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CRITERIA FOR PRESCRIBING OFF-LABEL DRUGS AND UNRESOLVED PROBLEMS IN THEIR USE

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Abstract

In past centuries, the doctor had the right to prescribe medications based only on his own professional experience and intuition. Nowadays, there are such medical technological documents as instructions for medical use, clinical protocols, formularies, national lists of essential drugs, which doctors are guided by when prescribing them. However, regardless of legal requirements, the doctor is obliged to select a drug for his patients, which must have high efficacy and acceptable safety. Currently, the use of off label drugs may be associated with changes in indications, age, dosage, routes of administration, i.e. anything that is not specified in the approved instructions for medical use. The journal covers all aspects of pharmacology. Manuscripts are accepted for consideration by Pharmacologyonline on the condition that they represent original material, have not been published previously, are not being considered for publication elsewhere, and have been approved by each author. In off label therapy, both prescription drugs and over-the-counter drugs can be used. In some countries, the use of off label drugs is regulated by law, their prescription does not violate ethical recommendations, the rules of safety and efficacy of drugs, the doctor knows how to use the drug correctly and takes legal and professional responsibility for its off-label prescription.

In general, off label drug use today is a controversial issue with significant legal, medical, ethical and economic arguments on both sides of the debate. 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 when used in this way. At the same time, it must be remembered that the safety and efficacy of drugs is determined by the requirements of the GCP, which is the "gold standard" of clinical medicine.

Keywords: *off-label drug use, criteria for prescribing off-label drugs, pharmacists.*

In past centuries, the doctor had the right to prescribe medications based only on his own professional experience and intuition. Nowadays, there are such medical technological documents as instructions for medical use, clinical protocols, formularies, national lists of essential drugs, which doctors are guided by when prescribing them. However, regardless of legal requirements, the doctor is obliged to select a drug for his patients, which must have high efficacy and acceptable safety. Currently, the use of off label drugs may be associated with changes in indications, age, dosage, routes of administration, i.e. anything that is not specified in the approved instructions for medical use [18, 19].

In off label therapy, both prescription drugs and over-the-counter drugs can be used. In some countries, the use of off label drugs is regulated by law, their prescription does not violate ethical recommendations, the rules of safety and efficacy of drugs, the doctor knows how to use the drug correctly and takes legal and professional responsibility for its off-label prescription.

There are no uniform standard rules for the use of off label drugs in the world. At a minimum, when prescribing an off-label drug, the doctor must justify: the patient's need for off label use, prophylactic or therapeutic properties, expected pharmacological effects, dose and mode of use. In this case, the physician should take into account the contraindications and the likelihood of PD and take all precautions to minimize the adverse effects of such drug use [20, 21, 22].

The optimal situation is when the use of off label drugs is regulated at the legislative level, and medical institutions monitor this use, in particular, by performing pharmacovigilance. At the same time, pharmaceutical companies must collect evidence that their drug, when used off label, is safe and necessary.

Since the problem of using drugs off label continues to be relevant for many nosology's, in 2007 the world medical community, together with representatives of drug manufacturers and regulatory authorities, developed criteria according to which drugs can be used outside of the label, namely:

Criterion 1: "The patient has a serious (life-threatening or seriously for a long time impairing his quality of life) disease."

Criterion 2: "Lack of approved specialty treatments".

Criterion 3: "There is scientific evidence to support the assumption that an effect (curative or palliative) can be achieved with the use of an off-label drug in a given patient" [1].

Also, an off-label drug can be prescribed if:

- there is convincing evidence of the effectiveness and safety of using drugs off label;
- informed consent was obtained from the patient;
- there is a need to prescribe a higher dose of the drug or another route of administration, but the reason for this prescription must be documented [1].

The Italian Supreme Court requires that three conditions be met for the use of off label drugs: informed consent of the patient; there should be no on label alternatives; off label use must be known in accordance with research published in internationally reputable scientific journals (exclude conference presentation or short abstract that could represent poorly substantiated results) [2, 3].

In the UK, there is no legal requirement for a physician to inform a patient that a drug is being prescribed off label. In this case, the patient should be provided with complete information about the treatment, including information about the expected benefits and possible risks off label of the drug, as well as whether there are alternative methods of treatment.

Also, these criteria indicate that it is clinical evidence that is the "gold standard" of pharmacotherapy, and doctors must responsibly make therapeutic decisions when using drugs off label.

In 2014, the American Academy of Pediatrics published criteria for the use of off label drugs for children. She advised pediatricians that their off-label use should not be exploratory, but based on strong scientific evidence, expert medical judgment, or published data in high-profile publications. This document also stated that clinical evidence remains the "gold standard" on which clinicians should base when making therapeutic decisions for their patients [4].

Pharmaceutical companies must create and submit to regulators proposals for the use of their drugs off label that meet strict criteria, namely:

1) an explanation why clinical trials or the path to official registration of a drug that is used off label are not possible;

2) an explanation of why the use of the drug off label will be beneficial for patients and for the healthcare system, despite the possible inevitable risks and increased costs to prove its safety and efficacy;

3) clear mechanisms for monitoring use, publishing, protocols and reporting to promote such use of the drug;

4) an indication of the conditions and time of possible registration of the drug that is used off label;

5) definition of marketing strategy and approval of all relevant materials, which must be approved by the regulatory body;

6) evaluation of the use of drugs off label according to the above criteria every 6 or 12 months in order to ensure monitoring of its use off label;

7) justification of the availability of funding potential for all of the above [3].

These criteria may seem overly restrictive, but given the risks to patients and the health system in general associated with uncontrolled off-label prescribing, they represent a fair trade-off between improving access to new therapeutic options for those who need them and maintaining high standards of health care and safety of drug use.

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. [5]. 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 [6, 7].

In fact, off label therapy is one of the ways to determine the new efficacy of drugs, i.e. innovation in modern pharmacotherapy, especially if information is communicated through peer-reviewed journals. However, off label therapy does not reflect the requirements of the current "standard of care".

This raises concerns of the doctor, pharmacist and patient about the risk if the patient receives an unwanted or poor treatment result [8].

Consequently, the use of off label drugs may pose risks that are not fully appreciated in terms of safety and efficacy. This makes it difficult for physicians to prescribe drugs off label without a sufficient evidence base, although such prescribing can be beneficial and even important in saving the lives of some patients.

Physicians working with special populations, such as children and pregnant women, sometimes have to refuse to prescribe a drug, either on label or off label, because sometimes drugs are not available for these populations. In addition, even if there are 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 regulatory approval [9].

Many of the new, repurposed drugs are, in fact, sometimes significantly improved versions of previously approved on-label drugs. For some of them, it is clinically proven that they are more effective and / or have less PR. For example, studies in the United States showed that antihypertensive therapy, when drugs were used off label, prevented 86,000 premature deaths from cardiovascular disease in 2001 alone [10, 11].

However, off label drug use does not have the same degree of scientific oversight and information as it does for approved indications. Although often information about them can help physicians make the necessary decisions, it may also be available from professional literature, which provides recommendations for prescribing off label drugs for specific indications or populations.

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 [12]. 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 [7].

Some off-label drugs are used to treat conditions that are very different from those for which the

drug has been approved by a regulatory authority, such as an anticonvulsant drug for chronic pain.

On the other hand, the lack of a convincing modern evidence base does not give grounds to recognize off label pharmacotherapy as innovative in all countries. For example, homeopathy is widely advertised and used in the treatment of many serious and even potentially fatal diseases, although there is no scientific evidence for the effectiveness and safety of this alternative therapy. Therefore, WHO made an official statement on the inadmissibility of advertising and the use of homeopathy in the treatment of serious, life-threatening diseases, thereby for the first time openly and unequivocally demonstrating its position in this regard [12].

In addition, while there are sometimes safety concerns about approved drugs, there is even greater uncertainty about the safety of off label drugs, especially in pediatrics, since most of the approved drugs for adults have not even been clinically tested in children. The main reason for this is that pharmaceutical companies tend to view the pharmaceutical market for children's drugs as relatively small and financially unprofitable, and pediatric clinical trials as complex and financially costly [13]. 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, for example, the recommended dose, which can both help and harm the child. Of course, it is better to rely on evidence-based medicine data so that the recommended doses are justified, but sometimes the course of the disease takes on an unforeseen turn and requires immediate non-standard decisions from practicing doctors. Therefore, when prescribing a drug off label, the doctor takes responsibility for his decision and is responsible for its consequences.

High competition in the pharmaceutical market creates a vicious practice for the promotion of off label drugs. Since the advertising of off label drugs is prohibited by law, pharmaceutical manufacturers are looking for ways to inform doctors about their use and sale, but at the same time refuse to be legally responsible for their actions.

Another problem with the use of off label drugs is that the off-label status may violate the conditions when they are introduced to various pharmaceutical markets on their mandatory study by conducting clinical trials in accordance with the requirements of world practice. Consequently, off-label drug use may impede the implementation of the gold standard of evidence-based medicine - mandatory clinical trials in accordance with the GCP.

The use of off-label drugs may even encourage firms 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 spreading information about off-label drug use [14].

Finally, in an era of ever-increasing health care costs, it must be remembered that off-label drug use can lead to financial losses, especially in the case of expensive drugs. For example, gabapentin is an expensive drug and is prescribed in about 50% of cases off label, including bipolar disorder, with no convincing evidence of efficacy in this condition or in the Warner Lambert regimen when used for neurological pain [15, 16, 17].

Particular attention should be paid to the indications of off label antibacterial drugs. Thus, the prescription of off label antibiotics for the treatment of ARVI is often inappropriate and leads to serious undesirable consequences that require additional drug therapy and sometimes increase the duration of hospitalization of patients [18].

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

- lack of clinical trials that have been approved by the regulatory / expert body;
- the likelihood of new PR manifestations;
- lack of motivation for 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.

Thus, the use of off label drugs is an important part of modern medicine and pharmacy, especially in pharmacotherapy in pediatrics, oncology, and psychiatry. While physicians can prescribe drugs approved by regulatory agencies for unauthorized

purposes, they should be aware that they are solely responsible for such prescribing.

In general, off label drug use today is a controversial issue with significant legal, medical, ethical and economic arguments on both sides of the debate. 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 when used in this way. At the same time, it must be remembered that the safety and efficacy of drugs is determined by the requirements of the GCP, which is the "gold standard" of clinical medicine.

References

1. Walton S. M., Schumock G. T., Meltzer D. et al. Prioritizing future research on off-label prescribing: results of a quantitative evaluation // Pharmacotherapy. – 2008. – Vol. 28 (Iss. 12). – P. 1443–1452.
2. Maratea D., Bettio M., Corti M. G. et al. The efficacy and safety of rituximab in treating childhood nephrotic syndrome: an Italian perspective // Ital. J. Pediatr. – 2016. – Vol. 42 (Iss. 1). – P. 1–3.
3. Stephanie M. Greence, Lars Noah, Debate, Off-label Drug Promotion and the First Amendment. – 2014. – P. 162.
4. Kumar P. Committee on Fetus and Newborn. American Akademy of Pediatrics. Use of inhaled nitric oxide in preterm infants // Pediatrics. – 2014. – Vol. 133 (Iss. 1). – P. 164–170.
5. Bennett W. M. Of-label use of approved drugs: therapeutic opportunity and challenges // J. Am. Soc. Nephrol. – 2004. – Vol. 15. – P. 830–831.
6. Levinson D. Medicare atypical antipsychotic drug claims for elderly nursing home residents. Department of Health and Human Services Office of Inspector General Report (OEI- 07-08-00150). (2001). – https://oig.hhs.gov/oei/reports/oei-07-08-00150.pdf
7. Morris J. The use of observational health-care data to identify and report on off-label use of biopharmaceutical products // Clin. Pharmacol. Ther. – 2012. – Vol. 91, N 5. – P. 937–942.
8. Dresser R., Frader J. Off-label prescribing: A call for heightened professional and government oversight // J. Law. Med. Ethics. – 2009. – Vol. 37, N 3. – P. 476–496.
9. O'Connell E., Rosebush L. H.FDA Published Guidance on Off-Label Use Communications. – 2017.
10. Ansel G. M., Jaff M. R. The "art" of medicine and the "smokescreen" of the randomized trial off label use of vascular devices // Catheter Cardiovasc. Interv. – 2008. – Vol. 72. – P. 998–1002.
11. Lai L. L., Koh L., Ho J. A. et al. Off-label prescribing for children with migraines in U.S. ambulatory care settings // J. Manag. Care Spec. Pharm. – 2017. – Vol. 23, N 3. – P. 382–387.
12. Cavalla D. Off-label Prescribing: Justifying Unapproved Medicine. Hoboken, NJ, Wiley-Blackwell, 2015, 216 p.
13. Tafuri G., Trotta F., Martini N. et al. Off-label use of medicines in children: can available evidence avoid useless pediatric trials? // Eur. J. Clin. Pharmacol. – 2009. – Vol. 65. – P. 209–216.
14. Demonaco H. J., Ali A., Ev H. The major role of clinicians in the discovery of off label drug therapies // Pharmacotherapy. – 2006. – Vol. 26 (Iss. 3). – P. 323–332.
15. Peckham A. M., Evoy K. E., Ochs L. et al. Gabapentin for off-label use: evidence-based or cause for concern // Substance Abuse: Research and Treatment. – 2018. – Vol. 12. Published online 2018 Sep 23. doi: 10.1177/1178221818801311.
16. Swaroop Vedula S., Li Tianjing, Dickersin Kay. Documents versus published trial reports: Comparisons in industry-sponsored trials in off-label uses of gabapentin (Differences in Reporting of Analyses in Internal Company Documents Versus Published Trial Reports: Comparisons in Industry-Sponsored Trials in Off-label Uses of Gabapentin) // PLoS Med. – 2013. – Vol. 31, N 9. – P. 1125–1127.
17. Silva D. I., Morais-Almeida Ansotegui M. Off-label prescribing for allergic diseases in children // World Allergy Organ J. – 2014.2014; 7(1): 4. Published online 2014 Feb 14. doi: 10.1186/1939-4551-7-4.

18. Tatochenko V.K. Rational therapy of acute respiratory infections // Attending physician. – 2011. – No 8. – P. 12.

19. Causes and legal aspects of off-label drugs emergence: literature review / Kalko K. O., Drogovoz S. M., Komarova A. P., Hailat I. A., Drogovoz K. V., Ivantsyk L. B. Pharmacologyonline. Vol. 3. 2021. P. 179-186. https://pharmacologyonline.silae.it/files/archives/2021/vol1/PhOL_2021_1_A024_Kalko.pdf

20. Frequency of off-label drug use in medicine / Drogovoz S. M., Shchokina K. G., Komarova A. P., Kalko K. O., Orlenko I. V., Belik G. V., Fesenko W. Yu. Pharmacologyonline. 2021. Vol. 2. P. 138-144. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A017_Drogovoz.pdf

21. Positive and negative aspects of the off-label drugs use / Drogovoz S., Kalko K., Tsyvunin V., Horoshko V., Levkov A., Verholias O., Zhurenko D. Pharmacologyonline. 2021. Vol. 2. P. 1179-1185. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A132_Drogovoz.pdf

22. Use of antidepressants in off label therapy / Drogovoz S. M., Belik G. V., Kalko K. O., Shtroblya A. L., Barus M. M., Taran A. V., Khomenko V. Pharmacologyonline. 2021. Vol. 2. P. 1186-1191. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A133_Drogovoz.pdf