Prescription off-label medicine for children at saras sehat pharmacy in tegal city

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**Abstract.** Use that does not correspond to drug information and marketing authorization is referred to as off-label drug prescribing. The child population is particularly at risk of off-label drug prescribing due to the specificity of the condition. This study was conducted to find out how the prevalence of off-label drug use in children in Saras Sehat Pharmacy in Tegal City.

This study is a descriptive study with data retrieval retrospectively. The study subjects in the form of recipes and medical record data of children aged 0-12 years in november 2021. Classification of off-label drugs is grouped with the ATC (AnatomicalTherapeutic Chemical)system. Identify off-label drugs using BNFC, DIH, PDH, and IONI.

The total prescribing of children during the study period was 1,495 prescriptions, a total of 368 prescriptions met the inclusion criteria. The total drug use of 368 prescribing was 2,743 drugs with 67 types of drugs. Based on the results of a study of 368 recipes found a total of 177 prescription sheets (48.10%) identified off-label. The prevalence of off-label drug prescribing categorized as off-label indications amounted to 40 (1.45%), off-label age 341 (12.43%), off-label contraindications 22 (0.80%), off-label dose 3 (0.11%), and no off-label category of route giving was found. The most widely prescribed off-label drugs are Decongestant drugs, namely Triprolidin and Pseudoephedrine as much as 124 (4.52%). Based on the results of this study it is known that off-label drug prescribing in children is still high enough that supervision related to the risk of drug use needs to be done.

**Keywords: off-label drugs, children, prescription, pharmacy.**

# Introduction

In the selection or drug regimen should be based on the disease, age, sex, weight, and physiology of the patient. However, sometimes doctors prescribe drugs outside the indications listed on the label, or better known as off-label drugs. Off-label drugs are drugs that are prescribed but not used according to the indicated drug indications. These discrepancies include drug indications that are not in accordance with those stated by the marketing authorization as well as dose, patient age, and route of administration [1]. One of the reasons for the use of off-label drugs is the lack of clinical response to previous treatment, contraindications to other alternative drugs such as the availability of approved drugs according to indications and patients with alternative treatments for clinical reasons[2]

In the study of Eri Destin et al 2020[3] it was found that the use of off-label in prescribing acute respiratory infections for pediatric patients was 23% with the off-label category of age (15.67%), off-label dose ( 5.70%) , off-label route of administration (1.22%) and off-label indication (0.40%) and there were no off-label cases in the contraindication category. The most commonly prescribed off-label drug for pediatric ARI is chlorpheniramine maleate.

Safety and effectiveness assessment is one of the key aspects of using off-label prescriptions. The FDA recognizes that, under certain circumstances, the use of off-label drug products is approved if rational, and acceptable to medical practice. In this context, it is important that doctors should have access to accurate information about the drugs used that are not as indicative or off-label [4].

Knowledge about off-label drugs is considered important to avoid the occurrence of medication errors or unwanted things. Drug selection in patients should be careful because not all drugs that are not given without indications can be used, in addition to having the advantage of off-label drug use also has disadvantages. Then medical personnel, especially pharmacists, are required to have more knowledge about drugs.

Before considering the off-label drugs used, safety support aspects and evidence of efficacy need to be evaluated to determine the risks and benefits that occur, especially drugs that have been approved by BPOM. Considering or reviewing the use of off-label drugs, health worker or medical personnel must be based on existing scientific evidence (evidence based) related to rational drug use.

The use of off-label drugs in Indonesia itself still has little evidence of prevalence data as well as known existence of its use. In a previous study, it was explained that the use of off-label drugs in prescribing acute respiratory infections was 23% in pediatric patients. One of the pharmacies in Tegal district that has a pediatrician practice is Saras Sehat pharmacy, where many pediatric patients carry out examinations at the site. Therefore, this study will identify how many off-label drug prescriptions in Indonesia, especially pediatric patients at the Saras Sehat Pharmacy in Tegal Regency.

# Methode

## Research design

This research is an observational study with retrospective data collection in the form of prescriptions from pediatricians. This study reviews or examines off-label drug prescribing and patterns of use. Identification of prescribed drugs including off-label categories or not based on the Drug Information Handbook, Pediatric Dosage Handbook, British National Formulary Children’s, and the Indonesian National Drug Informatory.

## Place and time

This research was carried out at the Saras Sehat Pharmacy, Tegal Regency, with a period of three months to collect research data, from October to December 2021.

## Data Types and Sources

The type of data in this study is in the form of secondary data taken retrospectively. The data source is a pediatrician's prescription for the period of November 2021 that meets the inclusion criteria.

## Population and Sample (Research Subject)

### Population

The population in this study is all prescriptions for pediatric patients for the period of November 2021 that were prescribed by Pediatricians at the Saras Sehat Pharmacy, Tegal Regency that met the inclusion and exclusion criteria. The population of children's prescriptions for the November 2021 period amounted to 1,495 prescription sheets, and those who met the inclusion criteria were 368 prescription sheets.

### Sample

The sample in this study was all population prescriptions for pediatric patients at the Saras Sehat Pharmacy, Tegal Regency for the period November 2021, which met the inclusion criteria. The sampling technique was carried out using the Total Sampling method, where all members of the population who had met the requirements were used as samples[5]. Inclusion and exclusion criteria in the population and sample of this study are as follows:

#### Inclusion Criteria

1. Prescription for pediatric patients for November 2021
2. Prescription for children aged 0-12 years
3. A complete prescription includes name, age, drug name, dose, dosage strength, instructions for use, duration of drug use and completeness of diagnostic data

#### Exclusion criteria

Research subjects who did not meet our inclusion criteria were excluded if the prescription was incomplete and damaged or illegible.

## Identification of Research Variables and Operational Definitions

### Research Variables

The research variable in this study is Prescribing Off-Label Drugs in pediatric patients at the Saras Sehat Pharmacy, Tegal Regency.

### Operational definition

1. A prescription is a written request from a doctor, dentist or veterinarian who is granted a permit based on the prevailing laws and regulations to a pharmacist managing a pharmacy to provide and deliver medicines for sufferers.
2. Off-label drugs are drugs prescribed by doctors outside the indications in the brochure or label that have been approved by the authorized agency or agency (BPOM or FDA) or are given in different dosage forms from those approved.
3. *Off – label* Age if used outside the approved age range
4. *Off - label* dose if used at a dose different from the approved dose
5. *Off - label* Indications if used beyond the indications stated on the label or approved brochure
6. *off-label* contraindicated if its use causes contraindications for patients whose age is not in accordance with the designation of the drug.
7. *0ff – label* route of administration Drugs are said to be off-label route of administration, i.e., if the drug is given through a method or route of administration that is not permitted or improperly as stated on the label.
8. Drug classification system ATC (Anatomical Therapeutical Chemical) is a system used to classify drugs in five different levels. Drugs are divided into fourteen main groups.

## Research Instruments

To determine the prevalence of off-label drug prescribing in pediatric patients at the Saras Sehat Pharmacy, Tegal Regency, the research instrument used was pediatrician prescriptions for the period November 2021.

Drugs are classified according to the ATC system. and references to determine off-label drug prescribing in children, including the Drug Information Handbook, Pediatric Dosage Handbook, British National Formulary Children’s, and the Indonesian National Drug Informatory.

## Procedure

1. Preparation

This preparatory stage includes making a research proposal according to the proposed title, then a preliminary study to determine the prevalence of off-label drug use, then proceeding with a proposal hearing and obtaining a research permit.

1. Permission

Permission to conduct research at Saras Sehat Pharmacy. The permit is issued by the Research and Development Center of the Harapan Bersama Tegal Polytechnic, then submitted to the Pharmacist in Charge of the Pharmacy.

1. Data retrieval

Collecting data is done by screening prescriptions and medical record data, namely identifying the patient's name, age, gender and disease diagnosis. The drugs in the prescriptions were reviewed to determine the number of uses and identification of drugs classified as off-label. Questions and answers were also conducted with pharmacists at the Saras Sehat Pharmacy to ask questions related to prescriptions that could not be read by researchers.

1. Data management

Prescription screening data and medical records were then characterized according to gender, age and diagnosis. Use Prescription drugs are classified by the ATC system and as a percentage, what class of drugs is most prescribed. Off-label drug prescriptions were identified based on off-label categories (Age, indication, dose, contraindication, and route of administration) with references to DIH, PDH, BNFC, IONI and other supporting references.

## Data analysis

Analysis of the data in the form of patient demographic data, drug use profiles, drug categories based on ATC and off-label drug prescriptions for indication categories, age, dose, contraindications and route of administration are presented in the form of tables and diagrams. Off-label drug identification refers to the reference DIH, PDH, BNFC, IONI.

Conclusions were drawn to determine the prevalence of off-label drug prescribing by percentage of what off-label categories were used the most.

# RESULTS AND DISCUSSION

## Characteristics of Research Subjects and Disease Diagnosis

In this study, the population of children's prescriptions for the November 2021 period was 1,495 prescription sheets. According to the inclusion criteria, 368 prescription sheets were obtained and 1,127 prescription sheets were excluded from the study because the patient's age data were incomplete. Recipes that met the inclusion criteria were used as samples.

**Table. 3. Characteristics of Research Subjects**

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| --- | --- | --- |
| NO | Patient Characteristics | Amount (%) |
| 1. | **Gender**  Man  Woman | 195 (52.99%)  173 (47.01%) |
| 2. | **Age**  0 – 5 years  5.1 years – 12 years | 271 (73.64%)  97 (26, 36%) |

The results of the study found that the number of male patients was more dominant (52.99%) than girls (47.01%). The dominance of patients aged under five (aged 0-5 years) was greater, namely 271 patients (73.64). Basically, the age of toddlers as a stage of development is quite vulnerable to various diseases. Several factors that trigger disease in toddlers include the structure and anatomy of the body's organs, the immune system is excessive so that it is easy to have allergies or deficiencies so that it is easy to become infected, infectious diseases that are not treated properly, genetic factors and geographical conditions[6].

## Disease Diagnosis

The results of the observation found that the distribution of disease diagnoses was ARI (25.54%), bronchitis (11.41%), diarrhea (11.41%), asthma (11.14%). The population of children is susceptible to respiratory tract diseases due to infection with pathogens (bacteria and viruses) and allergens.

The percentage of children aged 1–5 years is more likely to go to the clinic than children aged 6–12 years and more boys than girls (Table 3). This is because children aged 1-5 years are more susceptible to infection than children aged 6-12 years. In general, children aged 1-5 years have a low immune system compared to older children (Jadhav S et al, 2018). In infants to toddlers, ARI is generally the first occurrence of infection and the immune process has not been formed optimally so that immunity not perfect. In addition, children under five often put something in their mouth that can be an intermediary for the entry of germs into the body [7].

Based on the diagnostic data, the tendency for male patients is more often to develop respiratory tract diseases. Sex differences in the incidence of respiratory disease vary, depending on age and differences in biological characteristics. The role of genetics is very important in influencing the immune system, especially at an early age. The number of X chromosomes in women is more than in men, thus affecting the amount of micro-RNA that plays an important role in immunity. Another factor is that boys tend to be more active than girls so that they are more likely to be exposed to the causative agents of ARI. The incidence of respiratory disease in boys aged 2-5 years is 2 times more often than girls[8].

The results of our study are in line with the research of Maakh et al, as well as the results of Sujata Jadhav's study where non-pneumonia ARI patients were more common in boys aged 1-5 years than girls.

## Distribution of Patient Drug Use

During the study, from 368 prescription sheets, 67 items were found with a total use of 2,743 times.

The drug with the most use was Cefixime (10.93%) which was indicated as an antibacterial. Cefixime is a third-generation cephalosporin broad spectrum antibiotic used to treat a number of bacterial infections such as otitis media, urinary tract infections, strep throat, pneumonia, gonorrhea, and Lyme disease[9].

## Classification of Drugs Based on the ATC System

The use of drugs is then grouped based on the ATC (Anatomical Therapeutic Chemical) system, which is the system used to classify drugs. This system divides drugs into different groups according to the organ or system in which they provide activity or the therapeutic and chemical characteristics of the drug [10]

From the results of the analysis based on the ATC system, the highest drug prescription was for the respiratory system drug category (34.63%). This result is in accordance with the data on the diagnosis of the disease that most patients suffer from, namely respiratory tract diseases. At the age of toddlers are very susceptible to respiratory tract diseases such as ARI, bronchitis, asthma, common cold and pharyngitis. Basically, toddlers are quite vulnerable to the emergence of various kinds of infectious diseases. This is associated with the structure and anatomy of organs and the immune system that is not yet fully developed. Cyproheptadine, Triprolidine, Pseudoephedrine was more dominantly prescribed, followed by Erdostein HCl, Procaterol HCl, Cetirizin HCl and Ambroxol. The drug prescribing profile is in accordance with the dominance of the disease diagnosis, namely ARI.

*Cyproheptadine*is an antihistamine drug that is of great use in the treatment of nasal allergies, allergic rhinitis, to relieve red eyes, watery eyes, irritation, itching, sneezing, and runny nose caused by allergies, airborne irritation, and fever. Triprolidine and Pseudoephedrine are decongestant drugs that can be used to treat nasal congestion symptoms in cases of flu or colds, as well as other respiratory diseases. Erdostein HCl belongs to the class of mucolytic drugs, namely drugs that are useful for thinning phlegm. Usually, this drug is used to treat acute cough symptoms in people with chronic bronchitis. Procaterol HCl is a drug to treat shortness of breath due to asthma and Chronic Obstructive Pulmonary Disease or COPD. Ambroxol is a medicine to relieve cough with phlegm caused by several conditions, such as bronchitis or emphysema. In conditions of cough with phlegm caused by a bacterial infection, the use of ambroxol can be combined with antibiotics[11].

## Off-Label Drug Prescribing Characteristics

Based on research from a sample of 368 prescriptions, which were identified off-label were 177 prescription sheets (48.10%) and on-label were 191 prescription sheets (51.9%) (Fig. 1).

**Figure 1. Number of comparisons of Off-label and On-label prescriptions**

Category off-label indication (1.46%), off-label age (12.43%), off-label contraindication (0.80%), off-label dose (0.11%).

### Category Off-Label Indication

The most dominant use of off-label indicated drugs in children in this study was Ondansetron, which was 26 cases. Ondansetron is an anti-emetic drug class 5-HT3 blocker that works by blocking serotonin in the body to prevent nausea and vomiting. Some guidelines do not recommend antiemetics for the management of gastroenteritis in children. This is due to concerns about the side effects of anti-emetic drugs, namely sedation, extra pyramidal reactions, and diarrhea. *Food and Drug Administration* (FDA) also only recommends ondansetron to prevent and treat vomiting due to chemotherapy [12]

Cyproheptadine is used to relieve allergies, such as in cases of allergic rhinitis, allergic conjunctivitis, and mild allergic manifestations of the skin such as urticaria and angioedema. Cyproheptadine is also used in cases of vascular migraine [13]. Cyproheptadine is often used off-label to stimulate appetite and weight gain in children and adults; but only a few indications for clinical use[14].

### Category Off-Label Age

In this study, the off-label age category was the dominant one. Most pediatric patients get drugs with restrictions on use for a certain age. Types of decongestant and antihistamine drugs (Triprolidin, Pseudoephedrine, and Cyproheptadine) are drugs with restrictions on use for children under 6 years. Meanwhile, according to DIH [15] Triprolidine, Pseudoephedrine and Codeine are not intended for children under 2 years of age. The use of Tripolidin in children can cause hallucinatory effects.

Triamcinolone is a corticosteroid drug class as anti-inflammatory in various medical conditions, such as allergies, asthma, various skin diseases, adrenal insufficiency, and symptom relief in arthritis. Corticosteroids are used for the management of reversible and irreversible airway disease. British National Formulary of Children limits the use of triamcinolone for children less than 6 years. Some unwanted side effects if long-term use is that it can cause growth retardation in children and affect pubertal development. Long-term use of corticosteroids can increase susceptibility to infection and exacerbate or worsen the infection [16].

Salbutamol is also a drug within a certain age limit. Salbutamol is a beta-2 agonist drug that plays a role in the management of asthma or chronic obstructive pulmonary disease (COPD). Therapy with oral bronchodilators is not recommended in children because of the slower onset of action and the higher incidence of side effects compared to the inhalation route. Although the risk of ingestion is small, the side effects of oral salbutamol that may occur in children are hypokalemia, hypoglycemia, restlessness, tremor, tachycardia, and peripheral vasodilation[17]. The British Medical Association and the Royal Pharmaceutical Society of Great Britain [18] state that oral salbutamol is not recommended for children younger than 3 years and intravenously is not recommended for children younger than 12 years. IONI[19] states that the efficacy of Salbutamol for children aged <18 months is still in doubt.

Codeine is an opioid that is widely used for both analgesic and antitussive. Codeine has a detrimental effect that is fatal for pediatric patients, this is due to polymorphisms in the gene that metabolizes codeine. The UM (Ultrarapid Metabolizer) gene causes high levels of morphine in the patient's blood, causing respiratory depression and death. Therefore, the use of codeine in children is not recommended and the drug should be replaced with other drugs that are safer for pediatrics, namely Levodoprofizine and Moguisteine [20].

Cyproheptadine is a first-generation antihistamine and serotonin antagonist with anticholinergic effects. This drug is mainly indicated as an antiallergic drug with mild complaints, such as allergic rhinitis and cold urticaria, and can be used for migraines.. Cyproheptadine is only recommended for use in children aged 2 years and over. A significant side effect of cyproheptadine is central nervous system depression[21].

Dextromethorphan is a cough suppressant. This drug works by inhibiting the response or cough reflex in the brain. Please note that this drug is not effective for relieving cough with phlegm or cough caused by chronic bronchitis, asthma, emphysema. The main indication for dextromethorphan is as an adult antitussive in conditions associated with infection or allergies, such as upper respiratory tract infections (ARI). Use as an antitussive in children is not recommended, the use of dextromethorphan in children has not been proven effective and causes side effects of nausea, gastrointestinal disturbances, drowsiness, and dizziness[22].

### Category Off-label Contraindications

In this study, 22 cases of off-label contraindications were found, namely Loperamide HCl or about 0.8% of the total drug use. Loperamide is indicated for symptomatic relief in acute or chronic diarrhea, such as gastroenteritis, inflammatory bowel disease, or traveler's diarrhea. Its use is prohibited and not recommended for children[23].

Loperamide works by reducing bowel movements so that it stops diarrhea, in adults this mechanism may be used because the immune system is already good, but in children it is dangerous, because basically the cessation of bowel movements causes the viruses/bacteria that cause cannot get out of the body and can cause some things like fever and viral/bacterial growth becomes excessive. In addition, children's gastrointestinal nervous system that is not yet perfect will also be at risk of prolonged 'limp' due to this drug and cause paralytic ileus, and in some cases can 'skid' causing a condition called intussusception/invagination which is very dangerous

### Category Off-label Dosage

Dosage information is important in treatment because the pharmacokinetic and pharmacodynamic profiles of each individual age range are different. Drugs that are given at doses other than those listed in the marketing authorization or sales license are categorized as off-label drugs. In this study, an off-label dose category was found, namely the dose of Cefixime drug use.

Cefixime is indicated for the treatment of uncomplicated urinary tract infections, pharyngitis, tonsillitis, acute bronchitis and acute exacerbations of chronic bronchitis and uncomplicated gonorrhea with different doses for adults, children, and special populations. The general recommended dose for oral use is as a single dose once daily, or in 2 divided doses every 12 hours (twice daily). The results of the study found 3 cases of off-label doses or about 0.11% of the use of Cefixime, namely its use 3 times a day, not according to the dosage/rules of use recommended in the brochure or approved label[11].

The use of off-label drugs is generally carried out by doctors with a note if there is no standard dosage or use to treat certain diseases or if the standard treatment that has been carried out is not successful. The use of off-label drugs must be based on strong scientific evidence, especially regarding the evaluation, efficacy and safety of drugs.

Until now, the use of off-label drugs in Indonesia is still being applied so that off-label drug prescribing cannot be categorized as a prescription that violates the law. Because the use of off-label drugs may benefit the patient more when there are no other options for therapy. However, prescribing off-label drugs still carries a high risk because data on adverse drug reactions (ESOs) are likely to emerge.

# CONCLUSIONS

Based on the research that has been done, the following conclusions are obtained:

1. Off-label prescriptions for pediatric patients at the Saras Sehat Pharmacy, Tegal Regency are still quite high, with 48.10% off-label prescriptions and 51.9% on-label prescriptions.
2. The prevalence of off-label categories for age (12.43%), off-label indications (1.46%), off-label contraindications (0.80%) and off-label doses (0.11%). No category of Off-Label route of administration was found. The most widely prescribed Off-Label drugs are decongestant drugs, namely Triprolidine and Pseudoephedrine.

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