

1 **Abstract**

2 **Background**

3 There is evidence to suggest that adherence with prescribed medication is lower amongst
4 adolescents and children than in adults (1). Medication adherence rates between 11% and 93% in
5 paediatric patients have been reported (2). More research needs to be carried out in order to
6 understand why medicines adherence is low and how adherence can be improved in children with
7 long-term conditions. Personal communication with paediatricians in secondary care has highlighted
8 that problems are most likely to be encountered by parents, carers, nurses and children themselves
9 when administering medicines for prevalent long-term childhood conditions.

10 **Objective**

11 To explore problems with oral medicines prescribed to paediatric patients from the perspectives of
12 medical practitioners, pharmacists and nurses.

13 **Setting**

14 Two NHS trusts in the West Midlands, UK

15 **Method**

16 Four focus groups (FG) were conducted. 5 nurses, 8 medical practitioners and 6 pharmacists
17 participated in focus groups.. The themes explored were problems experienced when prescribing,
18 dispensing and administering oral medicines for children. Ethical approval was granted by the South
19 Birmingham Research Ethics Committee (REC), UK.

20 **Main outcome measure**

21 Themes evolving from Healthcare professionals reports on problems with administering medicines
22 to paediatric patients.

23 **Results**

24 Two main themes: sensory and non-sensory emerged from the data. Included within these were
25 taste, texture, colour, smell, size, swallowing, quantity, volume and manipulation with food. Taste
26 was the most commonly reported barrier to medicines administration. Texture was reported to be a
27 significant problem for the learning disability population. Medicines manipulation techniques were
28 revealed across the groups, yet there was limited knowledge regarding the evidence base for such
29 activity. Problems surrounding the supply of Specials medicines were discussed in-depth by the
30 pharmacists.

31 **Conclusion**

32 Organoleptic and physical properties of medicines were identified as key barriers to medicines
33 administration. A robust scientific evidence-based approach is warranted to inform standardised
34 protocols guiding healthcare professionals to support safe and effective medicines manipulation
35 across all settings. Pharmacists' knowledge of Specials medicines needs to be recognised as a
36 valuable resource for doctors. Findings of this study should help to optimise paediatric prescribing
37 and direct future formulation work.

38 **Keywords:** pediatrics;healthcare professionals;medicines administration;medicines
39 adherence;prescribing.

- 40 • A large number of issues are perceived by healthcare professionals to cause problems when
41 administering oral medicines to children. Taste was highlighted as the most significant issue.

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- Nurses had the greatest knowledge of bedside issues, whilst pharmacists understood the consequences of certain manipulations; wider sharing of this knowledge can help to ensure appropriate medicines are prescribed to minimise issues with administration.
- The scientific evidence base for medicines manipulation requires further development; it is evident that medical practitioners require more information when prescribing medicines to ensure supply, clinical effectiveness and to maximise cost efficiency.
- Addressing the education of healthcare professionals involved in prescribing, dispensing and administering oral medicines to children will be invaluable to improving the therapeutic treatment of paediatric patients.

63 **Ethical Approval**

64 Ethical approval was granted by the South Birmingham REC, UK (REC no: 10/H1207/47).

65

66 **Introduction**

67 There is evidence to suggest that adherence with prescribed medication is lower amongst
68 adolescents and children (0-17 years) than in adults (1). Medication adherence rates between 11%
69 and 93% in paediatric patients have been reported (2). A median rate of 58% medicine adherence in
70 youth has been estimated (3). As one in five children in the UK has a long standing illness or disability
71 (4) it is critical that more research needs to be carried out in order to understand why medicines
72 adherence is low and how adherence can be improved in children with long-term conditions.
73 Personal communication with paediatricians in secondary care has highlighted that problems are
74 most likely to be encountered by parents, carers, nurses and children themselves when having to
75 administer medication for prevalent long-term childhood conditions, notably: diabetes, Human
76 immunodeficiency virus (HIV), asthma, Tuberculosis (TB), rheumatic diseases amongst others. It is
77 predicted that issues experienced with medicines will be influenced by the child's age and disease
78 state.

79 Problems with children's medicines may be influenced by many factors. These include issues with
80 prescribing and the supply of medicines, the prevalence of unlicensed medicines and medicines
81 prescribed off-label (5,6), difficulties with administering medicines (including manipulation of
82 medicines – 7,8), behaviour around medicine taking (including influence of family, school and life
83 situation) (9), adverse effects of medicines and medicine adherence problems in specific patient
84 groups (i.e. age groups and chronic conditions). Particularly, research on juvenile diabetes,
85 haemophilia and rheumatoid arthritis has revealed the potential vulnerability of young people to
86 medication non-adherence (10).

87 Anecdotal parental reports suggest that healthcare professionals may not be aware of the specific
88 barriers and problems that patients and their parents and carers perceive and experience daily when
89 administering medicines to children. Medicines may be manipulated by parents, carers and young
90 people for which there is often a lack of robust scientific evidence. Parents, carers and young people

91 may decide to manipulate medicines of their own accord, unbeknown to the responsible medical
92 practitioner. Alternatively medicines manipulation may be performed following a recommendation
93 from a healthcare professional.

94 There is a paucity of research investigating healthcare professionals' perceptions of issues with
95 medicines used to treat paediatric patients with chronic conditions. Studies that have been
96 conducted include an exploration of healthcare providers' views on HIV adherence in paediatric
97 patients (11), an investigation in to nurses' knowledge and practice of mixing medicines with
98 foodstuffs (12) and those investigating unlicensed medicines use (13,14). The present study aimed
99 to have a more diverse approach, exploring the perspectives of allied healthcare professionals
100 (medical practitioners, nurses and pharmacists) with regard to problems with oral medicines
101 prescribed to children.

102 **Aim of the study**

103 The objective of the focus groups was to explore and understand the problems experienced when
104 prescribing, dispensing and administering oral medicines to children from the perspectives of
105 medical practitioners, pharmacists and nurses. The aim of this was to identify common and unique
106 themes across healthcare professional groups regarding problems with oral medicines prescribed to
107 paediatric patients and furthermore to compare their views with those of parents, carers and
108 children in the second part of the larger FIND OUT study (REC no: 10/H1207/47).

109 **Method**

110 Initial ideas generated by RV with the advice of the Professor of Clinical Pharmacy (JM) and a
111 Consultant Paediatrician (HS) were informed by healthcare professionals in pre-study hospital visits
112 and by study objectives. The different professional backgrounds of the individuals involved in study
113 design permitted the collaboration of a clinical and pharmaceutical input. Ideas were used to
114 develop a template plan of key topics for exploration in the focus groups. The same key topics
115 surrounding problems with oral medicines in children were highlighted in each focus group to
116 provoke participant interaction and discussion in the groups.

117 Children suffering from chronic conditions often have regular appointments in the secondary care
118 setting to review their condition and medicines. In the hospital environment, different members of
119 the healthcare team are responsible for providing care for patients. This multidisciplinary healthcare
120 team includes medical practitioners, nurses and pharmacists of varying expertise and with different
121 specialist interests.

122 This study was conducted with healthcare professionals at University Hospitals Coventry and
123 Warwickshire (UHCW) and Birmingham Children's Hospital (BCH), UK. Healthcare professionals were
124 invited to join a focus group by posters mounted on walls at UHCW and also contacted via the
125 UHCW email system and invited to respond to register an interest to participate. In addition,
126 targeted emails were sent to paediatric pharmacists in the West Midlands region. An information
127 sheet designed using guidance from the National Patient Safety Agency (NPSA) (15) was distributed
128 with the invitation email. General Practitioners (GPs) in Coventry and Warwickshire were informed

129 of the study via a study summary article in the clinical pharmacology e-newsletter, routinely
130 disseminated to all GPs in Coventry and Warwickshire.

131

132 Four uniprofessional focus groups were conducted involving nurses, medical practitioners,
133 pharmacists at UHCW, and a further group of pharmacists at BCH. The four focus groups were
134 conducted between September 2010 and February 2011. The second pharmacist focus group was
135 arranged for pharmacists at BCH. These pharmacists had generated interest in the study but were
136 unable to attend the UHCW session for logistical reasons. The introduction for each focus group
137 followed the same structure and included obtaining written consent from each participant to permit
138 publication of anonymised quotations, followed by a reminder about confidentiality issues. The
139 planning and conducting stages of the focus group sessions were carried out according to defined
140 procedures (16). Focus group design was informed by anecdotal information from parents, children
141 and healthcare professionals. The four focus groups were facilitated by RV and assisted by JM/HS.
142 The groups were digitally audio-recorded and complementary notes were taken during the sessions.

143

144 RV transcribed each focus group. Complementary notes recorded during the sessions were used to
145 optimise accuracy of the verbatim transcripts. The focus groups data was analysed using a
146 framework analysis approach, following published guidance (17). The template plan of topics was
147 used to explore and identify the themes revealed in each transcript. Following this, common themes
148 revealed across the groups and those unique to each group were identified. The thematic analysis
149 program QSR NVivo supported this analysis.

150

151 **Results**

152 Four focus groups were conducted with the following healthcare professionals:

- 153 1. Nurses (n=5: Neonatal nurse practitioners (n=2), a nurse with a specialist interest in CF, a
154 community-based nurse and a nurse practice educator),
- 155 2. Medical practitioners (n=8: Paediatric consultants with specialist interests (n=6), a paediatric
156 specialist registrar, and a GP with an interest in paediatrics)
- 157 3. Paediatric pharmacists (n=2)
- 158 4. Paediatric pharmacists (n=4).

159

160 Focus groups 1-3 were conducted at UHCW. Focus group 4 was conducted at BCH. The nurse and
161 medical practitioner groups were conducted at lunchtime and the pharmacist groups took place in
162 allocated study time. Groups lasted between 51 and 93 minutes.

163

164 Following the framework analysis, a structured thematic coding spine (see table 1) was created
165 based on two main themes: sensory and non-sensory (social and situational). Ten sub-themes
166 emerged from the focus groups. The coding spine includes themes revealed both independently and
167 across the focus groups. The results of the analysis are discussed systematically, using the thematic
168 headings and sub-headings listed in table 1.

169

170 *Sensory themes*

171 *Oral formulation-related barriers to medicines administration*

172 Commonly reported oral formulation-related barriers to the acceptance of medicines in children
173 across the four focus groups included taste, texture, size of solid dosage form, and volume. Taste
174 was the most prevalent oral formulation-related problem highlighted across the groups.

175 Flucloxacillin solution was perceived by all healthcare professional groups to be disliked by children
176 due to its taste.

177

178 Chloral hydrate solution, prednisolone soluble tablets and Movicol® (macrogol '3350') oral powder
179 were all highlighted with respect to taste in two of the focus groups.

180

181 Taste issues with specific formulations revealed in the focus groups in table 1.

182

183 All medicines reported with taste problems in the focus groups were perceived by participants to
184 cause problems with adherence.

185

186 All of the healthcare professional groups highlighted that children experience problems with the
187 textures of some medicines. The learning disability population were discussed as a problematic
188 patient population across the focus groups when regarding problems with texture.

189 All groups acknowledged that children taking antiretroviral tablets experience problems with their
190 size and also difficulties when swallowing them. In particular, Kaletra® (lopinavir/ritonavir) tablets
191 were mentioned to be problematic. Additionally, large dose volumes were perceived to be a barrier
192 to medicines administration and examples of formulations with large dose volumes were
193 volunteered across the groups.

194 The nurses reported the widest variety of oral formulation-related barriers to medicines
195 administration including those that affect sensory perceptions (colour and smell).

196 *Future medicines for children*

197 The nurses and medical practitioners prioritised the improvement of a variety of poorly palatable
198 medicines. However, the pharmacists perceived that an improvement to Specials medicines would
199 be ideal. In the UK, Healthcare professionals may consider it necessary to prescribe or advise the use
200 of an unlicensed medicine when no licensed, suitable alternative is available, and in which case the
201 medicine may be ordered from a Specials manufacturer (Specials medicine). Medicines legislation
202 (specifically, The Medicines for Human Use Marketing Authorisations Etc Regulations 1994/SI 3144)
203 states that medicinal products require a licence before they are marketed in the UK (19).

204 Pharmacists felt that providing Certificates of Analyses to assure the safety and stability of Specials
205 medicines and also licensing some medicines not commercially available in child appropriate
206 formulations should be considered in order to improve medicines for children. Improving Specials
207 medicines was not reported as an ideal medicine improvement by the nurses or medical
208 practitioners, suggesting that this problem is not such a concern for them.

209 Calpol® (paracetamol) suspension was presented as a favourite, well-liked medicine formulation in
210 all of the groups.

211 *Problems related to medicines administration*

212 All groups discussed *ad hoc* manipulation techniques that had been reported to them by parents and
213 carers and also those that they recommend to parents and carers to facilitate the administration of
214 medicines to children (see figure 1).

215

216 Manipulation techniques were discussed in detail by the nurses. The nurses provided examples of
217 medicines manipulation on wards and also highlighted how parents administer medicines at home.
218 Pharmacists showed most concern regarding pharmacokinetic effects. An example of this was their
219 unanimous appreciation of mixing medicines with food-stuffs (i.e. orange juice), and the potential
220 effects of altering pH on the drug. The nurse group also highlighted risks of altering drug stability
221 when mixing medicines with substrates prior to administration. The medical practitioners reported
222 more information on what parents actually do to the medicines.

223 *Non-sensory themes*

224 *Frequent issues experienced when treating paediatric patients, the supply of*
225 *medicines and liquid measuring devices*

226 “..the things I dread are when we have all these weird and wonderful specials” (Pharmacist 1 UHCW)

227 The problems with Specials and unlicensed medicines were discussed in all groups and extensively
228 amongst the pharmacists. Issues with omeprazole liquid Special were identified across the groups,
229 these included problems regarding: obtaining, costing (between £100 and £120), GP prescribing
230 (with reference to Primary Care Trust (PCT) guidance described first-hand by the GP in the medical
231 practitioners group, in relation to budget), storage and short expiries. An alternative omeprazole
232 formulation is Losec® MUPS (omeprazole) tablets. Problems with Losec® MUPS (omeprazole)
233 blocking feeding tubes were highlighted in all groups.

234 Problems with Specials medicines were a main focus of the pharmacist groups. Pharmacists
235 demonstrated their increased knowledge, awareness and enthusiasm regarding Specials medicines.
236 They discussed a variety of problems surrounding Specials which they frequently experienced first-
237 hand (e.g. unpredictable bioequivalence between different Specials medicines) compared to the
238 medical practitioners and nurses. The medical practitioners seemed to have the least understanding
239 and knowledge of the depth of issues with Specials and tended to identify Specials medicines and
240 issues with supply. The medical practitioner group suggested that some pharmacists may not be
241 aware that certain medicines can be ordered and query whether pharmacists remind patients about
242 the shortened expiries of Specials medicines and the need to frequently re-order. The nurses
243 expressed their concern towards extemporaneously dispensed products and the inconvenience of
244 frequent journeys to hospital pharmacy.

245 *Parental understanding of medicines*

246 Parental influence on medicines adherence and also limited parental understanding of medicines
247 was reported across all healthcare professional groups. The nurses emphasised the need for
248 parental education, whilst the BCH pharmacist group acknowledged the limited time available to
249 counsel patients effectively, resulting in their reliance upon nursing staff. Incorporating appropriate
250 information in to clinic appointments for parents, carers and children could improve the safety and
251 effectiveness of medicines use and also reduce medicines non-adherence.

252 'Pill-swallowing training' for groups of patients with specific chronic conditions was discussed by the
253 nurses and pharmacists. Mandatory 'Pill-swallowing training' for all children of a specific age was
254 reported to be implemented in Australia (no reference was provided with these reports).

255 The UHCW pharmacist group highlighted the plethora of social issues that prevail in the domiciliary
256 setting, implying that medicines adherence is not always prioritised in some social circumstances.

257 *Medicines adherence*

258 Pharmacists, medical practitioners and nurses reported that dosage form preference is influenced by
259 individual patient choice. The groups contended that parents can influence dosage form choice and
260 medicines adherence in paediatric patients. Reports of parents and carers influencing medicines
261 adherence in paediatric patients were frequently addressed in all groups. This included parents not
262 allowing young people empowerment and also parents not supporting medicines adherence.

263

264 The value of rationalising medicines in children who are prescribed multiple medicines
265 (polypharmacy) was proposed by a medical practitioner and BCH pharmacist. On the topic of
266 extemporaneous medicines, the pharmacists reported their unanimous negative attitude towards
267 preparation within community pharmacies and compared this to the rigorous approach adopted
268 within hospital pharmacies. The nurses discussed problems with short expiries of extemporaneous
269 preparations (sodium phosphate and sodium chloride solution), thus leading to inconveniences for
270 parents owing to frequent hospital visits.

271 *Adverse effects of medicines*

272 The medical practitioners and nurses identified key adverse effects of medicines with which they
273 were familiar.

274 Concerns regarding the safety of excipients were at the forefront of the BCH pharmacist session,
275 with specific reference to propylene glycol, alcohol, sweeteners and sugars.

276 *The supply of medicines and liquid measuring devices and medication errors*

277 Difficulty in freely obtaining oral syringes on the NHS was highlighted by all of the healthcare
278 professional populations. Nurse reports included comments on the reluctance of supply by
279 pharmacists - inferring that this is a financial problem, parents having to purchase oral syringes and
280 the paucity of oral syringe sizes available in the Drug Tariff. A medical practitioner addressed the
281 disallowance of prescribing oral syringes on FP10 prescriptions and reported lack of knowledge
282 regarding whether pharmacists are allowed to freely provide oral syringes or if it is out of their own
283 goodwill.

284 In addition, the pharmacists highlighted the risks of using inaccurate measuring devices (reports
285 included using a teaspoon).

286 The UHCW pharmacists perceived that the labelling of liquid medicines should be standardised, for
287 example, labelling all liquid medicines as the weight of drug in the same volume (i.e. Xmg in 1ml).
288 Both healthcare professionals and parents can become confused when different strengths are
289 printed on medicine labels and examples of this were provided by the UHCW pharmacists.

290 The risk of medication selection errors at GP practices was identified in the UHCW pharmacist focus
291 group.

292 *Problems with medicines at school*
293 Problems with medicines at school were reported across the groups. Unanimous reports suggested
294 that medicines should be prescribed to be administered outside of the school day (where this is
295 possible).

296 **Discussion**

297 Sensory characteristics: Taste, texture, size of solid dosage form, and volume were common themes
298 discussed in all of the focus groups. Problems with taste were reported most often. Oral flucloxacillin
299 was highlighted across all groups to be poorly accepted owing to palatability. One study similarly
300 reported that oral flucloxacillin is often considered unpalatable by children and suggested
301 conducting a taste-test with an individual child prior to prescribing flucloxacillin solution (20). Chloral
302 hydrate solution, prednisolone soluble tablets and Movicol® oral powder were all highlighted with
303 respect to taste in two of the focus groups. Similar findings were reported in other studies; oral
304 chloral hydrate (21), and taste of prednisolone oral solution superior to crushed tablets (22).

305

306 All healthcare professional groups reported texture as a barrier to medicines administration;
307 particularly amongst children with learning disabilities. Field and co-workers (2003) defined five
308 feeding problems (including one related to the texture of foodstuffs) and explored pre-disposing
309 factors to these problems. Over one quarter of children suffering from Down's syndrome, autism or
310 cerebral palsy refused to eat food textures that were considered to be developmentally appropriate
311 (23). Feeding problems (including those related to texture) should be considered carefully by
312 prescribers prior to making prescribing decisions.

313

314 The size of solid dosage forms was a common theme highlighted across the groups. Several studies
315 investigating children suffering from HIV support these findings and have reported the negative
316 attitudes of children regarding the size of antiretroviral tablets (24-30).

317

318 The nurses shared an in-depth knowledge on oral formulation-related barriers to medicines
319 administration that the medical practitioners and pharmacists did not discuss, highlighting the
320 importance of conducting focus groups with different healthcare professionals. This plethora of
321 knowledge mirrors the 'hands-on' experience that nurses have on administering medicines to
322 children. See table 1 for reports on the variety of formulation-related issues discussed across the
323 groups.

324

325 The pharmacists perceived that an improvement to Specials medicines would be ideal. Pharmacists
326 felt that providing Certificates of Analyses to assure the safety and stability of Specials medicines and
327 also licensing some medicines not commercially available in child appropriate formulations should
328 be considered in order to improve medicines for children. Improving Specials medicines was not
329 reported as an ideal medicine improvement by the nurses or medical practitioners, suggesting that
330 this problem is not such a concern for them. Supporting these findings, one study investigated the
331 opinions of GPs regarding off-label prescribing and found that less than 15% of GPs admitted to
332 specific concerns when prescribing off-label, including the risk of adverse effects and unevaluated
333 efficacy (31). Calpol® suspension was described positively across all groups; this is supported by
334 previous documentation stating that fruity, sweet formulations are preferred and in general citrus

335 and red berry flavours are favoured across Europe (32). Pharmaceutical companies should be fully
336 aware of medicines that are generally well-accepted by the paediatric population.

337

338 Study findings indicate that paediatric pharmacists' knowledge on risks of medicines manipulation
339 was better than that of the allied healthcare professionals in this study. This suggests that the
340 knowledge of paediatric pharmacists should be used to guide and educate healthcare professionals
341 when prescribing or administering medicines in paediatric patients. Communication is crucial and
342 each healthcare professional group should be utilised for the wealth of their knowledge, for example
343 it may be beneficial for medical practitioners and nurses to seek advice from hospital pharmacists on
344 drug-foodstuff incompatibilities. To support this, the knowledge and education of paediatric
345 pharmacists should be addressed to ensure that they have optimal understanding of key scientific
346 properties that may affect the dissolution and disintegration of a dosage form, properties including
347 the fat and dairy-protein content, pH and solubility of foodstuffs (12) Such factors, in addition to
348 food affecting gastric emptying rate, risk altering the bioavailability of a drug (33).

349

350 A plethora of medicines manipulation techniques were discussed in this study; similar practices have
351 been reported in previous studies (34,35). Findings of the focus groups indicate that the participating
352 healthcare professionals were unaware of the level of evidence supporting various *ad hoc*
353 manipulation techniques. Similar to the present study, one study observed that the majority of
354 nurses were unaware of potential drug stability and degradation issues when performing *ad hoc*
355 administration techniques and additionally some nurses were not conscious of a possible impact
356 upon clinical outcome (12). Further laboratory work is warranted to provide a robust scientific
357 evidence base to support safe and effective medicines manipulation; it should be recognised that
358 existing resources currently exist which provide guidance on medicines manipulation (36,37).

359

360 The risks of medicines interacting (through binding) with nutritional feeds and the potential effects
361 on drug absorption were discussed by the pharmacists and nurses. Examples provided were
362 phenobarbital, phenytoin and ciprofloxacin. Nurses declared their uncertainty regarding how and
363 when to administer the calcium binding drug ciprofloxacin, highlighting that advice is needed when
364 administering medicines and nutritional feeds to optimise therapy. More scientific evidence, based
365 on laboratory work investigating interactions between medicines and nutritional feeds (i.e.
366 identifying potential insoluble complex formation) should be used to direct and standardise
367 pharmaceutical advice in addition to sources that are already available, e.g. (38). It would be useful
368 to translate this scientific evidence in to appropriate sources for nurses and parents and carers.

369

370 The pharmacists had greater knowledge and understanding of Specials medicines compared to the
371 nurses and medical practitioners. Similarly, several studies have identified differences in the
372 knowledge on Specials, off-label and unlicensed medicines between allied healthcare professionals
373 (13,14,39). Further investigation is necessary to address the education and support that is needed to
374 improve knowledge of unlicensed medicines, Specials and off-label prescribing amongst healthcare
375 professionals. Educating doctors and allied healthcare professionals on the appropriate use of
376 Specials medicines at degree or equivalent level is fundamental to improving their understanding of
377 unlicensed medicines and optimising safe and cost-effective prescribing practices.

378

379 Improving time organisation to permit pharmacists to counsel patients effectively could help to
380 minimise problems that result from poor parental understanding as reported in the focus groups.
381 Pharmacists identified that staff shortages were a barrier to counselling patients. Government
382 funding bodies need to consider this when calculating financial budgets available to the NHS.
383 Several studies investigating solid dosage form training have found improvements in swallowing
384 abilities amongst children diagnosed with HIV (24,25). This may help to minimise difficulties with
385 tablet size and also support the use of novel formulations, e.g. mini-tabs (40,41) in paediatric
386 patients who would not generally be prescribed a tablet until they are older.

387

388 This study identified that family-related factors (including 'social circumstances') can influence
389 medicines adherence in children, this is supported by other studies (42-45). The impact of
390 polypharmacy on medicines adherence requires further investigation. The importance of medicines
391 adherence should be thoroughly explained to parents and children especially in circumstances
392 where an improvement of a chronic condition is not apparent. This may help to discourage parents,
393 carers and young people from discontinuing medicines without consulting healthcare professionals
394 and through this improve medicines adherence.

395

396 Study findings suggest that future work should investigate whether incorporating education for
397 parents, carers and young people within clinic sessions, on common and minor adverse effects of
398 medicines to support patients and manage their expectations of medicines has the potential to
399 improve adherence. In addition, concerns regarding the safety of excipients need to be addressed.
400 The draft guideline on pharmaceutical development of medicines for paediatric use (46) reinforced
401 the requirement for pharmaceutical companies to carefully select excipients when formulating
402 medicines for children. The final decision to include an excipient should be evaluated using a benefit
403 to risk ratio of the end pharmaceutical product (47). It should be recognised that some studies have
404 reviewed stability evidence and provide information regarding formulations and excipients (48,49).

405

406 Issues revealed with the supply of oral syringes on the NHS suggest that the Government should
407 address NHS funding in this area. Concern regarding the use of inaccurate measuring devices needs
408 to be addressed. Household teaspoons can vary between 2ml and 10ml and thus using a teaspoon
409 could result in a significant underdose or overdose (50). Pharmacists should be ensuring that the
410 correct dosing instrument is supplied to all patients and that counselling is provided to parents and
411 carers to assure accurate measurement of a dose.

412

413 Standardising the labelling of liquid medicines was reported as a potential method to minimise some
414 dosing errors. Studies are required to investigate if standardising the labelling of liquid medicines
415 could significantly improve patient safety. It is prudent that medicines labelling guidance provided to
416 pharmaceutical companies when applying for a Marketing Authorisation is addressed imminently.
417 Reports that medication selection errors are a problem at GP practices, suggest that safeguarding
418 measures and staff training need to be addressed.

419

420 Reports across the groups of some schools refusing to accept responsibility for medicines suggests
421 that medicines policies are not adopted uniformly across schools. Medicines adherence during
422 school hours may be sub-optimal if schools do not support medicines administration. Omitting doses
423 of medicines during the school day could have a significant impact on clinical outcome, therefore it is

424 critical that medicines administration is addressed correctly in schools. This is especially important
425 for paediatric patients suffering with chronic conditions and those requiring vital acute medicines.
426

427 *Study limitations*

428 Logistics created the greatest problem when recruiting participants. Time constraints resulting from
429 staff shortages restricted the availability of healthcare professionals and affected study recruitment.
430 A limitation of the focus group study was the low recruitment rate in the UHCW pharmacist group,
431 as this represented more a nominal group. It is acknowledged that group interaction is inevitably
432 minimised with low numbers of participants in a focus group. However, the information gathered
433 from the UHCW pharmacist focus group in collaboration with the BCH pharmacist group widened
434 the scope of pharmacist views in this study.

435

436 Although some healthcare professionals in the same setting were known to each other, the nature
437 of this focus group study was not perceived to be threatening; therefore it is unlikely that
438 participants would have contributed in a manner deemed to be more socially acceptable.

439

440 The study was conducted at two sites in the West Midlands, UK, therefore it cannot be generalised
441 and viewed as a nationwide perspective. Further investigation is required.

442

443 **Conclusion**

444 In summary, this study has identified a large number of issues perceived by healthcare professionals
445 to cause problems when administering oral medicines to children, however, these issues are not
446 always considered when using medicines in children. Taste was highlighted as the most significant
447 issue with specific examples, e.g. flucloxacillin solution, being reported across all groups.

448

449 Collaboration between doctors, nurses and pharmacists is essential to optimise patient care. Nurses
450 had the greatest knowledge of bedside issues, whilst pharmacists understood the consequences of
451 certain manipulations; wider sharing of this knowledge can help to ensure appropriate medicines are
452 prescribed to minimise issues with administration. Communication is crucial and each healthcare
453 professional group should be utilised for the wealth of their knowledge.

454

455 Findings of this study suggest that a paucity of scientific evidence is available to support the many *ad*
456 *hoc* manipulation techniques regularly used. Review of medicines manipulation data available in
457 literature confirmed that a robust scientific evidence base requires further development; this needs
458 to be addressed as it is evident that medical practitioners require more information when
459 prescribing medicines to ensure supply, clinical effectiveness and to maximise cost efficiency.

460

461 Addressing the education of healthcare professionals involved in prescribing, dispensing and
462 administering oral medicines to children and additionally counselling provided to parents, carers and
463 paediatric patients will be invaluable to improving the therapeutic treatment of paediatric patients.
464 Protocols detailing best practice guidance need to be developed. Further studies exploring the views
465 of healthcare professionals in different settings would complement this research.

466 **Conflicts of interest**

467 The authors declare that there are no conflicts of interest.

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473

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475 **References**

476 (1) Staples B, Bravender T. Drug compliance in adolescents: assessing and managing modifiable risk
477 factors. *Pediatric Drugs*. 2002;4(8): 503-513.

478 (2) Winnick S, Lucas DO, Hartman AL, Toll D. How do you improve compliance? *Pediatr*
479 2005;115(6):e718-24.

480 (3) Burkhart P, Dunbar-Jacob J. "Adherence research in the pediatric and adolescent populations: A
481 decade in review". In Hayman, L.;Mahon, M. & Turner, J. (Eds.) *Chronic illness in children: An*
482 *evidence-based approach*. 1st ed. New York: Springer 199-229;2002.

483 (4) Ernest TB, Elder DP, Martini LG, Roberts M, Ford JL. Developing paediatric medicines: identifying
484 the needs and recognizing the challenges. *J Pharm Pharmacol* 2007;59(8):1043-1055.

485 (5) Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A. et al. Survey of unlicensed and
486 off label drug use in paediatric wards in European countries. *BMJ* 2000;320(7227):79-82.

487 (6) Nunn, A. Making medicines that children can take. *Arch Dis Child* 2003;88(5):369-371.

488 (7) Skwierczynski C, Conroy S. How long does it take to administer oral medicines to children?
489 *Paediatr Perinat Drug Ther* 2008;8(4):145-149.

490 (8) Richey R, Donnell C, Shah U, Barker CE, Craig JV, Ford JL et al. An investigation of drug
491 manipulation for dose accuracy in paediatric practice: the modric study. *Arch Dis Child*
492 2011;96(4):e1-e1.

493 (9) Michaud P, Suris J and Viner R. The adolescent with a chronic condition. Part II: healthcare
494 provision. *Arch Dis Child* 2004;89(10):943-949.

495 (10) WHO. Adherence to long term therapies: Evidence for action. [online].
496 <http://whqlibdoc.who.int/publications/2003/9241545992.pdf> [Accessed 14/05/2010].

497 (11) Brackis-Cott E, Mellins CA, Abrams E, Reval T, Dolezal C. Pediatric HIV medication adherence:
498 the views of medical providers from two primary care programs. *J Pediatr Health Care*
499 2003;17(5):252-260.

500 (12) Akram G, Mullen AB. Paediatric nurses' knowledge and practice of mixing medication into
501 foodstuff. *IJPP* 2012;20(3):191-198.

502 (13) Mukattash T, Hawwa AF, Trew K, McElnay JC. Healthcare professional experiences and attitudes
503 on unlicensed/off-label paediatric prescribing and paediatric clinical trials. *Eur J Clin Pharmacol*
504 2011;67(5):449-461.

505 (14) Mukattash TL, Wazaify M, Khuri-Boulos N, Jarab A, Hawwa AF, McElnay JC. Perceptions and
506 attitudes of Jordanian paediatricians towards off-label paediatric prescribing. *IJCP* 2011;33(6):964-
507 973.

508 (15) NPSA. Information Sheets & Consent Forms. Guidance for Researchers and Reviewers. Version
509 3.5 May 2009. Available at: [http://www.nres.npsa.nhs.uk/applications/guidance/consent-guidance-](http://www.nres.npsa.nhs.uk/applications/guidance/consent-guidance-and-forms/?esctl1417026_entryid62=67013)
510 [and-forms/?esctl1417026_entryid62=67013](http://www.nres.npsa.nhs.uk/applications/guidance/consent-guidance-and-forms/?esctl1417026_entryid62=67013). Accessed 13/05/2010.

511 (16) Krueger RA, Casey MA. *Focus Groups: A practical guide for applied research*. 3rd ed. London:
512 Sage; 2000.

513 (17) Gale, N. K., Heath, G., Cameron, E., Rashid, S., & Redwood, S. Using the framework method for
514 the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol*
515 2013;13(1):117.

516 (18) BNF for Children. London: Pharmaceutical Press; (2011-2012).

517 (19) MHRA Medicines that do not need a licence (Exemptions from licensing): The manufacture and
518 supply of unlicensed relevant medicinal products for individual patients ('specials') [online].
519 <http://www.mhra.gov.uk/Howweregulate/Medicines/Doesmyproductneedallicence/Medicinesthatdonothonotneedallicence/index.htm> [Accessed 15/02/2012].

520

521 (20) Baguley D, Lim E, Bevan A, Pallet A, Faust SN. Prescribing for children - taste and palatability
522 affect adherence to antibiotics: a review. *Arch Dis Child* 2012;97(3):293-297.

523 (21) Chung T, Hoffer FA, Connor L, Zurakowski D, Burrows PE. The use of oral pentobarbital sodium
524 (Nembutal) versus oral chloral hydrate in infants undergoing CT and MR imaging—a pilot study.
525 *Pediatr Radiol* 2000;30(5):332-335.

- 526 (22) Lucas-Bouwman ME, Roorda RJ, Jansman FGA, Brand PLP. Crushed prednisolone tablets or oral
527 solution for acute asthma? Arch Dis Child 2001;84(4):347-348.
- 528 (23) Field D, Garland M, Williams K. Correlates of specific childhood feeding problems. J Paediatr
529 Child Health 2003;39(4):299-304.
- 530 (24) Czynewski D, Calles N, Runyan R, Lopez M. Teaching and maintaining pill swallowing in HIV-
531 infected children. AIDS READER-NEW YORK 2000;10(2):88-95.
- 532 (25) Garvie PA, Lensing S, Rai SN. Efficacy of a pill-swallowing training intervention to improve
533 antiretroviral medication adherence in pediatric patients with HIV/AIDS. Pediatr 2007;119(4):e893-9.
- 534 (26) Gibb DM, Goodall RL, Giacomet V, Mcgee L, Compagnucci A, Lyall H, et al. Adherence to
535 prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5
536 trial. Pediatr Infect Dis J 2003;22(1):56-62.
- 537 (27) Marhefka S, Farley J, Rodrigue J, Sandrik L, Sleasman J, Tepper V. Clinical assessment of
538 medication adherence among HIV-infected children: examination of the Treatment Interview
539 Protocol (TIP). AIDS Care 2004;16(3):323-337.
- 540 (28) Paranthaman K, Kumarasamy N, Bella D, Webster P. Factors influencing adherence to anti-
541 retroviral treatment in children with human immunodeficiency virus in South India—a qualitative
542 study. AIDS Care 2009;21(8):1025-1031.
- 543 (29) Reddington C, Cohen J, Baldillo A, Toye M, Smith D, Kneut C, et al. Adherence to medication
544 regimens among children with human immunodeficiency virus infection. Pediatr Infect Dis J
545 2000;19(12):1148-1153.
- 546 (30) Roberts KJ. Barriers to antiretroviral medication adherence in young HIV-infected children.
547 Youth Soc 2005;37(2):230-245.
- 548 (31) Ekins-Daukes S, Helms PJ, Taylor MW, McLay JS. Off-label prescribing to children: attitudes and
549 experience of general practitioners. Br J Clin Pharmacol 2005;60(2):145-149.
- 550 (32) EMEA Reflection paper: formulations of choice for the paediatric population
551 EMEA/CHMP/PEG/194810/2005 2006 [online].
552 [http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50000](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf)
553 [3782.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf) London [Accessed 01/10/2011].
- 554 (33) Bowles A, Keane J, Ernest T, Clapham D, Tuleu C. Specific aspects of gastro-intestinal transit in
555 children for drug delivery design. Int J Pharm 2010;395(1):37-43.
- 556 (34) Nguyen, T. M. U., Lau, E. T., Steadman, K. J., Cichero, J. A., Dingle, K., & Nissen, L.
557 Pharmacist, general practitioner, and nurse perceptions, experiences, and knowledge of
558 medication dosage form modification. Integr Pharm Res Prac 2014;3:1-9.
- 559 (35) Nissen, L. M., Haywood, A., & Steadman, K. J. Solid medication dosage form modification at the
560 bedside and in the pharmacy of Queensland hospitals. Journal of Pharmacy Practice and Research
561 2009;39(2):129-134.
- 562 (36) Burrige, N., & Deidun, D. Australian don't rush to crush handbook. Therapeutic options for
563 people unable to swallow solid oral medicines. The Society of Hospital Pharmacists of Australia,
564 Collingwood, Australia. 1st ed. Collingwood. 2011.
- 565 (37) Smyth, J. NEWT guidelines 2012 [online].
566 <http://www.newtguidelines.com/AdminOfTablets.html> Betsi Cadwaladr [Accessed 01/01/2013].
- 567 (38) Manrique-Torres, Y. J., Lee, D. J., Islam, F., Nissen, L. M., Cichero, J. A., Stokes, J. R., & Steadman,
568 K. J. Crushed tablets: does the administration of food vehicles and thickened fluids to aid medication
569 swallowing alter drug release?. J Pharm Pharm Sci 2014;17(2):207-219.
- 570 (39) Venables R, Stirling H, Marriott J. Poster 0073 Healthcare professionals' understanding of
571 children's medicines. IJPP 2012;20(Supplement 2):68-69.
- 572 (40) Spomer N, Klingmann V, Stoltenberg I, Lerch C, Meissner T, Breitzkreutz J. Acceptance of
573 uncoated mini-tablets in young children: results from a prospective exploratory cross-over study.
574 Arch Dis Child 2012;97(3):283-286.
- 575 (41) Thomson SA, Tuleu C, Wong IC, Keady S, Pitt KG, Sutcliffe AG. Minitablets: new modality to
576 deliver medicines to preschool-aged children. Pediatr 2009;123(2):e235-8.

577 (42) Gau SS, Shen H, Chou M, Tang C, Chiu Y, Gau C. Determinants of adherence to methylphenidate
578 and the impact of poor adherence on maternal and family measures. *J Child Adolesc*
579 *Psychopharmacol* 2006;16(3):286-297.
580 (43) Mackner LM, Crandall WV. Oral medication adherence in pediatric inflammatory bowel disease.
581 *Inflamm Bowel Dis* 2005;11(11):1006-1012.
582 (44) Mellins CA, Brackis-Cott E, Dolezal C, Abrams EJ. The role of psychosocial and family factors in
583 adherence to antiretroviral treatment in human immunodeficiency virus-infected children. *Pediatr*
584 *Infect Dis J* 2004;23(11):1035-1041.
585 (45) Shah CA. Adherence to high activity antiretroviral therapy (HAART) in pediatric patients infected
586 with HIV: issues and interventions. *Indian J Pediatr* 2007;74(1):55-60.
587 (46) EMA. 2013; Available at:
588 [http://nvkfb.nl/download/2013/Guideline%20on%20pharmaceutical%20development%20of%20me](http://nvkfb.nl/download/2013/Guideline%20on%20pharmaceutical%20development%20of%20medicines%20for%20paediatric%20use.pdf)
589 [dicines%20for%20paediatric%20use.pdf](http://nvkfb.nl/download/2013/Guideline%20on%20pharmaceutical%20development%20of%20medicines%20for%20paediatric%20use.pdf). Accessed 11/03, 2014.
590 (47) GRIP Webinar (online conference) GRIP Work Package 5 “Meet the Expert” on paediatric
591 formulations 2013.
592 (48) Glass, B. D., & Haywood, A. Stability considerations in liquid dosage forms extemporaneously
593 prepared from commercially available products. *J Pharm Pharmaceut Sci* ([www. cspsCanada.org](http://www.cspsCanada.org))
594 2015;9(3):398-426.
595 (49) Haywood, A., & Glass, B. D. Liquid dosage forms extemporaneously prepared from commercially
596 available products—considering new evidence on stability. *J Pharm Pharm Sci* 2013;16(3):441-455.
597 (50) McKenzie M. Administration of oral medications to infants and young children. *US Pharmacist*
598 1981;6:55-67.
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Table 1 Thematic coding spine detailing thematic headings and thematic sub-headings

Thematic headings	Thematic sub-headings 1	Thematic sub-headings 2
Sensory themes		
Oral formulation-related barriers to medicines administration	<ul style="list-style-type: none"> Taste-related problems <p>*Gastrografin® (sodium diatrizoate/meglumine diatrizoate) solution – Nurse 4. Oramorph® (morphine sulfate) solution – Nurse 1. Septrin® (trimethoprim and sulfamethoxazole) paediatric suspension – Pharmacist 2 UHCW. Rifampicin suspension – Pharmacist 1 UHCW. Kaletra® (lopinavir/ritonavir) solution – MP 7 describes burning sensation. Nitrofurantoin Special suspension – MP 5. Clarithromycin suspension – MP 2. Generic paracetamol suspension – Nurse 2.</p> <ul style="list-style-type: none"> Problems with texture <p>*Ciclosporin solution (pharmacist 1 UHCW described as oily). Lactulose solution (MP 1 described as oily). Topiramate sprinkle capsules (MP 1). Calcichew® (calcium carbonate) tablets (MP 2). Creon® (pancreatin) Micro gastro-resistant granules – inconvenience of transporting apple puree to mask texture (nurse 4).</p> <ul style="list-style-type: none"> Problems with colour and smell <p>*Rifampicin liquid – red colour described as “off-putting” (nurse 1). Klean-prep® (macrogol ‘3350’) liquid – “smell makes you wretch, it’s horrible” (nurse 4). Abidec® vitamin drops – bad smell and the colour stains bibs, yet tolerated (nurse 4). ‘Horrendous feeds’ and a smell that “pervades everything” (nurse 1).</p> <ul style="list-style-type: none"> Problems with size and swallowing <p>*Ethambutol tablets (pharmacist 2 described that often multiple small tablets are preferred). Slow sodium® (sodium chloride) tablets – “Like an old paracetamol tablet, they’re quite sticky to swallow down” (nurse 4). Temozolomide tablets – “I think they’re quite big drugs” (nurse 6). Antiretroviral tablets (all groups).</p> <ul style="list-style-type: none"> Problems with quantity and volume <p>*Chloral hydrate solution** described as having a “huge volume” (nurse 1 and pharmacist 1 UHCW). Movicol® (macrogol ‘3350’) oral powder*** (Pharmacists agree large volume). Soluble prednisolone tablets (nurse 3). Antiretroviral liquids – “liquid volumes are so high” (MP 7). Administering considerable volumes of medicines in addition to feeds in neonates, voiced by nurse 3.</p>	
Future medicines for children	<ul style="list-style-type: none"> Ideal improvements to medicines Well-accepted medicines 	
Problems related to medicines administration	<ul style="list-style-type: none"> Administration problems with specific medicines Interactions with foodstuffs and sub-optimal drug absorption Medicines manipulation 	(The knowledge of healthcare professionals regarding physicochemical effects of medicines manipulation, Evidence base for medicines manipulation)
Non-sensory themes		
Frequent issues experienced when treating paediatric patients	<ul style="list-style-type: none"> Specials medicines, unlicensed medicines and off-label administration Omeprazole formulations The knowledge and understanding of medical practitioners, pharmacists and parents regarding unlicensed medicine Extemporaneous dispensing 	(Omeprazole liquid, Losec® MUPS- licensed omeprazole formulation)
Parental understanding of medicines	<ul style="list-style-type: none"> Educating parents and children about medicines Social problems and language barriers 	
Medicines adherence	<ul style="list-style-type: none"> The relationship between age of child and dosage form preference Parental influence on dosage form choice and medicines adherence The relationship between age of child, disease status, diagnosis, miscellaneous variants and medicines adherence Polypharmacy 	
Adverse effects of medicines	<ul style="list-style-type: none"> Excipients 	

	<ul style="list-style-type: none"> • Adverse effects associated with specific medicines 	
The supply of medicines and liquid measuring devices	<ul style="list-style-type: none"> • Problems with the supply of oral syringes and the accuracy of measuring liquid medicines • 	
Medication errors in pharmacies and GP practices	<ul style="list-style-type: none"> • Standardising the labelling of liquid medicines • Medicine selection errors at GP practices 	
Problems with medicines at school	<ul style="list-style-type: none"> • Problems with medicines at school 	

*Problems with specific medicines or groups of medicines, as reported by the healthcare professionals indicated.

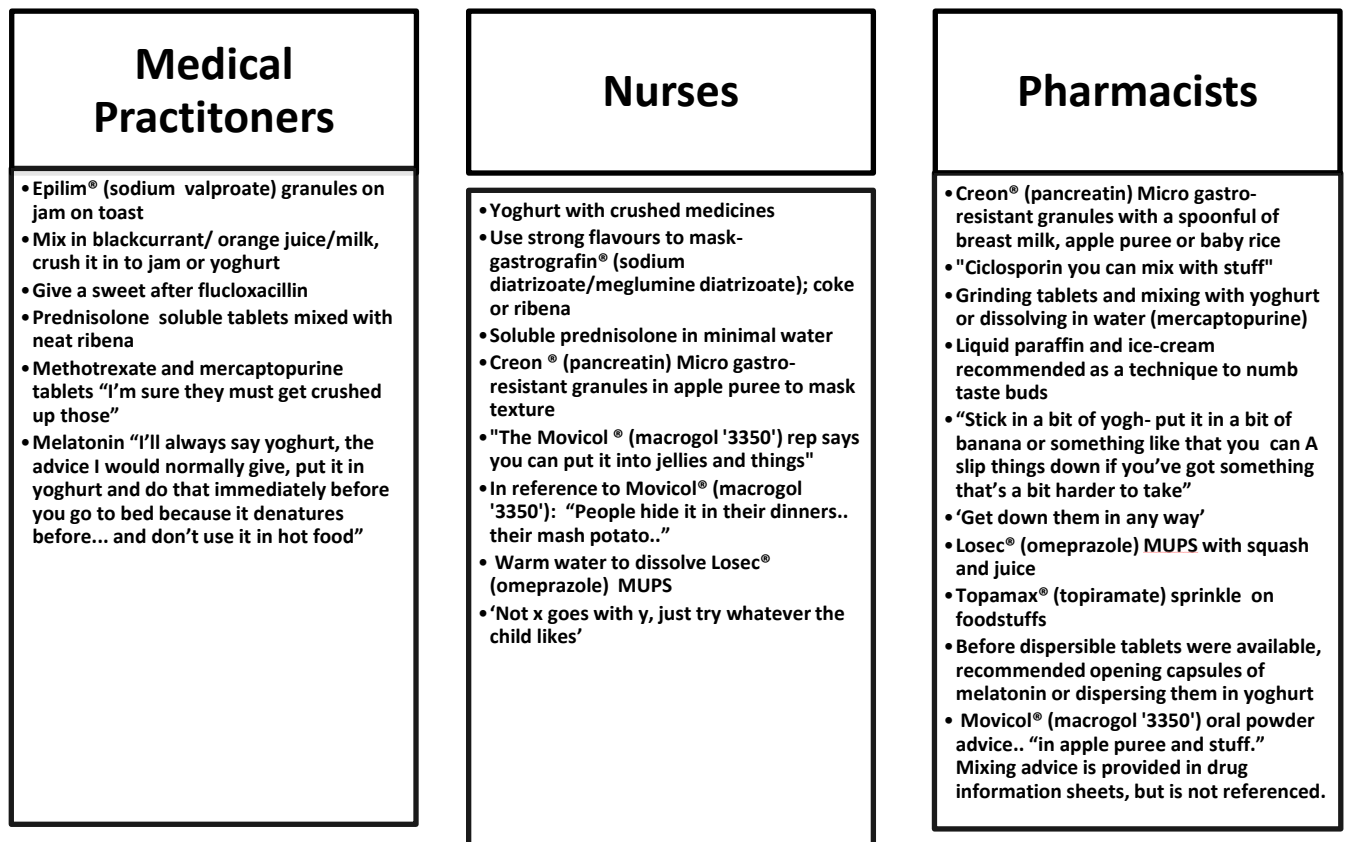
** Choral hydrate - dose for 1-12 year olds approximately 5-20mls 'well diluted with water' (18).

*** Movicol® (macrogol '3350') oral powder - each sachet added to 125mls of water (18).

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Figure 1: Examples of *ad hoc* administration techniques reported by the indicated healthcare professional groups.

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