

Awareness, knowledge and views of off-label prescribing in children: a systematic review

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AIM

The aim of this review was to provide an updated overview of awareness, knowledge and views of off-label prescribing in children.

METHOD

A literature search using electronic databases including PubMed, Medline, Scopus, Science Direct, Springer Link, Proquest, Ebsco Host and Google Scholar was conducted. Additional articles were identified by reviewing the bibliography of retrieved articles. The articles were searched with any of the following medical subject headings (MeSH) terms in the title: attitude, awareness, knowledge, experience, view, off-label, pediatric, paediatric and children. The inclusion criteria were full text articles published in English between January 2004 and February 2015 and reported outcome related to awareness, knowledge and views regarding off-label prescribing in children. Editorials, reviews, notes, conference proceedings, letters and studies reporting prevalence of off-label prescribing were excluded. The articles were scrutinized using thematic analysis.

RESULTS

Eleven studies conducted among doctors, community pharmacists, paediatric nurses, parents and children met the inclusion criteria. Nine themes were developed through document analysis which included main domains such as knowledge, awareness and views on off-label drug use in children, choice of information sources, reasons and suggestions to reduce off-label prescribing, concern regarding obtaining consent and participation in clinical trials.

CONCLUSION

The studies reviewed reported that the majority of doctors and community pharmacists were familiar with the term off-label prescribing but knowledge among parents was low. Awareness on off-label prescribing in children remains low among all study participants. There is a mismatch between views on off-label prescribing in children of study participants and the finding of previous studies.

Introduction

Prescribing in paediatric patients poses various challenges such as inadequate evidence due to limited studies done among the paediatric population, variation in drug disposition and off-label prescribing [1]. Off-label prescribing is defined as 'drugs prescribed and used outside their licensed indications with respect to dosage, age, indication or route' [2]. In general, off-label prescription rates ranged from 10.5–80%, and higher rates were found in younger vs. older paediatric patients and in the hospital vs. community settings [2–6]. The most common category of off-label prescribing in children was dosage [2, 4, 5].

Legislations, protocols, procedures, government circulars and local guidelines are all strategies implemented to help healthcare providers play their role in making sure off-label prescribing provides its intended benefit with minimum negative impact. But awareness, knowledge, views as well as attitude are crucial factors which will ensure actualization of these strategies. It is unclear to what extent these factors have been studied and no systematic review of awareness, knowledge and views of off-label prescribing in children is currently available. Therefore we undertook this systematic review to provide an updated overview of the awareness, knowledge and views of off-label prescribing in children.

The aim of this review is to provide an updated overview of the awareness, knowledge and views of off-label prescribing in children.

Method

Literature search

PubMed, Medline, Scopus, Science Direct, Springer Link, Proquest, Ebsco Host and Google Scholar were searched using text words and medical subject headings (MeSH) including attitude, awareness, experience, view, knowledge, off-label, paediatric and children. Additional articles were identified by reviewing the bibliography of the retrieved articles.

Inclusion and exclusion criteria

The inclusion criteria were full text articles published between January 2004 and February 2015, in English and reported outcome data related to awareness, knowledge and views of study participants regarding off-label prescribing in children. Editorials, reviews, notes, conference proceedings and letters as well as studies reporting the prevalence of off-label prescribing were excluded.

Article selection and review

The abstract of the articles was studied to determine inclusion of the article into this review if the title did not provide sufficient information to determine eligibility. The method used to select study articles for inclusion is summarized by adapting the PRISMA Group flow for study selection [7] (Figure 1). The following information was extracted from eligible studies: (i) identification of study, (ii) study details (study design, setting, study period, method), (iii) details of study participants, (iv) outcome measures, (v) results and (vi) limitations, strengths and recommendation discussed by the authors.

Quality assessment

Quality assessment of the eligible studies was evaluated independently by two review authors using a quality checklist for survey questionnaire [8] and a quality checklist for qualitative studies [9]. Disagreements between the reviewers were resolved by discussion.

Data analysis

Statistical pooling of data was not conducted due to the variations of studies in designs, participants and outcome measures. Rather, results of the included studies were scrutinized using thematic analysis [10] by

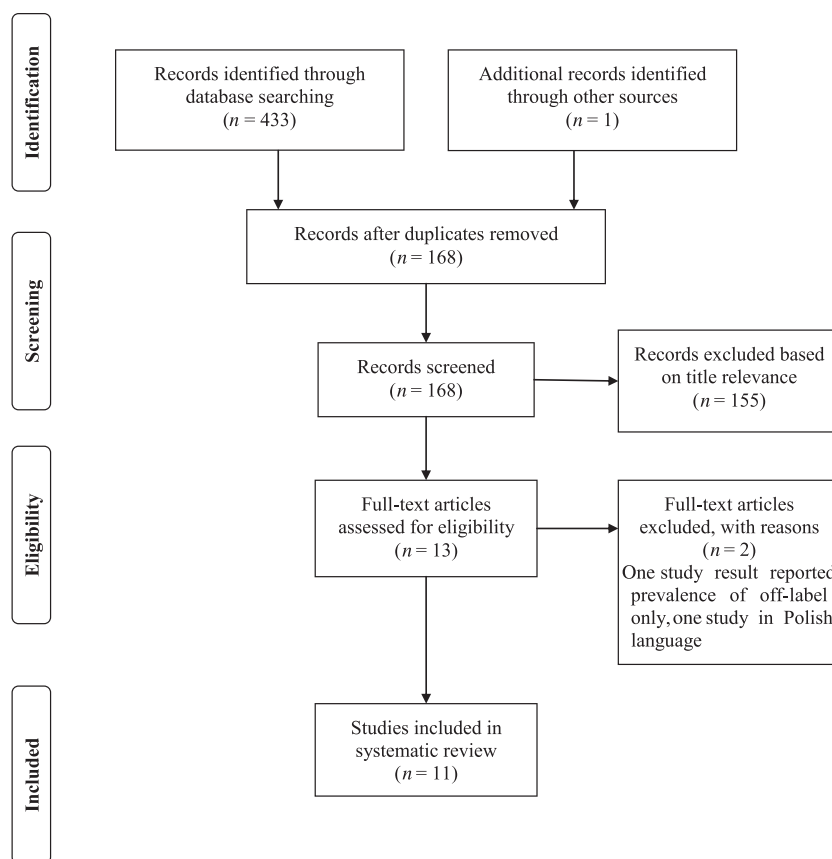


Figure 1

Quorum flowchart for study selection process

thorough reading and rereading in order to identify themes and groupings of similar themes (where appropriate) as they 'emerged' from the article [11]. The final process of refinement and modification of the themes was conducted by discussion with two other reviewers.

Results

Overview of the included studies

Eleven studies met the inclusion criteria. Ten studies used quantitative methods while one study utilized a qualitative method. The individual studies included in this review are presented in Table 1. The majority of eligible studies were found to be of good quality (Tables 2 and 3). Through the process of data analysis, nine themes were developed and are outlined in the following section.

Parents' knowledge and views on safe and labelled drug use in children

Three studies explored knowledge and views of parents on safe and labelled drug use in children [12–14]. In all three studies, parents without children were asked to assume that they had a child of their own. Results were also analyzed according to parents who had healthy children and those with ill children at the time the studies were conducted. Prior to knowing about off-label drug use, most parents thought that all medicines prescribed to children in both the hospital and primary care setting had undergone a similar testing and licensing process as in the case of medicines for adults [12, 14]. In a study conducted in India, 89.5% of parents felt that drugs prescribed to their children were either safe or extremely safe and parents with healthy children felt that drugs prescribed in the hospital were safe as compared with those prescribed by a family physician (89.4% vs. 81.3%, $P < 0.05$) [14]. The views of parents regarding safety of drug use in children dropped drastically after they knew about the concept of off-label prescribing [12, 14].

Knowledge on off-label drug use in children

Doctors Six studies [15–20] reported data on familiarity with the term 'off-label prescribing' among doctors, with the majority being familiar (69.2 to 92.8%) [15–19]. However, one study conducted in Italy [20] reported that 74% of paediatricians declared not to have a good knowledge about this practice. Specialist care doctors were more familiar with the term 'off-label prescribing' compared with their primary care counterparts [15, 17, 18]. Consultant paediatricians were found to be most familiar with the term 'off-label prescribing' (83.3%, $P < 0.05$) when compared with other healthcare professionals [16] and neonatologists were the most familiar among hospital-based paediatricians [17]. Most general practitioners (GPs) were unaware that off-label prescribing

was commonplace in general practice [19]. A study conducted in Jordan [17] reported more familiarity among hospital-based paediatricians trained in the United Kingdom compared with those trained locally or in other countries (USA and other European countries). Over half of the respondents in two studies [16, 17] reported that doctors gained their familiarity and knowledge regarding off-label prescribing through professional experience and post-graduate studies.

Pharmacists Two studies explored familiarity of community pharmacists with the term off-label prescribing among children [16, 21]. One study reported that 73% of community pharmacists admitted to being familiar with the concept of off-label prescribing [21]. However, a separate analysis of the latter study indicated that community pharmacists were more familiar with the term unlicensed medicines (93%) [16]. Familiarity with off-label prescribing was reported to be gained through dispensing experience (73%) [21] and undergraduate studies (50%) [16].

Parents Three studies conducted among parents identified that knowledge of parents regarding off-label drug use in children was relatively low (14 to 35%) [12–14]. There was no statistical significant difference observed amongst the different socioeconomic classes, parents and non-parents or between parents of sick or healthy children with regards to knowledge about off-label drug use [12–14]. A large proportion of parents also thought that off-label drug use was illegal [14] and associated with increased occurrence of side effects [12].

Children One study explored children's knowledge of off-label drug use [22]. This study combined the term 'off-label' and 'unlicensed' as 'unlicensed medicine use' since the distinction between these two terms were not discussed in detail with children. The children were able to link licensing to medicine safety and to permission for the medicine to be prescribed [22].

Awareness and views on off-label drug use in children

In this review, awareness is regarded as consciousness towards off-label prescribing i.e. knowingly or unknowingly prescribing or dispensing off-label medicines and views included inputs by study participants regarding categories of off-label prescribing, common age group involved and disease state where medicine was commonly prescribed off-label.

Doctors Six studies conducted among doctors reported that the percentage of prescriptions knowingly written in an off-label manner ranged between 25 to 90% [15–20]. All studies reported that most doctors prescribed off-label medicines unknowingly [15–20]. A lower percentage of

Table 1

An overview of the studies

Title (Author, year, reference)	Country	Study aim	Study design (duration)	Method	Target group	Survey instrument/tool characteristics	Outcome domains	Response rate (%)	Results
Awareness about parents and views of off-label drug use in children (Bang et al., 2014) [14]	India	To explore awareness among parents regarding both off-label drug use in children To explore willingness to allow their child to participate in clinical research	Cross-sectional study (1 year)	Face-to-face interview using structured questionnaire	Parents (n = 400)	Validated, structured questionnaire	Parental views on safety and labelled use of drugs in children	98.8 (400/405)	Participants felt that drugs used in children in hospital (89.5%) and community setting (80.3%) were either safe or extremely safe 30% parents were aware of off-label drug use in children 93% wanted to be informed whenever drug prescribed in off-label manner 73% felt the off-label drug use is illegal and 57% would ask for a change to labelled drug Participants not keen to allow their healthy children to participate in clinical trials
Results from the 2012-2013 paediatric national survey on off-label drug use in children in Spain (OL-PED study) (Pérez et al., 2014) [15]	Spain	To estimate the current state of knowledge on off-label use of drugs among Spanish paediatricians To assess the need to adopt measures to improve current practice To estimate how well informed they are about legal liabilities arising from off-label use of medications and to ascertain the sources paediatricians use to obtain information on drugs	Multicentre, cross-sectional study (8 months)	Online questionnaire	Paediatricians (n = 673)	Comprised of 10 questions Distributed via email	Knowledge and views on off-label prescribing Informing parents/guardians and documentation View on factors of support from the point of view of medical liability Sources of information used to obtain information on drugs	7.5 (673/9027)	75.1% of participants knew the meaning of off-label use 47% knew the importance of noting the off-label use in medical records. However only 22% wrote it in the medical records
A questionnaire-based study in Calabria on the knowledge of off-label drugs in paediatrics (Saullo et al., 2013) [20]	Italy	To evaluate the knowledge of off-label drugs in paediatricians of Calabria region in Italy	2-phase cross-sectional study (8 months)	Online anonymous questionnaire	Paediatricians (n = 85)	Comprised of 10 questions; all question had tick box answers	Drugs and their off-label use General guidelines on risk and limitation of off-label drugs in clinical practice	47.3 (85/180)	40% used off-label drugs 'sometimes' 74% did not have good knowledge about this practice

(Continues)

Table 1
(Continued)

Title (Author, year, reference)	Country	Study aim	Study design (duration)	Method	Target group	Survey instrument/tool characteristics	Outcome domains	Response rate (%)	Results
Children's view on unlicensed/off-label paediatric prescribing and paediatric clinical trials (Mukattash et al., 2012) [22]	Northern Ireland	To explore the views and perspectives of children on the use of medicines in children and on the participation of children in clinical trials	Cross-sectional study (not reported)	Focus group discussions	School children (n = 123)	Sessions moderated by trained researcher Facilitator was familiarized with focus group sessions by conducting 2 simulation sessions Study guide was used to ensure uniformity of focus group discussions	Views on the unlicensed use of medicines in children Informing parents/guardians and children Clinical trials and willingness to participate illness and participation in clinical trials	63.4 (123/194)	Pupils viewed unlicensed/off-label use of medicine in children as unsafe and unethical Pupils felt it is necessary to test medicines in children to improve availability of licensed products They felt that older children and parents should be informed when drug used in off-label manner
Healthcare professional experiences and attitudes on unlicensed/off-label paediatric prescribing and paediatric clinical trials (Mukattash et al., 2011) [16]	Northern Ireland	To investigate the knowledge and views of a range of healthcare professionals regarding the use of unlicensed/off-label medicines in children and the participation of children in clinical trials	Cross-sectional study (not reported)	Prospective questionnaire survey	Consultant paediatricians, general practitioners, community pharmacists, paediatric nurses (n = 563)	Survey instrument designed after an extensive review of the literature Comprised of 39 questions	Experiences and views of healthcare professionals regarding the use of unlicensed and off-label medicines in children Parental involvement in decision making regarding the medicine being prescribed for their child	46.5 (563/1212)	More familiarity with the term unlicensed compared to off-label prescribing 30.7% reported informing parents/guardians on the use of unlicensed/off-label medicines in children Willingness to be actively involved in clinical trials is highest among consultant paediatricians
						Questionnaire was piloted using a small number of healthcare professionals (n = 20; pharmacists and doctors) and respondents indicated that the questionnaire was clear and easy to understand Distributed via postal services and email 4-week window to complete the questionnaire	Information sources that healthcare professionals use when prescribing, dispensing and administering unlicensed/off-label medicines to children Paediatric clinical trials Dose-related issues when prescribing unlicensed and off-label medicines in children		

(Continues)

Table 1
 (Continued)

Title (Author, year, reference)	Country	Study aim	Study design (duration)	Method	Target group	Survey instrument/tool characteristics	Outcome domains	Response rate (%)	Results
Perceptions and attitudes of Jordanian paediatricians towards off-label paediatric prescribing (Mukattash et al., 2011) [17]	Jordan	To investigate the knowledge and views of Jordanian paediatricians regarding off-label prescribing in children	Cross-sectional study (not reported)	Prospective questionnaire survey	Hospital based paediatricians (n = 250)	Survey instrument designed after an extensive review of the literature	Experiences and views of paediatricians regarding off-label prescribing to children	83 (250/300)	69% of participants were familiar with the term off-label medicines but only 28% knowingly prescribed off-label medicine to children Majority did not obtain informed consent or tell parents when they prescribe off-label medicine
Off-label, off-limits? Parental awareness and attitudes towards off-label use in paediatrics (Lenk et al., 2009) [13]	Germany	To explore knowledge and view regarding off-label prescribing and participation in clinical trials	Cross-sectional study (4 months)	Questionnaire survey	Parents (n = 94)	Comprised of three sections	Knowledge and view of off-label use in paediatrics Participation in clinical trials	Parents of children with renal disease: 54 (43/80) Parents of healthy children 64 (51/80)	Knowledge about off-label drug use was poor in both groups Refusal to off-label drug use was low Parents with poor knowledge about off-label drug use tend to refuse to volunteer their child for participation in clinical trials
Public awareness and views on unlicensed use of medicines in children (Mukattash et al., 2008) [12]	Northern Ireland	To explore awareness and views of the general public on unlicensed use of medicines in children To explore participation of children in clinical trials	Multicentre, cross-sectional study (4 months)	Face-to-face interview using structured questionnaire	Parents (n = 1000)	Draft survey was examined for fitness for purpose and face validity in focus group Final version was piloted in a sample of 20 members of public Interview conducted by trained interviewer	Views on safety and labelled use of drugs in children Awareness regarding off-label use in children Communication from healthcare worker about off-label drug use in children Views on off-label drug use in children Willingness of allowing child participation in clinical trial	Not reported	Majority had no previous knowledge about unlicensed/off-label drug use Most parents felt that they should be told when drug prescribed unlicensed/off-label manner Views on clinical participation varied according health status of children

(Continues)

Table 1
(Continued)

Title (Author, year, reference)	Country	Study aim	Study design (duration)	Method	Target group	Survey instrument/tool characteristics	Outcome domains	Response rate (%)	Results
Attitudes and experiences of community pharmacists towards paediatric off-label prescribing: a prospective study (Stewart et al., 2007) [21]	United Kingdom	To identify community pharmacist experiences of, and attitudes towards paediatric off-label prescribing	Cross-sectional study (not reported)	Prospective questionnaire survey	Community pharmacists (n = 482)	Comprised of 21 questions with combination of tick-box responses and written comments Piloted prior to use	Knowledge of and reasons for paediatric off-label prescribing Classes of drugs dispensed off-label Most common reasons for concerns when dispensing off-label Sources of information for dispensing to children Transfer of information to parents and prescribers	32.1 (482/1500)	Familiarity with concept of off-label prescribing (73%), mainly gained through dispensing experience (64%) 40% knowingly dispensed off-label prescription to children Most common reason of off-label prescription was age (84.6%) Major concern regarding off-label drug use is lack of dosage data (60%) Majority feels that pharmacist should inform parents and prescribers if drug is used in off-label manner (66% and 78%)
A prospective questionnaire assessment of attitudes and experiences of off-label prescribing among hospital based paediatricians (McLay et al., 2006) [18]	Scotland	To assess current attitudes of hospital based paediatricians to off-label prescribing, and the performance of clinical trials in children	Cross-sectional study (1 year)	Prospective questionnaire survey	Hospital based consultants and specialist registrars (n = 151)	Comprised of 24 questions with combination of tick-box responses and written comments	Perceived reasons for off-label prescribing Concerns about off-label prescribing Parental and GP involvement Paediatric clinical trials	59 (151/257)	Familiarity with concept of off-label prescribing (92.8%) 90% knowingly prescribed off-label prescription to children Most common reason of off-label prescription was age Major concern regarding off-label drug use is lack of efficacy data (63.8%)
Off-label prescribing to children: attitudes and experience of general practitioners (Ekins-Daukes et al., 2005) [19]	Scotland	To identify experience with and attitudes towards paediatric off-label prescribing in primary care	Cross-sectional study (not reported)	Prospective questionnaire survey	General practitioners (n = 202)	Questionnaire was piloted prior to use Attempt to increase response rate was made Comprised of 13 questions Collected after 4 weeks	Prior knowledge of off-label prescribing and licensing recommendations Acknowledgement of and perceived problems with off-label prescribing Prescribing information sources used in practice Importance of proposed methods or reducing off-label prescribing	58 (202/346)	Majority familiar with off-label concept (705) but 40% admitted knowingly prescribing off-label drugs Ranked development of paediatric formulations and clearer dosage information highly as a means to reducing off-label prescribing

Table 2

Quality assessment of quantitative studies included in systematic review

Studies	Bang <i>et al.</i> [14]	Pérez <i>et al.</i> [15]	Saullo <i>et al.</i> [20]	Mukattash <i>et al.</i> [16]	Mukattash <i>et al.</i> [17]	Lenk <i>et al.</i> [13]	Mukattash <i>et al.</i> [12]	Stewart <i>et al.</i> [21]	McLay <i>et al.</i> [18]	Ekins- Daukes <i>et al.</i> [19]
Quality assessment domains										
Research question and design										
a) Was there a clear research question, and was this important and sensible?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
b) Was a questionnaire the most appropriate research design for this question?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sampling										
c) Was the sampling frame sufficiently large and representative?	✓	✓	?	✓	✓	✗	✓	✓	?	?
d) Did all participants in the sample understand what was required of them, and did they attribute the same meaning to the terms in the questionnaire?	✓	✓	?	?	?	?	✓	?	✓	?
Instrument										
e) Were the claims for reliability and validity made, and are these justified?	✓	✗	✗	✓	✓	✗	✓	✓	✗	✗
f) Did the questions cover all relevant aspects of the problem in a non-threatening and non-directive way?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
g) Were open-ended (qualitative) and closed-ended (quantitative) questions used appropriately?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
h) Was a pilot version administered to participants representative of those in the sampling frame, and the instrument modified accordingly?	?	✓	✗	✓	✓	✓	✓	✓	✗	✓
Response										
i) Have non-responders been accounted for?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Coding and analysis										
j) Was the analysis appropriate (e.g. statistical analysis for quantitative answers, qualitative analysis for open-ended questions) and were the correct techniques used?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
k) Were adequate measures in place to maintain accuracy of data?	✓	✓	?	✓	✓	✓	✓	✓	✓	✓
Presentation of results										
l) Have all relevant results ('significant' and 'non-significant') been reported?	✓	✓	?	✓	✓	✓	✓	✓	✓	✓
m) Is there any evidence of 'data dredging' (i.e. analyses that were not 'hypothesis driven')?	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Bias										
n) Is there evidence of any other bias (e.g. funding bias)?	?	✓	?	✓	✓	✓	?	✓	?	?

✓ = yes; ✗ = no; NR = not reported; ? = unclear

awareness was reported among hospital-based paediatricians even though they were reported to be more familiar with the concept of off-label prescribing [17]. Awareness among hospital-based consultant paediatricians and specialist registrars was reported to be higher [18].

Five studies highlighted the most common category of off-label prescribing [16–20]. Four of the studies found that most off-label prescribing happened for patients of younger age groups than for which the products were licensed [16, 18–20] while one study reported that use

of the product for a different indication than licensed as the most common category of off-label prescribing [17]. The majority of respondents in two studies reported neonates to be the most likely to receive off-label prescriptions [16, 17]. Respiratory and neurological diseases were found to be the two common disease states where drugs were prescribed off-label for children [18, 20].

Pharmacists The majority of community pharmacists were dispensing off-label medicine unknowingly [16, 21]. The most common category for a dispensed prescription

Table 3

Quality assessment of qualitative study included in systematic review

Screening questions	Mukattash et al. [22]		
	Yes	No	Cannot tell
1. Research question Did the paper address a clear research question?	/		
2. Design Was the study design appropriate to the research question? In particular, was a qualitative approach suitable and was the right design used?	/		
3. Context Was the context of the study sufficiently well described that the findings can be related to other settings?		/	
4. Sampling Did the researchers include sufficient cases/settings/observations so that conceptual rather than statistical generalizations could be made? Were the authors' preconceptions and ideology adequately set aside?			/
5. Data collection Was the data collection process systematic, thorough and auditable? Were attempts made to identify and explore disconfirming examples?	/		
6. Data analysis Were data analyzed systematically and rigorously? Did the analysis take account of all observations? Were sufficient data presented? Were disconfirming observations dealt with?	/		
7. Results Were there any unintended consequences?			/
8. Conclusions Did the authors draw a clear link between data and explanation (theory)?			/
9. Reflexivity Were the authors' positions and roles clearly explained and the resulting biases considered?	/		
10. Ethics Are there any ethical reservations about the study?		/	
11. Worth/relevance Was this piece of work worth doing at all, and has it contributed usefully to knowledge?	/		

being off-label was for a younger patient than the recommended age [16, 21]. The majority of community pharmacists indicated dispensing off-label medicines for infants (age 1 to 23 months) [16].

Parents The majority of parents (59%) involved in the study done in India thought that doctors would not knowingly prescribe drugs which were not fully tested for use in children [14]. Contrarily, 84.2% of parents from a study conducted in Northern Ireland thought that their doctors would knowingly prescribe a drug which was not fully tested for use in children [12].

Children Children trusted that doctors/pharmacists had adequate knowledge to decide the dose of medicines untested in children [22].

Choice of information sources

In the community setting, the British National Formulary (BNF) was the most commonly used by GPs and community pharmacists [19, 21]. In a study conducted among healthcare workers in Northern Ireland, the British National Formulary for Children (BNFc) was the most

commonly used information source [16]. Contrarily, Spanish paediatricians tended to use protocols or clinical guidelines more frequently [15]. Less frequently used information sources included the manufacturer's summary of product characteristics, Monthly Index of Medical Specialties, conference and meeting proceedings, colleagues' opinion, national guidelines and the local formularies [15, 16, 19, 21]. A study among Scottish primary care practitioners reported no respondent used any of the available paediatric formularies [19].

Reasons for off-label prescribing

Four studies evaluated the reasons for prescribing off-label medicines [18–21]. The reasons established were lack of paediatric dosage information [19, 21], lack of appropriate paediatric formulations [19, 20], hospital consultants' advice [19], lack of licensed alternative [18, 19] and lack of clinical trials data [21].

Suggestions to reduce off-label prescribing

Two studies highlighted measures to reduce off-label prescribing, which included increasing the number of

clinical trials in children, making more appropriate formulations available for young children and having clearer and consistent dosage information [16, 19]. The GPs placed clear and consistent labelling as the most important approach [19] but healthcare professionals, as a whole, ranked making more appropriate formulations available for younger children as the most important approach to reduce off-label prescribing [16].

Communication with parents and guardians

The majority of healthcare workers [16] and parents [12, 14] agreed that when a drug was prescribed in an off-label manner, the information should be disclosed to the parents. However, the rate reported for such practice remained low (4.8–32.4%) [15–18]. Hospital-based paediatricians felt that parents should not be told when a medicine had been prescribed in an off-label manner for their children [17, 18]. Only one third of hospital-based paediatricians admitted to informing a child's GP that they were prescribing an off-label medicine [18]. The community pharmacists felt that the pharmacist had a responsibility to inform the prescriber and parents when medicines were prescribed off-label for children [21]. However, the doctors were deemed to be the most appropriate personnel to inform the parents in both primary and specialist care settings [12, 14]. Once they knew that their children were prescribed off-label drugs, most parents would ask for a change of drugs to one that had been fully tested and licensed for use in children [14] or they would use the medicine for their child with caution [12]. The percentage of refusal of off-label use was higher among parents of healthy children compared with parents of ill children [13]. Besides parents, children also thought that the child should be told when off-label medicines were used to create alertness to potential side effects [22].

Concern regarding informed consent

Verbal consent was more common in both the community and hospital setting when informing parents about off-label prescribing [16, 17]. The majority of hospital-based consultant paediatricians and specialist registrars did not seek informed consent from parents when prescribing off-label medicine [18]. Spanish paediatricians felt that supporting actions from medical liability should include informing the parents, making a note of it in the medical records and to have protocols or clinical practice guidelines to endorse the action. However, most of them admitted not making a note in the medical records if the parents were verbally informed [15].

Participation in clinical trials

Doctors Two studies conducted among doctors evaluated their responses regarding clinical trials in children [16, 18]. Over half of the respondents in these two studies believed that all new medicines and medicines used in

off-label manner should undergo clinical trials in children [16, 18]. A third of the respondents in a study conducted in Scotland believed that generic medicines too should be tested in children [18]. Hospital-based paediatricians were more willing to be actively involved in clinical trials compared with GPs (53% vs. 20.1%) [16, 18]. Among all, consultant paediatricians reported the most willingness to help with clinical trials (94.4%) [16]. The majority stated that they would allow their own children to take part in clinical trials [16, 18] depending on the child's health status and the benefit from participating in such trials [16].

Community pharmacists The majority of community pharmacists (64.9%) believed that medicines used in off-label manner should undergo clinical trials in children but not all are willing to be actively involved in paediatric clinical trials (41.4%) [16]. Community pharmacists' willingness to consent for their children to take part in clinical trials was associated with the worsening of the child's health status and benefit from the clinical research [16].

Paediatric nurses The response from paediatric nurses regarding participation in clinical trials was limited and extracted from a study done among healthcare professionals [16]. The majority of paediatric nurses believed that off-label medicines should not undergo clinical trials in children and they were not willing to be actively involved in clinical trials (i.e. help in recruiting patients) [16].

Parents Three studies involving parents evaluated their response regarding participation of their children in clinical trials [12–14]. The majority of parents would allow their children to participate in clinical trials if their children were suffering from life-threatening conditions but their willingness reduced as the health status of the child improved [12, 14]. Well-informed parents were more willing to volunteer their children for participation in clinical trials [13]. Monetary incentives and the child's age were not factors influencing the decision of the parents to allow their child's participation in a clinical trial [12, 14].

Children School children were willing to take part in clinical trials only if they were seriously ill and if the medicine might help them but felt that those medicines should not be tested in babies [22]. Children also felt that they must give informed consent prior to their participation in clinical trials [22].

Discussion

This review was limited by the small number of studies (11 studies) which included responses from doctors, pharmacists, nurses, parents and children. Different

methods were used in the studies to explore awareness, knowledge and views of off-label prescribing among children, making a direct comparison impossible but some common points are worth highlighting.

Familiarity with off-label prescribing was assessed in doctors [16, 17], community pharmacists [16, 21] and parents [12–14] but the reason for familiarity was reported only for healthcare professionals, pointing out professional experience, post-graduate and undergraduate training [16, 17, 21] as the main reasons. The variation in reasons of familiarity was due to different rates of off-label drug use reported in different settings [2, 6] and difference in undergraduate and post-graduate curricula [23–27]. This review showed that most doctors did not reveal information regarding off-label drug use to parents [15–18], which could have resulted in a low level of familiarity to off-label prescribing among parents.

Five studies [16, 18–21] reporting views of study participants on off-label prescribing in children highlighted age as the common category of off-label drug use. Previous literature and systematic reviews [2, 3, 5], comprising a total of 78 studies, have concluded dose as the common category, accentuating a mismatch between views of study participants of this review and the finding of previous studies.

Even though various references were available specifically for paediatric patients [28–30], this review showed that most doctors and pharmacists tended to rely on other sources to obtain information regarding drug use in children, while expressing lack of paediatric dosage information as a major concern, an issue highlighted since the term ‘therapeutic orphan’ was coined by Shirkey in 1968 [31].

Doctors, pharmacists, parents and children were supportive of paediatric clinical trials to address the issue of off-label medicine use. Even though a clinical trial was the most valid means of obtaining data [32, 33], this review found that conducting clinical trials in children was not the most favoured means to reduce off-label prescribing.

Most studies included in this review used a self-reported, questionnaire-based method of data collection, resulting in low response rates which could have been overcome by face to face or focus group interviews. Further research should address possible gaps identified from the reviewed studies, such as lack of communication among healthcare providers and parents. Additionally, a structured intervention programme derived from learning needs assessment will foster awareness, knowledge and view of healthcare professionals.

Conclusion

This systematic review described major behavioural aspects of doctors, community pharmacists, paediatric

nurses, parents and children to off-label prescribing. In general, the studies reported that the majority of doctors and community pharmacists were familiar with the term off-label prescribing but knowledge among parents was low. Awareness regarding off-label prescribing in children remained low among all study participants. There seemed to be a mismatch between views of the study participants on off-label prescribing in children and the finding of previous studies.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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