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GUIDELINES

Connected Insulin Pens and Caps: An Expert's Recommendation from the Area of Diabetes of the Spanish Endocrinology and Nutrition Society (SEEN)

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ABSTRACT

Undoubtedly, technological advances have revolutionised diabetes management in recent years. The development of advanced closed hybrid loop insulin pumps or continuous glucose monitoring (CGM) systems, among others, have increased the quality of life and improved glycaemic control of people with diabetes. However, only some patients have access to such technology, and only some want to use it. CGM has become much more widespread, but in terms of insulin delivery, most people with type 1 diabetes (T1D) and almost all people with type 2 diabetes (T2D) on insulin therapy are treated with multiple-dose insulin injections (MDI) rather than an insulin pump. For these patients, using connected insulin pens or caps has shown benefits in reducing missed insulin injections and promoting correct administration over time. In addition, using these devices improves the quality of life and user satisfaction. The integration of insulin injection and CGM data facilitates both users and the healthcare team to analyse glucose control and implement appropriate therapeutic changes, reducing therapeutic inertia. This expert's recommendation reviews the characteristics of the devices marketed or in the process of being marketed and their available scientific evidence. Finally, it suggests the profile of users and professionals who would benefit most, the barriers to its generalisation and the changes in the care model that implementing these devices can bring with it.

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Key Summary Points
Most people with type 1 diabetes (T1D) and almost all people with type 2 diabetes (T2D) on insulin therapy are treated with multiple dose insulin injections (MDI) rather than an insulin pump
Several connected insulin pens or caps have been developed, with different characteristics summarized in this document
The use of connected insulin pens or caps can improve glycaemic control and quality of life by reducing missed and mistimed insulin injections
Integration of insulin injections and continuous glucose monitoring (CGM) data allows a comprehensive glucose dynamic analysis
Healthcare providers and users who are motivated to improve diabetes management and who are open to new technologies could benefit the most from using connected insulin pens and caps

THE CLINICAL ISSUE: AIMING TO IMPROVE ADHERENCE AND SELF-MANAGEMENT OF INSULIN THERAPY

Despite the pharmacological and technical advances in the last decades in type 1 (T1D) and type 2 diabetes (T2D) management, a high percentage of people with diabetes do not reach the therapeutic goals recommended by the clinical practice guidelines. Poor diabetes control implies a higher risk of long-term micro- and macrovascular complications resulting in a reduction in quality of life and mortality. Up to 70% of people with T1D in the T1D Exchange registry presented suboptimal HbA1c levels, with being 8.4% (68 mmol/mol) being the HbA1c average in the whole cohort and 9% (75 mmol/mol) in adolescents [1, 2]. Likewise, > 70% of people with T1D in Spain showed HbA1c > 7% (53 mmol/mol), with an average of 7.6% (60 mmol/mol) [3]. The available data in the T2D population also indicate the difficulty of optimising glycaemic control in > 50% of this population [4, 5].

Insulin is the main treatment in people with T1D and also in around 25% of the T2D population [4]. Adherence to the insulin regimens can be challenging, particularly when it requires multiple daily injections (MDI). Frequent dose adjustments driven by glucose monitoring add an additional burden. Usual follow-up comprised a massive amount of information regarding insulin therapy, glucose levels, meal content and lifestyle, among others.

Unfortunately, adherence to insulin therapy is poor and mainly affected by socioeconomic factors, treatment complexity and the fear of hypoglycaemia [6, 7].

Up to 43% of people with T1D miss more than one prandial bolus of insulin per week, according to data from the T1D Exchange registry [2]. Low adherence to prandial insulin administration represents a barrier to optimising glycaemic control, not only due to the omission of boluses but also by delaying its administration. Between 20 and 45% of patients inject prandial insulin at different times to prescribed [8, 9]. Insulin forgetfulness before unplanned intakes is also frequent in young people [10]. In addition, the omission of one or more doses of basal insulin every 14 days in people with T1D was 22% in a real-life observational study, reaching figures of up to 46% in those with greater glycaemic variability [11]. Omissions, as well as dosage errors, are often unnoticed in clinical practice due to the lack of information provided by the patient. Missed doses and late boluses clearly worsen glycaemic control, as measured by both HbA1c level and continuous glucose monitoring (CGM) derived metrics [time in target range (TIR), time above range (TAR), time below range (TBR), mean glycaemia and coefficient of variation (CV)]

[12]. It is estimated that the omission of 2 weekly prandial boluses would mean an increase of 0.3–0.4% in HbA1c, two doses of basal insulin per week of 0.2–0.3%, and the omission of 39% of all boluses would imply an increase of 1.8% [13]. Boluses after meals and excessive numbers of hyperglycaemia corrections cause difficult-to-manage hyperglycaemia and hypoglycaemia that impact the physical and mental health of people with diabetes. Maintaining a high glycaemic variability in the long term favours the development of endothelial dysfunction and, finally, cardiovascular events [14]. Low insulin adherence negatively influences quality of life and is associated with increased morbidity, mortality and hospitalisations due to acute complications [12, 15].

Connected Pens and Caps to Improve Adherence, Data Integration and Sharing with the Medical and Nursing Team

The technological evolution in diabetes is focused on reaching ecosystems integrating all the glycaemic data (from fingerstick and/or CGM), insulin therapy (dose, time, active insulin, carbohydrate/insulin ratios and insulin sensitivity), meals and physical activity. The software should also support predictive advice on insulin doses and alerts to avoid hyper- or hypoglycaemia [8, 9]. The support systems for insulin administration based on artificial intelligence (AI) have shown similar efficacy in reaching TIR goals as human specialists [10].

Given the significant burden that insulin therapy self-management represents, tools offering help during the process are demanded. Mobile Health (mHealth) technology is considered a promising way to ease chronic condition control by using daily life technology [11, 12]. Ideally, besides the device (connected pen or cap), the integrated system should offer alarms and reminders to the user, a complete tracking of the insulin and glycaemic data and a platform to share all the information with the caregivers and healthcare providers in a remote mode. The telemedicine tools in these platforms, including both synchronous and asynchronous functionalities, are appreciated [13–15]. In fact, diabetes can be seen as a digital condition paradigm because of the enormous amount of data generated, implying complex analysis to offer the best solutions to people with diabetes [16, 17].

Some of the digital devices potentially transforming diabetes management are connected insulin pens and caps integrated with the CGM sensors [8, 18]. These devices include functions to track the dose and time of insulin injections and send reminders about dose omissions or delays [19, 20]. They can offer a complete view of the relationship between the moment and dose of insulin and the postprandial glucose dynamic for both the user and professional caregiver [21].

Although the available evidence on these systems is still limited, and there are few clinical guidelines on their use, the data supporting the improvement of glycaemic control by reducing omitted and mistimed boluses are accumulating nowadays [22, 23]. Data suggesting a better quality of life and satisfaction with the treatment are also present [18].

Devices recording the insulin dose and time have been available for many years. However, only recently have some of them been able to download the memory and integrate this information with GGM data (“downloadable insulin pens”). Others can continuously share the information with specific software solutions and forward it to caregivers (“connected insulin pens and caps”). Additionally, some of the current systems offer advice to the user on insulin therapy management and can be properly named “smart pens or caps.” Since 2022, the Standards of Medical Care in Diabetes of the American Diabetes Association refers to these devices as “connected” insulin pens and caps“ instead of “smart pens” [24] (Fig. 1).

Connected Insulin Pens

Connected insulin pens are refillable pens with insulin cartridges including sensors that monitor dose administration as well as wireless communication to share data (NFC or Bluetooth®) [25].

They therefore allow:

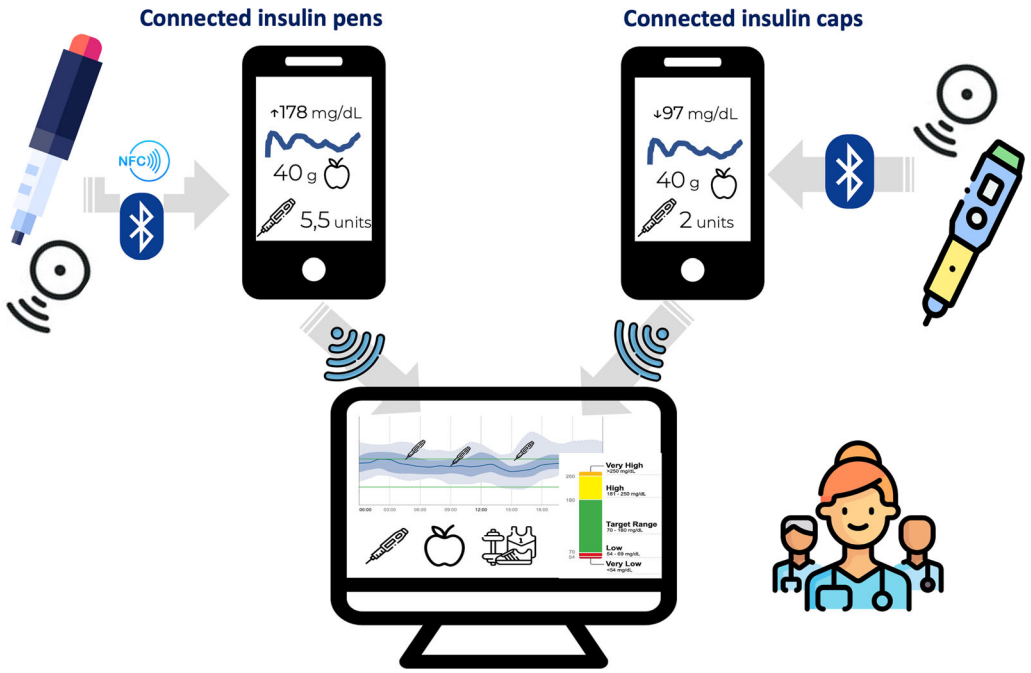

Fig. 1 Schematic representation of connected insulin pens and caps

1. Record information on the dose and time of insulin administered, and some also include information on insulin status (temperature, half-life).
2. Depending on the model, they can display information on the screen of the pen, or on an app, permitting integration with CGM or flash glucose monitoring (MFG) data platforms, etc.
3. Insulin administration reminders, bolus calculator and active insulin estimation are also available in some systems.

It has been postulated that connected pens should meet a series of requirements to be considered as such[26]:

- Absence of an additional device to send the information to the smartphone or laptop;
- Provide continued use for at least 12 months;
- Automatic time change according to time zone;
- Automatic recording of insulin injection dose and timing;
- Configurable automatic reminders for insulin injections;
- Ability to differentiate bolus insulin from priming insulin;
- Integration with other devices (CGM, digital therapeutic platforms, etc.);
- Provide decision support tools, such as a bolus calculator, active insulin estimation, etc.;
- Possibility of remote communication between patient and the medical team.

The most relevant general characteristics of CE-marked devices currently available or in the process of becoming so are shown in Table 1. The detailed characteristics of each are summarized below:

InPen®

This system, approved for people with diabetes over 7 years of age or younger with supervision, combines the Guardian™ 4 CGM sensor with the InPen™ smart pen system. CGM and pen data are sent to the InPen™ app via Bluetooth®, available for iOS and Android [27]. A review of the pen has been published analysing the potential benefits for the user prior to its integration with the CGM system [28].

Table 1 Marketed connected pens: main features

	ESYSTA BT pen®	**Pendiq 2.0®**	**NovoPen 6®**	**NovoPen Echo Plus®**	**InPen®**
Company	Emperra	Pendiq	Novo Nordisk	Novo Nordisk	Companion, Medtronic
Approval	EU marking	EU marking	EU marking	EU marking	FDA, EU marking
Compatible insulins	Any insulin in cartridge via adapter	Lilly, Sanofi and Novo Nordisk cartridges	Novorapid®, Fiasp®, Levemir®, Tresiba®	Novorapid®, Fiasp®, Levemir®, Tresiba®	Humalog®, Novorapid®, Fiasp®
Dose increments	1 UI	0.1 UI	1 UI	0.5 UI	0.5 UI
Maximum dose	60 UI	60 UI	60 UI	30 UI	30 UI
Shows last dose units	Yes	Yes	Yes	Yes	Yes
Connecting to apps or mobile	Yes	Yes	Yes	Yes	Yes
Active insulin dose	Not	Not	Not	Not	Yes
Bolus reminder	Not	Not	Not	Not	Yes
Bolus calculator	Not	Not	MySugr Social Diabetes in progress	MySugr Social Diabetes in progress	Yes
Integration with CGM	Not	Not	Glooko	Glooko	Guardian Connect System Glooko IOS; Dexcom Clarity iOS
Integration with FreeStyle LibreLink®/ Libreview ®	Not	Not	Yes	Yes	Not
Connectivity	Bluetooth®	Bluetooth®	NFC	NFC	Bluetooth®
Battery life	6–12 months	Rechargeable	5 years	5 years	1 year

Table 1 continued

	ESYSTA BT pen®	Pendiq 2.0®	NovoPen 6®	NovoPen Echo Plus®	InPen®
Web page	https://www.emperra.com/en/	https://pendiq.com/en/home/	https://www.novonordisk.com/our-products/smart-pens/novopen-6.html	https://www.novonordisk.com/our-products/smart-pens/novopen-6.html	https://www.medtronicdiabetes.com/products/inpen-smart-insulin-pen-system

FDA Food and Drug Administration, *CGM* continuous glucose monitoring, *NFC* near-field communication, *EU* European Union

The app shows the glucose values measured by the sensor and the dose and time of insulin injections. It has a configurable bolus calculator, including a view of the carbohydrates ingested. To suit all types of people with diabetes, the bolus calculator allows a simple option (fixed doses plus corrections, sliding scale type) and a more advanced option (carbohydrate estimation plus corrections) and an even more advanced option (insulin to carbohydrate ratio + insulin sensitivity factor). It also shows active insulin and bolus modified by the user instead of the suggested omitted boluses and capillary glycemia data (with a compatible glucometer). Insulin administration reminders, insulin expiration and temperature alerts are also available. Reports of up to 90 days can be generated and shared with the medical team.

The pen can be used for 1 year, does not need to be loaded and allows the administration of half units up to a maximum dose of 30 IU. More than one insulin pen can be attached to the app. Currently, it is only compatible with cartridges of rapid insulin analogues (except glulisine). The doses and time of injection of basal insulin can be introduced manually.

A study in 636 T1D people using InPen® showed a significant reduction in TBR < 70 mg/dl (2.54 to 2.27%; $p < 0.01$), the decrease being much more noticeable in subjects starting from TBR < 70 mg/dl over 4% (8.02 to 6.27%; $p < 0.01$) [29].

In another observational study including 529 participants with T1D on suboptimal glycemic control (423 showing GMI > 8% and 106 with GMI > 9.5%), glucometric data were analyzed after 90 days of InPen® use compared to the previous 90 days. Participants with GMI > 8% significantly increased their TIR by 2.3% (0.6 h/day), with a decrease of GMI of 0.1% and a decrease of TAR of 2.4% (TBR unchanged). Patients with previous GMI > 9.5% obtained a more significant benefit, with an increase in TIR of 5.1% (1.2 h/day), a decrease in GMI of 0.4% and a reduction of TAR of 5.1%, with no change in TBR[30].

NovoPen® 6 and NovoPen® Echo Plus

These two memory downloadable insulin pens allow the use of different types of NovoNordisk insulins in a cartridge (Penfill®). They show the last dose of insulin administered and the time since its administration on a little screen on the top (example: 12 IU, 00:45.13; this means that the last dose of insulin injected was 12 IU 45 min 13 s ago). Both pens allow storing information about the last 800 doses [31].

These pens have a duration of 5 years, allow sending data to any device with NFC (computer, tablet, smartphone, glucose monitor, etc.) and have a compatible app. In some countries, agreements have already been established with Diasend, Glooko-Diasend and MySugr to integrate pen information into their platforms and apps. The memory of insulin injections can be downloaded and integrated into the FreeStyle LibreLink app and LibreView web platform.

The NovoPen® system does not have a bolus calculator, although integration with apps like MySugr could facilitate it.

NovoPen® 6 (grey) allows up to 60 IU to be delivered in a single injection in 1-IU increments, while NovoPen® Echo Plus (red) allows a maximum dose of 30 IU in 0.5-IU increments. Therefore, NovoPen® 6 is intended for basal insulin administration and NovoPen® Echo Plus for prandial insulin boluses.

A real-life multicenter, observational prospective study conducted in Sweden recruited 94 people with T1D, users of CGM or FGM. During the follow-up (at least five visits according to the protocol of each centre) it was observed that the use of NovoPen® 6 significantly improved glycaemic control by increasing TIR by 1.9 h/day, decreasing TAR by 1.8 h/day and TBR < 54 mg/dl by 0.3 h/day and decreasing glycaemic variability. The number of missed insulin boluses was also reduced by 43% compared to baseline ($p = 0.002$) [32].

An observational study in a group of children with T1D who use CGM ($n = 39$) showed that after 12 months of using NovoPen® 6 for basal insulin or prandial insulin administration, TBR < 54 mg/dl was significantly reduced, with a decrease in the number of total and nocturnal hypoglycaemic events[33].

Jendle et al. conducted an economic evaluation study in Sweden using the IQVIA CORE model to estimate the cost-effectiveness of NovoPen 6® in people with T1D. Its use could be associated with an increase in life expectancy of 0.9 years and an increase in quality-adjusted life expectancy of 1.15 years. Direct cost savings were SEK 124,270 and indirect cost savings were SEK 373,725 [34].

Pendiq® 2.0

These pens show the last dose and time of insulin injection on an illuminable OLED screen on their upper part as well as the battery level. They are rechargeable insulin pens via USB cable. They can store up to 1000 doses of insulin and transfer the data wirelessly, via Bluetooth® or directly with a USB cable to an app (Dialife® app for iOS). It uses specific needles, allowing increments of 0.1 IU and a maximum dose of 60 IU per injection [35].

Low battery, blocked needle or low insulin level alarms are available (any insulin cartridge from Lilly, Novo Nordisk or Sanofi can be used, if available).

ESYSTA® BT Pen

This pen displays the last dose of insulin administered and automatically transfers the data (dose, date and time; storage of up to 1000 doses) via Bluetooth to the ESYSTA app (compatible with iOS and Android). It has an adapter compatible with any insulin cartridge and has a countdown system during injection [36].

The app is also compatible with some glucometers. In addition, it is possible to synchronise with the web platform to share data with the health team (including blood glucose data and statistics with values inside and outside the range). However, there is no integration with any CGM or FGM system.

ESYSTA® BT pen uses a replaceable battery with an approximate duration of 6 months. It requires specific insulin needles and allows increments of 1 unit and a maximum dose of 60 IU per injection.

Other connected pens

Other devices developed are YpsoMate SmartPilot (from the company YpsoMed), Vigipen (Diabnext Co.), Tempo (Lilly) and KiCoPen (Cambridge Consultants), whose availability in the short term are to be determined.

Connected Insulin Caps

Connected insulin caps are small devices adaptable to insulin pens that allow monitoring of administered insulin doses. They have been developed to obtain all the functionalities of the connected pens but add versatility because they are compatible with different pens and insulins on the market.

Although numerous options are described on the internet, not all of them are available in every country and scientific literature is scarce on several of them. Additionally, an essential aspect of assessing the connected insulin pens and caps is the existence of a smartphone/computer application allowing to share and analyse the data obtained and integrate the information from glucometers and CGM.

Table 2 Marketed connected caps: main features

	GoCap	Insulcheck Connect	Clipsulin	Mallya	InsulClock
Country of origin	US	Ireland	US	France	Spain
Approval	FDA	EU marking FDA		EU marking (medical device, class IIb)	EU marking
Insulin compatibility	SoloStar, FlexPen, KwikPen	FlexPen, KwikPen, SoloStar, NovoPen 3/4/5/Echo, Luxura HD, Savvio, ClikSTAR	SoloStar, ClikSTAR, KwikPen, Luxura, FlexPen, FlexTouch	Solostar, Kwikpen, Flexpen	KwikPen, FlexTouch, Flexpen SoloStar
Compatible smartphone	Apple, Android	Apple, Android	Apple, Android	Apple, Android	Apple, Android
Connectivity	Bluetooth	Bluetooth	Bluetooth	Bluetooth	Bluetooth
Temperature monitor	Yes	Yes	Not	Not	Yes
Insulin Injection reminder	Yes	Not	Not	Yes	Yes
Bolus dose calculator	Not	Not	Not	Not	Not
Integration with CGM	FreeStyle Libre	Socialdiabetes	Glooko	MySugr	Dexcom, CSV user data from others
Battery life	1 year	Replaceable	1,800 injections	Rechargeable for 2 years, then replaceable	Rechargeable for 2 years, then replaceable

CGM continuous glucose monitoring, *FDA* Food and Drug Administration, *EU* European Union

Table 2 summarises the fundamental technical characteristics of the most representative devices.

Insulclock®

Insulclock® system is a very advanced and scientifically sounded product owing to an ambitious development programme [37]. Insulclock® is a cap fitted into commercially available insulin pens which tracks the date, time and dose of insulin injections as well as the type of insulin, duration of injections and temperature of insulin [38]. Additionally, Insulclock® is a complete technological system (software and hardware) composed of the connected cap, a mobile application and a web platform for medical use. The app synchronises wirelessly with the device via Bluetooth. In addition, it obtains and integrates the glucose

level data from both CGM and FGM or capillary blood glucose from glucometers in its reports.

The system has been tested in two randomized controlled clinical trials in T1D [19, 39] and another randomized crossover trial in T2D [40]. Overall, these studies have shown improved glycaemic control (up to 6% increase in TIR and decreased glucose variability) and increased adherence to insulin administration (up to 20% increase in total and timely doses) with high user satisfaction. Recently, a cost-effectiveness analysis of the Insulclock® system use in the long term has confirmed savings of up to € 35,658 during the lifespan in the T1D Spanish population vs. the standard care [41].

GoCap®

GoCap® is a cap connected to a smartphone app [42]. It allows the recording of dose, type and temperature of insulin administered. It has reminders and alerts and shows the average insulin dose used. It is registered with the Food and Drug Administration (FDA). An observational study of 75 participants with diabetes showed that non-adherence to insulin dosage and timing can be objectively assessed using attached caps and is associated with poorer glycaemic control [20].

Mallya®

Another European system is Mallya® [43], which automatically captures injection data (dose, date and time) and sends the information in real time to a software application using Bluetooth technology.

Which User Profile Can Benefit the Most from Connected Pens and Caps?

To date, no well-designed randomised clinical trials have identified which patients will benefit the most from connected pens or caps. In general, due to the defined characteristics of these digital devices and their functionalities, any patient with diabetes under insulin treatment is a potential candidate for their use. These systems should facilitate communication between health professionals and people with diabetes by sharing integrated glucose and insulin therapy data. Nevertheless, individuals who voluntarily or involuntarily omit or delay insulin prandial doses, and those with suboptimal glycaemic control, will benefit from incorporating these tools into their therapeutic regimen (see Table 3). Reasons for initiating this technology include:

- Low adherence to treatment:
  - Missed doses of insulin (basal or bolus);
  - Mistimed boluses;
  - Incorrect insulin overcorrections.
- Difficulty adjusting treatment:
  - Need for a more precise adjustment of insulin ratios;
  - Bolus calculation;
- Patient preference;
  - The added value of digital integration of all glucometric and insulinometric parameters;
- Social determinants;

Table 3 Proposal of patient profiles that can benefit from using connected pens and caps

Difficulty of metabolic control	Suboptimal glycaemic control
	Hypoglycaemia
	Glycaemic variability
Poor adherence	Missed doses of insulin (basal/bolus)
	Mistimed bolus
	Insulin overcorrections
Difficulty in adjusting treatment	Need for more precise adjustment of insulin ratios
	Bolus calculation
Patient preferences	Added value of digital integration of all glucometric and insulinometric parameters
Social determinants	Dependents with caregivers who administer insulin

- Individuals depending on caregivers who manage their insulin;
- Children, to ease care given by parents or teachers.

Healthcare Professional Profile for Connected Pen and Cap Management

The development and implementation of new technologies and digital advances in recent years are key to supporting and improving the management of chronic diseases such as diabetes [44]. The technological commitment facilitates communication between people with diabetes and health professionals. With optimal use, it also increases the satisfaction of both parts by contributing to improved glycaemic control and quality of life [45].

However, the benefits obtained with the new digital devices would be more significant if the health professional profile could maximize the system functionalities [26]. The characteristics of this profile could be the following (see Table 4):

- Endocrinologists, diabetologists and educators integrated in Diabetes Units, familiar with the use of technologies applied to diabetes and open to innovation.
- Those having disposition and motivation to continuously update and train as new advances in this field arrive.
- Those feeling the need for more information regarding insulin treatment, with the assurance that this is accurate.
- Those interested in improving communication with patients and willing to increase treatment adherence.
- Professionals who want to avoid therapeutic inertia and who are looking to optimize and intensify the treatment earlier as one of their priorities.
- Other professionals within a collaborative workgroup, in which they have the support of advanced and qualified educators for diabetes management to empower the patient's decision making.

Table 4 Healthcare professional profile for using connected pens and caps

Highly qualified health personnel familiar with the use of technologies applied to diabetes and who are open to innovation
Having the disposition and motivation to continuously update and train as new advances in this field arrive
Needing more information about the treatment of people with DM and the dose of insulin administered, with the assurance that it is accurate
Willing to improve the way of communicating with persons with diabetes and interest in improving their adherence to the treatment
Professionals who want to avoid therapeutic inertia and for whom treatment optimization and early intensification are one of their priorities
Professionals within a collaborative work environment, in which they have the support of therapeutic education in advanced and quality diabetes as a fundamental pillar to empower the patient in the decision-making process
Willingness to improve the quality of life and satisfaction of people with diabetes under their care

- Those willing to improve the quality of life and satisfaction of people with diabetes in their care.

Integrated Report Minimums

Connected pens and caps provide a wealth of information on diabetes management. Standardization of integrated insulin therapy and glucose data analysis and reports is needed to facilitate decision making. Rodbard and Garg [46] have developed the first standardised report proposal for users of connected pens and caps. In 2021, Bergenstal [47] presented another proposal for a standardized report that includes (see Table 5):

Table 5 Suggested minimums of integrated report derived from connected pens and caps

Graph of stacked bars with time objectives results, either standardized or personalized
Glucometric data: mean blood glucose, glucose management indicator (GMI), percentage coefficient of variation
Insulin metrics: mean daily insulin dose, mean basal insulin, mean prandial insulin, basal insulin dose administered, mean boluses per day, use of the bolus calculator (also indicating whether the dose administered was higher or lower than calculated)
Ambulatory Glucose Profile (AGP) and, on this profile, personalized data on insulin ratios, insulin sensitivity factor and personalized glycaemic targets, based on time slots throughout the day
Basal insulin analysis, including mean dose of basal insulin, time of administration, nocturnal blood glucose < 70 mg/dl (3.9 mmol/l), mean blood glucose from bedtime to rising
Insulin bolus analysis, including the analysis of boluses in each intake and average dose, ratio of insulin-carbohydrates, time of administration of the bolus and omitted boluses
Daily profiles that include shaded glucose percentiles integrating information on carbohydrate intakes, basal insulin, prandial boluses, corrective boluses, system-proposed insulin dose versus administered, active insulin duration, times in different goal range AGP bar, total daily carbohydrate and distribution of insulin (basal/bolus)

- Graph of stacked bars with TIR, TAR and TBR goals, either standard or personalized, depending on the patient;
- Glucometric data: mean glucose levels, glucose management indicator (GMI), coefficient of variation;
- Insulin metrics: mean total daily dose of insulin, mean dose of basal insulin, mean dose of prandial insulin, mean boluses per day and use of the bolus calculator (also indicating whether the dose administered has been higher or lower than calculated);
- Ambulatory Glucose Profile (AGP) with personalized data on insulin ratios, insulin sensitivity factor and personalized glycaemic target for different time slots throughout the day;
- Basal insulin analysis, including mean dose of basal insulin, time of administration, nocturnal blood glucose < 70 mg/dl (3.9 mmol/l) and mean blood glucose from bedtime to rise;
- Analysis of insulin boluses. This includes the analysis of boluses at each intake, average dose, carbohydrates-insulin ratio, time of administration and omitted bolus;
- Daily profiles that include shaded glucose percentiles integrating information on carbohydrate intakes, basal insulin, prandial boluses, corrective boluses, system-proposed insulin dose versus administered, active insulin duration, times in different goal range AGP bar, total daily carbohydrate and distribution of insulin (basal/bolus)

Challenges for Implementation of Connected Pens and Caps

The possible barriers can be described depending on the patient, professionals, health system or device itself:

- Patient preference for improving the usability of those systems;
- The economic burden when they are not reimbursed by the health systems;
- Need for an advanced diabetes education support;
- Minimum digital knowledge;
- Availability of compatible mobile phones as well as updated maintenance of applications;
- Lack of training on digital tools for the healthcare providers;
- Informed motivation of the user and their health team.

It is a general claim that these devices and systems, hardware and software, should be "agnostic", compatible with any glucose

monitoring system and "interoperable": they work in user applications and in electronic medical record systems.

A challenge for the future of these devices is the move from connected to smart devices. This would involve the inclusion additional support functions in the user and professional software such as individualizable bolus calculators or predictive alarms, similar to those functions available for current advanced closed loop insulin infusion systems.

Scientific societies are positioning the connected insulin therapy systems as a basic tool for people with diabetes who receive treatment with multiple doses of insulin [48, 49]. Ongoing studies with connected pens and caps will provide more data on their benefit in glycaemic control, adherence, cost-effectiveness and quality of life.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Limitations

Some possible limitations of this document must be stated. A comprehensive review of all the products under the connected pen and cap denomination worldwide is impossible and out of scope. Additionally, the continuously evolving nature of technology and the timing of the scientific publication process imply that some described features of the systems could need to be updated at the time of the document's publication. Lastly, the suggested user's and healthcare provider's profile and clinical recommendations could not be universally accepted or not completely fit different populations. As with any clinical guideline, they cannot substitute clinical judgement and an individualized approach to the use of technology in diabetes.

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DATA AVAILABILITY

The authors make themselves available to readers in case of any doubt, suggestion or question.

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