

Parents' awareness and perspective on off-label medicines use in children

Sir,

The lack of pediatric drug labeling is a long-standing problem for prescribers and drug regulatory bodies. As a result, medicines are prescribed in an off-label manner, which is inconsistent with its approved prescribing limits. The magnitude of off-label prescribing is accounted to be between 18% and 60% in pediatric wards. However, off-label prescribing may denote best evidence-based medicine, but, in several cases, benefit–risk is not well established. There are reports that suggest that off-label use is associated with adverse drug reactions and, hence, patient safety is jeopardized.^[1] Most clinicians recognize off-label prescribing as proper and believe that the benefits outweigh the risks and even their understanding of consequences appears to be negligible, with a low level of worry about the risk of side-effects, unevaluated efficacy and issues relating to informed consent.^[2,3] Parents are generally considered most suitable for conveying children therapy information, but are not specifically told about the off-label use of medicines in children. Hence, we aimed to evaluate their knowledge and attitude to off-label medicines.

A cross-sectional study-based questionnaire (Appendix) was used comprising 18 questions on several aspects of off-label medicine use in children. The survey participants were selected randomly from various areas of Ahmedabad and Gandhinagar city of the state of Gujarat. We presumed that parents might not be aware of the drug development and approval procedure; hence, we presented a “slide-show” to explain invention of medicine, animal testing, clinical trials, licensing procedure, how and why drugs are used as “off-label” and benefit and risk of off-label medicine use. The research study followed ethical guidelines as per the Declaration of Helsinki. The responses of 407 parents representing various socioeconomic groups, children's health status and education backgrounds were taken.

Of the 407 parents, 229 (56.3%) were male and 178 (43.7%) were female; 233 (57.2%) belonged to the age group of 20–40 years, 117 (28.7%) were in the 41–60 years age group and the remaining 57 (14%) were aged above 60 years. Many parents (290, 71.2%) held a bachelors degree while 86 (21.1%) had a masters degree and 31 (7.6%) did schooling; 301 (74%)

had one child and 106 (26%) had more than one child. Among the parents, 215 (52.86%) had healthy children whereas 192 (47.14%) had diseased children. The majority of diseased children were having a minor condition [147 (76.56%)], while 19 (9.9%) were having a life-threatening condition and 26 (13.54%) had a major but not life-threatening condition.

Majority of the participants, 366 (89.9%), were unaware about the concept of off-label medicines, and 384 (94.34%) parents felt that their child is not mature enough to understand the benefit–risk associated with off-label use. Most parents (86%) were solely responsible to decide their children's therapy. Parents of healthy children were markedly more skeptical toward the efficacy of off-label medicines than parents of diseased children (75% vs. 70%, $P > 0.05$) [Table 1]. It was important to note that 382 (94%) parents were more concerned about the safety of the off-label medicines [Table 1].

The 386 (95%) parents felt that the doctor should inform them regarding off-label medicines and take an approval before using it. The most reliable mode for permission was found to be written informed consent, 252 (62%). Among the participants, majority of the parents, 338 (83%), would visit a doctor who uses off-label medicines and 395 (97%) would ask their doctor about off-label medicines. A significant proportion of the parents, 334 (82%), believed that it is the responsibility of the doctor to inform them about off-label medicines.

Of the parents participating in the survey, 326 (80%) felt that doctors should consider risk first then benefit to children [Table 2]. Most parents, 376 (92.3%), felt that use of off-label medicines carries the risk of adverse drug reaction in comparison with labeled usage [Table 2]. When parent were asked what they would do if their child was having a life-threatening condition like cancer or heart failure and off-label medicine was necessary for survival, but that it also caused an adverse drug reaction like hair loss or anemia, then 252 (62%) parents said that they would continue with therapy for the sake of benefit the child would receive.

Most, 324 (80%), parents supported clinical trials in the pediatric population, but 388 (95%) were unwilling to let their children undergo clinical trials. A significant proportion of parents (77%) would let their children participate in clinical trials when alternate treatment was unavailable. Among the participants, 54% parents felt that regulatory bodies are primarily responsible for off-label medicines, whereas 36% felt that pharmaceutical industries were accountable. The majority of the parents (53%) supported

Table 1: Parents' views on efficacy and safety of off-label medicines

	Health condition of children (%)		P value (Chi square test)
	Parents of diseased children	Parents of healthy children	
Worry about efficacy and safety of medicines	182 (95)	195 (91)	0.1146
Worry about efficacy of off-label medicines	135 (70)	162 (75)	0.7491
Worry about safety of off-label medicines	182 (95)	200 (93)	0.9571

Table 2: Parents' views on benefit-risk of off-label medicines

	Health condition of children (%)		P value (Chi square test)
	Parents of diseased children	Parents of healthy children	
Risk first then benefit	171 (89)	155 (72)	<0.0001
Risk of adverse drug reaction	182 (95)	195 (91)	0.078
Continue use of off-label medicines despite ADR	140 (73)	152 (52)	<0.0001

ADR: Adverse drug reaction

the idea of investigating the benefit–risk of off-label use in clinical practice.

The present study found that 89.9% of the parents surveyed were ignorant about the concept of off-label medicines use in children. The findings are consistent with an earlier study in which 86% of the general public also lacked the knowledge of off-label medicines.^[4] The situation is not surprising as there is little attention being paid by media and even doctors and pharmacists often prefer not to inform parents about off-label medicines.^[5] Shared clinical decision making, in which the doctor and parents work together to select a high-quality evidence-based option, is often viewed as ideal and could improve the clinical outcome. The practice of taking consent from parents can avoid medico-legal issues, increase the confidence in prescriber and improve patient's access to medicines. At the prescriber level, publishing and disseminating experiences with the practice of informing about off-label use could motivate other healthcare professionals to adopt the same practice. Majority of the parents believed that doctors should inform them regarding off-label medicines, but there should be “uniformity” in the type of information delivered by various healthcare professionals on use of off-label medicines without causing uncertainty or confusion so as to avoid negatively impacting on medicines.^[6]

Of the parents surveyed, the majority (80%) stressed that doctors should consider the risk associated with off-label medicines first. When medicines are used as off-label, each

patient is unique and risk–benefit pertaining to him should be assessed by high-quality evidence. The prescriber can critically appraise therapeutic studies for grading of “strength of evidence” and for deciding about the applicability of research evidence to individual patient circumstances. There is a growing concern about the safety of off-label medicines, and many studies implicated off-label medicines as a risk factor of adverse drug reactions.^[7] But, meticulous explanation of benefit and risk associated with off-label use could help to improve clinical decision, especially in chronic diseases like cancer, where off-label use and risk of side-effects is high. Also, sometimes, the prescriber might not be fully convinced about the particular off-label use due to lack of clinical studies. However, the clinical condition of the patient may necessitate off-label use, and this uncertainty could deprive the patient of potentially beneficial therapy. Such participation is often observed when, after a period of aggressive chemotherapy has failed to treat the disease, parents are faced to cure the disease like enrolling in phase I/II clinical trials.^[8] The current status of off-label medicines can be improved by motivating companies to perform pediatric clinical trials through incentive schemes, better informed consent procedures in clinical practice and improved product labeling for the pediatric population.

The present study reflects the fact that there is a lack of knowledge among parents about off-label medicines, and a higher concern about its safety. The issue of informed consent is important during clinical practice and also the likely views of parents that researchers will be faced with when conducting pediatric trials. Further qualitative work is required, particularly the views of children themselves on off-label use and participating in clinical trials for the benefit of others.

Mohd Masnoon Saiyed, Aaroohi Prajapati, Gaurang Shah

Department of Pharmacology and Clinical Pharmacy, KB Institute of Pharmaceutical Education and Research, Gandhinagar, Gujarat, India

Address for correspondence:

Mohd Masnoon Saiyed, Department of Pharmacology and Clinical Pharmacy, KB Institute of Pharmaceutical Education and Research, Gh-6, Sector-23, Gandhinagar - 382 023, Gujarat, India.
E-mail: saiyed78@gmail.com

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APPENDIX

Parents' awareness and perspective on off-label medicines use in children

Dear Parents,

We request you to complete this questionnaire for assessing your awareness and perspective toward the use of off-label medicines in children. This is a descriptive, cross-sectional study carried out in Ahmedabad and Gandhinagar cities. The study will contribute to better understanding and judicious practising of off-label medicines.

Name

Profession: _____ Highest Qualification: _____

Age: _____ Gender: Male/Female

Phone Number: (M) _____ (O) _____

No. of Children: Boy(s) _____ Age: _____

Girls(s) _____ Age: _____

Any disease to your children

Instructions: [1] For each question circle the appropriate option. [2] You have to fill only one choice unless specified [3] If you want to mention other information, please use space below the question.

1. Did you know "Off-label Medicine Use" before you saw our presentation?

A: Yes B: No if yes please specify the source.....

2. Do you think that children are enough mature to understand the benefit and risk of the use off-label medicines?
A: Yes B: No
3. Who takes part in clinical decision making along with the doctor?
A: Children only B: Parents only C: Parents with children D: Parents, children and other
4. After learning about the concept of off-label medicines, are you worried about children's medicine?
A: Very Much B: Somewhat C: Not at all
5. Are you worried about efficacy (efficiency) of off-label medicines?
A: Very Much B: Somewhat C: Not at all
6. Are you worried about safety of off-label medicines?
A: Very Much B: Somewhat C: Not at all
7. How should doctor take permission before prescribing off-label medicine?
A: Written permission B: Verbal permission C: Not required
8. Will you visit a doctor who uses off-label medicines?
A: Yes B: No
9. Will you ask doctor about off-label medicines?
A: Yes B: No
10. As per your view, who should inform patients regarding the use of off-label medicines?
A: Doctor B: Pharmacist C: Nurse D: Regulatory Bodies
11. What should doctor consider while balancing benefit-risk of off-label medicine?
A: Benefit first then risk B: Risk first then benefit

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12. Do you believe that if medicines are used as off-label, they carry additional risk of side-effects as compared to approved use?
A: Very Much B: Somewhat C: No Additional risk
13. Will you continue to use off-label medicines for life threatening conditions like cancer, heart failure even if they cause adverse drug reactions like hair loss, anemia?
A: Yes, if it treats my child B: No, even though it treats my child C: Stop use, irrespective of the outcome.
14. Do you think that new medicines should be tested on children?
A: Yes B: No
15. Will you allow your children to participate in clinical trials for off-label medicines?
A: Yes B: No
16. What will be the motivating factor to participate in clinical trials for off-label medicines?
A: Receipt of new medicine B: Benefit to other children C: Non-availability of treatment in market D: Other
17. Who is responsible for the use of off-label medicines?
A: Doctors B: Pharmaceutical industries C: Regulatory bodies D: None
18. According to you, what step does regulatory bodies need to undertake to safeguard the use of off-label medicine?
A: carryout clinical trials B: should investigate its benefit-risk in real-life C: allow D: stop it.

Thanks for your participation in this study.