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MODERN MEDICAL AND PHARMACEUTICAL PROBLEMS OF OFF LABEL DRUG USE: LITERATURE REVIEW

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Abstract

The off-label use of drugs (beyond the instructions) is an important part of modern medicine and pharmacy, especially in the pharmacotherapy of pediatric, oncological, psychiatric patients. The term was established in the United States in 1997. Off-label therapy is one of the ways to identify new drug indications, i.e. innovation in modern pharmacotherapy. However, the off-label use of drugs does not have the same degree of scientific control and information as drugs for approved indications (on-label). The lack of an adequate and generalized informative database of off-label therapy in the world is one of the main problems associated with the assessment of such drug use. As a result, no matter from what angle the off-label use of drugs is viewed, problems arise. However, this use of drugs has gained momentum: one drug in five is prescribed off-label, so this is not a trivial problem. In addition, side effects from off-label drugs are about two to three times more likely than from on-label drugs. All of the above is the reason and necessity for professional, ethical, and legal control over the regulation of the use of off-label drugs. Official medicine can use existing clinical evidence regarding the use of off-label drugs, and should also monitor their safety in the framework of pharmacovigilance. Today, the use of off-label drugs has become a reality of pharmacotherapy, so it must be properly regulated at the legislative level.

Keywords: off-label use of drugs, official medicine, legislative level.

The off-label use of drugs (beyond the instructions) is an important part of modern medicine and pharmacy, especially in the pharmacotherapy of pediatric, oncological, psychiatric patients [1-4]. The term was established in the United States in 1997. Off-label therapy is one of the ways to identify new drug indications, i.e. innovation in modern pharmacotherapy, especially if this information is presented in highly scientifically indexed journals. Many off-label drugs are, in fact, significantly improved versions of previously approved on-label drugs. Some have been clinically proven to be more effective and/or have fewer adverse reactions (ARs). For example, studies in the United States have shown that off-label antihypertensive therapy, in 2001 alone, prevented 86,000 preterm deaths from cardiovascular diseases [5, 6]. However, the off-label use of drugs does not have the same degree of scientific control and information as drugs for approved indications (on-label). Although often information about them can help physicians make necessary decisions for the patient, it can also be available from professional literature, which provides recommendations for prescribing drugs off-label for specific indications or patient populations. However, off-label therapy does not reflect all the requirements of the current "standard of care". The latter raises concerns for the doctor, pharmacist, and patient, especially about the risk of the patient receiving an unwanted or poor treatment result from off-label therapy [7].

Currently, despite the widespread off-label use of drugs, their prescription is considered illegal, since it can lead to an increase in the frequency of prescribing drugs that do not meet the approved global requirements of the regulatory framework for drugs. In addition, there are currently no criteria in the world to determine when the use of off-label drugs is positive and when it is negative.

The off-label use of drugs is therefore a controversial issue with significant legal, medical, ethical, and economic arguments on both sides of the debate: the pros and cons of off-label pharmacotherapy.

In particular, the existing practice of using off label drugs, in addition to positive ones, has some negative (unresolved) consequences, namely:

- lack of clinical trials, which would be approved by the regulatory/expert body;
- the likelihood of new AR manifestations;
- lack of motivation of drug manufacturers to conduct clinical trials to justify changes to the approved instructions;
- disappointment of the patient and the doctor with a negative assessment of the safety and efficacy of the off-label drug used;
- clinical trials of most off-label drugs in children and elderly patients have not been conducted [8-10].

The lack of an adequate and generalized informative database of off-label therapy in the world is one of the main problems associated with the assessment of such drug use [11]. The Internet contains an abundance of information about the use of off-label drugs, but doctors, pharmacists, and patients do not always have the opportunity to find out if this information is accurate, professional, truthful, approved by regulatory authorities and whether it can be used [12, 13]. In addition, the off-label use of drugs may pose risks that have not been fully assessed for safety and efficacy. In this regard, it is sometimes difficult for doctors to prescribe drugs off-label without a sufficient evidence base, although such prescription can be useful and even be important or the only one to save the lives of some patients.

As a result, no matter from what angle the off-label use of drugs is viewed, problems arise. However, this use of drugs has gained momentum: one drug in five is prescribed off-label, so this is not a trivial problem. In addition, side effects from off-label drugs are about two to three times more likely than from on-label drugs.

One study analyzed widely used off-label drugs. It turned out that about 21% of off-label drugs used were ineffective, of which 15% had no scientific evidence of therapeutic efficacy [14]. At the same time, the use of off-label drugs with limited or no scientific justification was most common among psychotropic (96% of cases) and antiallergic (89% of cases) drugs [13].

Some off-label drugs are used to treat conditions that are way different from those for which the drug has been approved by the regulatory authority, such as the anticonvulsant drug gabapentin for the treatment of chronic pain [6].

The lack of a convincing modern evidence base for off-label drugs in the world does not give grounds to recognize off-label pharmacotherapy as innovative in all countries. In addition, even in the presence of positive clinical results from the use of an off-label drug in a new environment (new indications, dose, routes of administration), a pharmaceutical company cannot quickly obtain official approval from the regulatory authority [15].

If there are sometimes safety concerns regarding approved drugs, and this is indicated in the instructions, then there is even greater uncertainty about the safety of off-label drugs, especially in pediatrics, since most of the approved drugs for the adult population have not undergone clinical trials in children. The main reason for this situation is that pharmaceutical companies tend to consider the pharmaceutical market, which provides drugs for children as relatively small and unprofitable, and clinical trials in pediatrics, complex and costly [16]. At the same time, pediatricians have to treat a sick child, sometimes prescribing off-label drugs and not knowing many of the features of their use in children, for example, the recommended dose, which can either help or harm the child. Of course, it is better to rely on evidence-based medicine data so that the recommended doses, routes of administration, and other conditions for administration of medicinal products are justified, but sometimes the course of the disease takes on an unforeseen turn and requires practitioners to make immediate non-standard decisions. Therefore, prescribing a drug off-label, the doctor takes responsibility for the decision and is responsible for its consequences [17, 18].

Another problem with the use of off-label drugs is that their off-label status violates the conditions for drugs to enter various pharmaceutical markets: their mandatory study by conducting clinical trials following the requirements of world practice. Consequently, the use of off-label drugs violates the implementation of the "gold standard" of evidence-based medicine - the mandatory conduct of clinical trials following the requirements of the GCP [18].

However, the use of off-label drugs may enable companies to seek regulatory approval for other indications for which clinical trials are less complex and less expensive, or the pharmaceutical company may simply support doctors' messages in disseminating information about the off-label use of drugs [18].

Also, today there are no clear approaches to controlling the regulation of off-label drug turnover. When introducing a new drug, regulatory authorities carefully assess both the safety and the effectiveness of its use. But off-label drugs are used based on perceived efficacy and safety, without regulatory review. This approach, unfortunately, may not only fail to justify the expected results of treatment but also cause serious safety issues.

The lack of clear medical, pharmaceutical, legal, economic, and ethical regulation of off-label therapy can carry great risks to the health of patients, the activities of the doctor and pharmacist. Therefore, the choice of using drugs off-label today is the responsibility of the attending physician.

All of the above is the reason and necessity for professional, ethical, and legal control over the regulation of the use of off-label drugs. In particular, a common solution needs to be found, especially in areas such as pharmaceutical law and health insurance legislation. In addition, it is necessary to

establish rules for prescribing off-label drugs and monitoring their safety. For this, it would be optimal to create a coordinating structure in the world or individual countries, as is customary for on-label drugs.

Official medicine can use existing clinical evidence regarding the use of off-label drugs, and should also monitor their safety in the framework of pharmacovigilance. Improvement of the situation with the use of off label drugs can be achieved by approving, as a result of consensus, a list of drugs used off label, supported by convincing scientific data, which will partially facilitate the work of doctors and pharmacists in this area (for example, in the EU, such a list can be approved by the EMA with the scientific support of countries - members), as well as by evaluating and approving specific recommendations for the use of off label drugs by an official expert group (as is the practice in France) [19, 20].

This experience of using off label worldwide pharmacotherapy was taken into account when the Supreme Council of Ukraine adopted on March 30, 2020 the Law "On Amendments to Certain Laws of Ukraine Regarding the Provision of Coronavirus Disease (COVID-19) Treatment", when Ukraine was allowed to use the experience of off label pharmacotherapy of others countries taking into account the positive and side effects of off-label drugs [21-25].

Finally, in an era of ever-increasing health care costs, it must be remembered that the use of off-label drugs can lead to financial losses, especially in the case of expensive drugs [26-28]. Particular attention should be paid to the indications of off-label antibacterial drugs. Thus, the off-label prescription of antibiotics for the treatment of acute respiratory viral infections is often inappropriate and leads to serious undesirable consequences that require additional drug therapy and sometimes increase the duration of hospitalization of patients.

Consequently, today there is a need to create a regulatory framework for the use of off-label drugs, where targeted information on these drugs will be summarized as a method of increasing knowledge about alternative options for pharmacotherapy. Therefore, the creation of a regulatory framework for off label drugs is an urgent task of pharmacotherapy in modern conditions when reforming the medical sector, and the inclusion of off label drugs in the standards of disease treatment protocols is a guarantee that off label therapy will not mislead the doctor, patient, and pharmacist. Since today there are no official mechanisms for assessing the feasibility of pharmacological, economic efficiency, and safety of the use of off label drugs, as well as advertising and legal measures on this issue, this may lead to an increase in the frequency of such prescriptions without clinical trials or sufficient positive experience, which may negatively affect the health status of both an individual patient and a certain category of patients [29, 30].

Today, the use of off-label drugs mainly has its own specific therapeutic niches. The reason for this is the lack of interest of pharmaceutical companies in this off-label segment of the pharmaceutical market due to insufficient funding for the creation of new drugs and difficulties in conducting their clinical trials. In Ukraine, as elsewhere in the world, there is no regulatory framework for the use of off-label drugs [21-25].

Thus, there are currently four trends in modern medicine that make off-label prescribing a problem.

First, there is a growing demand for the safety of the drugs we take. When analyzing the benefit/risk ratio, regulators, the medical community, patients, and their representatives pay more and more attention to assessing the risks and their impact on the benefits of a drug, and not vice versa. Nobody is deceived about the results obtained if the risks have a significant adverse effect on the patient's health and/or quality of life [7].

Secondly, the nature of the relationship between the patient, the doctor, and the pharmacist has changed dramatically recently. The latter are still

respected, of course, patients have become more educated and have more access to information about the medicine. In addition, their expectations of 100% benefit from pharmacotherapy have changed. In addition, informed consent from patients before starting treatment has gained significant weight.

Thirdly, the information evidence base of pharmacotherapy as the basis of modern medical practice has increased. Previously obtained data are disputed, sometimes new evidence refutes existing treatment standards. Legal discussion in European countries regarding the use of drugs off label is mainly focused on the risks to the safety of patients taking off label drugs, or deviations from the methodological official information in pharmacotherapy (for example, on posology, dosage form, age, side effects, contraindications, etc.) [19, 20].

Fourth, since the use of drugs off-label has become widespread over the past 10–15 years, the key to solving this problem lies in the legal/legislative plane and provides for the existence of laws and by-laws regarding the regulation and control of off label therapy [20].

Consequently, the problem of using drugs off-label is far from being solved, but it has attracted the interest of doctors, pharmacists, patients, and other specialists who are both "pro" and "contra". However, proponents and opponents of off-label drug use believe that, in any event, such drug use should be legally regulated and "off label" therapy should only be used in the absence of an approved alternative treatment. There should also be specific clinical trials/data that confirm the efficacy and safety of using a particular drug off label: in a different dosage, form, or for a different age group. In this case, the justification for the need for off-label therapy must be documented in the patient's medical documentation. At the same time, it must be remembered that any drug can be completely safe and effective when used in one patient, but this does not mean at all that the same drug will be equally effective and safe for another patient.

To regulate the process of using off label drugs, it is necessary to collect information:

- on clinical evidence of effective and safe use of drugs off label;
- on the regulatory framework of off label drugs from various states and stakeholders (healthcare professionals, pharmaceutical industry, doctors, and pharmacists);
- on the rules and rights to use off label drugs in different countries and where there is no official permission for their use;
- side effects of off label drugs and their cost in comparison with the drugs used;
- on measures taken for patient safety when using off-label drugs.

Healthcare regulators are aiming to open up new opportunities to promote any beneficial innovation in medicine and pharmacy, including off-label drug use. Therefore, they must formulate laws and administrative rules for the use of drugs off-label for the benefit and protection of the patient, physician, and pharmacist. Today, the use of off-label drugs has become a reality of pharmacotherapy, so it must be properly regulated at the legislative level. The purpose of these proposals is not to prevent off-label use, but to reserve it for the rare, exceptional case when nothing else meets the needs of the patient, and to prevent off-label marketing by pharmaceutical companies.

Drug manufacturers, regulators, physicians, and pharmacists must continue to work together to define the pharmacotherapeutic niche for off-label drug use, as well as strike a balance between physician and patient freedom to innovate pharmacotherapy, clinical feasibility, and cost-effectiveness, and mandatory harmlessness at the use of medicines off-label. At the same time, it must be remembered that the safety and efficacy of drugs are determined by the requirements of the GCP, which are the "gold standard" of clinical medicine.

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