Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2016, Volume 4, Issue 10
ISSN: 2321–3647(online)

Are unlicensed and off labelled drugs being practiced safely in Pediatric population? – A Systematic review

Muhammad A Hamid[1*], Jabeen Fayyaz[2], Sohaib Siddiqui[1], Arif Haque[1], Christina Yeung[1], Dennis Scolnik[3]

1. Assistant Professor Pediatrics, University of Toronto & Consultant Paediatrician Rouge Valley Health Services, 2867 Ellesmere Road, Toronto

2.Clinical Fellow Paediatric emergency Medicine , The Hospital for Sick Children

3. Associate Professor, Pediatrics, University of Toronto, Staff Physician Pediatric Emergency Medicine & Clinical Pharmacology and Toxicology, The Hospital for Sick Children

ABSTRACT

The aim of this systematic review is to analyze after that is the 'unlicensed ' and 'off labelled 'drugs prescribed for children are being used safely in pediatric after population. A systematic search was made in Medline PubMed, CINAHL and Cochrane Library from 1998 to 2014 addressing the use of unlicensed and off labelled drugs in pediatric population. After that process of identification 29 studies fulfilled the criteria to be included . Total number of pediatric patients covered in the review of 29 selected publications is 3589061. Data from 16 countries are included. Unlicensed use of drug in pediatric age group starting from neonates were found to be from 1.26% - 16.8% with a maximum of 90% use of off-label use of drug in the age group of 23-36 weeks. Almost 34-36% off-label use of these drugs and 62.3% for unlicensed or off-label use of the drugs were found in critical care areas. A range of 3.3% to 76% off-label and 1.26-33% unlicensed or unapproved drugs usage was found in the OPD and Clinical settings. The drug categories found to be used mostly are analgesic drugs 26.9% and antispasmodic drugs (31.5%). Paracetamol had 25-49% off-label use. A considerable off- label and unlicensed use is observed in pediatric population. The increase in number of studies and awareness is also evident through this review. The regulatory agencies apart from stringent rules to control unapproved use of drugs have to ensure pharmacovigilance of existing drugs. Healthcare providers should be prudent in the use of drugs weighing the risk-benefit analysis and practice informing the parents about the off- label use and start after their consent.

Keywords: Healthcare providers, Pediatric, drugs

*Corresponding Author Email: mahamid@rougevalley.ca
Received 03 October 2016, Accepted 13 October 2016

Please cite this article as: Hamid MA *et al.*, Are unlicensed and off labelled drugs being practiced safely in Pediatric population?–A Systematic review. American Journal of Pharmacy & Health Research 2016.

INTRODUCTION

The intention of licensing is to certify that the medicines are available in the market only after having been studied for safety, efficacy, and quality.[27] The regulatory agencies like Food and Drug Administration (FDA), European Medicines Agency (EMEA), Health Canada, Therapeutic Goods Administration (TGA) and Medicines & Healthcare products Regulatory Agency (MHRA) has shown considerable effort to provide rational prescribing for children[30, 31, 32, 33]. Many of the prescribed drug labeling are also changed by including pediatric information like efficacy and safety data.[1,9, 11,12,15,16,18] However, off-label and unlicensed drug prescription is one of the major public health issue for children having chronic and critical illness due to lack of information for pediatric use[3,5,6,9,27] This insufficiency is because of the complications for conduction of clinical trials in this population which include practical adversity and ethical issues, as children are considered as vulnerable subjects.[26] Clinician prescribed the off-label or unlicensed medications for benefit of the individual patient, but before prescribing the off-label or unlicensed medications, mostly clinicians do not discuss with parents and they are unaware regarding the concept of off-label drug use in children.[19] Off-label prescription are legally accepted and clinically appropriate when patient or parents are informed accordingly.[22]

Clinicians prescribed these medications on the basis of previous experience and even this trend is so popular that some of them are unknowingly practicing prescribing off-label or unlicensed medications.[26]

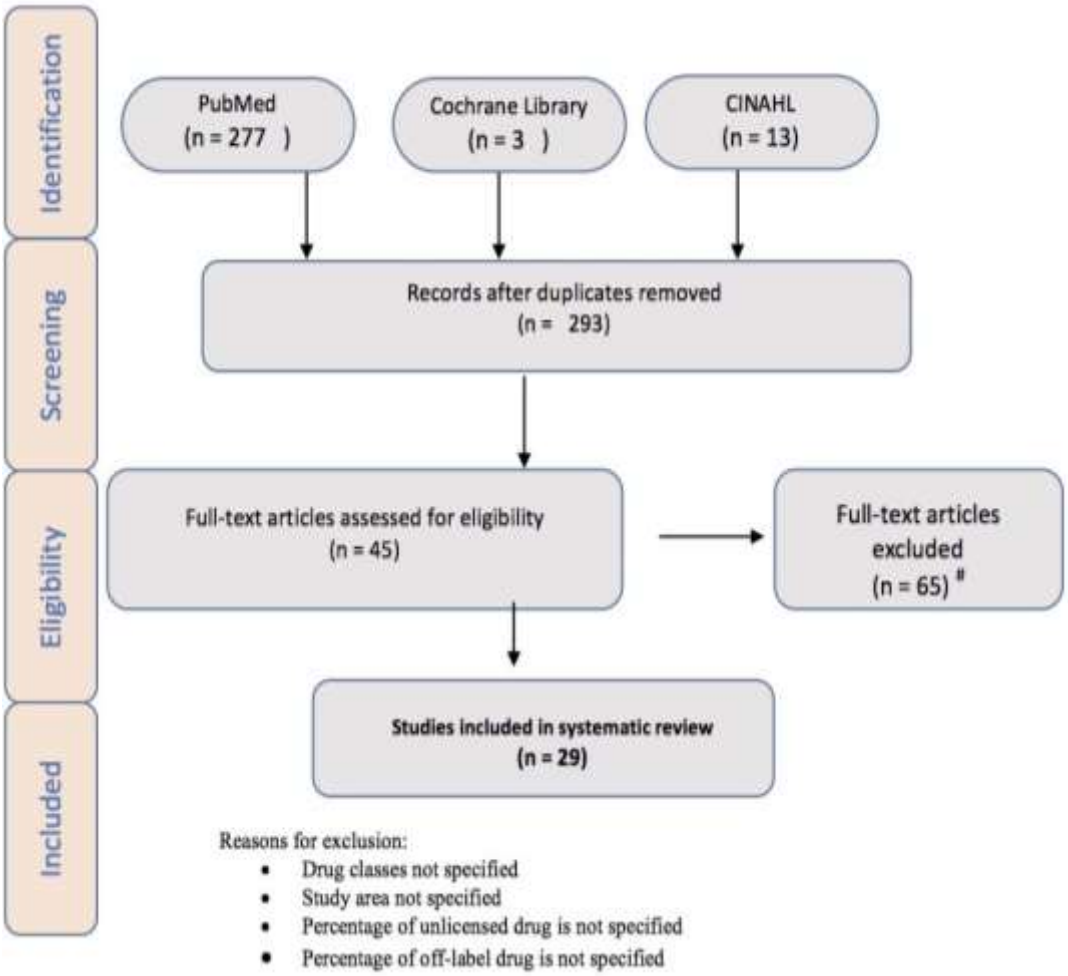
Off- label drug use can be defined in terms of the usage of medicines beyond the provision of the product license in terms of dosage, age of the patient, mode of administration, indication for use, as mentioned in the package insert or the patient information list[7]. *Unlicensed drugs* can be defined in terms of its use before granting the license of the medication or any alteration of licensed medication.[7] In the 90's, there has seen an increased initiation of implementing a number of measures in the developed world, e.g. USA and Europe to inspire the drug industry to provide accurate information (in drug labels and package inserts) for prescribing doctors with a special focus for the drugs used in children. It also has encouraged clinical investigators in carrying out clinical trials with children and to ensure that children are taken into consideration throughout the regulatory process.[23]

Objective

The primary objective of this systematic review is to analyze the trend of 'off-label' and 'unlicensed drugs' prescribed for children and the role of different regulatory agencies in terms of off-label and unlicensed drug prescription in children.

The secondary objective is to explore the regulatory changes during the selected study period.

MATERIALS AND METHOD



Flowchart for literature search procedure

The process of identification was done through search in PubMed, CINAHL and Cochrane Library, which date back to January 1998 to December 2014, followed by screening to avoid duplicity and sorting the eligibility Through find the best fit to include in this review (Flowchart). Title/ Abstract searches were used involving the term 'unlicensed drug' and 'off-label drug'. For narrowing down the search result, included filters were 'publication dates', 'language', 'age' and 'full text' and taking into consideration the fact that some of the filters used by the individual databases varied. Selected studies considering the age group of participants was from neonates to adolescent age group (0 years to 18 years). For better understanding of the details of the study,

the selected language is English and considering only full text. The resulting article titles or abstracts were scanned for relevance; those regarding studies on the off-label/unlicensed use of drugs in children were obtained and included in the review.

Keywords the selection of the studies were done keeping in mind that all the settings of care can be covered e.g., neonatal ICU (NICU), pediatric ICU (PICU), pediatric ward/in-patient department (IPD), operation theater (OT), out-patient department (OPD), general physician's clinic and pharmacies. These publications were selected in a span of 17 years (1998 to 2014) and was research conducting in European countries including the U.K, North America countries including the U.S. and Australia. The regulatory guidelines of these countries were followed in order to understand the requirements and restrictions for unauthorized use of drug(s).

RESULTS

Through the process of identification, 29 publications were considered for evaluation (Table-1). Total number of pediatric patients covered in the review of 29 selected publications was 3589061. Data from 16 countries were included. There were 13 publications from European countries (n=2701636), 7 publications from USA (n=881029), 7 from UK (n=5868) and 1 each North America (n=228) and Australia (n=300).

Table 1: Off- Label and Unlicensed Use of drugs in pediatric population from 29 studies between 1998-2014

Setting of Care	Sl No.	Author(s)	Year	Country	n (patients/ no. of drugs)	Age Group	Drug(s) or drug classes involved	% of off label and/or unlicensed drug use
PICU, NICU and Operating room	1	Doherty DR, Pascuet E	2010	Canada	228	Less than 18 years of age	Not specified (3391 drug prescription in study duration)	59.7% off-label
ICU	2	Oguz SS, Kanmaz HG, Dilmen U.	2011	Turkey	464	32. 5 +/- 4.7 weeks	penicilin, amikacin, vancomycin, ampicillin, theophyllin	62.3% unlicensed or off-labeled
	3	Maltz LA, Klugman D et al	2013	US	82	Less than 18 years of age	Analgesics, diuretics, antibiotics, antihypertensives,steroids, bronchodilators, anticoagulants, sedatives, anesthetics, antiarrythmics, GI Drugs, paralytics, vasoactives and endocrine drugs	36% off-label
Pediatric ward	4	Turner S, Longworth A et al.	1998	UK	609	4 days - 20 years	Paracetamol, Cefotaxime, Diclofenac sodium, Morphine, Salbutamol, Metronidazole, Prednisolone, Cefaclor, Trimethoprim and Lactulose	25% (unlicensed or off label use)
	5	Turner S, Nunn AJ et al	1999	UK	936	Less than 18 years of age	Antibiotics, Morphine and other opiates, Diuretics, Corticosteroids, Antihypertensive/vasodilators, Sedatives, Bronchodilators, TPN, Inotropic agents and other commonly used drugs	48% unlicensed/off-label drugs
	6	Conroy S, Newman C, Gudka S et al	2003	UK	51	0.6–16.3 years	Cytotoxic, Antibiotic, Antifungal, Antiviral, Anti-emetic, Corticosteroid, Analgesic, Laxative, Electrolyte supplements, Sedative, Antihistamine, Diuretic, Antacid, Folinic acid, Allopurinol, Urokinase, Salbutamol, Emollient, Antitussive, Sucralfate, Filgrastim and Gabapentin	19% (unlicensed) and 26% (off label)
	7	Dick A, Keady S et al	2003	UK	308	20 days - 17 years	Omeprazole, Paraffin oil, Domperidon, Ranitidine, Picosulphate, Cisapride, Azathioprine, Prednisolone, Tacrolimus, Metronidazole, Polyethylene glycol, Mesalazine, Senna, Mebeverine,	49% unlicensed/off-label use

							Amoxicillin, Gaviscon, Ciprofloxacin, Lactulose and Vancomycin	
	8	Bajcetic M, Jelisavcic M et al	2005	Serbia (Europe)	544	4 hours-18 years	Frusemide, catopril, digoxin, spironolactone, licomycin, amoxycillin, paracetamol, propranolol, ibuprofen and acetylsalicylic acid	Unlicensed 11% or off label 47%
	9	Shah SS, Hall M et al	2007	US	355409	Less than 18 years of age	central or autonomic nervous system agents or as fluids or nutrients, or gastrointestinal tract agents were most commonly used off-label	off-label or unlicensed drug use ranged from 33% to 76%
	10	Ring JC. Et al	2008	US	31432	less than 18 years	dopamine, lidocaine, and milrinone (off label), enalapril, sotalol, lisinopril, amlodipine, losartan, and fenoldopam (off label dose)	dopamine (26.6%), lidocaine (22.7%), and milrinone (19.1%): un-approved for pediatric use. enalapril, sotalol, lisinopril, amlodipine, losartan, and fenoldopam: 62.1% (off-label)
	11	Dos Santos L1, Heineck I.	2011	Brazil	342	Less than 14 years	analgesics and antisposmodics	Analgesic drugs (26.9%) and antispasmodic drugs (31.5%) were the most frequently issued off-label drugs
	12	Ballard CD1, Peterson GM	2012	Australia	300	Less than 12 years.	oxycodone, salbutamol and paracetamol	31.8% off-label
	13	Ribeiro M, Jorge A, Macedo AF.	2012	Portugal	700	4 days to 18 years	Amoxicillin/clavulanic acid, paracetamol, amoxicillin, ibuprofen and salbutamol	32.2 % off-label
	14	Palčevski G, Skočibušić N,	2012	Croatia	691	Less than 18 years	PPI	46% unlicensed or off-label manner
	15	Kimland E, Nydert P	2012	Sweden	2947	0 and 18 years	Paracetamol	49% off label

	16	Bellis JR, Kirkham JJ et al	2014	UK	3869	New born - 16 years	Metronidazole Infusion/Oral suspension, Gentamicin Infusion, Spironolactone Oral liquid, Chloral hydrate, Diclofenac, Sodium chloride 0.9% Nasal drops,Ondansetron, Dexamethasone, Hyoscine hydrobromide, Ibuprofen, Melatonin, Omeprazole, Sodium feredetate, Ranitidine hydrochloride, Folic acid, Morphine sulphate, Paracetamol and Salbutamol	Off label amongst neonates (58.3%), amongst adolescents (29.5%) and above 70% in all other age categories
Operating room	17	Smith MC, Williamson J	2012	US	10782	Less than 18 years	ondansetron, hydromorphone, and neostigmine	34% off labeled
only OPD	18	Carnovale C, Conti V et al	2013	Italy	1708755	0-18 years	antibiotics	3.3 % off-label.
	19	Ruíz-Antorán B, Piñeiro R et al	2013	Spain	695	22 days–15.6 years	antacids, PPI, antibiotics, laxatives and antihistaminics	33.2% off-label
	20	Langerová P, Vrtal J, Urbánek K	2014	Czech Republic	4282	0-15years	ramipril and enalapril	1.26% unlicensed and 9.01% off label
General practice Clinic	21	Martin RM, Wilton LV, Mann RD et al	1998	UK	25	less than 12 years	fluoxetine capsules	76% off label
	22	t Jong GW, Eland IA et al	2004	Netherland	13426	New born-16 yrs	corticosteroids (18.0%), selective β2-sympathomimetics (17.1%), systemic antihistamines (14.8%), sympathomimetics (12.7%) and phenothiazine derivates (8.9%)	16.8% unlicensed 20.3% off-label.
	23	Manthripragada AD, Pinheiro SP et al	2013	US	482906	Less than 20 years	tacrolimus and pimecrolimus	The proportion of new users younger than 2 years of age significantly decreased for both tacrolimus (36.7% to 22.5%, P < .001) and pimecrolimus (47.0% to 33.7%, P < .001) after regulatory actions

	24	Palmaro A, Bissuel R et.al	2014	France	2313	0 -16 years	Analgesics, Antibacterials for systemic use, Antiinflammatory and antirheumatic products, Nasal preparations and other commonly used	56.4% unapproved indication, lower dosage 26.5%, higher dosage 19.5% than specified, age not labeled 7.2%, incorrect route of administration 3.5% and contraindication 0.3%
General practice Clinic, pharmacies, family physician	25	Eiland LS; Knight P	2006	US	403	3 days - 18 years	Ondansetron, Albuterol, Ranitidin, Ipratropium–albuterol, Ipratropium, Lorazepam, Lactobacillus acidophilus/Lactobacillus bulgaricus, Budesonide, Metoclopramide, Nalbuphine, Polyethylene glycol, Aspirin, Prednisolone, Dexamethasone, Diphenhydramine, Metronidazol, Paroxetine, epinephrine and others	31% was classified as off-label due to indication or age.
	26	Ellul IC, Grech V.	2013	Malta (Eurpoe)	209	2-11-years	76 drugs during study period	54.1% off-label and unlicensed
Pharmacy	27	Sharon Conroy et al	1998	UK	70	26 - 36 weeks	Gentamicin, Benzylpenicillin, Caffeine, Folic acid, Dalivit, Albumin, Vitamin K, Frusemide, Flucloxacillin, Morphine	90% off label
	28	Olsson J, Kimland E	2011	Sweden	968465	0 - 18 years	sex hormones, cardiovascular drugs, antidepressants, hypnotics and several NSAIDs	13.5% off label and 1.6% unlicensed
	29	Edwards G, Gill A	2014	US	15	newborn - 2 years	N-acetyl cysteine	86% off label use

Age Group

The search resulted age groups from neonates to adolescent ranging from new-born (0-30 days of age), infant (1 month-2 years), young children (2 years-12 years) and adolescent (12-18 years). The publications encompassing the neonatal population (n=2704686) were found to be 10 studies[8,15,16, 18, 20,22,24,27-29]. Unlicensed use of drug is pediatric age group starting from neonates are found to be from 1.26% [20] to 16.8% [22] with a maximum of 90% use of off-label use of drug in the age group of 23-36 weeks[5].

Setting of Care

As per the area/settings for pediatric care, different facilities areas were included that serve to dispense prescription medications. These included neonatal ICU (NICU), pediatric ICU (PICU), pediatric ward, operation theater (OT), out-patient department (OPD), in-patient department (IPD), general physician's clinic or private clinics and pharmacies. The closely monitored and critical care and intervention units like NICU, PICU and operating rooms were grouped to obtain a sample size of 11,092 patients. Total 4[1, 2, 3, 17] publications were found to reflect the data which ranged from 34-36% off-label use of these drugs and 62.3% for unlicensed or off-label use of the drugs.

The other subset for hospital maintenance care and follow up are done from pediatric specialty wards, general care and day care wards, IPD and OPD clinics which has the maximum of publications including 16 studies. A total of 2,110,137 patients in age group of neonates to adolescents are treated in these settings. A range of 3.3% to 76% off-label uses of drugs are found in these settings while 1.26%-33% unlicensed/unapproved uses of drugs are found in this category. UK study done by Bellis JR, Kirkham JJ *et al* [27] in 2014, resulted off-label use amongst neonates (58.3%), amongst adolescents (29.5%) and above 70% in all other age categories.

There were 4 studies which were included are carried out in general physician's or private childcare clinics (n=498670). The evaluation is segregated in settings wise where the patients catered to general physicians and that of catered in pediatric clinics are included together as there is evidence[16] that off-label prescriptions are more prevalent in children who receive a greater number of prescriptions from their GPs, similar to that of a pediatric clinic[1, 7, 25, 28].

A maximum of 76% off-label use and 56.4% unlicensed or unapproved use of drugs are observed. Pharmacies prove to be a critical component in this review as they dispense most of the drugs prescribed from different facilities. 3 studies with patient number 968,550 are done only in pharmacies. It is observed that 1.6% of unlicensed use and up to 90% of off-label use is

observed. There were 2 studies done which included patients from both general physician's clinics and pharmacies (n=612) shown off-label use of 31% - 54.1% and nil unlicensed use[9, 24].

Drug(s) or drug classes involved

The nature of prescription ranged from anesthetics to penicillin, amikacin etc. and drug classes like analgesics, diuretics, antibiotics, antihypertensive, steroids, bronchodilators, anticoagulants, sedatives, anesthetics, antiarrhythmic etc. 48-62.3% of commonly used drugs are unlicensed[2,5] . Paracetamol has 25-49% off-label use[5,12,13,15]. Antibiotics has a both off-label and unlicensed use. A 2011 study conducted in 342 patients (below 14 years) by Dos Santos L, Heineck I[14] showed that analgesic drugs (26.9%) and antispasmodic drugs (31.5%) were the most frequently issued off-label drugs. In this category of settings a good proportion of off-label and unlicensed use of drug is observed. Analgesics, antibacterial for systemic use, anti-inflammatory and anti-rheumatic products, nasal preparations are the common treatment areas shown by Palmaro A, Bissuel R et.al in 2014 study in France (n=2313) which shown evidence of 56.4% unapproved indication, lower dosage 26.5%, higher dosage 19.5% than specified, age not labeled 7.2%, incorrect route of administration 3.5% and contraindication 0.3%[28].

Distribution of studies according to year

1998-2003: Six studies are conducted in six years with a population of 1999. All the six studies that are involved for this review are done in UK[1-6]. With a maximum of 96% off-label use of drug is observed.

2004-2008: Five studies are selected in a span of five years. 20.3-47% off-label use is observed[8,10,22,25] . Study conducted by Shah SS, Hall M et al in USA included 355409 patients in pediatric ward in which use of off-label and unlicensed drug use ranged from 33-76%[10] .

2009-2014: In the last six years 19 studies are selected for this review with a total population of 7212967. The studies are done in 14 countries and at different setting. A study conducted in 2013 by Manthripragada AD et al has shown a considerable decrease in use of topical calcineurin inhibitor in children. After USFDA action in 2005 against off-label use, a significant decrease in topical off-label use for both tacrolimus (36.7% to 22.5%, $P < .001$) and pimecrolimus (47.0% to 33.7%, $P < .001$) is found in new users younger than 2 years of age.[25]

Discussion

This systematic review was done to determine the nature and extent of such use in pediatric population with respect to geographic location, age of children prescribed, setting of care and class of drugs prescribed for off-label and unlicensed use. The result showed a lower off-label

drug usage in the neonatal population (1.26%[29] to 1.6%[15]) while a major off-label use (maximum of 90%) in the age group of 23-36 weeks[5] .

On the other hand, there was a higher off-label use (34-36%) and 62.3% for unlicensed/off-label use observed in common and widely prescribed drugs in NICU, PICU and operating rooms. This again reflects the emergence to explore the new use of drugs in critical care for the caregivers in the interest for the patients. A considerable amount of off-label use is observed amongst neonates (58.3%) than the adolescents (29.5%)[12, 13, 18, 21].

In terms of specific drug classes it is observed that analgesic drugs (26.9%) and antispasmodic drugs (31.5%) were the most frequently issued off-label drugs. 48-62.3% of commonly used drugs are unlicensed.[2, 5] Paracetamol has 25-49% off-label use [5,7,13,15]while antibiotics has a both off-label and unlicensed use.

A maximum number of studies to identify the off-label and unlicensed use of drug are conducted in European countries followed by USA. The aim of this review is also to understand the regulatory environments of different agencies in America, Europe, Australia, Canada and United Kingdom where the maximum number of studies and review conducted in last 17 years.

United States: The FDA has shown their stand by making it a mandate to ask the pharmaceutical companies to obtain complete, comprehensive and credible data for the use of the drugs in pediatric population as part of their submission and to review their data in a regular basis to modify or continue the labeling requirement 'pediatric use only' for their products.[30]

Health Canada: The Standing Senate committee on Social Affairs, in their Jan 2014 report, discussed the role of Health Canada in approving all drugs after determining that the benefits outweigh the risks associated with a drug's use before they can be sold in the country. While Health Canada has the authority to conduct post-market surveillance, it does not have jurisdiction over the prescribing practices of physicians, which is provincially/territorially regulated.[31]

European Legislation does not require Member States to prohibit the prescription or administration of medicines outside their authorized indications. As per the Article-5 of Directive 2001/83/EC, a Member State may not prohibit the use beyond the prescription limitations and to preserve clinical freedom to act in the best interest of the individual patient.[32]

MHRA-UK has published an update on *Off-label or unlicensed use of medicines: prescribers' responsibilities* on 1st April 2009 where it is mentioned that there may be situations where the prescribers has to judge the necessity of use of off-label and unlicensed drugs especially in case of pediatrics where difficulties in the development of age-appropriate formulations means that many medicines used in children are used off-label or are unlicensed.[33]

New South Wales Therapeutic Advisory Group (NSW TAG) of Australia to promote Quality use of medicines (QUM), has recommended routine off-label use in Australia can be justified if there is high-quality evidence supporting efficacy or effectiveness, and sufficient evidence about the medicine's safety profile to suggest an overall reasonable benefit–risk ratio for a given clinical context.[34]

The percentage of only off-label usage of medicine is high in Pharmacy[3,26] and highest unlicensed drug used in pediatric ward (19%).[5] The above regulatory environment directs the health care providers to be more cautious in practicing prescription habits for children. They should analyze the risk benefit scenario prudently in different point of care. If need emerges, no alternative therapy is available, the parents of the children should be informed and proper consenting to be taken before practicing off-label, unlicensed use of certain drugs for the benefit of the patient.[19,22] For reinforcing the pediatric clinical trial, encouragement of parents play a vital role[19]. The second stake holder, the manufacturer or the marketing authority holder should regularly carry out pharmacovigilance of already marketed drug to understand the adverse reactions and new indications. Time to time notifying the regulatory agencies and performing regular clinical studies for new drugs or new indications are utmost necessity.

Pediatricians and other treating physicians must become aware of the licensing status of the medications that they prescribe and propagate the information to all involved in the care of children receiving these medications through peer inspirations and different CMEs. In some regions there are local prescribing policies, which govern GP choice of prescription to only licensed medications. Pediatric specialists should provide information to families on drugs that are likely to cause particular problems. This can then be disseminated to local practitioners, nurses and pharmacists.[7]

The limitation of this systematic review is that the data collected from various settings followed different assessment method to determine the percentage of off-label and unlicensed drug for pediatric population.

The most important stakeholder, the regulatory agencies, should be vigilant on reviewing safety data and supporting the industry with time-to-time update about the use of drugs in pediatric populations. The concept of parental oral consent before the use of off-label and unlicensed drug should be explored in parallel.[19] The last and the final stakeholder is the parents who should always make sure to go through the package inserts, product monographs of drug prescribed to minimize the off-label use[14] . They have all the rights to ask their health care givers about the pros and cons of the drug prescribed to their children.

Abbreviation:

CINAHL: Cumulative Index to Nursing & Allied Health

EC: European Commission

EMEA: European Medicines Agency

FDA: Food and Drug Administration

GI: Gastro Intestinal

ICU: Intensive Care Unit

IPD: In Patient Department

MAH: Marketing Authorization Holder

MHRA: Medicines & Healthcare products Regulatory Agency

NICU: Neonatal Intensive Care Unit

NSAID: Non Steroidal Anti-inflammatory Drug

NSW TAG: New South Wales Therapeutic Advisory Group Inc.

OPD: Out Patient Department

OT: Operation Theatre

PICU: Pediatric Intensive Care Unit

PPI: Proton Pump Inhibitor

QUM: Quality use of medicines

TGA: Therapeutic Goods Administration

UK: United Kingdom

USFDA: United States Food and Drug Administration

US: United States

REFERENCE

1. Martin RM, Wilton LV, Mann RD, Steventon P, Hilton SR. (1998) Unlicensed and off label drug use for paediatric patients. General practitioners prescribe SSRIs to children off label. BMJ 1998;317:204
2. Turner S, Longworth A, Nunn AJ, Choonara I. (1998) Unlicensed and off label drug use in paediatric wards: prospective study.BMJ. 1998 Jan 31;316(7128):343-5
3. Conroy S, McIntyre J, Choonara I. (1998) Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal E.1999 Mar;80(2):F142-4; discussion F144-5.

4. Turner S, Nunn AJ, Fielding K, Choonara I (1999). Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. ActaPaediatr. 1999 Sep;88(9):965-8.
5. Conroy S, Newman C, Gudka S(2003) Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children.Oxford Journals Ann Onc.2003 Jan;14(1):42-7
6. Dick A, Keady S, Mohamed F, Brayley S et al (2003) Use of unlicensed and off-label medications in paediatric gastroenterology with a review of the commonly used formularies in the UK. Aliment PharmacolTher. 2003 Feb 15;17(4):571-5.
7. 't Jong GW, Eland IA, Sturkenboom MC,(2004) Unlicensed and off-label prescription of respiratory drugs to children.EurRespir J. 2004 Feb;23(2):310-3.
8. Bajcetic M, Jelisavcic M, Mitrovic J (2005) Off label and unlicensed drugs use in paediatric cardiology.Eur J ClinPharmacol. 2005 Nov;61(10):775-9. Epub 2005 Sep 8.
9. Eiland LS; Knight P (2006), Evaluating the off-label use of medications in children. A merican Journal of Health-System Pharmacy, 2006 Jun 1; 63 (11): 1062-5.
10. Shah SS, Hall M, Goodman DM et al (2007). Off-label drug use in hospitalized children. Arch PediatrAdolesc Med. 2007 Mar;161(3):282-90.
11. Ring JC. (2008). Pharmacotherapy for pediatric cardiovascular diseases: the role of off-label drug use in the 21st century.CircCardiovascQual Outcomes.2008 Nov;1(2):69-71. doi: 10.1161/CIRCOUTCOMES.108.830935
12. Doherty DR, Pascuet E, Ni A (2010). Off-label drug use in pediatric anesthesia and intensive care according to official and pediatric reference formularies. Can J Anaesth.2010 Dec;57(12):1078-88. doi: 10.1007/s12630-010-9395-0.
13. Oguz SS, Kanmaz HG, Dilmen U (2011) Off-label and unlicensed drug use in neonatal intensive care units in Turkey: the old-inn study. Int J Clin Pharm. 2012 Feb;34(1):136-41. doi: 10.1007/s11096-011-9604-0
14. Dos Santos L, Heineck I (2011)Drug utilization study in pediatric prescriptions of a university hospital in southern Brazil: off-label, unlicensed and high-alert medications. Farm Hosp. 2012 Jul-Aug;36(4):180-6. doi: 10.1016/j.farma.2010.12.008. Epub 2011 Oct 24.
15. Olsson J, Kimland E, Pettersson S, Odlind V (2011) Paediatric drug use with focus on off-label prescriptions in Swedish outpatient care--a nationwide study. ActaPaediat. 2011

Sep;100(9):1272-5. doi: 10.1111/j.1651-2227

16. Ballard CD, Peterson GM, Thompson AJ, Beggs SA. (2012) Off-label use of medicines in paediatric inpatients at an Australian teaching hospital. J Paediatr Child Health.2013 Jan;49(1):38-42. doi: 10.1111/jpc.12065.
17. Ribeiro M, Jorge A, Macedo AF. (2012) Off-label drug prescribing in a Portuguese paediatric emergency unit. Int J Clin Pharm. 2013 Feb;35(1):30-6. doi: 10.1007/s11096-012-9699-y. Epub 2012 Sep 28.
18. Smith MC, Williamson J, Yaster M, Boyd GJ, Heitmiller ES.(2012) Off-label use of medications in children undergoing sedation and anesthesia.AnesthAnalg. 2012 Nov;115(5):1148-54
19. Palčevski G, Skočibušić N, Vlahović-Palčevski V. (2012) Unlicensed and off-label drug use in hospitalized children in Croatia: a cross-sectional survey. Eur J ClinPharmacol. 2012 Jul;68(7):1073-7.
20. Kimland E, Nydert P, Odlind V, Böttiger Y, Lindemalm S.(2012) Paediatric drug use with focus on off-label prescriptions at Swedish hospitals - a nationwide study.Acta Paediatr.2012 Jul;101(7):772-8.
21. Maltz LA, Klugman D, Spaeder MC, Wessel DL. Off-label drug use in a single-center pediatric cardiac intensive care unit. World J PediatrCongenit Heart Surg.2013 Jul;4(3):262-6. doi: 10.1177/2150135113481042.
22. Carnovale C, Conti V, Perrone V. et al (2013) Paediatric drug use with focus on off-label prescriptions in Lombardy and implications for therapeutic approaches.Eur J Pediatr.2013 Dec;172(12):1679-85. doi: 10.1007/s00431-013-2111-7
23. Ruíz-Antorán B, Piñeiro R, Avendaño C, Román E et al (2013). Drug utilization and off-label drug use in Spanish pediatric gastroenterology outpatients.JPediatrGastroenterol Nutr.2013 Feb;56(2):173-7
24. Ellul IC, Grech V (2013). Off-label and unlicensed paediatric prescribing in a community setting: a prospective longitudinal cohort study in Malta.PaediatrInt Child Health. 2014 Feb;34(1):12-8. doi: 10.1179/204690513X13656734979929. Epub 2013 Dec 6.
25. Manthripragada AD, Pinheiro SP, MaCurdy TE et al (2013). Off-label topical calcineurin inhibitor use in children. Pediatrics. 2013 Nov;132(5):e1327-32. doi: 10.1542/peds.2013-0931. Epub 2013 Oct 14.
26. Edward G. and Gill A (2014). Use of n-acetylcysteine for bowel obstruction in children. Archives of disease in childhood 2014, 99 (8)e3. Publication Year: 2014

27. Bellis JR, Kirkham JJ, Nunn AJ, Pirmohamed M (2014). Adverse drug reactions and off-label and unlicensed medicines in children: a prospective cohort study of unplanned admissions to a paediatric hospital.Br J ClinPharmacol. 2014 Mar;77(3):545-53. doi: 10.1111/bcp.12222.
28. Palmaro A, Bissuel R, Renaud N, Durrieu G. (2014) Off-label prescribing in pediatric outpatients. Pediatrics. 2015 Jan;135(1):49-58. doi: 10.1542/peds.2014-0764. Epub 2014 Dec 15.
29. Langerová P, Vrtal J, Urbánek K. Incidence of unlicensed and off-label prescription in children. Ital J Pediatr. 2014 Feb 4;40:12. doi: 10.1186/1824-7288-40-12.
30. 21 CFR Part 201: Specific Requirements on Content and Format of Labeling for Human
31. Prescriptions of Pharmaceuticals in Canada-Off label Use, Jan 2014
32. DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67) 2001L0083 — EN — 16.11.2012 — 011.001 — 18
33. MHRA-Government of UK: Off-label or unlicensed use of medicines: prescribers' responsibilities Dated: 1 April 2009
34. Med J Aust 2006; 185 (10): 544-548. Off-label use of medicines: consensus recommendations for evaluating appropriateness.