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Knowledge and attitude about off-label prescription of drugs amongst healthcare students and professionals: A cross-sectional questionnaire based study

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Abstract

Introduction: Off-label drug use (OLDU) is use of drugs outside of its licensed indication with respect to dose, age, indication and route of administration. OLDU is often due to lack of effective alternatives or exhaustion of approved drugs in certain cases. **Objective:** To analyze the knowledge, awareness and perceptions regarding OLDU amongst those medical students. **Methodology:** This questionnaire-based study was conducted amongst the healthcare professionals and medical students in a healthcare university, after obtaining ethical clearance. Second year to final year students from MBBS, dental, nursing, occupational therapy, physiotherapy, allied health sciences, postgraduates, recent MBBS graduates (passed last year) and healthcare practitioners who were willing to participate in the study were included. A total of 18 questions were asked in the English language and the answers were recorded. **Results:** Out of 123 respondents, 102 (82.92%) belonged to the MBBS stream. A total of 101 (82.1%) participants thought that they were aware of the term "off- label use" in medicine. Sixty-five (52.8%) participants were fully aware of the definition of OLDU. According to 52 (42.28%), the main cause of a rise in OLDU is the use of drugs in a condition with similar symptoms. Ninety (73.17%) stated that keeping updated knowledge regarding a medicine's approved indication and taking informed consent after explaining the correct reason behind prescribing off label are important measures to minimize the misuse of OLDU. **Conclusion:** Although most of the participants claimed that they were fully aware of the definition of OLDU, not all of them could answer the definition correctly. According to most of the participants, the main cause of a rise in the number of doctors prescribing off-label is the use of drugs for an indication that is symptomatically similar to the labeled indication.

Keywords: Off-label use, prescription, knowledge, adverse drug events

INTRODUCTION

Off-label drug use (OLDU) is prescription of drugs and its use outside of the licensed indications with respect to dose, age, indication and route of administration.[1] These drugs are mainly prescribed based on the data published from the clinical studies supporting its unapproved use due to lack of effective alternatives or exhaustion of approved drugs.[2] Sometimes, the OLDU is also based on the personal experience or experience shared by experts or peers.

OLDU has been most commonly found in the pediatric, geriatric population and pregnant women [2]. OLDU is prevalent not only due to absence of medications but also due to diseases sharing similar pathologic or physiologic features. Selective serotonin reuptake inhibitors, tacrolimus, gabapentin , tacrolimus, gabapentin are some of the examples used off-label. [3, 4] Many drugs are used in the pediatric population without formal FDA approval. [3]

The most important aspect of OLDU is to fulfill the unmet needs of the conventional therapeutic approaches and increasing the access of medication for special categories of patients. Studies have shown that off-label drug use has often led to drug repurposing. [5,6]

The promotion of OLDU by the manufacturers is illegal. [5] In order to limit legalities, physicians should prescribe off-label only for indications that they believe are in the best interest of the patient's health [3] and only after informing the patients. Sometimes, especially in critical patients, decisions are often urgently taken with the intent to minimize derangements in these patients. In such situations also clinicians should inform the relatives. Health care professionals should know the possibilities of adverse reactions, drug interactions and risks/benefits associated with OLDU. They should also keep themselves educated about the updated guidelines.

OBJECTIVES

The primary objective of this study was to evaluate the knowledge and attitude of healthcare students towards 'off label" prescription of drugs. The secondary objective was to compare knowledge and attitude of 'off label' prescription of drugs among students from different healthcare streams.

MATERIALS AND METHODS

The study was conducted amongst the medical students in a healthcare university, after obtaining ethical clearance from the Institutional Ethics Committee. Second year to final year students from MBBS, dental, nursing, occupational therapy, physiotherapy, allied health sciences, postgraduates and MBBS graduates (who passed MBBS last year) and willing to participate in the study were included in the study. Voluntary anonymous participation was invited after taking consent from each participant. Participants were subjected to a predesigned pre-validated questionnaire. Demographic data of the participants including age, gender and year of their study (undergraduate/postgraduate) and stream were noted. A total of 18 multiple choice questions were asked in the questionnaire. In seven questions, multiple answers could be selected by the participants. The questionnaire was in English and the answers were recorded in Google sheets.

Statistical Analysis:

Data entry was done using Google sheets. Descriptive statistics was applied. Data were analyzed by proportion and percentages. Wherever necessary, the results were depicted in the form of tables and graphs.

RESULTS

In our study, a total of 123 participants participated. A total of 102 (82.92%) participants belonged to MBBS stream, rest 21 (17.08%) participants belonged to- physiotherapy, allied health sciences, dentistry and post-graduation distribution (Table 1). Overall, 45 (36.59%) participants were interns and 71 (57.72%) out of 123 participants were females.

Parameter	**Result N (%)**
Stream of Study	
Allied health sciences	6 (4.87%)
Dental	5 (4.06%)
Physiotherapy	9 (7.31%)
MBBS	102 (82.92%)
Post graduate student	1 (0.81%)
Year of study	
II year	31 (25.20%)
III year	12 (9.75%)
IV year	14 (11.38%)
Intern	45 (36.59%)
I year (PG students)	1 (0.81%)
Practicing physician	20 (16.26%)
Gender	
Female	71 (57.72%)
Male	52 (42.28%)

A total of 101 (82.1%) participants thought that they were aware of the term "off- label use" in medicine, rest 22 (17.9%) participants claimed that they were either unaware or unsure about the same (Figure 1).

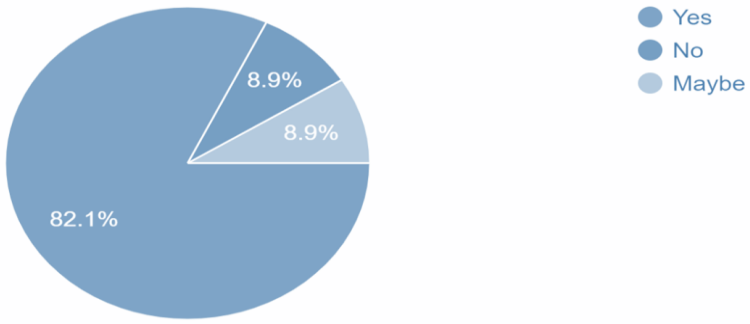

Figure 1. Awareness of the term off-label use of drugs

Only 65 (52.8%) participants were fully aware of what the actual definition of OLDU was, and answered the question correctly. When asked about what could be the potential cause that causes doctors to prescribe off label, 70 (56.9%) answered that according to them the cause could be "Inadequate knowledge about approved indication, dose and age" (Figure 2).

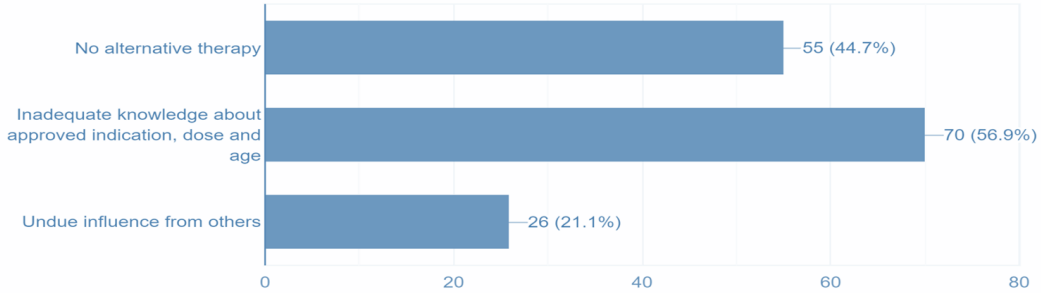

Figure 2. Common causes of OLDU

The sources of awareness about the term OLDU amongst the students were theory classes 50 (40.65%), clinical postings 40 (32.52%), reference books 28 (22.76%), professional encounters and internet 4 (3.25%) each.
A total of 81(65.85%) of them said that the most common age group in which OLDU is practiced is amongst adults, others being elderly and children.

A total of 87 (70.73%) students were unsure whether OLDU and over the counter drugs (OTC) are the same thing or not. A total of 36 (29.27) % of participants reported witnessing OLDU in a hospital setting. A total of 92 (74.80%) participants were unaware of the legislation to curb off-label prescription in medicine. According to 78 (63.41%) participants, OLDU can be a potential legal threat for the practicing doctors. A total of 109 (88.6%) mentioned that OLDU can have some serious consequences.

Table 2: Opinions of the participants about OLDU

Variable	**Response**	**Result N (%)**
Adequate knowledge amongst students and healthcare professionals about OLDU	Yes	72 (58.5%)
	No	15 (12.20%)
	Not sure	36 (29.27%)
Can off label drug use be a source of legal trouble for doctors?	Yes	78 (63.41%)
	No	40 (32.52%)
	Maybe	5 (4.07%)
Are OTC & OLDU the same?	Yes	11 (8.94%)
	No	25 (20.33%)
	Maybe	87 (70.73%)

The consequences of OLDU mentioned by the participants included increased risk of adverse drug reactions, 16 (13%), increased risk of drug interactions 12 (9.8%), increased risk of administration error 7 (5.7%) and inadequate efficacy 5 (4.1%). A total of 109 (88.6%) mentioned that all of these can be consequences of OLDU (Figure 3).

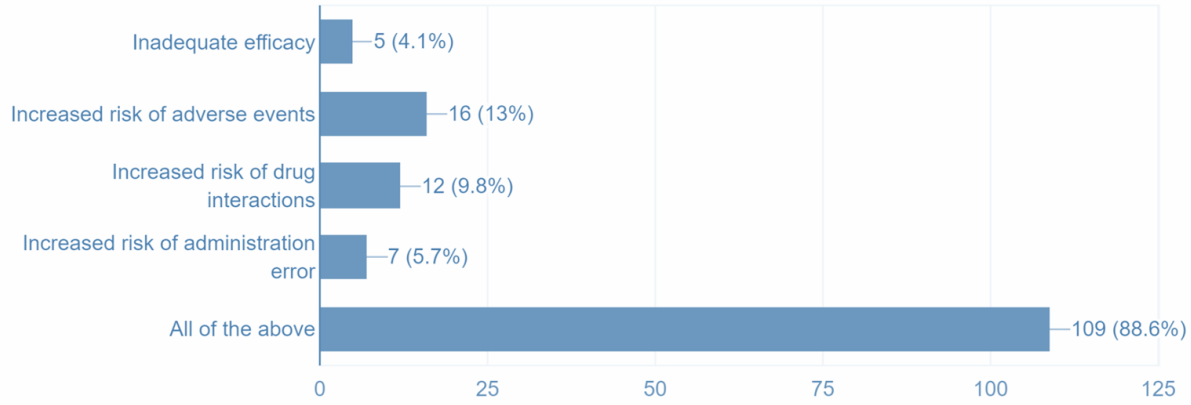

Figure 3. Consequences of OLDU

A total of 58 (47.2%) participants thought that patients would end up asking for an alternative therapy instead if informed consent for OLDU is requested (Figure 4). A total of 43 (35%) participants were of the opinion that if informed consent is requested, patients will refuse the treatment.

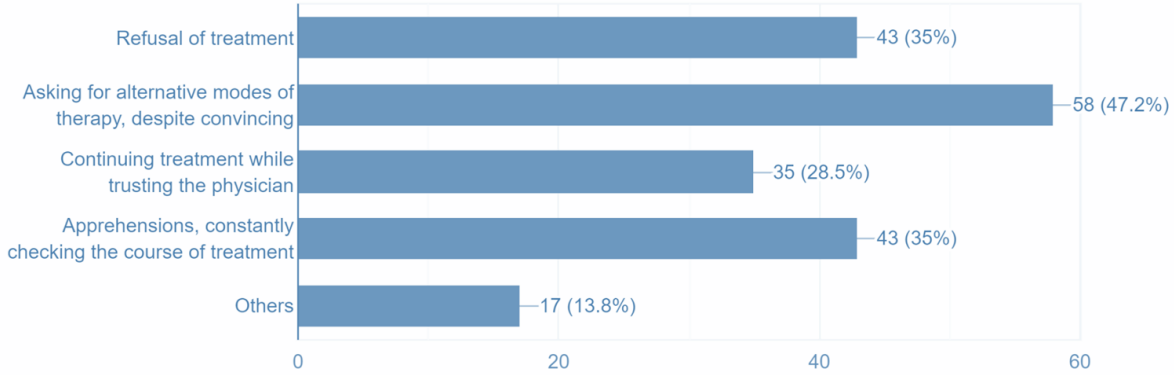

Figure 4. Impact of informed consent on OLDU

According to 52 (42.28%) participants the main cause of a rise in the number of OLDU is treatment of unapproved conditions with similar symptoms as approved indication (Table 3). Other causes reported by the study participants are listed in table 3.

Table 3. Causes of increasing use of OLDU amongst doctors

Parameter	**Result N (%)**
Free samples provided by physicians to the patients	34 (27.64%)
Drug samples being used for clinical trials	43 (34.96%)
Influence of CMEs	41 (33.33%)
Use of drugs indicated for different diseases, used for ones with similar symptoms	52 (42.28%)
Others	59 (47.96%)

A total of 90 (73.17%) participants stated that all the measures like- keeping updated regarding a medicine's approved indication, taking informed consent after explaining the correct reason behind prescribing off label, reporting the adverse drug reactions resulting from the drugs were equally important to minimize the misuse of OLDU.

DISCUSSION

This study was conducted in order to check the awareness of medical students and recently graduated practitioners about OLDU. Demographically, the maximum number of participants belonging to MBBS were interns and females.

Maximum number of participants thought that they were aware about off label drug use. A little less than half of the population who claimed that they were fully aware of the term OLDU, ended up incorrectly answering the definition of the same. Most of the incorrect answers claimed that OLDU meant only "Prescription and use of the drug outside their approved indication". In another study conducted in the Kingdom of Saudi Arabia, wherein a total of 398 participants participated from various cities, 43% of them heard about off-label drugs for the first time during their undergraduate program, while 31% heard about off-label drugs during their clinical practice. [7] However, we found similar results in a study based in Iran, wherein a questionnaire was sent to 257 hospital-based pediatricians, wherein it was found that over 90% of responders were familiar with the concept of, and knowingly prescribed, off label drugs. [8]

Most common causes of OLDU by doctors was thought to be inadequate knowledge about the approved indication/dose/age for a drug and lack of alternative therapy. Maximum number of students learnt about OLDU from their theory classes and clinical postings. According to many study participants, doctors practice OLDU mainly amongst patients of the adult population. The study conducted in a pediatric hospital had 55% of responders stating that such prescribing can have disadvantages in children, and 47% expressed concerns about the efficacy of off label medicines and it should be discouraged. The study observed that 70% of responders expressed concerns about safety, only 17% of the physicians had observed an adverse event, and 47% a treatment failure. [8] According to the results of another study, the prevalence of OLDU is higher in the pediatric population (mainly the neonatal, infants, low birth weight babies).
Maximum number of participants were unsure and hence unaware about the difference between OLDU and over the counter (OTC) drugs, whereas some incorrectly thought them to be the same thing. Even though OLDU these days is highly prevalent in today's practice amongst doctors, only a few students have witnessed it being practiced and understood that it was being practiced with their indications.

Some licensed medicines are prescribed for indications outside of their labeled indication in order to treat health problems for which there are currently no or lesser number of approved medications. However, such use can sometimes be associated with adverse events. OLDU without a patient's consent can lead a doctor into legal trouble, however not many physicians and upcoming doctors are aware of the same. Most of the participants mentioned that OLDU can have serious consequences and the reasons behind them.

The promotion of off-label uses by a drug manufacturer company is considered to be illegal. Safety and efficacy in off-label indications of drugs is not formally evaluated, and hence are an area of controversy. According to the records retrieved from a database that contained all the electronic prescriptions (151,305 prescriptions) from Canada in a 4-year time period, 11.8% constituted an off-label indication. The adverse events noted correlated with off-label indications and were 40% more frequent than those associated with on-label recommendation cases. Moreover, the study also stated that, in 80.9% of the cases, these recommendations were not based on strong scientific evidence. [5] Findings from their study suggested that there is limited awareness of, unsupportive research data about off-label uses and side effects amongst physicians. More research should be done to understand the ideal extent of details to provide as a part of informed consent and reasons why physicians are unaware of unsupportive data.[9] The participants in our study responded that taking informed consent from the patients before OLDU would most likely result in problems like - patients asking for alternative therapy, refusal of treatment, would also result in apprehensions in the minds of patient, constantly rechecking the course of treatment and visiting multiple doctors for the same. However, research suggests that legal problems associated with OLDU can be curbed with the help of informed consent. [4] A shared comprehensive discussion regarding the risks and potential benefits in case of OLDU in any scenario can lead to better decision making.[10] In a study, about 69% physicians did not obtain informed consent or tell parents they were prescribing off-label. The study also recommended making guidelines like the, "Recommendation for Use (RTU)" in France and the positive list in Belgium. It also supported the thought of taking the permission of the hospitals' ethics and therapeutics committees before prescribing off-label medicines.[8] In European Countries, the main focus is towards increasing safety and decreasing risk, especially in off-label use. Regulatory framework to safe practice and allow controlled off-label drug use can be created.[5] In another study conducted in Pakistan, they mention that off-label drug prescribing is common in current medical practice. It emphasizes training of health care professionals on adverse effects and legislations of off-label use is necessary.[11] When asked for solutions to this emerging problem most of the participants stated that keeping yourself

updated as a physician regarding a medicine's approved indication, taking informed consent after explaining the correct reason behind prescribing off label, reporting the ADRs resulting from the drugs being prescribed. All of these measures are equally important. We also observed, divided opinions amongst practicing clinicians regarding informing the patients about the off label use for their awareness. Some believed that it is essential to inform them about the approved and unapproved indications; whereas others believed that informing the patients might add on to the confusion and can often be mistaken as some type of a trial that is being done on them. In such a situation, having a guideline in place for guiding the clinicians about do's and don'ts would help.

Studies have reported common off-label prescription of psychotropic drugs.[12,13] In order to understand more about off-label use in psychiatry, we consulted some practicing psychiatrists. Atypical antipsychotics are mainly used for psychotic disorders like schizophrenia and bipolar disorder; often they are also prescribed for children and adolescents with behavioral issues, borderline personality disorders, eating disorders, autism; amongst the few.[14] Insights after discussion with practicing psychiatrists, revealed that patients on some second generation psychotics (eg. olanzapine) tends to gain weight. Weight gain caused by antipsychotics raises the risk of comorbidities like obesity, diabetes mellitus and cardiovascular disorder. [14]

In order to manage this the consultant psychiatrists sometimes prescribed metformin or topiramate off label. However, a study reported that topiramate may not be very effective in preventing weight gain.[15] They also used bupropion, an atypical antidepressant to decrease the appetite of the patient in cases of binge eating disorders.[16]

They also mentioned that antipsychotics like olanzapine and aripiprazole are also used for patients presenting with hyperactivity, aggression and increasing appetite. A systematic review suggested that atypical antipsychotics cause hunger and appetite in patients by causing a tendency of fat and carbohydrate cravings. Therefore, causing a small increase in appetite in those with eating disorders. [17] Antidepressants can also be used in patients with sleeping disorders, like insomnia. Insomnia is a disorder of unsatisfactory sleep leading to delayed sleep onset, poor maintenance of sleep, early waking, impairment of daytime functioning. This impairs quality of life and is also associated with an increased risk of physical and mental health problems. Even though hypnotic medications like benzodiazepines are licensed for sleep promotion in such cases, they cannot be used much due to dependence and tolerance caused by them. Hence in clinical practice, antidepressant use for insomnia is widespread, as an off-label prescription; in order to avoid long term side effects of hypnotic medications.[18] Off-label prescription of pramipexole and ketamine in cases of resistant depression, has also been used by the consultant psychiatrists in recent practice. [19,20]

OLDU can be called a double-edged sword. OLDU can help patients who are non-responsive to most of the first- or second-line approved therapies, in order to decrease their sufferance. However, sometimes, it can be problematic, especially when practiced without patient's informed consent

Our study highlights the need for increasing awareness about OLDU in medical students and professionals. Questionnaire based study design, small number of respondents are some of the limitations of our study. More studies to perform gap analysis involving physicians and pharmacists can be performed.

CONCLUSION

In our study, most of the participants claimed to be aware of the definition of OLDU, but not all of them could answer the definition correctly. The main reason for rise in OLDU is the use of drugs for an indication that is symptomatically similar to the labeled indication. There are mixed opinions of participants regarding taking informed consent for OLDU.

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