Title: A systematic review of patients' perspectives on the subcutaneous route of medication administration.

Authors: Colin H Ridyard[1] PhD, Dalia M M Dawoud[2] PhD, Lorna V Tuersley[1] PhD MRPharmS and Dyfrig A Hughes[1] PhD, MRPharmS

[1] Centre for Health Economics and Medicines Evaluation, Bangor University

[2] Clinical Pharmacy Department, Faculty of Pharmacy, Cairo University

Corresponding Author: Professor Dyfrig A. Hughes, Centre for Health Economics and Medicines Evaluation, Bangor University, Ardudwy, Normal Site, Holyhead Road, Bangor LL57 2PZ, UK

Tel: +44 (0)1248 382950

E-mail: d.a.hughes@bangor.ac.uk

Keywords: Subcutaneous drug administration, administration, subcutaneous injections, injection devices, systematic review, patient preference, patient satisfaction

Running Head: Review of patient perspectives on subcutaneous medications

Acknowledgements: This research is supported the MRC North West Hub in Trial Methodological Research: G0800792

Conflict of Interest: CR, DD, LT, DH declare no conflict of interest. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any

organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Contributions: CHR and DAH contributed substantially to the conception and design of the work. All authors made contributions to the acquisition, analysis, or interpretation of data. CHR and LT drafted and DAH redrafted the paper; all authors revised it critically for important intellectual content, and gave their final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Key points for decision makers

- Subcutaneous drug administration is used increasingly in place of intravenous drug delivery and is an alternative to oral dosing for some treatments
- Studies of patients' perspectives typically assess ease of use, patient satisfaction and fear of adverse reactions relating to treatment administration
- Among the studies assessed, oral, subcutaneous infusion, intramuscular injection, and needle-free injection devices were not favoured over subcutaneous injections

Abstract

Background: Subcutaneous injections allow for self-administration, but consideration of patients' perspectives on treatment choice is important to ensure adherence. Previous systematic reviews have been limited in their scope for assessing preferences in relation to other routes of administration

Aim: To examine patients' perspectives on subcutaneously administered, self-injectable medications when compared with other routes or methods of administration for the same medicines.

Methods: Nine electronic databases were searched for publications since 2000 using terms pertaining to methods of administration, choice behaviour and adverse effects. Eligibility for inclusion was determined through reference to specific criteria by two independent reviewers. Results were described narratively.

Results: Of the 1,726 papers screened, 85 met the inclusion criteria. Studies were focused mainly on methods of insulin administration for diabetes but also included treatments for paediatric growth disorders, multiple sclerosis, HIV and migraine. Pen devices and autoinjectors were favoured over administration with needle and syringe; particularly with respect to ergonomics, convenience and portability. Inhalation appeared to be more acceptable than subcutaneous injection (in the case of insulin), but it is less certain how subcutaneous infusion, intramuscular injection, and needle-free injection devices compare with subcutaneous injections in terms of patient preference.

Conclusions: The review identified a number of studies showing the importance of the methods and routes of drug delivery on patient choice. However, studies were prone to bias

and further robust evidence, based on methodologically sound approaches, is required to demonstrate how patient choice might translate to improved adherence.

Introduction

Patients' attitudes towards their medicines are influenced by many factors, including their perceived (or real) benefits and harms, previous experience of use, perceptions of their illness, satisfaction with treatment and personal preferences [1]. Thus achieving optimal treatment outcomes requires that the right patients get the right choice of medicine at the right time [2]. This notion of "medicines optimisation" also encompasses encouraging patients to take their medicines correctly, avoid taking unnecessary medicines, reduce wastage of medicines, and improve medicines safety [2,3]. For some medicines, offering patients different methods or routes of drug administration may help achieve a patient-centred approach to care thereby improving medication adherence, especially in the context of parenteral administration [4-6].

While oral dosing is the posology of choice for chronic disease management, this may not be possible for some medicines (e.g. because of low bioavailability) or desirable for others (e.g. because of poor targeting of the site of action). The subcutaneous (SC) route of administration is being used increasingly, particularly as alternative formulations of biologics are developed for conditions such as cancers and inflammatory diseases [7]. Treatments including trastuzumab and rituximab –previously only available for intravenous administration– are now licensed for SC use. Compared with other routes of parenteral administration, subcutaneously-injectable formulations may offer advantages in terms of convenience, ease of use and the possibility of self-administration, which can also save health professionals' time and, thus, reduce costs. However, barriers to the use of SC injections, such as anxiety [8] and adverse, injection-site reactions [9] may have a negative impact on adherence and the benefits of such treatments.

There also exists several methods of SC administration, and patients' satisfaction with, or preferences towards delivery devices are likely to differ. In the case of insulin, for instance, patients consider pen devices to be a more acceptable method of administration than conventional vial and syringe or pre-filled syringes [10]. These offer improved portability, convenience and ease of use and reduced injection-site pain leading to better patient satisfaction. Compared to vials and syringes, use of insulin pen devices may consequently improve adherence and reduce healthcare resource use and associated costs [11].

Whilst differences in the pharmacokinetics and efficacy of competing methods and routes of drug administration are well documented, less is known of patients' perspectives. Relevant research methods include the use of self-reported outcomes, such as from rating and ranking scales, willingness-to-pay studies, discrete choice experiments, conjoint analyses and best-worst scaling exercise.

This review aims to examine patients' perspectives on subcutaneously administered, self-injectable medications. It focuses on study methodologies and on examining how patients' choices compare for different devices and routes of administration.

Methods

The systematic review protocol was registered with the All Wales Systematic Reviews Register [12,13], conducted according to the methods of the Centre for Reviews and Dissemination [14] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

Sources searched: The following databases were searched during July 2013, using a combination of MeSH and free text searches: Embase (Ovid), CINAHL (EBSCO Host), Pubmed, Cochrane (including the Cochrane Database of Systematic Reviews), TOXLINE (ProQuest), PsycARTICLES (ProQuest), PsycINFO (ProQuest), Health & Safety Science Abstracts (ProQuest), Physical Education Index (ProQuest).

Search terms: Free-text or MeSH heading terms pertaining to (i) the route of administration were combined using the Boolean operator AND with terms relevant for (ii) identifying choice behaviour and methods of elicitation, and (iii) (perceived) adverse injection-site reactions or process utility:

(i) subcutaneous drug administration OR subcutaneous injections OR subcutaneous injection OR subcutaneous drug administration OR injection devices OR self injection
(ii) Prefer* OR “trade-off” OR “patient participation” OR “patient satisfaction” OR “decision making” OR elicit* OR assess* OR “choice behaviour” OR “choice behavior” OR (Conjoint OR choice* AND (analys* OR experiment* OR elicit* OR assess* OR measurement)
(iii) injection site pain OR injection pain OR adverse drug reaction OR injection site reaction OR cutaneous reaction OR “process utility” OR ((“treatment related attributes” OR “drug administration” OR “dose frequency”) AND (utilities OR “utility measurement”))

Inclusion criteria: Studies were included if they reported on a comparison(s) of administration of a medicinal product via SC with a different route of administration, or using a different SC

device, including hypothetical scenarios; in patients currently or likely to become responsible for self-administration of SC medication; and which measured patients' perspectives towards to the health technology, adverse effects attributable to the method / route of administration such as pain or injection site reactions, or satisfaction.

Exclusion criteria: Studies were excluded if they: were published prior to 2000; written in a language other than English; were reviews, case studies, decision models, news, correspondence, commentaries; were published as conference abstracts or posters or in books, trade journals; were animal, mechanistic or pharmacokinetic studies; assessed vaccines, anaesthesia or palliative care; or considered injection drug users or non-ambulatory patients.

Review methods: Titles and abstracts were read and eligibility assessment was performed independently by two reviewers. The full manuscripts of potentially eligible studies were retrieved and assessed by both reviewers against the inclusion and exclusion criteria. Disagreements in the application of inclusion or exclusion criteria were resolved by consensus and/or consultation with two other reviewers.

Outcome measures: A wide range of outcomes was considered, to reflect the various dimensions that influence patient choice:
(i) Health technology-related outcomes (including ease of use, portability and convenience);
(ii) Behavioural outcomes (including perceived benefits, perceived barriers, satisfaction and fear/discomfort of needles);
(iii) Adverse reactions (including fear of pain and injection site reactions)

Data extraction: Data were extracted on: (1) description of study; (2) characteristics of the population and intervention; (3) types of outcome measures; (4) any measured revealed preferences (adherence); (5) comparators; (6) study type; (7) results and (8) characteristics of study sponsors and links to authors.

Data analysis: Results were primarily presented narratively [14] with strength of patients' choices assessed from the statistical significance reported or inferred from individual studies.

The potential to perform a quantitative (meta)-analysis was specified *a priori*, conditional on a rigorous assessment of clinical, methodological and statistical heterogeneity between studies. We were cognisant of the dangers of synthesising results from diverse studies as this could lead to biased assessments and give rise to misleading results. We therefore limited any quantitative analysis of the data to studies that: (i) compared a common drug, (ii) made the same comparison among 2 (or more) devices /routes of administration (we excluded studies in which comparators were not described in full), (iii) reported a common outcome, and (iv) used a common method of assessing outcomes (methods that were not validated or not reported were excluded). Meta-analyses of eligible studies were performed in RevMan version 5 (Cochrane Collaboration) using random effects modelling to assess the pooled mean difference (for continuous variables) or odds ratio (for dichotomous variables).

Results

Number of studies: A total of 2,337 articles relating to patient preferences for SC medications were identified. Following de-duplication and screening, 85 were judged suitable for inclusion. The PRISMA flow diagram of the search and screening process is presented in Figure 1. A summary of the main characteristics of each paper is presented in Supplementary Online Appendix 1.

Study populations: Sample sizes ranged from 19 to 6,528 people. The majority involved administration of insulin for the management of diabetes (n=51 studies), followed by growth hormone deficiency (n=10), migraine (n=5) and multiple sclerosis (n=4). Other areas included HIV, infertility, contraception, chronic kidney disease, and rheumatoid arthritis. The age range of patients from whom views were obtained directly was 3.5 to 95 years.

Study characteristics: The studies described 102 separate comparisons (Figure 2), with the majority considering alternative means of SC administration (Table 1). No details on the type of SC device were given for 16 comparisons, and there was incomplete information on how multiple daily injections (MDI) were achieved in a further 16 comparisons involving insulin.

A variety of study designs were described. Forty-three were randomised studies, 29 were cross-over trials and 18 were parallel arm studies. The duration of clinical studies ranged from 1 week to 2 years. The majority used generic or disease-specific questionnaires; 16 used open-ended questioning or semi-structured interviews. Nine studies used Likert scales, and 12 studies used other rating scales, including a visual analogue scale. Five studies sought to elicit stated preferences for routes of administration using choice-based methods including discrete choice experiment (DCE), adaptive conjoint analysis (ACA) and time trade-off (TTO) analysis. Some studies used simulated injections to obtain information on ease of administration. Table 2 summarises the methods used to elicit preference.

The majority of studies stated links with one or more organisations likely to have commercial interest in the outcomes. The level of involvement ranged from provision of specific costs such as translation or equipment, to direct study funding and/or authorship, receipt of grants or being an advisory board member.

Main study findings: Results from four studies comparing SC administration with intramuscular (IM) injection [16-19] were mixed. While one observational study of interferon-beta-1a in patients with multiple sclerosis found a significant difference in patients' desire to change or discontinue treatment adherence at 1-year in favour of IM with the number of injection site reactions reported as an important factor [16], another suggested a preference towards SC administration [17]. The findings of two studies of the contraceptive

medroxyprogesterone acetate were similarly inconclusive, with one indicating a tendency towards higher satisfaction with SC [18], and the other showing no statistically significant difference in in reported measures of satisfaction [19].

Inhaled insulin was preferred to SC insulin in all included studies [20-26]. However all studies reported ties with the manufacturers of inhaled insulin technologies. The possibility of publication bias could not be rejected.

Comparisons of SC injection with oral administration did not reveal any statistically significant differences in preference. In two surveys presenting hypothetical scenarios to patients with migraine, there was a tendency for the oral route being preferred, [31] and for formulation type to be more important than speed of onset [27]. However two clinical comparisons of sumatriptan suggested the opposite, with SC formulation tending to be preferred [28,29]. A DCE among patients with osteoporosis indicated that patients would be willing to pay €142 a month for a daily SC injection rather than a daily or weekly tablet [30].

Four of the comparisons of oral and SC formulations in migraine also considered nasal administration but none demonstrated any statistically significant difference in preference [27-29,31].

Two studies compared SC with transdermal administration [31,32]. In a crossover study of insulin delivery, significantly more patients with type 1 or 2 diabetes stated that they would switch to a patch treatment, if available [32].

Among studies comparing needle-free injector devices (NFID) with SC injections, four compared enfuvirtide delivered via NFID and needle and syringe in patients with HIV. All found significant differences in favour of NFID in terms of patient-rated ease of use [33],

preference [35], or a desire to continue with the NFID at the end of the study [34, 36]. However, there was no significant difference in patient satisfaction among women self-administering gonadotropin for infertility treatment [37], or in three studies of children receiving growth hormone therapy [38-40].

Nine comparisons of autoinjector devices with vial and syringe and/or pre-filled syringes (PFS) or other auto-injectors were identified. An adaptive conjoint analysis of users of growth hormone therapy revealed autoinjection to generate higher utility [38]. Autoinjectors for adalimumab were preferred to PFS and associated with less injection site pain in patients with rheumatoid arthritis [41,42]. Autoinjectors were similarly preferred for darbopoetin in chronic kidney disease [43] and for sumatriptan in migraine [48]. While one study of autoinjector devices for growth hormone found a preference among both patients and parents [45], another found less favourable scores compared with pen devices, largely due to the requirement for reconstitution [44]. Studies of interferon beta 1a autoinjectors in multiple sclerosis yielded varying results. One found no significant changes from baseline in a disease-specific treatment concern questionnaire [46] while another suggested a preference for autoinjectors [47].

Of 12 papers comparing insulin via SC catheter (mainly continuous SC infusion) with multiple daily injections (MDI) [49-60], 9 found significant differences in favour of administration by infusion, through a range of largely disease-specific measures [49-54,57-59].

Eighteen studies compared SC administration using pen devices with syringes, 17 using traditional syringe and vial. These were largely for insulin in diabetes, but also treatments of psoriasis [61], growth hormone deficiency [62], infertility [63,64] and hepatitis C [65]. Pens

were significantly preferred in 15 studies, particularly with respect to ease of use, convenience and portability [61-64,66-74,76-78].

The largest number of comparisons was between different pen devices, including 22 for administration of insulin [74-75,77-96], and 4 for growth hormone [97-100]. However, 13 insulin and 3 growth hormone studies used simulated injections and no clinical study of pen devices was longer than 12 weeks. All claimed advantages for the novel device over comparators, with statistically significant differences in 19, but all were authored and/or sponsored by manufacturers.

Among all the studies examined, only 12 assessed adherence or persistence as a revealed preference [16,19,26,35,36,40-42,62,65,71,73], and most of these relied on patient self-report.

Meta analyses: Four groups of studies were considered eligible for meta-analyses, each of which compared insulin delivered using pen devices versus some alternative method (see Supplementary Online Appendix 2). These were: (i) the assessment of patients' satisfaction compared with continuous SC infusion [51,57], (ii) patient preference for a new pen device versus their existing pen device [80,81,83,92,94], (iii) preference compared with SC needle and syringe [68,71], and (iv) preferences in comparison to any existing method of administration [74,78-79].

The comparison of pen devices with SC needle and syringe yielded a pooled odds ratio of 6.7 (95% confidence interval 4.6, 9.7; heterogeneity I^2=0%) for patients favouring pen devices. However as this represented only 2 of 13 studies making this comparison the potential for selection bias cannot be excluded. All other comparisons we statistically heterogeneous ($I^2 \geq 98\%$) and therefore deemed unreliable.

Discussion

An understanding of patients' perspectives on the methods and routes of drug delivery is an important consideration for maximising the effectiveness of medicines. Our systematic review identified wide-ranging evidence using a range of methods of assessing patients' stated and actual choice for SC versus alternative routes of drug administration, as well as between different SC injectable devices. The principal findings were: increased satisfaction and preferences with respect to the ergonomics, convenience and portability of insulin pen devices and autoinjectors as compared to needle & syringe, and more satisfaction with inhaled insulin; but no clear favouring of oral, SC infusion, intramuscular injection, and needle-free injection devices when compared with SC injections.

A significant number of studies meeting our inclusion criteria were of methods of insulin delivery, reflecting developments in pen devices and the (now discontinued) inhaler, Exubera. Satisfaction with, and preference for different insulin devices and routes of administration may relate more to the necessity for a convenient and pain-free method, given the need for punctual and life-long therapy. By contrast, studies in migraine, where the need for medication is intermittent and unpredictable, having available options of routes of administration for use in different circumstances may be more important to patients than any single preferred option. These contrasts suggest that factors important for patient choice of a given route of administration will vary with the clinical situation and context of use.

The number of studies comparing SC administration with oral, nasal, transdermal and intramuscular administration were each very small, and covered different therapeutic areas. None of the studies compared SC self-administration with intravenous administration by health care professionals in a clinical setting, which we perceive to be increasing with the

335 introduction of novel biologic therapies. The comparison with clinic-administration by IM
336 injection of medroxyprogesterone acetate as a contraceptive was perhaps the closest
337 situation, but neither study revealed any difference from a patient's perspective [18,19].

338 Whilst our review complied with best methodological practice, the strength of our findings is
339 limited by the weaknesses of the research identified and the variety of approaches
340 employed. The number of studies comparing SC injection with non-SC routes was small for
341 each route and many studies were observational, unmasked, had small sample sizes and
342 short follow-up periods. There was general inadequacy in the descriptions of the
343 technologies being assessed, or of the methods of analysis. Although some studies did not
344 disclose a source of funding, the majority were supported by (or linked to) pharmaceutical
345 companies seeking to differentiate their products from those of competitors. As more
346 biopharmaceutical products are developed, and treatments previously administered
347 intravenously are formulated for SC administration, more patient-centred evaluations are
348 likely to emerge, however this should not be at the expense of methodological rigour.

349 Reviewed studies employed a range of methods, including direct questioning of patients,
350 typically with responses on Likert scales, for their satisfaction with or preference to different
351 treatment options. Such surveys employed a variety of questionnaire designs, only some of
352 which were recognised as validated. The discrete choice experiments or conjoint analyses
353 employed in a small number of studies are a more appropriate choice-based method of
354 preference elicitation grounded in theory [101]. There was considerable heterogeneity
355 among studies, in terms of populations, treatments, methods of drug administration,
356 outcome measure and measurement, to enable unbiased pooled estimates to be determined
357 through meta-analyses in all but one comparison [102]. Combining heterogeneous studies
358 could compromise the systematic and scientifically rigorous representation of empirical
359 evidence that could be more accurately reported in our narrative synthesis [14].

Our systematic review has extended previous reviews [10,103], which were restricted to comparisons of pen versus needle and syringe insulin for diabetes. Our findings suggest that differences in patients' perspectives between methods and routes of drug delivery will affect choice of delivery device across a whole spectrum of diseases. But while evidence of patient preference – in addition to all features/attributes of medicines (such as efficacy, safety, route of administration) – may potentially add value to treatments, health technology assessments require evidence on how this improves health outcomes and /or cost-effectiveness to justify any increases in pricing. These were outside the scope of the present review, but even so, very few studies considered patient adherence to treatment that might mediate improvements in health outcomes.

The implications of our findings are: firstly, that medicines may be optimised by considering patient choice in the clinical decision to prescribe a particular method or route of administration. Prescribers should be alert to the alternative options for subcutaneously administered medicines, and consider the range of factors that are likely to influence patients' adherence with treatment. Secondly, pharmaceutical companies often cite patient preference as a justification for price premiums. Their value dossiers and health technology assessment reports typically suggest that patients favour some methods or routes of drug administration more than others, and that this can lead to improvement in health outcomes. Our review illustrates that evidence underpinning such claims is weak.

Conclusions

The review identified a number of studies showing the importance of the methods and routes of drug delivery on patient choice. To improve the evidence base, however, we propose that future studies of patients' perspectives of injectable devices should consider using validated preference measures, combined with a choice-based experiment for stated preference

386 elicitation, and reliable adherence measurement [5] for revealed preferences. Studies need
387 to be unbiased and appropriately powered for demonstrating statistical significance.
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