ORIGINAL ARTICLE

A prospective questionnaire assessment of attitudes and experiences of off label prescribing among hospital based paediatricians

J S McLay, M Tanaka, S Ekins-Daukes, P J Helms

Arch Dis Child 2006;**91**:584–587. doi: 10.1136/adc.2005.081828

See end of article for authors' affiliations

Correspondence to:
Dr James S McLay,
Department of Medicine
and Therapeutics,
University of Aberdeen,
Polwarth Buildings,
Foresterhill, Aberdeen
AB25 2ZD, UK; j.mclay@
abdn.ac.uk

Accepted 16 January 2006
Published Online First
27 January 2006

Objective: To assess current attitudes of hospital based paediatricians to off label prescribing, and the performance of clinical trials in children.

Design: A prospective, questionnaire based study.

Setting: 257 hospital based consultants and specialist registrars in paediatric practice in Scotland during 2003–2004.

Results: A 25 item questionnaire was sent to 257 hospital based paediatricians and 151 (59%) were returned completed. Over 90% of responders were familiar with the concept of, and knowingly prescribed, off label drugs; 55% of responders stated that such prescribing disadvantaged children, and 47% expressed concerns about the efficacy of off label medicines. Although 70% of responders expressed concerns about safety, only 17% had observed an adverse event, and 47% a treatment failure, while 69% did not obtain informed consent or tell parents they were prescribing off label, and 67% did not inform the family's general practitioner. Many respondents did not believe it was necessary to carry out clinical trials in children for new (46%) or generic (64%) medicines. However, 52% of respondents stated that they would be willing to undertake clinical studies and recruit their own patients (61%) or children (73%) to take part in such studies.

Conclusions: Among Scottish paediatricians there is concern about off label prescribing, although the majority do not consider it necessary to inform parents or GP colleagues. The need for clinical trials in children was recognised but there was a less than wholehearted acceptance of the need for such studies, at variance with the current drive to promote clinical trials in this age group.

Paediatric drug treatment relies on the use of both unlicensed (medicines which have not been licensed for human use) and off label drugs (licensed drugs prescribed without their marketing authorisation). Off label prescribing, which is more common than unlicensed drug use, often occurs because of a lack of appropriate clinical trials data and licensed alternatives. At least one third of children admitted to hospital and 90% of children in neonatal units are prescribed off label medicines,^{1–4} which recent evidence suggests may be associated with an increased level of adverse drug reactions, and possible treatment failure.^{5–8} Although in the United Kingdom, prescribing a medicine off label is not illegal,⁹ there is concern over the extent and possible effects of such prescribing in this vulnerable population. In the USA these problems have been tackled by the introduction of the 1997 FDA Modernisation Act (FDAMA), the 1998 “Pediatric Rule”, the 2002 Best Pharmaceuticals for Children Act (BPCA), and the 2003 Pediatric Research Equity Act (PREA). These Acts not only ensure appropriate reward for pharmaceutical companies willing to undertake paediatric studies, but also that the appropriate legislative framework and funding is available to ensure the assessment of drugs for paediatric use.^{10–11} In the European Union there has been a slower paced development of guidelines to encourage the pharmaceutical industry to perform appropriate clinical studies in children but as yet no legislative framework,^{12–13} although an additional period of market exclusivity for companies that undertake appropriate studies is proposed.¹⁴

As we have previously investigated the attitudes and experiences of general practitioners to off label prescribing in the community, where it is frequently initiated by a hospital

based paediatrician, we sought to assess the attitudes and experiences of the latter to off label prescribing and to paediatric clinical trials.

METHODS

A 25 item questionnaire comprising 24 questions with a combination of tick box responses or 5–6 point scale questions, three of which also allowed written comment, and one free text question were sent to all 259 hospital based consultant paediatricians and paediatric specialist registrars in Scotland during 2003–2004 (appendix A). In addition to the acquisition of baseline demographic data, questions focused on knowledge of and reasons for off label prescribing, actual and potential concerns about off label medicines, communication with parents, guardians, and GPs, and attitudes towards the need for and the performance of clinical studies in children. The joint Grampian ethics committee approved the study.

RESULTS

The responses to the questionnaire are detailed in table 1.

Demographics

Two hundred and fifty seven questionnaires were distributed to 188 consultant paediatricians and 69 specialist paediatric registrars in Scotland; 151 (59%) were returned completed and 23 uncompleted. Fifty nine per cent (59.6%) of consultants, and 56.5% of trainees replied. Of the 112 consultants who returned completed questionnaires, 61%

Abbreviations: ADR, adverse drug reaction; SPR, specialist registrar

Table 1 Respondents' replies to the questionnaire

Question	Yes (n)	No (n)	No answer/don't know (n)
Familiarity with OLM prescribing	92.8% (140)	4.6% (7)	2.6% (4)
Knowingly prescribe OLM	90% (136)	7.3% (11)	2.6% (4)
Do OLM disadvantage children?	55% (83)	37.7% (57)	7.3% (11)
Concerns about the efficacy of OLM	47% (71)	49% (74)	4% (6)
Concerns about the safety of OLM	70% (106)	26% (39)	4% (6)
Have you experienced ADRs due to OLM?	17.2% (26)	78.8% (119)	4% (6)
Have you experienced treatment failure due to OLM?	47% (71)	43% (65)	10% (15)
Do you request consent for OLM usage?	25.9% (39)	68.9% (104)	5.3% (8)
Do you inform the GP?	33.1 (50)	58.9% (89)	7.9% (12)
Do you inform the parents?	32.4% (49)	60.3% (91)	7.3% (11)
Are specific paediatric formulations required?	33.1% (50)	58.9% (89)	8% (12)
Should all new medicines be trialled in children?	54% (81)	36.7% (56)	9.3% (14)
Should incentives to pharmaceutical companies be available?	78.1% (118)	17.9% (27)	4% (6)
Should off-patent medicines be trialled?	35.8% (54)	62.9% (95)	1.3% (2)
Would you like to be involved with clinical trials?	53% (80)	25.8% (39)	21.2% (32)
Would you recruit for clinical trials?	60.9% (92)	20.5% (31)	18.6% (28)
Would you allow your children to take part in clinical trials?	72.8% (110)	19.2% (29)	8% (12)
Do paediatric trials involve ethical issues?	94.7% (143)	2% (3)	3.3% (5)

Only questions with a yes, no, or don't know answer are listed.
ADR, adverse drug reaction; OLM, off label medicines.

(68) had been in post for more than 10 years. The specialties reported by all respondents included general paediatrics (28%, 42), neonatology (16.6%, 25), community (16.6%, 25), mixed (21.9%, 33), intensive care (1.3%, 2), and others (15.9%, 24).

Perceived reasons for off label prescribing

The majority of respondents admitted to being familiar with the concept of off label prescribing, and to prescribing off label drugs to children, citing younger age, higher dose, or for a different indication than that licensed as the most common reasons. Sixty six per cent (100) respondents also gave medical reasons for off label prescribing, which included neurological conditions such as epilepsy, sleep disorders, or migraine (27%), gastrointestinal disease (15%), asthma/cystic fibrosis (12%), and infection (7%). Only 26% of respondents cited lack of a suitable licensed alternative as the reason for off label prescribing.

Concerns about off label prescribing

Just over half of all respondents believed that the use of off label medicines disadvantaged children, citing lack of efficacy data (63.8%), lack of safety data including risk of long term side effects (48.3%), and lack of appropriate pharmacokinetic/dosage data (13.8%). Only 10% cited possible parental, GP, or legal issues as reasons for concern. Although safety and efficacy issues were of concern to the large majority of paediatricians, among neonatologists the overall levels of concern appeared to be low, with 64% (15) responding that they had no concerns about efficacy, and 48% (12) about the safety of off label medicines. Furthermore no neonatologist admitted to having observed any adverse drug reactions (ADRs), and only 24% to having observed treatment failure because of the use of off label medicines. Overall, however, approximately one fifth of respondents had observed ADRs, and almost half had observed treatment failure with off label medicine usage.

Parental and GP involvement

The majority of paediatricians did not seek informed consent, or inform the parents or guardian that they were prescribing an off label medicine. Only one third of respondents admitted

to informing a child's GP that they were prescribing an off label medicine.

Paediatric clinical trials

When asked about the need for paediatric clinical trials, just over half the respondents believed that all new medicines should undergo clinical trials in children, and a third believed that generic medicines should undergo clinical trials in children. However, over three quarters of respondents agreed that incentives should be offered to the pharmaceutical industry to stimulate drug research in children. Just over half of all respondents would be willing to take part in, and recruit their own patients for, appropriate clinical studies. The majority, however, stated that they would allow their own children to take part in such studies.

DISCUSSION

The majority of hospital paediatricians were familiar with the concept of off label prescribing and knowingly prescribed medicines in this manner, citing as the most common reasons prescribing for a younger age, at a higher dose, or for a different indication than recommended—findings consistent with the results of previous studies of off label prescribing in the United Kingdom.^{2-4 16}

Although only about half the respondents believed that the use of off label medicines disadvantaged their patients, a larger number expressed concerns about safety and efficacy issues, reporting high levels of treatment failure and ADRs. These responses clearly highlight current deficiencies in paediatric practice and the need for more extensive efficacy, outcome, and safety data. Neonatologists were the least concerned, which is surprising considering their high usage of off label or unlicensed drugs.^{3 17 18} While these responses could reflect a greater experience and confidence with off label prescribing, they may also reflect the difficulties in identifying ADRs in sick neonates.

Unexpectedly only a third of respondents thought that specific paediatric formulations were required, highlighting an unawareness of the current situation where pharmacists overcome the lack of paediatric formulations by supplying extemporaneous preparations, imported medicines, or unlicensed special products.

What is already known on this topic:

- Paediatric off label prescribing is common in both primary and secondary care
- Off label prescribing is reportedly associated with increased levels of adverse drug reactions
- There is a European Union initiative to ensure appropriate assessment of all paediatric medicines

In contrast to veterinary practice, where informed consent is strongly advised,¹⁹ only about a third of paediatricians sought parental consent, or informed parents or the child's GP that an off label medicine was being prescribed. These issues have been partially addressed by a recent policy statement by the Royal College of Paediatrics and Child Health, which states that it is not necessary to take additional steps beyond those normally taken in obtaining consent, although recognising the need for communication with parents and other professionals when the continuing care of a child prescribed an unlicensed or off label drug is handed over to others.²⁰

Despite concerns over the safety and efficacy of off label medicines, only half the respondents believed that medicines should undergo trials in children, citing as the reasons for this less than enthusiastic attitude "that there was already a significant level of empirical knowledge available", and possible ethical issues regarding informed consent. These attitudes are at variance with those expressed by Scottish GPs,²¹ who, while less concerned about the safety issues (15% v 70% of hospital paediatricians), were more convinced of the need for appropriate clinical trials (79% v 54%). The ethical concerns surrounding informed consent also need to be reconciled with the current unsatisfactory situation in which the use of off label drug treatment is associated with levels of treatment failure and ADRs that would be unacceptable in adults.²⁻⁸ Consideration of this ambivalent attitude may become an important issue when legislative actions to promote clinical trials in children are taken, although the establishment of the UK Medicines for Children Research Network should help to allay some of the concerns and apparent lack of enthusiasm.

Authors' affiliations

J S McLay, M Tanaka, S Ekins-Daukes, Department of Medicine and Therapeutics, University of Aberdeen, Polwarth Buildings, Foresterhill, Aberdeen, UK

P J Helms, Department of Child Health, University of Aberdeen, Polwarth Buildings

Competing interests: none declared

REFERENCES

- 1 Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. *BMJ* 2000;**320**:79-82.
- 2 Turner S, Longworth A, Nunn A, et al. Unlicensed and off label drug use in paediatric wards: prospective study. *BMJ* 1998;**316**:343-5.
- 3 Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. *Arch Dis Child Fetal Neonatal Ed* 1999;**80**:F142-4.
- 4 Conroy S. Developments in relation to unlicensed and off label drug use. *Paediatr Perinat Drug Ther* 1998;**2**:23-6.
- 5 Choonara I, Conroy S. Unlicensed and off-label drug use in children: implications for safety. *Drug Safety* 2002;**25**:1-5.
- 6 Turner S, Nunn AJ, Fielding K, et al. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr* 1999;**88**:965-8.
- 7 Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. *Br J Clin Pharmacol* 2002;**54**:665-70.

What this study adds:

- The majority of paediatricians have concerns about the safety and efficacy of off label medicines
- Paediatricians express the view that off label prescribing is associated with both adverse drug reactions and treatment failure in their patients
- A significant number of paediatricians expressed both concerns and less than wholehearted support towards the current EU drive to extend efficacy and safety data by promoting paediatric clinical trials

- 8 Impicciatore P, Choonara I, Clarkson A, et al. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* 2001;**52**:77-83.
- 9 Bendall C. The prescription and supply of drugs in children from a legal viewpoint. *Paediatr Perinat Drug Ther* 1999;**3**:49-54.
- 10 Spielberg S. Paediatric therapeutics in the USA and internationally: an unparalleled opportunity. *Paediatr Perinat Drug Ther* 2000;**4**:71-4.
- 11 Lamprill J. Paediatric clinical trials: A wake-up call for pharmaceutical companies in Europe. *Monitor*, Summer, 2004.
- 12 Committee for Proprietary Medicines (CPMP). Clinical investigation of medicinal products in children, 17-03-97. Report CPMP/EWP/462/95. The European Agency for the Evaluation of Medicinal Products. London: Human Medicines Evaluation Unit).
- 13 Committee for Proprietary Medicines (CPMP). Clinical investigation of medicinal products in the paediatric population. CPMP/ICH 2711/99. The European Agency for the Evaluation of Medicinal Products. London, Human Medicines Evaluation Unit (<http://www.emea.eu.int/pdfs/human/ich/271199EN.pdf>).
- 14 European Commission. Better medicines for children. Unit F2-Paediatric Initiative. Brussels: The European Commission, DG Enterprise, 2002.
- 15 Choonara I, Conroy S. Unlicensed and off-label drug use in children. Implications for safety. *Drug Safety* 2002;**25**:1-5.
- 16 Ekins-Daukes S, Simpson CR, Helms PJ, et al. Off label prescribing to children in primary care. Retrospective observational study. *Eur J Clin Pharmacol* 2004;**60**:349-53.
- 17 Gill AM, Leach HJ, Hughes J, et al. Adverse drug reactions in a paediatric intensive care unit. *Acta Paediatr* 1995;**84**:438-41.
- 18 Conroy S, McIntyre J. The use of unlicensed and off label medicines in the neonate. *Semin Fetal Neonat Med* 2005;**10**:115-22.
- 19 Bartle DG, Finlay FO, Guillon S. Off label prescribing in children. *BMJ* 2002;**325**:338.
- 20 Royal College of Paediatrics and Child Health. The use of unlicensed medicines or licensed medicines for unlicensed applications in paediatric practice. Policy statement produced by the joint RCPCH/NPPG Standing Committee on Medicines (http://www.rcpch.ac.uk/publications/formulary_medicines/Unlicensed_Medicines.pdf).
- 21 Ekins-Daukes S, Helms PJ, Taylor MW, et al. Off label prescribing to children: attitudes and experiences of general practitioners. *Br J Clin Pharmacol* 2005;**60**:145-9.

APPENDIX

QUESTIONNAIRE: "OFF LABEL" MEDICINES IN CHILDREN

1. Are you a consultant or SPR in paediatrics?
Consultant ☐ SPR ☐
2. How long have you been working as a paediatrician?
0-4 years ☐ 5-10 years ☐ more than 10 years ☐
3. What is your current main speciality?
Neonatology ☐ Community ☐ Intensive Care ☐ General ☐ Other ☐
4. Which age groups do you see the most?
Please score 1-5, with 5 the most frequent and 1 the least.
0-11 months ☐ 1-2 years ☐ 3-6 years ☐
7-11 years ☐ 12-16 years ☐
5. How familiar are you with the concept of 'off-label' prescribing of medicines?
Very familiar ☐ Reasonably familiar ☐ Unfamiliar ☐
6. Do you knowingly prescribe medicines off-label?
Yes ☐ No ☐
7. Please indicate which of the following is the most important and which is the least important cause for

off-label prescribing. Please score 1–6, with 6 the most important and 1 the least.

- Use of lower than recommended dose ☐
- Use of higher than recommended dose ☐
- Use at a younger age than recommended ☐
- Use via a different route of administration ☐
- Use of a different formulation ☐
- Use of a different indication ☐

8. Do you believe that off-label prescribing may disadvantage children?

Yes ☐ No ☐

If **yes**, please give reasons.

9. Do you have concerns about the efficacy of off-label medicines?

Yes ☐ No ☐

10. Do you have concerns about the safety of off-label medicines?

Yes ☐ No ☐

11. Have any of your patients, to your knowledge, ever experienced an adverse drug reaction following the use of an off-label medicine?

Yes ☐ No ☐

12. Have you ever experienced treatment failure due to the use of an off-label medicine?

Yes ☐ No ☐

13. What are your most common medical reasons for prescribing off-label medicines? (e.g., pharyngitis/ tonsillitis, ear ache, parental pressure)

14. Do you request informed consent from a parent or guardian before prescribing an off-label medicine?

Yes ☐ No ☐

15. Do you inform the GP that you have recommended an off-label medicine when you discharge a child from hospital or clinic?

Yes ☐ No ☐

16. Do you routinely inform parents that you are prescribing an off-label medicine for their child?

Yes ☐ No ☐

17. What sources of prescribing information do you use?

British National Formulary (BNF)

Medicines for Children (by Royal College of Paediatrics and Child Health)

Colleagues' experience

All of the above

Others

16. Is it important to develop more paediatric formulations?

Yes ☐ No ☐ Don't know ☐

17. Should all new medicines be trialled in children prior to use?

Yes ☐ No ☐ Don't know ☐

18. Should the UK government provide an incentive to stimulate pharmaceutical companies to perform clinical trials in children?

Yes ☐ No ☐ Don't know ☐

19. Should all **current** medicines which have not been studied in children undergo trialling in a paediatric population?

Yes ☐ No ☐ Don't know ☐

If **yes**, please give reasons.

If **no**, do you believe that medicines in common paediatric use could continue to be used safely without detailed clinical trials? Please give reasons and the class of medicines.

20. Would you like to be actively involved in clinical trials?

Yes ☐ No ☐ No opinion ☐

21. Would you like to recruit subjects for clinical trials from your patients?

Yes ☐ No ☐ No opinion ☐

22. Would you allow your own child to participate in a clinical trial?

Yes ☐ No ☐ No opinion ☐

23. Do you believe that clinical trials in children involve ethical issues?

Yes ☐ No ☐ No opinion ☐

Please give reasons.

THANK YOU VERY MUCH FOR COMPLETING THIS QUESTIONNAIRE

If you would like to be identified and receive a copy of the results, please write your name and address here:

Name:

Address: