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**Growth hormone delivery devices: current features and potential for enhanced treatment adherence**

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## **Abstract**

**Introduction:** Adherence to daily growth hormone (GH) injections optimizes treatment benefit; however, adherence rates are sometimes poor. Reasons for poor adherence and persistence are multifaceted. GH injection devices are undergoing continual improvement to enhance adherence.

**Areas covered:** This review evaluates published data on the evolution of GH injection devices to meet patients' needs and preferences, patients' perception of new devices and the projected impact of device developments on adherence. Published studies were identified through literature database searches including EMBASE and PubMed (January 1985–November 2015).

**Expert opinion:** Patient needs and preferences trend towards convenient, easy-to-use devices that enable self-injection, minimize injection preparation steps by reducing the medication reconstitution and storage requirements, and reduce injection pain. In comparative studies, devices that patients considered easier to use than comparator devices were associated with reduced handling errors, fear of injection (needle anxiety/needle phobia) and pain upon needle insertion, and were thus preferred. A combination of the following items are expected to increase patient motivation to better adhere to therapy and improve treatment outcomes:

advances in GH injection devices, educating patients regarding injection device and injection technique and ongoing support from healthcare professionals, including comprehensive education about their condition, medication and expected outcomes.

**Keywords:** accuracy; adherence; device; growth hormone; pen; somatropin; treatment; usability, non-adherence

### Article highlights box

- Poor adherence to GH therapy is more common than we think.
- Sub-optimal adherence to GH therapy results in poorer than predicted clinical outcomes.
- Poor adherence and its associated costs are the driving force behind new innovations in GH delivery devices and product features.
- Patients have shown a preference for easy-to-use GH device features that reduce injection pain, facilitate ease of use and offer minimal disruption to their daily routine or lifestyle.
- Direct comparisons between individual GH injection device features are limited, but where available, easy-to-use pens with liquid GH are often preferred to electronic devices and other available injection pens with GH requiring reconstitution.
- Advances in GH injection devices coupled with educating patients in terms of the injection device and injection technique and in conjunction with ongoing support from healthcare professionals, including comprehensive education about their condition, medication and expected outcomes, may motivate patients to better adhere to therapy and improve treatment outcomes
- Future research is likely to continue towards developing GH products that require less frequent administration as well as injection devices and formulations that improve usability and convenience.

ACCEPTED MANUSCRIPT

## **Abbreviations:**

GH, growth hormone

GHD, growth hormone deficiency

IPAQ, Injection Pen Assessment Questionnaire

MeSH, medical subject heading

PDC, proportion of days covered

VAS, visual analogue scale

## ***1. INTRODUCTION***

Growth hormone (GH) therapy is licensed to treat short stature in children across a number of indications and in adults with growth hormone deficiency (GHD) [1]. In children with short stature, the primary aims of GH therapy are to facilitate catch-up growth, normalise height during childhood and enable patients to achieve an adult height within the normal range [2]. In adults, the aims of GH replacement therapy are to correct metabolic dysfunction, including abnormal body composition [3] and adverse cardiovascular risk [4, 5], and to improve quality of life [6, 7] and bone mineral density [8, 9, 10].

Currently, GH therapy usually involves daily subcutaneous injections of GH, which may lead to avoidance of therapy in many patients [11]. In addition, it is widely acknowledged that many patients with long-term conditions do not take their medicines as prescribed [12]. Although the effects may not be immediate, missing a large number of GH doses is likely to have a substantial long-term impact, including reduced adult height, suboptimal efficacy in adults with GHD and cost inefficiencies for the health care system [13, 14, 15]. Various factors may cause patients to miss GH doses, including a lack of understanding of the disease and the importance of regular GH administration, and inadequate contact with health care providers [15, 16].

For optimal treatment outcomes, long-term persistence and adherence with GH treatment is vital [15]. Although some children only receive GH therapy until adult height is achieved, persistent GHD may require lifelong GH substitution. The principle of adherence may be described as: “compliance”, “concordance” or “adherence”. In this review, “adherence” is defined as “Persistence in a practice or tenet; steady observance or maintenance” [17].

Adherence implies a need for agreement between patient and physician rather than a subservient relationship [18]. Persistence, which describes how long a patient continues to use a prescribed therapy, may also impact on treatment outcomes.

Approximately 25% of patients treated with GH miss >2 injections per week [16, 19].

Adequate adherence is defined as >80–95% of the prescribed dose of the medication actually taken by the patient [20]. Treatment adherence rates are higher among children than in adolescents and adults [16]. In younger children, who need more help from their parents or carers to inject [21], poor adherence may reflect a lack of understanding of their treatment by their parents. The adolescent period is frequently marked by a rebellious period, and this coupled with their desire for a normal life could influence their compliance. Adults, especially those in middle-age, are also less likely to be compliant with therapy than younger children due to other priorities in their life [16, 22]. Adherence and persistence decrease with treatment duration [23]; up to 52% of paediatric patients may cease GH treatment earlier than they are required to [24].

Poor adherence to GH therapy in children with growth retardation is associated with substantial reductions in linear growth [19, 23, 25, 26]. An unbiased, anonymised national survey of GH compliance in New Zealand of all children and adolescents receiving publicly funded GH in a single 4-month interval in 2007 showed that 66% of patients missed  $\geq 1$  injection per week and that this was associated with a reduction in their growth [25].

Non-adherence may also result in increased healthcare costs due to an increased duration of GH therapy and GH dose, and requirement of additional diagnostic tests to determine the reason for poor growth in an effort to improve height outcomes [15]. Indeed, it has been proposed that effectively improving adherence may have a greater effect on treatment outcomes than any treatment by itself [27].

Practical and perceived barriers to treatment may result in intentional and unintentional low adherence. Inadequate levels of knowledge and support as well as injection discomfort are often cited as causes of poor adherence and low persistence with treatment [16, 28, 29, 30]. One reason for low adherence to GH therapy is that there is no real-time feedback loop; patients do not feel unwell if they miss an injection. Poor responders may be especially susceptible to non-persistence [24], as patients perceive that their treatment is not working due to insufficient knowledge or misconceptions about their disease and GH treatment [16, 30]. Unintentional low adherence may result if a patient is unable to follow the agreed treatment regimen due to obstacles beyond their control, including understanding instructions and difficulties with administration [29]. Alternatively, the patient may deliberately not take their medication [29], or even forget to take their medication; a steady decline in adherence is reported with increasing length of therapy [15]. Strategies to combat a poor treatment response, which may lead to poor adherence, as well as poor adherence for other reasons have been developed [14, 31, 32, 33]. Regular clinic visits and comprehensive therapy education have been shown to translate into better adherence [29]. Reducing physical barriers to good adherence by educating the patient in terms of the injection device and injection technique to minimise the impact of treatment on daily life and reduce injection pain [31, 32] is also important. Here, we summarise the development of GH injection devices in response to patient needs and preferences as part of a strategy to improve adherence.



### ***1.1 Search strategy and results***

EMBASE and PubMed were searched extensively to identify all relevant articles published between January 1985 and November 2015. The following medical subject heading (MeSH) terms were used: medication adherence and patient compliance. In addition, the following key words were also searched in the title or abstract: “growth hormone [Title]”, “device(s)”, “pen(s)”, “force”, “accuracy”, “precision”, “acceptability”, “preference”, “intuitiveness”, “ease”, “acceptance”, “easy”, “friendliness”, “adherence”, “compliance” and “persistence”. The restrictions “human”, “core clinical journal”, “English” and “clinical trial” were applied and articles were required to have an abstract written in English. No limitations were implemented on publication status or study design. Abstracts of the identified articles were retrieved and manually searched to identify original studies and review articles most relevant to the aims and objectives of the article. The key topics of interest were factors that influence therapeutic non-adherence or compliance, strategies to improve patient compliance, as well as the extent of non-compliance with GH treatment. Original studies that included an insufficient number of patients (<10) and validation studies to identify factors influencing compliance were excluded. If the abstract was not clear enough to determine whether the inclusion criteria were met, full articles were read to enable a decision to be made. In total, 1,307 publications were identified in the initial search. After the selection process, 85 published articles were identified that met the inclusion criteria. A further 22 articles were excluded after obtaining full articles for reasons such as small sample size or not focusing on factors that affect compliance. The remaining 63 articles were included in this review.

### ***1.2 The continuing development of GH injection devices***

Devices for GH administration have evolved considerably since the 1960s, when patients were treated two or three times a week at clinics with intramuscular injections of GH [34].

During the 1980s, daily subcutaneous injections of GH, which could be self-administered at home by patients, were shown to result in higher growth rates than the less frequent intramuscular injections [35]. Although both methods of delivery involve a needle and syringe, patients preferred subcutaneous injection as it required shorter needles and was less painful [36].

GH delivery devices have progressed from conventional syringes and needles to injection pens, electronic injectors and needle-free injectors. The underlying goals of GH device development include simplification of drug delivery and reduction of injection anxiety and anticipated injection pain. Improving ease of use may also save time and reduce costs; in a micro-cost analysis, GH devices that required more time to learn to use and prepare GH for injection were associated with higher net costs [37]. Injection pens, usually operated by dialling the dose using a scale on the side of the pen then pressing a button to deliver the dose, are easier to operate and more convenient than a needle and syringe, with a greater proportion of patients being able to self-inject with a pen injector [38, 39]. Needle visibility, which is problematic for patients who suffer from needle anxiety, can be reduced with needle covers that hide the needle before and during the injection. Automatic needle insertion systems, which insert the needle via a spring-loaded mechanism, may also help to reduce anxiety and are reported to be less painful than manual needle insertion [40].

GH injection devices that simplify the injection process or eliminate the need for mixing of GH prior to injection might improve the ability of patients to self-administer their treatment and indirectly improve their adherence. Errors in dilution and mixing GH prior to injection may be more prevalent among patients with a poor understanding of their treatment [30].

However, efforts to simplify the injection process have been addressed with the introduction of disposable pen injectors and ready-to-use GH formulations that do not require reconstitution before use, as well as single-use, fixed-dose injection pens. Needle-free

injection systems, which use a small nozzle to expel GH at high pressure and force via the skin for subcutaneous dispersion, were designed to reduce problems with conventional needle delivery, such as needle fear, and to reduce safety issues such as accidental needle stick injury. Among 631 children receiving GH by needle and syringe (305 children) or a needle-free device (cool.click; Merck Serono, Rockland, MA, USA) (326 children), significantly more patients using a needle and syringe failed to take more than half of their prescribed GH dose (13.4% in the needle and syringe group vs. 6% in the needle-free group,  $p=0.002$ ) [41]. Compliance data in this study was based on physician reports. Simplifying the complexity of product storage requirements, e.g. allowing storage outside of the refrigerator, may also impact positively on adherence.

Introduction of the fully automated and programmable easypod (Merck Serono, Rockland, MA, USA) injection device marked the first electronic GH injection device to come to market. Easypod features preset dosing and adjustable injection settings, to make injections more comfortable, via electronic skin sensors. Easypod also features an injection log that can be accessed later at the clinic to provide a complete record of treatment adherence [40]. In an open-label observational study in 1,972 paediatric patients in Canada, France and Nordic countries (Norway, Sweden and Finland), adherence was  $\geq 80\%$  after 1 year [42]. Adherence was defined as days with injections received divided by days with injections planned, presented as percentage.

Both correct injection technique and selection of injection device are important to promote good adherence, with research indicating that involving the patient in the selection of the injection device results in increased adherence to treatment [43]. Principal features for patients regarding injection devices are ease of use and convenience, including lack of bruising and/or pain on injection and a ready mixed GH preparation [43, 44, 45, 46]. A “willingness to pay” study, which determined the monetary value parents would place on

specific device features, showed that the most valued features were those facilitating ease of use, especially no requirement for mixing GH before use and flexible storage of GH, and no requirement for refrigeration of the device when in use [47].

## **2. FEATURES OF GH DEVICES THAT MAY HELP IMPROVE ADHERENCE**

There is a wide variety of GH injection devices currently available to patients. Table 1 summarises the available GH administration devices and their key features. Available GH devices include: reusable (durable) injection pens that use GH cartridges to replenish the GH supply, such as the NordiPen (Novo Nordisk, Bagsvaerd, Denmark), Genotropin Pen (Pfizer, New York, NY, USA), HumatroPen (Eli Lilly, Indiana, IN, USA), Omnitrope Pen (Sandoz, Kundl, Austria) and SurePal (Sandoz, Kundl, Austria); disposable, multidose, prefilled injection pens such as Norditropin FlexPro (FlexPro; Novo Nordisk, Bagsvaerd, Denmark), Norditropin NordiFlex (NordiFlex; Novo Nordisk, Bagsvaerd, Denmark), Norditropin NordiLet (NordiLet, Novo Nordisk, Bagsvaerd, Denmark), Nutropin AQ NuSpin (Roche, Mississauga, ON, Canada) and Genotropin GoQuick (Pfizer, New York, NY, USA); needle-free devices such as ZomaJet 2 Vision (Ferring, Saint-Prex, Switzerland), one.click (Merck Serono, Rockland, MA, USA) and Needle-free Tjet (Teva, Petach Tikva, Israel); electronic devices, such as easypod; and single-dose syringes, such as MiniQuick (Pfizer, New York, NY, USA). The majority of GH injection devices now include, or are packaged with, an optional needle guard. While adherence to stringent storage and reconstitution requirements are essential to provide a stable GH with optimum efficacy, storage is simplified with the FlexPro, NordiFlex and NordiLet devices and cartridges for Norditropin NordiPen (Novo Nordisk, Bagsvaerd, Denmark), as well as cartridges for liquid Saizen (Merck Serono, Rockland, MA, USA). The FlexPro, NordiFlex and NordiLet devices and the NordiPen cartridges offer storage flexibility and after first use can be stored for up to 21 days at up to 25°C in the EU, USA and International Operations [48], or up to 10 days at 30°C in Costa

Rica, El Salvador, Guatemala, Honduras and Panama [49]. More approvals for up to 10 days at 30°C are expected within the coming year [50]. Pens must be refrigerated prior to first use. Cartridges with liquid Saizen (Merck Serono, Rockland, MA, USA) can be stored during use for 7 consecutive days at up to 25°C [51]. When stored outside the refrigerator for up to 7 consecutive days, the cartridges must be returned to the refrigerator and used within 28 days after first injection [51]. Alternatively, Genotropin MiniQuick may be stored unrefrigerated for up to three months at 25°C before reconstitution and for 24 h after reconstitution [52]. Several studies have demonstrated that patient satisfaction is improved by addressing patient preferences and needs through the innovation of injection devices, as summarised in Table 2 [21, 38, 40, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73]. The following sections review some specific features of current GH injection devices and how these features may help improve adherence.

### ***2.1 Ease of use***

Evidence supports that patients prefer devices that are easy to prepare for use and easy to use [62, 63, 65, 66, 68, 69, 70, 71, 72, 74, 75, 76, 77]; these qualities may instil confidence to self-inject. In a multicentre questionnaire-based study involving 473 paediatric (mean age 12.6 years), Spanish patients treated with GH, those who self-injected showed significantly higher adherence rates (assessed by the number of dose units missed) than those who did not ( $p < 0.01$ ) [71]. Furthermore, although concordance did not vary among GH injection devices, a free choice of GH injection device among paediatric patients was associated with better concordance [19], suggesting that adherence may be improved when patients are allowed to use their preferred device.

The key goals underlying GH device development include simplification of drug delivery and reduction of injection anxiety and anticipated injection pain. In a randomised, open, multicentre, crossover trial involving 67 paediatric patients receiving GH, a prefilled pen

removed the reconstitution preparation step and enabled young patients (<10 years) to perform injections [59]. In a 2-week open questionnaire trial in 39 GH-treated children and 39 GH-treated adults (all self-injecting), 95% expressed preference for the multi-dose Genotropin Pen over its predecessor (Genotropin Kabi Pen). This improved device has a digital display for greater certainty of dosing, offering the ability to correct the set dose and lock the injection function after successful injection and a more ergonomic design than its predecessor [67]. Patients preferred the ease of handling of the new pen; patient preference was reported using an end-of-study questionnaire, which incorporated a visual analogue scale (VAS).

Other design improvements aimed at improving ease-of use include reducing the size of the device or moving the dosing buttons so they are easier to reach for patients with small hands or limited dexterity. FlexPro is a prefilled, ready-to-use, multidose, disposable pen injection device that is 11 mm shorter than its predecessor, NordiFlex [74], and has a spring-loaded dosing mechanism to reduce the extension of the dose button so it is easier to reach and press for patients with reduced muscle strength, such as those with GHD [75]. In a laboratory-based study, dose force, the force required to push down the dose button to deliver a dose, measured using a tensile testing machine in compression mode and a transducer, was lower with FlexPro than with either NordiFlex or Genotropin GoQuick [74].

In a non-interventional, open-label, sham injection, uncontrolled study of three GH delivery devices involving 70 children (mean age, 14 years) who were self-injecting GH, 99% reported on the end-of-study 21-item questionnaire that FlexPro was easy to use, with approximately two-thirds reporting the device as no more difficult to use with wet hands [62]. Patients reported that it was “easy” or “very easy” to hear the “click” sound to confirm the dose was delivered; 97% being confident the correct dose had been delivered and 96% being comfortable with the idea of future self-injection [62]. In comparison with their current

injection device, 92% of patients reported that they were more confident that FlexPro had administered the correct GH dose and 64% preferred this device to their current device [62].

In an open-label, non-interventional, multicentre usability study involving 106 participants (61 adults; 45 children and adolescents) of whom approximately 50% were naïve to injections, the SurePal injection device, a reusable (durable) needle-based injection system, was rated as “very easy” or “easy” to use by 92% (95% of adults, 89% of children/adolescents) in an end-of-study interview [65]. The device possesses a number of features designed to improve ease of use such as auto-priming and reduced injection force, as well as safety features to ensure correct dosing and a feature to reduce drug wastage by ensuring that the remaining doses from an existing cartridge can be used and complemented to the full dose when a new cartridge is inserted [65].

In two non-interventional, randomised, open label, crossover studies (n=56, mean age 13.6 years [63]; n=64, mean age 13.1 years [66]) that assessed the ability of patients already using GH injection devices to perform injections with GH injection devices without prior training by assessing time taken to inject and patient-reported outcomes by questionnaire, the majority of patients rated FlexPro as the most intuitive and the easiest device to learn to use (whether patients had received full device training or only brief verbal instruction) compared with easypod and Genotropin Pen [63], or NordiFlex and GoQuick [66] (Table 2). In both studies, FlexPro was the preferred device, specifically due to device features that enabled ease of handling, ease of preparation and overall ease of use [63, 66]. Importantly, in a single-centre, single-arm, open-label, questionnaire-based survey of 108 paediatric patients undergoing GH treatment who were scheduled to switch from Norditropin NordiFlex (Novo Nordisk A/S) to FlexPro, the proportion of patients able to self-inject increased from 34.1% to 43.9%, and the proportion of patients with self-reported ‘complete adherence’ increased from 53.7% to 63.0% [76]. Compared to the responses regarding NordiFlex, an approximate increase of

20% in positive responses occurred with FlexPro for all questionnaire items related to handling, except 'dialling up the dose' and 'reverse-dialling' [76].

For patients with diabetes, where subcutaneous injections are generally a mainstay of therapy, insulin pens provide a means for subcutaneous injection that is convenient, accurate, less painful and more patient-friendly than a conventional needle and syringe [78].

## ***2.2 Storage flexibility***

Patients report a high treatment burden when using devices that require refrigeration [77, 79].

In a web-based survey of 239 caregivers and 61 patients (aged  $\geq 13$  years), more than one-third of respondents considered the storage of GH to be burdensome [79]; the primary reason given for missing GH doses was "away from home or traveling" [79]. Easier storage requirements may have a positive impact on adherence by easing product storage requirements, reducing waste due to spoiled product and decreasing time needed for injection by avoiding time needed for product to warm up to room temperature before injection.

Although the majority of GH products require refrigeration, storage is simplified with devices containing Norditropin SimpleXx (Novo Nordisk A/S): FlexPro, NordiFlex and NordiLet, with Genotropin MiniQuick and with Saizen, all of which can be stored at room temperature for certain periods as described above. Using an interviewer-guided, web-based interview, the impact of storage-flexible GH products and refrigeration-only GH products on the daily lives of patients (n=48) and caregivers (n=98) injecting GH at least once-weekly was assessed [80]. The survey used was developed specifically for the study using research questions selected from a proprietary library and assessed for usability in pilot interviews. Study results illustrated that storage-flexible products were associated with significantly shorter mean (SD) injection times (10.9 min [14.2] vs. 20.5 min [16.1];  $p < 0.001$ ) and significantly greater adherence; 24% of patients using storage-flexible products reported missing at least one



injection per month vs. 43% of patients using refrigeration-only products ( $p<0.05$ ) [80]. Significantly lower wastage (disposal of GH due to potential spoilage) ( $p<0.01$ ) was reported with storage flexible versus refrigeration-only products. Furthermore, a higher proportion of patients using refrigeration-only products (40%) versus storage flexible products (22%) reported missing activities as a consequence of having to manage storage or supplies for their GH product. Among patients offered a choice of device at treatment start, 65% of patients and caregivers chose a storage-flexible product vs. 35% who chose a refrigeration-only product, with 86% of patients currently using a refrigeration-only product indicating a strong preference for a storage-flexible product; 74% of those using a storage-flexible product stated that they were content with their choice.

### **2.3 Reducing injection pain**

Discomfort with injection, which may be exacerbated by poor injection technique, the GH product solution (buffers and preservative) or the injection pen, is an enduring problem with subcutaneous drug administration and may affect adherence [53].

The preservative used in the formulation, the buffer substance, concentration of GH and injection volume affect injection pain and local tissue reactions [81, 82]. In a double-blind randomised study, significantly more volunteers (38/54) reported more pain immediately after a subcutaneous injection of a citrate-buffered solution than after that of a histidine-buffered solution ( $p<0.002$ ). Injection pain was assessed using a validated verbal rating score [82]. In addition, the preservative *m*-cresol was reported as more painful than benzyl alcohol when included in solutions for injection; however, benzyl alcohol appeared less painful than phenol-containing solutions [81]. Variations in the type of preservative and buffer exist among GH products. For example, Norditropin Simple Xx contains a histidine buffer and a phenol preservative, Nutropin AQ Nuspin uses a citrate-buffered GH solution and the GH products in Genotropin Pen, HumatroPen and click.easy for easypod and cool.click 2 use the

preservative *m*-cresol. The Genotropin MiniQuick syringe has no preservative and must therefore be used within 24 h of reconstitution.

Reducing the outer diameter of the injection needle is associated with decreased injection pain [83], while automatic needle insertion systems that hide the needle during injection aim to reduce needle phobia and the perceived pain of the injection. A number of injection devices carry a recommendation to attach a new needle for each injection, as this may reduce injection pain; however, it is unclear if patients adhere to this recommendation. In one of the first studies to directly compare an injection pen system with the conventional needle and syringe injection system, the injection pen (KabiPen) was considered less painful due to its finer, sharper needle and smaller injection volume, and was selected for continued use by 34 of 40 families enrolled in a one-month trial of the new pen [38].

Although three studies demonstrated patient preference for automatic needle insertion systems that can be used with existing pen injection devices [39, 56, 70], a fourth, 12-week open-label uncontrolled study showed that although 82% of 85 paediatric patients who were GH-naïve or currently using an alternative GH delivery system wished to continue using an auto-injector GH delivery system, 18% preferred using the injection pen without the auto-injector as it was smaller and easier to use, despite being more painful [54]. Patients' impression of the device was recorded by questionnaire at baseline and at study completion. Among studies comparing needle-free injector devices with subcutaneous injections, no significant difference in patient satisfaction was observed in children receiving GH therapy [43, 46, 60], although they were reported to be as effective as needle- and syringe-based GH delivery devices [84, 85]. In a retrospective cohort study, data from 6,061 children receiving either Zomacton (somatropin) via the ZomaJet jet-delivery device or one of six brands of GH, all administered via needle-based devices, were evaluated for persistence (interval between first and last home-delivery of GH) and for adherence (only for patients using ZomaJet who

had appropriate data, measured by proportion of days covered) [28]. Significantly longer persistence with GH therapy was observed in patients using ZomaJet compared to needle-based devices (599 days vs. 535 days, respectively,  $n=4,093$ ;  $p<0.001$ ). More than half (58%) of patients using ZomaJet were classed as adherent ( $n=728$ ). Adherence was estimated using a validated and extensively studied measure known as proportion of days covered (PDC); a PDC score  $>0.8$  indicates high adherence. Side effects of needle-free injection might include occasional pain, discomfort and local reactions due to the high-pressure drug delivery [85]. No difference in injection pain between needle-free and needle-based devices was reported in one study [73], and needle-free devices were preferred over needled devices by paediatric patients in one study [21], but not in another [60].

#### **2.4 Electronic GH devices**

Easypod is currently the only commercially available electronic injector. Of 824 children who were dissatisfied with their current injection device and started using easypod, 91.8% reported that they wished to continue using this device [40]. The children were enrolled in a multicentre, multinational, observational 3-month study covering 15 countries ( $n$  numbers for countries with  $>50$  participants: Argentina,  $n=155$ ; France,  $n=143$ ; Italy,  $n=112$ ; Spain,  $n=100$ ; Germany,  $n=72$ ; Portugal,  $n=58$ ). Adherence to treatment was measured using data recorded by the injection device. In this study, overall adherence ( $>92\%$  of prescribed doses) was 87.5%. For countries with  $>50$  participants, adherence was greatest in Spain (97%) and lowest in Argentina (75%) [40]. With the exception of the Nordic countries (Finland, Norway and Sweden), Portugal and Spain, where adherence rates were similar between treatment-naïve and treatment-experienced children, adherence rates were generally higher in patients new to treatment than in those with some previous experience of treatment [40]. In two open-label uncontrolled studies, treatment naïve or GH-treated paediatric patients ( $n=61$  [72];  $n=20$  [68]) started on easypod, the majority of previously treated patients reported by questionnaire

that they preferred easypod compared to their current auto-injector pens [68, 72]. A valuable and unique feature of easypod is that health care providers can download data on device use and review patient adherence to the injection schedule [68]. This is useful as patient recall of adherence does not necessarily provide a complete picture [86, 87] and frequently underestimates non-adherence [88]. Adherence rates measured with easypod may reflect the fact that the patient knows their injection history is recorded on the device. Other features of easypod include the ability to preset the GH dose by a physician or nurse, as well as the possibility to split the dose over two cartridges and customise the injection speed, depth and duration, which may reduce waste or inaccurate dosing [87]. Potential limitations of easypod include the longer training period compared to other devices, difficulties with mixing and reconstitution of GH and problems handling the device for patients with smaller hands.

### ***2.5 No GH reconstitution required***

Among 51 paediatric patients (treatment naïve, n=15; treatment experienced, n=36) treated with liquid GH subcutaneously for 6 months, 85% of treatment-experienced patients preferred the convenience of the liquid form over GH that required reconstitution before first use, when evaluated by questionnaire at study end [55]. Similarly high patient preference (94%) for liquid GH compared to their previous treatment was reported among 103 treatment-experienced paediatric patients following 12 weeks of treatment [59]. Patient preference was evaluated via a nurse-administered questionnaire.

Studies assessing the usability of GH injection devices with ready-to-use cartridges have shown that patients rate these devices as easy to use [38, 63, 64, 66, 89]. Further, shorter injection times are reported with devices that are fitted with ready-to-use cartridges of GH [38, 63, 66].

### ***2.6 Disposable injection devices***

Prefilled disposable GH injection devices can reduce the number of steps required before an injection as they are ready to use and simply disposed of after use. A multicentre, single-arm, open-label study was conducted to compare the ease of use and preference in treatment-experienced patient–caregiver dyads for a new disposable GH injection pen with previous use of a reusable pen [61]. The validated self-reported Injection Pen Assessment Questionnaire (IPAQ) was administered at baseline and at 2 months and after 2 months of use of the new disposable pen to assess ease of use of the individual pens (rated on a 5-point Likert-type scale), the comparative ease of use of the 2 pens, and pen preference. In this study, 60% of the 132 children or parents who were surveyed preferred the disposable pen and almost two-thirds of patients and caregivers reported that the new disposable pen was easier to use than the reusable pen [61].

Similar results were also reported in a randomised, crossover, multinational study comparing the reusable Genotropin Pen with the disposable GoQuick pen [64]. In this randomised, crossover, multicentre, multinational, open-label study, ease-of-use of and preference for the two pens were assessed via use of IPAQ after 2 months of at-home-use experience in the following three treatment-naïve populations: parents of very young children, parent–child dyads and adults. Overall, 51.3% of all subjects found the disposable pen easier to use than the reusable pen [64].

### **3. CONCLUSIONS**

Sub-optimal adherence to prescription medicine for chronic disease is a common problem.

Reasons cited for non-adherence or non-persistence across a variety of diseases include fear or experience of side effects, generic concerns about treatments, lack of perceived need for the medication and financial hardship [90]. There are two main approaches that may help improve adherence to GH therapy by addressing these factors. First, improving therapeutic support and patient education might be especially valuable in managing patient expectations

of treatment, reducing the likelihood of stopping treatment through perceived lack of efficacy or adverse events. To our knowledge, however, there is little available evidence regarding the impact of health beliefs, psychological and social factors as predictors of adherence in patients prescribed GH. Future efforts to improve adherence to GH require research into adherence interventions using a patient-centred focus. Second, increasing treatment acceptability by minimising adverse events, pain, injection site reactions, injection anxiety and difficulty with self-injection through training and support may also play a part in promoting good adherence and optimising treatment efficacy. The present article reviews developments in injection devices for GH therapy, which have become more convenient and easier to use to meet the needs and preferences of patients. Studies show that more recent pen injection devices developed to meet the needs and preferences of patients are well accepted and provide most of the desirable features of a GH injection device. Evidence suggests that, in addition to regular clinic visits and comprehensive education about their condition and medication, educating patients in terms of the injection device, injection technique and expected outcomes will likely motivate patients to better adhere to therapy and thus have a good growth response.

#### **4. EXPERT OPINION**

Following the transition of routine administration of GH therapy from nurses to patients, GH injection devices have evolved towards easy-to-use devices that are well accepted by patients, offering improved portability, convenience, ease of use and reduced injection site pain, leading to better patient treatment satisfaction. Compared with conventional syringes and needles, more recent injection devices may improve adherence and reduce healthcare utilisation and associated costs. A strength of the available research is the thorough assessment of the acceptance of each new device and the features that have been developed to meet patient needs and preferences. The majority of these adaptations have been generally

well accepted by patients, with a preference to continue using the new device or feature over the current injection device. In this regard, discerning the true value or potential impact of each individual device feature might be difficult due to the indirect nature of the comparisons made. Where more direct comparisons have been made, easy-to-use pens with liquid GH are often preferred over electronic devices and other available injection pens with GH requiring reconstitution [63, 66]. A substantial weakness of the available research is that many of the studies are observational, unmasked and had small sample sizes and short follow-up periods. Several of the studies that involved direct questioning of patients regarding preference or satisfaction with treatment employed a variety of questionnaire designs, only some of which were identified as validated. Among studies that have attempted to establish the impact of a device on adherence, patient preference was often cited as an indication of the potential effect on adherence; it is of interest, however, that almost without exception patients express a preference for GH injection devices that are comparatively easier to use [63, 66].

Matching an injection regimen and device to the preferences and needs of a patient is likely to maximise treatment tolerability and adherence. Discussions with patients and their families and involving them in decision-making may help provide crucial motivation to adhere to their therapy and enable nursing staff to determine which regimen and device characteristics may make taking GH most acceptable. All of these actions must be supported by ongoing patient education in terms of the injection device, injection technique and expected outcomes.

Current research highlights that features associated with ease of use are preferred by patients [45] and that they may encourage correct injection technique [76] and confidence in device handling [63, 66]. Notably, the adoption of an easy-to-use device with reduced number of preparation steps may increase the proportion of patients who are able to self-inject [76] and are confident with the device [63, 66]. Together with improved storage requirements, this

adoption might also benefit patients with busy lives who resent the time burden imposed by daily injections [37] and have a positive impact on adherence [71].

There is substantial variation in the methods used to assess adherence to GH. Indirect measures of adherence, such as patient self-reporting, cartridge counts and prescription refills, do not provide all the information needed to accurately evaluate adherence. The most accurate method to determine actual adherence is to monitor injections via a patient diary (indirect observation) or using an injection-recording device (direct observation). Electronic devices such as easypod can record the timing and dose taken with minimal disruption to the injection routine of the patient [87]. Reminding patients about injections via text message or an alarm on the injection device might help patients with erratic schedules or poor memory. In this regard, communication is crucial in detecting poor adherence. The patient must feel confident enough to discuss openly any treatment issues with their physician. In addition, indications of unease with treatment, such as pain or bruising, should be carefully investigated.

Switches in device may occur if patients have to move to another product due to differences in licensed indications between brands, due to health plan and/or patients' insurance demands or, as seen in some European countries, as a result of pressure to contain healthcare expenditure a new treatment plan may be mandated on economic grounds that requires children receiving GH treatment to switch GH product. Such changes may be implemented irrespective of any inconvenience caused to the patients or health system. Data collected from a 9-question, anonymous, internet-based survey with multiple-choice and yes/no answers to active members of the Paediatric Endocrine Society to explore the effects of insurance-mandated brand switches during the course of paediatric GH treatment on clinical practice revealed that brand switches were common (208/231 respondents reported brand switches) [91]. The reported effects of GH brand switches ranged from effects directly relating to the



drug or device, logistics, or patient autonomy and brand switches were associated with decreased effectiveness, safety concerns, and reduced compliance, as well as additional work for healthcare staff such as paperwork, training to use the new device and patient reassurance [91]. The observation of a willingness to pay for the features of GH devices that are regarded to reduce the burden of injection [92] support that cost saving measures may not necessarily impact positively on treatment outcomes.

As GH therapy continues for many years for most patients, cumulative costs can be substantial over the course of treatment. Using a model-based approach applied to a population of GH-treated patients in Italy, GH wastage at a single device level was shown to account for up to 15% of drug consumption costs [93]. The ability of a device to select finer dosing increments enables a more accurate dose selection, resulting in less product wastage compared to injection devices with larger dosing increments [94, 95]. Moreover, it is crucial to consider the last dose available with multiuse pens and a strategy to better match the prescribed dose with the ability of the pens to deliver is an additional way to reduce waste.

For the foreseeable future, the trend towards more convenient GH administration and easy-to-use GH devices is likely to continue. The daily regimens associated with most current GH products may be burdensome and inconvenient to patients, promoting low adherence, treatment abandonment and sub-optimal therapeutic outcomes. A simplified dosing regimen could potentially aid in reducing low adherence and maximise therapeutic end results. Long-acting GH preparations allowing for reduced injection frequency have been designed to provide improved treatment adherence and to decrease the distress and inconvenience associated with daily injections. Oral delivery and hydrogel delivery options may also prove feasible in reducing the overall burden of GH administration.

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**Table 1. Available growth hormone injection devices**

<b>Manufacturer</b>	<b>Device</b>	<b>One-step injection</b>	<b>No reconstitution required</b>	<b>Preservatives/buffer reduces injection pain</b>	<b>Measure adherence</b>	<b>Disposable</b>	<b>Storage flexibility</b>	<b>Needle-free</b>	<b>Auto-injector</b>
Eli Lilly (Indiana, IN, USA)	HumatroPen	✓							
Ferring (Saint-Prex, Switzerland)	Zomajet 2 Vision							✓	
	Zomajet Vision X	✓						✓	
Merck Serono (Rockland, MA, USA)	cool.click	✓						✓	
	easypod	✓				✓	✓		✓
	one.click	✓							✓
Novo Nordisk (Bagsværd, Denmark)	FlexPro	✓	✓	✓		✓	✓		
	NordiFlex	✓	✓	✓		✓	✓		
	NordiLet	✓	✓	✓		✓	✓		

Manufacturer	Device	One-step injection	No reconstitution required	Preservatives/buffer reduces injection pain	Measure adherence	Disposable	Storage flexibility	Needle-free	Auto-injector
	NordiPen	✓	✓	✓			✓		
Pfizer (New York, NY, USA)	Genotropin Pen								
	GoQuick					✓			
	MiniQuick	✓	✓			✓ <sup>a</sup>			
Roche (Mississauga, ON, Canada)	Nutropin AQ NuSpin	✓	✓	✓		✓			
	Nutropin AQ Pen	✓	✓	✓					
Sandoz (Kundl, Austria)	Omnitrope Pen	✓	✓						
	SurePal	✓	✓				✓		
Teva (Petach Tikva, Israel)	Needle-Free Tjet	✓						✓	

<sup>a</sup>Daily disposable; One-step injection: needle insertion and dose delivery in a single step; No reconstitution required: GH formulation is provided ready to use; Preservative/buffer reduces injection pain: following injection, pain perception is reported to be similar between formulations

Manufacturer	Device	One-step injection	No reconstitution required	Preservatives/buffer	reduces injection pain	Measure adherence	Disposable	Storage flexibility	Needle-free	Auto-injector
<p>containing phenol and benzyl alcohol m-cresol was associated with more painful injections than benzyl alcohol. Furthermore, patients reported more pain following injection of a citrate-buffered solution than after a histidine-buffered solution [81]; Measures adherence: Injection device automatically records the patient's adherence to treatment; Disposable: Prefilled, ready to use device that is disposed of when GH has been dispensed; Storage flexibility: Injection pen may be stored unrefrigerated after the first use for up to 21 days at not more than 77°F; Needle-free: devices use a small nozzle to expel GH at high pressure, forcing the medication through the skin where it disperses subcutaneously; Autoinjector: Medical device designed to deliver a dose of a particular drug. Autoinjectors are designed to be easy to use and are intended for self-administration by patients</p>										

**Table 2. Adaptations to GH injection devices and patient responses**

<b>Adaptation</b>	<b>Study</b>	<b>Study population</b>	<b>Participant response</b>
<b>Injection pen</b>			
	Jørgensen & Susgaard [56]	27 children with GH abnormalities	Nearly two-thirds of patients felt less injection pain with the injection pen vs. needle and syringe  All patients found the injection pen more convenient and wished to continue using it instead of a needle and syringe
	Albertsson-Wikland [38]	40 children (including parents/guardians)	All participants found the injection pen more convenient, less time consuming and easier to travel with, and 34/40 participants wished to continue using the injection pen
<b>Auto-injection</b>			
	Main et al. [53]	18 children	Automatic needle insertion was associated with lower mean and maximum pain scores compared with manual needle insertion
	Stanhope et al. [57]	30 children (previously untreated)	82% wished to continue with the auto-injector

Hokken- 85 children 88.4% found the PenMate automatic  
Koelega et needle insertion system 'very easy' or  
al. [54] 'easy' to use  
64% wished to continue using  
PenMate

### Liquid GH

Iyoda et al. 51 patients 85% preferred the convenience of  
[55] liquid GH to GH requiring  
reconstitution

Müller et al. 67 children 98% found liquid GH and PenMate  
[58] system easier to use overall  
75% wished to continue using the  
liquid GH system

Stanhope et 103 children 94% preferred liquid GH system  
al. [57] 92% found SimpleXx more  
convenient

### Needle-free

Dörr et al. 133 children More than 20% of children preferred  
[60] the needle-free device (Genotropin  
ZipTip) to their current device

Kaptein [21] 73 children The needle-free device (Zomajet  
Vision X) combined with a new  
formulation of GH that resulted in a  
lower injection volume was associated

with greater patient satisfaction than that with their previous device

### Disposable

Hey-Hadavi et al. [61]	133 children/parents who administered the injection	73.7% rated the disposable pen as easy to use or no different from the reusable pen 65.2% preferred the disposable pen to the reusable pen or had no preference
Pleil et al. [64]	120; 42 adults, 50 child-caregiver pairs, and 28 very young children (<8 years of age)	67.2% found the disposable pen (GoQuick) to be no different or easier to use than the reusable pen (Genotropin Pen)

### Easy-to-use

Sjöblom et al. [67]	78; 39 children and 39 adults	Genotropin Pen was considered more comfortable to hold, less painful and provided greater certainty that the correct dose was administered 95% wished to continue using Genotropin Pen instead of the KabiPen
Rapaport et al. [65]	61 adults, 45 children/adolescents	After the second use of SurePal, 87–97% of patients rated SurePal as



			‘easy’ or ‘very easy’ to use
Fuchs et al. [62]	70 children/adolescents		99% considered FlexPro ‘very easy’ or ‘quite easy’ to use when delivering their usual dose 64% preferred FlexPro to their current GH injection device
Pfützner et al. [63]	56 children/adolescents		70% considered FlexPro the most intuitive device compared with easypod and Genotropin Pen FlexPro was considered easier to learn to use than easypod and Genotropin Pen in both uninstructed and instructed patients 50% of uninstructed patients identified FlexPro as the device of overall preference vs. 7% for easypod and 43% for Genotropin Pen. 73% of instructed patients identified FlexPro as the device of overall preference vs. 23% for easypod and 4% for Genotropin Pen
Rohrer et al. [66]	64 children/adolescents		63% of patients identified FlexPro as the most intuitive device FlexPro and NordiFlex were

considered easier to learn to use than

GoQuick in both uninstructed and

instructed patients

60% of uninstructed patients identified

FlexPro as the device of overall

preference vs. 28% for NordiFlex and

12% for GoQuick. 56% of instructed

patients identified FlexPro as the

device of overall preference vs. 16%

for easypod and 28% for Genotropin

Pen

Kappelgaard 74

et al. [69]

children/adolescents

99% found FlexPro easy to handle,

reporting no technical complaints

81% preferred FlexPro compared with

their current device

Kappelgaard 50

et al. [70]

children/adolescents

80% preferred to use the FlexPro

PenMate system (considered more

user friendly) than the NordiFlex

PenMate system

### Electronic

Bozzola et

824 children

al. [40]

91.8% wished to continue using

easypod

>90% found it easy to use and 90.2%

of patients missed  $\leq 2$  injections per

		month
Dahlgren et al. [68]	61 patients	87% preferred easypod to their current device (one.click or cool.click)
Tauber et al. [72]	20 children	All patients (17/17) wished to continue using easypod

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GH, growth hormone

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