

# Off-label use and designation of age group-specific contraindications for pharmacotherapy in children in Korea

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Children should be treated with medicines that have been tested for efficacy and safety in the given age groups. In reality the majority of drugs being used in children lack such information, inevitably leading to the “off-label use.” Over decades there have been concerns regarding risk of adverse effects with such off-label uses. However, in most countries rational application of off-label uses have not been prohibited, since it may be the only available and perhaps the best possible treatment option. In contrast, in an effort to minimize such use and per se ‘protect’ children from possible harm associated with it, Korea has launched “Drug Utilization Review” system, which included age group-specific contraindications, based on the labeling information approved by Ministry of Food and Drug Safety. The problem lies in the definition and scope of ‘contraindication.’ Lack of evidence for safety and concern for risk of serious adverse drug reactions are the basis for contraindication. This leads to branding of off-label uses as contraindications in certain age groups. This policy is restricting the already scarce treatment options and suffocating the initiative for developing better pharmacotherapy for children. We should learn from other countries that have travelled more to provide better medicines to children. Clinical trials of new drugs as well as existing drugs in pediatric populations are strongly encouraged. Simple prohibition of off-label use is not the answer, but rather systematized management of off-label use as well as conduct of clinical trials in pediatric age groups must be encouraged and supported.

## Introduction

“Pediatric patients should be given medicines that have been appropriately evaluated for their use. Safe and effective pharmacotherapy in pediatric patients requires the timely development of information on the proper use of medicinal products in pediatric patients of various ages and, often, the development of pediatric formulations of those products.”[1]

Unfortunately, in our daily practice of medicine, children are quite commonly subject to exposures to drugs that have not been appropriately tested for their efficacy and safety in the relevant age groups. Even though there are a few cases in which unlicensed drugs might have to be prescribed as in rare diseases,

depending on the regulations of each country, most of the times the drugs used in children are licensed and made available for prescription based on the discretion of the healthcare providers. The labels usually contain clinical data for the evidence of efficacy and safety in the general adult populations in which the drugs most commonly will be prescribed. But in majority of drugs, there is a lack of information for pediatric use or data on efficacy and safety in certain pediatric age groups.

It is the off-label use of licensed drugs. The frequencies of off-label uses in pediatric age groups worldwide range between 11 and 80%;[2] relatively higher in younger patients and in hospital settings.[3] Almost 80% of the pediatric patients hospitalized at tertiary care hospitals received at least one “off-label” or unlicensed prescription of medication.[4]

However, the major concern stemming from the prevalence of off-label use of drugs in children is the increased risk of adverse

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drug reactions.[5-7] Quite a number of reports have been published regarding this issue. Unfortunately, or rather fortunate enough, most of them were lacking in statistical significance or power and inconclusive, showing only the trends of association between off-label use and ADR. In one of the studies conducted in the US, the investigators utilized the FDA administrative database containing inpatient resource utilization data from tertiary care pediatric hospitals, where off-label use is quite commonly done. But it was difficult to determine whether certain off-label uses are unsafe or ineffective and which result in substantial benefit.[4,8]

“Off-label use” of licensed drugs is not the same as illegal use or indiscreet use. It is widely accepted that off-label uses may be the only available option and perhaps the best possible choice. Based on the review of literature regarding the off-label use, it is obvious that pediatricians around the world are facing the same challenges and taking a similar approach to solve the problems; that is, most pediatricians would decide to use drugs off-label to meet the needs of the patients at hand for their best interests. [9] Medical necessity would be the primary reason for their decision. With the full understanding of the fact that efficacy and safety of the drugs used off-label have not been established through adequate clinical trials in the relevant age groups at the time of licensing, physicians and parents have to make a choice, because their children must be treated for the diseases at hand against the lack of proven efficacy and safety in these age groups.

It is important to protect our children from the potential harm associated with the off-label use of drugs. But at the same time children should be given the best possible treatment options available. There is a fine line between these two big propositions. It would be best to pick out only those off-label uses that are safe and effective. But what about those that seem effective based on previous experience of off-label uses and data collected so far but questionable in safety? Or those that have shown safety but questionable efficacy?

### Current schemes of designation of age group-specific contraindications in Korea

In 2008 a pilot program of Drug Utilization Review (DUR) was started by Health Insurance Review and Assessment Service (HIRA). The program has been extended nationwide since 2010, and currently it is officially utilized throughout the healthcare institutions for the guidance of prescription behaviors of the prescribers, based on the databases built to check contraindications for concomitant use due to drug-drug interactions, age group-specific contraindications, duplicate prescriptions, over- or under-doses, and others. HIRA uses in the DUR program the labeling information of Korea Ministry of Food and Drug Safety (MFDS) as the basis for the criteria of the aforementioned parameters.

It is a helpful tool in a sense that prescriptions can be screened for apparent prescription errors or possible risks for toxicities.

There is a mechanism that allows prescribers to override the warnings of the system when in need, seemingly supportive and educational to the healthcare providers helping to avoid human errors. However, any practices outside the criteria and guidelines set by HIRA, endorsed by MFDS, will have to be justified with the submission of the evidence for efficacy and safety, or the reimbursement will be denied. This scheme for controlling the prescription behavior might be the strongest measure that can effectively discourage most of the off-label uses, and as the regulatory agency and HIRA believe, protect patients from indiscreet drug uses. Added to the scheme, public relations and propaganda revealing simple numbers of prescriptions made outside the criteria, leading to the blame in the healthcare community for its irresponsible actions, further stifle even the good intentions and perhaps the chances of giving the best treatment options to the patients, not to mention the opportunities for developing new indications and uses of the licensed drugs.

### Definitions and Scope of Contraindication

According to the guidelines of MFDS, “active pharmaceutical ingredients contraindicated for use at certain age groups are those that should not be used because safety has not been established or there is concern for risk of serious adverse drug reactions in the given age groups.”[10] The dictionary definition of contraindication is ‘sign that someone should not continue with a particular medicine or treatment because it is or might be harmful’.[11] When a drug is contraindicated, there should be enough evidence that the drug is or might be harmful. The clause “because safety has not been established” means that there is lack of information on safety. Most common cause for the lack of information is because clinical trials have not been carried out in the given age groups for a variety of reasons. In a real sense, it does not mean that if you use the drug in a given age group, it will be or most likely be harmful. It just means that you do not know whether the drug is or might be harmful. However, in most cases in the labeling information approved by MFDS, the lack of information on safety as well as efficacy is regarded as contraindications. In fact it is critical that the current labeling practice by MFDS should be revisited. “Contraindications” are ‘misused’ and ‘overused’ too often and inappropriately in the MFDS-approved labeling information. This practice misleads the public that off-label prescriptions might be viewed as something that should not be done because the regulatory agency has designated as contraindicated. Simply put, this rule is literally saying that you are prohibited from prescribing drugs outside the labeling information officially approved by the MFDS. No off-label use allowed. But is banning the off-label use by branding it as “contraindication” the best possible way to protect children from indiscreet off-label uses?

In the past children were excluded from clinical trials with the intention of protecting them from the possible harm of being in the trials. This attitude, along with financial, technical and regulatory hurdles that are inherent in pediatric drug development,

left children vulnerable to the harm that arises from the lack of information or “ignorance” about the drugs, when off-label use is inevitable or seems promising. Now children are excluded from off-label uses with the intention of protecting them from the possible harm of off-label use. This policy will definitely save children from harm of off-label uses. But will it save children from illness or suffering that require treatment options better than the currently available approved pharmacotherapy?

Based on this definition, the presence of concern for risk of serious adverse drug reactions is another important criteria for contraindication. Designation or branding of contraindications should be based on more sound scientific grounds than simple reasons like “don’t know because not tested” or “concern for risk”. Most of the associations based on reports of isolated cases can be described in the warnings or precautions sections rather than in the contraindications. If concern is real, presence of such concern must be substantiated with enough evidence. Just by raising a concern without scientific basis, it will lead to unnecessary restriction of use of drugs that might be useful when in need.

### Examples of Unsubstantiated Designation of Drugs as Age group-specific Contraindication in Korea

There are currently 129 items that are designated to be contraindicated based on age. These are supposed to be selected based on an algorithm. The flow of reasoning seems quite reasonable at a glance. However, when delved into depth, appropriateness of the translation or interpretation of the expressions used in the labels in other countries may have to be questioned. Furthermore, inconsistent and irrational over-designation of contraindications in the labeling information by MFDS may pose serious problems. Moreover, there are no reasons given at all why these drugs have been designated contraindications in certain age groups. Another important issue is that the information that the judgment of designation of contraindication is based on the information that is not up to date. Except for a few that have been known to cause serious adverse effects in children over the past several decades, most do not have logically acceptable basis for designating any of these to be contraindicated in the given age groups.

One example is lorazepam in injection form, which in general medical practice and in many textbooks for neonatal care of refractory neonatal seizure is indicated as a third line choice for short acting anticonvulsant after phenobarbital and phenytoin failed. However, according to the DUR guidelines, it is contraindicated in neonates less than 4 weeks old. The main reason for this designation is that lorazepam in injection form contains benzyl alcohol, which is associated with life-threatening respiratory distress in premature infants. Based on the drug label of the original product,[12] lorazepam is a nearly white powder almost insoluble in water. Each mL of sterile injection contains either 2.0 or 4.0 mg of lorazepam, 0.18 mL polyethylene glycol 400 in pro-

pylene glycol with 2.0% benzyl alcohol as preservative. The label clearly indicates in the “Precautions” section that the “gasping syndrome,” characterized by CNS depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine, has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Although normal therapeutic doses of Ativan injection contain very small amounts of these compounds, premature and low-birth-weight infants as well as pediatric patients receiving high dosages may be more susceptible to their effects. On the other hand, in the “Contraindications” section, it is contraindicated in patients with a known sensitivity to benzodiazepines or its vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol), in patients with acute narrow-angle glaucoma, or in patients with sleep apnea syndrome. American Academy of Pediatrics Committee on Drugs published a position paper regarding “Inactive” Ingredients in Pharmaceutical Products: Update.[13] In the report, it states that “a number of neonatal deaths and severe respiratory and metabolic complications in low-birth-weight premature infants have been associated with use of this agent in bacteriostatic saline intravascular flush and endotracheal tube lavage solutions.” “At low doses, such as those present when medications preserved with benzyl alcohol are administered, benzyl alcohol is safe for newborns.” The usual dosage of lorazepam is 0.05 to 0.1 mg/kg/dose IV slow push, repeated based on clinical response. For each such dose, it contains 0.5 mg/kg benzyl alcohol. You will have to use 200 doses per day and get 100 mg/kg/d of benzyl alcohol. It is a well-known pharmacological principle that “any drug can be a poison if given too much.”

There are many drugs on the list that should be removed based on up-to-date information. Ciprofloxacin either tablets or injection is contraindicated under 18 in the DUR Age group-specific Contraindication guidelines. USFDA label indicates that ciprofloxacin is contraindicated for “history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components.” The label also clearly states that “ciprofloxacin causes arthropathy and histological changes in weight-bearing joints of juvenile animals resulting in lameness” and that “although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to the controls, including events related to joints and/or surrounding tissues.” However, at the same time, it describes specific pediatric dosage guidelines for certain conditions such as complicated urinary tract infection or pyelonephritis in patients from 1 to 17 years of age, based on the information obtained from clinical trials in these age groups. Levofloxacin is another one that is quite similar to ciprofloxacin. Levofloxacin either tablets or injection is contraindicated under 18 in the DUR Age group-specific Contraindication guidelines. USFDA label has a boxed warning that fluoroquinolones, including levofloxacin, are associated with an increased risk of tendinitis

and tendon rupture in all ages. However, it contains the dosage information for pediatric patients less than 50 kg and greater than or equal to 6 months of age.

Fentanyl injection is contraindicated under 2 years of age in the DUR Age group-specific Contraindication guidelines. USFDA label shows that it is contraindicated only for known intolerance to the drug or other opioid agonists. It clearly states that “safety and efficacy of fentanyl citrate in children under 2 years of age have not been established. Rare cases of unexplained clinically significant methemoglobinemia have been reported in premature neonates undergoing emergency anesthesia and surgery which included combined use of fentanyl, pancuronium and atropine.”

The approach that regulatory agencies like USFDA take to prevent indiscreet use of drugs off-label is quite different from what is being done in Korea. It is quite evident in the example of venlafaxine. It is contraindicated under 18 in the DUR Age group-specific Contraindication guidelines. The USFDA label describes in the ‘Pediatric Use’ section that “Safety and effectiveness in the pediatric population have not been established. Two placebo-controlled trials in 766 pediatric patients with MDD and two placebo-controlled trials in 793 pediatric patients with GAD have been conducted with Effexor XR, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Effexor in a child or adolescent must balance the potential risks with the clinical need.” The labeling gives relevant information for the guidance of healthcare providers to decide, rather than simply prohibiting the use by contraindicating it.

## Survey

In the survey conducted in 2011 involving physicians in Korea,[14] most physicians were favorable to “off-label” use of drugs when medical necessity was acknowledged in cases where there were no other treatment options or where “off-label” use was expected to be superior to other available drugs. Based on the workplaces, 37% worked at local clinics, 17% at secondary hospitals, and 46% at tertiary care hospitals including university hospitals. Internal medicine specialists comprised 33%, followed by 28% of pediatricians. 62% had experience in medical practice for over 10 years and 24% over 5 years. While the majority treated adults, 39% practiced medicine for children, including 31% who took care of infants less than 6 months.

In terms of understanding of the scope of the off-label use, 85% regarded the use outside the approved disease conditions as off-label use, followed by use of drugs outside approved dosages, duration, subtypes of disease conditions or age groups. Most respondents were favorable to off-label uses in certain situations such as when there is no available drug for a given indication (67%), followed by conditions where the off-label use can maximize the scope of utility or usefulness of the approved drugs. About a half of the respondents answered their reason for off-label uses as the lack of treatment options in a given age

group. 42% responded that it was physicians’ rights to prescribe the already approved drugs off-label. On the contrary, safety issues, lack of evidence on safety and efficacy, and risk of liability were main reasons for negative attitude toward off-label uses.

In terms of experience of the off-label use, 73% respondents issued at least one prescription off-label during the past year. Two thirds of the physicians answered the major factor that caused hesitation in their off-label use was the fear of denial of reimbursement from the insurance agency, but at the same time 61% responded that they used the drugs off-label despite the hindering factor in cases where there were no available treatment options. The most common rationale for their use of drugs off-label was the personal judgment that it was the most appropriate treatment option (49%), followed by medical textbooks and literature as the evidence (45%), and personal experience (38%).

The majority of the respondents agreed on the necessity for generating evidence for the current off-label uses as well as need for prescription guidelines. For the question asking whether it would be appropriate to use drugs off-label when evidence is lacking, the responses were distributed in a normal distribution curve around the neutral position in the middle.

The respondents picked the treatment guidelines provided by academic societies or medical professional organizations as the most reliable and appropriate source of evidence for off-label use (78%), followed by review articles (57%), meta-analysis article (52%), and reports of individual randomized control trials (48%). For the generation of scientific data for the supportive evidence of off-label uses, many agreed that randomized control trials should be conducted, while some considered the report and database of off-label uses as the most needed. 93% favored the support from regulatory agencies in acquiring evidence. 61% answered the primary objective for conducting clinical trials should be for safety data. But in general, prescriptions were issued based on KFDA approved labels and criteria for National Health Insurance Guidelines.

## Situations in Other Countries

One common feature among the off-label use-related regulations of the countries studied in this article is that none of them designated drugs as contraindications based on the lack of evidence for safety in certain pediatric age groups. On the contrary, unless there is a strong signal that is suggestive of close association between the off-label use of a drug and a serious adverse event and requires in-depth investigation, off-label uses are generally permitted based on the discretion of the healthcare providers.

## US

In principle, USFDA does not control the use of licensed drugs by physicians as long as the drugs are used for the best interest of patients based on the knowledge and discretion of physicians either on- or off-label. However, when a physician uses a drug off-label, the decision must be based on the supportive evidence

that is derived from sound scientific principles and medical needs. At the same time, a physician must keep the records of individual responses to the drug regarding its efficacy and safety. When a licensed drug is used either on- or off-label, it is not required to submit applications to or obtain approval from either USFDA or IRBs. Depending on the institutions' policies, off-label uses can be subject to review by IRB or other reviewing bodies.[15] It is important that the promotion of off-label uses as a new intended use without USFDA approval or clearance is regarded as violation of the law. However, it is also acknowledged by USFDA that healthcare professionals are entitled to lawfully use or prescribe off-label, recognizing that the off-label uses may be important therapeutic options and may be a medically recognized standard of care.[16]

In the case where there is a request for investigation into the association of off-label use of a drug with serious adverse effects, USFDA may launch an investigation and publish its reports as seen in the case of misoprostol for the off-label use for cervical ripening or labor induction petitioned by Tatia Oden French Memorial Foundation.[17,18] Safety information obtained from the review of off-label uses may be updated in the label. For example, terbutaline, approved for prevention and treatment of bronchospasm in patients with asthma, bronchitis or emphysema, has been used off-label in acute obstetric conditions such as for the treatment of preterm labor or uterine hyperstimulation, or for the prevention of recurrent preterm labor. USFDA reviewed the postapproval adverse event reporting system (AERS) and medical literature and reported its decisions that IV terbutaline not to be used for the purpose of preventing preterm labor and not to be used over 48 to 72 hours for the treatment of preterm labor. Oral terbutaline was advised against use for prevention or treatment of preterm labor because of the proven lack of efficacy as well as the concern for safety issues as with IV terbutaline. These decisions were updated in the label, which were consistent with the official statements by American College of Obstetricians and Gynecologists (ACOG).[19]

USFDA's policies on the approved drugs are towards the life-cycle management through risk management and more strict rules to be imposed on off-label uses. However, it is made clear and emphasized that the basic policy of USFDA that it does not intrude on or interfere with individuals' health decisions is upheld. The rights of patients and physicians for the use of drugs at their discretion should be maintained. But at the same time USFDA realized that there should be a mechanism that can help wiser decisions based on more available information on efficacy and safety when faced with difficult medical decisions.[20]

In line with the aforementioned policy statement, US launched pediatric initiatives that resulted in legislative acts for obtaining efficacy and safety information on pediatric populations through clinical studies. Starting with FDAMA/Pediatric Exclusivity Provision in 1997, followed by Best Pharmaceuticals for Children Act in 2002 and Pediatric Research Equity Act in 2003 required and encouraged pediatric studies to be conduct-

ed. These rules were extended in 2007 under FDAAA and made permanent under FDASIA in 2012.[21] Roberts R et al reported that these rules stimulated pediatric clinical studies and contributed to the improved understanding of drugs used in children and improved safety.[22]

### The Netherlands

Medicines Evaluation Board (MEB) and Dutch Health Care Inspectorate (IGZ) do not, in principles, object to the responsible uses of drugs off-label. However, if adequate evidence cannot be given for the uses, the off-label use is prohibited. Appropriate off-label use is defined as the use with scientific evidence for a given indication even though it has not been evaluated by MEB and not included in the label. Most of the evidence for off-label indications are those published in the scientific journals. The decision whether the proposed off-label use is the best possible treatment for the patient is the responsibility of the physician. But it is required for the physician to give information on the pros and cons of the suggested off-label use to the patient. To this end MEB and IGZ make effort to provide relevant and up-to-date information on off-label uses to the physicians. In addition, MEB and IGZ collect adverse events information on off-label uses and provide them to the healthcare providers.

### Australia

Off-label use of approved drugs is not a violation of Therapeutic Goods Act. If there is appropriate evidence with quality data for the use, it is regarded as valid. On the other hand, in certain cases where the drug is not used off-label despite the fact that there exist sufficient amount of acceptable evidence with quality data for the off-label indications, the physicians may be held accountable for malpractice. Furthermore, the use of unlicensed drugs can be legal with sufficient evidence. However, individual medical institutions should make provisions to ensure maximizing the safety and efficacy of such off-label uses.

### Conclusion

We always say children are not miniature adults. It means children are different in many ways qualitatively or quantitatively from adults, even though children share most of the common physiologic principles and features with adults. There are more similarities than differences. Inasmuch as we know about the developmental changes, there is a possibility of extrapolating adult data into pediatric age groups to a certain extent. However, the time that we must spend to attain the knowledge and information on these developmental changes, which may vary according to the drugs in use, is not allowed to the patients at hand. In order for us to come up with better guidelines for pharmacotherapy in pediatric age groups as quickly as possible, we need to find out and confirm what we believe and anticipate from knowledge and information so far gathered or what we have seen through our past years' experience of off-label uses. Prohibiting and simply minimizing off-label uses

will be a short-sighted approach, and may not be a solution to the underlying problems. Conducting clinical trials in pediatric age groups could be an answer. As US and EU are leading the movement, we will have to participate, collaborate, cooperate, and contribute to the generation of data that will be used as evidence for or against specific current off-label uses of drugs. The responsibility lies in all of us, healthcare providers, industry and government, to provide better medicines to children.

## Conflict of Interest

Nothing to declare

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