

Half-Unit Insulin Pens: Disease Management in Patients With Diabetes Who Are Sensitive to Insulin

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Abstract

Background: Insulin pens represent a significant technological advancement in diabetes management. While the vast majority have been designed with 1U-dosing increments, improved accuracy and precision facilitated by half-unit increments may be particularly significant in specific patients who are sensitive to insulin. These include patients with low insulin requirements and in those requiring more precise dose adjustments, such as the pediatric patient population. This review summarized functional characteristics of insulin half-unit pens (HUPs) and their effect on user experience.

Methods: The literature search was restricted to articles published in English between January 1, 2000, and January 1, 2015. A total of 17 publications met the set criteria and were included in the review.

Results: Overall, studies outlined characteristics for 4 insulin HUPs. Based on their functionality, the pens were generally similar and all met the ISO 11608-1 criteria for accuracy. However, some had specific advantageous features in terms of size, weight, design, dialing torque, and injection force. Although limited, the currently available user preference studies in children and adolescents with diabetes and their carers suggest that the selection of an HUP is likely to be influenced by a combination of factors such as these, in addition to the prescribed insulin and dosing regimen.

Conclusions: Insulin HUPs are likely to be a key diabetes management tool for patients who are sensitive to insulin; specific pen features may further advance diabetes management in these populations.

Keywords

Half-unit insulin pen, HumaPen Luxura HD™, JuniorSTAR®, NovoPen Echo®, NovoPen Junior

Patients with diabetes who are sensitive to insulin (eg, children and the elderly) have low insulin requirements and so are more susceptible to dosing errors.¹ A small volume error will represent a high additional percentage of total administered volume. Accuracy may be limited in low-dosage insulin users from rounding up or down to the nearest 1U.² In this context, accuracy refers to the closeness of the administered value to the dialed/true value.³ Conversely, precision refers to the level of reproducibility of dosing facilitated by different insulin pens, that is, level of deviation between different doses administered.³ The improved accuracy and precision afforded by insulin half-unit pens (HUPs) compared with 1U pens and vial/syringe administration may potentially benefit patients sensitive to insulin through improved glycemic control.

Children and adolescents often use low doses of insulin and could therefore be vulnerable to dosing errors.¹ Insulin requirements are determined based on body weight, age and pubertal status, and children with newly diagnosed type 1

diabetes mellitus (T1DM) may require an initial total daily dose as low as ~5-10 units/24 h administered in multiple low doses during the day.^{4,6} The high level of hypoglycemia observed in this population may be due to errors of administering small amounts of insulin¹ or due to dosing limitations when adjusting to the nearest 1U dose with either mealtime or long-acting insulin.² Similar to the pediatric population, elderly patients with diabetes who are sensitive to insulin may benefit from half-unit dosing accuracy.¹ Half-unit dosing accuracy may also prove useful in patients who use

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carbohydrate counting to determine their mealtime insulin^{2,7} by precisely titrating their insulin dose to their dietary intake, and patients with concomitant Addison's disease, hypopituitarism, chronic kidney disease, or chronic pancreatitis.²

The Diabetes Control and Complications Trial (DCCT) demonstrated the significance of intensified methods of blood glucose control in T1DM, as this was shown to delay the onset and slow the progression of diabetes-related complications.⁸⁻¹⁰ In TEENS, the largest worldwide study assessing T1DM management in youth aged 8-25 years, optimal glycemic control was only achieved by 28% of participants.¹¹ Therapy adherence, central to optimal glycemic control, can impart significant treatment burden and worsen the quality of life (QoL) for people with T1DM.¹² Adherence to therapy may be particularly challenging in the pediatric T1DM population, with lower compliance reported compared with adults.¹³ Traditionally, insulin has been administered subcutaneously by using a syringe manually filled from a vial.⁷ For many patients, this method presents barriers to treatment because of inaccuracy, pain, anxiety, inconvenience and problems with social acceptability.¹³⁻¹⁸ Alternative delivery methods, such as insulin pens, have been designed to help overcome these barriers,¹⁸⁻²¹ and HUPs may be particularly beneficial in achieving therapy adherence and optimal glycemic control in an insulin-sensitive population.

Since the first launch of a half-unit insulin pen (HUP) in 1992,¹⁵ other HUPs have been developed, for example, HumaPen Luxura HD™ (Eli Lilly and Company, Indianapolis, IN, USA; HPL), JuniorSTAR® (Sanofi, manufactured by Haselmeier, Stuttgart, Germany; JS), NovoPen Echo® (Novo Nordisk A/S, Bagsvaerd, Denmark; NPE), and NovoPen Junior (Novo Nordisk A/S; NPJ). The different functional characteristics and how these affect user experience and preference are outlined in the "Factors Affecting the User Preference for an HUP" section.

Objective

The objective of this review was to summarize the available literature on functional characteristics of HUPs and their effect on user experience and preferences.

Literature Review Methodology

This systematic review adheres, where relevant, to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement on developing a systematic review. The search was restricted to articles published in English between January 1, 2000, and January 1, 2015. Key search inclusion terms included half-unit insulin pen, half-unit insulin dose, half-unit insulin injection device, glycemic control, diabetes management, injection force, accuracy, patient preference, clinical outcomes, comparison, outcomes, and insulin sensitivity. Additional references not listed on the PubMed database were added if known to the authors and applicable to the review objective. These also included the

user guides of HUPs identified through the literature search. Retrieved references were evaluated for suitability. Exclusion criteria included studies not relating to diabetes or insulin delivery devices, those assessing suitability of injection needles, studies of alternative insulin delivery devices, comparison of vial/syringe–pen use and articles describing disposable/prefilled insulin pens or 1U insulin pens. A total of 17 publications met the criteria outlined above and are reviewed in detail below.

Results

The literature was split broadly into 2 categories: (1) functional characteristics of HUPs and (2) factors affecting the user preference for an HUP.

Functional Characteristics of HUPs

This section outlines the main features and technical characterization of HUPs (Table 1), their accuracy, and injection forces required to perform an injection.

Main Features and Technical Characterization of HUPs

Pen weight, dimensions, and design. The overall size and weight of an insulin pen can greatly affect the convenience of every day transportation and ease of operation.¹⁶ Of the 4 HUPs examined, JS had the lowest weight (Table 1), NPE was the shortest with the cap on, while JS was the shortest without the cap.²² The sizes of the dosing display and digits may be of particular significance for populations with impaired visual acuity.²³ HPL had the largest dose display and JS had the largest digits.²² Dimensions of the injection button will be particularly significant in populations with limited manual dexterity. HPL and JS had the dose buttons of largest dimensions.²² JS, NPJ, and NPE are also available in multiple colors, which may be beneficial for users who require different insulin variants. Further individualization is offered for the NPE with different skins which may be particularly relevant for the pediatric population.²⁴

Durability/robustness. Reusable insulin pens are designed to withstand everyday use, and lifetime simulation is required as part of the ISO 11608-1 criteria.²⁵ Kristensen and Lilleore conducted a study of simulated lifetime use of NPE, which maintained dosing accuracy at all doses throughout the simulated lifetime use test.²⁶ Clark et al investigated the accuracy of the initial half-unit dose dispensed using the HPL over 3 different temperatures as specified in the ISO 11608 criteria (5°C, room temperature, and 40°C).²⁷ All delivered doses satisfied the ISO 11608-1 criteria for accuracy of needle-based injection systems.²⁷

Dialing torque. Dialing torque of an insulin pen refers to the strength needed to adjust the dose-setting dial.²³ Greater ease of use contributes to the confidence a user has in the

Table 1. Summary of Half-Unit Insulin Pen Characteristics.

		NovoPen Echo	NovoPen Junior	JuniorSTAR	HumaPen Luxura HD
Company		Novo Nordisk	Novo Nordisk	Sanofi (manufactured by Haselmeier)	Eli Lilly and Company
Weight with cartridge, g (\pm SD)	With cap	59.3 (\pm 0.17) ²²	61.3 (\pm 0.33) ²²	41.7 (\pm 0.16) ²²	64.2 (\pm 0.34) ²²
	Without cap	44.1 (\pm 0.15) ²²	44.1 (\pm 0.20) ²²	27.4 g (\pm 0.04) ²²	44.3 (\pm 0.34) ²²
Injection volume range (U)		0.5-30 U ^{24,26}	1-35 U ^{37,56}	1-30 U ^{42,57}	0.5-30 U ⁴³
Insulin type		Penfill® 3 mL insulin cartridges ²⁴	Penfill 3 mL insulin cartridges ⁵⁶	Sanofi insulin cartridges ^{28,57}	Lilly insulin cartridges (Insulin lispro, Insulin lispro protamine suspension/insulin lispro injection) ^{27,37,43}
Cartridge replacement mechanism		A simple twist with auditory feedback once cartridge is secure ²⁴	Several revolutions ⁵⁶	Several revolutions ⁵⁷	Several revolutions ⁴³
Lowest dose (U)		0.5 ^{24,40}	1 ³⁷	1 ⁵⁷	1 ⁴³ (accuracy at 0.5 dose demonstrated) ²⁷
Memory function		Last dose and time elapsed (up to 12 h) ^{24,40,53}	None ^{14,56}	None ⁵⁷	None ^{40,43}
Recommended in situ time (s)		6s ²⁴	6s ⁵⁶	10s ⁵⁷	5s ⁴³
Dial back		Dial-without insulin loss ²⁴	Requires partial disassembly ^{37,56}	Dial-back without insulin loss ⁴²	Dial back without insulin loss ^{37,43}

dose setting and accuracy of a pen,²³ and may be of particular significance in pediatric patients and patients with limited hand strength. Dialing torque has only been reported for JS, where the mean dialing torque for both dialing and correcting a dose was between 5 and 6 N cm.²⁸ A dialing torque of this magnitude is expected to allow easy dose dialing and correction for pediatric patients.²⁹

Accuracy. Dose accuracy is vital for maintaining glycemic control and minimizing the risk of complications in people with diabetes.^{30,31} All HUPs have been shown to meet ISO 11608-1 criteria for accuracy of needle-based injection systems, so fluctuations within these criteria are unlikely to be of clinical significance.^{26,27,31-35}

Injection Force. Injection force is defined as the peak force reached when pushing the injection button during administration of an insulin dose.^{20,36} While not confirmed in a clinical trial, a lower injection force is expected to facilitate simpler operation and reduced injection-site pain.^{16,32,33,37-39} JS had the lowest mean injection force of the HUPs investigated (5.94 N for the flow rate 6.00U/s).²² All HUPs required a smaller mean injection force than the maximum force that can be exerted on such devices by the pediatric population (>21 N).²⁹ Therefore all HUPs are suitable for use by this population.

Factors Affecting the User Preference for an HUP

This section summarizes 3 studies examining patient experience in the use of different HUPs (Table 2) and outlines how

the pen features translate into usability preferences. Olsen et al compared the usability and functionality of NPE, NPJ, and HPL for children and adolescents with T1DM, as well as parents and health care professionals working as diabetes nurse educators or physician/pediatricians.⁴⁰ Wong et al conducted a randomized, 2-period, cross-over, open-label study to compare functional usability and preference of HPL and NPJ in 65 adult caregivers of children aged 3-12 years with T1DM.⁴¹ Klonoff et al conducted a noncomparative assessment of JS in 168 HUP users from 5 European countries.⁴²

Overall Preference. Noncomparative assessment of JS by both pediatric nurses and patients/parents (n = 167) found that the majority agreed JS was easy to use overall, convenient for everyday use and suitable for the lifestyle of a young person with T1DM.⁴² When the usability of HPL versus NPJ was tested, the majority of caregivers preferred HPL.⁴¹ Similarly, the majority of participants rated HPL easy/very easy to use, compared with NPE and NPJ.⁴⁰

Injection Force. The majority of participants (both pediatric nurses and patients/parents) found the injection force of JS suitable for young people with diabetes.⁴² Olsen et al found that more participants using NPE and HPL found the injection force “ideal,” compared with users of NPJ ($P = .005$).⁴⁰

Ease of Dose Dialing and Correction. To correct a dose that has been set higher than needed, NPJ requires the barrel and cartridge holder to be separated, followed by pressing the dial-up button back to 0, before the pen is assembled again and

Table 2. Summary of Surveys Examining the Usability of Different Half-Unit Insulin Pens.

	Olsen et al ⁴⁰	Wong et al ⁴¹	Klonoff et al ⁴²
Study type	Face-to-face interviews and functionality testing	Randomized 2-period cross-over, open-label simulated injection study	Face-to-face interviews
Location	Germany, France, Canada	Not reported	France, UK, Germany, Italy, Spain
Population	Children and adolescents aged 7-18 years with T1DM (n = 79), parents (n = 78), and health care professionals (n = 48)	Adult caregivers of children aged 3-12 with T1DM (n = 65)	Nurses working with children with T1DM (n = 109), parents of children with T1DM aged 0-5 years (n = 16), parents of children with T1DM aged 6-12 years (n = 20), adolescents with T1DM (aged 13-18 years (n = 22)
Method	Usability assessment: setting up the pen, adjusting, injection into a foam cushion and use of memory function Preference assessment: Rating scales on a standardized nonvalidated online questionnaire	Each item was answered on a 7-point scale for specific pen features as well as proportions of caregivers with a pen preference were used to assess the overall ease of use, ease of changing the insulin cartridge and ease of correcting the insulin dose	The performance of JS was rated for 18 attributes on a 5-point scale depending on question type: 1 (very poor, very difficult, completely disagree), 2 (somewhat poor, somewhat difficult, somewhat disagree), 3 (neither poor nor good, neither easy or difficult, not sure), 4 (somewhat good, somewhat easy, somewhat agree), or 5 (very good, very easy or completely agree)
Pens included	NPE, NPJ, HPL	HPL, NPJ	JS
Selecting dose to be delivered	Successful setting of the pen: 84% NPE, 88% NPJ, 91% HPL Rated easy or very easy: 77% NPE, 75% NPJ, 87% HPL	Preference of ease of use: 94.7% HPL, 5.3% NPJ	Dialing the dose rated as easy by 87% of nurses and 66% of parents/adolescents (total 80%) Reading the dose rated as easy by 94% of nurses and 98% of parents/adolescents (total 96%)
Injecting a dose	Proportion of participants completing injections: 95% NPE, 97% HPL, 60% NPJ		Rated easy to inject by 87% of nurses and 97% of parents/adolescents (total 90%)
Injection force	Rated as ideal: About 70% for NPE and HPL, 58% for NPJ		Rated suitable by 84% of nurses and 93% of parents/adolescents (total 87%)
Size	Ideal in size: 70% NPE, 54% NPJ, 20% HPL		
Weight	Rated as ideal: 53% NPE, 42% NPJ, 36% HPL		Weight rated as suitable by 71% of nurses and 67% of parents/adolescents (total 69%) Pen rated as easy to carry by 86% of nurses and 81% of parents/adolescents (total 84%)
Changing the cartridge		Preference: 94.1% HPL, 5.9% NPJ	Rated easy to change by 65% of nurses and 83% of parents/adolescents (total 71%)
Dose correction		Preference: 94% HPL, 6% NPJ	Rated easy to dial back a dose by 92% of nurses and 78% of parents/adolescents (total 87%) Mechanism of dialing back was found to give flexibility in dialing the correct dose by 94% of nurses and 95% of parents/adolescents (total 94%)
Memory function	Rated as easy to use: 89% of pediatric subjected and 94% of parents		
Overall	80% favored NPE ⁴⁰	80% HPL	Rated as easy to use by 94% of nurses and 93% of parents/adolescents (total 93%)

HPL, HumaPen Luxura; JS, JuniorSTAR; NPE, NovoPen Echo; NPJ, NovoPen Junior; T1DM, type 1 diabetes mellitus.

the correct dose can be dialed.^{19,37} In all other HUPs, an incorrect dose can be corrected by reversing the dial without any insulin loss.^{24,37,42,43} Overall, the majority of participants found it easy to dial and to dial back a dose using JS in terms of dial tactility and auditory feedback, and found that these pen features afford flexibility in dialing the correct dose.⁴² In terms of ease of correcting a dose, participants preferred HPL to NPJ.⁴¹ Similarly, NPE and HPL were rated better compared with NPJ.⁴⁰ The lower preference of NPJ reported in these studies was likely due to the more complex dial-back mechanism compared with other HUPs. The studies indicate that a simple dial-back mechanism that does not waste insulin is preferable.

Ease of Reading Dose/Display. The majority of participants (children/adolescents/parents, 98%; nurses, 94%) rated JS as somewhat good/very good (top 2 options of a 5-point scale) in terms of ease of reading a dose, which may be because of the large dose digit measurement previously reported.⁴² The majority of participants also found the dose easy to read when comparing HPL, NPJ, and NPE in a pediatric population.⁴⁰ This feature may be of particular significance for patients with sight impairments.

Changing of the Cartridge. Most HUPs require several revolutions to screw the cartridge holder onto the pen with the exception of NPE, which requires a single-movement twist. The majority of study participants (children/adolescents/parents, 83%; nurses, 65%) agreed that JS was somewhat good/very good for ease of changing the cartridge.⁴² In the direct comparison of HPL and NPJ, of the caregivers with a preference, the majority preferred HPL.⁴¹ No usability preference has been reported for NPE.⁴⁰

Transportation and Handling. The majority of study participants (children/adolescents/parents, 81%; nurses, 86%) found JS easy to carry on a daily basis,⁴² which is important for insulin-sensitive patients who may need to keep the pen on them at all times and monitor insulin requirements regularly. A low weight and smaller size of the pen may be particularly important in light of smaller hands of children as well as for elderly patients with neuromuscular impairments, or hand fatigue.^{16,32,33,36,37,44}

Memory Function. This feature has been developed as a safety feature to address user anxiety over a forgotten dose and risk of hypoglycemia through double-dosing.^{14,45-48} NPE is the only HUP with this feature and records the last dose volume and time (<12 h).^{24,40,49} The majority of pediatric users (89%) and parents (94%) rated this feature as very easy or easy to use.⁴⁰ The memory function of NPE was also tested in the REMIND study, which included 2- to 18-year-old participants with T1DM.⁴⁹ Overall, 83% of participants stated that they used the memory function during the study.⁴⁹ Compared with the previously used device,

forgotten injections were significantly reduced (51% vs 27%, respectively; $P < 0.0001$).⁴⁹ However, switching from a previous device to an HUP with a memory function was not associated with improved glycemic control.^{49,50} Furthermore, only 42% of health care professionals rated this as a very important feature.⁴⁶

Discussion

Clinical Significance

Inadvertent medication overdoses have been cited as “a common problem among children” by American Academy of Pediatrics.⁵¹ Accuracy to half-unit dose facilitated by HUPs may therefore be particularly significant in the pediatric population and adult patients who are sensitive to insulin.^{15,44} The outlined characteristics and features of the HUPs support a role for HUPs in improved adherence to treatment,³⁷ leading to improved clinical outcomes and improved QoL.^{21,52} However, no interventional or comparative studies on clinical outcomes (glycemic control) using HUPs were identified in this literature search. Additional studies are required to investigate whether HUP use results in improved glycemic control, and how this feature translates into patient outcomes. Overall, while many of the benefits of HUPs may improve clinical outcomes for young patients with diabetes, real-world studies are required to determine whether this is the case.

Choosing an HUP

Insulin pen characteristics will affect injection procedure and user experience, and may ultimately affect treatment outcome (Figure 1). As insulin pens are manufactured for use with specific insulins, the choice of an insulin pen could also be determined by the insulin prescribed.⁴⁴ Since the main objective of using insulin pens is to facilitate optimization of a patient's diabetes management,⁵³ pen characteristics should be matched with a user's requirements and lifestyle.

The choice of an insulin pen facilitating half-unit versus 1U dosing may be of particular significance to patients with T1DM who are more sensitive to insulin when accuracy at lower doses is crucial, as well as when requiring dose precision and accuracy to a half-unit. Other functional features of HUPs should be matched with user needs and preferences. HUP features affecting dose dialing, correction and dose reading may increase the confidence a user has in dose accuracy. Features facilitating ease and convenience of use, as well as discreetness, could improve treatment flexibility and social acceptance. The main objectives of HUPs are to enable accurate dose delivery to an insulin-sensitive patient, as well as reducing the physical, cognitive and emotional burden of diabetes management.⁵³ Therefore, all the various features of HUPs and their impact on users' lifestyle should be considered by health care professionals when prescribing insulin.

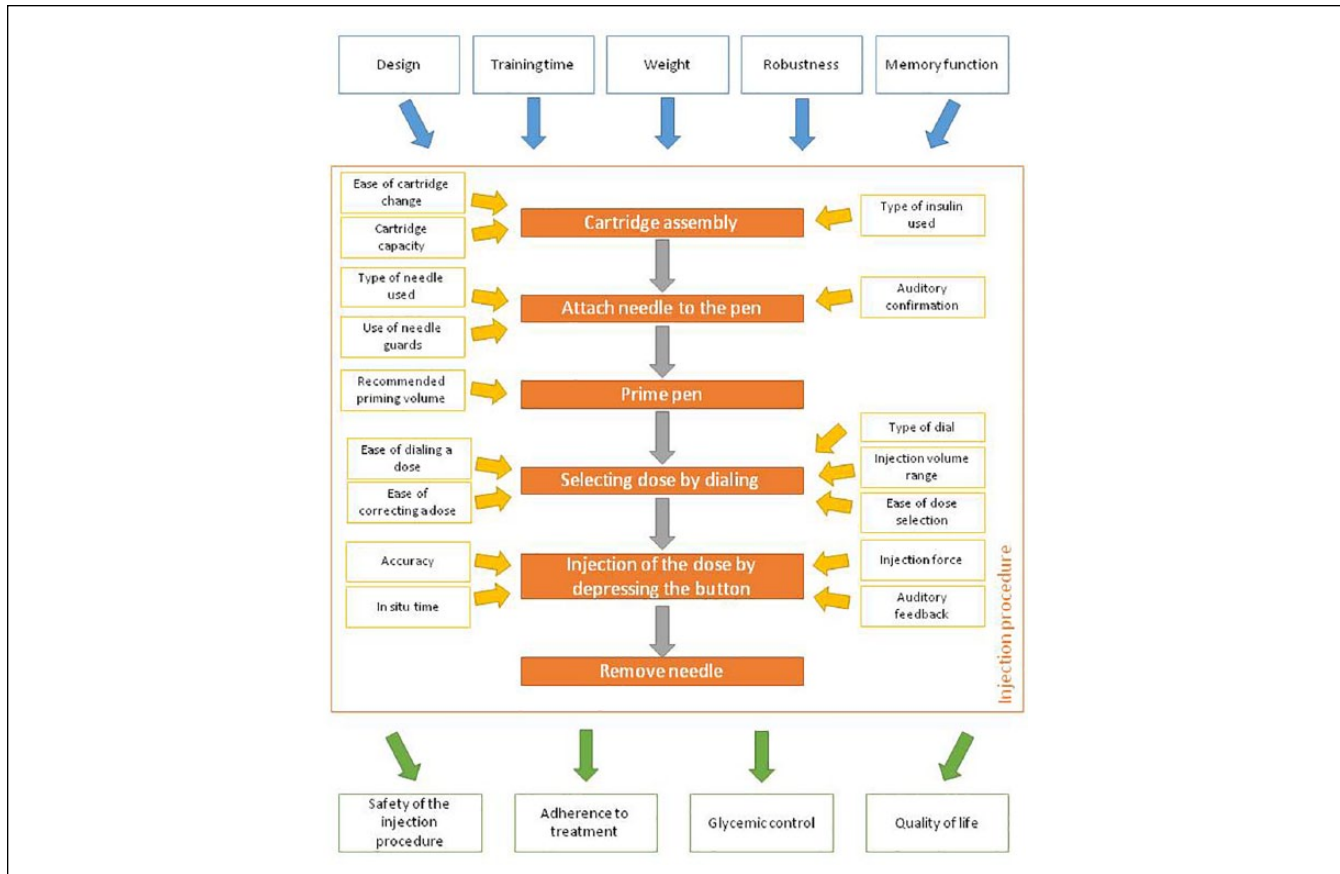


Figure 1. Summary of the different characteristics that may influence the user preference for an insulin pen and how these may impact the management of diabetes.

The most recent development in insulin pens is the development of a “reusable wireless pen” facilitating half-unit increment for mealtime insulin for people with diabetes age 12 years and older, where a Bluetooth connection facilitates transfer of data from the insulin pen to a smartphone app.⁵⁴ The app is designed to manage and catalog the insulin dose data, and provide a dose calculator to aid mealtime insulin dose calculations.⁵⁴ It is likely that this type of technologic developments represent the future of insulin therapy in this patient population.

In the absence of head-to-head comparison studies across the available HUPs, no conclusion can be drawn on overall user preference.

Beyond Half-Unit Accuracy

U20 insulin preparations (20 units/mL) facilitated insulin dosing to 0.2U and were termed “toddler-friendly” insulins because of the small dose increments that could be administered.⁵⁵ Since the standardization of U100 insulin preparations (100 units/mL), U20 (20 units/mL) have been withdrawn, leaving a gap in the market for insulin dosing accuracy below 1U.⁵⁵ HUPs aid in addressing the lack of

small dosing increments by enabling 0.5U dosing increments. Currently, precision and accuracy beyond 0.5U can only be achieved through the use of insulin pumps or by insulin dilution.⁵⁵ However, these approaches have drawbacks, because the availability of pumps is limited and insulin dilution necessitates the use of a syringe,⁵⁵ introducing the risk of contamination if a patient mixes their own parenteral medications. Pens delivering more accurate insulin dosing with 0.1U precision could benefit certain patient populations, such as insulin-sensitive patients using carbohydrate counting who may only require very low doses of insulin per day.

Conclusions

The development of HUPs has provided improved precision and accuracy of insulin dosing. This feature of HUPs may be relevant to patients requiring lower doses of insulin (eg, pediatric and populations who are sensitive to insulin) as well as others requiring more precise insulin dose adjustments. Currently available HUPs are generally similar in terms of technical characteristics, although some have specific advantageous features and these should be carefully

considered for any individual's needs. Although limited, the currently available studies suggest that the selection of an HUP is likely to be influenced by a combination of these aforementioned factors as well as the insulin and dosing regimen prescribed to the user. In summary, HUPs fill a need in insulin dosing and are likely to be a key diabetes management tool for the foreseeable future.

Abbreviations

DCCT, Diabetes Control and Complications Trial; HPL, HumaPen Luxura HD; HUP, half-unit insulin pen; ISO, International Organization for Standardization; JS, JuniorSTAR; NPE, NovoPen Echo; NPJ, NovoPen Junior; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL, quality of life; T1DM, type 1 diabetes mellitus.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: DK is a consultant for Insulet, Lifecare, SANOFI, and Voluntas. US, HO, and CD are employees of SANOFI. The other authors have no disclosures to report.

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