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

Ridyard, Colin; Dawoud, D.M.; Tuersley, L.V.; Hughes, D.

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4 **Authors:** Colin H Ridyard[1] PhD, Dalia M M Dawoud[2] PhD, Lorna V Tuersley[1] PhD

5 MRPharmS and Dyfrig A Hughes[1] PhD, MRPharmS

6

7 [1] Centre for Health Economics and Medicines Evaluation, Bangor University

8 [2] Clinical Pharmacy Department, Faculty of Pharmacy, Cairo University

9

10 **Corresponding Author:** Professor Dyfrig A. Hughes, Centre for Health Economics and

11 Medicines Evaluation, Bangor University, Ardudwy, Normal Site, Holyhead Road, Bangor

12 LL57 2PZ, UK

13

14 Tel: +44 (0)1248 382950

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

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21

24

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31

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35 important intellectual content, and gave their final approval of the version to be published. All

36 authors agree to be accountable for all aspects of the work in ensuring that questions related

37 to the accuracy or integrity of any part of the work are appropriately investigated and

38 resolved.

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40

41 **Key points for decision makers**

42 - Subcutaneous drug administration is used increasingly in place of intravenous drug

43   delivery and is an alternative to oral dosing for some treatments

44 - Studies of patients' perspectives typically assess ease of use, patient satisfaction and

45   fear of adverse reactions relating to treatment administration

46 - Among the studies assessed, oral, subcutaneous infusion, intramuscular injection, and

47   needle-free injection devices were not favoured over subcutaneous injections

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3

50   **Abstract**

51

52   **Background:** Subcutaneous injections allow for self-administration, but consideration of

53   patients' perspectives on treatment choice is important to ensure adherence. Previous

54   systematic reviews have been limited in their scope for assessing preferences in relation to

55   other routes of administration

56

57   **Aim:** To examine patients' perspectives on subcutaneously administered, self-injectable

58   medications when compared with other routes or methods of administration for the same

59   medicines.

60

61   **Methods:** Nine electronic databases were searched for publications since 2000 using terms

62   pertaining to methods of administration, choice behaviour and adverse effects. Eligibility for

63   inclusion was determined through reference to specific criteria by two independent

64   reviewers. Results were described narratively.

65

66   **Results:** Of the 1,726 papers screened, 85 met the inclusion criteria. Studies were focused

67   mainly on methods of insulin administration for diabetes but also included treatments for

68   paediatric growth disorders, multiple sclerosis, HIV and migraine. Pen devices and

69   autoinjectors were favoured over administration with needle and syringe; particularly with

70   respect to ergonomics, convenience and portability. Inhalation appeared to be more

71   acceptable than subcutaneous injection (in the case of insulin), but it is less certain how

72   subcutaneous infusion, intramuscular injection, and needle-free injection devices compare

73   with subcutaneous injections in terms of patient preference.

74

75   **Conclusions:** The review identified a number of studies showing the importance of the

76   methods and routes of drug delivery on patient choice. However, studies were prone to bias

4

77   and further robust evidence, based on methodologically sound approaches, is required to

78   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.

6

105 There also exists several methods of SC administration, and patients' satisfaction with, or

106 preferences towards delivery devices are likely to differ. In the case of insulin, for instance,

107 patients consider pen devices to be a more acceptable method of administration than

108 conventional vial and syringe or pre-filled syringes [10]. These offer improved portability,

109 convenience and ease of use and reduced injection-site pain leading to better patient

110 satisfaction. Compared to vials and syringes, use of insulin pen devices may consequently

111 improve adherence and reduce healthcare resource use and associated costs [11].

112

113 Whilst differences in the pharmacokinetics and efficacy of competing methods and routes of

114 drug administration are well documented, less is known of patients' perspectives. Relevant

115 research methods include the use of self-reported outcomes, such as from rating and

116 ranking scales, willingness-to-pay studies, discrete choice experiments, conjoint analyses

117 and best-worst scaling exercise.

118

119 This review aims to examine patients' perspectives on subcutaneously administered, self-

120 injectable medications. It focuses on study methodologies and on examining how patients'

121 choices compare for different devices and routes of administration.

122

123 **Methods**

124

125 The systematic review protocol was registered with the All Wales Systematic Reviews

126 Register [12,13], conducted according to the methods of the Centre for Reviews and

127 Dissemination [14] and reported according to the Preferred Reporting Items for Systematic

128 Reviews and Meta-Analyses (PRISMA) statement [15].

129 *Sources searched*: The following databases were searched during July 2013, using a

130 combination of MeSH and free text searches: Embase (Ovid), CINAHL (EBSCO Host),

131 Pubmed, Cochrane (including the Cochrane Database of Systematic Reviews), TOXLINE

132 (ProQuest), PsycARTICLES (ProQuest), PsycINFO (ProQuest), Health & Safety Science

133 Abstracts (ProQuest), Physical Education Index (ProQuest).

134 *Search terms*: Free-text or MeSH heading terms pertaining to (i) the route of administration

135 were combined using the Boolean operator AND with terms relevant for (ii) identifying choice

136 behaviour and methods of elicitation, and (iii) (perceived) adverse injection-site reactions or

137 process utility:

138 (i) subcutaneous drug administration OR subcutaneous injections OR subcutaneous

139 injection OR subcutaneous drug administration OR injection devices OR self injection

140 (ii) Prefer* OR "trade-off" OR "patient participation" OR "patient satisfaction" OR "decision

141 making" OR elicit* OR assess* OR "choice behaviour" OR "choice behavior" OR (Conjoint

142 OR choice* AND (analys* OR experiment* OR elicit* OR assess* OR measurement)

143 (iii) injection site pain OR injection pain OR adverse drug reaction OR injection site reaction

144 OR cutaneous reaction OR "process utility" OR (("treatment related attributes" OR "drug

145 administration" OR "dose frequency") AND (utilities OR "utility measurement"))

146 *Inclusion criteria*: Studies were included if they reported on a comparison(s) of administration

147 of a medicinal product via SC with a different route of administration, or using a different SC

8

148 device, including hypothetical scenarios; in patients currently or likely to become responsible

149 for self-administration of SC medication; and which measured patients' perspectives towards

150 to the health technology, adverse effects attributable to the method / route of administration

151 such as pain or injection site reactions, or satisfaction.

152 *Exclusion criteria*: Studies were excluded if they: were published prior to 2000; written in a

153 language other than English; were reviews, case studies, decision models, news,

154 correspondence, commentaries; were published as conference abstracts or posters or in

155 books, trade journals; were animal, mechanistic or pharmacokinetic studies; assessed

156 vaccines, anaesthesia or palliative care; or considered injection drug users or non-

157 ambulatory patients.

158 *Review methods*: Titles and abstracts were read and eligibility assessment was performed

159 independently by two reviewers. The full manuscripts of potentially eligible studies were

160 retrieved and assessed by both reviewers against the inclusion and exclusion criteria.

161 Disagreements in the application of inclusion or exclusion criteria were resolved by

162 consensus and/or consultation with two other reviewers.

163 *Outcome measures*: A wide range of outcomes was considered, to reflect the various

164 dimensions that influence patient choice:

165 (i) Health technology-related outcomes (including ease of use, portability and convenience);

166 (ii) Behavioural outcomes (including perceived benefits, perceived barriers, satisfaction and

167 fear/discomfort of needles);

168 (iii) Adverse reactions (including fear of pain and injection site reactions)

169

170 *Data extraction*: Data were extracted on: (1) description of study; (2) characteristics of the

171 population and intervention; (3) types of outcome measures; (4) any measured revealed

172 preferences (adherence); (5) comparators; (6) study type; (7) results and (8) characteristics

173 of study sponsors and links to authors.

174   *Data analysis*: Results were primarily presented narratively [14] with strength of patients'

175   choices assessed from the statistical significance reported or inferred from individual studies.

176   The potential to perform a quantitative (meta)-analysis was specified *a priori*, conditional on

177   a rigorous assessment of clinical, methodological and statistical heterogeneity between

178   studies. We were cognisant of the dangers of synthesising results from diverse studies as

179   this could lead to biased assessments and give rise to misleading results. We therefore

180   limited any quantitative analysis of the data to studies that: (i) compared a common drug, (ii)

181   made the same comparison among 2 (or more) devices /routes of administration (we

182   excluded studies in which comparators were not described in full), (iii) reported a common

183   outcome, and (iv) used a common method of assessing outcomes (methods that were not

184   validated or not reported were excluded). Meta-analyses of eligible studies were performed

185   in RevMan version 5 (Cochrane Collaboration) using random effects modelling to assess the

186   pooled mean difference (for continuous variables) or odds ratio (for dichotomous variables).

187

188   **Results**

189

190   *Number of studies*: A total of 2,337 articles relating to patient preferences for SC

191   medications were identified. Following de-duplication and screening, 85 were judged

192   suitable for inclusion. The PRISMA flow diagram of the search and screening process is

193   presented in Figure 1. A summary of the main characteristics of each paper is presented in

194   Supplementary Online Appendix 1.

195

196   *Study populations*: Sample sizes ranged from 19 to 6,528 people. The majority involved

197   administration of insulin for the management of diabetes (n=51 studies), followed by growth

198   hormone deficiency (n=10), migraine (n=5) and multiple sclerosis (n=4). Other areas

199   included HIV, infertility, contraception, chronic kidney disease, and rheumatoid arthritis. The

200   age range of patients from whom views were obtained directly was 3.5 to 95 years.

10

201

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

11

228 medroxyprogesterone acetate were similarly inconclusive, with one indicating a tendency

229 towards higher satisfaction with SC [18], and the other showing no statistically significant

230 difference in in reported measures of satisfaction [19].

231

232 Inhaled insulin was preferred to SC insulin in all included studies [20-26]. However all

233 studies reported ties with the manufacturers of inhaled insulin technologies. The possibility of

234 publication bias could not be rejected.

235

236 Comparisons of SC injection with oral administration did not reveal any statistically

237 significant differences in preference. In two surveys presenting hypothetical scenarios to

238 patients with migraine, there was a tendency for the oral route being preferred, [31] and for

239 formulation type to be more important than speed of onset [27]. However two clinical

240 comparisons of sumatriptan suggested the opposite, with SC formulation tending to be

241 preferred [28,29]. A DCE among patients with osteoporosis indicated that patients would be

242 willing to pay €142 a month for a daily SC injection rather than a daily or weekly tablet [30].

243

244 Four of the comparisons of oral and SC formulations in migraine also considered nasal

245 administration but none demonstrated any statistically significant difference in preference

246 [27-29,31].

247

248 Two studies compared SC with transdermal administration [31,32]. In a crossover study of

249 insulin delivery, significantly more patients with type 1 or 2 diabetes stated that they would

250 switch to a patch treatment, if available [32].

251

252 Among studies comparing needle-free injector devices (NFID) with SC injections, four

253 compared enfuvirtide delivered via NFID and needle and syringe in patients with HIV. All

254 found significant differences in favour of NFID in terms of patient-rated ease of use [33],

255 preference [35], or a desire to continue with the NFID at the end of the study [34, 36].

256 However, there was no significant difference in patient satisfaction among women self-

257 administering gonadotropin for infertility treatment [37], or in three studies of children

258 receiving growth hormone therapy [38-40].

259

260 Nine comparisons of autoinjector devices with vial and syringe and/or pre-filled syringes

261 (PFS) or other auto-injectors were identified. An adaptive conjoint analysis of users of growth

262 hormone therapy revealed autoinjection to generate higher utility [38]. Autoinjectors for

263 adalimumab were preferred to PFS and associated with less injection site pain in patients

264 with rheumatoid arthritis [41,42]. Autoinjectors were similarly preferred for darbopoetin in

265 chronic kidney disease [43] and for sumatriptan in migraine [48]. While one study of

266 autoinjector devices for growth hormone found a preference among both patients and

267 parents [45], another found less favourable scores compared with pen devices, largely due

268 to the requirement for reconstitution [44]. Studies of interferon beta 1a autoinjectors in

269 multiple sclerosis yielded varying results. One found no significant changes from baseline in

270 a disease-specific treatment concern questionnaire [46] while another suggested a

271 preference for autoinjectors [47].

272

273 Of 12 papers comparing insulin via SC catheter (mainly continuous SC infusion) with

274 multiple daily injections (MDI) [49-60], 9 found significant differences in favour of

275 administration by infusion, through a range of largely disease-specific measures [49-54,57-

276 59].

277

278 Eighteen studies compared SC administration using pen devices with syringes, 17 using

279 traditional syringe and vial. These were largely for insulin in diabetes, but also treatments of

280 psoriasis [61], growth hormone deficiency [62], infertility [63,64] and hepatitis C [65]. Pens

281 were significantly preferred in 15 studies, particularly with respect to ease of use,

282 convenience and portability [61-64,66-74,76-78].

283

284 The largest number of comparisons was between different pen devices, including 22 for

285 administration of insulin [74-75,77-96], and 4 for growth hormone [97-100]. However, 13

286 insulin and 3 growth hormone studies used simulated injections and no clinical study of pen

287 devices was longer than 12 weeks. All claimed advantages for the novel device over

288 comparators, with statistically significant differences in 19, but all were authored and/or

289 sponsored by manufacturers.

290

291 Among all the studies examined, only 12 assessed adherence or persistence as a revealed

292 preference [16,19,26,35,36,40-42,62,65,71,73], and most of these relied on patient self-

293 report.

294

295 *Meta analyses*: Four groups of studies were considered eligible for meta-analyses, each of

296 which compared insulin delivered using pen devices versus some alternative method (see

297 Supplementary Online Appendix 2). These were: (i) the assessment of patients' satisfaction

298 compared with continuous SC infusion [51,57], (ii) patient preference for a new pen device

299 versus their existing pen device [80,81,83,92,94], (iii) preference compared with SC needle

300 and syringe [68,71], and (iv) preferences in comparison to any existing method of

301 administration [74,78-79].

302

303 The comparison of pen devices with SC needle and syringe yielded a pooled odds ratio of

304 6.7 (95% confidence interval 4.6, 9.7; heterogeneity $I^2=0\%$) for patients favouring pen

305 devices. However as this represented only 2 of 13 studies making this comparison the

306 potential for selection bias cannot be excluded. All other comparisons we statistically

307 heterogeneous ($I^2 \geq 98\%$) and therefore deemed unreliable.

14

308

Discussion

310

311 An understanding of patients' perspectives on the methods and routes of drug delivery is an

312 important consideration for maximising the effectiveness of medicines. Our systematic

313 review identified wide-ranging evidence using a range of methods of assessing patients'

314 stated and actual choice for SC versus alternative routes of drug administration, as well as

315 between different SC injectable devices. The principal findings were: increased satisfaction

316 and preferences with respect to the ergonomics, convenience and portability of insulin pen

317 devices and autoinjectors as compared to needle & syringe, and more satisfaction with

318 inhaled insulin; but no clear favouring of oral, SC infusion, intramuscular injection, and

319 needle-free injection devices when compared with SC injections.

320

321 A significant number of studies meeting our inclusion criteria were of methods of insulin

322 delivery, reflecting developments in pen devices and the (now discontinued) inhaler,

323 Exubera. Satisfaction with, and preference for different insulin devices and routes of

324 administration may relate more to the necessity for a convenient and pain-free method,

325 given the need for punctual and life-long therapy. By contrast, studies in migraine, where the

326 need for medication is intermittent and unpredictable, having available options of routes of

327 administration for use in different circumstances may be more important to patients than any

328 single preferred option. These contrasts suggest that factors important for patient choice of a

329 given route of administration will vary with the clinical situation and context of use.

330

331 The number of studies comparing SC administration with oral, nasal, transdermal and

332 intramuscular administration were each very small, and covered different therapeutic areas.

333 None of the studies compared SC self-administration with intravenous administration by

334 health care professionals in a clinical setting, which we perceive to be increasing with the

15

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].

360   Our systematic review has extended previous reviews [10,103], which were restricted to

361   comparisons of pen versus needle and syringe insulin for diabetes. Our findings suggest that

362   differences in patients' perspectives between methods and routes of drug delivery will affect

363   choice of delivery device across a whole spectrum of diseases. But while evidence of patient

364   preference – in addition to all features/attributes of medicines (such as efficacy, safety, route

365   of administration) – may potentially add value to treatments, health technology assessments

366   require evidence on how this improves health outcomes and /or cost-effectiveness to justify

367   any increases in pricing. These were outside the scope of the present review, but even so,

368   very few studies considered patient adherence to treatment that might mediate

369   improvements in health outcomes.

370   The implications of our findings are: firstly, that medicines may be optimised by considering

371   patient choice in the clinical decision to prescribe a particular method or route of

372   administration. Prescribers should be alert to the alternative options for subcutaneously

373   administered medicines, and consider the range of factors that are likely to influence

374   patients' adherence with treatment. Secondly, pharmaceutical companies often cite patient

375   preference as a justification for price premiums. Their value dossiers and health technology

376   assessment reports typically suggest that patients favour some methods or routes of drug

377   administration more than others, and that this can lead to improvement in health outcomes.

378   Our review illustrates that evidence underpinning such claims is weak.

379

380   **Conclusions**

381

382   The review identified a number of studies showing the importance of the methods and routes

383   of drug delivery on patient choice. To improve the evidence base, however, we propose that

384   future studies of patients' perspectives of injectable devices should consider using validated

385   preference measures, combined with a choice-based experiment for stated preference

17

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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389

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