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TYPES OF OFF-LABLE DRUG USE AND INFORMED CONSENT DOCTRINE WHEN PRESCRIBING THEM

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Abstract

Today, medicine does not have a sufficient arsenal of drugs for the personalized treatment of cancer, neurological, psychiatric, pediatric patients, HIV-infected patients. An important aspect of informed consent when prescribing drugs off label is informing patients about potentially unknown risks, as well as about the existence of a rationale for such prescription of the drug. Thus, the doctrine of informed consent means, on the one hand, the doctor provides the patient with complete information about the use of an off label drug, an alternative method of treatment, the risks and potential benefits of such an alternative, and on the other hand, the patient decides whether he is ready to be treated with a drug that will be used off label, and confirms this with informed consent.

In modern good medical practice, the patient's rights take precedence over the opinion of the medical practitioner. Informed consent is an integral component of the modern relationship between doctors and their patients and a means of ensuring that the doctor's beliefs do not override the patient's right to self-determination and personal integrity.

Keywords: *off-lable drug use, informed consent doctrine*

Today, medicine does not have a sufficient arsenal of drugs for the personalized treatment of cancer, neurological, psychiatric, pediatric patients, HIV-infected patients [18, 19, 20]. Considering the above, the use of off label drugs can be considered as a spare niche in modern pharmacotherapy, which solves the problems of not only the range of drugs, but also the individual characteristics of the patient.

Individual patient factors influencing his response to drug administration:

- body weight, sex of the patient, age, race, ethnicity;
- variability of the processes of adsorption and excretion of drugs;
- variety of metabolic processes and their characteristics;
- patient behavior, lifestyle, habits and diet;
- comorbid conditions.

Considering the above individual characteristics of the human body, the dosage, the mode of administration and even the route of administration of the drug may change, which will not be indicated in the instructions, and therefore, it will be used off label.

The use of drugs off label can occur in connection with their use:

1) for indications that are not specified in the instructions for medical use approved by the regulatory body (hereinafter - instructions);

2) in an unapproved dose;

3) by introduction, which differs from that indicated in the instructions;

4) for unapproved duration of treatment and frequency of drug use;

5) in combination with another drug that is not provided for by the approved instructions;

6) in an unapproved age / target group.

With regard to off-label drug use off-label, the following situations occur: the drug is approved for one specific disease / condition, but is used to treat others. For example, topiramate is indicated for the treatment of seizures and is also used to treat neurological pain or depression. Below are a number of other examples when drugs are used to treat diseases / conditions that are not listed in the instructions:

- clonidine (clonidine) - an α2-adrenergic agonist, antihypertensive drug, used as an analgesic or in the treatment of attention deficit disorder;
- risperidone, an antipsychotic drug used to treat autism;
- azithromycin - an antibiotic used as an anti-inflammatory drug for cystic fibrosis;
- indomethacin - an NSAID, used for nephrogenic diabetes insipidus;
- folic acid - vitamin Bc, used for seizures in newborns.

If the used dose of the drug differs from the recommended instruction for medical use, then, in fact, it is used off label. For example, the dose used in actual clinical practice for atypical antipsychotic drugs may be much higher (risperidone, aripiprazole) or lower (quetiapine) than the FDA-approved dose, depending largely on the severity of the disease and the tolerability of the treatment [2]. Doses in which calcitriol is used off label in the treatment of hypocalcemia, secondary renal failure, exceed those recommended for the treatment of osteoporosis.

In the event that the route of administration of the drug differs from that indicated in the instructions, the use of drugs also refers to off label.

For instance:

- diazepam in solution for parenteral administration is prescribed rectally for the treatment of status epilepticus;
- the injectable form of tobramycin is used as inhalation for cystic fibrosis;
- Acetylcysteine inhalation solution is given orally for kidney disease.

Changes in the frequency and duration of drug use are also considered off label. In this case, the duration and frequency of drug use can both increase and decrease. Most often this happens with the use of antibiotics, fluoroquinolones, antifungal drugs, proton pump blockers and antihistamine receptors (vancomycin, theophylline, ciprofloxacin, amikacin, fluconazole, ranitidine, omeprazole).

It should be noted that when a drug is used differently from the recommendations in the instructions (dose, duration, frequency and route of administration), this is considered an off label application, both for approved indications and for

unapproved indications (Table 1). The use of the drug is considered off label and when it is combined with another drug that is not provided for in the approved instructions. One of the most frequent uses of off label drugs is their use in those categories of patients for whom they are not indicated or contraindicated. Particularly vulnerable in this regard are children, pregnant women, lactating women, elderly patients, as well as patients with diseases of the metabolizing and excretory organs.

Types of use of off label drugs in pediatrics:

1) prescribing drugs for children studied in clinical trials for a different age group;

2) the use of drugs in a different dosage than indicated in the instructions;

3) long-term use of drugs, which has been studied in short-term clinical trials;

4) prescribing drugs for the treatment of diseases not specified in the officially approved indications.

National requirements for informed consent differ from one EU country to another, but in general it is believed that physicians should inform their patients that the proposed treatment will be off label, the reasons why such treatment is offered, the potential side effects, risks and benefits. as well as any alternatives available. Informed consent is a European law and all EU member states are obliged to respect and protect it. The requirement for informed consent, in accordance with the Oviedo Convention and the European Charter, is declared for any type of treatment. For off label therapy, informed consent means that the patient must have adequate information about the risks and benefits of using the drug [3].

In Ukraine, the provision of any medical care is carried out only with the informed consent of the patient, regardless of whether it is diagnostics, prevention or treatment. Requirements for informed consent of the patient are presented in the Fundamentals of Healthcare Legislation, Art. 43 «Consent on medical involvement». It should be noted that «in non-emergency cases, if there is a real threat to the life of a sick person explicitly, for someone who is sick, either medical involvement is not required» [3].

If the lack of consent can lead to serious consequences for the patient, the doctor is obliged to explain this to him. If after that the patient refuses treatment, the doctor has the right to take a written confirmation from him, and if it is impossible to receive it, to certify the refusal by an appropriate act in the presence of witnesses.

A patient who has acquired full legal capacity, realizes the significance of his actions and can direct them, has the right to refuse treatment [4].

If the refusal of treatment is given by the patient's legal representative and this may have serious consequences for the patient, the doctor must inform the guardianship and guardianship authorities about it [3].

Informed voluntary consent is a modern doctrine in medical ethics and medical law, according to which for medical intervention, especially one that carries risks, the patient's consent must be obtained and its receipt must be subject to certain conditions.

Moreover, informed consent is necessary when it comes to prescribing off label drugs [5]. The decision of whether to prescribe a drug off label to a particular patient is a matter of medical judgment by a physician, not a decision of regulatory authorities. The most difficult issue in such prescribing of drugs is the role and responsibility of the doctor about the use of drugs off label and obtaining informed consent from the patient for this treatment.

In the United States, the rule that a patient's consent to treatment must be informed was formalized about 60 years ago. The concept of "informed consent" was first applied in 1957 by the California Court of Appeals, which clarified that the doctor is violating his duty to the patient and is responsible if he withholds from the patient any facts necessary to form an informed consent to medical intervention [6].

In the United States, courts are not very strict about the opinion that the informed consent doctrine requires physicians to inform their patients about off-label drug use. However, American law recognizes the principle of informed consent. The US Congress explicitly prohibited the FDA from regulating the practice of a doctor, and the use of drugs off label is considered the prerogative of a

doctor. However, this is not the same as claiming that FDA information is irrelevant to medical practice.

Consequently, the doctrine of informed consent is that the patient must be provided with the following information:

characteristics of the proposed treatment (drug);

characterization of the risk and benefit of the recommended treatment measures, highlighting the degree of danger of the most unfavorable outcomes (death or severe disability);

about alternative methods of treatment, characteristics of their usefulness and risk, the danger of adverse outcomes;

the consequences of postponing or refusing treatment;

a description of the likelihood of a successful outcome;

an explanation of the probable difficulties of treatment, the length of the rehabilitation period and the patient's return to his normal volume of activity;

presentation of similar cases from the experience of the doctor or his colleagues.

Risks and complications of the treatment and diagnostic process should be discussed only those that significantly affect the patient's choice of consent or disagreement with the proposed treatment. It is logical to assume that the patient will quite easily agree to a treatment procedure, provided that death as a result of it occurs in one in 10,000 patients, and will think about it if during the procedure, risks arise in 33% of patients.

Therefore, before prescribing an off label drug, the physician must provide the patient with complete information about it, including that it is not approved for the proposed use, that the risks associated with its use are not fully understood or are unknown and what is possible. failure in treatment, the losses from which may not be reimbursed. Compliance with this requirement may allow patients to disagree with treatment or make claims for damages. One way or another, it is considered optimal that after such information, the patient should fill out a document in which he will express his decision on off label treatment.

At a minimum, an informed consent form should contain information:

- the nature of the proposed treatment;
- about potential PR (the most dangerous and common);
- about treatment alternatives, including their potential side effects;
- about the patient's prospects without treatment;
- the cost of such treatment.

Thus, the doctrine of informed consent means that the physician must provide the patient with full information about the proposed use of drugs off label, existing alternatives, as well as the risks and potential benefits of alternatives, and then allow the patient to decide which pharmacotherapy he will consent to.

From a medical point of view (taking into account the information contained in available drug guides, authoritative medical literature and accepted standards of medical practice), the more information the doctor provides to patients about alternative therapies, about their risks and benefits, the more informed the decision will be. the patient about the use of the drug off label.

An important aspect of informed consent when prescribing drugs off label is informing patients about potentially unknown risks, as well as about the existence of a rationale for such prescription of the drug. The physician should also discuss with the patient why any conventional medications available are not suitable for the patient. This discussion should be well documented in the medical history. The doctor should not hide from the patient the fact that he plans to prescribe a medicine, which is, in fact, an experiment in treatment. The inability of the doctor to disclose the idea and the need to use the drug off label negatively affects the essence of the concept of informed consent [7].

Each state sets its own criteria for determining what information is essential for the patient. For example, in China there is a mandatory requirement

that the doctor inform the patient about his condition and the results of treatment, about any risks of alternative treatment, and obtain written consent to carry it out. However, the law does not specify when the patient is required to obtain informed consent. If the doctor, without obtaining the informed consent of the patient, carried out a treatment that harmed the patient, the latter has the right to sue for compensation for the damage caused [8, 9, 10, 11].

In pediatrics, there is an ethical problem with the amount of information provided to the patient and parents regarding the use of off label drugs: is it necessary to fully inform parents about the drugs prescribed for their child? If so, is their verbal consent sufficient or should it be provided in writing? Obtaining informed consent for off label drug use in a pediatric patient will not only protect the clinician in the event of an adverse drug reaction, but also respect parental autonomy [8, 9, 10, 12].

In oncology, the difficulty of informed consent is that it is difficult to establish a framework for how truthful and voluminous the information provided by the doctor to the patient should be, about his health status, diagnosis, and further treatment, including the use of off label drugs. It is very difficult to determine the line after which complete truthful information can harm the patient's psychological state, lead him to a wrong decision, for example, to stop treatment, i.e. harm a person [13, 14, 15, 16].

Given that professional obligations in the UK generally require physicians to inform patients about off label prescribing, in fact, patient awareness is very low. A survey of 1,000 members of the public in Northern Ireland showed that 86% of the surveyed population did not have sufficient knowledge about the use of unlicensed drugs in children and 81% of them were concerned about it [17].

If a healthcare facility does not require informed consent, then it may have an increased risk of legal liability for medical malpractice, for the fact that its doctors do not inform patients about the prescription of off label drugs and do not obtain written consent from the patient. To avoid potential off label prescribing irregularities, a healthcare facility should require its physicians to prescribe drugs with appropriate scientific evidence and to follow established informed consent procedures.

In turn, in accordance with the concept of informed consent, if it is planned to use the drug off label, the patient can ask the doctor the following questions:

- Are there clinical trials on the safety and efficacy of this drug off label?
- What is the evidence that this drug should be taken off label?
- Is the doctor confident that the drug will be helpful?

Most allegations of medical malpractice in the use of off label drugs are related to cases of lack of informed consent, where the physician has failed to disclose the nature and risks of the likely outcomes and alternatives of the intended treatment [6, 7]. However, not a single court decision has yet established the fact that the doctor, without taking informed consent from the patient, committed a criminal offense. Therefore, the overwhelming majority of courts on this issue were resolved in favor of doctors, since when using off label drugs, speech is about the chances of the safety and effectiveness of treatment, as well as when prescribing them on label. When evaluating alternative therapies, where one drug is used off label and the other is used on label, there are risks in both cases, especially with regard to their safety issues.

The informed consent form must be kept in the patient's medical history, which indicates: the name of the drug, the dose and frequency of taking the drug, the indications for its use. In addition, the informed consent form should include the following points:

1) I was given oral information on the above medication;

2) I have been advised of alternative treatment options (if any);

3) I understand that my decision is voluntary;

4) I understand the risks and benefits and give my consent to treatment with an unregistered drug or for an unregistered indication;

5) I have had ample time to consider the risks and benefits of using this medication;

6) I had the opportunity to ask questions and all my questions were answered satisfactorily;

7) signatures of the patient or close relatives;

8) date;

9) a document proving the doctor's identity, his name, signature and official seal, as well as the appointment of the drug and the date.

Thus, the doctrine of informed consent means, on the one hand, the doctor provides the patient with complete information about the use of an off label drug, an alternative method of treatment, the risks and potential benefits of such an alternative, and on the other hand, the patient decides whether he is ready to be treated with a drug that will be used off label, and confirms this with informed consent.

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Table 1.**Examples of *off label* drugs for various body systems**

Systems	***Off label***	**International non-proprietary drug name**
Gastrointestinal tract	Indications	Ondansetron
Nervous	Indications	Lorazepam
Respiratory	Dose	Chlorphenamine
Respiratory	Age, dose	Phenylephrine, dextromethorphan, ipratropium bromide