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OFF LABEL DRUGS USED IN PEDIATRICS: REVIEW ARTICLE

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ABSTRACT

Background: Off-label and unlicensed drugsuse in children is popular since trials in children were typically not done during the phase of drug creation.This has led to concerns that children can receive medicines at doses that either lack effectiveness or that pose safety problems. **Objective:** To review the level of drug use off label and the most widely used off label drugs. **Method:** Medline search of titles and abstracts from 2006 to the present was performed using the search in (scholar google , Science daily , Science direct , research gate, pub Med, up-to-date)Information from these studies were summarized in relation to number of prescribed off label drug, condition and disease in which off label drug used for, age group that taking this medication **Conclusions:** This review reveals a large proportion of off-label medications was prescribed for children, and this leads us to recommend that the availability of up-to - date pediatric drug information must be a national priority

INTRODUCTION

In children, most prescribed drugs are still notproperly studied in this population and most are not approved to be used in children. Off-label prescribing is troubling due to lack of information on drug safety, effectiveness and appropriate use in children (dose, interaction). In addition, adverse drug outcomes were associated with off-label prescribing. Thelack of datain pediatric can lead to the prescribing of potentially harmful treatments or to withholding of potentially beneficial treatments. Despite recent facts, the Food and Drug Administration (FDA) gave authority to allow assessment of some new drugs for children and to promote evaluation of others through patent extensions. The FDA has therefore registered a rise in the number of medicinal products licensed for use in children.

Off-label rates reported worldwide for children range from 11% to 79%.Nevertheless, there is little research on the level of off-label drug usage in children, the kinds of drugs most commonly used off-label and the characteristics of children who receive off-label drugs.[1] Using the word "off-label" refers to the use of a medication in a way that is not included for that medication in the product insert (approved labelling).Off-label use is intended to benefit an individual patient. It is vital to remember that the word "off-label" doesn't really mean a use that is inappropriate, unlawful, contraindicated or investigative. It is permissible to use drugs off-label and report out-of-label findings. The lack of labelling for a particular age group or for a specific medical condition doesn't actually indicate that the use of the drug is inappropriate for that age or condition. Rather, it just means that the FDA has not approved the evidence needed by law to warrant inclusion in the label. In addition, a

lack of labeling does not in any way indicate that medication is not validated by clinical practice or research in children. Rather, it simply means that evidence of drug effectiveness and safety in pediatric was not submitted to be reviewed by the FDA or was not compliant with regulatory requirements of "substantial evidence" forFood and Drug Administration approval. [1]

The status of off-labels was determined using the following criteria:

- Age;Medications were regarded off label by age when requested for any indication for children with age less than the permitted age.
- Weight;Medications were deemed off label by weight where weight was defined in the product labeling, and medications were prescribed for any age or reason for a child with weigh lower than the approved weight.When weight was absent, drugs were considered possibly off label.
- Indication;Medications were regarded off label by indication if requested during visits without a recorded condition according to an indication approved by the FDA [2]. Table (1) show summary of the off label drug categories

Risks of Off-label Drug Use

Studies found a strong correlation between off-label drug and adverse drug effects.[3] (Aagaard et al., 2012) In a research, 17 percent of adverse drug reactions (ADRs) due to drug use off-label was reported and 60% of which were serious. [3]Several other studies revealed correlation between adverse drug reactions and drug use off-label.[4], (Palmaro et al., 2015) in study on off-label prescribing to pediatric patients, 736 (37.6%) of the 2313 patients were treated with an off-label medication, which was correlated with 23 adverse drug reactions in the research population, mainlydue to unapproved indications and dosages.[5] In a review by (Mason et al 2012), the predisposition of adverse drug reactions with the use of off-label drugs in children was reported.[6]

(Bellis et al. 2014) The study concluded that there was a 23% rise in adverse drug reactions for each additional off-label drug being administered. [7]The adverse drug reactions have been found to be more correlated to the use of oncological drugs off-label.Topical drug use off-label was also associated with ADRs but with a lower impact than drugs administered systemically.Incorrect applications of drugs outside of its Summery Product Characteristics were also associated with adverse drug reactions[8]

- Current off-label medication use trials of hospitalized children are constrained by the few patients surveyed, the emphasis on patients seeking specialized care, and the general presence of patients treated both in hospital and outpatient settings.The aim of this review was to determine the extent of off-label drugs use, detect off-label drugs most widely used and recognize factors associated with off-label drugs use in pediatrics.Since most medicines are not approved for use in children, we decided to focus on those medicines that were either commonly prescribed or proposed by (FDA) for further research in children.

METHODS: Medline searches for titles and abstracts from 2006 to the present was performed using the search in (scholar google , Science daily , Science direct , research gate, pub Med, up-to-date) and terms unlicensed/ off-label/ license/ pediatrics /label/ approved/ approval/prescription /prescribe/ inappropriate and adverse effect /ADRs reporting systems/pharmaceutical preparations/drug therapy andchild/child preschool. The limits Human and English Language were applied to both searches.Papers and articles relating to off label drug (prescribing /use/ risk / most common medication / classification) were included. Information from these studies were summarized in relation to number of prescribed off label drug, condition and disease in which off label drug used for, age group that taking this medication.

RESULTS

Worldwide studies on the use of off-label drugs in pediatrics: Use of drugs off-label is very common among neonates and children.There have been many studies in different parts of the world that have shown different prevalence rates of drug use off-label. LEA S. elland and Patrice knight in 2006 in a study for 403 patients revealed that 31% of patients received an unlicensed or off-label medicine. [9], Samir et al in 2007 study in USA Hospitalized children showed 79% of patients were give off-label.[10] Hsien et al 2008 study Stated that 67 percent of children got off-label or unlicensed drugs [11]. Table (2) show summary of studies done in different countries and for different types of patient from 2006 to 2020. Another study for Bazzano et al 2009 reported 62% use of off-label drugs in Spain. Carnovale et al. 2013 in study for 1708755 in Italy for outpatient clinic showed that about 3.30% take off label drug [18]. .Jain et al 2014 in study for India in neonate intensive care unit showed 26% of patients have off label drugs used [25] , a study by Joret-Descout et al. 2015 in France showed 36.50% of patients taking off label drugs [31] .Aamir et al. 2017 study in Pakistan reported 48.2% [40], while Andrea et al 2018 in Spain showed 59.50% of patients taking off label drugs [43] and in 2019 Katelyn et al study in USA report 28.20% [45] and 2020 study done by Tukayo et al in Indonesia reported 71.50% of hospitalized patients were given a medicine that are aff label [46] According to many studies there were a several drugs that were most frequently prescribed as off label drug and the table (3) showed examples of these off label drugs and their uses

DISCUSSION

This review demonstrates that off-label use of medications in pediatric patients is a common practice, with a significant number of children, inpatient and outpatient, receiving an off-label medication. Though most of the articles reviewed were from European countries, all continents were represented. The historical practice of using off-label medications in children is a frequent worldwide occurrence and continues to be an issue despite the increased awareness and passed legislation. Eighteen of the reviewed studies were conducted in European countries. The reason for off-label use varies among studies. The studies included in this review were throughout the world. The review included studies from multiple countries, a broad age range and settings such as inpatient and outpatient, which we felt would give us a current global perspective on off-label medication use but perhaps introduced bias as each setting and country defined off-label based on their local regulatory board. The number of off-label medications in hospital wards was highest, while the most widely prescribed drugs were antibiotics then respiratory drugs. Methodology was observed varying between authors and a specific description of off-label and an unlicensed drug was not established.Most of the papers included in this analysis stated that drug usage under off-label conditions occurred when medications were administered beyond the scope of the marketing authorization, i.e. where age, frequency, route of administration differed. Nevertheless, other authors were considereddrugs unlicensed oroff-label when there is a different formulation or contraindication.This underlines the idea that the off-label and unlicensed drugsdefinition is of great importance, especially in the situation of the pediatric population, in ensuring the correct use of terminology, in promoting understanding with in the scientific community as a whole and to enable the comparison of different studies and different nationalities. The main drawback of the review of agreement on the off-labeland/or unlicensed medicinesdefinitionwas lacked, something that makes direct comparison of findings difficult, as other studies have shown [47, 48].This, in effect, shows the need to undertake an international study with common assessment criteria, as proposed by Pandolfini et al. and Lindell Osuagwu et al.[47,48], and to reach to a general off-label and unlicensed medications definition, that should then be rendered statutory. [49] . Another explanation for the difficulty of direct comparison among studies is that prescribing patterns appear to differ not just between the countries at which the studies are conducted, but also between the doctors themselves.

Table (1) summary of the off label drug categories

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 pediatric information	No mention at all in the SmPC regarding pediatric use
Lack of pediatric clinical data	Stated lack of evidence of efficacy and safety in pediatric 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): Summary of studies done in different countries and for different types of patient from 2006 to 2020

Author	Year Publish	NO. Patient	Age Range	Country of Origin	% Off-Label Prescription	type of patient
LEA S. elland and patrice knight[9]	2006	403	<18	USA	31.00%	General Pediatrics-NICU
Samir et al[10]	2007	355409	<18	USA	79%	Hospitalized
Hsien et al[11]	2008	417	All ages	Germany	31%	Multiple wards
Muhlbauer et al[12]	2009	289000	0-16	Germany	3.20%	outpatient clinic
Bazzano et al[13]	2009	7901	<18	Spain	62%	General Pediatrics
Morales-Capri et al[14]	2010	462	<14	Spain	27%	Emergency department
Lass et al[15]	2011	151476	<19	Estonia	31%	outpatient clinic
Olsson et al[16]	2011	1911417	0-18	Sweden	13.50%	outpatient clinic
Palcevski et al[17]	2012	691	0-19	Croatia	13.30%	Multiple wards
Carnovale et al.[18]	2013	1708755	0-18	Italy	3.30%	outpatient clinic
Ballard et al.[19]	2013	300	<12	Australia	32%	General Pediatrics
Maltz et al.[20]	2013	82	<18	USA	36%	CVICU
Ribeiro et al.[21]	2013	700	<18	Portugal	32.20%	Emergency department
Lee et al[22]	2013	192	<18	Malaysia	34.10%	PICU
Knopf et al[23]	2013	17450	0-17	Germany	40.20%	outpatient clinic
Kieran et al.[24]	2014	110	neonate	Ireland	39%	NICU
Jain et al[25]	2014	156	neonate	India	26%	NICU
Langerova et al[26]	2014	4282	0-15	Czech Republic	9.01%	outpatient clinic
Lindell- Osuagwu et al.[27]	2014	123	<18	Finland	42%	Multiple wards
Blanco-Reina et al[28]	2014	81	0-14	Spain	52%	PICU-NICU

Palmaro et al.[29]	2015	2313	0-16	France	37.60%	outpatient clinic
Czarniak et al[30]	2015	699	all ages	Australia	25.70%	Inpatient &outpatient
Joret-Descout et al[31].	2015	120	0-18	France	36.50%	Multiple wards
Taylor et al.[32]	2015	3343	0-17	Australia	30.50%	Outpatient clinic
Abdulah et al[33]	2015	4936	0-5	Indonesia	18.60%	Outpatient clinic
Silva et al[34]	2015	218	<28 day	Portugal	25.70%	NICU
Pereira Gomes et al.[35]	2015	320	18-Feb	Brazil	57.20%	Inpatient ward
de Souza et al.[36]	2016	192	<28 days	Brazil	95.70%	NICU
Schweigertova et al.[37]	2016	202	<29 days	Slovakia	43%	NICU
Cuzzolin et al[38]	2016	220	neonate	Italy	59%	NICU
Berdkan et al[39]	2016	500	1 day-16 yrs	Lebanon	30.20%	multiple wards
Aamir et al.[40]	2017	895	<18yrs	Pakistan	48.20%	Surgical wards
Teigen et al[41]	2017	400	0-17yrs	Australia	30.50%	Multiple wards
Chauthankar et al[42]	2017	460	neonate	India	12.30%	NICU
Andrea et al[43]	2018	5060	<18	Sicilian	8.97%	Multi wards
Katelyn et al[44]	2019	2773770	<18	USA	28.20%	Multiple wards
DivyaHoon et al[45]	2019	1000	neonate	USA	83%	Ambulatory setting
Tukayo et al[46]	2020	200	>18	Indonesia	71.50%	Hospitalized

Table (3): List of most common off label drugs used in pediatrics.

Author	year of publish	Most common drug
Hsien et al[11]	2008	60% cardiovascular drugs , 42% anti-infectives , 30% drugs for respiratory system, 25% drugs for alimentary tract and metabolism and 3% analgesics and antipyretics
Olsson et al[16]	2011	drugs for the respiratory tract and antibiotics
Palcevski et al[17]	2012	Proton pump inhibitors.
Carnovale et al[18]	2013	antibiotics for systemic use , alimentary tract and metabolism
Ballard et al[19]	2013	oxycodone, salbutamol and paracetamol
Jain et al[25]	2014	anti-infective and antiepileptic
Langerova et al[26]	2014	Anti-histamines and bronchodilators.
Blanco-Reina et al[28]	2014	anti-infectious, systemic use nervous system and cardiovascular
Palmaro A, et al[29]	2015	Paracetamol, ibuprofen, and amoxicillin
Taylor et al.[32]	2015	Salbutamol, ondansetron, ipratropium, fentanyl and oxycodone
Abdulah R, et al[33]	2015	doxycycline and domperidone
Silva et al[34]	2015	gentamicin , ampicillin , cholecalciferol , morphine , paracetamol , caffeine citrate , multivitamins , clotrimazole , furosemide
Pereira Gomes et al.[35]	2015	The most commonly used and prescribeddrugwas the NSAIDsmetamizole(90 percent)of the studiedpatients, followed by metoclopramide (37.5 percent) and fenoterol (33.7 percent)
de Souza et al[36]	2016	Anti-infectives for systemic use, blood, alimentary tract
Schweigert et al.[37]	2016	Anti-infectives and alimentary drugs
Teigen et al[41]	2017	ampicillin, caffeine, racemic adrenaline
Chauthankar et al [42]	2017	Antibiotics (69.6%) followed by non-steroid anti-inflammatory drugs
Andrea et al[43]	2018	Anti-infectives drugs, followed by drugs for alimentary tract and metabolism and drugs for blood or blood forming organs
DivyaHoon et al[44]	2019	GI drugs
Katelyn et al[45]	2019	CNS medications and respiratory and/or ENT medications
Tukayo et al[46]	2020	Ranitidine was the most frequent drug

"NSAIDs= Non-Steroidal Anti Inflammatory Drugs"

Taking the percent of off-label prescriptions along with the percent of unlicensed prescriptions offered an overall image of the situation and showed that the prescribing of off-label and/or non-licensed drugs was both popular and widespread.[47, 48, 50]. Overall, as stated by Lindell-Osuagwu et al.[47], the prescribing of off-label and unlicensed drugs was the highest in wards and intensive care units since the majority of pediatric hospitalized patients received at least one medication under off-labeland/or unlicensed condition[47,50]. Several research on the age of the study population found that the use of off-label and/or non-licensed drugs was highest in younger patients, with the highest rate of off-label and/or unlicensed drugs use among newborns. [48,50]. In fact, lack of a pediatric license or information was the key explanation for prescriptions drugs off label.The lack of studies on the quality, efficacyandsafety of prescribed drugs to children indicated that information on guidelines for drugs used in the pediatric population was lacking, And because the drug quality ,efficacyand safety observed in the adult population are commonly believed to be the same as in the pediatric population, these same drugs were prescribed to pediatric patients[51]. As also stated by Pandolfini et al. and Lindell Osuagwu et al.[47,48], drugs given beyond the dosage and age range of the marketing authorization is another explanation found for off-label prescribing in pediatric patients.This may be because a drug, while approved for use in pediatric patients, may be administered in different doses and administered to different age groups of the pediatric patients with differences in metabolicand physiological development.However, an increase in the number of well-studied pediatric medications was reported in study[52] carried out after ten years of European Medicines Agency (EMA) activity , thus generating valid pediatric data and demonstrating that the shortage of drugs in specific areas can be overcome. Owing to the EMA, in 2012 the proportion of pediatric trials that are part of an approved Pediatric Investigation Program increased to 23 percent[53].Following legislative and regulatory changes, there is still a shortage of substitute medicines with marketing authorization for use in paediatric patients, which ensures that off-label and unlicensed products in medical practice tend to be administered [54]And that new studies are therefore needed to evaluate the current scope of off-labeland/or unlicensed prescription. Another problem related to the use of off-labeland/or non-licensed medications are the prevalence of adverse drug reactions.Some research [49,54,55,56] suggest that a very high percentage of adverse drug reactions in the pediatric patients are linked to off-labeland/or non-licensed medications use. Furthermore, several studies have reported that the risk of adverse drug reactions associated with the use of off-label and/or non-licensed drugs in the pediatric patients is 3 times higher than that for the adult population[56,57] . Additionally, theproblem of the prescriptions of off-label drug are not only inhospitalized patients but it also occurin primary care, thus further researches on the use of off-label drugs in primary careand the correlation between this use and the occurrence of adverse drug reactions are needed .

CONCLUSION

This review reveals a large proportion of off-label medications were prescribed for children. Despite legislation designed to improve pediatric labeling and thereby minimize the use of off- label drugs,the high incidence of off-label prescriptions across various categories of drugs leads us to recommend that the availability of up-to - date pediatric drug information must be a national priority.Studies efforts must focus on the unstudied drugs and conditions for which some off-label drugs were prescribed.Further studies should focus on assessing the conditions and appropriateness of off-label prescribing.Developing off-label prescription guidelines can help to guide clinical practitioners.

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