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REASONS FOR AND FREQUENCY OF *OFF* – *LABEL* DRUG USE

RAZLOZI I UČESTALOST *OFF* – *LABEL* PRIMENE LEKOVA

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Summary

Introduction. The application of drugs in accordance with the marketing authorization issued by the regulatory authority is considered *on-label* use, while *off-label* drug use frequently occurs in medical practice. It includes the application of drugs beyond approved indications, for unapproved age group, with different dosage regimens or different administration route. Medical specialists frequently prescribe an *off-label* drug in pediatrics, neonatology, geriatrics, psychiatry and oncology. Some countries have established registers of *off-label* drugs and guidelines for their prescribing and administration. The aim of the paper is to review practices in *off-label* drug use in order to satisfy the attitude of regulatory bodies and professional associations regarding the *off-label* use of drugs. **Material and Methods.** The sources of information used are articles published in scientific journals and information from the official websites of regulatory agencies. **Results and Discussion.** The most common reasons why physicians decide to prescribe *off-label* drugs are primarily the absence of drugs for a particular indication or those for a particular age group. In their daily work, doctors prescribe drugs for an *off-label* use based on their own or other colleague's experience. There is no general agreement on *off-label* use of drugs at the national or international level, but more and more doctors' associations and regulatory bodies approve *off-label* drug use in compliance with certain scientific and legal requirements. **Conclusion.** *Off-label* drug use has its place in practice and it has been widely accepted by the medical community and by itself it is not a violation of the standards of healthcare. *Off-label* use is common in our country and worldwide, and it is necessary to establish a registry for *off-label* drug use.

Key words: *Off-Label* Use; Drug Prescriptions; Physician's Practice Patterns; Registries

Introduction

Administration of drugs in compliance with the marketing license specifying the formulation, dosage and age-category, issued by a relevant authority is referred to as *on-label* use. However, the practice

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Sažetak

Uvod. Primena leka u skladu sa dozvolom za promet koju je izdao regulatorni organ predstavlja *on-label* primenu, dok se u praksi često sreće i *off-label* primena lekova, koja podrazumeva primenu leka mimo odobrenih indikacija, za neodobreanu starosnu grupu, sa drugim režimom doziranja ili drugačijim načinom primene. Lekari često propisuju *off-label* lekove u pedijatriji, neonatologiji, gerijatriji, psihijatriji i onkologiji. Neke zemlje imaju registre upotrebe *off-label* lekova i vodiče za njihovo propisivanje i primenu. Cilj rada je bio da se prikažu iskustva iz prakse u *off-label* primeni lekova. **Materijal i metode.** Izvori podataka su radovi objavljeni u naučnim časopisima i zvaničnim internet stranicama regulatornih tela. **Rezultati i diskusija.** Razlozi zbog kojih se lekari odlučuju za *off-label* propisivanje lekova su nedostatak lekova za određenu indikaciju ili za određenu starosnu grupu. U praksi, lekari propisuju lekove za *off-label* primenu na osnovu vlastitog ili iskustva drugih kolega. Nema jedinstvenog stava o *off-label* primeni lekova kod nas i u svetu ali sve više udruženja lekara i regulatornih tela odobrava *off-label* primenu lekova uz poštovanje određenih stručnih i zakonskih uslova. **Zaključak.** Primena *off-label* lekova ima svoje mesto u praksi i široko je prihvaćena među lekarima, te nije u suprotnosti sa zdravstvenim standardima. *Off-label* primena je zastupljena kod nas i u svetu i neophodno je formirati registre za *off-label* primenu lekova.

Glavne reči: *Off-label* primena; Primena lekova; Lekarsko iskustvo; Registri

of *off-label* prescribing is very common. It implicates the use of a medication in a manner not listed in the approved prescribing guidelines with respect to indications, age-category, and dosage regimen or administration route. *Off-label* drug use is to be distinguished from the application of unlicensed and thereby unregistered drugs. Unregistered drugs are those that have not been evaluated or approved by a relevant authority responsible for putting the drug in the market. This category in-

Abbreviations

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| AIDS | – Acquired Immune Deficiency Syndrome |
| ALIMS | – Medicines and Medical Devices Agency of Serbia |
| EBM | – Evidence Based Medicine |
| EU | – European Union |
| FDA | – Food and Drug Administration |
| USA | – United States of America |

cludes drugs undergoing the registration procedure and/or clinical trials, particular *ex-tempore* preparations intended for individual patients, modified forms of registered drugs in view of their formulation or strength (e.g. the preparation of a suspension from capsules or tablets, the preparation of a topical product from a peroral preparation, modification of the preparation to the one with different pharmacokinetic profile, etc.), repackaged drugs (the drugs that are removed from their original container and placed into another container during storage or dispensing process), chemicals used for the treatment of particular diseases [1].

Are there Legal Regulations relating to Off-Label Prescription and Promotion of Drugs?

A treatment is commonly defined as a discipline that includes preventive, diagnostic and therapeutic measures in line with relevant legislation, which are primarily aimed at improving, recovering and maintaining of health. However, medicine is often described not as a science, but as an „art of healing” – literally translated from Latin „*ars medicinae*“. Therefore, as artists tend to resist censorship, so doctors tend to fight against some legislative decrees that seem to them as a barrier to their freedom of prescribing [2]. Undoubtedly, enforcement of certain legal guidelines is inevitable in order to provide safe and effective health protection.

Are Doctors Granted Freedom in Prescribing Drugs?

European Medicines Agency (EMA), Food and Drug Administration of the United States of America (FDA) and other national regulatory authorities, as well as the Medicines and Medical Devices Agency of Serbia (ALIMS) are responsible for ensuring the quality, safety and effectiveness of the drug put on the market and its compliance with the approved guidelines. However, such authorities do not generally regulate the administration of drug in everyday practice. Thus, doctors are entitled to freedom in prescribing drugs. Such prescription-freedom must be in accordance with fundamental postulates of medicine – a doctor's responsibility and care for the patient's well-being. Doctors must keep in mind their professional liabilities and responsibilities towards relevant national legislation and obey medical ethical principles. In line with novel scientific accomplishments, doctors should prescribe an *off-label* drug only if this *off-label* prescribing (according to

their professional judgment) is the safest and most effective therapeutic option for the patient [3].

The aforementioned facts clearly indicate that the *off-label* practice of drug prescribing is legal and very common in many countries worldwide. This also pertains to opioid analgesic drugs (morphine, methadone, pethidine, etc.), the marketing of which is governed by special regulations. It is a worldwide known fact that the lack of adequate registered and approved (*on-label*) therapy makes the *off-label* prescribing inevitable. Even Hungary, being one of the countries in which *off-label* prescription had not been permitted, initiated the process of official legal recognition of the *off-label* drug prescribing [4, 5]. According to the data from the available international literature, it is evident that *off-label* prescribing is legitimate [6]. The question that inevitably arises is when the *off-label* prescribing can be considered an appropriate approach. Regrettably, a universal answer does not exist. Doctors are entitled and responsible to estimate what could be considered the “appropriate” *off-label* application in each individual case.

Legal Regulations and Criteria for Off-Label Drug Prescription in the European Union, the United Kingdom of Great Britain, the United States of America and in our Region

Certain standards for *off-label* prescribing are regulated by relevant legislation and medical and health-related bodies in the majority of countries.

Different opinions on this issue could be summarized as following:

1. It is frequently emphasized that *off-label* drug prescribing is justifiable under certain specific circumstances when convincing clinical evidence for its application is available. If an *on-label* drug is likely to produce a similar effect for particular indication as an *off-label* drug, the doctor should undoubtedly choose the registered one, i.e. an *on-label* drug.

2. Professional standards and guidelines must be followed. *Off-label* prescribing should be based on scientific evidence, except in case of extreme emergency, when no alternative is available.

3. Each *off-label* treatment should guarantee a high level of respect of the patients' needs and rights and written consent to the treatment should be obtained. Although standards vary substantially among the relevant authorities, it is generally believed that doctors are obligated to inform their patients about the nature and details of suggested therapy (i.e. to emphasize that the drug is *off-label* and not registered for this particular indication), to explain clearly their reasons for suggesting the treatment, potential adverse reactions, risks and benefits. In addition, they must mention available alternatives for the treatment. Ideally, such information should be communicated to the patient personally, in private conversation. Afterwards,

the doctor should ask and obtain the written consent from the patient.

4. The doctor is obligated to keep clear, accurate and legible records on the application and effects of the drug, including the lists of all prescribed drugs and the reasons for their prescribing. It is of paramount importance in order to provide adequate monitoring of the effects of *off-label* prescribed drugs and obtain an overview of the extent and effectiveness of such treatment [6].

Legal Regulations Pertaining to Off-label Drug Promotion

Contrary to drug prescribing, which is regulated by somewhat more flexible regulations, promotion of drugs is strictly regulated by national laws. Strict regulatory restrictions on drug promotion, i.e. advertising, come from the fact that drug advertising is a powerful tool that might result in massive adverse impact on public health if inadequately applied. To prevent such negative effects on human health, *off-label* promotion is declared illegal in all countries worldwide. However, it is to be emphasized that, whereas promotion of *off-label* drug is distinctly prohibited, providing information on *off-label* application is not [6].

Legal Regulations in the European Union

The European regulations governing the marketing of medicines do not offer a universal definition for "appropriate application of the *off-label* drugs", yet defining the number of situations where *off-label* prescribing is allowed:

- products currently undergoing clinical trial
- exceptions from European Union (EU) Directive and Regulation (e.g., compassionate use for terminally ill patients)
- *off-label* use under the individual decision of a treating doctor while applying appropriate procedure to protect patients' health [7]

In the majority of EU member countries, the patient's right is to obtain information about available alternative treatments to the one proposed by their treating doctor, that is, available *on-label* therapies when their doctor has suggested an *off-label* treatment option. Besides the aforementioned circumstances pertaining to the EU as a whole, Ethics Committees of each individual member state provided the opinion on the *off-label* drug application and declared the binding (or not binding) regulations on the prescription thereof [7].

Legal Regulations in Great Britain

Off-label prescribing is legal and accepted in Great Britain. This concept is regulated by *Good practice in prescribing and managing medicines and devices* of the British Medical chamber that represents the core guidance for drug prescribing

for all registered doctors. This Guidance, issued in 2006, states the principles that must be followed by doctors when prescribing drugs. The Guidance indicates that a doctor may prescribe medicines for the purpose other than the one they were registered for. Besides a wide range of circumstances when *off-label* prescribing is possible, the Guidance emphasizes that it is most likely in pediatric practice. When prescribing medicine outside the terms of their license the doctor has to:

- assess whether an *off-label* drug will better meet the specific needs of the patient than the licensed therapeutic alternative
- assess whether there is sufficient evidence on the safety and effectiveness of relevant *off-label* medicine or experience on its application. In some cases, the information provided by the manufacturer might be insufficient, thus, more information should be provided from other sources.
- take full responsibility for *off-label* prescribing and monitoring of the patient's care, and follow up treatment, or ensure that arrangements are made for another suitable doctor to do so (in case of hospitalized patients)
- keep clear, precise and legible records on all prescribed medicines; indicate the reasons for prescribing an *off-label* drug in case of not complying with common practice [8, 9]

The Guidance also addresses the issue of patient's being informed about the use of drugs within or outside the terms of their license. Accordingly, if an authoritative guidance supports the *off-label* drug application, the patient does not have to be alerted about the drug being or not being used in line with its original license. The doctor should give the patient sufficient information about the therapy that he considers relevant and important. However, if the patient or his caregiver (parents, family members, etc.) expresses any concern about *off-label* prescribed drug, the doctor must provide the explanation for his decision. Such explanation may be supported by written information, e.g. the brochure about the application of unregistered drugs or application of registered drugs beyond their proposed use in pediatric patient population published by the Royal College of Pediatrics and Child Health. On the other hand, if there is not enough supporting evidence relying on authoritative prescribing practice, the doctor should explain the reasons for prescribing an *off-label* medicine. The same applies to drugs not yet registered but whose administration is indispensable.

Legal Regulations in the United States of America

In the United States of America (U.S.A.), *off-label* prescribing is not prohibited by any federal regulation. The discretion of doctors and other health-care-team members who are licensed for prescribing drugs (pharmacists and specially trained and qualified nurses) to prescribe products off label is recog-

nized. The FDA approves a product for marketing, yet it does not have the legal authority to regulate the prescribing practice of the medicine. That is, the *off-label* prescribing practice is beyond the authority of this regulatory body. According to the official statement of the FDA dated April 1982, once a product is approved and registered for marketing in the U.S.A., doctors are legally entitled to prescribe it for indications beyond the registration limit and age categories, as well as to prescribe doses or administration routes other than those included on the label. *Off-label* drug prescribing must rely on the doctor's professional assessment of the effectiveness and safety of such drug application. The FDA considers that *off-label* drug administration is justified and rational in some instances and that it reflects therapeutic approaches reported in the relevant medical literature [9].

Legal Regulations Pertaining to *Off-label* Prescribing and Promotion in Serbia and Neighboring Countries

Similar to the neighboring countries, the issue of *off-label* drug prescribing in Serbia has not been addressed in relevant legislation. Although the *off-label* prescribing practice is evident from the data on everyday medical practice, the ALIMS has not yet publicly communicated any official data. Contrary to Great Britain where the registry of *off-label* drugs applied in pediatrics or neonatology is available, there are neither regulations regarding the *off-label* drug prescribing nor relevant registries of *off-label* medicines in our country. Moreover, promotion and advertising of *off-label* medication is not regulated, i.e. directly prohibited by any law or subordinate legislation except for the general prohibition on advertising and promotion of drugs other than over-the-counter drugs (OTCs). The provisions of the Law on Medicines and Medical Devices indirectly indicate that *off-label* promotion is not legal. Advertising of a prescription drug to professional community is allowed under conditions stipulated in the license, and in accordance with the previously approved summary of product (drug) characteristics [10].

Reasons for *Off-label* Drug Administration

One of the major reasons why doctors choose *off-label* prescribing is the unavailability or absence of licensed, effective and safe therapeutic options for particular conditions and diseases. It is particularly evident in some rare conditions, carcinoma (because of resistance of malignant cells towards the range of medicinal substances), infectious diseases (human immunodeficiency virus (HIV)/*Acquired Immune Deficiency Syndrome* (AIDS)), complex psychiatric disorders, etc. Sometimes, *off-label* prescribing is the ultimate choice of doctors, particularly after the approved treatment options have failed. Absence of therapeutic alternatives for specific patient populations (newborns, children, pregnant or lactating women, the elderly,

patients with severe kidney or liver diseases, etc.) often results in *off-label* drug prescribing to unapproved patient population in spite of potential contraindications stated in the Summary of Product Characteristics (SmPC) or Patient Information Leaflet (PIL). Children, pregnant women and the elderly are often excluded from clinical trials for a number of legal, ethical or practical reasons, thus, a wide range of drugs is neither approved nor specifically intended for such populations. Consequently, *off-label* prescribing is often practiced in pediatric, geriatric and obstetric practice. Another common reason for prescribing medicines outside the limits of their original license is convincing evidence on their effectiveness and safe application in particular situations. Positive and encouraging results of randomized clinical studies often represent a starting point for considering the *off-label* drug as a therapeutic option. In that respect, doctors may take into consideration novel developments in the field of medicine and pharmacy when prescribing medicine beyond the approved indications, contraindications, recommended dose and dosage regimen, administration route or age category. Doctors' decisions on *off-label* prescribing are often justified by the clinical and scientific facts relying on Evidence-Based Medicine (EBM). The EBM concept represents "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients", that is, "integrating individual clinical expertise with the best available external clinical evidence from systematic research" [11, 12]. This very definition of EBM encourages some doctors to administer *off-label* drugs if such administration is appropriate in given circumstances. Having in mind the fact that information on drugs is widely available to patient population, it is not surprising that patients and their families often initiate the *off-label* prescribing. Obviously, it occurs most commonly in terminally ill patients or patients with degenerative diseases, who desperately seek any information about potentially effective treatment option. Easily accessible information on the effects of an *off-label* medication is not necessarily supported by sound and valuable scientific evidence. Thus, insufficiently valid results of particular studies might often be misleading for the patients and their families with regard to therapeutic effectiveness of particular *off-label* medication. One should bear in mind that, even when the patient initiates the *off-label* prescribing, the doctor is the one to take the responsibility for prescribed therapy. Thus, the doctor should decide about the best available therapeutic option for the patient while providing the patient's consent for its application.

Prevalence of *Off-label* Drug Prescribing

Off-label drug prescribing is very common in medical practice. Most frequently, drugs are prescribed outside their licensed indications or to different age categories. Studies have revealed that *off-label* prescribing is more common by special-

ists than by general practitioners [13, 14]. Psychiatric and malignant diseases are often associated with *off-label* prescribing, which is not surprising having in mind that unknown etiology and factors influencing disease progression require highly complex approach to the treatment and selection of an effective therapy. Administration of drugs outside their original license is evident in obstetrics, psychiatry as well as in treatment of some infectious diseases (particularly AIDS).

Off-label prescribing is common in pediatrics practice, which is due to the specific age of the patients. The most commonly prescribed *off-label* drug categories include drugs used in the therapy of cardiovascular diseases, anticonvulsive drugs, antipsychotics, antidepressants and antiasthmatics. The extent of *off-label* prescribing of particular drugs is best illustrated in the following example. Fentanyl, a powerful, rapid-acting opiate analgesic is registered in American market for the treatment of severe pain in patients with carcinoma. However, available data indicated that only 1% of Fentanyl prescriptions were issued by oncologists in the first half of the 2006. It was established that 80% of the drug was prescribed *off-label* predominantly to treat migraine and back pain. In 2006, a study aimed at investigating the prevalence of off-label prescribing to outpatients was published in the U.S.A. [15, 16]. That research encompassed 160 mostly prescribed drugs in the U.S.A. The rates of *on-label* and *off-label* prescribing were investigated, as well as the existence of sound scientific justification for their *off-label* prescribing. The obtained results revealed that as many as 20% of drugs registered and licensed in the U.S.A. were prescribed *off-label*. The research revealed that 50-90% of drugs prescribed as "*off-label*" and "*unlicensed*" and used in pediatric and neonatological practice had never been evaluated for application in children and newborns [14, 17, 18]. The research revealed that the rates of *off-label* medications ranged from 62% (pediatric departments), 80% (primary pediatric practice) to even 88% (neonatology hospital departments) in the period 1990-2010. Numerous studies conducted in various therapeutic fields, among different age groups and geographic regions indicated that the newborns are the population most commonly treated with medications that are beyond the license for this particular age group. According to these studies, the percentage of children who have received at least one *off-label* or unregistered drug ranges between 36%–92% at pediatric departments, 80%–97% at neonatology department and 11%–37% in primary health care [19–26]. *Off-label* prescribing is very common in oncol-

ogy. According to available data, particular antineoplastics are more frequently associated with unlicensed and *off-label* drug prescribing than with the licensed one. It has been estimated that 50–75% of drug administered in oncology practice in the U.S.A. are prescribed *off-label* today.

A study conducted in the U.S.A. in 1991 revealed that one third of the drugs administered to oncology patients were prescribed *off-label*, while more than a half of the patient received at least one drug beyond its licensed indication. Another study done in 1997 with 200 participating oncologists, members of the American Society of Clinical Oncology, revealed that 60% of members prescribed drugs outside the relevant license [17, 26].

Conclusion

Doctors' freedom in prescribing *off-label* drugs is associated with substantial advantages. It enables an innovative approach in clinical practice, particularly in cases when approved therapeutic options are unsuccessful. In other words, *off-label* drug prescribing offers possibilities of adopting novel evidence-based treatment practices. On the other hand, such policies facilitate patients' early access to potentially valuable medication. The fact that *off-label* prescribing often represents the only available therapeutic option for specific patient groups or patients with rare diseases is an important advantage of this approach. However, the drawbacks of *off-label* prescribing practice should not be neglected. Potential problems associated with the *off-label* drug prescribing include the following:

- a) adverse reactions associated with *off-label* drug prescribing
- b) increased responsibilities of health care providers in view of patient's well-being
- c) impossibility to compensate health care expenses because of *off-label* drug use
- d) promotion of *off-label* drugs by the manufacturers

Major drawback of the *off-label* drug use is an increased probability of adverse effects of the drug. It is attributed to the fact that safety and effectiveness of an *off-label* drug have not been confirmed. Thus, implementation of more precise legislation defining appropriate prescribing and application of *off-label* drugs as well as stipulating the responsibilities of all parties participating in such therapeutic approach is highly demanded in our country. Creation and regular update of a registry of off-label drugs applied in daily healthcare practice is of vital importance.

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