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Review Article

Insulin delivery by injection in children and adolescents with diabetes

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Type 1 diabetes is treated with insulin, which has traditionally been delivered by vial and syringe. However, for many patients, dosing inaccuracy, pain, anxiety, inconvenience, and social acceptability present barriers to this method of administration (1–5). This has contributed to the increased popularity of alternative insulin delivery systems, including pen delivery devices (4, 6).

Evidence suggests that discreet devices, such as insulin pens, facilitate adherence to intensive insulin therapy regimens, help improve lifestyle flexibility, and reduce injection pain compared with the conventional syringe-based regimens, as shown in studies in adults and adolescents (7). In addition, compared with the vial and syringe method of insulin administration, pens may provide more accurate dosing – which is particularly important in children – thereby improving short-term blood glucose control and potentially improving long-term outcomes (5, 8). Children, in particular, may benefit from insulin pens that are simple to use as adherence issues may be more evident in this patient group (9). Pens for insulin delivery in children with type 1 diabetes have been used for a long time in Europe, and have recently gained in popularity in many other places around the world (4, 10). Furthermore, the conventional vial and syringe method of insulin delivery is beginning to be considered as obsolete (11). Moreover, there is a continued drive to improve insulin pen technology, to refine and enhance the functionality and usability of these pens. However, despite recent advances in pen design and function, the selection of pens available especially for children is limited.

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This review will explore the features of the available insulin pens and consider how these may address the needs of the paediatric population.

Features and benefits of insulin pens

Modern insulin delivery devices have numerous advantages compared with traditional vials and syringes. Notably, insulin pens have been found to be easier to use and transport, provide more accurate dosing, reduce the fear associated with needles, reduce injection pain when used with the short, fine (5–6 mm and 30–32 gauge) needles, and reduce the embarrassment of injecting in public (1, 4, 5, 8, 12–16). Furthermore, insulin pens are associated with patient preference and improved adherence compared with the vial and syringe method of insulin delivery (4). In a study conducted in the USA, Lee et al. (14) investigated the impact on medication adherence when converting from the vial and syringe method of insulin administration to FlexPen® (Novo Nordisk A/S, Bagsværd, Denmark), a prefilled insulin pen, in 1156 adult patients with type 2 diabetes. Adherence was measured by a medication possession ratio (MPR; denoting the proportion of time a patient had a supply of medication during the follow-up period) ≥80%. MPR values of <80% are frequently used in the literature on chronic diseases to define poor adherence to medication. Medication adherence significantly improved after switching to insulin pen devices (from 62% with vials and syringes to 69% with insulin pens, $p < 0.01$). In addition, the proportion of patients who were adherent (MPR ≥80%) was significantly higher after switching to insulin pens compared with before (54.6% vs. 36.1%, respectively, $p < 0.01$), indicating that switching from vials/syringes to insulin pens improves medication adherence.

The first insulin pen device, NovoPen® (Novo Nordisk A/S), was launched in 1985 and revolutionised insulin administration for people with diabetes. Current pen device manufacturers include Berlin-Chemie AG, Eli Lilly and Company, Novo Nordisk A/S, Owen Mumford Ltd, and Sanofi-Aventis. Since the mid-1980s, insulin pens have evolved into more sophisticated devices. Some pens have specific features such as dose delivery confirmation (an audible click). This reduces the potential for dosing errors and also alerts visually impaired individuals to the insulin dose being dialled, allowing them continued independence (17). Modern pens also have dose selectors with dial-up/down features that allow easy adjustment or correction of dialled doses. Moreover, the dose selectors are designed in an ergonomic fashion, with different textures to fit better in the hand and ensure ease of use (17). In 2007, the first insulin pen with a memory function, HumaPen® Memoir™ (Eli Lilly and Company, Indianapolis, IN, USA) was launched. The memory function addresses the common issue of anxiety over a missed dose (18).

Insulin pens are constantly being developed in order to improve their usability, potentially simplifying the management of diabetes. They may be durable (i.e., the insulin cartridge is replaceable) and larger cartridges have been designed to reduce the number of cartridge replacements required. In addition, disposable insulin pens have been produced for individuals who have difficulty in changing the cartridges (17, 19, 20).

Other benefits of insulin pen devices include the discreet appearance, ease with which patients can learn to use them, and the resulting user confidence (17). These features may help to improve the quality of life of people with diabetes, particularly in the paediatric setting (Table 1) (21).

Table 1. Insulin pen features

Key features of insulin pens for the management of diabetes
Long-term feasibility of MDI (40)
More convenient and easier to transport than traditional vial/syringe (14, 21)
More accurate doses/greater precision (4, 5, 13)
Easier to use for those with visual or fine motor-skill impairments (17)
Less injection-site pain (21)
May be used discreetly in public (4, 21)
Slim, lightweight, and 'stylish' design (17)
Helps improve lifestyle flexibility (4, 21)
Improves quality of life (21)

MDI, multiple daily injections.

Use of insulin pens in the paediatric population

The Diabetes Attitudes, Wishes, and Needs (DAWN) Youth Survey, initiated by Novo Nordisk in cooperation with the International Diabetes Federation, was conducted between 2007 and 2008 to investigate the effect of diabetes on the lives of children, adolescents, and their families living with diabetes. In total, 60% of children with diabetes were reported as not managing their diabetes successfully at school, whilst children with adequate support from their school had a better quality of life and were less burdened by their condition (22). In practice, schools may fail to train staff in diabetes care and there may be a widespread lack of legislative effort in most countries to ensure equal and safe access to education for children with diabetes (23). Evidently, social support from multiple domains is very important for children with diabetes. Consideration of the process by which diabetes is managed, namely insulin delivery, is also integral to improving quality of life. It is noteworthy that it may be easier to train school staff to use insulin pens rather than vials and syringes, which may aid in facilitating the management of diabetes at school or in day care for the very young child living with diabetes.

Adherence to insulin therapy is an important issue in children and adolescents with diabetes (9). There is evidence to show that some children and adolescents develop ketoacidosis as a result of poor adherence to insulin therapy (24, 25). The level and need for self-care also differs with age; children with diabetes who were diagnosed at an older age have been reported to have more success with self-care (22). The consequences of forgetting or omitting doses of insulin may lead to a deterioration of metabolic control and include increasing levels of haemoglobin (Hb)A1c (26, 27), which lead to an increased risk of diabetes-related complications. There is a need to improve self-care in children and adolescents as long-term poor metabolic control will increase the risk of diabetic complications and cardiovascular disease (28, 29).

A study of children and adolescents with type 1 diabetes investigated their attitudes towards insulin injections, needle phobia, and the experience of pain when using different types of insulin devices. Study participants ($n = 158$) answered a questionnaire using Visual Analogue Scale (VAS) scores for various

Table 2. Comparison of insulin pens commonly used in children with diabetes

Device	Manufacturer	Memory function	Dose increments (units)	Choice of colours	Ability to customise pen
AutoPen® Junior	Owen Mumford, Oxford, UK	No	1.0	Yes	No
ClikSTAR®	Sanofi-Aventis, Paris, France	No	1.0	Yes	Yes
FlexPen®§	Novo Nordisk A/S, Bagsværd, Denmark	No	1.0	No*	No
HumaPen® Luxura™	Eli Lilly and Company, Indianapolis, IN, USA	No	1.0	Yes	No
HumaPen® Luxura™ HD**	Eli Lilly and Company, Indianapolis, IN, USA	No	0.5	No	No
HumaPen® Memoir™	Eli Lilly and Company, Indianapolis, IN, USA	Yes	1.0	No	No
KwikPen™§	Eli Lilly and Company, Indianapolis, IN, USA	No	1.0	No	No
NovoPen 3 Demi®	Novo Nordisk A/S, Bagsvaerd, Denmark	No	0.5	No	No
NovoPen® 4	Novo Nordisk A/S, Bagsvaerd, Denmark	No	1.0	No	No
NovoPen Echo®**	Novo Nordisk A/S, Bagsværd, Denmark	Yes	0.5	Yes	Yes
NovoPen® Junior	Novo Nordisk A/S, Bagsværd, Denmark	No	0.5	Yes	No
SoloStar®§	Sanofi-Aventis, Paris, France	No	1.0	No*	No

*Different color depending on type of insulin.
§Prefilled, disposable pens (not for reuse).
**Manufacturer assures accuracy from 0.5 U dosing.

statements including injection pain and needle phobia. The median VAS score of injection pain/fear was rated lower with insulin pens than with syringes. A total of 8.3% of the subjects scored themselves as having pronounced needle phobia (1). Insulin pens may therefore be preferable and help to facilitate adherence in the paediatric population as they were found to cause less fear and less injection pain than syringes in this study. Today, pen device needles are available in 4–6 mm lengths (30), while the shortest syringe needle is 8 mm (5). The pen needles are also thinner than syringe needles; the gauge of syringe needles is usually 30 (0.30 mm) (5), while pen needles designed for the paediatric population are available in 31 or 32 (0.25 or 0.23 mm) gauge (31).

There are several insulin pens available, in both disposable and durable forms, that are commonly used for insulin delivery in children with diabetes (Table 2). An automatic injection device [Penmate® (Novo Nordisk A/S)] in which a pen injector is used has been shown to decrease insertion pain (32).

Numerous crossover comparison studies of insulin pens have been conducted in adult patients (20, 33–38) and although there has been a widespread acceptance of insulin pens among both adults and children (10), there are fewer comparative studies in children.

A select number of studies over the last decade have explored the advantages of insulin pens in children (39). The long-term feasibility of multiple daily injections (MDI; before meals) with insulin pens in children and adolescents has been demonstrated (40), and a later study by Lteif and Schwenk (41) showed that insulin pens are more accurate than syringes at delivering low insulin doses in children with type 1 diabetes. Results from the Diabetes Control and Complications Trial (only vials/syringes were used in this study) (42) and the UK Prospective Diabetes Study (28) highlight the importance of striving to achieve and maintain the best possible glycaemic control. Insulin pens potentially offer substantial improvements in convenience, freedom, and flexibility for children and adults with diabetes (43). Indeed, children are a key treatment group and, as such, developing pens with this patient population in mind is crucial.

Correction added after online publication 27 July 2011: corrections have been made on the table to complete data on insulin pens and manufacturers.

Memory function

Despite the recent advances in insulin pen technology, there are currently no insulin pens available with memory functions that have been designed specifically for the paediatric population. Forgetfulness can hinder treatment adherence in children and adolescents with diabetes; therefore, an insulin pen with a memory function would be beneficial to this patient population.

Currently, HumaPen Memoir is the only insulin pen available with a memory function; it records the 16 most recent doses administered. The functionality and acceptability of HumaPen Memoir was investigated in a multicentre, open-label, single-arm study lasting 6–10 wk involving adult patients with type 1 or type 2 diabetes (n = 290) and healthcare professionals (HCPs; n = 16). The study participants rated the memory function of HumaPen Memoir as important. When asked to select two aspects of the memory function they considered to be most important, patients and HCPs chose the ability to confirm that an injection had been taken (55 and 63%, respectively), the ability to view the number of units of the previous insulin dose (38 and 44%, respectively), and the ability to check when the previous insulin dose was taken (25 and 44%, respectively) (18, 44).

Results from the study of HumaPen Memoir are promising as it may be speculated that children are more likely to forget to treat themselves than adults and they may become unsure or confused about the details of their last insulin dose – these factors must be considered when developing a pen specifically for children.

The results of a recent usability study, involving children, their parents, and HCPs treating children, showed a strong preference for a new paediatric insulin pen with a simple memory function [NovoPen Echo® (Novo Nordisk A/S)] compared with two other marketed insulin pens without a memory function [HumaPen® Luxura™ HD (Eli Lilly and Company) and NovoPen® Junior (Novo Nordisk A/S)]. In particular, the memory function scored highly for meeting participants' needs and being easy to use (45). However, it should be noted that NovoPen Echo can provide details of only the most recent dose administered, while HumaPen Memoir can provide details of the 16 preceding doses. The Innovo(R) (Novo Nordisk A/S) system was an insulin delivery device that had a similar memory function to NovoPen Echo, which showed the last dose administered and the time elapsed since the last dose. However, the Innovo system has been discontinued.

Insulin pen devices with a memory function designed specifically for children may provide added security for parents, who need to be assured that their child has not missed a dose or received a double dose of insulin. This is particularly important in younger children with multiple caregivers. The consequences of double dosing can lead to severe hypoglycaemia, neurological impairments, or death if not identified and treated rapidly (46).

Although parents may be ready to hand over the responsibility for their child's care to other people (such as school staff/personal day carers or grandparents), it has been shown that parents worry about their children having low blood glucose levels at school. The consequence may be that parents give their children insufficient insulin in the morning to try to prevent hypoglycaemia at school (47). As there is often a lack of adequate support and care in this environment (22, 47), the memory function of an insulin pen may be beneficial for parents/caregivers because they will be able to check if and when the child had a dose of insulin while at school. Furthermore, parents/caregivers can check if the dose their child received was appropriate.

Parents can also use a feature like the memory function as a form of age-appropriate education to teach their children about the importance of insulin injections, dosing, and timing, which may remind and reinforce the importance of taking medication. This may provide the children with an increased sense of independence, allowing them to gain confidence in their ability to self-manage their diabetes.

Dosing accuracy

Insulin pens are known to provide more accurate dosing than vials and syringes, especially when delivering low doses of insulin, thereby improving short-term glycaemic control and potentially improving long-term outcomes for people with diabetes (4, 5, 8, 13, 41).

Lteif and Schwenk (41) compared the accuracy of insulin pens with syringes in children and demonstrated that insulin pens were more accurate than syringes at delivering insulin doses of <5 U. A total of 32 children with type 1 diabetes and 16 parents of children with type 1 diabetes (all of whom measured out the insulin doses) were included in the study. In total, 24 children (mean age: 14.1 yr) were on MDI and were familiar with both insulin pens and vials/syringes, and 24 children (mean age: 9.8 yr) administered a mixture of regular and Neutral Protamine Hagedorn insulin via syringe only (16 parents routinely drew up their child's insulin dose in this group and were therefore included in the study). The accuracy and precision of the doses (morning doses measured three times from vials/syringes or cartridges containing radio-labelled glucose and saline) were determined by scintillation spectroscopy. In this non-randomised study, the absolute error for doses <5 U with insulin syringes [Becton Dickinson and Co U100 (BD, Franklin Lakes, NJ, USA) and Terumo® U100 (Somerset, NJ, USA) syringes] was significantly greater than with pen devices [AutoPen® (Owen Mumford Ltd, Oxford, UK) and NovoPen 1.5]: $9.9 \pm 2.4\%$ with syringes vs. $4.9 \pm 1.6\%$ with pen devices, $p < 0.01$. For doses >5 U, the absolute error with syringes was comparable to that of insulin pens ($3.2 \pm 0.6\%$ vs. $2.2 \pm 0.4\%$, respectively). This was a small study that employed scintillation technology instead of weight measurement (actual insulin was not used); however, it was the first study to compare the accuracy of syringes vs. insulin pens in children.

A study by Gnanalingham et al. also compared the accuracy of insulin pens with syringes. The 1, 2, 5, and 10 U insulin doses were drawn up by one investigator (five each of the Becton Dickinson pen and the NovoPen) and five paediatric nurses (using 30 U syringes) at a paediatric diabetes clinic (8). The insulin dose was deposited onto a polystyrene container and weighed immediately using an analytical balance. The percentage errors for all doses studied were significantly lower for the Becton Dickinson pen (3%) and NovoPen (4%) than for the syringes (9%), $p < 0.0001$. This was also true for the smaller insulin doses of 1, 2, and 5 U ($p < 0.01$). In general, the insulin pens underdosed; however, the nurses had a tendency to overdose the small insulin doses with the 30 U syringe. This study was also small, uncontrolled, and non-randomised, and compared syringe doses drawn up by five different nurses, thus potentially introducing error. However, it is one of the few studies that have looked at accuracy relating specifically to insulin pen use in children.

Such findings are important as there is a need for accurate and fine-tuned dosing in the paediatric population which may require small doses of insulin. Insulin pens that dispense half-increment doses, such as BerliPen® Junior (Berlin-Chemie AG, Berlin, Germany), HumaPen Luxura HD, and NovoPen Junior may therefore be beneficial in this patient group (48). Insulin sensitivity also differs between patient subgroups, exemplified by insulin pump studies showing that younger children (≤6 yr) require smaller doses of insulin/kg compared with older children (>6 yr) (49, 50). This emphasises the importance of accurate and convenient insulin delivery devices that can tailor dosing according to the requirements of all paediatric age groups.

For patients receiving MDI, the accuracy of the insulin pen device is essential for continued confidence in treatment. As the principal aim of diabetes management is to achieve adequate glycaemic control and reduce the long-term complications of hyperglycaemia, dose accuracy and precision should be the first consideration when choosing an insulin pen (4). Although half-increment dosing may be more important for bolus administration of rapid-acting insulin, highly insulin-sensitive young children may also benefit from half-increment dosing with respect to administration of basal insulin. If a patient/caregiver is certain that the pen device is delivering insulin in accurate doses, it may help to improve adherence to treatment. Studies in adults and adolescents with diabetes show that improving adherence is associated with improved HbA1c levels, whilst decreasing the incidence of hypoglycaemia and the number of hypoglycaemia-associated hospital and physician visits (14, 24).

Of the insulin pens currently available that provide insulin in half-unit increments, none have a memory function, a feature that is also highly important for the paediatric population, as discussed previously.

Design aspects

An insulin pen for children should be suitable for small hands as children will be required to perform certain functions, including dialling the dose, checking the selected dose, pulling off the needle cap, pressing the injection button, and replacing the cap (21). The ability to self-inject insulin may depend on the size of the device, especially in small children; therefore, such a device should be relatively small, slim, and lightweight for portability, simplicity, and ease of handling. If the pen device is the correct size for the paediatric population, it will be easy to operate and therefore may improve acceptance of and adherence to treatment regimens, which may aid in promoting self-care.

In the above-mentioned study (45), NovoPen Echo received the most favourable rating for design and overall appearance compared with HumaPen Luxura and NovoPen Junior. Child-friendly coverings on insulin pens are more likely to encourage children to use their insulin pen devices and reduce the embarrassment of performing injections. This may aid in promoting adherence to treatment. Different colours of pen devices and/or the use of 'skins' (i.e., decorative/protective covers typically used for mobile phones and MP3 players) allows easy differentiation in case different types of insulin are used in identical devices, which may reduce the risk of patients administering the wrong type of insulin (48). This feature would be especially advantageous for children using different kinds of insulin (e.g., basal and bolus).

Other insulin delivery devices

Insulin pumps

Unlike insulin pens, continuous subcutaneous insulin infusion (CSII) or insulin pump therapy mimics the physiological delivery of insulin by using a portable electromechanical pump to infuse insulin at a slow, basal rate over 24 h. In addition, insulin pumps also have a memory function; it is possible to download details of all doses administered during the previous month or more (49). In this regard, the functionality is therefore not comparable to insulin pen devices. Insulin pump therapy is recommended as a possible treatment for children and adolescents with type 1 diabetes if treatment with MDI is not practical or not considered appropriate (51), for example, if HbA1c is persistently above the individual goal, hypoglycaemia is a major problem or quality of life needs to be improved (16). It is also a feasible mode of insulin therapy in very young children, and is increasingly used from the onset of diabetes in this age group.

An increasing number of studies have shown a beneficial effect on glycaemic control with CSII compared with MDI (52–57). In addition, observational trials in children have shown a decrease in the rate of severe hypoglycaemic episodes with CSII, despite decreasing HbA1c values (55, 58–60). Furthermore, evidence indicates that quality of life and patient satisfaction with CSII therapy are at least equal to or greater than that achieved with MDI (61–64).

However, CSII is not the preferred solution for all children; success with a pump requires proactivity, commitment, and motivation which may be lacking in this patient group and their support structure. A multidisciplinary staff/centre is required to utilise the full potential of CSII treatment (65). Also, young children are unable to manage their own treatment and may need parental support to adjust pump settings. In many schools, teachers and school nurses may be reluctant to use insulin pumps and refuse to help young children who are receiving CSII therapy (47). In some situations, the parent and paediatric diabetes team have to provide time-consuming training sessions for school staff before allowing a young child using an insulin pump to attend school. When adolescents use pump therapy, it is not uncommon for them to forget to administer bolus insulin before/after eating a meal (27). Besides, children and adolescents tend to eat irregularly, and missed bolus insulin doses may counterbalance the advantage of the basal insulin replacement offered by CSII (25). Indeed, parents play a key role in CSII management (66) and lack of support for parents or proper training may prevent improvements in glucose control. Despite insulin pumps improving adherence to medication, they tend to be expensive and hence less accessible to some patients (19).

Subcutaneous indwelling catheters/injection ports

Subcutaneous indwelling catheters/injection ports, such as Insuflon® (Unomedical, Roskilde, Denmark) and I-port® (Patton Medical Devices, Austin, TX, USA), were originally devised to overcome problems with injection pain at the onset of diabetes. Insuflon is inserted and rests against the skin while the I-port requires insertion at a 90° angle. Both devices have a dead space (the hollow inside that will be filled with insulin with the first injection) of approximately 0.5 U of 100 U/mL, which can be added to the first dose after replacement. They can be used with both pens and syringes, even for administering small doses as low as 0.5 U. For a review of the use of indwelling catheters, see reference (67). Insuflon is inserted in the abdomen using a topical local anaesthetic cream (68). Insuflon is used in an increasing number of centres for the introduction of MDI and its use does not affect metabolic control (69). In children who have problems using injections, HbA1c has been decreased by using Insuflon (70). Patients who dislike injections may therefore benefit from using Insuflon as it may help to improve adherence to medication.

Jet injectors

A jet injector uses very high pressure to form a thin jet stream of insulin that penetrates the skin. The insulin is absorbed quickly and glucose control achieved using this method can equal that achieved by an insulin pump (71, 72). Jet injectors have been reported to decrease injection pain (73), but this finding has been contradicted in other studies (74, 75). Bleeding, bruising, and delayed pain after the injection have been described (74).

Conclusions and future directions

The incidence of type 1 diabetes in the paediatric population is a growing concern, and the development of adequate treatment to maintain lower blood glucose targets is of paramount importance. As a consequence, demand for insulin delivery devices that are simple, accurate, and tailored for the paediatric population will also increase.

Insulin pens are well established as a delivery device in children and adults with diabetes, and offer improvements in adherence, freedom, and flexibility over more conventional means of administration using syringes. Further advances in pen technology are necessary to improve upon these features and there is a continued drive to develop pens that are specifically targeted at children.

Memory functions in insulin delivery devices have much to offer. Clinical experience gained from the use of insulin pumps has shown benefits in the ability to download details of all doses administered during the previous month or longer. We anticipate that developing a similar memory function in insulin pens should help to improve the long-term management of diabetes in the future.

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Conflict of interest

R. Hanas has participated in advisory board meetings for Novo Nordisk, Eli Lilly, and Unomedical. He has received lecture honoraria from Eli Lilly and Novo Nordisk. C. de Beaufort has participated as a speaker for Novo Nordisk. H. Hoey has participated in an advisory committee for Novo Nordisk. B. Anderson has served as a DAWN Youth Survey supervisor and has received lecture honoraria from Novo Nordisk.

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