



## A Survey of Off-label and Unlicensed Antibiotic and Respiratory Medications Prescribed for Toddler Patients

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### ABSTRACT

**Background:** Many medications are unlicensed for use in toddlers and many drugs are prescribed as off-label in this age group. Different studies showed high prevalence of prescribing such medications in children. Prescribing off-labeled or unlicensed drugs can cause adverse drug events (ADEs) and harm to the patients. We conducted this study to evaluate the rate of off-label and unlicensed drugs prescribed for toddlers.

**Methods:** Out-patient prescriptions within the electronic database from a main governmental health insurance company in Tehran, Iran were evaluated for off-label and unlicensed drugs in a two-month period (November-December 2019).

**Results:** 5358 prescriptions for toddlers reached to the insurance database, of these, 461 prescriptions were randomly selected. Three hundred and fifty prescriptions contained antibiotics and/or respiratory medications, from them, 183 (52.3%) had at least one off-labeled or unlicensed medication.

**Conclusion:** Our study showed high rates of off-label and/or unlicensed medication use in pediatric population.

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### Introduction

It is well known that children are more vulnerable to medication related problems, including adverse drug effects (ADEs)(1). Safety and efficacy of drugs in pediatric population are less examined as compared to adults (2). Many medications are unlicensed for use in toddlers and many drugs are prescribed as off-labeled in this age group. Different studies showed high prevalence of prescribing such medications in children; even half of prescriptions were reported to be off-labeled or unlicensed (3). In neonatal intensive care units this problem occurs in even 85 percent of the patients (4). Prescribing off-labeled or unlicensed drugs can cause ADEs and harm to the patients, including death (5, 6). To overcome this problem, governmental regulatory bodies give incentives to the pharmaceutical manufacturers

to conduct clinical trials in pediatric population (7, 8). In this study we investigated the prevalence of off-labeled or unlicensed medications prescribed for out-patient toddlers.

### Methods

Out-patient prescriptions within the electronic database from a main governmental health insurance company in Tehran, Iran were used. In a two-month period from November to December 2019, all of the prescriptions for toddlers were collected for further analysis. Toddlers were described as children between 28 days and 2 years of age. A random sample of these prescriptions was selected. If antibiotic or respiratory medications exist in the prescription, then it would evaluate for being off-label or unlicensed.

We considered any inhaled corticosteroid, inhaled

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bronchodilator, systemic antihistamine, decongestant, bronchodilator, mast cell stabilizer, Leukotriene inhibitor, mucolytic, cough suppressant, intranasal corticosteroid and decongestant as “respiratory medications”. Also we considered any antibacterial, antifungal, anthelmintic, and antiviral as “antibiotic medication”.

British National Formulary (BNF) and Food and Drug Administration (FDA) licenses for each medication were used to describe off-labeled or unlicensed medications. Prescribers' specialty, age of the patient, and name of medications were recorded for further analysis. Identities of the patients were not recorded due to ethical considerations. Microsoft Office Excel 2007 was used for analyzing descriptive statistics.

### Results

In the study period 5358 prescriptions for toddlers reached to the insurance database, of these, 461 prescriptions were randomly selected. Three hundred and fifty (75.9%) prescriptions had at least one antibiotic or respiratory medication. In these 350 prescriptions, 287 antibiotics and 285 respiratory medications were identified. The five most common prescribed medications were azithromycin (13.8%), cetirizine (10.8%), cefixim (7.1%), amoxicillin-clavulanic acid (6.1%), and ketotifen (4.9%). Fifty-two percent of prescriptions were prescribed by pediatricians, 35.5% by general practitioners, and 12.5% by other specialties.

One hundred and thirty-nine (39.7%) of the prescriptions had at least one unlicensed medication. A total of 572 medications were prescribed, of these 157 were unlicensed (20 antibiotics and 137 respiratory medications). The top three unlicensed medications were cetirizine (18.5%), pseudoephedrine and chlorpheniramine combination (16.6%), and salbutamol syrup (12.7%). Sixty percent of unlicensed medications were prescribed by pediatricians, 32.5% by general practitioners, and 7.5% by other specialties.

Fifty-nine (16.9%) of the prescriptions had at least one off-labeled medication. A total of 572 medications were prescribed, of these 61 were off-labeled (4 antibiotics and 57 respiratory medications). The top three off-labeled medications were cetirizine (54.1%), diphenhydramine (36.1%), and ketoconazole (3.3%). 59% of off-labeled medications were prescribed by pediatricians, 34.5% by general practitioners, and 16.5% by other specialties.

In summary, from 350 prescriptions that contained antibiotics and/or respiratory medications, 183 (52.3%) had at least one off-labeled or unlicensed medication.

### Discussion

In this study we investigated off-labeled or unlicensed medication in a large outpatient database. We found that

prescribing such medications is a common practice (52.3%) in the treatment of toddlers. This is a global problem and the rate of prescribing off-label and/or unlicensed drugs ranges from 9% to 51% (3-5, 9-11). In a large survey which was done in Estonian national prescription database, Lass et al., investigated 467,334 ambulatory prescriptions of children, they found that 31% of prescribed medications were off-label and 0.05% was unlicensed drugs. They also found that toddlers were the highest in all age groups that received off-labeled drugs. They concluded that limited number of pediatric trials and lack of up-to-date information in the Summaries of Product Characteristics is the reason of their observation (11).

In a study of in-patient children, 2145 prescriptions were analyzed. Unlicensed and off-label medications were prescribed in 8.3% and 38.2% of the prescriptions, respectively. They found that reasons for off-label drug use were unapproved age group (53.2%), dosing (27.6%), frequency (25.2%), indication (5.5%) and route of administration (5.6%). The authors compared off-label uses with scientific data using Pediatric Dosage Handbook, and Micromedex®. Only in 39% of the cases, robust scientific evidence supports off-label uses (10).

A study in Brazil analyzed 342 in-patient pediatric prescriptions, the results showed that 12% of the prescriptions had unlicensed drugs and 39% had at least one off-label drug. Authors warned about long term safety of such medications. They suggested implementation of protocols for the prevention of prescribing off-label and unlicensed drugs (12).

Off-label respiratory medicines were prescribed in 60% of 220 outpatient pediatrics in a study by Mohamad et al. Diphenhydramine was the most prescribed off-label drug. The most frequent reason for off-label use was wrong indication, higher than the recommended dose, and lower than the licensed frequency. The study also showed that patients who received more medications are more likely to receive off-label drugs (13). In our study we did not have access to the indication, because writing indication on paper prescriptions are not mandatory for the physicians.

In a systematic review of 31 studies, off-label medication uses in children in a 10-year period was reviewed by Allen et al. They found off-label prescription rate from 3.2 % to 95%. One of the studies showed increased ADEs secondary to off-label use of medications. They concluded that off-label prescribing is a common practice in both in-patient and out-patient settings, and although legislations were established to overcome the problem, it still continues to be a high rate of off-label medication use (2).

In conclusion, our study and other studies show high rates of off-label medication use in pediatric population. Although some studies showed increased harm with this kind of practice, off-label prescribing does not necessarily cause

harm. Factors such as limited trial data and inadequate incentives for the pharmaceutical companies to conduct such trials may be the reasons for this practice.

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