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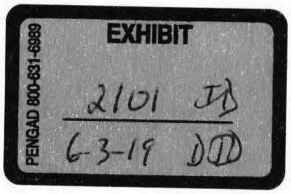
REVIEW

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).

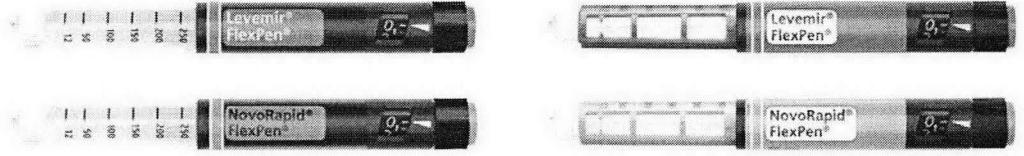

Figure 1 View of FlexPen Levemir and FlexPen NovoRapid (left) and Next Generation FlexPen Levemir and Next Generation FlexPen NovoRapid (right).

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

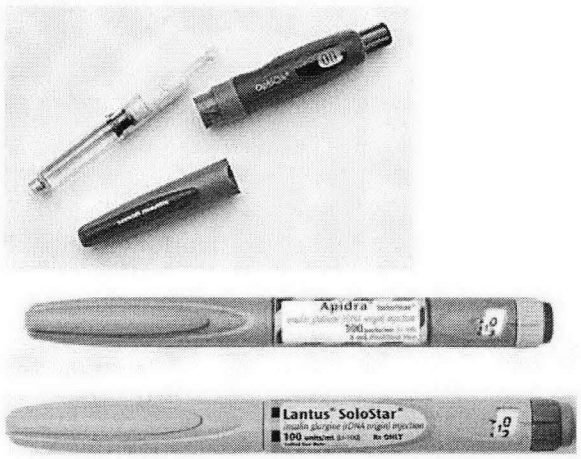

Figure 2 View of OptiClik (top) and SoloSTAR (bottom) pens.

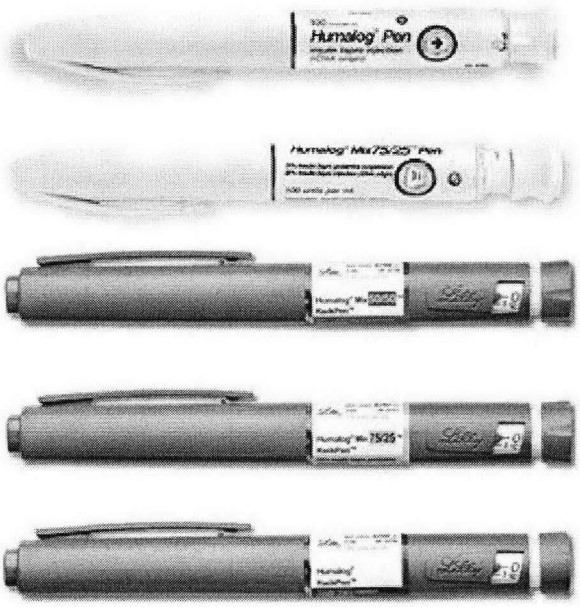

Figure 3 View of Humalog pen (top) and KwikPen (bottom).

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 $1.63\% \pm 0.84\%$ and $2.11\% \pm 0.92\%$, respectively ($P < 0.001$). This was also seen at a dose of 30 U, with an absolute deviation of $1.23\% \pm 0.76\%$ and $1.54\% \pm 0.84\%$, 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

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