Journal of Diabetes Science and Technology
Volume 5, Issue 6, November 2011

REVIEW ARTICLE

What Can We Learn from Patient-Reported Outcomes of Insulin Pen Devices?

Barbara J. Anderson, Ph.D.,[1] and Maria J. Redondo, M.D., Ph.D.[1,2]

Abstract

Although a variety of effective treatment options are available for patients with type 1 or type 2 diabetes, many patients in the United States have difficulty reaching their glycemic goals. Patient adherence to insulin therapy, which often involves self-administered subcutaneous injections of insulin using either a vial and syringe or an insulin pen device, is often poor. Various factors associated with the type of injection device have been shown to influence the rate of patient adherence to insulin therapy. This article reviews patient-reported outcome (PRO) evidence from pediatric and adult studies that compared insulin pen devices with vial and syringe use. In a majority of these cases, patients preferred the pen devices over vial and syringe, stating advantages such as ease of use, convenience, greater confidence in their ability to properly administer the drug, and a greater perceived social acceptance. The pens were considered less painful than syringes and were associated with less needle fear. In addition, PRO evidence has directed pen technology design, leading to development of more advanced insulin pen devices. By appreciating the correlation between adherence to insulin regimens and a patient's device preference, clinicians can make improved treatment recommendations to facilitate achievement and maintenance of glycemic targets.

J Diabetes Sci Technol 2011;5(6):1563-1571

Introduction

Despite the availability of effective treatments, many youth with diabetes[1] as well as 40% to 60% of U.S. adults with diagnosed diabetes do not achieve their glycemic goals.[2,3] Insulin, when properly dosed, can decrease hemoglobin A1c from almost any baseline level to close to the 6.5% target level recommended by the American Association for Clinical Endocrinologists[4] and also has beneficial effects on triglycerides and high-density lipoprotein cholesterol.[5] However, adherence rates are poor. For example, in one claims analysis, greater than 80% of patients who were prescribed a prandial insulin for the first time had a 90-day gap in prescription refill during the first year following insulin initiation.[6]

Most patients with diabetes who require insulin self-administer their treatment by subcutaneous injection using either a vial and syringe or an insulin pen device. Worldwide, pen devices are used by approximately 60%

Author Affiliations: [1]Baylor College of Medicine, Houston, Texas; and [2]Texas Children's Hospital, Houston, Texas

Abbreviations: (DiabMedSat) Diabetes Medication Satisfaction, (OAD) oral antidiabetic drug, (PRO) patient-reported outcome, (QOL) quality of life

Keywords: adherence, diabetes, insulin therapy, pen, syringe

Corresponding Author: Maria J. Redondo, M.D., Department of Pediatrics, Endocrinology, and Metabolism, Texas Children's Hospital, 6701 Fannin St., Suite 1020, Houston, TX 77030; email address redondo@bcm.edu

of insulin users, although usage varies greatly among countries.[7] For example, in Japan, China, and Australia, pen devices are used by 95% of insulin users, whereas, in the United States, they are used by only approximately 20% of patients taking insulin.[7] A review showed that usage of pen devices was associated with improved adherence to insulin therapy and reduced costs compared with vial and syringe.[8] The greater adherence to insulin therapy associated with such devices may help patients achieve their glycemic goals. The focus of this review is insulin pens as they compare with vial and syringes; other insulin delivery devices (e.g., insulin pumps) are not reviewed in this article.

Compared with vial and syringe, insulin pens have additional advantages, including better dosing accuracy,[9] easier dosing and administration, convenience, and increased patient acceptance and satisfaction.[10–12] The pens are discreet and easily portable,[12] which lessens social embarrassment.[10] Furthermore, patients with impaired vision or compromised manual dexterity—common problems among adults with poorly controlled, long-term diabetes—are likely to find insulin pens easier to use.[13] While pens may have higher upfront pharmacy costs compared with vial and syringe,[11,14] the use of insulin pens may result in decreased need for oral antidiabetic drugs (OADs; and their associated costs),[14] reduced costs associated with fewer primary care and outpatient facility visits,[14] lower diabetes-related costs,[8,14] and lower all-cause health care costs.[8] Furthermore, pens typically contain more units of insulin than vial and syringe (e.g., 1500 versus 1000 U, respectively), allowing patients to obtain more insulin for the same copay.[13]

Outcomes such as treatment satisfaction, ease of injection, convenience, flexibility, discreetness of injection, and injection pain can be important determinants of adherence to insulin therapy in patients with diabetes. Outcomes data collected directly from patients are termed patient-reported outcomes (PROs). Patient-reported outcomes are typically assessed using questionnaires, which may be administered at the clinic, online, or via the mail. Many different PRO instruments have been used to assess the multifactorial impact of treatment on the quality of life (QOL) of patients with type 1 or type 2 diabetes.[15] The instruments include generic instruments such as the Short Form-36[16] as well as disease-specific questionnaires such as the diabetes treatment satisfaction questionnaire,[17–19] insulin treatment satisfaction questionnaire,[20,21] and the Diabetes Medication Satisfaction (DiabMedSat) questionnaire.[22,23] In addition, some investigators have utilized novel questionnaires containing questions of interest, often involving Likert scales to assess patients' experiences, opinions, and preferences.

This review evaluates the PRO evidence collected over 25 years since the introduction of the first insulin pen device in 1985[24] from studies that compared insulin pen devices with vial and syringe use. By better understanding patient preferences, clinicians can make treatment recommendations that will help patients to remain adherent to insulin regimens, thus facilitating achievement and maintenance of glycemic targets.

Methods

A PubMed search was conducted for pediatric and adult references published between 1985[24] and January 2011 using the terms "insulin" and "pen," in combination with one of the following terms: "syringe," "needle," "patient-reported outcome," "questionnaire," "survey," "satisfaction," "acceptability," "quality of life," "preference," "convenience," "ease of use," and "pain."

Results

Patient-Reported Outcomes of Insulin Pen Devices versus Vial and Syringe

Since the introduction of the insulin pen, numerous studies have examined PROs for insulin pen devices compared with vial and syringe use (**Table 1**). Across these studies, many vastly different questionnaires were used, some of which are not validated.

Although the studies differed in methodology, they were highly consistent in their results. Of the 43 studies summarized in **Table 1**, only two studies reported PROs that did not favor pen devices over vial and syringe. One of these two studies showed pen devices to be equivalent to vial and syringe with regard to self-reported scores on a self-esteem inventory, an assessment of health beliefs, a questionnaire about type A behavior, and the Hamilton Depression Rating Scale in 10 patients with type 1 diabetes.[29] In the other study, 9 of 18 patients preferred vial and syringe, 8 preferred pen devices, and 1 was undecided.[43] Both studies were conducted when pen technology was less advanced. Among the rest of the studies, a preference for insulin pen devices was found in various patient groups, including community-dwelling adults with type 1 or type 2 diabetes, children and adolescents with type 1 diabetes, pregnant women

Table 1.
Summary of Patient-Reported Outcome Studies of Insulin Pen versus Vial and Syringe Use in Types 1 and 2 Diabetes[a]

Reference	Patient population	Summary of main PRO results	Device preference
17	DTNS (*n* = 1622)	Pen > VS for all DTSQ items, including satisfaction, convenience, flexibility, likelihood of recommendation, satisfaction to continue, and perceived frequency of hyperglycemia and hypoglycemia	Not stated
25	Children and adolescents with T1DM (*n* = 20)	Pen > VS for satisfaction	Pen
26	T2DM (*n* = 62)	Pen > VS for convenience, overall ease of use, ease of setting the insulin dose, portability, ease of storing, and improvement in lifestyle	Not stated
27	T1DM (*n* = 16)	Pen > VS	Not stated
28	T1DM (*n* = 136) and T2DM (*n* = 179)	Pen > VS for preference, ease of complying with insulin treatment, ease of use, ease of reading dose numbers, comfort with public use, convenience	Pen
29	T1DM (*n* = 10)	Pen = VS	Pen
30	T1DM (*n* = 77)	Pen > VS for treatment satisfaction	Not stated
31	T1DM (*n* = 19)	Pen > VS for convenience	Pen
32	T1DM and T2DM (*n* = 60) over 60 years old	Pen > VS for ease and speed of use; 90% preferred pen for future treatment	Pen
33	T1DM (*n* = 10)	Pen > VS for simplicity of injections and flexibility	Pen
34	Hospitalized patients with T1DM (*n* = 10) or T2DM (*n* = 65)	Pen > VS for patient recommendation and preference for continued use	Not stated
35	T1DM (*n* = 27)	Pen > VS for preference, ease of use, and quicker to use	Pen
36	T1DM (*n* = 40)	95% of patients chose to continue with pen rather than VS	Pen
37	T2DM (*n* = 86)	Pen > VS	Pen
38	T1DM and T2DM (*n* = 1310)	Pen > VS for injection pain, social acceptability, convenience, ease of use, flexibility, and overall preference	Pen
39	Children and adolescents with T1DM (*n* = 158)	Pen > VS for injection pain	Not stated
40	T1DM (*n* = 72)	Pen > VS for QOL	Not stated
41,42	T1DM (*n* = 16)	81% of patients chose to continue with pen rather than VS	Pen
43	T1DM (*n* = 6) or T2DM (*n* = 12)	More patients preferred VS (50%) than pens (44%) for future use	VS
44	T1DM (*n* = 14) or T2DM (*n* = 218)	Pen > VS	Pen
45	T1DM (*n* = 50)	96% of patients chose to continue with pen rather than VS	Pen
46	T2DM (*n* = 78)	Pen > VS for injection pain, acceptance, ease of setting and drawing up the dose, and overall preference	Pen
47	T1DM (*n* = 19)	Pen > VS for ease and speed of use	Pen
48	T1DM (*n* = 14) or T2DM (*n* = 107)	Patient preference questionnaire: pen > VS for preference, ease of use, confidence in glycemic control, more stable, more discreet in public, confidence in injecting correct dose and in setting dose, ease of reading dose; on all DTSQ items, no major differences between pen and VS	Pen
16	T1DM (*n* = 4) and T2DM (*n* = 61)	Pen > VS for QOL	Not stated
49	T1DM and T2DM (*n* = 72; previous VS users)	Pen > VS for convenience, comfort, and ease of use; 74% of syringe users preferred to continue with the pen	Pen
23	T2DM (*n* = 349)	Pen > VS for treatment satisfaction	Not started

Continued →

Table 1. Continued

Reference	Patient population	Summary of main PRO results	Device preference
50	T1DM (*n* = 78)	95% of patients preferred pen over VS and continued with the pen	Pen
51	Children and adolescents with T1DM (*n* = 40)	95% preferred pen over VS	Pen
52	T1DM and T2DM (*n* = 100)	100% of patients preferred pen over VS	Pen
53	T2DM (*n* = 372)	Pen > VS for convenience, flexibility, perceived clinical efficacy, QOL, and preference	Not stated
54	DTNS (*n* = 16)	Pen > VS for ease and speed of use	Not stated
55	Adolescents (aged 12–18 years) with T1DM (*n* = 19)	Pen-based basal–bolus insulin regimen preferred by all patients over previous syringe-based twice-daily insulin regimen	Not stated
56	T1DM (*n* = 93; women in pregnancy)	Pen > VS for ease of use	Not stated
57	T1DM (*n* = 37)	Pen > VS for flexibility	Not stated
58	T1DM (*n* = 21)	Pen > VS portability, speed of use, and overall preference	Not stated
59	T1DM and T2DM (*n* = 70)	74% preferred to continue using pen; 75% expressed preference for the pen over VS	Pen
60	T1DM and T2DM (*n* = 330)	Pen > VS for convenience and ease of use	Not stated
61	T1DM and T2DM (*n* = 99 insulin users; *n* = 143 insulin nonusers)	Overall preference appeared to be higher for pens compared with VS	Not stated
62	T1DM (*n* = 18)	Pen > VS for flexibility of meal times and an increased experience of freedom	Not stated
63	Children and adolescents with T1DM (*n* = 15)	Pen > VS for convenience, ease of use, portability, discreetness, and QOL	Pen
64	Homeless patients with T1DM (*n* = 2) or T2DM (*n* = 21)	Pen > VS for convenience, ease of use, and perceived dose accuracy	Not stated

[a] Study participants were adults unless otherwise specified. >, favored over; =, no significant difference between insulin pen and vial/syringe; DTNS, diabetes type not specified; DTSQ, diabetes treatment satisfaction questionnaire; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; VS, vial and syringe. Studies of discontinued devices were excluded from this table.

with type 1 diabetes, hospitalized patients, and homeless patients.[25,34,51,55,56,63,64] Patients cited various reasons why they preferred insulin pen devices: they found pens more convenient, easier and simpler to use, more portable, more socially acceptable, and quicker to use than vial and syringe. They also reported that pen devices allowed greater lifestyle flexibility and caused less injection pain than the alternative. Of these 43 studies, only 11.6% (*n* = 5) studied pediatric patients. Whenever a pediatric study is reviewed, this is indicated in the text.

Overall Preference

Of the 43 studies summarized in **Table 1**, 24 studies inquired about patient preference (rather than a proxy such as "ease of use") for either a pen device or vial and syringe. In 23 out of these 24 studies, the majority of patients preferred insulin pen devices (**Table 1**), mainly because pen devices were believed to simplify the injection procedure.

Patients also favored pen devices over vial or syringe when asked to express their degree of preference using Likert scales. In one postal survey of expectations of device attributes, patients with type 1 or 2 diabetes rated preference scores on a five-point rating scale where 1 = "not prefer" and 5 = "prefer." Preference scores were higher for insulin pen devices compared with vial and syringe among 99 insulin users (3.58 and 2.98, respectively) and 143 patients who were prescribed insulin for the first time (4.22 and 2.10, respectively).[61]

Acceptability, Ease of Use, Convenience, and Quality of Life

In addition to direct questioning on the delivery option preferred overall, other questions focused on the acceptability, satisfaction, and convenience of pen devices, including any impact on ease of use, portability, speed of use, ease of setting the dose, lifestyle flexibility, and overall QOL. In most trials, PROs favored insulin pens over vial and syringe injection (**Table 1**).

In an open-label, crossover study, patients with type 1 (n = 14) or type 2 (n = 107) diabetes were randomly assigned to use either vial and syringe or a prefilled pen to inject an insulin analog premix for 4 weeks, followed by 4 weeks of use of the other injection device using the typical once-daily or twice-daily injection schedule.[18] Upon completion of the study, patients evaluated each injection method using an eight-question patient preference questionnaire. Overall, 74% of patients preferred the pen while 20% preferred the vial and syringe. Numerical values for responses to six of the eight questions showed that patients favored the pen device over vial and syringe in terms of being "easier to use" (74% versus 21%), "confidence in glycemic control" (61% versus 16%), "more discreet in public" (85% versus 9%), "confidence in injecting correct dose" (73% versus 19%), "confidence in setting dose" (82% versus 11%), and "easier to read dose" (85% versus 10%). In addition, preference for the pen device was observed with regard to being "more stable" and "easier to handle" compared with vial and syringe, although the percentages of patients expressing such preferences was not reported.

In addition to evaluating device attributes, more general aspects, such as well-being, satisfaction, and QOL, were assessed in other studies. For instance, QOL was assessed in 93 patients with moderately to poorly controlled type 2 diabetes who were randomized to continue taking OADs for 24 weeks (group A), administer twice-daily fixed mixture of human soluble and human isophane insulin using a standard syringe for 12 weeks followed by a pen device for another 12 weeks (group B), or vice versa (group C).[26] While scores for general well-being were very similar in all three groups, significantly more patients believed the insulin pen improved their lifestyle compared with the syringe (33.8% versus 4.8%; $p < .001$).

Patient satisfaction was also assessed in an observational study of 349 patients with type 2 diabetes who switched from prior therapy to administration of biphasic insulin aspart via a prefilled or refillable insulin pen.[23] This study used the DiabMedSat questionnaire, a 21-item patient self-administered assessment that includes an overall score plus subscales on the burden, efficacy, and symptoms/tolerability of medications used for type 2 diabetes. Results showed that patient satisfaction was significantly improved from baseline to final visit in the overall scale and in each of the three subscales ($p < .001$ for each).

Most studies used diabetes-specific questionnaires, but one study used the generic Short Form-36 to assess QOL.[16] In this two-arm, parallel-group, open-label, nonrandomized study, 32 patients with diabetes receiving insulin therapy were switched to administration of insulin via a pen device for 12 weeks, as suggested by their physician. A group of 33 age-matched controls continued to administer insulin using a vial and syringe for the same period. The Short Form-36 questionnaire was administered prior to and after the 12-week study period. This questionnaire consisted of eight categories of subscales, including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and psychological health. The score for each subscale ranged from 0 to 100: the higher the score, the better the functional health status. After 12 weeks, the insulin pen group showed a significant improvement in the summary scale of the physical components of the Short Form-36 questionnaire compared with the vial and syringe group (+3.9 versus -1.0; $p = .037$). A similar trend was shown on the mental component summary scale but was not statistically significant (+1.3 versus -0.8; $p = .291$).

Perceived Clinical Efficacy

Although questionnaires that measure PROs are not able to determine effects on glycemic control, three studies assessed patients' perceived glycemic control/clinical efficacy or their confidence in their ability to maintain glycemic control using pen devices. In one study of 1622 insulin users, switching from vial and syringe administration to a prefilled insulin pen device was reported to produce a significant improvement in perceived hypoglycemia and hyperglycemia status, as assessed by the diabetes treatment satisfaction questionnaire, although numerical data were not presented.[17] In another study, perceived clinical efficacy was assessed using the "diabetes treatment satisfaction questionnaire–change" and "quality of life–status and change" instruments for 600 patients with type 2 diabetes, including 300 who administered insulin using a vial and syringe and 300 who used a pen device. Results showed patients perceived that insulin pen devices facilitated improved diabetes self-care compared with vial and syringe use (odds ratio 20.15; $p < .001$).[53]

As previously discussed, the 4-week crossover study conducted by Korytkowski and colleagues[18] reported that more patients felt confident in their ability to maintain glycemic control with a pen device (61% patients) than vial and syringe (16% patients). However, differences in mean fasting plasma glucose, serum fructosamine, or four-point glucose profile between the two forms of insulin administration were not statistically significant.

Needle Fear and Pain

For patients with diabetes, fear of needles can be a barrier to adherence to insulin therapy, leading to poor glycemic control.[48,65-67] The pain involved in self-injection of insulin is partially related to characteristics of the needle, particularly diameter.[68-71] Pen needles may be sharper and thinner than syringe needles because they do not have to penetrate the insulin vial stopper prior to injection.[65] The mode of administration may also influence psychological distress. Often, pen devices induce less fear because less of the needle is visible during injection and because, unlike the syringe, patients may not associate the pen-shaped device with memories of childhood immunizations.[72] Using an insulin pen device with an attachment that conceals the needle during injections has been shown to reduce pain perception.[73]

Patients in several studies reported less injection pain associated with insulin pen devices than with vial and syringe.[38,39,46] Reduced injection pain associated with the ultrafine needles of insulin pen devices may be especially beneficial in young children. In a study of 158 children and adolescents with type 1 diabetes, the levels of needle phobia and injection pain were inversely correlated with patient age, with younger patients reporting greater needle phobia and injection pain.[39]

Improvements in Pen Technology Based on Patient-Reported Outcomes

The design of insulin pen devices has been modified to further simplify insulin injection and enhance its acceptability to patients. Results of PRO studies of existing devices have prompted many of these design modifications.

Pen needles have become thinner and shorter to reduce injection pain and needle fear. Several studies demonstrated that patients preferred to use insulin pen devices fitted with thinner needles (32 G or "thin wall" 31 G) because they were associated with less injection pain and considered easier to use than pen devices fitted with regular 30 or 31 G needles.[68–71] Shorter needles are also favored, with one study reporting that a 4 mm needle was significantly less painful than either a 5 mm or an 8 mm needle (both $p < .01$).[70]

Injection force has also been reduced to improve acceptability. This reduction allows the patient to initiate the injection with less pressure on the dose button, which was previously a problem for some.[74] Results have shown that a pen modified to deliver a 28% relative reduction in injection force was simpler and more comfortable for patients to use and was more likely to receive a rating of "good" or "very good" injection force.[10]

Color-coding of labels, packaging, and cartridges have also been introduced to facilitate patient selection of the correct insulin. One pen design was modified to have a mean dosage display more than four times larger than its predecessor.[75] The authors concluded that patients with diabetes who have manual or visual impairment should find insulin dosing easier with the modified device. Also, pen devices have been designed with a memory function that allows the dose and time of the last injection to be recorded, thus avoiding double dosing and other dosing errors.

Several pen device modifications may be particularly useful for children and their parents.[76,77] In one study, pediatric patients, their parents, and health care professionals assessed usability, functionality, and preference for a pen with a memory function compared with two other designs. The memory function device scored well for meeting participants' needs, with 78% of children, 83% of parents, and 79% of health care professionals rating it as either 1 or 2 on scale of 1 to 6 (where 1 = "meets my needs completely" and 6 = "does not meet my needs").[78] In addition, the pediatric pen is available in two colors, allowing patients to distinguish between two types of insulin they may use. Another feature of pen devices designed to meet the needs of very young children with type 1 diabetes is the ability to set doses in half-unit increments.[79-81]

Discussion

In 43 studies comparing PROs for insulin pen devices versus vial and syringe (**Table 1**), patients generally preferred the pen devices. Overall patient satisfaction ratings were higher with insulin pens than with vial and syringe.

The PROs in these studies confirmed that patients believe insulin pens to be advantageous over vial and syringe. Patients found the pen devices more socially acceptable and easier to use because they were more convenient and portable. The doses were easier to read, increasing patients' confidence in their ability to set and administer the correct dose and to achieve glycemic control. Pens were considered less painful than syringes and were associated with less needle fear. Patients found it more discreet to use pen devices in public, and consequently,

they felt that they had greater lifestyle flexibility. Patient-reported outcomes have helped guide pen technology advancements, leading to current pens with shorter and thinner needles, reduced injection force, color-coded insulin cartridges and packaging, and built-in memory function. Aspects of insulin pens that are particularly useful in pediatric patients include device modifications to reduce injection fear and pain, memory functions, and the ability to set doses in small increments.

One disadvantage of pens is that patients on high doses of insulin may require two injections versus one injection needed when using a syringe.[12] Insulin pens deliver a maximum dose of 16 to 80 U in a single injection, whereas the largest insulin syringes can inject up to 100 U of U-100 insulin. In addition, most insulin pens deliver a minimum dose of 1 U and deliver doses in 1 U increments, so these particular models are not suitable for patients requiring very small doses. Other drawbacks include the potential for mechanical failure and the fact that it is not possible to mix insulin types when using pen devices.[13]

Potential explanations for the lower usage of insulin pens in the United States than in other countries[7] may include difficulties with health insurance coverage, greater use of insulin pumps, and habits of practicing physicians.

Given patient preference for pens over vial and syringe, physicians should discuss the option of using a pen device and explain its advantages and disadvantages when initiating insulin therapy for patients with diabetes. In addition, when patients taking insulin are not meeting glycemic goals, clinicians should assess adherence and reasons for any nonadherence.[8] Switching to the insulin pen may help overcome some patients' barriers to adherence, which include impaired vision or manual dexterity, injection pain, and the inconvenience and social stigma of injecting with a syringe. By helping to promote adherence to insulin therapy, insulin pens may improve patients' potential to achieve their glycemic goals.[8]

Acknowledgments:

Writing and editorial support was provided by Reza Sayeed and Lauren Cerruto of Bioscript Stirling Ltd.

Funding:

Research was supported by Novo Nordisk.

References:

1. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, Deeb L, Grey M, Anderson B, Holzmeister LA, Clark N; American Diabetes Association. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care. 2005;28(1):186-212.
2. Hoerger TJ, Segel JE, Gregg EW, Saaddine JB. Is glycemic control improving in U.S. adults? Diabetes Care. 2008;31(1):81-6.
3. National Committee for Quality Assurance. The state of health care quality. *http://www.ncqa.org/Portals/0/State_of_Health_Care/2010/SOHC 2010 - Full2.pdf*. Accessed March 1, 2010.
4. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, Handelsman Y, Horton ES, Lebovitz H, Levy P, Moghissi ES, Schwartz SS. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract. 2009;15(6):540-59.
5. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32(1):193-203.
6. Bonafede MM, Kalsekar A, Pawaskar M, Ruiz KM, Torres AM, Kelly KR, Curkendall SM. Insulin use and persistence in patients with type 2 diabetes adding mealtime insulin to a basal regimen: a retrospective database analysis. BMC Endocr Disord. 2011;11:3.
7. Perfetti R. Reusable and disposable insulin pens for the treatment of diabetes: understanding the global differences in user preference and an evaluation of inpatient insulin pen use. Diabetes Technol Ther. 2010;12 Suppl 1:S79-85.
8. Asche CV, Shane-McWhorter L, Raparla S. Health economics and compliance of vials/syringes versus pen devices: a review of the evidence. Diabetes Technol Ther. 2010;12 Suppl 1:S101-8.
9. Luijf YM, DeVries JH. Dosing accuracy of insulin pens versus conventional syringes and vials. Diabetes Technol Ther. 2010;12 Suppl 1:S73-7.
10. Pfützner A, Asakura T, Sommavilla B, Lee W. Insulin delivery with FlexPen: dose accuracy, patient preference and adherence. Expert Opin Drug Deliv. 2008;5(8):915-25.
11. Dang DK, Lee J. Analysis of symposium articles on insulin pen devices and alternative insulin delivery methods. J Diabetes Sci Technol. 2010;4(3):558-61.
12. Goldstein HH. Pen devices to improve patient adherence with insulin therapy in type 2 diabetes. Postgrad Med. 2008;120(3):172-9.
13. Pearson TL. Practical aspects of insulin pen devices. J Diabetes Sci Technol. 2010;4(3):522-31.
14. Lee LJ, Li Q, Reynolds MW, Pawaskar MD, Corrigan SM. Comparison of utilization, cost, adherence, and hypoglycemia in patients with type 2 diabetes initiating rapid-acting insulin analog with prefilled pen versus vial/syringe. J Med Econ. 2011;14(1):75-86.
15. Molife C, Lee LJ, Shi L, Sawhney M, Lenox SM. Assessment of patient-reported outcomes of insulin pen devices versus conventional vial and syringe. Diabetes Technol Ther. 2009;11(8):529-38.

16. Lee IT, Liu HC, Liau YJ, Lee WJ, Huang CN, Sheu WH. Improvement in health-related quality of life, independent of fasting glucose concentration, via insulin pen device in diabetic patients. J Eval Clin Pract. 2009;15(4):699-703.

17. Albano S; Orbiter Study Group. Assessment of quality of treatment in insulin-treated patients with diabetes using a pre-filled insulin pen. Acta Biomed. 2004;75(1):34-9.

18. Korytkowski M, Bell D, Jacobsen C, Suwannasari R; FlexPen Study Team. 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(11):2836-48.

19. Bradley C. The diabetes treatment satisfaction questionnaire: DTSQ. In: Bradley C, ed. Handbook of psychology and diabetes: a guide to psychological measurement in diabetes research and practice. Chur: Harwood Academic Publishers; 1994, 111-32.

20. Anderson RT, Skovlund SE, Marrero D, Levine DW, Meadows K, Brod M, Balkrishnan R. Development and validation of the insulin treatment satisfaction questionnaire. Clin Ther. 2004;26(4):565-78.

21. Stockl K, Ory C, Vanderplas A, Nicklasson L, Lyness W, Cobden D, Chang E. An evaluation of patient preference for an alternative insulin delivery system compared to standard vial and syringe. Curr Med Res Opin. 2007;23(1):133-46.

22. Brod M, Skovlund SE, Wittrup-Jensen KU. Measuring the impact of diabetes through patient report of treatment satisfaction, productivity and symptom experience. Qual Life Res. 2006;15(3):481-91.

23. Mukherjee AK, Reddy VS, Shah S, Jhingan AK, Ramakrishnan P, Prusty V, Singh NS. Quality of life as a key indicator of patient satisfaction and treatment compliance in people with type 2 diabetes mellitus in the IMPROVE study: a multicentre, open label, non-randomised, observational trial. J Indian Med Assoc.2009;107(7):464-70.

24. Rex J, Jensen KH, Lawton SA. A review of 20 years' experience with the NovoPen family of insulin injection devices. Clin Drug Investig. 2006;26(7):367-401.

25. Arslanoğlu I, Saka N, Bundak R, Günöz H, Darendeliler F. A comparison of the use of premixed insulins in pen-injectors with conventional patient-mixed insulin treatment in children and adolescents with IDDM. Is there a decreased risk of night hypoglycemia? J Pediatr Endocrinol Metab.2000;13(3):313-8.

26. Barnett AH, Bowen Jones D, Burden AC, Janes JM, Sinclair A, Small M, Tindall H. Multicentre study to assess quality of life and glycaemic control of Type 2 diabetic patients treated with insulin compared with oral hypoglycaemic agents. Pract Diabetes Int.1996;13(6):179-83.

27. Berger AS, Saurbrey N, Kühl C, Villumsen J. Clinical experience with a new device that will simplify insulin injections. Diabetes Care.1985;8(1):73-6.

28. Bohannon NJ, Ohannesian JP, Burdan AL, Holcombe JH, Zagar A. Patient and physician satisfaction with the Humulin/ Humalog Pen, a new 3.0-mL prefilled pen device for insulin delivery. Clin Ther.2000;22(9):1049-67.

29. Buysschaert M, Janne P, Mpoy M, Reynaert C, Pirson F, Cassiers L, Lambert AE. Metabolic and psychological evolution of insulin dependent diabetic patients during a 6 months insulin-pen treatment. Diabete Metab. 1988;14(2):75-9.

30. Chantelau E, Schiffers T, Schütze J, Hansen B. Effect of patient-selected intensive insulin therapy on quality of life. Patient Educ Couns. 1997;30(2):167-73.

31. Chen HS, Hwu CM, Kwok CF, Yang HJ, Shih KC, Lin BJ, Ho LT. Clinical response and patient acceptance of a prefilled, disposable insulin pen injector for insulin-treated diabetes. Zhonghua Yi Xue Za Zhi (Taipei). 1999;62(7):455-60.

32. Coscelli C, Lostia S, Lunetta M, Nosari I, Coronel GA. Safety, efficacy, acceptability of a pre-filled insulin pen in diabetic patients over 60 years old. Diabetes Res Clin Pract. 1995;28(3):173-7.

33. Dahl-Jorgensen K, Hanssen KF, Mosand R, Sandvik L. The "insulin pen": Comparison with multiple injection treatment with syringe. Pract Diabetes Int. 1986;3(2):90-1.

34. Davis EM, Christensen CM, Nystrom KK, Foral PA, Destache C. Patient satisfaction and costs associated with insulin administered by pen device or syringe during hospitalization. Am J Health Syst Pharm. 2008;65(14):1347-57.

35. Dunbar JM, Madden PM, Gleeson DT, Fiad TM, McKenna TJ. Premixed insulin preparations in pen syringes maintain glycemic control and are preferred by patients. Diabetes Care. 1994;17(8):874-8.

36. Engström LH. Insulin pen for administration of isophane insulin. Pract Diabetes Int. 1990:7(4):162-4.

37. Fox C, McKinnon C, Wall A, Lawton SA. Ability to handle, and patient preference for, insulin delivery devices in visually impaired patients with type 2 diabetes. Pract Diabetes Int. 2002;19(4):104-7.

38. 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(3):486-96.

39. Hanas R, Ludvigsson J. Experience of pain from insulin injections and needle-phobia in young patients with IDDM. Pract Diabetes Int. 1997;14(4):95-9.

40. Hörnquist JO, Wikby A, Andersson PO, Dufva AM. Insulin-pen treatment, quality of life and metabolic control: retrospective intra-group evaluations. Diabetes Res Clin Pract.1990;10(3):221-30.

41. Houtzagers CM, Berntzen PA, van der Stap H, van Maarschalkerweerd WW, Lanting P, Boen-Tan I, Heine RJ, van der Veen EA. Efficacy and acceptance of two intensified conventional insulin therapy regimens: a long-term cross-over comparison. Diabet Med. 1989;6(5):416-21.

42. Houtzagers CM, Visser AP, Berntzen PA, van der Stap H, van Maarschalkerweerd WW, Heine RJ, van der Veen EA. Multiple daily insulin injections improve self-confidence. Diabet Med.1989;6(6):512-9.

43. Hung CT, Wang FF. Pen injector for insulin-requiring diabetic patients. J Formos Med Assoc.1992;91(10):1026-9.

44. Ignaut DA, Schwartz SL, Sarwat S, Murphy HL. Comparative device assessments: Humalog KwikPen compared with vial and syringe and FlexPen. Diabetes Educ.2009;35(5):789-98.

45. Jørgensen JO, Flyvbjerg A, Jørgensen JT, Sørensen HH, Johansen BR, Christiansen JS. NPH insulin administration by means of a pen injector. Diabet Med. 1988;5(6):574-6.

46. Kadiri A, Chraibi A, Marouan F, Ababou MR, el Guermai N, Wadjinny A, Kerfati A, Douiri M, Bensouda JD, Belkhadir J, Arvanitis Y. Comparison of NovoPen 3 and syringes/vials in the acceptance of insulin therapy in NIDDM patients with secondary failure to oral hypoglycaemic agents. Diabetes Res Clin Pract. 1998;41(1):15-23.

47. Kølendorf K, Beck-Nielsen H, Oxenbøll B. Clinical experience with NovoPen II and insulin Protaphane HM Penfill. Postgrad Med J.1988;64 Suppl 3:14-6.

48. Korytkowski M. When oral agents fail: practical barriers to starting insulin. Int J Obes Relat Metab Disord. 2002;26 Suppl 3:S18-24.

49. Martin JM, Llewelyn JA, Ristic S, Bates PC. Acceptability and safety of a new 3.0 ml re-usable insulin pen (HumaPen) in clinical use. Diabetes Nutr Metab.1999;12(5):306-9.

50. Murray DP, Keenan P, Gayer E, Salmon P, Tomkin GH, Drury MI, O'Sullivan DJ. A randomized trial of the efficacy and acceptability of a pen injector. Diabet Med.1988;5(8):750-4.

51. O'Hagan M, Greene SA. Pre-mixed insulin delivered by disposable pen in the management of children with diabetes. Diabet Med.1993;10(10):972-5.

52. Rowe BR, Pizzey M, Barnett AH. A clinical evaluation of the B-D Pen. Pract Diabetes Int. 1992;9(4):138-9.

53. Rubin RR, Peyrot M. Factors affecting use of insulin pens by patients with type 2 diabetes. Diabetes Care.2008;31(3):430-2.

54. Saurbrey N, Berger A, Kühl C. The NovoPen--a practical tool for simplifying multiple injection insulin therapy. Acta Paediatr Scand Suppl.1985;320:64-5.

55. Schönle EJ. [Intensive insulin therapy in adolescents with type 1 diabetes mellitus: initial experiences with a semiautomatic insulin injection device (the insulin pen)]. Schweiz Med Wochenschr.1987;117(45):1756-60.

56. Schuster MW, Chauhan SP, McLaughlin BN, Perry KG Jr, Morrison JC. Comparison of insulin regimens and administration modalities in pregnancy complicated by diabetes. J Miss State Med Assoc.1998;39(2):51-5.

57. Small M, MacRury S, Boal A, Paterson KR, MacCuish AC. Comparison of conventional twice daily subcutaneous insulin administration and a multiple injection regimen (using the NovoPen) in insulin-dependent diabetes mellitus. Diabetes Res.1988;8(2):85-9.

58. Spijker AJ, Hoekstra JB, Erkelens DW. The insulin pen: a new device for multiple insulin injections. Transplant Proc.1986;18(6):1689-90.

59. Stocks A, Perry SR, Brydon P; Australian HumaPen Collaborative Research Group. HumaPen Ergo(R): a new 3.0ml reusable insulin pen: evaluation of patient acceptability. Clin Drug Invest. 2001;21(5):319-24.

60. Sucic M, Galic E, Cabrijan T, Ivandic A, Petrusic A, Wyatt J, Mincheva N, Milicevic Z, Malone J. Patient acceptance and reliability of new Humulin/Humalog 3.0 ml prefilled insulin pen in ten Croatian diabetes centres. Med Sci Monit. 2002;8(3):PI21-6.

61. Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. Clin Ther. 2004;26(9):1498-505.

62. Tallroth G, Karlson B, Nilsson A, Agardh CD. The influence of different insulin regimens on quality of life and metabolic control in insulin-dependent diabetics. Diabetes Res Clin Pract. 1989;6(1):37-43.

63. Tubiana-Rufi N, Levy-Marchal C, Mugnier E, Czernichow P. Long term feasibility of multiple daily injections with insulin pens in children and adolescents with diabetes. Eur J Pediatr. 1989;149(2):80-3.

64. Wilk T, Mora PF, Chaney S, Shaw K. Use of an insulin pen by homeless patients with diabetes mellitus. J Am Acad Nurse Pract. 2002;14(8):372-9.

65. Meece J. Dispelling myths and removing barriers about insulin in type 2 diabetes. Diabetes Educ. 2006;32 (1 Suppl):9S-18S.

66. McConnell EM, Harper R, Campbell M, Nelson JK. Achieving optimal diabetic control in adolescence: the continuing enigma. Diabetes Metab Res Rev. 2001;17(1):67-74.

67. Khan H, Lasker SS, Chowdhury TA. Prevalence and reasons for insulin refusal in Bangladeshi patients with poorly controlled Type 2 diabetes in East London. Diabet Med. 2008;25(9):1108-11.

68. Iwanaga M, Kamoi K. Patient perceptions of injection pain and anxiety: a comparison of NovoFine 32-gauge tip 6mm and Micro Fine Plus 31-gauge 5mm needles. Diabetes Technol Ther. 2009;11(2):81-6.

69. McKay M, Compion G, Lytzen L. A comparison of insulin injection needles on patients' perceptions of pain, handling, and acceptability: a randomized, open-label, crossover study in subjects with diabetes. Diabetes Technol Ther. 2009;11(3):195-201.

70. Hirsch LJ, Gibney MA, Albanese J, Qu S, Kassler-Taub K, Klaff LJ, Bailey TS. Comparative glycemic control, safety and patient ratings for a new 4 mm x 32G insulin pen needle in adults with diabetes. Curr Med Res Opin. 2010;26(6):1531-41.

71. Siegmund T, Blankenfeld H, Schumm-Draeger PM. Comparison of usability and patient preference for insulin pen needles produced with different production techniques: "thin-wall" needles compared to "regular-wall" needles: an open-label study. Diabetes Technol Ther.2009;11(8):523-8.

72. Taddio A, Chambers CT, Halperin SA, Ipp M, Lockett D, Rieder MJ, Shah V. Inadequate pain management during routine childhood immunizations: the nerve of it. Clin Ther. 2009;31 Suppl 2:S152-67.

73. Diglas J, Feinböck C, Irsigler K, Winkler F, Egger T, Weitgasser R, Pieber T, Lytzen L. Reduced pain perception with Pen Mate, an automatic needle insertion device for use with an insulin pen. Pract Diabetes Int. 1999;16(2):39-41.

74. Sommavilla B, Jørgensen C, Jensen KH. Safety, simplicity and convenience of a modified prefilled insulin pen. Expert Opin Pharmacother. 2008;9(13):2223-32.

75. Donsmark M, Herold L, Kristensen CM. A comparison of injection force and dosage scale size between NovoPen 3 and NovoPen 4. Diabetes Technol Ther. 2009;11(9):581-5.

76. Venekamp WJ, Kerr L, Dowsett SA, Johnson PA, Wimberley D, McKenzie C, Malone J, Milicevic Z. Functionality and acceptability of a new electronic insulin injection pen with a memory feature. Curr Med Res Opin. 2006;22(2):315-25.

77. Olsen BS, Lilleøre SK, Korsholm CN, Kracht T. Novopen Echo® for the delivery of insulin: a comparison of usability, functionality and preference among pediatric subjects, their parents, and health care professionals. J Diabetes Sci Technol. 2010;4(6):1468-75.

78. Olsen BS, Lilleøre SK. NovoPen Echo™ for the delivery of insulin in paediatric patients: a comparison of usability, functionality and preference among patients, their parents and healthcare professionals. Pediatr Diabetes. 2009;10 Suppl 11:30-109.

79. Clark PE, Okenfuss CR, Campbell M. Half-unit dose accuracy with HumaPen Luxura HD: an insulin pen for patients who need precise dosing. J Diabetes Sci Technol. 2010;4(2):353-6.

80. Hyllested-Winge J, Jensen KH, Rex J. A review of 25 years' experience with the NovoPen family of insulin pens in the management of diabetes mellitus. Clin Drug Investig. 2010;30(10):643-74.

81. Magnotti MA, Rayfield EJ. An analysis of the HumaPen Luxura HD pen: what is the role of 0.5-unit insulin dosing? J Diabetes Sci Technol. 2010;4(2):357-8.