

## Evaluation of Knowledge, Attitudes and Experience of off-label Drug Prescribing Practice among Physicians in Baghdad City Hospitals

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### Abstract

The objective of this study was to assess the knowledge, attitude, and experience of off-label prescribing practice among physicians working in public hospitals in Baghdad city. This cross-sectional study was performed from November 1<sup>st</sup> 2018 to March 2019 in 17 public hospitals in Baghdad, Iraq. The targeted hospitals were randomly selected at different regions in Baghdad City. A self-administered questionnaire was utilized to collect data from the physicians. Out of the 400 distributed paper questionnaires to a convenience sample of physicians, 383 of them were returned completed. More than half of the participants (57.2%) indicated that they were reasonably familiar with the term "off-label drug", 57.7% mentioned that the most common medical reason for the prescribing off-label drugs was unavailability of alternatives. About two thirds had concerns regarding off-label drug safety and efficacy. 62.7% agreed that the Ministry of Health authority should provide an incentive to pharmaceutical companies to perform clinical trials in Iraqi patients, 49.1% believed that clinical trials that recruit volunteers involve ethical issues. Extensive efforts are required to make programs, regulations and guidelines to control the off-label prescribing practice among the Iraqi healthcare providers at different healthcare settings.

**Keywords:** Attitude, Prescribing practice, off-label prescribing.

### تقييم العلمية والسلوك والخبرة لممارسة صرف الأدوية خارج الأستطببات المحددة لها بين الأطباء في مستشفيات مدينة بغداد

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### الخلاصة

هذه الدراسة تهدف الى تحديد العلمية والسلوك والخبرة لممارسة صرف الادوية خارج الاستطببات المحدده لها بين المستشفيات أساسها الاطباء في مدينة بغداد. هذه الدراسة الاستقصائية انجزت خلال الفترة من ١ تشرين الثاني ٢٠١٨ الى ١ مارس ٢٠١٩ في ١٧ مستشفى حكومي في مدينة بغداد، العراق. استبيان ذاتي التقديم استخدم لجمع المعلومات من الاطباء. المستشفيات الحكومية اختيرت بصورة عشوائية من مختلف مناطق مدينة بغداد. من اصل ٤٠٠ استمارة استطاع موزعه على الاطباء، ٣٨٣ منهم عادت منجزه، ٥٧,٢% منهم بينوا انهم على معرفة بما تعني كلمة خارج الأستطببات المحددة لها بشكل معقول، ٥٧,٧% ذكروا بأن أكثر سبب شائع لوصف الادوية الغير مصرح بها كان عدم توفر البديل، ٦٢,٧% اتفقوا ان يتوجب على وزارة الصحة توفير دوافع لتحفيز الشركات الدوائية لانجاز تجارب سريرية على المرضى العراقيين، ٤٩,١% يؤمنون بأن التجارب السريرية التي تجند متطوعين تتضمن قضايا اخلاقية. جهود مكثفة مطلوبة لتأسيس ورش توعية، تنظيمات، توجيهات لتنظيم ممارسة وصف الادوية الغير مصرح به بين العراقيين مقدمي العناية الصحية المسموح لهم بوصف الادوية في مختلف أقسام الرعاية الصحية. الكلمات المفتاحية: سلوك ، ممارسة ألصرف ، صرف خارج الأستطببات المحددة لها .

### Introduction

The term off-label drug use (OLDU) is widely used in the medical literature and the media<sup>(1)</sup>. Off-label drug prescribing has not undergone the type of advantage-disadvantage assessment required in the process of medicines' marketing authorization. However, it has been noted that healthcare professionals commonly prescribe medicines off-label with levels of evidence considered to be low. This is principally problematic because off-label use with inadequate strong scientific evidence may be associated with higher rates of adverse events that may harm the patient<sup>(2-4)</sup>. Off-label prescribing is not certainly bad. It can be beneficial, particularly when the patients have no other approved options like in cancer chemotherapy. Off-label prescribing of a drug or combination of

drugs usually represents the standard of care in such cases<sup>(5)</sup>. Off-label prescribing can represent different forms including prescribing drug outside the age range or weight for which the product is licensed<sup>(6)</sup>, for indications not approved in the Product Information Leaflet (PIL)<sup>(7)</sup>, utilizing alternative routes of administration other than that indicated for that formulation in the PIL<sup>(8)</sup>, the use of doses or dose frequencies other than those stated in the PIL<sup>(9,10)</sup>, and using different formulation other than approved one<sup>(11,12)</sup>. As lately reported on the off-label use of medications in the European Union (EU), the prevalence of off-label use in the pediatric and adult population is high in a wide range of therapeutic regions, particularly oncology, psychiatry, neurology and rheumatology<sup>(13)</sup>.

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Many controversies existed and the healthcare professionals generally agree that more work and efforts are needed to prescribe suitable off-label drugs for patients with rare diseases. <sup>(14)</sup> However, they also concur that potential improper promotion, as well as possibly hazardous prescribing use for these drugs should be obviated <sup>(14)</sup>. The present study was designed to assess the knowledge, attitude, and experience of off-label prescribing practice among physicians in Baghdad city hospitals and clarify the acceptability of this practice among prescribers at different medical specialties in addition to the reasons behind accepting or rejecting this approach.

## Methods

A quantitative cross-sectional study design was used. A self-administered questionnaire was utilized to collect data from the physicians at different healthcare branches in Baghdad City, Iraq. A 25 item questionnaire comprised questions with a combination of tick box responses, 5–6-point scale questions and four open-ended questions were sent to 17 public hospitals. The survey focused on physician knowledge of and reasons for off-label prescribing, concerns about off-label medicines, communications between patients and physicians, and attitudes towards the need for performance of clinical studies. The recruitment process was carried out from November 1, 2018 to March 1, 2019. No incentive was offered to the participants.

### Questionnaire development

In the present study, an English questionnaire especially was developed to evaluate the off-label prescribing practice among Iraqi clinicians. The questionnaire contents were formulated based on questionnaire previously used elsewhere to explore the views, attitudes, knowledge, and perceptions of the prescribers towards the off-label prescribing of medicines <sup>(15)</sup>. Most questions had pre-formulated answers, except few with partially open-ended answers. The questionnaire consisted of 25 questions. The questionnaire was divided into four sections addressing different topics of interest including the participant demographic information, physician familiarity of off-label prescribing practice and its consequences, the reasons behind off-label prescribing, patient involvement in the prescribing process and physician sources of information about off-label drugs. Finally, the questionnaire focused on the clinical trials and the issues associated with dosage determination of off-label medicines to young patients.

### Validation of the study tool

The study questionnaire was pilot tested on a convenience sample of 40 randomly selected physicians to predict the validity and reproducibility of the designed questionnaire. Using the Cronbach alpha, reliability tests yielded good internal

consistency for the overall questionnaire items ( $\alpha=0.782$ ). Test-retest reliability was evaluated by Pearson correlations between time 1 and 2 scores (2-3 weeks later) on the two completed questionnaires. Test-retest reliability for the overall score was acceptable ( $r = 0.83$ ). All the participants declared that the questionnaire was clearly understood.

### Physicians

Physicians were recruited from 17 different hospitals that cover the healthcare services at different regions of Baghdad. Four-hundred physicians participated in this cross-sectional study (74 consultants, 72 general practitioners and 254 permanent registrars) who practiced in different disciplines of medicine (32 Internists, 115 Surgeons, 7 Nephrologists, 8 Intensive Care unit, 76 pediatric, 50 General and 95 represented other miscellaneous fields).

### Inclusion criteria

The inclusion criteria of the current study included physicians from different specialties at different hospitals in Baghdad with minimum practicing experience of 3 years who provided verbal consent to participate in the study.

### Exclusion criteria

The exclusion criteria of the current study included the rotators and junior physicians with prescribing practice experience of less than 3 years.

### Statistical analysis

Statistical analyses were performed using the IBM Statistical Package for Social Sciences SPSS (version 24.0) and GraphPad Prism version 5.1 software with significance levels set at  $P<0.05$ . Categorical variables were expressed as numbers and percentages, while continuous variable were expressed as mean $\pm$ SD. Non-parametric tests were utilized to compare knowledge scores, perspectives, and off-label prescribing practices across the different selected clinician demographics (Mann-Whitney U test for 2 groups and Kruskal-Wallis for more than 2 groups). Validity and reproducibility of the questionnaire were measured by Cronbach's alpha. Chi square test and Exact Fisher's test were used to compare the differences in the perceptions of clinicians who have practiced off-label drug prescribing and those who have the idea and knowledge but do not practice off-label drug prescribing.

## Results

### Demographics

Out of the 400 distributed questionnaires to the physicians, 383 (95.8%) of them were returned completed, while 17 (4.2%) were uncompleted and excluded during analysis. A total of 18.3% of the participants were consultants, 17.5% general practitioner, 39.9% of them were permanent registrar and 24.3% of them were specialists.

Regarding the practice field, 8.4% of them were internist, 30% surgeons, 1.8% nephrologists, 2.1% intensive care, 13.1% general, 19.8% pediatricians and 24.8% represent other miscellaneous specialties. Regarding the duration of practice, 29.25% of respondents practiced as physicians for 1-4 years, 27.9% for 5-10 years and 42.8% for more than 10 years in service.

#### Knowledge and views about off-label medicines

The majority of respondents (219; 57.2%) indicated that they were reasonably familiar with the term "off-label drug" and found to be significantly greater ( $P < 0.05$ ) than those who are either unfamiliar or highly familiar, 62 (16.2%) mentioned that they were highly familiar with the term "off-label" drug and 102 (26.6%) were found unfamiliar with this term (Figure 1).

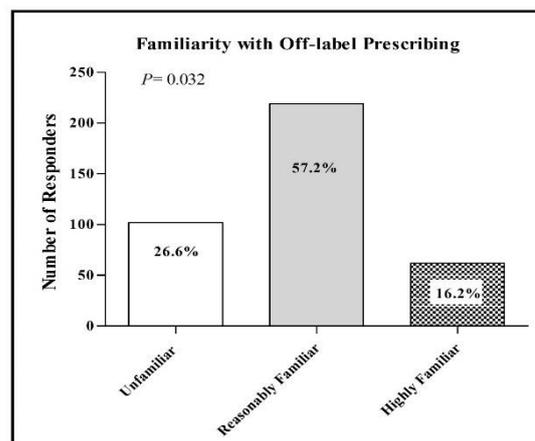
The present study indicated that the forms of the off-label prescribing include prescribing a drug for younger age (56.9%), lower than recommended dose (66.6%), higher than recommended dose (57.2%), choosing an alternative different formulation (60.3%), prescribing a drug of different indication (64.8%) or utilizing different route of administration (59.8%) (Table 1).

**Table 1. Forms of off label-drugs**

Most important forms for off-label prescribing	Frequency <i>n</i> (%)	Score from 6 (mean $\pm$ SD)
Lower than recommended dose	255(66.6)	2.15 $\pm$ 2.03 <sup>a</sup>
Higher than recommended dose	219(57.2)	1.65 $\pm$ 1.71 <sup>a</sup>
At a younger age than recommended	218(56.9)	1.86 $\pm$ 1.90 <sup>a</sup>
Via a different route of administration	229(59.8)	2.20 $\pm$ 2.06 <sup>a</sup>
Different formulation	231(60.3)	2.26 $\pm$ 2.06 <sup>a</sup>
Different indication	249(64.8)	2.56 $\pm$ 2.11 <sup>a</sup>

Values are expressed as frequencies, percentage and mean  $\pm$ SD; mean score values with non-identical superscripts (a, b) among groups are significantly different (Kruskal-Wallis test with Dunn's post hoc test).

In addition, the majority of respondents reported patients (> 40 years of age) and patients (1 day -15 years) to be the most likely seen by the targeted physicians (41.5% and 37.6%; respectively). On the other hand, patients (16-20 years), patients (21-30years) and (31-40 years) were characterized by the respondents to be less likely seen by the targeted physicians (32.1%, 32.9% and 36.8%; respectively) (Table 2).



**Figure 1. Rating of the targeted physicians according to their familiarity with the off-label prescribing practice. *n*=383 total number; (chi-square test).**

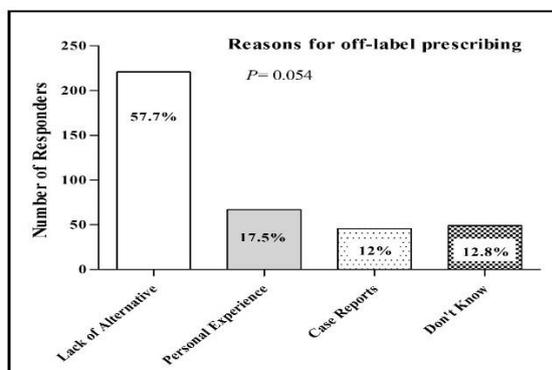
The present study indicated that the forms of the off-label prescribing include prescribing a drug for younger age (56.9%), lower than recommended dose (66.6%), higher than recommended dose (57.2%), choosing an alternative different formulation (60.3%), prescribing a drug of different indication (64.8%) or utilizing different route of administration (59.8%) (Table 1).

**Table 2. The age ranges of patients mostly seen by the targeted physicians (*n*= 383 physicians)**

Age range of patients (Years)	Frequency <i>n</i> (%)	Score from 5 (mean $\pm$ SD)
1-15 years	144(37.6)	2.19 $\pm$ 2.0 <sup>a</sup>
16-20 years	123(32.1)	1.84 $\pm$ 1.7 <sup>a</sup>
21-30 years	126(32.9)	1.85 $\pm$ 1.8 <sup>a</sup>
31-40 years	141(36.8)	1.86 $\pm$ 1.87 <sup>a</sup>
Over 40 years	159(41.5)	2.32 $\pm$ 2.18 <sup>a</sup>

Values are expressed as frequencies, percentage and mean  $\pm$ SD; mean score values with non-identical superscripts (a, b) among groups are significantly different (Kruskal-Wallis test with Dunn's post hoc test).

According to the physician's answers, the most common medical reasons for prescribing off-label drugs were 57.7% unavailability of alternatives, 17.5% personal experience, 12% case reports and 12.8% mentioned that they don't know (all of the last group don't prescribe off-label drug for their patients) (Figure 2).



**Figure 2.** The reasons behind off-label prescribing practice.  $n=383$  total number; values of last three options are significantly different (*chi-square test*).

#### Views about the safety and efficacy of the off-label medicines

**Table 3.** Physicians views about the safety and efficacy of the off-label medicines ( $n= 383$  physicians)

Questions	Response $n(\%)$		P-value
	Yes	No	
Do you knowingly prescribe drugs off-label?	230(60.1)	153(39.3)	<b>0.03</b>
Do you realize that off-label prescribing may disadvantage the patients?	200(52.2)	183(47.8)	0.24
Do you have concerns about the efficacy of the off-label drugs?	251(65.5)	132(34.5)	<b>0.021</b>
Do you have concerns about the safety of the off-label drugs?	259(67.6)	124(32.4)	<b>0.02</b>
Have any of your patients experienced ADR after using off-label drugs?	131(34.2)	252(65.8)	<b>0.02</b>
Have any of your patients experienced treatment failure due to the off-label drug use?	212(55.4)	171(44.6)	0.18

Values are expressed as frequency and percentage;  $n$ : number of the responders;  $P$ -value indicates significant differences according to *Fisher's exact test*.

In the present study, only 35.8% of respondents declared that they request verbal consent from the patient or the patient's parents, 38.6% of them ask for the consent of their supervisor and only 40.7% of the interviewed physicians routinely inform their patients that they dispensed an off-label drug for them and inform them about its use and the expected outcome (Table 4). There was a significant relationship between the

The majority of respondents had major and/or minor concerns regarding the safety (67.6%), while those who concerned about the efficacy of the prescribed off-label medications represent around 65.5% of the respondents (Table 3). There was no significant difference between the familiarity of off-label prescribing and concerns about the safety of off-label medicines during prescribing to their patients; ( $p=0.449$ ) (*chi-square test*).

About half of the respondents (52.2%) felt that the use of off-label medicines increased the likelihood of disadvantages to the patient for several reasons. As they mentioned, it may disadvantage the patient and cause serious ADRs. At the same time other mentioned that they do not have close monitoring or follow up to their patients after administering the drug to observe the ADRs. About 34.2% of respondents have observed ADRs after using off-label drugs to their patients (Table 3).

Declaring their own practice, approximately half of healthcare providers (55.4%) admitted to having experienced treatment failure; in spite of that 60.1% of the physicians knowingly prescribe drugs off-label for their patients (Table 3).

familiarity of off-label drug prescribing and asking for consent from the patient and informing the patient about the off-label drug ( $p= 0.008, 0.01$ ) respectively. While the result showed that there was no significant relationship between the familiarity and asking consent from the supervisor, ( $p=0.7$ ) (*chi-square test*).

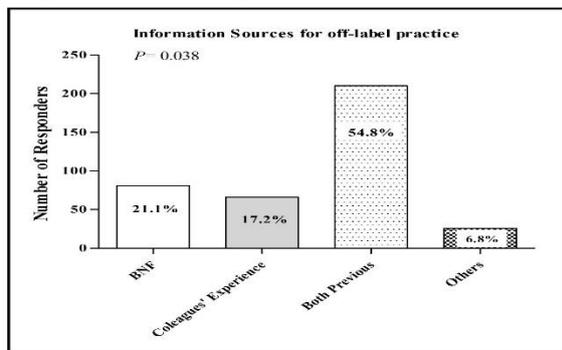
**Table 4. concerns of the physicians about ask for consent for prescribe off-label drug (n= 383 physicians)**

Questions	Response n(%)		P-value
	Yes	No	
Do you request a patients' consent before prescribing off-label drugs?	137(35.8)	246(64.2)	<b>0.02</b>
Do you inform the institution authority that you have recommended off-label prescribing practice?	148(38.6)	235(61.4)	<b>0.03</b>
Do you routinely inform the patients that you are prescribing an off-label drug for their treatment?	156(40.7)	227(59.3)	0.11

Values are expressed as frequency and percentage; *n*: number of the responders; *P*-value indicates significant differences according to *Fisher's exact test*.

#### Information sources

When the healthcare providers were asked how they became familiar with the terminology of off-label drugs, 21.1% of the respondents mentioned that they had gained their knowledge from the BNF, 17.2% from a colleagues' experience, 54.8% from all the mentioned before and 6.8% from other non-recognized sources (Figure 3).



**Figure 3. The information sources for the off-label prescribing practice. n=383 total number; values of BNF, colleague experience and others are significantly different (*chi-square's test*)**

#### Clinical trials on volunteers

In this section, when the healthcare providers were asked about the need for more clinical trials to address the issue of off-label drugs use, 71% of them mentioned that it is important to provide more drug formulations, 44.4% of the respondents believed that all current drugs that have not been evaluated in younger ages should be trialed in those populations and 67.6% thought that all new drugs should be trialed in different age groups prior to use. Moreover, approximately more than half of the respondents (62.7%) agreed that the Ministry of Health (MOH) authority should provide an incentive to stimulate pharmaceutical companies to perform clinical trials in Iraqi patients (Table 5).

There is limited information about their efficacy in younger age patients which consider riskiest group. Younger patients have different physiology, Basal Metabolic Rate, metabolism, surface area and different body weight. About 49% of the respondents do not believe that all current drugs that have not been evaluated in younger ages should be trialed in those populations. Some of the respondents disagreed with trying new drugs in different age groups prior to use for ethical considerations and nature of our society.

**Table 5. Views of the physicians about the need for more drug formulations and trialing all new drugs in different age groups prior to use (n= 383 physicians)**

Questions	Response n(%)		
	Yes	No	Do not know
Is it important to develop more drug formulations?	272(71)	42(11)	69(18)
Should all new drugs be trialed in different age groups prior to use?	259(67.6)	49(12.8)	75(19.6)
Should the MOH authority provide incentives to stimulate pharmaceutical companies to perform clinical trials on Iraqi patients?	240(62.7)	59(15.4)	84(21.9)
Should all current drugs that have not been evaluated in younger ages trialed in those populations?	170(44.4)	78(20.4)	135(35.2)

Values are expressed as frequency and percentage; *n*: number of the responders.

However, only 43.4% of the respondents indicated that they have the willingness to be actively involved in a clinical trial, and about 44.6% of them accepted the idea of recruiting their own patients for

a clinical research. There was no significant relationship between willingness to be involved in clinical trial and the specialty of the physicians. The participants were also asked if they accepted to

enroll their relatives in the clinical trials. Only 37.6% of the respondents agree to allow their relative to participate in a clinical trial. About half of physicians (49.1) believed that clinical trials that recruit volunteers involve ethical issues (Table 6).

Several reasons make the physicians believed that clinical trials that recruit volunteers

involve ethical issues including believing that uncertain efficacy of off-label drug may lead to unexpected result that may harm the patient; for social and religious consideration, to avoid personal problem with the patients.

**Table 6. Views of the physicians about clinical trials in Iraqi patients (n= 383 physicians)**

Questions	Response n(%)		
	Yes	No	No opinion
Would you like to be actively involved in conducting clinical trials?	166(43.4)	138(36)	79(12.6)
Would you like to recruit your patients for a clinical trial?	171(44.6)	107(27.9)	105(27.5)
Would you allow your own relatives to participate in a clinical trial?	144(37.6)	155(40.5)	84(21.9)
Do you believe that clinical trials that recruit volunteers involve ethical issues?	188(49.1)	112(29.2)	83(21.7)

Values are expressed as frequency and percentage; n: number of the responders.

## Discussion

The data of the present study showed that the majority of respondents mentioned that they were either familiar or reasonably familiar with the term "off-label drug". The most common form of prescribing off-label drug was prescribing lower than the recommended dose. The results were approximately equivalent to the results of prevalence of off-label use in Jordan and North Ireland<sup>(16,17)</sup>. However, it is possible that a decrease in the dose could significantly increase risk of treatment failure. The other causes related to the increases in dose, frequency, or duration of administration, compared with the approved dosing regimens, can actually increase the risk of toxicity of a marketed drug<sup>(18-20)</sup>.

Prescribing modified formula (dosage form) of the drug for patients who have difficulty in swallowing like in Parkinson patients or patient with mandibular fracture is considered as a common solution to ease the administration of the drug; e.g., crushing the tablets or open the capsules. However, the clinical consequences of such practice can be inappropriate and may harm the patient. Such alteration of formula may affect the drug's absorption and can result sometimes in fatal overdose, or oppositely under dosing, rendering the treatment inefficient<sup>(21-24)</sup>. Similarly, the change in the route of drug administration may create series of new problems. The modified routes of administration may create problems concerned with increased local concentrations, sterility, pyrogenicity, hypersensitivity (e.g., airway reactivity), difference in pharmacokinetic and pharmacodynamics, which can seriously increase the risks of toxicity or adverse effects<sup>(25)</sup>.

In the present study, the respondents reported patients (>40 years) (41.56%) and patients (1-15 years) (37.6%) to be the most likely seen by the targeted physicians. In other study show that

geriatric and pediatric patients remain poorly participate in clinical trials that evaluate the pre-marketing efficacy and safety of novel therapies. It is perhaps not unpredictable that off-label prescribing is particularly common in these groups<sup>(26)</sup>.

The present study showed that around half (52.5%) of the respondents felt that prescribing off-label medicines increased the likelihood of disadvantages to the patient. The majority of respondents (67.6%) had major and/or minor concerns regarding the safety, while those who had concerned about the efficacy of the prescribed off-label medications represent about two third of the respondents (65.5%). This result was in tune with many previously reported data that focus on the concerns of disadvantaging the patient's health<sup>(27,28)</sup>.

Approximately more than half of healthcare providers (55.4%) admitted to having experienced treatment failure, while third of them (34.2%) experienced ADR after using off-label drugs to their patients. In spite of that, more than half of the physicians (60.1%) knowingly prescribe drugs off-label for their patients as a usual practice. This unusual behavior needs to be thoroughly evaluated to uncover the exact reasons behind such attitude. Attentiveness to medicines safety is very important, although there is an evidence that off-label use is frequently inappropriate and may expose patients to a very high risk of ADRs<sup>(4,29)</sup>. Moreover, this high percent of off-label drug misuse may lead to waste of economic resources<sup>(30)</sup>.

Regarding the prescribers' practices, the present study revealed that only third of the respondents (35.8%) mentioned that they request verbal consent from the patient or the patient's relatives; while more than third of them (38.6%) ask for the consent of their supervisor and only 40.7% of the interviewed physicians routinely informed

their patients that they dispensed an off-label drug for them and informing them about its use and the expected outcome. Nowadays, the prescribers have a corresponding legal and ethical duty to acknowledge all of the facts that are relevant to their patients' treatment decisions. Patients deserve to know any inherent risks of a prescribed medication. Also, asking for informed consent for off-label medication use will protect physicians against legal issue<sup>(31)</sup>.

When the healthcare providers were asked about the reasons behind prescribing off-label drug, more than 50% of the respondents (57.7%) mentioned that they prescribe off-label drug as a result of unavailability of alternatives; while about 17.5% referred to their personal experience and 12% case reports. In addition, 12.8% did not declare the reasons for its use. Approximately all the later 12.8% of physicians did not prescribe off-label drug during their practice history. Also, 21.1% of prescribers had gained their knowledge from the BNF, 17.2% from a colleagues' experience, 54.8% responded from all the mentioned before and other 7% not recognized sources.

Unfortunately, the physician's attitude toward off-label prescribing has no strong scientific evidence. This could be explained by the absence of awareness of such prescribing approach. Case reports are not considered as well-trusted sources; meanwhile, the frequent use of personal experience, previous patient prescription notes and colleague experience, all of which may lead to inaccurate off-label prescribing. BNF can be useful, but offer obvious guidance only after high-quality research has evaluated a specific off-label use<sup>(32)</sup>. According to the FDA, approved drugs that are allowed for an unapproved use are misbranded<sup>(33)</sup>.

In the present study, the healthcare providers addressed the need for more clinical trials to clarify the issue of off-label drugs use; nearly 71% of them mentioned that it is important to provide more drug formulations, two thirds of the respondents (67.6%) believed that all the current drugs that have not been evaluated in younger ages should be trialed in those populations to make sure they are safe. Approximately two thirds of the respondents (62.7%) agreed that the MOH authority should provide an incentive to stimulate pharmaceutical companies to perform clinical trials in Iraqi patients. Clinical trials introduce 'a way to pool controlled observations in an objective and scientific way, helping clinicians to decide what is the best therapy for the patient'<sup>(34)</sup>.

In spite of that about 20.4% of the physicians make objections to conducting clinical trials in Iraq for several reasons including either for social, religious and economic considerations, or low education. However, in considering the idea of taking part in clinical trials, only 43.3% of respondents indicated that they have the willingness

to be actively involved in a clinical trial and about 44.6% of them accept the idea of recruiting their own patients for a clinical research. There was no relationship between willingness to be involved in clinical trial and the specialty of the physicians.

The participants were also asked if they accepted to enroll their relatives in the clinical trials; only 37.6% of the respondents agreed to enroll their relative to participate in a clinical trial and approximately half of physicians believed that clinical trials that recruit volunteers involve ethical issues.

Strategies to encourage physician participation in clinical trials include financial and nonfinancial stimulus, sufficient training, research questions that are in agreement with physician interests and have clear potential to improve patient health care<sup>(35)</sup>.

The development of new health care management models where patients involve in clinical trials and the expansion of information technology are additional factors that contribute to enhance this change<sup>(36)</sup>. Patient-centered medicine cannot be practiced without patients involving in their own health care decisions and in the research that needs such decisions<sup>(37)</sup>.

Ethics and regulatory review procedures are essential for protection the safety and interests of the participants. However, overly strict ethical and regulatory systems could limit research capacity<sup>(38,39)</sup>.

After all, all drug treatment, all cases involving the use of drugs in an off-label use should be thoroughly documented in the medical report of the patient, including the clinical outcomes of such therapy, could extremely improve the knowledge in this area<sup>(40)</sup>.

#### **Study limitations**

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, arguments by the prescribers, and importance of treatment. Other potential limitation of the present study could be the absence of clinical outcome follow-up for dispensing off-label medications, which could help in assessing their efficacy.

#### **Conclusion**

The majority of participants were reasonably familiar with the concept of off-label medicines and prescribe off-label drug knowingly. They believed that this practice may disadvantage the patient due to concerns about efficacy and safety that may be associated with increased risks of ADRs. Although the respondents very well recognized the ethical issue of the off-label drugs, most of them do not request consent neither from the patients nor from the health authority seniors. Extensive efforts are required to make programs,

regulations and guidelines to control the off-label prescribing practice among the Iraqi healthcare providers who are authorized to prescribe medications at different healthcare settings.

### Acknowledgments

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