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POSITIVE AND NEGATIVE ASPECTS OF THE OFF-LABEL DRUGS USE

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Abstract

A way of using the dug that goes beyond the approved prescriptions by the regulatory authorities is called «off-label use». Today's healthcare problem is the problem of off-label drug prescribing.

Aim of study – analyze the positive and negative aspects of the off-label drug use.

Materials and methods. Analysis of scientific publications at the PubMed platform regarding the positive and negative aspects of off-label drug use.

Results. The world experience of using off-label drugs indicates a great desire of doctors to increase knowledge about the effectiveness and safety of drugs. Off-label therapy allows patients and doctors to use approved drugs in new ways, driven by knowledge of the drugs. The main purpose of this use of drugs is to provide effective patient healthcare. At the same time, the use of off-label drugs has higher risks for the patient and the doctor than their usage in accordance with the approved instructions and does not guarantee that the success of pharmacotherapy from such use of drugs.

Conclusions. Given the risk of liability for prescribing drugs for unapproved indications, doctor should only use this type of therapy if they are fully convinced that the potential benefits of an off-label use of drug outweigh the risks.

Keywords: *drugs, the use of medicines outside the indications in the instructions, on-label use, off-label use.*

Introduction

Atherosclerosis and atherothrombosis of blood

In modern world medical practice, all drugs must obtain permission from regulatory authorities (for example, FDA - in the USA, EMA - in the European Union, MoH - in Ukraine) so that doctors, pharmacists and patients could use them [32]. Authorization is granted if there is evidence of efficacy and safety of the drug, and then it can be used in accordance with the approved indications for use in the instructions (on-label prescription). According to WHO, half of all medicines are prescribed for indications that are not in the instructions [8]. A way of using the drug that goes beyond the approved prescriptions by the regulatory authorities is called «off-label use».

The term "off-label use" means the use of drugs outside the instruction. This term was given by the American Food and Drug Administration (FDA) in 1997 and meant «the use of a drug in dosage form, dosage regimen, for a population (for example, for an age group, for pregnant women) or for other parameters of use not listed in the approved drug instructions» [2, 36].

As a rule, the use of off-label drugs does not imply abuse for unapproved indications or their use in toxic doses to the detriment of patients. The main purpose of this use of drugs is to provide effective patient care [27]. However, minor deviations from the recommendations indicated in the instructions for the drug are sufficient to consider its use as off-label. In countries where the circulation of drugs is regulated by law, their widespread use is limited for indications that are not in the instructions. Despite that, the prescription of off-label drugs is very common in all areas of medicine and for some drugs it is becoming common practice [19, 10, 33].

In clinical practice, especially in pediatrics, oncology, psychiatry and obstetrics, doctors and patients sometimes cannot manage without prescribing off-label drugs for the following reasons:

to limit participation in clinical trials for certain populations of patients (for example, children, pregnant women);

due to limited alternatives of drugs approved by regulatory authorities for the pharmacotherapy of a number of diseases and conditions;

there is a proven efficacy of the drug in the absence of an official approval of its use;

there is a vital need for the use of the drug in the absence of dosage forms, indications for use, method of administration for certain categories of patients (children, pregnant women, breastfeeding women, the elderly, etc.) [35, 39, 34].

For over 35 years, the international medical and pharmaceutical scientific community and authorities have been trying to find the best approach to resolve the problem of off-label drug use, including at the legislative level.

Therefore, the current task of public health is the search for a solution to the problems of prescribing drugs in violation of the recommendations in the officially approved instructions.

What is the risk of the off-label drug usage for a patient?

There is no definite answer to this question. It is also impossible to know with 100% certainty what the outcome of a clinical trial of a drug could be [4, 11]. Published data show that the off-label use of drugs greatly increases the risk of adverse reactions, including serious and life-threatening reactions [22]. Because in this situation, the drug is in an «unstudied (unlicensed) field». At the same time, Internet contains an abundance of information on the use of off-label drugs, but this should not be enough for a doctor, pharmacist and patient.

The world experience of using off-label drugs indicates a great desire of doctors to increase knowledge about the effectiveness and safety of drugs. When prescribing off-label drugs, doctors can be guided by professional experience, scientific curiosity, economic and personal interests of the patient, and should understand what responsibility they take upon themselves. The off-label use of drugs can be beneficial for the treatment of diseases, and sometimes it is the only treatment or a chance available for the patient [1, 5, 7]. Unfortunately, despite widespread use, off-label treatment outcomes are generally not comprehensively evaluated. There is a complete lack of data to assess the scale of off-label drug usage, which is especially important in relation to drugs used in oncology, psychiatry and pediatrics.

Consequently, arguments about the benefits or harms of off-label drugs usage are contradictory, as are the views of the medical and pharmaceutical

community about whether this approach to the use of drugs should be criticized or the issues of its legalization should be resolved at the legislative level.

Off-label therapy allows patients and doctors to use approved drugs in new ways, driven by knowledge of the drugs. For some categories of patients (most often children), off-label drug use is the only treatment available [12, 24].

In clinical practice, off-label pharmacotherapy sometimes produces unexpected positive effects when compared to approved prescription drugs. The potential of off-label therapy allows to form a new understanding of the pharmacodynamics of the drug, and how it can be used in the pharmacotherapy of other diseases. Off-label drugs prescription may be logical and useful for another related indication with pathogenesis similar to the approved one (for on-label use), even if clinical trials have not been conducted for the new indication (for off-label use) [9, 16].

New pharmacological properties or side effects of approved drugs when used off-label can be very important for the treatment of diseases or certain categories of patients and can be effectively used in clinical practice in the future [38].

Sometimes the results of clinical trials and legal approval of the use of drugs have to be expected for years, while their off-label use allows you to speed up this process. A classic example of this is β-blockers approved for the treatment of hypertension when their off-label use has been shown to be beneficial in treating of heart attacks at people with diabetes [18, 21].

Sometimes, when creating new drugs, ethical standards may be associated with the inability to conduct clinical trials in certain categories of patients (children or pregnant women). In addition, the inclusion of patients in clinical trials is sometimes not possible due to the decision of the ethics committee of the hospital [27, 13]. In such situations, the use of off-label drugs may be an alternative, provided there is adequate evidence-based positive pharmacotherapeutic justification for the drug. Therefore, the off-label use of drugs may be the only alternative for pharmacotherapy in those clinical situations. More often than not, generics that find their new use are prescribed off-label, which is not formally approved, but can be inexpensive and effective treatment.

There is another positive aspect of off-label use of drugs: when a drug has already been approved for use for a specific indication after clinical trials and its production standards meet GMP criteria, therefore, the safety issues of its off-label use will not be related to quality as such. In this case, the priority issues may be the dangers of using drugs for unapproved indications, since there are no clinical trials with reliable scientific data. However, as a result of clinical observation and accumulated clinical data, the off-label use of drugs has allowed doctors, for example, to treat adolescent alopecia with minoxidil, which has been approved as an antihypertensive drug [14, 30].

Balancing the rapid development of affordable and effective drugs for new indications with limited information on the benefit / risk ratio remains a major challenge today. There are other approaches for regulating off-label prescribing. For example, to allow usage of innovations in clinical practice for off-label use when approved treatments have failed, in such cases an off-label drug is the only available treatment option for the patient [29].

The off-label use of drugs is not always a negative phenomenon in pharmacotherapy. According to the American Cancer Society, oncological diseases are often treated by off-label chemotherapy drugs, especially if the chemotherapy drug is approved for one type of tumor and can be used for some other types of tumors [17]. This use of drugs can be especially useful when the potential of existing formal approaches to treatment has been exhausted [3].

There are other advantages of off-label therapy: they can fill pharmacological niches at the market to meet the needs of practical health care [26].

Thus, the off-label use of drugs in certain cases allows doctors to improve the results of medical care. This becomes possible due to alternative approaches to pharmacotherapy, the use of drugs previously approved for use for other indications, the re-profiling of their use, especially when the officially approved approaches to the treatment of a particular patient have exhausted their potential [6]. Sometimes empiric off-label therapy for serious and life-threatening conditions or in certain patient is the only treatment. Thus, the drugs can be used

for off-label to treat for children, pregnant women, elderly, which are usually are not involved in clinical trials.

Nowadays, there is still a shortage of drugs at the pharmaceutical market for the treatment of acute and life-threatening conditions (infectious and rare diseases for which drugs are technically, economically or ethnically difficult to create). This leads to a situation where some diseases do not have effective treatment [13].

The off-label use of drugs makes it possible to treat diseases and conditions for which they are unlikely to be developed, and if they are, then only for narrow groups of patients with limited indications for which they can be approved by authorities [20].

Therefore, the off-label use of drugs is advisable and justified if there is convincing clinical evidence for such use.

This wide spectrum of different levels of evidence justifies the off-label use of drugs for new indications that are not officially approved. Although much of the off-label use of drugs occurs without any good scientific evidence, sometimes the usefulness and irreplaceability of such use is well known and may even be the standard treatment.

The presence of evidence of the clinical feasibility of off-label use of drugs, in the absence of an official assessment of these data, does not guarantee that such usage of drug should always be expected to be successful in pharmacotherapy.

The issue of drug safety for off-label use of drugs should be considered simultaneously with the assessment of their effectiveness. Particular attention in this assessment is drawn to potential side effects that arise from overdose or inadequate dose, from the use of drugs not according to indications; conditions associated with the procedure of administration (frequency and route), with the use of drugs in pediatric and geriatric populations.

Off-label drugs are not a concern as long as they are effective, safe, well tolerated and relatively inexpensive. However, off-label use of drugs has higher risks for patient and doctor than their use in accordance with approved instructions. There are a number of factors that contribute to the risks associated with the use of off-label drugs. According to statistics, in many countries 70% of drugs are used off-label, without scientific justification and convincing explanation of side effects and contraindications [31, 23, 15]. Given the risk of liability for prescribing a drug for unapproved indications, doctor should only use this type of therapy if they are fully convinced that the potential benefits of off-label drug use outweigh the risks. Nowadays there is no minimum standard for testing the safety for off-label drug use. The result of off-label drug studies show that doctors are not always aware of the side effects of these drugs [25]. Therefore, the lack of such information leads to an increase in both the very likelihood of side effects and their frequency. This is confirmed by the results of numerous studies. In 2004 pediatric study in the UK showed that 35% of reported side effects were associated with the off-label use of drugs or because of 87 unlicensed drugs [37].

The presented data indicate that side effects are most often associated with the practice of off-label drugs usage and are of a more serious nature. When using off-label drugs, the patient's age, dose range, features of pharmacokinetics and pharmacodynamics, as well as the conditions for the simultaneous use of several drugs may differ from those studied and recommended for their on-label use, and therefore may affect the efficacy and safety of drugs when used off-label. For example, the off-label dose used, the frequency or duration of therapy can lead to the development of drug resistance. Particularly dangerous are the consequences of drugs interactions in therapy.

There are many examples where drugs that are safe for short-term use can cause safety problems at long-term use. The use of drugs in lower or higher doses than indicated in the instructions can lead to safety problems.

Since there are not many alternatives in pediatric pharmacotherapy, it remains an area of medicine where off-label drugs are widely used, despite the fact that there may be insufficient information about the safety and efficacy of their use in children, especially in newborns [28].

Pediatric drugs are commonly used off-label by extrapolating efficacy, dosing, administration, and side effect of adult's profile. However, children pharmacokinetically differ from adults and drugs for adults cannot simply be administered in smaller doses. There are many examples in pediatric

pharmacology where new drugs may don't have fully understood safety profiles, which makes their use inappropriate for children, because of unknown side effects. British studies have shown that drug's side effects were more frequent at hospitalized children with off-label drugs than with on-label drugs (6% vs. 3.9%) [40]. The lack of therapeutic efficacy when the dose is too low is also a concern [41]. The problem of safety and efficacy of the off-label use of drugs is important not only in connection with its influence on the course of the underlying disease and the results of treatment, but this problem also affects the financial side of pharmacotherapy. Knowledge of the various risk factors and the spectrum of side effects of off-label drugs for children can help development of strategies for their safe prescribing in the future [24].

Drugs, regardless of whether they are used on-label or off-label, are always xenobiotics for the body, so their use may be accompanied by side effects.

The instruction of the drug is the most reliable and accessible source of information about it. But the instructions can only contain information that has been approved by the authorities and does not apply to off-label drugs.

The negative aspects of off-label therapy include examples when, contrary to existing rules and legal requirements, drug manufacturers are engaged in hidden promotion of their off-label use, which is contrary to the principles of ethical business processes.

Off-label drug prescribing is usually not in line with the «standard of healthcare». The responsibility for prescribing an off-label drug rests entirely with the doctor. However, when using an off-label drug, neither the patient nor the doctor are always aware of the possible consequences of the effects of such pharmacotherapy on the patient's health. Therefore, doctors should resort to this use of drugs only if they are convinced that the benefits of using an off-label drug outweigh the risks.

Despite the above, off-label therapy may be acceptable for treatment, taking into account the patient's condition, capabilities and safety. In any case, off-label therapy is completely unacceptable when patient safety is at stake.

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