

Original Research Article

The pattern of off-label and unlicensed drug use in adult and pediatric patients in the Kingdom of Saudi Arabia: multicenter retrospective study

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ABSTRACT

Background: Screening approved medications to identify therapeutics for drug repurposing is an effective tactic, and a deep research into off label drug use (OLDU) is required. Unfortunately, OLDU has not been extensively studied in Middle East. Our study aimed to evaluate the extent of OLDU in Saudi Arabia.

Methods: Retrospective study carried out during 12 months period at six tertiary hospitals in Saudi Arabia. Each prescription was evaluated as unlicensed or OLDU based on the product information or based on Food and drug Administration (FDA) approval.

Results: A total of 288 prescriptions were analyzed, where the reasons for off-label prescribing were OLDU by indication (94.42%), OLDU by different age group (2.09%), and other reasons represented (3.48%). Adults/geriatrics (≥18 years) received (89.05%) of the orders, and children (1-11 years) received (7.78%) of the orders. Both adolescents (12-18 years) and neonates (1-29 days) received (1.42%) of the orders per each category, while infants (1 month-1 year) received (0.36%) of the orders. The therapeutic classes most often prescribed were antidepressants (21.88%), antidiabetics (17.71%), and atypical antipsychotics (10.06%).

Conclusions: Off-label prescribing was found in most adults/geriatrics suffering from depression, and diabetes mellitus. The most common reason for off-label prescription was off-label by indication. The results call for the need to conduct more studies with larger sample size, do more investigations on the OLDU in the whole kingdom, and develop policy for OLDU across hospitals.

Keywords: Off-label medication, Guidelines, Prescriptions

INTRODUCTION

Off-label drug use (OLDU) refers to the prescription of a currently available and marketed medication for a use that has never been approved by Food and Drug Administration (FDA).¹ Reasons for off-label prescriptions of a medication include that the medication is used for a different indication than the ones registered, administered via a different route, given with a different dose, or given to a patient of a different age range than registered.²

Adverse drug reactions (ADR) of some off label medications were still not been reported and documented, here comes the integral role of expert pharmacists in the medication review process, patient guidance, safety and adverse drug issues.³⁻⁷

In most countries, pharmaceutical companies are not allowed to issue prescribing information and promotional materials that contain non-approved indication. However, physicians can prescribe any approved medication for any indication, regardless of the fact that such indication is not approved by regulatory bodies.⁸ In fact, few countries such as the USA and France have taken an initiative and have come up with the regulations about off-label use of medicine.

Screening approved medications in order to identify therapeutics for drug repurposing is an effective tactic, and a deep research into OLDU is required as well as studies to monitor and evaluate the prevalence rate of OLDU. Unfortunately, OLDU has not been extensively studied in Middle East.⁹

In a study that was published in 2014, a library of 290 compounds was screened for antiviral activity against Middle East respiratory syndrome coronavirus (MERS-CoV) and acute respiratory syndrome coronavirus (SARS-CoV).¹⁰ Interestingly, a total of 27 compounds with activity against both viruses were identified. These compounds belong to 13 different therapeutic classes, including dopamine antagonists used as antipsychotics.

Perceptions and attitudes of pediatricians in Jordan towards off-label pediatric prescribing have been studied.⁹ Another study was conducted in Jordan to analyze the prevalence and nature of off-label antibiotic prescribing for children in a tertiary setting.¹¹ The rates of prescribing Antipsychotic medications for off-label uses, including treatment of posttraumatic stress disorder (PTSD) in returning Iraq and Afghanistan veterans with PTSD have been analyzed in a study that was published in 2015.¹² In a study that was conducted to assess the rational drug use of dabigatran at a tertiary care hospital in United Arab Emirates, it was found that some patients received it for off-label indications. In addition, a study was conducted in Palestine in to determine the extent and nature of unlicensed/off-label prescribing patterns in hospitalized children.^{13,14}

In Saudi Arabia, A retrospective analysis was conducted to study the use of Intravenous immunoglobulin (IVIG) in a tertiary care teaching hospital.¹⁵ In this study, the indications of IVIG were categorized into FDA-labeled, off-label recommended as first line, off-label recommended as alternative, and not recommended. The results showed that there was a relatively high amount of IVIG dispensed at the study institution for inappropriate indications, which had a great cost burden on the hospital. The authors concluded that implementing an approval form and obtaining expert permission to use IVIG for off-label indications particularly when science-based evidence is limited or not conclusive may improve this behavior. Another study was conducted in Saudi Arabia to report the indications and safety of biologic agents used in treatment of children with rheumatic diseases at a tertiary hospital.¹⁶ The study found that off-label use of biologic agents was common.

A study that was conducted in a Saudi tertiary care hospital showed that OLDU in hospitalized neonates seems to be a common practice.¹⁷ Nevertheless, there is no information available regarding the extent of use of unlicensed and off-label drugs in Saudi Arabia and Middle East. Therefore, this study was conducted to address this issue, cover this literature gap, and provide data about the prevalence rate and prescribing pattern of off-label use at different hospitals in the Kingdom of Saudi Arabia.

METHODS

Study design

A retrospective study was conducted at six different hospitals in Saudi Arabia including secondary and tertiary hospitals around the kingdom. Data were collected from the medical records of patients who visited or were admitted to the study hospitals between January 2016 and July 2018 and were then transferred into data collection forms. Data included demographic data, diagnosis, the number of medications prescribed, and the complete regimen for each drug prescribed (dose, frequency, indication, route of administration, and formulation).

Objectives

- Evaluating the rate of off-label drugs usage.
- Identifying the percentage of morbidity and mortality by using off-label medications.
- Classifying the most common off-label use medications in Saudi Arabia's hospitals.
- Determining the availability of policy and procedures behind prescribing the off-label medications.
- Measure the prevalence of adverse drug reactions associated with off-label prescribing and evaluate it as a risk factor for the development of serious adverse reactions.

Reasons for OLDU

All drug prescriptions were evaluated as unlicensed or off-label use based on the product information or based on FDA approval. A medicine is classified as an off-label prescription for any of the following reasons:

1. Contraindicated in children of all age ranges.
2. Off-label use by indication.
3. Off-label use by different age group.
4. Off-label use by route of administration.
5. Lower than the approved licensed dose.
6. Higher than the approved licensed dose.

Patients' age classification

Patients' ages were classified into six groups:

1. Neonates (1-29 days).
2. Infants (1-month-1 year).
3. Children (1-11 years).
4. Adolescents (12-18 years).
5. Adults/geriatric (18 years and older).

Sampling technique

A consecutive sampling technique was applied to collect prescriptions from each site, where every subject that met the criteria of inclusion was enrolled till the required sample size was achieved.

The study sites

Data were collected from six tertiary hospitals in Saudi Arabia after getting the institutional review board approval from each one:

- Prince Mohammed bin Abdulaziz Hospital-Riyadh (N=100).
- Security Force Hospital-Riyadh (N=58).
- Alyamamah Hospital-Riyadh (N=45).
- Maternity and Children Hospital-Makkah (N=34).
- Prince Sultan Cardiac Center-Riyadh (N=30).
- Prince Imam Abdulrahman Alfaisal Hospital-Riyadh (N=21).

RESULTS

Demographics and comorbidities

Data of a total of 288 patients were collected. Table 1 shows that females and males represented (69.04%) and (30.97%) respectively. According to age classification, adults/geriatrics represented (89.05%) while children represented (7.78%). Both adolescents and neonates represented (1.42%), whereas infants represented (0.36%). The most comorbid conditions were diabetes mellitus (17.37%), polycystic ovary syndrome (16.67%), migraine (15.63%), and hypertension (14.94%).

Frequency of prescribed medications

Table 2 shows that antidepressants were the most frequently prescribed (amitriptyline 21.88%), followed by anti-diabetic agents (metformin 17.71%), atypical antipsychotics (AAPs) (10.06%) where quetiapine was the most frequently prescribed medication, drugs for treatment of infertility (clomiphene 9.72%), drugs for Treatment of enlarged prostate and androgenic alopecia (finasteride 7.99%).

Female and adults/geriatric predominance regarding the prescription of the top three OLDU antidepressants, anti-diabetic agents, and AAPs is described in Table 3; while the most common prescribed medication among children was sildenafil (50.09%), followed by spironolactone (22.73%), folic acid (13.64%), and montelukast (4.55%) as shown in Table 4.

Table 1: Demographics and comorbidities.

Variables	Count	Percentage
Gender*		
Female	194	69.04
Male	87	30.97
Age classification **		
Adult/geriatric	252	89.05
Adolescent	4	1.42
Children	22	7.78
Infants	1	0.36
Neonates	4	1.42
Comorbidities		
Diabetes mellitus	50	17.37
PCOS	48	16.67
Migraine	45	15.63
Hypertension	43	14.94
Cardiac disease	29	10.07
Hypothyroidism	21	7.3
androgenic alopecia	20	6.95
Dyslipidemia	18	6.25
Smoking	16	5.56
diabetic neuropathy	16	5.56
Fibromyalgia	9	3.13
LV thrombus	9	3.13
Preeclampsia	7	2.44
bronchial asthma	4	1.39
Hair fall	4	1.39
Endocrinology	4	1.39
Stroke	3	1.05
Renal diseases	3	1.05
Neuropathic pain	3	1.05
Parkinson	3	1.05
IBS	3	1.05
Preterm baby	3	1.05
IHD	3	1.05

*7 patients with missing data; ** 5 patients with missing data.

Table 2: Frequency of prescribed medications.

Medication	No. of prescriptions	Percentage
Antidepressant		
Amitriptyline	63	21.88
Antidiabetic		
Metformin	51	17.71
Atypical antipsychotic		
Quetiapine	20	6.94
Olanzapine	3	1.04
Clozapine	3	1.04
Risperidone	3	1.04
Treatment of infertility		
Clomiphene	28	9.72
Treatment of enlarged prostate and androgenic alopecia		
Finasteride	23	7.99
Anticoagulants		
Rivaroxaban	17	5.90
Treatment of erectile dysfunction and PAH		
Sildenafil	17	5.90
Anticonvulsants		
Gabapentin	14	4.86
Lamotrigine	3	1.04
Antiplatelet		
Aspirin	12	4.17
Treatment of folate deficiency		
Folic acid	12	4.17
Antihypertensives		
Propranolol	5	1.74
Spiroglactone	6	2.08
Treatment of circulation disorders		
Pentoxifylline	2	0.69
SNRI antidepressant		
Duloxetine	2	0.69
Desvenlafaxine	1	
Anticancer		
TPA NEB	1	0.35
Anti-asthmatic		
Montelukast	1	0.35
Treatment of cystic fibrosis		
Pulmozyme	1	0.35
Total	288	

Regarding the reasons behind OLDU use, out of 288 off-label prescriptions, 271 (94.42%) were off-label by indication, and 6 (2.09%) were off-label by different age group as shown in Table 5.

Table 6 shows that the most frequent outcome indicator was absence of symptoms 165 (57.29%), followed by absence of complications 160 (55.56%), cured/controlled disease 105 (36.46%), and improved laboratory parameters 6 (2.08%).

Table 3: Pattern of prescription according to gender and age.

Therapeutic class	Pattern of prescription according to gender (%)	Pattern of prescription according to age (%)
Antidepressants	Females: 79.37 Males: 20.63	Adults/geriatrics: 98.41 Adolescents: 1.5
Anti-diabetic agents	Females: 100 Males: 0	Adults/geriatrics: 100
Atypical antipsychotic	Females: 79.31 Males: 20.69	Adults/geriatrics: 100

Table 4: Off-label medications prescribed for children.

Medication	Number of prescriptions	%
Sildenafil	13	59.09
Spiroglactone	5	22.73
Folic acid	3	13.64
Montelukast	1	4.55
Total	22	

Table 5: Reasons for off-label prescriptions.

Reason for OLDU	Number of prescriptions	%
OLDU by indication	271	94.42
OLDU by different age group	6	2.09
OLDU for other reasons	10	3.48
Total*	287	

*1 medication with missing data.

Table 6: Outcome indicators.

Outcome indicator	Number of cases	%
Absence of symptoms	165	57.29
Absence of complications	160	55.56
Cured/controlled disease	105	36.46
Improved lab. parameters	6	2.08

DISCUSSION

Antidepressants were the most frequently prescribed, followed by anti-diabetic agents, and AAPs. It is not easy to relate or compare these results to those of other studies

since most of the published studies were conducted to analyze the prevalence of OLDU of a certain therapeutic class. Antidepressants are frequently off-label prescribed. In the current study, amitriptyline was prescribed for (21.88%) of the cases for migraine, diabetic neuropathy, fibromyalgia, and IBS. In a study that was conducted to analyze off-label indications for antidepressants, amitriptyline was associated with a high off-label prescribing rate (93%, 89.6% to 95.7%). Metformin was prescribed for (17.71%) of cases in our study. This may be because it is known to induce weight loss in overweight patients even without glucose abnormalities.^{18,19} AAPs were prescribed for (10.06%) of the studied cases. This is justified since AAPs are frequently prescribed as off-label medications.²⁰ Gabapentin was prescribed for (4.86%) of the cases. In another study that was conducted to analyze the prevalence of OLDU of anticonvulsants at a private hospital in Indonesia, it was prescribed for (18.28%) of cases.²¹

Among studied children, the most common frequent medications were phosphodiesterase (PDE) inhibitors (sildenafil for pulmonary hypertension), and diuretics (spironolactone). These results differ from those published by Luedtke and Buck in a study that was conducted to evaluate the off-label prescribing at the Kluge Children's Rehabilitation Center, Virginia, USA, where the highest percentages of off-label prescribing was for drugs of the cardiovascular system (40.6%), respiratory system (39.4%), genitourinary system/sex hormones (36.8%) and alimentary tract (34.1%).²² Also, it differs from the results reported by Czarniak et al.²³ where the highest frequency of off-label prescribing was associated with nervous system drugs in a study that was conducted to estimate the prevalence of off-label prescribing at a major pediatric teaching hospital in Western Australia.

The most common reason for OLDU in our study was OLDU by indication 271 (94.42%), while OLDU by different age group only represented 6 (2.09%). These results differ from those of a study that was conducted in Brazil where the main reason was OLDU by a different dose, followed by OLDU by different age range.²⁴ This is due to the difference of age among the studied populations, where most of our studied patients were adults/geriatrics, while the patients studied in the Brazilian study were children.

Although neither adverse event nor serious side effects have been reported, (20.49%) of the used off label medications were used with no guidelines to govern their use.

Our study has an obvious limitation; a low sample size that hindered a deep analysis of the actual prevalence of OLDU in the Kingdom of Saudi Arabia.

CONCLUSION

Off-label prescribing was found in most adults/geriatrics suffering from depression, and diabetes mellitus. The most common reason for off-label prescription was off-label use by indication.

Recommendations

1. We recommend a strong collaboration between hospitals and academic institutions in conducting more studies for extensive analysis of the pattern of off-label and unlicensed drug use in adult and pediatric patients in the Kingdom of Saudi Arabia.
2. These studies would be drug and age specific in order to deeply understand the efficacy and estimate the risk of the off-label prescribing of each medication with respect to different age groups.
3. Moreover, we recommend that such results be promptly reported to the Saudi Food and Drug Authority (SFDA) to start planning for regulations regarding off-label use of medicine around the kingdom.
4. Pharmacists can play a major role in the off-label review process based on their medication experience and the high demand toward prescribing OLDU.
5. A well-defined policy across hospitals must be established to manage the use of OLDU in proper way.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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