

The use of off-label drugs in medicine: ethical and legal issues.

Biomedicine and Surgery

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ABSTRACT

The term off-label drug describes the use of a particular drug outside its approved indication, dose, frequency and route of administration of that patient group for which it is registered. Despite the stated definition indicating a certain risk for their application, off-label application is part of everyday medical practice and is often the only treatment option for patients when no suitable approved drug is available. Possible legal-ethical-medical problems for a physician may arise if after such a therapy an adverse outcome occurs, not necessarily due to a given therapy. Drug Commission and Clinical Pharmacologists from the physician's institution could be the first instance to which a doctor might address if his intended treatment includes off-label medication.

KEY WORDS: off-label drug use; pharmaceuticals; prescribing

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INTRODUCTION

The term off-label drug describes the use of a particular drug outside its approved indication, dose, frequency and route of administration of that patient group for which it is registered (1,2).

Despite the stated definition indicating a certain risk for their application, off-label application is part of everyday medical practice and is often the only treatment option for patients when no suitable approved drug is available. The frequency of this practice is the result of a situation in which all the processes involved in the development, approval and marketing of medicines do not follow the needs of everyday clinical practice. Approved drugs are only tested for a limited number of indications and most often their pharmacological properties have not been investigated in certain groups of patients such as children, patients with rare diseases, patients with various co-morbidities, geriatric, oncological and psychiatric patients and pregnant women, and hence the patients from the mentioned groups often treated with off-label medicines (2,3).

Given the administratively complex and expensive process of developing and approving new drugs, pharmaceutical companies are often not interested in developing a new drug (or supplementing indications for the existing one) if they do not have the appropriate financial gain (2,3). In this gap between medical demand, immediate needs and economic gain, the prescription of off-label medication is often the only rational solution exerted by a physician in order to provide adequate medical care to the patient. However, by prescribing them, the doctor assumes a special responsibility because the consequences of his decision may end up as a complex medical-ethical-legal situation in which the doctor has to defend himself and prove that he has not violated the rules of profession even though he „de facto“ prescribes the medicine that the regulatory body did not confirm as safe and effective (2–4).

Many studies have been conducted in the European Union to determine the extent to which off-label medicines are used in hospitals and outpatient treatment. The largest number of studies

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has been conducted for the therapeutic area of pediatrics where there is the most prominent lack of approved medicines. Data from 32 studies involving research in 16 European countries for a different age of hospitalized children showed that 13-69% of the drugs were off-label (3). Forty studies from 12 EU countries that were conducted at the level of outpatient treatment showed that the off-label drug coverage was 2-100% (3). In the adult population, 23 studies were conducted in 6 EU countries showing that the range of off-label drug use was 7-95% in hospital treatment, while in 13 studies from 6 countries for the outpatient treatment, this range was 6-72% (3). In both hospital and outpatient treatment, high incidence of off-label drug use has been reported in certain therapeutic areas such as cardiology, rheumatology, neurology, psychiatry, hematology and oncology (2-4).

The results of research in different EU member states regarding the use of off-label medicines in pregnant women are not uniform: from the statement that there is no specific data and the problem is not so significant because it only applies to certain drugs to the opinion that use of off-label medicines during pregnancy is significant (the study from France has shown that 10 out of 20 drugs used during pregnancy are off-label) (3). One of the studies conducted in Germany lists 91% of physicians specializing in gynecology and ophthalmology that prescribed off-label medications (3,5). The UK study (Liverpool Women's Hospital) showed that 83 percent of all medicines prescribed during pregnancy are off-label medications (6).

From the legal point of view, European (EU) and Croatian legislation do not directly regulate the way the medicine will be used in medical practice (3). A decision is made by a doctor about how to heal the patient and it comes from his conscience and acquired knowledge of what is best for the patient. Accordingly, the law does not oblige the doctor to prescribe only approved drugs (on-label). On the other hand, EU legislation through Directive 2001/83 / EC and Regulation (EC) 76/2004 harmonizes national legislation and regulates drug marketing and marketing in the EU (3). The European Commission, the European Medicines Agency (EMA) and the regulatory bodies in Member States (Croatia: the Agency for Medicinal Products and Medical Products - HALMED) set joint standards for safety, quality and efficacy of medicines in the EU. Although EU legislation does not regulate the use of off-label medicines, their use is covered by a new legislation in the field of pharmacovigilance (3,7).

However, directives and laws regulating the pharmaceutical industry, i.e. their products, do not regulate the medical profession at the same time, and often regular approvals are not aligned with an adequate medical approach to treatment. The use of off-label medicines is not forbidden for doctors, but in the case of unexpected events due to their application neither the pharmaceutical company nor the law have any legal or ethical responsibility and all the responsibility is on the prescribing doctor (2-4).

Therefore, increasing use and legal and ethical questions in relation to the use of off-label medicines in clinical practice led to the drafting of Directive 2010/84 / EC of the European Parliament and of the Council that recognizes the use of off-label medicines and cites those responsible for approvals for placing a finished medicinal product in use and providing all available information on their products, including the results of clinical or some other studies and any use of the product outside the marketing authorization conditions (8). Pursuant to the aforementioned directive, the Pharmacovigilance Risk Assessment Committee has drawn up guidelines for marketing authorization holders requesting them to collect and submit information on the off-label use of their medicines to ultimately define two groups: off-label medicines that may harm patients and off-label medicines that do not harm patients (1). Similarly, the European Parliament, in adopting Council Recommendation (2009 / C 151/01), calls on the European Medicines Agency to draw up a list of off-label medicines in use and to develop guidelines for their use, taking into account both the law and patient protection (3). In order to ensure the fastest availability of appropriate medicines in the market, incentives to the pharmaceutical industry are also approved (2,3).

Legislation allows for the extension of their patent rights if a new indication is introduced in the first eight years after the marketing authorization that brings significant benefits over the existing treatment (3). A number of activities initiated by the EU legislation at Member State level are also reflected in the creation of the national frameworks in which individual Member States define the use of off-label medicines, thus facilitating their doctors' work and providing patients with the best treatment. Some of the EU member states (10 out of 21 countries participating in the survey: France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Spain, Sweden and the United Kingdom) have certain regulations and measures

at the public health level regulating the use off-label medicines (3).

Of course, there is no consistency between the member states, because in addition to legal measures regulating EU medicines and the work of pharmaceutical companies, the creation of national measures is an important factor in the economy of a particular country, its public health and social welfare system and the national drug-treatment process. For example, France has developed a legal framework for prescribing and use of off-label medicines, “Temporary Referrals for Use (RTU)”, for which the physician must justify his choice and inform the patient in detail about the mode of treatment as well as all the risks and benefits (2,3). Similarly, in Hungary the legal framework works so that doctors and their organizations must request the license from the competent state administration authority to use the off-label medicine (3). Furthermore, the United Kingdom has developed guidelines for doctors such as GMC Guidance (Good practice in prescribing and managing medicines and devices, 2013)(3). In the Netherlands, the prescription of off-label medicines is permitted only if the relevant body has developed protocols and professional standards in relation to their use. It is important to note that all the protocols in Netherlands require informed consent of the patient, but also that the physician must specifically record the treatment chosen by the patient (3).

The EU member states that were involved in the study and did not develop specific legal measures regarding the use of off-label medicines are Austria, Belgium, Bulgaria, the Czech Republic, Denmark, Estonia, Finland, Ireland, Malta, Portugal and Slovenia. Their common attitude is that the use of off-label medication is a matter that needs to be solved at the physician-patient level, not at the regulatory or health system level (3). However, there is still a question of liability in relation to the prescription of off-label medicines, and the importance of proper information and obtaining consent of the patient for said treatment (2,3).

Croatia was not included in this study of the 21 EU member states, but like the countries described above, there are no elaborated legal measures regarding the use of off-label medicines. Using off-label medicines is the responsibility of a physician, who often inherits this practice as a part of health guidelines for particular therapeutic areas that apply to institutions. Physicians are often unaware of the use of an off-label drug because certain therapies are considered “quite understandable and normal”

in some situations because the patient is thus successfully treated or even rescued. Additionally, the use of off-label medication can be justified also for economic reasons because an equally effective, yet significantly cheaper drug can provide treatment for a larger number of patients (9). Possible legal-ethical-medical problems for a physician may arise if after such a therapy an adverse outcome occurs (not necessarily due to a given therapy). How will a physician then defend his professional decision in relation to an unauthorized treatment procedure before the competent institutions? Will then the legal service and colleagues stand in his defense?

These are issues that have a significant impact on the medical decision in clinical practice, leading to many dilemmas. Should treatment be based on the availability of registered medicines or on the basis of clinical evidence of safety and efficacy of the drug? What if an available registered drug is ineffective and is not more secure than a significantly more effective drug that has no approval? In the field of gynecology and obstetrics, one example is the use of dexamethasone or betamethasone for the purpose of prevention of respiratory distress syndrome in premature babies. Both drugs are not approved for the indication used and their prescribing physician enters the “unsafe zone” of the disapproved drug. On the other hand, not prescribing them may have life-threatening consequences for a premature child for whom the doctor will again be responsible, but this time due to non acting.

A physician who decides on the possible use of an off-label drug should ask two key questions: i) is the use of off-label medication necessary for treating the patient? and ii) are there clinical and scientific evidence described in the professional literature on the efficacy of off-label medication? In addition, the physician should inform the patient in detail about the possible treatment that he/she should give and his/her written consent.

Maybe the Drug Commission and Clinical Pharmacologists from the physician’s institution could be the first instance to which a doctor might address if his intended treatment includes off-label medication? The Commission would then be able to allow the use of the said drug for a particular patient or particular groups of patients on the basis of relevant evidence of efficacy, safety or cost-effectiveness of the use of off-label medication. In the above-mentioned studies conducted in the EU Member States, some of them have already developed guidelines regarding the use of off-label medicines. These may be of use especially in cases where an already approved drug is used, but

has not been further registered for the particular indication, mode of administration or group of patients because of the inertness and/or the lack of interest in the pharmaceutical industry.

This option would protect doctors when deciding on how to treat patients, which would result in better clinical practice and safer treatment of patients.

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