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REVIEW

An evaluation of prefilled insulin pens: a focus on the Next Generation FlexPen®

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Abstract: Insulin pen delivery systems are preferred by patients over the traditional vial and syringe method for insulin delivery because they are simple and easy to use, improve confidence in dosing insulin, and have less interference with activities and improved discretion with use. Insulin manufacturers have made numerous improvements to their first marketed pen devices and are now introducing their next generation of devices. Design modifications to the newest generation of prefilled insulin pen devices are intended to improve the ease of use and safety and continue to positively impact adherence to insulin. This review focuses on the Next Generation FlexPen® with regard to design considerations to reduce injection force, improve accuracy and ease of use, and evaluate the preference of patient and health-care provider compared with other disposable, prefilled insulin pen devices.

Keywords: diabetes, dose accuracy, injection force, patient preference, insulin pen device

Introduction

Global estimates indicate the total number of individuals with diabetes will increase from 171 million in 2000 to a projected 366 million people by 2030, likely due to the population growth, aging, urbanization, and increasing prevalence of obesity and lack of physical activity.[1] Estimates from 2007 indicate the prevalence of undiagnosed and diagnosed patients with diabetes in the United States alone to be 23.6 million people or 7.8% of the population.[2]

Studies show that maintaining glycosylated hemoglobin (HbA_{1c}) goals close to the range of nondiabetic patients reduces the risk of microvascular complications.[3–8] In order to achieve HbA_{1c} goals and maintain glycemic control, insulin remains the cornerstone of therapy for patients with type 1 diabetes.[9] Furthermore, insulin administration is recommended as an additional method to intensify therapy when other antidiabetic agents and lifestyle modifications are insufficient to meet the HbA_{1c} goals for patients with type 2 diabetes.[10,11]

A treatment algorithm, formulated by a consensus panel of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), to manage patients with type 2 diabetes recommends an option of additional therapy with insulin after monotherapy with metformin does not achieve the HbA_{1c} goals.[10]

The treatment algorithm, formulated by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), stratifies patients with type 2 diabetes based on their current HbA_{1c} value with a goal of monitoring therapy every 2–3 months and intensifying therapy until the HbA_{1c} goal

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has been reached. It recommends that for patients with HbA_{1c} values >9% and on antidiabetic medications or if medication naive and symptomatic, insulin therapy should be considered. For patients with HbA_{1c} values <9% and combinations of dual or triple antidiabetic medications fail to achieve the HbA_{1c} goal of ≤6.5%, insulin therapy should be considered as an additional method of intensification.[11]

Despite these recommendations, it is estimated that only 27% of the adult American population diagnosed with diabetes are on some type of insulin treatment, whereas 73% take either oral medication or no medication at all.[2] Further research is needed to assess the percentage of patients with type 2 diabetes who should have augmentation with insulin therapy according to these guidelines.

Multiple patient factors and attitudes regarding insulin contribute to the overall reluctance to initiate therapy. Certain patient attitudes presenting a barrier to insulin use include: fear of hypoglycemic complications, increased complexity of managing diabetes, lifestyle restrictions, social unacceptability, and fear of self-injecting.[12,13] A survey validation study confirmed a positive correlation among three main pen product attributes that relate to the preference for insulin pens compared with vials and syringes including ease of use, less activity interference, and social acceptability.[14] Since the first introduction of insulin pens to the market, consideration of these three main attributes permeates throughout the design and evaluation of various pen devices in an effort to positively influence patient preference and ultimately adherence to insulin regimens.

Although the traditional vial and syringe method is available for the delivery of insulin, this method requires extensive training and the patient must have the appropriate visual acuity, manual dexterity, and coordination to properly prepare and administer an insulin injection.[15] Studies have shown patients with diabetes prefer insulin pens over vials and syringes because of the improvements in the following features: ease of use, confidence in dosing, discretion with use, compliance, quality of life, and independence of administration in patients with visual or motor disabilities.[15–24] Furthermore, national health-care benefit studies revealed the transition from vials and syringes to insulin pens improves medication adherence and reduces overall health-care costs, emergency department and physician visits, and the likelihood of experiencing a hypoglycemic event.[25–27]

The purpose of this review is to present an evaluation of the Next Generation FlexPen® (NGFP) (Novo Nordisk, Bagsvaerd, Denmark) compared with other disposable, prefilled insulin pen devices. Emphasis will be placed on evaluating the utility of this device regarding the design considerations to improve accuracy, reduce injection force, and evaluate the preference of patient and health-care provider with NGFP compared with other disposable, prefilled insulin pen devices.

A Pubmed search was conducted to identify studies published from 1985 to February 2010 using the search terms *flexpen*, *next generation flexpen*, *prefilled pen*, *insulin pen*, and *insulin delivery device*. References of identified articles and pharmaceutical websites were also reviewed for additional pertinent articles.

The evolution of new-generation prefilled insulin pens

Insulin pen device delivery systems were created in 1985 with the intent to overcome barriers of the vial and syringe method. Insulin pen devices combine an insulin reservoir cartridge and syringe into a single component in an effort to overcome barriers to adherence with insulin self-administration and improve convenience and ease of use for patients.[28] Insulin pen devices are typically classified as being either durable (reusable) or prefilled (disposable). Durable insulin pen devices use replaceable and disposable insulin cartridges that are loaded and removed from the insulin delivery pen by the patient. Prefilled insulin pen devices require no installation of an insulin reservoir cartridge by the patient. The entire device including the body of the pen and prefilled insulin cartridge can be discarded once it is empty. Both types of devices contain 3 mL of insulin (100 U/mL), for a total of 300 U of insulin and require attachment of an insulin pen needle to administer a dose.[29]

Dose preparation and insulin administration are simplified with prefilled insulin pens compared with the vial and syringe method. Pen device preparation and insulin administration with new-generation prefilled pens share broadly similar techniques. Patients would follow the following basic steps: correctly identifying the insulin analog for use, removing the pen cap, placing an insulin pen needle on the insulin end of the pen, and "dialing-up" or setting the insulin dose by twisting a dosage selector. At this point, patients can visualize their numerical insulin dose and concurrently hear audible clicks for each incremental dose increase from zero. Patients typically perform a 2 U safety airshot of insulin to verify whether the needle is working. Once this is confirmed and the patients have dialed up their insulin dose, they insert the pen at a 90° angle into subcutaneous tissue and depress the injection button on the end of the dosing knob of the pen. The dosing window returns to zero, resulting in delivery of

insulin. Patients should be instructed to wait for a few seconds to allow the absorption of the appropriate amount of insulin and withdraw the insulin pen from the subcutaneous tissue. Due to the ease of administration, patients can correctly dial up and administer their insulin with minimal instructions using pen devices.[30–33]

All three manufacturers of insulin dispensed in the United States. (Novo Nordisk; Eli Lilly and Company, Indianapolis, Indiana, USA; sanofi-aventis, Bridgewater, New Jersey, USA) have disposable, prefilled insulin pens to facilitate the administration of their corresponding rapid- or long-acting insulin analogs and premixed insulin analog preparations from the devices (Table 1). Insulin manufacturers have made improvements to their first marketed pen devices and are now introducing their next generation of devices by making design modifications that are intended to improve the ease of use and safety and continue to positively impact adherence to insulin.

New-generation pen devices: product improvements

Compared with the original FlexPen® (FP) (Novo Nordisk) design, the NGFP device has product modifications producing a lower injection force, improved accuracy of dose delivery, and an easier pen needle interface requiring a single-luer lock type of twist to secure a NovoTwist® (Novo Nordisk) needle to the pen. These features were implemented to enhance convenience and ease of use. To improve patient safety, the NGFP imitated the color coding of the pen injection button found in the original FP, but the design has been modified to continue the color coding throughout the entire pen body (Figure 1). The color coding assigned to labeling and packaging of insulin aspart (NovoRapid®; Novo Nordisk) is orange, insulin detemir (Levemir®; Novo Nordisk) is green, and insulin aspart protamine/aspart 70/30 mix is blue with a clear cartridge.

To enhance the ease of use, compared with the original durable OptiClik® (OC) pen (sanofi-aventis), the SoloSTAR® (SS) (sanofi-aventis) pen has been modified to a prefilled, disposable pen device (Figure 2). The OC and SS are the only pens that allow a maximum dose administration of 80 U. During development of the SS pens, the manufacturers wanted to maintain the ability to allow the maximum insulin dose, but retain a manageable "thumb reach" distance, defined as the dial extension distance from holding the pen in one hand to extending the thumb, and low injection force.[34] Compared with older-generation prefilled pens marketed at the time, the SS pen had the lowest mean injection force[35] and was preferred by patients with diabetes.[36] These changes were implemented to enhance convenience and ease of use. If a patient wants to minimize the number of injections required for high doses that exceed 60 U but are less than 80 U, SS pen may be the ideal disposable pen device.

In 2006, the Institute for Safe Medication Practices (ISMP) reported that the digital display for the insulin dose, which is near the dial used to set the dose on the OC pen for the injection of insulin glargine and insulin glulisine, had the potential for dosing errors and patient harm if the pen was oriented in the wrong direction. For example, if a left-handed practitioner or patient held the pen upside down, with the needle to the right, away from the hand, a dose that is actually 52 U may appear as 25 U. ISMP believed that the design of the pen was potentially dangerous and could lead to a significant overdose or a subtherapeutic dose of insulin, and thus ISMP did not recommend clinical use of the device until safety issues were resolved.[37] Therefore, the SS pen was designed without the digital display. Additional improvements were

Table 1 Prefilled disposable insulin pen devices available in the United States

Manufacturer	Pen devices	Insulin aspart	Insulin aspart protamine/ aspart 70/30 mix	Insulin detemir	Insulin glulisine	Insulin glargine	Insulin lispro	Insulin lispro protamine/lispro 75/25 and 50/50 mix	Delivery range (units)
Novo Nordisk	FlexPen[a]	✓	✓	✓					1–60
	Next Generation FlexPen	✓	✓	✓					1–60
sanofi-aventis	SoloSTAR				✓	✓			1–80
Eli Lilly and Company	Humalog pen						✓	✓	1–60
	KwikPen						✓	✓	1–60

[a]Currently Novo Nordisk manufactures only the Next Generation FlexPen; however, it is possible that both the original FlexPen may still be available in some areas (depending on use).

Figure 1 View of FlexPen Levemir and FlexPen NovoRapid (left) and Next Generation FlexPen Levemir and Next Generation FlexPen NovoRapid (right).

made utilizing a different coloring scheme of pen labeling to help distinguish between rapid- and long-acting insulin analogs. The rapid-acting analog, insulin glulisine, is dark navy blue, and the long-acting analog, insulin glargine, is gray. These color schemes were validated in studies including patients with poor visual acuity or color blindness.[34] An additional change to help differentiate between insulin glargine and glulisine is a raised ring on the dose button of the insulin glulisine pen to assist with tactile differentiation of the two insulin analogs. These design changes to the SS pen were implemented to improve patient safety.

To enhance the ease of use, compared with the original Humalog®/Humulin® pen (HP) (Eli Lilly and Company), the KwikPen® (KP) (Eli Lilly and Company) device was modified to simplify dialing doses (Figure 3). The HP required the user to line up an arrow in the dosing window and pull out the dose knob to perform the priming step until a diamond appeared. After the pen was properly primed, the user lined up the arrow in the dosing window again and had to pull out the dose knob to set the insulin dose. These steps were quite cumbersome and often led to poor satisfaction in comparison with other insulin pen devices.[36] Similar to the other new-generation insulin pens, now the KP only requires dialing the dose, which improves the convenience and ease of use. The KP is the shortest new-generation prefilled pen. Hence, the HP and KP devices have the shortest "thumb reach" distance overall.[35,38] This device may be an ideal choice for a patient with dexterity issues. The KP has been modified to have a lower injection force and is color coded to distinguish between rapid and long-acting analog mixes. The rapid-acting insulin lispro is burgundy, lispro protamine/lispro 75/25 mix is yellow, and lispro protamine/lispro 50/50 mix is red. Patients who are pen naive prefer the KP over vials and syringes and FP possibly due to these design modifications.[39]

Notably, Novo Nordisk and Eli Lilly and Company no longer manufacture human insulin in their new generation of disposable pen devices. The regular or Neutral protamine hagedorn (NPH) human insulin alone or combined mixes were provided in disposable insulin pen models of the discontinued InnoLet® (Novo Nordisk, or Princeton, New Jersey, USA) and Humulin pens. The AACE/ACE guidelines do not recommend the use of short-acting regular human insulin or intermediate-acting NPH, if possible, for patients with type 2 diabetes.[11] This recommendation is due to human insulin preparations' unpredictable time course, inability to mimic

Figure 2 View of OptiClik (top) and SoloSTAR (bottom) pens.

Figure 3 View of Humalog pen (top) and KwikPen (bottom).

the normal physiologic profile, and increased risk of hypoglycemia.[11] Similarly, the ADA standards recommend the use of rapid- and long-acting insulin analogs for patients with type 1 diabetes since they are associated with less hypoglycemia and similar HbA_{1c} lowering compared with human insulin.[9,40,41] The ADA/EASD consensus statement and algorithm for patients with type 2 diabetes recognizes the use of insulin analogs results in lower risk of hypoglycemia. However, their recommendations include use of either intermediate- or long-acting basal insulin and use of either short- or rapid-acting prandial insulin. Interestingly, the algorithm omits inclusion of short-acting human insulin for prandial coverage. Despite their recognition of insulin analogs in reducing the risk of hypoglycemia compared with human insulin, they do not conclude the analogs lower the HbA_{1c} value more effectively than the human insulin.[10] Therefore, it can only be assumed that ceasing the production of human insulin preparations in prefilled pen devices was done in response to consensus statements discouraging their use and the shift toward the use of insulin analogs.

Dose accuracy

The accuracy of an insulin delivery system is of utmost importance in avoiding diabetes-related complications due to either hyperglycemia or hypoglycemia. The new-generation insulin pens available today have been shown to be exceedingly accurate.

Dosing accuracy for insulin pens is based on the regulations set by the International Organization for Standardization (ISO). To define positive accuracy for insulin pen-injectors for medical use, the ISO standard allows for a deviation within 1 U of insulin when administering 20 U or less and no greater than 5% deviation for doses greater than 20 U.[42]

Only three studies have evaluated the NGFP compared with the original FP or other new-generation pens.[43–45] The first study aimed to compare NGFP with FP using a total of 180 delivered doses.[43] It was found that neither of the pens delivered any doses outside the predefined ISO limits when tested at 1, 30, or 60 U. The NGFP was more accurate than FP at delivering 30 U ($P < 0.05$) and 60 U based on the mean absolute deviation from the set doses. In addition, NGFP was more precise than FP at delivering 30 and 60 U ($P < 0.05$). Both NGFP and FP had similar accuracy in delivering 1 U of insulin.[43]

The second study compared NGFP with SS using a total of 66 delivered doses.[44] NGFP was outside the predefined ISO limits for 1 dose (0.2%) at 10 U and 1 dose (0.6%) at 30 U. The SS pen was outside the predefined ISO limits for 2 doses (0.4%) at 10 U and 3 doses (1.8%) at 30 U. The NGFP was more accurate than SS at delivering 10 U, with an absolute deviation of 1.63% ± 0.84% and 2.11% ± 0.92%, respectively ($P < 0.001$). This was also seen at a dose of 30 U, with an absolute deviation of 1.23% ± 0.76% and 1.54% ± 0.84%, respectively ($P < 0.05$).[44]

The most comprehensive study to evaluate the accuracy of NGFP compared with the newer generation of prefilled, disposable insulin pens was conducted by Krzywon et al.[45] The accuracy of NGFP, FP, SS, and KP was evaluated at doses of 1, 10, 30, 40, and 60 U and SS alone at 80 U using a total of 1,260 delivered doses. All pens at every dose tested were within the predefined ISO limits, and absolute average deviation of all insulin pens ranged between 0.09 and 0.81 U. The authors concluded that the dosing accuracy was excellent for all pens studied and there was no significant difference from one pen device to the next.[45]

The aforementioned studies were conducted in controlled laboratory settings, by trained professionals. However, when patients with or without diabetes, not dependent on insulin therapy, and naive to pen device were instructed on FP and SS pen use, the results demonstrated that the participants were able to administer a 20 U dose accurately.[46] A small amount of dosing errors occurred in this study, with less than 2% of doses from each pen delivered below the predefined ISO limits.[46] Another study in patients with diabetes, with approximately 90% of patients reporting pen device experience, found that patients were able to accurately administer six different doses (range, 5–80 U) with the SS pen, with no measurements outside the predefined ISO limits.[47] An interesting study evaluated the accuracy of administering injections with the SS pen under varying temperature conditions from 5°C to 40°C and found the SS pen dosed accurately according to ISO standards at 1, 40, and 80 U.[35]

All new-generation pens have excellent accuracy in a controlled laboratory setting[45] and only the SS can claim its pen to be accurate under varying temperatures.[35] No accuracy studies have been conducted using the NGFP or KP in patients with diabetes; however, studies show that patients can dose FP and SS accurately. Further studies are needed to determine if patient administration of insulin using other new-generation pens impacts their accuracy and/or clinical patient outcomes.

Injection force

Insulin pens have grown in favor amongst providers and patients for a number of reasons. One of the identified qualities affecting patient preference is the amount of force

necessary to inject insulin through a pen device (injection force).[48] It has been established that pen devices require less injection force to deliver an equivalent dose, in general, than insulin syringes because of the wide bore associated with the pen needles.[49] Injection force, measured in Newtons (N), is determined in clinical trials by mounting pens ready to deliver a set dose on a testing machine that is programmed to deliver the dose and depress the push button at a set speed. Injections are made into cushions designed to mimic adipose tissue in climate-controlled laboratories.[48] Injection force has been frequently validated with older insulin pens, and design modifications have been made that enable pens to require less injection force while maintaining accuracy. After the emergence of the SS insulin pen, a study comparing it with FP found that the FP required higher injection forces than SS to deliver equal amounts of insulin for numerous doses and speeds.[35] This validated survey data describing complaints from patients with manual dexterity problems in depressing the push button to deliver insulin doses with the FP.[43,50]

Thus, the NGFP was developed with a goal of requiring lower injection force for dose delivery to improve user satisfaction.[48] Three studies have evaluated the injection force of NGFP compared with FP and other new-generation pens.[43,48,49]

A study comparing the injection force of NGFP with its predecessor, the FP, evaluated 20 pens using a standard flow rate of 10 U/s with 1 standard needle size (30G). NGFP was superior to FP with a relative reduction in injection force by 29.8%.[43]

The injection force of NGFP was also compared with SS in delivering a dose of 60 U at 3 constant injection speeds of 4, 6, and 8 mm/s.[49] Twenty-four pens were tested using the following combinations of pens and needle sizes: NGFP with a 32G needle, SS with a 32G needle, and SS with a 31G needle. Various injection speeds were evaluated to mimic the possible range of injection speeds at which a patient may perform self-administration of insulin, and two needle sizes were used to examine any influence of injection force from needle bore size. The NGFP with a 32G needle had significantly lower mean injection force compared with SS with either a 32G or 31G needle ($P < 0.0001$). Over the range of injection speeds, the NGFP with 32G needle reduced the injection force by 18%–28% compared with the SS with 32G needle and by 36%–45% compared with the SS with 31G needle. Therefore, using a smaller-gauge (32G) needle reduced the injection force to the greatest extent and that increasing the injection speed required higher injection force using either pens.[49]

The most comprehensive study to evaluate the injection force of NGFP compared with the newer generation of prefilled, disposable insulin pens was conducted by Asakura et al.[48] A head-to-head comparison of NGFP, SS, and KP was conducted at 3 constant injection speeds with 2 needle sizes of 31G and 32G. The set injection doses for this study were 20 U instead of 60 U doses delivered in the Rissler et al[49] study. Results demonstrated similar findings showing superiority of NGFP over SS in requiring lower injection force by 12%–25% at both needle sizes and at all injection speeds (Tables 2 and 3). NGFP was also superior to KP requiring lower injection force by 35%–41% at both needle sizes and at all injection speeds (Tables 2 and 3). This study also confirmed that increasing the injection speed and gauge size of the needle significantly increased the injection force with all pens tested.[48]

Head-to-head comparisons of current insulin pen devices demonstrate clear superiority of NGFP to either SS or KP in requiring lower injection force needed to deliver a set dose of insulin.[48,49] Because injection force has been described in patient survey data as a factor affecting satisfaction, it may be inferred that improving this could result in improved patient preference. Further studies are needed to determine if improved injection force with the NGFP improves clinical patient outcomes.

Patient-focused perspectives

Patient perceptions of injection force, ease of use, product identification, and handling can influence pen preference. Only 2 studies evaluating patient preference of NGFP compared with other pen devices have been completed. Patient perceptions of injection force were evaluated in the study by Pfutzner et al.[43] Fifty patients with type 2 diabetes who had insulin pen experience were asked to complete a survey after delivering 1 dose each of 20, 40, and 60 U with NGFP and FP devices into an injection pillow in a randomized

Table 2 Comparative injection force (N) at various speeds using a 31G pen needle and NGFP, SS, and KP insulin pens[48]

Pen device	Speeds of injection (mm/s)		
	3.3	5	8.3
Next Generation FlexPen[a,b]	8.1 ± 0.7	10.7 ± 1.4	15.6 ± 0.9
SoloSTAR[b]	9.2 ± 0.5	13.3 ± 0.8	20.7 ± 2.4
KwikPen[a]	12.5 ± 1.6	16.9 ± 1.2	24.5 ± 2.6

Note: All values are given as mean ± SD.
Abbreviations: N, Newton; NGFP, Next Generation FlexPen; SS, SoloSTAR; KP, KwikPen.
[a]$P < 0.05$ for all comparisons made between NGFP and KP; [b]$P < 0.05$ for all comparisons made between NGFP and SS.

Table 3 Comparative injection force (N) at various speeds using a 32G pen needle and NGFP, SS, and KP insulin pens[48]

Pen device	Speeds of injection (mm/s)		
	3.3	5	8.3
Next Generation FlexPen[a,b]	5.7 ± 0.4	8.2 ± 0.7	12.7 ± 0.5
SoloSTAR[b]	6.7 ± 0.3	10.4 ± 2.1	16.3 ± 1.1
KwikPen[a]	9.1 ± 1.3	13.1 ± 0.8	21.6 ± 2.0

Note: All values are given as mean ± SD.
Abbreviations: N, Newton; NGFP, Next Generation FlexPen; SS, SoloSTAR; KP, KwikPen.
[a]$P < 0.05$ for all comparisons made between NGFP and KP; [b]$P < 0.05$ for all comparisons made between NGFP and SS.

order. Significantly more patients rated the injection force as "good" or "very good" using the NGFP at all 3 tested doses of 20, 40, and 60 U compared with the FP (80%, 72%, and 38% vs 48%, 32%, and 20%, respectively, $P < 0.0001$). In addition, significantly more patients found the NGFP to be "simpler and more comfortable to use" than the FP (76% vs 24%, respectively, $P = 0.0002$).[43]

Sixty-four patients with type 1 or type 2 diabetes were enrolled in a survey study to evaluate the visual appearance and perceptions of NGFP compared with FP.[50] All patients were shown the range of FPs and NGFPs prefilled with three types of analogs (insulin aspart, insulin detemir, or insulin aspart protamine/aspart mix) along with their packaging and asked to answer nine survey questions corresponding to their ability to identify the type of insulin. Patients were also asked to attach a NovoFine® (Novo Nordisk) needle on the FP and NGFP, then attach a NovoTwist needle on NGFP (NovoTwist is not compatible with FP), and answer three survey questions about the ease of attaching the needle. Finally, the patients were asked to inject 1 dose of 20, 40, and 60 U of insulin detemir into an injection pillow and were randomized to inject either FP followed by NGFP or NGFP followed by FP. They then answered 22 additional survey questions relating to the injection force and device handling. Significantly more patients found the insulin analog type with the NGFP was easier to identify with regard to labeling ($P < 0.001$), packaging ($P < 0.001$), and cartridge ($P < 0.001$) compared with the FP. Significantly more patients rated that attaching the NovoTwist needle on NGFP was easier than attaching a NovoFine needle on either FP or NGFP ($P < 0.001$), and significantly more patients preferred using the NovoTwist needle over the NovoFine needle with the NGFP (77% vs 6% respectively, $P < 0.001$). The NGFP was easier to inject than FP at all 3 doses of 20, 40, and 60 U of insulin ($P < 0.001$). In addition, significantly more patients believed it was "easy" or "very easy" to push down the injection button on the NGFP compared with the FP for the 20 U (91% vs 67% respectively, $P < 0.001$), 40 U (72% vs 22% respectively, $P < 0.001$), and 60 U doses of insulin (38% vs 2% respectively, $P < 0.001$). More patients rated the NGFP as "very easy" for overall use ($P < 0.001$), the most convenient pen ($P < 0.001$), and the simplest pen to use ($P < 0.001$) compared with the FP. Patients were more confident that the full dose of insulin was delivered using the NGFP than with the FP ($P < 0.001$). Accordingly, 83% of patients perceived that the NGFP was the safest to operate. Overwhelmingly more patients preferred the NGFP compared with the FP (95% vs 5% respectively, $P < 0.001$) if they had to use the pen on a daily basis.[50]

Unfortunately, there are no studies currently available that examine patient preference of NGFP compared with other new-generation prefilled pens, and further research is needed in this area.

Health-care providers' perspectives

Studies have shown that health-care providers' attitudes toward insulin pens are powerful predictors of pen use in their patients. Physicians presenting insulin pens as an option for insulin administration (odds ratio [OR] = 14.09; $P < 0.001$), encouraging their use (OR = 135.63; $P < 0.001$), patients' perception that the pen facilitates diabetes self-care (OR = 20.15; $P < 0.001$) and is less expensive (OR = 4.79; $P < 0.05$) were the strongest determinants of pen users from nonusers.[51]

Health-care providers' attitudes toward insulin therapy can also contribute negatively and positively to the overall use of insulin therapy and pen devices. An international survey evaluating the resistance to starting insulin therapy among patients with diabetes and diabetes care providers found that US patients reported lower belief in insulin efficacy and more self-blame for needing insulin therapy than patients from all other countries.[12] The study also found that 50%–55% of nurses and general practitioners delay insulin therapy until absolutely necessary, but specialists and opinion leaders were less likely to do so. The delay of insulin therapy was also significantly less likely when physicians and nurses see their patients as more adherent to medication or appointment regimens, view insulin as more efficacious, and when they are less likely to delay initiation of oral diabetes medications.[12]

Only two studies have evaluated the health-care providers' perspectives of insulin pens using older-generation HP pens[52] and the SS pen.[53] Satisfaction surveys given to health-care providers using older Humalog/Humulin insulin pen devices found more physicians agreed that it was easier to start patients on insulin therapy using the pen, believed

patients were less intimidated by the pens, took less time to teach the patients how to use the pen, and found patients were more confident in their ability to accurately administer the insulin dose compared with vial and syringe method.[52] The only study evaluating the health-care providers' perspectives using a new-generation insulin pen was with SS devices.[53] A survey given to physicians and diabetes educators found that approximately 80% of respondents reported SS pens were easy to use, very easy to teach their patients how to use, and also reported it took less than 10 minutes to train their patients to use the insulin pen.[53]

Further research is needed to determine the health-care providers' perspectives by comparing all new-generation insulin pen devices. It is also important for the health-care providers to be aware of and/or advise their patients to check with their health-care plan provider and/or prescription benefit plan to clarify coverage of insulin pens and their supplies, if necessary.

Medication adherence and clinical outcomes

No studies have been conducted to evaluate if improvements to any of the new-generation pens in dose accuracy, injection force, and patient or health-care provider satisfaction would affect medication adherence. The only studies that have examined this particular type of outcome were from the analysis of medical and prescription claims databases.[25,27]

One study examined medication adherence and total health-care costs among type 2 diabetes patients enrolled in a Medicaid program from 2001 to 2006.[27] The authors found that diabetes-related and overall medication adherence was comparable for patients initiating insulin therapy with a pen (FP or NovoPen®; Novo Nordisk) vs a syringe (53% vs 50% and 94% vs 94%, respectively).[27]

The other managed care study followed patients who newly initiated insulin pen or vial and syringe, for a minimum of 2 years, to evaluate outcomes retrievable through an integrated medical and pharmacy claims database of 57 managed care health plans in the United States.[25] After transition to insulin pens (FP), they found medication adherence was significantly improved, the likelihood of experiencing a hypoglycemic event was significantly reduced, and the incidence of hypoglycemia in adherent patients decreased by nearly two-thirds. There were significant reductions in emergency department and physician visits, whereas hypoglycemia-attributable (HA)-related hospitalizations and outpatient visits remained similar after transition.[25]

A similar evaluation of 468 privately insured patients with insulin-dependent type 2 diabetes, who were previous users of insulin vials and syringes, was identified from 57 commercial health plans in the United States.[26] They were followed for a 6-month period before and for a 2-year or longer period after transition from a human or insulin analog vials and syringes to a biphasic insulin analog pen (FP). Adherence, measured by the medication possession ratio (MPR), significantly increased from 59% to 68% after transition to the pen device ($P < 0.01$). A significant decrease in the likelihood of experiencing a hypoglycemic event was also observed after the transition (OR = 0.40; 95% confidence interval [CI], 0.27–0.61), with hypoglycemic events reduced by nearly two-thirds among patients with optimal adherence (MPR of 80% or greater). There were significant reductions in HA – related emergency department visits (OR = 0.36; 95% CI, 0.16–0.84) and physician visits (OR = 0.39; 95% CI, 0.22–0.77).[26]

Beyond overall reductions in the likelihood of experiencing hypoglycemic events and their related hospital or physician visits after transition from vials and syringes to insulin pens from studies previously mentioned,[25–27] there are no studies that have evaluated these types of clinical outcomes comparing one pen device with another.

Similarly, no studies have been conducted to evaluate if improvements to any of the new-generation pens in dose accuracy, injection force, and patient satisfaction would result in any benefit in reducing the HbA_{1c} value. Only 1 study has done a comparative evaluation for the outcome of HbA_{1c}. They evaluated an older-generation prefilled human insulin NovoLet® (Novo Nordisk) pen and compared it with vials and syringes for an 8-week treatment period in patients older than 60 years. Patients using insulin pens had a significant reduction in the mean HbA_{1c} values by 1.1% compared with a 0.6% reduction using the vial and syringe method (baseline value of HbA_{1c}, 8.4%; value of HbA_{1c} after treatment, 7.3% vs 7.8%, respectively, $P < 0.02$).[22]

Conclusion

Many design modifications have been made to prefilled insulin pens to produce devices that are highly accurate, have low injection force, and are simple for patients with diabetes to use. Dosing accuracy appears excellent for all new-generation prefilled insulin pens, and no one pen claims superiority over another. The NGFP has the lowest injection force needed to deliver a set dose of insulin, at various injection speeds using common needle gauge sizes, compared with either SS or KP. Almost twice the amount of patients

rated the NGFP better in injecting insulin compared with the FP and believed it was easier to push down the injection button. More patients perceived that the NovoTwist needle was easy to use with the NGFP and preferred using it over the NovoFine needle with the NGFP. NGFP was superior to FP in simplicity, ease of use, convenience, confidence in delivering the full dose of insulin, identification of insulin analog from labeling and packaging, and overall preference. Further studies are needed to determine what impact the design modifications to improve pen accuracy, injection force, and patient or health-care provider preference to new-generation prefilled pens would have on improving the glycemic control and other clinical outcomes.

Disclosure

The authors disclose that they have no financial interests, arrangements, or affiliations with the manufacturers of any products discussed in the article or their competitors.

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