related complications. The time horizon for the simulation was set to 60 years to capture the remainder of a type 1 diabetes patient's lifetime. Continuous subcutaneous insulin infusion was associated with an improvement in quality-adjusted life years (QALYs) gained of 1.061 versus MDI for adults and 0.799 versus MDI for children/young adults. The incremental cost-effectiveness ratio for CSII versus MDI in adults was $16,992 per QALY gained and in children/young adults was $27,195 per QALY gained. Assuming a cost-effectiveness threshold of $50,000 per QALY gained, CSII is thus estimated to be a cost-effective option for U.S. patients with type 1 diabetes.

Conclusions

Important advances have been made both in the ability to mimic physiologic insulin secretion using insulin analogs tailored to this purpose and in devices to administer these insulins. The advantages of pens over syringes include greater accuracy and ease of use and improved patient satisfaction, quality of life, and adherence. United States claims database analyses indicate that the improved adherence made possible by use of an insulin pen has the potential to reduce diabetes care costs when compared with using a vial and syringe. A cost-effectiveness analysis using a Markov model has estimated that CSII is a cost-effective option for U.S. patients with type 1 diabetes, with an incremental cost-effectiveness ratio for CSII versus MDI of $16,992 per QALY gained in adults and $27,195 per QALY gained in children/young adults. However, even with the most sophisticated insulin delivery devices, BG control still falls short of normality for most patients.[51] The development of more physiologic routes of insulin administration, use of an artificial pancreas, or pancreas/beta-cell transplantation are therefore important ongoing areas of research. Moreover, the low rate of insulin pen usage in the United States compared with European countries and the fact that many patients report that they are not offered the option of an insulin pen by their physician suggest that there is a need to increase patient and provider awareness of the latest devices for insulin administration to enable the maximum number of patients to benefit from the important developments of the past three decades.

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