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Awareness about and views of parents on the off-label drug use in children

V. Bang[a], A. Mallad[a], S. Kannan[a], S.B. Bavdekar[b], N.J. Gogtay[a] and U.M. Thatte[a,*]
[a]*Department of Clinical Pharmacology, Seth GS Medical College & KEM Hospital, Parel, Mumbai, India*
[b]*Department of Pediatrics, TNMC and BYL Nair Hospital, Mumbai, India*

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Abstract.
BACKGROUND: Off-label use of drugs is widely prevalent in children mainly due to a limited data generated in children during drug development process. Parents play a critical role in giving consent for their child to participate in clinical trials. Very few studies have assessed the opinion of the parents regarding such use and permitting their child to participate in clinical trials.
OBJECTIVE: In view of lack of information about the awareness among parents regarding both off-label drug use in children as well as about allowing their child to participate in clinical research especially from a developing country, this study was conducted.
METHODS: Adults accompanying patients in a tertiary care hospital were administered a validated, structured questionnaire following written informed consent. The questionnaire consisted of 18 items broadly divided into 5 themes - parental views on safety and labelled use of drugs in children, awareness of off-label drug use in children, communication from healthcare worker about it, parental views on off-label drug use in children and willingness to allow their child to participate in a clinical trial. Chi-square or Fisher's exact probability test and McNemar's test were used for analysis.
RESULTS: Initially, a majority of the participants felt that the drugs used in children in hospital (89.5%) and prescribed by a family physician (80.3%) were either safe or extremely safe while after the concept of off-label drug use is explained, a significant reduction in the proportion (59.3% in hospital and 59.8% by family physician) of parents felt the same. Only 30% parents were aware of off-label drug use in children. Ninety-three percent of the parents wanted to be informed whenever a doctor prescribes a drug in an off-label manner and a similar percentage felt the off-label drug use would increase the side-effects. Seventy three percent parents felt the off-label drug use is illegal and 57% would ask for change to a labelled drug in case of such prescription in their children. A majority of the parents would allow their child to participate in case of a life-threatening condition (59.8%) or in case of a chronic illness (51.3%) but significantly less when their child is healthy.
CONCLUSION: The present study has found a low level of awareness regarding the concept of off-label drug use in children amongst the public. Our study also shows that parents expect that the doctor explains the fact to them, although they appear to vest a large amount of trust in the doctor's judgement in doing the best for their sick child. Parents were more willing to allow their child's participation in clinical research if their child was seriously ill than if healthy, indicating the need to educate the society about the need for clinical research so that they could take more informed decisions.

Keywords: Awareness, children, clinical trials, off-label drug use, parents

*Address for correspondence: Dr. Urmila M. Thatte, Professor and Head, Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Acharya Donde Marg, Parel, Mumbai 400012, India. Tel.: +91 22 24133767; E-mail: urmilathatte@gmail.com.

1. Introduction

Off-label drug use is the administration of a drug, biologic or device for conditions outside the product license with respect to the dose, age, route of administration, indication or contra-indication [1, 2]. Although, this entails use of a drug when its efficacy and safety have not been proven, it is considered neither illegal nor unethical [3]. The extent of off-label drug use in children ranges from 26–70% in various countries [4–8], including India [9, 10]. Limited data generated in the paediatric population during the drug development process is the main reason that compels physicians to use drugs in an off-label manner in children [11]. To ensure that children get medications that have been tested for efficacy and safety in them, various national regulatory agencies have taken steps to encourage, coax and compel pharmaceutical companies to carry out clinical trials in children [12, 14] to ensure that regulatory and clinical decisions in children are based on evidence.

Although paediatric clinical trials face several ethical challenges [15], if off-label drug use is to be reduced, clinical trials will have to be conducted in children. The population at large, and especially parents, need to be aware of this fact so that they can make informed choices regarding enrolling their child in a clinical trial when the opportunity arises. There is limited literature [16, 17] from the world and none from India about the awareness among parents regarding both off-label drug use in children as well as about allowing their child to participate in clinical research. This study was therefore designed to explore these issues.

2. Methods

The study was conducted between April 2009 and June 2010 in a tertiary care hospital in a metropolitan city after obtaining institutional review board approval (Institutional Ethics Committee – Seth GS Medical College and KEM Hospital). Individuals above the age of 18 years, accompanying patients in the General Medicine outpatient and inpatient departments were approached for the study and were enrolled after obtaining a written informed consent. These individuals essentially consisted of those who had children and those who did not. The latter were requested to answer the questions as if they had children.

A previously published structured questionnaire [16] was used after obtaining permission from the author. The questionnaire was administered by a trained interviewer and consisted of 18 items eliciting information on parental perception of off-label drug use in children and clinical trials in them. The items in the questionnaire were broadly divided into 5 themes. The first was related to parental views on safety and labelled use of drugs in children. After obtaining these views, the parents were provided information regarding the concept of off-label drug use and they were then requested to answer questions related to the other themes which were awareness of off-label drug use in children, communication from healthcare worker about it, parental views on off-label drug use in children and willingness to allow their child to participate in a clinical trial. In the last theme, an additional option (If money was given) for allowing their child to participate in the trial was added by us as the research participants were expected to be from the disadvantaged sections of the society. The translated versions (Hindi and Marathi languages) of the original English version of the Questionnaire [16] were used after establishing the face validity in a sample of 10 parents. Demographic details of the participants including socioeconomic status based on Kuppuswamy scale 2007 [18] were also noted.

In the absence of literature from India on this topic, no formal sample size calculations were made.

2.1. Statistical analysis

For the purpose of quantitative analysis, participants were divided into two broad categories; namely, those with children and those who did not have children but were requested to pretend they had. The former group was further categorized into those that had healthy children at the time of interview and those whose children were sick.

The responses to the 5 broad themes are presented as qualitative data. The responses to individual items are presented as proportions with 95% confidence intervals (95% CI) represented in square brackets ([]). The Chi-square test or Fisher's exact probability test was used to analyze differences between categories. McNemar's test was used to find out significant difference in the responses of the participants before and after they were made aware about the concept of off-label drug use as well as the parental opinion of the safety of the drugs prescribed in hospital as compared to those prescribed by the family physician. Chi-square for trend analysis was used to analyze the participants' willingness to allow their child to participate in clinical trials under various hypothetical situations. McNemar's test was performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL) and all other statistical analyses were performed using GraphPad Instat 3.0 (GraphPad Instat version 3.0 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com). A p value of <0.05 was considered significant.

3. Results

3.1. Demographic details

Of the 405 individuals approached, 400 (267 men, 133 women) consented to participate in the study. A majority (69%) of the individuals belonged to the 21–40 year age-group and to the middle class (70.5%) (Table 1). Eighty two percent (328/400) had children of their own while the rest answered questions as if they had children.

Table 1
Demographics of the study participants [n (%)]

Gender distribution	
Male: Female	2:1
Age distribution (in years, $n = 400$)	
18 – 20	20 (5)
21 – 40	276 (69)
41 – 60	97 (24.3)
>60	7 (1.8)
Parents who had children on their own	328 (82.0)
Individuals who were assumed to have children	72 (18.0)
Socio-economic status	
Upper class	7 (1.8)
Upper middle class	135 (33.5)
Lower middle class	148 (37.0)
Lower class	110 (27.5)

3.1.1. Parental views on safety and labelled use of drugs in children

Prior to being told what off-label drug use is, parents felt that the drugs prescribed to their children in the hospital were either safe or extremely safe (358/400, 89.5% [86.1, 92.1]). Only 10/400 (2.5%, [1.4, 4.5]) said that the medicines prescribed in the hospital were unsafe or extremely unsafe. Thirty two (8% [5.7, 11.1]) said they did not know. A similar response was obtained for drugs prescribed by the general physician except in the case of parents of healthy children where a significantly higher proportion of parents (89.4% [84.8, 92.7] vs. 81.3% [75, 85.5], $p < 0.05$) felt that the drugs prescribed in the hospital were safe as compared to those prescribed by a family physician (Table 2).

A majority of the participants thought that all medicines prescribed to children in the hospital (241/400, 60.3% [50.5, 69]) or by their family physicians (213/400, 53.3% [43.5, 62.7]) have undergone a testing and licensing process similar to those in adults.

3.1.2. Parental awareness regarding off-label drug use in children

After being explained about the concept of off-label drug use, 121/400 (30.3% [22.2, 40]) participants said that they had heard about this concept. There was no significant difference observed amongst different socioeconomic classes, parents (29.3% [21.3, 38.9]) and non parents (34.7% [26, 44.4]) or between parents of sick (31.2% [23, 40.8]) or healthy children (28.5% [20.58, 38]) with regards to this awareness.

3.1.3. Communication from healthcare worker about off-label drug use in children

After having learnt what off-label drug use in children means, an overwhelming majority of parents (372/400, 93% [90.1, 95.1]) said that they should be informed about prescribing an off-label drug to their child and this information should be provided by the doctor in the hospital {331/400 (82.8% [78.7, 86.1])} and outside the hospital settings {345/400 (86.3% [82.5, 89.3])}.

3.1.4. Parental views on off-label drug use in children

Only 164/400 (41% [36.3, 45.9]) participants thought that doctors would knowingly prescribe a drug not fully tested for use in children, 18 of these chose more than one reason for the doctor's prescribing off-label drug use. Eighty nine (54.3% [46.6, 61.7]) of these participants felt that this happened because the doctors have enough experience to do so, 75/164 (45.7% [38.3, 53.4]) felt that the doctors did so as they believed benefits outweighed the risks and 22/164 (13.4% [9, 19.5]) thought that lack of availability of a labelled alternative led to off-label prescribing.

The participants' perception regarding the safety of medicines changed enormously once the concept of off-label drug use was explained to them: Now, only 237/400 (59.3%; [54.4, 64.0]) (when prescribed in the hospital) and 239/400 (59.8% [54.8, 64.4]) (when prescribed by a family physician) felt the drugs to be safe or extremely safe. This was significantly ($p < 0.0001$) less than the proportion who felt that drugs were safe or extremely safe before they knew about off-label drug use in all categories of parents except for those who had assumed that they had children for the drugs prescribed by family physician (Table 2). In addition, 371/400, 92.8% [86, 96.4] participants felt that the off-label drug use would increase the extent of side-effects. A large proportion of parents and non-parents (293/400, 73.3%, [64, 81]) felt that such use was illegal.

The participants were then given three choices related to actions they would take when they found that their child was prescribed a drug not fully tested for use in children. We excluded 12 participants from analysis as they gave more than one answer to the question. Over half (220/388, 57% [51.7, 61.5]) said they would ask for a change of drug to one that has been fully tested and licensed for use in children, 88/388, 23% [18.8, 27.1] said they would simply accept the treatment because the doctor knows best and

Table 2
Parental views about the safety of medicines used in children before and after they were made aware of off-label drug use n(% [95% confidence interval])

Before or after the concept of off-label drug use has been explained		In hospital				By family physician			
		Parents with sick child* ($n=93$)	Parents with healthy child* ($n=235$)	Individuals who were assumed to have children* ($n=72$)	Total* ($n=400$)	Parents with sick child* ($n=93$)	Parents with healthy child* ($n=235$)	Individuals who were assumed to have children ($n=72$)	Total* ($n=400$)
Before	Safe or extremely safe	88 (94.6 [88, 97.7])	210 (89.4 [84.8, 92.7])**	60 (83.3 [73.1, 90.2])	358 (89.5 [86.1, 92.1])	76 (81.7 [72.7, 88.3])	191 (81.3 [75.8, 85.5])	54 (75 [63.9, 83.6])	321 (80.3 [76.1, 83.9])
	Unsafe or extremely unsafe	0	7 (3 [1.5, 6])**	3 (4.2 [1.4, 11.6)	10 (2.5 [1.4, 4.5])	5 (5.4 [2.3, 12.0)	21 (8.9 [5.9, 13.3])	6 (8.3 [3.9, 17.0])	32 (8 [5.7, 11.1])
After	Safe or extremely safe	38 (40.9 [31.4, 51.0])	150 (63.8 [57.5, 69.7])	49 (68.1 [56.6, 77.7])	237 (59.3 [54.4, 64])	39 (41.9 [32.4, 52.1)	146 (62.1 [55.8, 68.1])	44 (61.1 [49.6, 71.5])	239 (59.8 [54.8, 64.4])
	Unsafe or extremely unsafe	40 (43.01 [33.4, 53.2)	62 (26.4 [21.2, 32.4])	17 (23.6 [15.3, 34.6])	119 (29.8 [25.9, 34.4])	38 (40.7 [31.4, 51.0])	59 (25.1 [20, 31])	19 (26.4 [17.6, 37.6])	116 (29 [24.8, 33.6])

*$p<0.05$ for proportion of parents who would consider the drugs safe/extremely safe or unsafe/extremely unsafe for drugs prescribed in hospital/family physician before and after the concept of off-label drug use has been explained. **$p<0.05$ for proportion of parents whose children are healthy that consider drugs prescribed are safe/extremely safe or unsafe/extremely unsafe in hospital as compared to prescription by a family physician.

Table 3
Participants' willingness to volunteer their child to participate in a clinical trial under various situations [*n* (%)]

Hypothetical health situations	Participant's Categorization			Overall* ($n = 400$)
	Parents		Individuals who were assumed to have children ($n = 72$)	
	Sick child ($n = 93$)	Healthy child ($n = 235$)		
Child suffering from a life threatening condition	59 (63.4) [53.6, 72.2]	141 (60) [50, 69]	39 (54.1) [44.4, 63.5]	239 (59.8) [54.9, 64.4]
Child suffering from a chronic but not life threatening condition	50 (53.8) [44.1, 63.3]	119 (50.6) [41, 60.2]	36 (50.0) [40.4, 60]	205 (51.3) [46.4, 56.1]
Child in hospital	49 (52.7) [43, 62]	112 (47.7) [38.2, 57.4]	35 (48.6) [39, 58.3]	196 (49) [44.1, 53.9]
Child suffering from a minor condition	44 (47.3) [37.8, 57]	111 (47.2) [37.7, 57]	25 (34.7) [28.8, 47.5]	180 (45) [40.2, 50]
Child in good health	23 (24.7)** [17.3, 34]	99 (42.1) [32.9, 52]	30 (41.7) [32.5, 51.5]	152 (38) [33.4, 42.9]
If money was given	17 (18.3) [11.7, 27.3]	56 (23.8) [16.5, 33]	16 (22.2) [15.2, 31.3]	89 (22.3) [18.5, 26.6]

* - $p < 0.0001$ (significant) for different hypothetical situations. ** - $p = 0.01$ (significant) between parents of sick children and others.

the rest (80/388, 21% [16.9, 24.9]) said although they would allow use of the drug in the child, they would check carefully for side-effects. These responses did not differ significantly amongst the three groups of participants (parents with sick children, those with healthy children and individuals who were requested to assume they had children).

3.1.5. Willingness for allowing the child to participate in a clinical trial

The majority of participants said they would allow their child to participate in a clinical trial if the child was suffering from a life-threatening condition (239/400, 59.8% [54.9, 64.4]) ($p < 0.05$, χ^2 test for Association). There was a significant reduction in the proportion of parents who would allow their child's participation in a clinical trial as the child in the scenario became healthier when analyzed by Chi-square test for trend analysis (Table 3). Only 89/400, 22.3% [18.5, 26.6] parents said they would allow their child's participation if they were given money. As compared to parents with healthy children or individuals who have been asked to pretend to have children, less parents of sick children would allow their child to participate in a clinical trial in the scenario of their child being healthy ($p = 0.01$). In all other imagined scenarios, these parents were no different from the others.

When we analyzed the responses of parents who would insist on substitution of a licensed drug in place of an off-label drug, we found that a significantly ($p < 0.05$) smaller number (73/220, 33.2% [27.3, 39.6]) would opt for enrolment of their child in a clinical trial when their child is in good health as against those who would allow off-label drug use in their child (41/88, 46.6% [36.5, 56.9]) and those who would allow off-label drug use, but would carefully check for side-effects (35/80, 43.8% [33.4, 54.7]). In case their child was suffering from a life-threatening disorder, a significantly ($p < 0.05$) more number of parents who would ask for change to a labelled drug in their child (135/220, 61.4% [54.8, 67.6]) and those who would allow off-label drug use but would carefully check for side-effects (54/80, 67.5% [56.6, 76.8])

Table 4
Influence of the action expressed by the participants following the prescription of an off-label medicine for their child on their willingness to volunteer their child in the clinical trials *n* (%) [95% CI]

Hypothetical situation in which the parents will allow their child to participate in the clinical trial	To change the medicine to a fully tested and licensed medicine ($n = 220$)	Accept the prescribed off-label medicine ($n = 88$)	Use the medicine in the child, but check carefully for side-effects ($n = 80$)
Child suffering from a life threatening condition*	135 (61.4) [54.8, 67.6]	43 (48.9) [38.7, 59.1]	54 (67.5) [56.6, 76.8]
Child suffering from a chronic but not life threatening condition	103 (46.8) [40.3, 53.4]	47 (53.4) [43.1, 63.5]	49 (61.3) [50.3, 71.2]
Child suffering from a minor condition*	85 (38.6) [32.5, 45.2]	45 (51.1) [40.9, 61.3]	43 (53.8) [42.9, 64.3]
Child in hospital	107 (48.6) [42.1, 55.2]	39 (44.3) [34.4, 54.7]	46 (57.5) [46.4, 67.7]
Child in good health*	73 (33.2) [27.3, 39.6]	41 (46.6) [36.5, 56.9]	35 (43.8) [33.4, 54.7]
If money were to be given*	41 (18.6) [14.1, 24.3]	31 (35.2) [26.1, 45.6]	14 (17.5) [10.7, 27.3]

*$p < 0.05$ (significant), χ^2 test for Association.

would allow their child's participation in a clinical trial as compared to those who would simply accept the off-label drug use because the doctor knows best (43/88, 48.9% [38.7, 59.1] (Table 4).

Less than a quarter of the participants (87/400, 21.8% [18, 26.1]) said that their decision to allow their child's participation in a clinical trial would be influenced by their child's age.

4. Discussion

The present study assessed the awareness and views of parents regarding off-label drug use in children and their willingness to allow their child to participate in clinical trials. We found a low level of awareness of off-label drug use (30%) which was similar to that previously reported from Northern Ireland [16] and Germany [17], both developed countries. Interestingly, in our study (as also in others [16, 17]), a similar proportion of parents with sick children were unaware of off-label drug use as were those with healthy children or those who did not have children. This suggests the possibility that information regarding off-label drug use is not being disseminated by doctors to parents who are visiting the hospital/physician for their sick child. This situation can possibly be in part due to lack of awareness of off-label drug use even amongst physicians [19, 20].

Once explained about off-label drug use, the proportion of participants who felt that the medicines prescribed for children were unsafe or extremely unsafe increased exponentially and further, many parents felt that such use was illegal. More importantly, a vast majority (93%) also said that such use should be communicated to the parents. Although, it is not legally mandatory that parents be informed that the prescribed drug is off-label, it is only ethically correct that this information be communicated to parents to the best of their ability to understand [21, 22]. In view of the fact that studies have found relative lack of awareness even amongst physicians [19, 20], it appears that these issues should be mandatorily covered during both the undergraduate and postgraduate medical training.

Our observations that more than half of the participants said that they would ask the physician to consider switching to a labelled medicine for their children emphasises the increasing trend of shared decision making about choice of treatment [23–25]. This reinforces the need to have more and more drugs used in children based on labelled indications in turn based on evidence generated from clinical trials. Hence, it was important to know whether our participants would allow their children to participate in clinical trials.

We found that the largest proportion of the participants (60%) were willing to allow their child to take part in clinical trials if the child was suffering from life-threatening conditions corroborating the findings of a previous study [16]. As the scenario shifted from serious illness to no illness, a significantly fewer proportion of parents were willing to allow their child to participate. This, coupled with a generally poor awareness about clinical research in India [26, 27] particularly emphasises challenges one would face in recruiting healthy children for vaccine trials or pharmacokinetic research.

The participants were largely from the lower middle socio-economic class (with an average monthly income ranging from INR 5,000 to 10,000 ($82 to 164) [18, 28]). In spite of this, only a fifth of the participants said they would allow their child to participate in a trial if there was a monetary benefit. This is contrary to what we found in a study in healthy adults [29] who participated in non-therapeutic clinical trials, where financial reward was the most common motivating factor for their participation.

The finding that the parents who would ask for the use of a licensed drug in their child would allow their child to participate in a clinical trial only in the scenario when the child was suffering from a life-threatening condition further re-emphasises the possible lack of understanding of the need for clinical research. It has been shown that parents who had earlier allowed their child to participate in a clinical trial understood better about clinical trials than those who had not [30].

This is probably the first study that has attempted to elicit the degree of awareness and opinions regarding off-label drug use in children and parental views regarding children's enrolment in the clinical trials from a developing country in Asia. The use of a previously validated Questionnaire (translated and revalidated), inclusion of socioeconomic status data, assessing the influence of monetary compensation on willingness to enrol children are some of the strengths of the study. Enrolling participants who did not have children at the time of interview expecting them to answer questions assuming that they had children was done to represent the general societal view which is an important aspect. This is a single centre study and we did not assess the reasons behind the responses we obtained – this could be addressed using other qualitative research methods in further studies.

To conclude, the present study has found a low awareness of the concept of off-label drug use in children amongst the public. Our study also shows that parents expect that the doctor explains the fact to them, although they appear to vest a large amount of trust in the doctor's judgement in doing the best for their sick child. Parents were more willing to allow their child's participation in clinical research if their child was seriously ill than if healthy, indicating the need to educate the society about the need for clinical research so that they could take more informed decisions.

Conflict of interest

The authors declare that there is no conflict of interest.

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