



Pattern of Use Unlicensed Medication in Pediatrics: A Retrospective Study at Major Tertiary Care Hospital in Saudi Arabia

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AA and HA prepared the plan for the study and supervised the design and execution. Authors YB, BA and SA facilitated hospital communication and provided data. Authors AA and WM wrote the paper and performed the statistical analysis of collected data. Authors HA and HM reviewed it. All authors read and approved the final manuscript.

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ABSTRACT

Background: Unlicensed medication use (off label use) is common in pediatrics practice. There are more than 75% of drugs which approved for using in adults, data of efficacy and safety in pediatric population is not completely available, and missed data might be due to some reasons mainly ethical consideration. Our study aimed to assess practicing of using of unlicensed medication in pediatrics at major tertiary care hospital in Saudi Arabia.

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Methods: A retrospective review of pediatrics prescriptions that were prescribed as unlicensed medication use by collection of all unlicensed use forms that known as form B which approved by pharmacy and therapeutics (P&T) committee at Prince Sultan Military Medical city (PSMMC). Data collection started from January 2018 until the end of 2020. Children up to 14 years of age and administered at least one medication were eligible to participate in the study.

Results: The total collected off label prescriptions (both in and out patients) was 128 from January 2018 till end of 2020. Prescription for females were 39.84% while their male counterparts were 60.16%. Ophthalmology, Oncology and both Otorhinolaryngology and general pediatrics were the most frequent specialties prescribed unlicensed medications by 34.38%, 19.53% and 8.59% respectively. Overall, unlicensed medicine use was highest (33.6%) for products belong to monoclonal antibodies class. Surgical intervention was the commonest indication for using unlicensed medication (35.94%) followed by infectious diseases treatment (14.06%). Represented as the cumulative off-label frequency percentage, the most common reason of off-label use was by indication (35.94%), frequency (33.18%), Dose (19.82%), while for the route was almost (11.06%). The highest frequency of off label prescriptions according to pharmacological class split by gender and age category showed significance level of 0.045 in males and 0.001 in infants respectively.

Conclusion: Class variability of unlicensed medications in this study, sought us to confirm that physician using this therapeutic option yet ethically, but in a disorganized manner. Thus, prescribing unlicensed drugs specifically in pediatric needs to be better validated by current and new evidence. The findings of this study call for further research across the kingdom to start off label legislation process under SFDA authority. Current off-label dosage amounts pose concerns about drug safety exceptionally in children.

Keywords: Un-licensed medication use; pediatrics; Saudi Arabia; safety.

1. INTRODUCTION

Unlicensed medication (Off-label medication) use is known as the use of approved medication by Food and Drug administration (FDA) with the unauthorized indication, dose, route, frequency, or duration in children [1-4]. There are more than 75% of drugs which approved for using in adults, data of efficacy and safety in pediatric population is not completely available [5]. This missed data might be due to some reasons mainly changing in physiological, pharmacokinetics of body during ages development as well as some ethical considerations [6]. The major concern of off-label using is having low quality evidence which might predisposed patient to any types of medication errors [7-9].

The number of off-label prescribing estimated to be between 18% and 60% in infants and it might be reach to 90% in neonates [10-16]. The probability of receiving an off-label prescription is reduced by 3% for every year of increasing in age [17]. Safety concerns usually explored with unlicensed medications [18]. Safe prescribing is especially difficult in children since many therapeutic agents have not been adequately tested in this population group and their benefit-to-risk ratio is commonly ascertained by insufficient proof. Children are most vulnerable to medication errors due to unlicensed medications

[19]. It is worth notable that 23% up to 60% of all adverse drug reactions ADRs in children were caused by unlicensed use of medicine [20]. However, health care providers may repurpose some medications for treating certain clinical conditions [21].

Usually medications' pamphlet and advertising materials done by pharmaceutical companies in most countries lack information regards unlicensed indication. Physicians can, however, recommend any licensed medication for any indication, regardless of the fact that such an indication is not approved by regulatory authorities [22].

Only few countries like France and United States of America their regulatory authorities issued regulations concerning unlicensed medications [23]. In Saudi Arabia, Saudi Food and Drug Authority (SFDA) is the regulatory authority responsible for authorizing and registering medications [18]. In conjunction with Saudi vision 2030, for carrying the health needs or health status of Saudi people to the maximum and highest possible standard, in terms of equity and dignity in the provision of healthcare, national studies at level of tertiary hospitals are essentially needed to help regulatory authorities to issue policies and regulations regarding use of unlicensed medications. Therefore, this study

was designed assess the percentage of unlicensed pediatric drugs utilization in real practice by exploring the most common prescribed unlicensed medication at major tertiary care hospital in Saudi Arabia.

2. METHODS

2.1 Study Design and Data Collection

A retrospective review of pediatrics' prescriptions of unlicensed medications by collecting all off-label use forms known as form B which approved by Pharmacy & Therapeutic (P&T) committee at Prince Sultan Military Medical city (PSMMC) to proceed unlicensed medication prescription. Study was conducted from January 2018 until end of 2020 to all prescriptions of inpatient and outpatient pharmacy. Data collected under supervision of clinical pharmacists of drug information and poison center (DPIC). Data are continuously validated and reviewed by DPIC team. Only after this, data were gathered and demographic data, specialty who request off-label use, the number of medications prescribed as off-label use, most common pharmacology and indications classes, and most common reasons of un-licensed use of medication are collected. Children up to 14 years of age and administered at least one medication were eligible to participate in the study where older children or adolescents were excluded.

2.2 Statistical Analysis

Demographic data and prescriptions collected were described using descriptive statistics (frequencies and percentages for categorical variables, means and standard deviations for continuous variables whenever applicable). Comparisons of the age and pharmacological class categories between drugs listed as off-label was performed using Chi-square statistics.

Analyses were performed using the SPSS version 20 statistical software. A p-value < 0.05 is considered as statistically significant.

3. RESULTS

From January 2018 till end of 2020, total of 51817 medications that had been prescribed by electronic prescription system, only 128 (0.25%) prescriptions which proceed by attaching the form b with prescription from (both out and inpatients) to pediatric population who was included in our study. Medications were prescribed as un-licensed medication use by attaching form B as per hospital policy with evidence based approved by clinical pharmacist to be given. Patient age ranged from 36 weeks to 14 years, the average age was 4 years and the median was 1 year with infants consisted 43.75%. Females constituted 39.84% of patients while males were 60.16% (Table 1).

The most specialty requested off-label medications was ophthalmology 44 (34.38%), oncology 25 (19.53%) and both oto-rhino-laryngologists and general pediatricians prescribed 11 (8.59%) orders. Highest proportion of un-licensed medication use among indication classes was using for surgical intervention (35.94%), followed by 14.06% and 13.28% for treatment of infections and tumors respectively (Table 2).

Un-licensed medication with the highest rate of prescription was Ranibizumab (26.56%) followed by Palifermin (9.38%) and mometasone (5.47%) (Table 3). Regarding overall unlicensed medication monoclonal antibodies class of medication was top in the list (33.6%), followed by chemotherapy class (28.9%), general antibiotics classes (13.3%), immune suppressants class (8.6%) and miscellaneous medications class were 15.6% (Tables 5 and 6).

Table 1. Demographic characteristics of patients

	Characteristic	Number n=128	(%)
Gender	Male	77	60.16
	Female	51	39.84
Ages	0 - <28 days (neonates)	3	2.34
	28 days- 11 months	56	43.75
	1-10 year	49	38.28
	11-14 year	20	15.63

Table 2. Un-licensed medication use classification by specialty and indication

Classification	Characteristic	Number n=128	(%)
Specialty	Dermatology	7	5.47
	Otorhinolaryngology	11	8.59
	General pediatric	11	8.59
	Hematology	2	1.56
	Infectious diseases	6	4.69
	Nephrology	6	4.69
	Neurology	3	2.34
	Oncology	25	19.53
	Ophthalmology	44	34.38
	Pediatric gastroenterology	4	3.13
	Pediatric surgery	1	0.78
	Intensive care	4	3.13
	Rheumatology	3	2.34
Urology	1	0.78	
Indication	Tumors	17	13.28
	Endocrine	7	5.47
	Genetics	7	5.47
	Infections	18	14.06
	Gastroenterology	5	3.91
	Surgical intervention	46	35.94
	Autoimmune diseases	10	7.81
	Miscellaneous	18	14.06

Table 3. Most commonly un-licensed prescribed medication list

Drug name	n=128	(%)
ganciclovir	4	3.13
Gentamicin	3	2.34
Bleomycin	6	4.69
Palifermin	12	9.38
Mitomycin	5	3.91
Tofacitinib	3	2.34
Ranibizumab	34	26.56
Tocilizumab	5	3.91
Anakinra	5	3.91
Sirolimus	3	2.34
Cinacalcet	6	4.69
mometasone	7	5.47

3.1 Reasons of Using Un-licensed Medication

Frequently drugs are classified as off-label for more than one reason. The most evidence that we used in our study to define un-licensed use (off label) was Micromedex, Food and Drug Authorization FDA and some case reports [21,22]. The most common reason in our study was by indication (73.43%), frequency (64.84%), and dose (39.84%), while for the route was (25%). This is demonstrated by a cumulative off-

label frequency percentage of about 203% shown in Table 4.

Table 4. Cumulative frequency and percentage of off-label medications

Type of off-label	Frequency	%
Dose	51	39.84
Route	32	25
Frequency	83	64.84
Indication	94	73.43
Cumulative	260	203.11

The highest frequency of off-label prescribing occurred in infants with significant difference according to pharmacological class prescribed ($p < 0.001$) on the other hand males in general irrespective of the age also differ significantly than females according to the same variable ($p = 0.045$) as shown in Tables 5 and 6 respectively.

4. DISCUSSION

This Study focused on processing of un-licensed use of medication (off-label medication) in real practice meaning the prescription of off-label medication might processing without approval of P&T committee based on some evidence that

reviewed by pharmacist to give patient even it is not FDA labeled. In this study, prescription of off-label medications followed standards of unlicensed medication use prescribing policy of hospital, while the related studies didn't clarify some thoughts into off-label prescriptions regard to the drugs being prescribed, and how they are being used off-label. Regrettably, the information in these studies also didn't not capture a true sense of what is happening in really practice.

Aldebasi and his colleague stated that almost 2% of all premature babies with ROP might need treatment every year. They attributed this high incidence of ROP to the development in neonatal healthcare [24]. A recent secondary analysis of data from the Postnatal Growth and Retinopathy of Prematurity, the authors found 3224 infants (43.1%) with retinopathy of prematurity (ROP). These two studies may explain the great rate of ranibizumab prescription by ophthalmologists in our study [25].

Bazzano et al. analyzed data from the 2001–2004 National Ambulatory Medical Care Surveys and found that in 7901 outpatient visits of children ages 0 to 17, just 2% of visits utilized off-label drug therapy. Of these prescriptions, 90% of the cardiovascular-renal medications, 80% of pain and gastrointestinal medications, 75% of pulmonary and dermatologic medications, and 42% of anti-infective uses were considered off-label [26]. So, it might difficult to manage or

control to un-licensed medication use by these huge numbers of medications which treated most of chronic diseases.

In contrast to this study, Tefera and his colleagues classified off-label used based on pharmacology classes, found antimicrobials was the highest by 60.6%, followed by drug working on central nervous system 14.3%, cardiovascular system 8.6%, while ophthalmologic and blood-forming agents were the least group of drugs 0.3% [21]. On the other hand, in 2019 Nagham and her colleagues agreed almost to our results as they studied pattern of off label and unlicensed drug use in Saudi Arabia included all groups of ages, percentage of data of prescriptions for peditrics was less than 10% of total prescriptions, and study found the most common reason of off label use is indication [23].

Our study agrees with related studies which by developing with ages, the number of off-label use was decreased. This study comparing to related studies found the most common reason for unlicensed medication use was due to indication.

This study has some limitations as it was conducted only in one center, included only pediatric patients' pharmacy data, difficult estimation of number of patients who was admitted through study periods and in interpreting data collection by correlate data with each other.

Table 5. Frequency of off label prescriptions according to pharmacological class split by gender

Class	Gender (p=0.045)		
	M	F	Total
Antibiotics	13	4	17
% of total	10.2	3.1	13.3
Chemotherapy	15	22	37
% of total	11.7	17.2 %	28.9
Monoclonal Antibodies	29	14	43
% of total	22.7	10.9	33.6
Immunosuppressant	6	5	11
% of total	4.7	3.9	8.6
Miscellaneous	14	6	20
% of total	10.9	4.7	15.6
Total	77	51	128
% of total	60.2	39.8	100.0

Table 6. Frequency of off label prescriptions according to pharmacological class split by age category

Age category	Pharmacological class (p<0.001)					Total
	Antibiotic	Chemotherapy	Monoclonal antibodies	Immunosuppressant	miscellaneous	
Less than 28 days (Neonates)	0	0	3	0	0	3
% of total	0.0	0.0	2.3	0.0	0.0	2.3
28 days- 11 months (infants)	7	4	31	4	10	56
% of total	5.5	3.1	24.2	3.1	7.8	43.8
1-10 years	6	19	8	6	10	49
% of total	4.7	14.8	6.3	4.7	7.8	38.3
11 -14 years	4	14	1	1	0	20
% of total	3.1	10.9	0.8	0.8	0.0	15.6
Total	17	37	43	11	20	128
% of total	13.3	28.9	33.6	8.6	15.6	100.0

5. CONCLUSION

Class variability of unlicensed medications in this study, sought us to confirm that physician using this therapeutic option yet ethically, but in a disorganized manner. Since our study reported indication as the most common reason for unlicensed medications use and literature emphasized no data as regards neither efficacy nor safety for pediatric ages. Prescribing off label pediatric drugs needs to be better validated by current and new evidence. Since this was a single-center study, the results could not be applicable to other hospitals in Saudi Arabia. Our research did not examine the benefits and adverse effects of using unlicensed drugs. Certainly, the findings of this study call for further research across the kingdom to start off label legislation process under SFDA authority. Current off-label dosage amounts pose concerns of unintended toxicity and adverse drug consequences in children.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approval of this study was obtained from scientific research center at Prince Sultan Military Medical city (PSMMC) with a reference of PSMMC (HP-01-R079).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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