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## OFF-LABEL USE OF MEDICINES IN CHILDREN

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**ABSTRACT:** Although plenty of information relating to drug utilization among adults is available, the literature pertaining to children is scarce. The majority of drugs prescribed have not been tested in children and safety and efficacy of children's medicines are frequently supported by low quality of evidence. This is explained by the lack of clinical research in this population, caused by ethical, scientific and technical issues, besides commercial priorities. Therefore, most of the therapies prescribed to children are on an off-label or unlicensed basis. The off-label and unlicensed use of medicines is widespread and variable depending on the level of health care available, speciality concerned and patient characteristics. In the recent years, various laws and guidelines from the competent authorities have come up regulating the drug use and clinical research among children. This article reviews various pros and cons of the off-label use of medicines in children including various types, incidence rates, reasons, risks, consequences, management modalities, national and international guidelines related to the same.

**INTRODUCTION:** Children are not small adults. Their age, weight and surface area which may change quickly need to be accurate for appropriate dosing. During development different physiological changes occur in terms of body composition (body water, body fat, plasma proteins and hormones) which affect the drug disposition and dosage requirements. Some of the intrinsic factors such as gender, race, heredity and inherited diseases and extrinsic factors such as acquired diseases, diet may also affect the drug disposition.

Pharmacokinetic and pharmacodynamic characteristics change over a child's development, and important stages, such as drug absorption, distribution, metabolism, and clearance that can be influenced by hydrogen potential (pH) fluctuations, gastrointestinal motility, enzyme deficiency, and liver immaturity.<sup>1</sup>

The majority of drugs prescribed by doctors have not been tested in children and safety and efficacy of children's medicines are frequently supported by low quality of evidence.<sup>2</sup> This is explained by the lack of clinical research in this population, caused by ethical, scientific and technical issues, besides commercial priorities<sup>3, 4</sup> as a result of which prescribers often feel constrained on account of non-availability of suitable formulations of various paediatric medications in strengths required for this population. Therefore, most of the therapies

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prescribed to children are on an off-label or unlicensed basis.<sup>2</sup>

### Drug-Related Problems in Children:

A drug-related problem is any event or circumstance involving drug treatment that interferes or potentially interferes with the patient achieving an optimum outcome of medical care.<sup>5</sup> There are various types of drug related problems in children like heterogeneous nature of paediatric population, lack of standard dosage, inability to swallow solid dosage forms, off-label and unlicensed drug use, less acceptance of bitter oral formulations, stability and safety of excipients, needle phobias, calculation errors by prescribers, pharmacists or nurses, poor adherence, lack of available dosage forms and concentrations which necessitate additional calculations and manipulations of commercially available dosage forms or preparation of extemporaneous formulations, lack of familiarity between adult and paediatric guidelines, confusion between adult and paediatric preparations, limited published information, administration errors and use of inappropriate measuring devices.<sup>6</sup>

Therefore various factors which need consideration for selecting a drug dosage regimen and route of administration include age, weight, body surface area, appropriate dose, appropriate dosing interval, appropriate strength of drug formulation, appropriate route of administration, drug interactions, legal considerations, expected response and monitoring parameters.<sup>6</sup>

### Off-Label/Unlicensed Use of Medicines:

Off-label use is the use of pharmaceutical drugs outside the product licence for an unapproved indication, an unapproved age group, unapproved dosage, or unapproved form of administration<sup>7</sup> and the use of medication that is not approved for use by the relevant national authority is referred to as unlicensed drug use.<sup>8</sup> Both prescription drugs as well as over-the counter drugs can be used in off-label ways, although most of the studies focus on off-label use of prescription drugs. Off-label is generally legal unless it violates the ethical guidelines or safety regulations, but it does carry health risks and differences in legal liabilities.

Following definitions related to off-label use of drugs have also been proposed:

“Off-label use” means ‘all uses of marketed drug not detailed in the Summary of Product Characteristics (SmPC) including therapeutic indication, use in age-subsets, appropriate strength (dosage), pharmaceutical form and route of administration’.

“Paediatric off-label use” specifically includes: ‘all paediatric use of a marketed drug not detailed in the SmPC with particular reference to:’<sup>9</sup>

Therapeutic indication

Therapeutic indication for use in subset

Appropriate strength (dosage by age)

Pharmaceutical form

Route of administration

“Unlicensed use” means all uses of a drug which has never received a European Marketing Authorization as medicine for human use either in adults or children’. The most common form of off-label drug use involves the prescribing of currently available and marketed medication but for an indication (disease and symptoms) that has never received necessary regulatory approval.<sup>7</sup>

### Worldwide studies on Off-Label Drug Use in Children:

Off-label use of drugs among neonates and children is very common. Many studies have been conducted in various parts of the world which have shown different rates of prevalence of the off-label use of drugs. Conroy et al (1999) in a study showed that 90% of the patients were given a medicine that was either an unlicensed or used in an off-label way<sup>15</sup> while another study in Australian neonatal intensive care unit showed 47% of prescriptions were off-label.<sup>16</sup> Another study conducted in France reported 42% use of off-label drugs.<sup>17</sup>

Radley et al (2006) reported that 21% prescriptions were off-label among a group of commonly used medications<sup>18</sup> while another study reported that

78.9% of discharged children were taking at least one off-label drug.<sup>13</sup> In a survey of unlicensed and off-label use of drugs in paediatric wards of five European countries, Conroy et al (2000) reported that 67% of admitted children received drugs prescribed in off-label or unlicensed manner. Analgesics and bronchodilators were the most common off-label drugs prescribed. The commonest category of off-label drug use was pertaining to dose and frequency in three centres (Uppsala, Marburg, Bergamo) accounting for more

than half of off-label use. Among 2262 prescriptions administered to 624 children, almost half of all prescriptions (1036;46%) were either unlicensed or off-label out of which 872 were off-label and 164 were unlicensed.<sup>19</sup>

A literature review done by Pandolfini et al (2005) reported that out of 30 studies conducted between 1985 to 2004, off-label and unlicensed prescription rates ranged from 11% to 80% with higher rates found in younger patients than older ones.<sup>20</sup>

**TABLE 1: CATEGORIES OF OFF-LABEL DRUG USE**<sup>10</sup>

Off-Label Category	Description
Age	Drug not recommended in the SmPC below a certain age
Weight	Drug not recommended in the SmPC for children below a certain weight
Absence of Paediatric Information	No mention at all in the SmPC regarding paediatric use
Lack of paediatric clinical data	Stated lack of evidence of efficacy and safety in paediatric patients in the SmPC
Contraindication	Statement in the SmPC that the drug is contraindicated in children
Indication	Drug prescribed for indications outside of those listed in the SmPC
Route of Administration	Drug administered by a route not described in the SmPC

\*SmPC = Summary of Product Characteristics.

**TABLE 2: EXAMPLES OF COMMON OFF-LABEL USES OF DRUGS IN CHILDREN**

Drug	Off-Label Use(s)
Amoxicillin (high dose)	Otitis media in children <sup>11</sup>
Atenolol	Hypertension in children <sup>11</sup>
Sildenafil	Pulmonary hypertension in children <sup>11</sup>
Intranasal Desmopressin	Nocturnal enuresis <sup>12</sup>
Morphine	Pain in children <sup>13</sup>
Salbutamol	Used 2 hourly (12times daily), licensed 4 times daily <sup>14</sup>
Rifampicin	Used for enzyme induction in infant with biliary atresia <sup>14</sup>
Tobramycin	Used once daily in neonate. Licensed for twice daily <sup>14</sup>
Cyclizine	To be used in children over 6 years of age <sup>14</sup>
Belcomethasone	Used in infants under 12 months. Licensed for 2 years and above in Italy <sup>14</sup>

**TABLE 3: SUMMARY OF SOME STUDIES ON OFF-LABEL USE OF MEDICINES IN CHILDREN**

Reference	No. of Prescriptions evaluated (patients)	No. of off-label prescriptions (Percent)
Turner et al(1998) <sup>21</sup>	2013 (609)	203 (10)
Turner et al (1999) <sup>22</sup>	4455 (936)	2138 (48)
Conroy et al (2000) <sup>19</sup>	2262 (624)	882 (39)
t Jong et al (2001) <sup>23</sup>	2139 (237)	385 (18)
Gavrilov et al (2000) <sup>24</sup>	222 (132)	75 (34)
Craig et al (2001) <sup>25</sup>	237 (77)	54 (22.8)
Conroy et al (2001) <sup>26</sup>	715	236 (33)
Schrim et al (2003) <sup>27</sup>	66222 (18943)	24502 (37.2)
Neubert et al (2004) <sup>28</sup>	740 (178)	167 (22.7)
Bazzano et al (2009) <sup>29</sup>	7901	4897 (62)

Recently various studies have been conducted on the off-label use of medicines in children. Olsson et al (2011) while examining Swedish Prescribed Drug Register reported that 64% paediatric patients were dispensed with an off-label drug once.<sup>30</sup> Tansarli et al (2012) in a systematic review on the

off-label use of antibiotics in clinical practice observed that fifteen studies conducted on the paediatric patients showed that the percentage of off-label prescriptions varied between 1% to 94%.<sup>31</sup> Paediatric national survey on off-label drug use in children in Spain (2012-13) showed that out of

673 Spanish paediatricians, 75.1% knew the off-label drug use meaning, 61% doctors prescribed medicines outside the summary of product characteristics, 47% knew the need of maintaining the record of off-label drug use.<sup>32</sup> Knopf et al (2013) reported that prevalence rate of off-label medicine was 40.2% and it was found to be highest in preparations of drugs affecting cardiovascular system<sup>33</sup> while a review concluded that respiratory and allergic medicines are the most prescribed off-label drugs in children.<sup>34</sup> Scheimdl et al (2014) reported a high off-label use of respiratory system drugs among paediatric patients which were off-label due to age and indication.<sup>35</sup>

Corny et al (2015) in a review of 48 studies reported that global off-label medicine use in children in Europe was found to be 0.2% to 36% among in-patients and 0.3% to 16.6 % for out-patients.<sup>36</sup> Ian et al (2015) in a study conducted in Malta reported that 721 medicines out of 1507 were prescribed in an off label manner among 924 paediatric patients which accounted for 47.8% use of drugs in off-label manner.<sup>37</sup>

#### **Studies on Off-Label Drug Use in India:**

Off-label drug use is also common in India in sick neonates<sup>38</sup> and in paediatric practice.<sup>39</sup> A study was conducted by Saiyed et al (2014) at a paediatric general ward of public teaching hospital on 320 patients. Out of 1645 prescriptions 310 (19%) received at least one off-label drug (antibiotics, cold preparations, bronchodilators). The study reported a total of 70% off-label drug use which was mainly due to higher dosage and restricted age limits.<sup>40</sup>

Jain et al (2014) in a study on off-label drug use conducted in Neonatal Intensive Care Units across north India showed prescription of drugs which were not approved in neonates. Proportion of off-label prescriptions was 50.3% out of which 75% were not approved by FDA in neonates, 12% prescriptions had unavoidable medication errors<sup>38</sup> while another study reported that alteration in dosage form was the most common reason for off-label drug use followed by indication and age.<sup>41</sup> Bavdekar et al (2009) also reported high prevalence of off-label use of drugs among paediatric age groups. In this study 300 patients received 2237

prescriptions out of which 1573 (70.58%) prescriptions were off label in nature.<sup>42</sup> Most commonly used off-label drugs reported were anti-infectives (Ceftriaxone, Amikacin),<sup>38, 40</sup> drugs acting on respiratory system (Dextromethorphan, Chlorpheniramine, Salbutamol), nervous system (Lorazepam, Paracetamol).<sup>42</sup> Bhadiyadara et al in 2012 in a study on 170 patients also reported off-label use of drugs to the extent of 10%, Amoxicillin being the commonest.<sup>43</sup>

#### **Clinical Trials in Children:**

Clinical trials in children are essential to develop age-specific, empirically-verified therapies and interventions to develop and improve the best medical treatment available.<sup>44</sup> However, there are variety of obstacles to be overcome in this special field of medicine and development like ethical hurdles (difficulty in obtaining informed consent), need for non-invasiveness, need for micro-assays because blood samples available are very small, stratification of the patient population into at least five categories (preterm neonates, full-term neonates, infants and toddlers, older children and adolescents), difficulty in predicting long-term effects during the maturation process, rare diseases (making patient recruitment difficult and small market size providing lower return on investment), necessity for training of paediatricians to assess protocols for research, high regulatory requirements.<sup>45</sup>

European Union *ad hoc* group has issued recommendations for implementing guidelines under Directive 2001/20/EC relating to good clinical practices in the conduct of clinical trials on medicinal products for human use and also provides recommendations on various ethical aspects of clinical trials performed in children from 0 to 18 years. This will contribute to the protection of children who are the subject of clinical trials in the European Union (EU).

The third recital of Directive 2001/20/EC (The Clinical Trials Directive) in particular recognizes the need for investigation of medicinal products in the vulnerable population of children (i.e., minors in the meaning of the Clinical Trials Directive) whilst ensuring their protection.<sup>46</sup>



### Reasons for Off-label Drug Use in Children:

One of the most important reasons for off-label use of medicines is the non-availability or absence of the standard, licensed, effective and safe therapeutic options for a specific disease or condition for children and absence/inconsistent paediatric information in SmPC.<sup>47</sup> Other reasons include failure of the standard therapy, lack of alternate forms of therapy for specific age groups, lack of clinical trials in special age groups like neonates, infants, pregnant women, elderly etc. Another common reason for prescribing medicines outside the limits of their original license is availability of convincing evidence on their effectiveness and safe application in particular situations.

Some other arguments that have often been used in support of off-label use of drugs in children include the following:

The prohibitive cost of obtaining FDA approval is not involved which can be otherwise expensive and also time consuming.

Faster availability of drugs because obtaining FDA approval for legal use of drug can very much time consuming.

Physicians know their patient quite well and have got the right to prescribe an off-label drug for an immediate and better patient care.

### Consequences of off-label use of drugs:

Off-label or unlicensed drug use may exert a good therapeutic effect, fail to produce the intended effect, or may result in adverse drug effect and at the same time if prescriber is reluctant to prescribe off-label drug, the paediatric patient may be deprived of potentially effective medication.<sup>8</sup> In off-label use, children may be receiving the drugs at unapproved dosages, for unapproved indications or age that either lack safety or present safety problems. Turner et al (1999) have shown that one third to one half of adverse drug reactions (ADRs) occurring in paediatric hospital involved

1. **Off-label drug use.**<sup>22</sup> Aagaard et al (2012) in a study reported that 17% of the adverse drug reactions were associated with off-label drug

use, 60% of them being serious.<sup>48</sup> Many other studies have shown association of adverse drug reactions with off-label drug use.<sup>17, 49, 50</sup> Palmaro et al (2015) in a study conducted on off-label prescribing to paediatric out patients reported that out of 2313 patients, 736 (37.6%) patients were prescribed with an off label drug which were linked to 23 ADRs among study patients which were mainly due to unapproved indications and dosage.<sup>51</sup> Mason et al (2012) in a review reported the predisposition of ADRs with the use of off-label drugs in children.<sup>52</sup> Bellis et al (2014) concluded in the study that there was 23% increase in ADRs with prescribing of each additional off-label drug. The ADRs were found to be more related with off-label use of oncological drugs.<sup>53</sup>

### Risks of Off-label Drug Use:

Off-label drug use allows the unregulated experimental use of drugs.

2. There is lack of research standards because there is no physician standard for drug study design, documentation, data collection methods and statistical analysis.
3. Studies have shown significant association between the off-label medicine and adverse drug effects.<sup>17, 48, 49</sup> Topical off-label drug use has also been linked to adverse drug reactions but of lower impact than systemically administered drugs.<sup>50</sup> Incorrect use of drugs beyond its SmPC has also been linked to adverse drug reactions.<sup>54</sup>

### Management of Off-label Drug Use:

Due to increased and widespread off-label use of drugs, there is a need to improve the drug use by developing medicines which are suitable for children with regard to strength, taste, and formulation.<sup>21, 55, 56, 57</sup>

Pharmaceutical manufacturers need to be prohibited from marketing any off-label product for purposes that FDA has not found safe and effective. Physicians prescribe off-label much more frequently than is justifiable and risk harming their patients. In fact, 70% of off-label uses lack significant scientific support. Physicians usually

prescribe the off-label drug due to incentives of the pharmaceutical manufacturers which in-turn increases their sales turnover.

### **Guidelines and recommendations on medication use among children:**

World Health Organization has published guidelines on use of medicines in children entitled 'Promoting Safety of Medicines for Children' in the year 2007. These guidelines are intended to improve awareness of medicine safety issues among everyone who has an interest in the safety of medicines in children and to provide guidance on effective systems for monitoring medicine safety in the paediatric populations.<sup>45</sup>

In 2006, WHO and the United Nations Children's Fund (UNICEF) held a consultation on essential medicines for children in Geneva. The meeting brought together interested partners to identify ways to address the lack of essential medicines for children and to review a draft work plan for WHO and UNICEF, which became the 'Better Medicines for Children' programme. Topics discussed included availability, suitability, regulatory issues, safety and treatment guidelines.<sup>58</sup>

In 2007, the 60th World Health Assembly reviewed a report prepared by WHO on 'better medicines for children' and passed resolution WHA60.20 calling for specific actions by WHO and Member States to address the global need for children's medicines.<sup>59</sup> In December of 2007, WHO together with stakeholders launched 'make medicines child-size', to raise awareness and promote global action to ensure that children receive the right medicine in the right dose at the right time.<sup>60</sup> International organizations, governments, industry, researchers, health-care providers, professional associations, academia, and civil society have endorsed the initiative.

The American Academy of Paediatrics encourages paediatricians to advocate for research of drugs for children, and supports the publication of drug trials, including negative studies, in academic journals.<sup>61</sup> Food and Drug Administration (FDA) advocates that good medical practice in the best interests of the patient requires that physicians use legally available drugs, biologicals, and devices according

to their best knowledge and judgment for which USFDA issued statement on "Off-Label and Investigational Use of Marketed Drugs, Biologicals and Medical devices."<sup>62</sup> Best Pharmaceuticals for Children Act (BPCA) and the Paediatric Research Equity Act, 2003(PREA) have collectively resulted in an improvement in rational prescribing for children in USA. The BPCA and the PREA are two complementary federal laws that have substantially increased clinical evaluation and labelling of drugs in children both by the pharmaceutical industry and through government-sponsored trials. The PREA mandates that almost all new drugs and certain approved drugs must be studied in children for approved uses of the product if there is potential for use of that drug in children and that the application for new drug approval include the results of adequate paediatric studies unless the studies are deferred or waived by the FDA.<sup>62</sup>

European Union (EU) Paediatric Regulation has granted responsibilities which enable the European Medicine Agency to stimulate research into the uses of medicines in children and to lead to their authorisation in all age groups.<sup>63</sup> This Paediatric Regulation came into force in the European Union (EU) on 26 January 2007. Its objective is to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0 to 17 years and aims to ensure that medicines for use in children are of high quality, ethically researched and authorised appropriately and improving the availability of information on the use of medicines for children. It aims to achieve this without subjecting children to unnecessary trials or delaying the authorisation of medicines for use in adults.<sup>64</sup>

The Indian Council of Medical Research (ICMR) has issued draft guidelines for biomedical research on children, a move aimed at ensuring safe trials on children who are sensitive to side effects and adverse reactions. The draft guidelines state that drugs should be tested for safety, pharmacokinetics, and at least initial indications of efficacy in adults before being tested on children. It may often be appropriate to defer paediatric testing until adult testing has reached phase 3 or beyond, when substantial data is available on the safety and efficacy of a drug in adults.<sup>65, 66</sup>

**Concluding Remarks:**

Children have all the right to receive safe and effective drugs in proper strength, dosage, route of administration and indication. Off-label drug use is significantly associated with adverse drug reactions in children. Critically ill neonates and infants are more vulnerable to development of adverse effects. More clinical trials should be conducted in children and there is also need for vigilant post-marketing surveillance. Drug related problems should be continuously documented and more research should be done on the older drugs also in order to make medicines safer for children.

Clinical decision making should always be guided by the best available evidence and the well-being of the individual patient. Clinicians use their professional knowledge and judgment to determine drug utilization in children. In such situations, a clinician may play a significant role in adding to therapeutic information by publishing his or her experience with off-label uses of drugs. These reports can serve as the basis of more formal efficacy and safety studies and can serve as a therapeutic decision-making resource for other physicians also.

Drug utilization studies in neonates, paediatrics and adolescents need to be persistently conducted to ascertain the patterns of drug usage in these patient populations and suggest changes wherever required. These studies should be a regular exercise on perennial basis in every hospital for the sake of generating evidence and devising appropriate policies required for promoting rational use of medicines in children.

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