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Physician-pharmacist agreement about off-label use of
medications in private clinical settings in Baghdad, Iraq

Original Research

Physician-pharmacist agreement about off-label use of medications in private clinical settings in Baghdad, Iraq

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Abstract

Objective: 1) To evaluate the relationship between physician-pharmacist agreement about the off-label drug use and 2) and to identify the most common off-label medication category/indications and prescriber clinical disciplines in private settings in Baghdad area, Iraq
Methods: This study evaluated 980 off-label use requests in the private clinical settings within Baghdad area, Iraq from October 2013 to September 2015. The efficacy, safety, and convenience of each drug request and its alternative options were evaluated according to the patient health and demographic characteristics and standard guidelines.
Results: Of the 980 physician off-label requests, only 22.7% were approved by the pharmacists. Rheumatology and Nephrology accounted for the highest ratio of off-label use requests for adults (30.3% and 26.3%). The pharmacist rejection ratio of off-label use was comparable between the two groups (p>0.05). Most of the issued requests were attributed either to unapproved indication or to combination of more than one drug (38% and 35.3%). A low acceptance rate was reported in the requests issued for treatment in different clinical lines to the authorized one (11.9%). The lowest rate of acceptance was reported in the requests that had very low evidence level (9.1%). The mostly prescribed medications were musculoskeletal agents (28.9%). Finally, 78.2% of the requests came from clinical branches for adults. Although the agreement rate for requests in adults was higher than that in pediatrics, the two rates were not significantly different.
Conclusion: Community pharmacists should effectively take responsibility for assessing off-label drug requests in Iraqi private settings. The quality of evidence does not represent the major factor influencing the approval rate of off-label drug use. The availability of safer and/or affordable alternatives and prescribing for a different patient age category highly impacted the pharmacists' approval rate.

Keywords

Off-Label Use; Interprofessional Relations; Physicians; Pharmacists; Practice Patterns, Physicians'; Attitude of Health Personnel; Prospective Studies; Iraq

INTRODUCTION

Off-label prescribing practice of medications refers to the use of drugs for unapproved indications or in an unapproved age group, dosage, or route of administration.[1] It is commonly recognized in most of the medical specialties in developed countries; however, it is more frequent in communities with low experience of patient inclusion in clinical trials.[2,3] Although some off-label medications may benefit the patients, in certain conditions, this approach may be a source of serious medical problems, especially when safety and effectiveness data for off-label use are scanty.[4,5] Unlike drugs prescribed for Food and Drug Administration (FDA) approved indications, off-label uses may not exactly follow the required effective scientific scrutiny. Accordingly, the rational off-label prescribing should be based by on solid and scientific evidences to ensure safe and effective outcomes.[6] Ideally, prescribing practice should rely on evidenced-based idea and the results of controlled clinical trials rather than what is mentioned in the product leaflet. While the leaflet can be a source of valuable information about the given medication, it is not an exclusive determinant of the medical practice nor is it a substitute for sound clinical decision.[7]

In the U.S., the FDA approves an appreciable number of off-label uses annually.[8] This pathway can be a valuable approach to ensure that health care is based on solid evidence-based clinical practice, and associated with patient safety and cost effectiveness. However, many screening studies and surveys have indicated that supporting evidence is not widely available for most off-label uses for various types of medications.[3] Despite the concerns regarding patient safety and cost effectiveness to the total community and health care system, limited data are available in Iraq regarding the clinical significance of off-label drug uses. Moreover, the level of scientific evidence that support these uses in medical practice is inadequate. Off-label prescribing rate is well characterized in out-patient practice, including 21% in USA[3] and 11.8% in Canada[9]; however, no similar data were reported in Iraq. According to our knowledge, this study is the first of its kind to be conducted in Iraq that highlights the off-label

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prescribing practice in private medical services. The objectives of this study were 1) to evaluate the relationship between physician-pharmacist agreements about the off-label drug use and 2) identify the most common off-label medication category/indications and prescriber clinical disciplines in private settings in Baghdad, Iraq.

METHODS

Study design, settings and participants

This study included the evaluation of 980 off-label medication use requests issued by physicians in 50 private outpatient clinics within the Baghdad area during the period from October 1, 2013 to September, 30, 2015. Physicians, private general practitioners with a minimum of 5 practice years, were randomly selected and invited to participate through direct contact (in person). In total, 50 physicians agreed to participate and fulfilled the study inclusion criteria: Prescribe drugs during routine practice, and have documented patients' data. The participating physicians were fully informed about the study aims and design. The physicians were asked to prepare the medication requests in a form to facilitate pharmacist evaluation. The research protocol was approved by ethics committee at the University of Baghdad, College of Pharmacy. The research committee included three specialist pharmacists who were responsible for reviewing the prescriber off-label requests. The review committee received technical support from the Clinical Pharmacy Unit, Al-Kindy Teaching Hospital/ Baghdad, which engaged in a clinical pharmacy training program that related to off-label drug uses.

Measurement of outcomes

According to the study protocol, a physician had to complete a drug prescribing request form with patient demographics, previous treatments, alternative treatments, and reasons justifying the off-label indication, and attach any bibliographic references requested by the research team, which included three pharmacists. The research team followed a standardized evaluation procedure based on the one designed by the GENESIS Group (Group for Innovation, Assessment, Standardization and Research in the Selection of Drugs) from the Spanish Society of Hospital Pharmacy.[10] The research team considered 7 days as time-period to evaluate the efficacy, safety, and convenience of the physician requested medication and its alternative options. The evaluation decision depends on patient health and demographic characteristics, the U.S. FDA and the National Institute for Health Care Excellence (NICE) guidelines. The study did not include drugs subject to off-label protocols at the time of their approval, as well as individualized off-label treatments at the time of receiving the indication by regulatory agencies: Iraqi National Board of Drug Selection (NBDS), and the U.S. FDA. Treatment agreement rate was considered as the primary variable, and data analyses also included patients' demographic data, medication therapeutic category and clinical indication. Medication efficacy and safety data were taken in consideration in reviewing decision of off-label requests. The reasons for any drug or combination to be considered off-label were

ranked into four groups: 1) Indication is not licensed at the Product Specifications (PS), 2) Indication is not approved for the patient's age, when patient did not fall into the specific age group targeted by the treatment (e.g., adults vs pediatrics) 3) Indication for a treatment approach differs from that approved in the PS. 4) Prescriptions including combination of drugs are not matching that approved in the PS. Scientific evidences of the off-label indications were classified according to the GRADE system (Grading of Recommendations, Assessment, Development and Evaluation), into high, moderate, low, and very low evidence.[11] High Evidence includes meta-analyses, randomized controlled trials (RCTs), systematic review of RCTs. Moderate Evidence includes non-randomized controlled clinical trials, randomized clinical trials in other lines of treatment or population, but could be extrapolated, studies of cohorts and high quality centers. Low Evidence includes studies of cases and controls, and multiple series compared over time. Very Low Evidence includes series of cases, and experts' opinion.[11]

Statistical analyses

Statistical analyses were conducted using the SPSS (Statistical Package for the Social Sciences) Program for Windows, version 19.0 (IBM, USA). Frequencies were used to summarize the gender, number of prescribed drugs, approved, unapproved and off-label prescribed drugs. Chi square test was used to measure the relationship between scientific evidence and the decision by the evaluators, and the relationship between the agreement rate between adults and pediatrics.[2] The relationship between evaluator's decisions was calculated through Student's t-test. The statistically significant value was $p < 0.05$.

RESULTS

Study participants and settings

In the present study, we have successfully evaluated 980 individualized prescriptions ordered over 3 years (from 2013 to 2015) by specialists in private clinical disciplines, who complied with required criteria established by the research team regarding the off-label treatment practice. Only 22.7% of the drug requests were approved by the pharmacists' revision committee, and 53.4% of them were issued for male patients. The median age of the included patients was 48 years (Table 1). Table 2 shows that Rheumatology and Nephrology account for the highest ratios among the clinical branches that issue drug requests for adult patients (30.3% and 26.3%, respectively).

Table 1. Characteristics of the patients and drug requests		
Age. mean (range)	46 years	(1 month-80 years)
Gender. n(%)		
	Male	522 (53.4)
	Female	458 (46.6)
Age group. n(%)		
	Adults	766 (78.2)
	Pediatrics	214 (21.8)
Off-label drug requests. n(%)		
	2013	298[†] (30.4)
	2014	312 (31.8)
	2015	370[*] (37.8)
Total		980 (100)
n= number; [†] Since October 1st; [*] Until December 1s		

Table 2. The distribution of off-label drug requests according to adult and pediatric clinical branches and the decision of the revision committee. n(%)

Clinical branch	Total	Accepted	Rejected
Adults			
Rheumatology	232 (30.3)	62 (26.7)	170 (73.3)
Nephrology	201 (26.3)	63 (31.4)	138 (68.6)
Gastroenterology	165 (21.5)	49 (29.7)	116 (70.3)
Neurology	112 (14.6)	28 (25.0)	84 (75.0)
Surgery	40 (5.2)	15 (37.5)	25 (62.5)
Other	16 (2.1)	13 (81.3)	3 (18.7)
Total	766 (100)	230 (30.0)	536 (70.0)
Pediatrics			
Rheumatology	88 (41.1)	21 (23.9)	67 (76.1)
Neurology	56 (26.2)	10 (17.8)	46 (82.2)
Dermatology	45 (21.1)	11 (24.4)	34 (75.6)
Cardiology	20 (9.4)	11 (55.0)	9 (45.0)
Surgery	5 (2.3)	3 (60.0)	2 (40.0)
Total	214 (100	56 (26.2)	158 (73.8)

Table 3. The off-label drug requests (OLP) according to the indication, drug combination, patient age, line of medicine and the decision of the revision committee. n(%)

OLP type	Total	Accepted	Rejected
Unlicensed Indication	372 (38.0)	99 (26.2)[a]	273 (73.4)
Drug Combination	346 (35.3)	85 (24.6)[a]	261 (75.4)
Patient Age	145 (14.8)	28 (19.3)[b]	117 (80.7)
Clinical Line	117 (11.9)	11 (9.4)[b]	106 (90.6)
Total	980 (100)	223 (22.7)	757 (77.3)

Values with non-identical superscripts ([a,b]) are significantly different (p<0.05) (p= 0.03 vs patient age; p= 0.01 vs clinical line). Unlicensed Indications may have safer and/or cost-effective (affordable) alternatives.

Prescribe medication classification

The distribution of requested drugs was performed according to the Anatomical Therapeutic Chemical classification (Table 5). This study found the most prescribed medications were those utilized for treatment of musculoskeletal disorders (28.9%). The medications with the highest level of off-label use requests were: diclofenac (n=126), celecoxib (n=106), domperidone (n=72), and ceftriaxone (n=62) (Figure 1). The most frequent indications appeared in Table 6, with their acceptance or rejection rates by the revising committee. The most repeated indications were: osteoarthritis (n=142), post-operative infections (n=92), gastrointestinal (GI) ulcers (n=64), and neuropathic pain (n=62). Finally, 78.2% of medication requests came from clinical branches for adults, and 21.8% from pediatric practice. Although the agreement rate for requests in adults (30%) was higher than that in pediatrics (26.2%), they are not significantly different (p>0.05, chi squared test).

Physician-pharmacist agreement rate

Only 30% of these requests were approved by the revision committee (Table 2). Meanwhile, Rheumatology and Neurology specialties account for the highest ratios among the clinical branches that issued drug requests for pediatric patients (41.1% and 26.2%, respectively). The revision committee rejected 73.3% of pediatric drug requests (Table 2), and the rejection ratio of off-label drug requests was comparable between the two (rejected and accepted) groups (p>0.05, chi squared test). Concerning the claim behind considering the treatment off-label, most of the issued drug requests were attributed either to unapproved indication by the recommended global regulatory authorities, or to combination of more than one drug (38% and 35.3%, respectively; p>0.05). However, only 26.2% and 24.6% of these drug requests were approved. Some of the off-label requests (14.8%) included medications for patients within an age range that was not indicated in the product specification. The revision committee approved only 19.3% of these requests. The lowest off-label drug prescription was reported in the requests issued for treatment of different indication than the authorized ones (11.9%) and only 9.4% of these requests were approved (Table 3). The agreement rate of the later types of OLP requests was significantly lower than the drug indication and combination types (p<0.05, chi squared test). Regarding the level of evidence available at the prescribing time, Table 4 summarizes the distribution of these evidence levels. The evidence level influenced the revision committee decisions. The requests with high and moderate evidence received significantly higher acceptance rate than those with low and very low evidence level (p<0.05, chi squared test). The lowest rate of acceptance was reported in the requests that had very low evidence level (9.1%). Taken together, 22.7% of acceptance was reported when drug requests were evaluated according to the available evidence.

DISCUSSION

This is the first study of its kind to investigate off-label prescribing practices in private medical settings in Iraq. It covered a period of 3 years and included more than 900 physician requests of medications prescribed off-label. Although there are many studies that cover the off-label uses of drugs across the world[12,13], they mostly focus on inpatient settings (hospitals).[3] Hospital-based studies indicate that various medications used in inpatients setting are either unlicensed or are prescribed beyond the requirements of the product license.[4,14] However, scanty data are available regarding the rate of such practice in outpatient clinics.[15,16] Accordingly, there is a high potential for many patients to receive off-label medications and may be subjected to the inherent risks of adverse reactions associated with this practice. However, the incidence of these risks is difficult to follow in outpatient settings, which

Table 4. The available evidence of off-label drug requests (OLP) and decision of the revision committee. n(%)

Evidence	Total	Accepted	Rejected
High evidence	135 (13.8)	75 (55.6)[a]	60 (44.4)
Moderate evidence	129 (13.2)	31 (24)[b]	98 (76)
Low evidence	254 (25.9)	75 (29.5)[b]	179 (70.5)
Very low evidence	462 (47.2)	42 (9.1)[c]	420 (90.9)
Total	980 (100)	223 (22.7)	757 (77.3)

Values with non-identical superscripts ([a,b,c]) are significantly different (p<0.05).

Table 5. The Anatomical Therapeutic Chemical (ATC) classification of the prescribed medications and the decision of the revision committee. n(%)

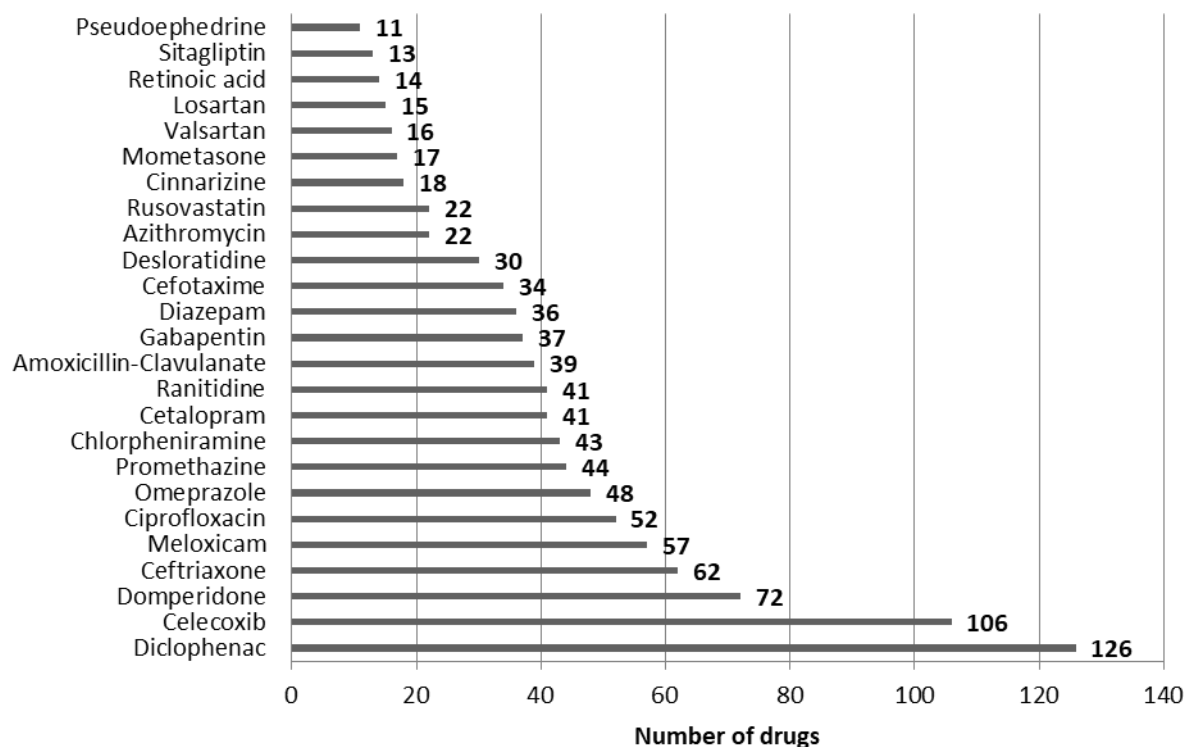| ATC classification	Total	Accepted	Rejected
Musculoskeletal	283 (28.9)	70 (24.7)	213 (75.3)
Anti-bacterial	233 (23.8)	43 (18.4)	190 (81.6)
Nervous system	108 (11.0)	20 (18.5)	88 (81.5)
Cardiovascular	47 (4.8)	12 (25.5)	35 (74.5)
Gastrointestinal	212 (21.6)	25 (11.8)	187 (88.2)
Respiratory	48 (4.9)	20 (41.7)	28 (58.3)
Various	49 (5.0)	33 (67.3)	16 (32.7)
Total	980 (100)	223 (22.7)	757 (77.3)

Figure 1. Frequency of drugs that are off-label requested by the prescribers (n=1016)*.
*(total number of drugs was higher than number of requests because in some cases more than one drug was included in the same prescription).

can be a potential limitation of the present study and may be recognized in others performed elsewhere.

Our study identified an extremely high level of off-label prescribing practice among Iraqi physicians in private outpatient clinics in the absence of strong evidence for a substantial number of drugs. The study also revealed a high rate of rejection according to the standard global criteria and the rejection included several classes of drugs particularly pain killers, antibiotics, CNS drugs, and others. The availability of data that correlate prescribed drugs to their indications of use is a fundamental issue in the evaluation of off-label use. The study was able to answer the objectives because the prescriber mentioned the off-label indication of the prescribed drugs, which is not common in routine prescribing practice in private clinics. This approach is directly related to the existing policy regarding the issue of prescriptions. Currently, the vast majority of Iraqi physicians do not mention the indication for which a medication is prescribed in the drug prescription. Moreover, reporting the specific diagnosis for each drug prescribed is likely to be of high value and feasible, and at the same time could reduce prescribing errors.[17] In the present study, the agreement rate is far less than that reported by other studies elsewhere[18,19] that cover shorter duration (less than 2 years) and include a smaller number of drug requests.

Regarding the clinical units which present more requests, our results are quite different from most of the previously reported[20], and this may be attributed to the relatively more comprehensive approach followed in the present study. Although many data have been reported in this regard based on local authority legislations, the case in Iraq was unfortunately quite different, because there are no well-established local authorities that define and regulate off-label drug use. Hence, we relied mostly on the international guidelines to establish our conclusions. In this study, we included various types of medical specialties and population groups in private clinic settings; while most of the published studies in this field focus on partial aspects of therapeutic interventions[18] and in specific group of population[10,21], or cover only certain classes of drugs.[22,23] In contrast to what could be expected, the present study does not show a direct correlation between the quality of published evidence and the likelihood of medication approval. This can be attributed to the fact that, even though drug selection could be supported by solid evidence from clinical trials, there are many other types of treatments with the same evidence of efficacy and safety at a lower cost. In other circumstances, unavailability of other alternatives led physicians to prescribe medications using only limited supporting evidence. Meanwhile, the urgent need to initiate treatment due to a case severity led to the off-label use of medications. Another factor that impacts the revising committee's decision regarding an off-label treatment is the patient age. Clinical studies are mostly conducted in adults; therefore, certain medications have no approved indication for pediatric patients, and the vast majority of drugs from this type were approved regardless of the available evidence quality in this regard. When the off-label requests based on indication for clinical disciplines other than the approved ones, they received a high rejection rate compared to other causes. Moreover, the availability of other alternatives which are more cost-

effective and well recognized for efficacy and safety was another reason for the majority of rejected requests.

Limitations

This study had some limitations. The sample size of the participants was relatively small. There have been other variables difficult to control, that may impact the results and not included in the study, including availability of alternatives for the prescribed medications, clinical picture of the patient, influence of relatives, insistence by the prescribers, and urgency of treatment. Moreover, other potential limitation of the present study could be the lack of clinical outcome follow-up of the administered off-label medications, which could help in assessing their efficacy.

CONCLUSIONS

Community pharmacists should effectively take responsibility for assessing off-label drug requests in private settings in Iraq. This study indicated that the quality of evidence does not represent the major factor influencing the approval off-label drug use. The availability of safer and/or affordable (cost-effective) alternatives and prescribing for a different patient age category highly impacted the pharmacists' approval rate.

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