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Assessment of Awareness and Experience of Using off-label Drugs by Doctors of Clinical Specialties

Aim	To evaluate the frequency of off-label prescription of medicines in practice of clinical specialists and the awareness of respondents of the procedure of justified off-label prescription.
Material and methods	The sample included 542 clinical specialists who worked in definite medical organizations in 26 entities of the Russian Federation. The respondents were proposed to fill in remotely an anonymous questionnaire to evaluate the experience of prescribing medicines off-label to adult patients.
Results	Prescribing medicines not in consistence with the officially approved instruction for medical use (off-label or «outside instruction») is a relevant issue of global medical care since convincing scientific evidence for safety of such use is scarce. Analysis of information about off-label prescription is one of current tasks of national medical research centers according to the Federal Project «Development of a network of national medical research centers and implementation of innovative medical technologies». According to the responses about the frequency of off-label prescriptions 67.5% of respondents reported of no experience of off-label prescription, 27.7% said «rarely» or «sometimes», and 4.8% said «frequently» and «very frequently». Specialties of physicians who have more often used medicines off-label (50% and more) included obstetrics and gynecology, pediatrics, rheumatology, hematology, and pulmonology. Cardiologists, neurologists and clinical pharmacologists use medicines off-label relatively rarely (19.6%, 28.6%, and 22.2%, respectively). 40% of medicines used off-label were those designed for the treatment of coronavirus infection SARS-CoV-2. The medicines most frequently used off-label included metformin, rituximab, and thioctic acid. 65% of respondents assessed their knowledge of off-label prescription as insufficient. In addition, 75% of respondents consider it useful to receive additional information about risks and benefits of off-label prescription in clinical practice.
Conclusion	The survey revealed the need of physicians for information about risks of the off-label use of medicines in clinical practice.

Keywords	Off-label; "outside instruction"; off-label medicines; clinical specialists; survey
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The off-label administration of drugs (i.e., their use for an unapproved indication, dosage form, population, or other parameters not mentioned in the approved labeling) is a relevant problem concerning world health care practices due to the lack of conclusive scientific evidence of the safety of such use.

In clinical practice, it commonly occurs that a physician performs an off-label prescription of a drug that has been officially approved in the Russian Federation based on knowledge about its potentially high clinical efficacy. The reasonable decision must consider the main factors determining the benefit of the drug: patient characteristics (e.g., older age, pregnancy, lactation, etc.), the severity of the disease, evidence of the drug's potential benefits, as well as likely adverse reactions. The predominance of potential benefits over the harm is most evident subject to the following conditions: patient rarely has adverse reactions; disease is severe; the high efficacy of the drug is documented; adverse reactions are well studied, unlikely, and insignificant. When deviating from specified methods of administration, it is of crucial importance that a prescribing physician take such nuances into account [2, 3].

While off-label prescription of drugs is not legally prohibited, the practice increases the personal responsibility of an HCP for possible risks to a patient's health, for which reason such a decision must be reasonable and justified [4–8]. The criteria for appropriate off-label drug prescription are most clearly described in German pharmaceutical law. According to the Declaration on Good Off-Label Use Practice

(GOLUP Declaration) developed by the expert group of the European Medicines Agency in 2016, the off-label drug administration is considered reasonable subject to specific criteria (Figure 1, adapted from GOLUP Declaration [9]).

Although not formalized, the following criteria for reasonable off-label drug administration are widely used in Russian clinical practice:

- the presence of a severe or life-threatening disease, or disease significantly deteriorating quality of life;
- the absence of a drug approved for the indication or the age group;
- evidence-based grounds to expect that a therapeutic or palliative effect can be achieved using the drug in a particular patient and particular clinical situation.

From a legal point of view, off-label drug administration in Russia should be justified in source medical records (often accompanied by a protocol or consensus report of the medical commission), as well as by informed consent signed by a patient [10].

Analysis of information concerning the off-label administration of drugs is one of the objectives of the national medical research centers (NMRCs) under the federal project Development of a Network of National Medical Research Centers and the Introduction of Innovative Medical Technologies. In Russia, off-label drug administration data are typically collected in cases of adverse reactions [11]. However, according to international estimates, the frequency of off-label drug administration in adults varies from 7–95% in hospitals and from 6–72% in outpatient facilities [12], i.e., the off-label administration of drugs is common in clinical practice.

Open-label, observational, prospective, non-randomized clinical trial was designed and carried out in the National Medical Research Center of Internal and Preventive Medicine to collect data on the off-label drug administration.

Objective

To evaluate the frequency of off-label drug administration in clinical practice in various medical specialties and the knowledge of the respondents about the procedure of reasonable off-label drug administration.

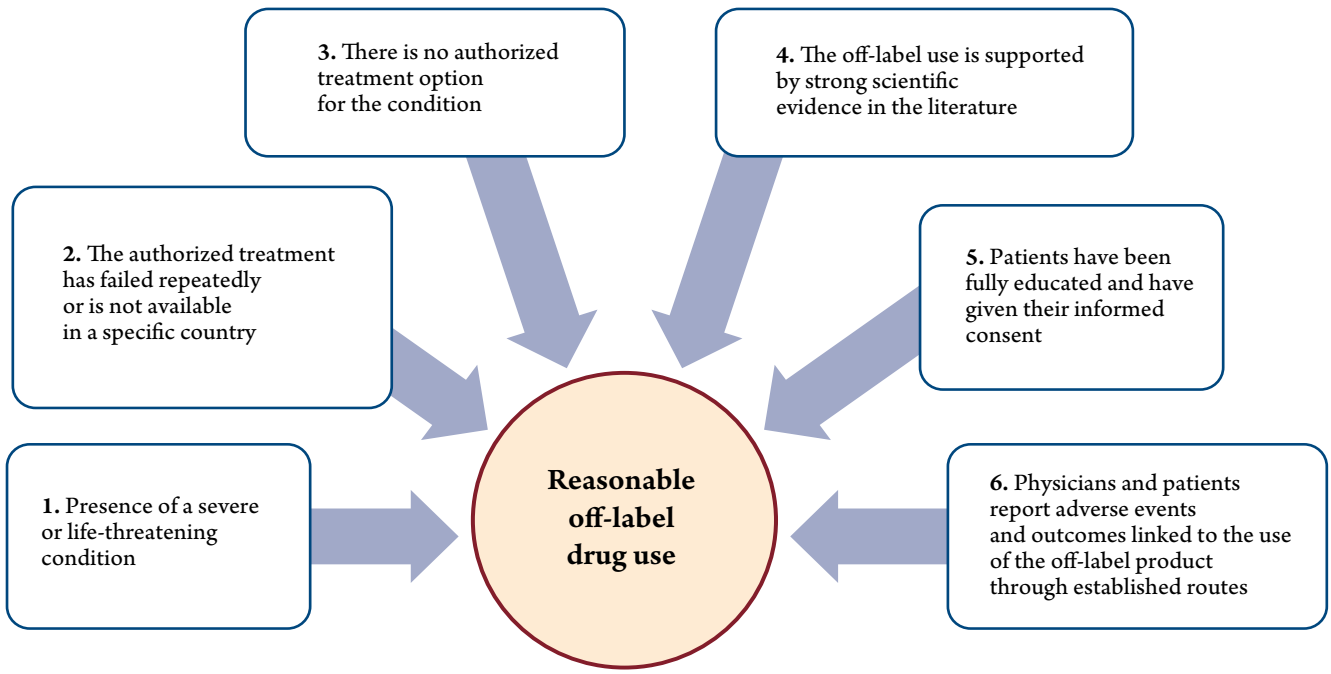
Material and Methods

The trial was carried out following good clinical practice guidelines. The protocol was approved by the ethics committee of the National Medical Research Center of Internal and Preventive Medicine.

The sample included physicians with clinical specialties working in healthcare facilities in 28 subjects of the Russian Federation.

The inclusion criterion was clinical practice in the healthcare facility selected for the trial. The exclusion criterion was refusal to participate in the trial. Respondents were enrolled with the support of senior internal medicine specialists of the relevant federal subjects and districts. Respondents were asked to undergo a remote anonymous survey (Table 1).

Figure 1. Criteria of reasonable off-label drug administration according to the Declaration on Good Off-Label Use Practices



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The obtained data were statistically processed using the IBM SPSS Statistics 20.0 (USA) and Microsoft Office Excel 2016 (USA) software suites. The normality of distribution was detected using the Kolmogorov–Smirnov test and the Shapiro-Wilk test. The qualitative parameters were compared using the 2×2 contingency tables and Pearson's test. The differences were considered significant at $p<0.05$ in all types of analyses.

Results

The trial was conducted from August to September 2020. The questionnaire was completed by 542 respondents from the following subjects of the Russian Federation: Vologda Region, Chelyabinsk Region, Kaliningrad Region, Kamchatsky Krai, Kemerovo Region, Khanty-Mansi Autonomous Area, Kursk Region, Moscow Region, Murmansk Region, Nizhny

Table 1. Questionnaire to assess the experience of off-label drug administration in adult patients by clinicians (based on a questionnaire on the knowledge of off-label drugs in pediatrics [13])

Question	Answer option (if available)
1.1. Subject of the Russian Federation	List of the Subjects
1.2. Place of employment	☐ Outpatient facilities (non-24-hour settings of medical care and treatment), including house-calls
	☐ Day-care facilities (day-time care and treatment not requiring 24-hour medical supervision and treatment)
	☐ Inpatient facilities (24-hour medical care and treatment)
	☐ Others (please specify)
1.3. Your specialty	
2. How often do you prescribe drugs off-label?	☐ Very frequently
	☐ Frequently
	☐ Occasionally
	☐ Rare
	☐ Never
3. Which drugs did you prescribe off-label? (please specify one or more)	3.1. International nonproprietary name (INN) (please specify active substance)
	3.2. Trade name (please specify)
	3.3. What is/are the parameter(s) of the drug use that was/were off-label (please select one or more)?
	☐ Special population (pregnant women, elderly, etc.)
	☐ Indications
	☐ Contraindications
	☐ Dosage frequency
	☐ Doses
	☐ Method (route) of administration
	☐ ПDuration of treatment
	☐ Others (please specify)
	3.4. What is the main reason for prescribing this drug off-label? (please specify)
4. To what extent does your off-label prescription of drugs affect treatment efficacy?	☐ Significantly
	☐ Slightly
	☐ Marginally
	☐ No effect
5. What are the risks associated with your off-label administration of drugs?	☐ Adverse reactions
	☐ Lack of treatment efficacy
	☐ Others (please specify)
6. Do you consider your knowledge on the off-label administration of drugs to be adequate?	☐ Yes
	☐ No
7. Would you like to get more information about the risks and benefits of off-label administration of drugs in clinical practice?	☐ Yes
	☐ No

Novgorod Region, Novosibirsk Region, Omsk Region, Orenburg Region, Penza Region, Primorsky Krai, Republic of Altai, Republic of Chuvashia, Republic of Dagestan, Republic of Mari El, Republic of Mordovia, Republic of Tatarstan, Rostov Region, Ryazan Region, Sakhalin Region, Sevastopol, Tyumen Region, Voronezh Region, Zabaykalsky Krai.

General respondent characteristics

The questionnaire was completed by physicians of 25 specialties: 297 (55%) – internal medicine; 56 (10%) – cardiology; 35 (6%) – neurology; 29 (5%) – general practice (Figure 2).

334 respondents worked as outpatient physicians (62%), while 176 (33%) were employed in hospitals (Figure 3).

The proportion of outpatient physicians among respondents who specified «internal medicine» and «neurology» was comparable to the general structure. Of respondents who specified «internal medicine», 67% worked in an outpatient facility, 28% worked in hospitals, while 5% were employed in day hospitals. Among the physicians who specified «neurology», the distribution according to place of work was similar: 66% in outpatient facilities, 23% in day hospitals, and 11% in hospitals. Among the respondents specializing in «cardiology», the proportion in hospitals and outpatient facilities were comparable (43 and 46%, respectively). Among physicians who specified «general practice», 66% worked in outpatient facilities, 23% in hospitals, and 11% in day hospitals (Figure 4).

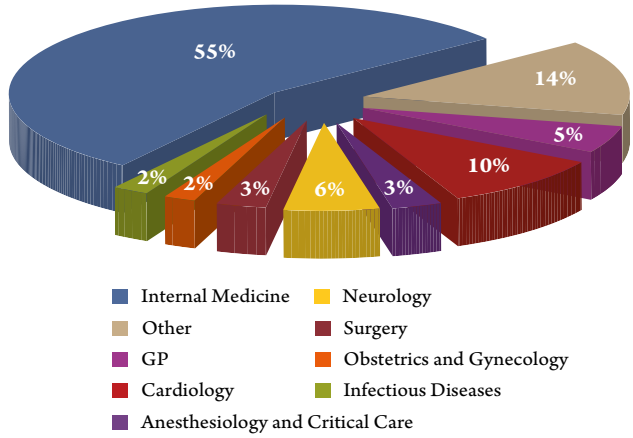
Respondent's experience of the off-label drug administration

According to the responses on the frequency of the off-label drug administration, 366 (67.5%) respondents said that they had no experience of off-label prescription, while only 4.8% (n=26) prescribed drugs off-label frequently or very frequently (Figure 5). In most cases, the drugs had been administered off-label to treat patients with COVID-19. In a few cases, internal medicine specialists reported the following cases of off-label prescriptions: administration of omeprazole for the prevention of erosion and ulcers associated with the use of nonsteroidal anti-inflammatory drugs; metformin for the treatment of obesity.

Experience of off-label drug administration depending on the specialties of respondents

A comparison of the structure of respondents' specialties depending on off-label use of pharmaceutical drugs showed a close to critical level of significance

Figure 2. Respondent specialty structure



GP, general practitioner.

of the differences between the investigated parameters (p=0.064). The respondents of the following specialties administer drugs off-label more often (50% or more respondents prescribed drugs off-label): Obstetrics and Gynecology, Pediatrics, Rheumatology, Hematology, Pulmonology (Table 2). Medications are administered off-label comparatively rarely by cardiologists (19.6%), neurologists (28.6%), and clinical pharmacologists (22.2%).

In «obstetrics and gynecology» (50% of respondents adminster drugs off-label), the off-label pres-

Figure 3. Places of employment

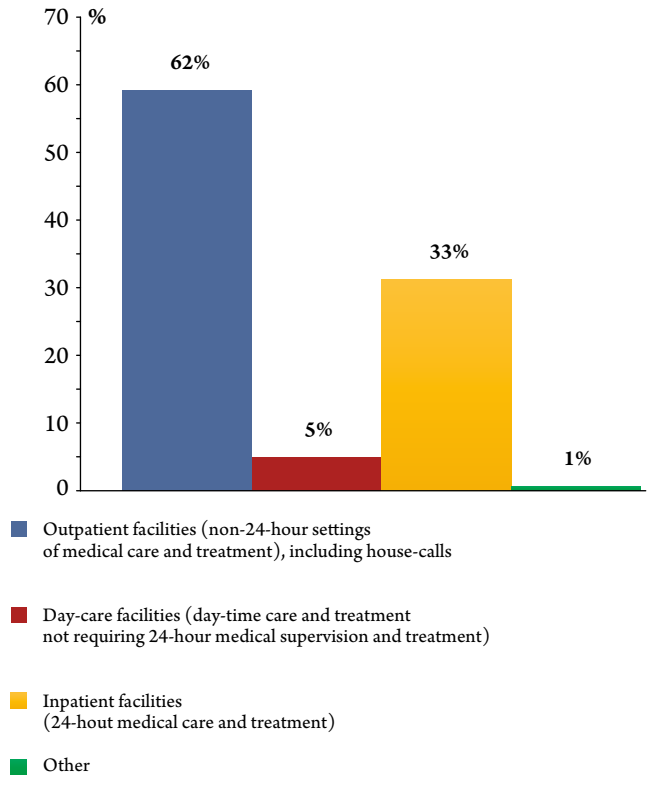


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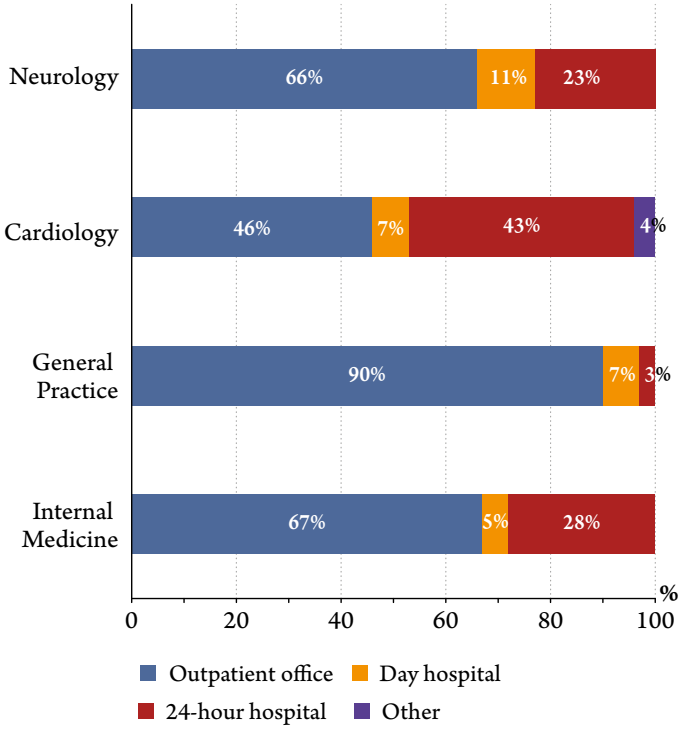
Figure 4. Structure of places of employment of the respondents in «Internal Medicine», «General Practice», «Cardiology», «Neurology"

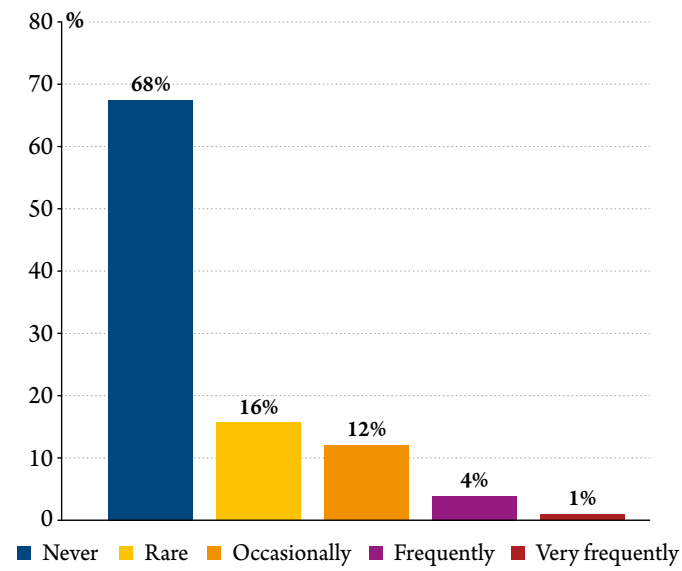


criptions concerned special patient populations (pregnant women, etc), duration of treatment, and indications for the use of homeopathic drugs.

Among pediatricians (55.6% of respondents use drugs off-label), the main causes of off-label prescription are the age-related characteristics of patients; in one case, route of administration was cited.

Off-label use by rheumatologists (60% of respondents prescribe drugs off-label) included unapproved indications and a special patient group (in one case).

Figure 5. Frequency of off-label drug use



Hematologists (83.3% of respondents use drugs off-label) prescribe medications off-label on unapproved indications in all cases.

Among physicians who specialize in «pulmonary medicine» (83.3% of respondents administer drugs off-label), the off-label use included unapproved indications, as well as a special patient population (in one case), and the duration of drug use (in one other case).

Drugs most commonly administered off-label

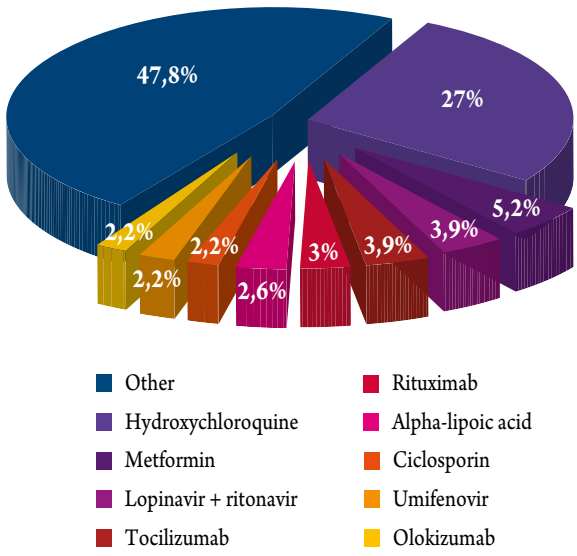
The detailed analysis of the use of specific drugs off-label showed that they were used in 40% of cases to treat COVID-19; this can be attributed to the trial having been conducted during the COVID-19 pandemic period.

The pharmaceutical drugs most frequently used off-label were hydroxychloroquine (27.0%), metformin (5.2%), lopinavir + ritonavir (3.9%), tocilizumab (3.9%), rituximab (3.0%) (Figure 6). 47.8% were

Table 2. Differences in frequency of the off-label administration of drugs in clinical practice by the respondents depending on a specialty

Respondent specialty	Off-label drug administration in clinical practice			
	Not used, n=366		Used, n=176	
	n	%	n	%
Internal Medicine	204	68.7	93	31.3
General Practice	17	58.6	12	41.4
Cardiology	45	80.4	11	19.6
Neurology	25	71.4	10	28.6
Infectious diseases	5	55.6	4	44.4
Anesthesiology and Critical Care	9	60.0	6	40.0
Obstetrics and Gynecology	5	50.0	5	50.0
Pediatrics	4	44.4	5	55.6
Rheumatology	2	40.0	3	60.0
Pulmonary medicine	1	16.7	5	83.3
Hematology	1	16.7	5	83.3
Clinical Pharmacology	7	77.8	2	22.2
Gastroenterology	3	75	1	25
Surgery	10	66.7	5	33.3
Endocrinology	6	75	2	25
Otorhinolaryngology	4	100	0	0
Genetics	0	0	1	100
Oncology	2	66.7	1	33.3
Ophthalmology	4	57.1	3	42.9
Physical therapy	1	100	0	0
Nephrology	1	100	0	0
Traumatology and Orthopedics	2	66.7	1	33.3
Dentistry	5	100	0	0
Trainee doctor	1	100	0	0
Other	1	50	1	50

Figure 6. Administration of individual drugs used off-label



various rarely used pharmaceutical drugs, which were prescribed in less than 2% of all cases.

In addition to the drugs prescribed off-label to treat COVID-19, the most frequent uses of off-label pharmaceutical drugs off-label were metformin, rituximab, and thioctic acid.

Comparative assessment of the frequencies of off-label drug prescription in clinical practice by the respondents depending on a place of employment

There were no significant differences (p=0.375) when comparing off-label drug administration practices depending on the places of work (Table 3). The number of physicians in each specialty administering or not administering pharmaceutical drugs off-label was broadly equivalent.

Assessment of the effects of administering drugs off-label on treatment efficacy

The analysis on the effects of using pharmaceutical drugs off-label on treatment efficacy was carried out: 236 (44%) of respondents thought that the use of drugs off-label significantly affected treatment efficacy, including those who had no experience of off-label drug administration (64% of respondents); 109 (20%) reported that the off-label use of pharmaceutical drugs did not affect treatment efficacy; it should be noted that 87% of them had no experience of off-label drug administration (Figure 7).

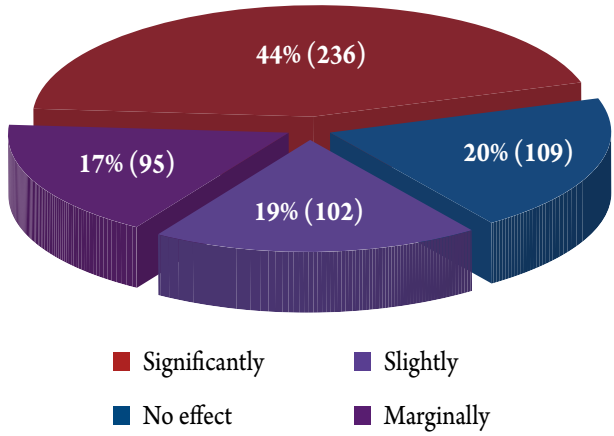
Structure of risks associated with off-label administration of drugs

Regarding the risks of off-label adminstration of pharmaceutical drugs, 88 (50%) of 176 physicians

Table 3. Frequency of off-label drug administration in clinical practice by respondents depending on place of employment

Place of employment	Off-label drug administration in clinical practice			
	Not used, n=366		Used, n=176	
	n	%	n	%
Outpatient office	233	63.7	101	57.4
Day hospital	20	5.5	8	4.6
24-hour hospital	111	30.3	65	36.9
Other	2	0.5	2	1.1

Figure 7. Structure of responses by effects of off-label drug administration on the treatment efficacy



who had the experience of administering drugs off-label reported the development of adverse reactions, 73 (41%) reported a lack of efficacy of the prescribed drug (Figure 8). At the same time, 10 (6%) of physicians believe that there are no risks of off-label drug administration, while 5 (3%) thought that a healthcare facility could be held legally responsible for such practices.

Self-evaluation of respondents' knowledge and interest in increasing their knowledge of off-label administration of drugs in clinical practice

Interestingly, 355 (65%) of respondents assessed their knowledge about the off-label adminstration of drugs as insufficient.

Even more physicians (75%) consider it useful to receive more information about the risks and benefits of off-label drug prescription in clinical practice.

Discussion

In this trial, a relatively low frequency of off-label prescription of pharmaceutical drugs was reported. In

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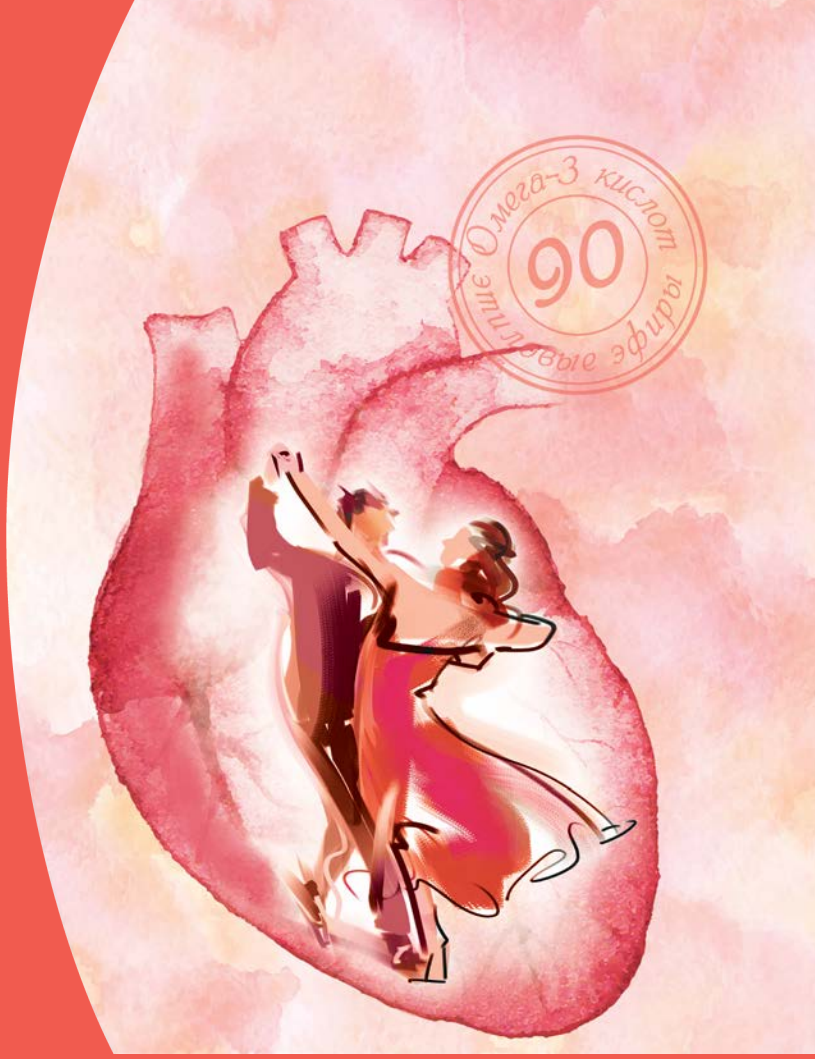
Abbott

- Способствует восстановлению клеток сердца*, 1, 2
- Снижает риск внезапной сердечной смерти на 45%*, 3
- Хорошо переносится при длительной терапии*, 4, 5



* У пациентов после инфаркта миокарда (в составе комбинированной терапии): в сочетании со статинами, антиагрегантными средствами, бета-адреноблокаторами, ингибиторами ангиотензинпревращающего фермента (АПФ).

ОМАКОР ДЕЛО ЖИЗНИ

ДЛЯ ВТОРИЧНОЙ ПРОФИЛАКТИКИ ПОСЛЕ ИНФАРКТА МИОКАРДА*, 6

Омакор. Регистрационный номер: ЛС-000559. **Международное непатентованное или группировочное наименование:** Омега-3 кислот этиловые эфиры 90. **Лекарственная форма:** капсулы, 1000 мг. **Фармакологические свойства*.** Полиненасыщенные жирные кислоты класса омега-3 – эйкозапентаеновая кислота (ЭПК) и докозагексаеновая кислота (ДГК) – относятся к незаменимым (эссенциальным) жирным кислотам (НЭЖК). Результаты клинического исследования GISSI-Prevenzione, полученные за 3,5 года наблюдений, показали существенное снижение относительного риска смертности от всех причин, нефатального инфаркта миокарда и нефатального инсульта на 15 % ([2-26] p=0,0226) у пациентов после недавно перенесенного инфаркта миокарда, принимавших препарат Омакор по 1 г в сутки. Дополнительно, относительный риск смерти по причине сердечно-сосудистой патологии, нефатального инфаркта миокарда и нефатального инсульта снижался на 20 % ([5-32] p=0,0082). Результаты клинического исследования GISSI-Heart Failure, в котором пациенты с хронической сердечной недостаточностью получали препарат Омакор по 1 г в сутки в среднем в течение 3,9 лет, показали снижение относительного риска смертности от всех причин на 9 % (p=0,041), снижение относительного риска смертности от всех причин и госпитализации по причине сердечно-сосудистых патологий на 8 % (p=0,009), снижение относительного риска первичной госпитализации по причине желудочковых аритмий на 28 % (p=0,013). **Показания к применению.** Гипертриглицеридемия: эндогенная гипертриглицеридемия IV типа по классификации Фредериксона (в монотерапии) в качестве дополнения к гиполипидемической диете при ее недостаточной эффективности; эндогенная гипертриглицеридемия IIb или III типа по классификации Фредериксона в комбинации с ингибиторами ГМГ-КоА редуктазы (статинами), когда концентрация триглицеридов недостаточно контролируется приемом статинов. Вторичная профилактика после инфаркта миокарда (в составе комбинированной терапии): в сочетании со статинами, антиагрегантными средствами, бета-адреноблокаторами, ингибиторами ангиотензинпревращающего фермента (АПФ). **Противопоказания.** Повышенная чувствительность к действующему веществу, сое, арахису или любому из вспомогательных веществ, входящих в состав препарата. Возраст до 18 лет (эффективность и безопасность не установлены). Беременность и период грудного вскармливания. Омакор не следует применять у пациентов с экзогенной гипертриглицеридемией (гиперхиломикронемией I типа). **С осторожностью.** Установленная гиперчувствительность или аллергия на рыбу; возраст старше 70 лет; нарушения функции печени; одновременный прием с пероральными антикоагулянтами; геморрагический диатез; пациенты с высоким риском кровотечений (вследствие тяжелой травмы, хирургической операции); вторичная эндогенная гипертриглицеридемия (особенно при неконтролируемом сахарном диабете). **Применение при беременности и в период грудного вскармливания*.** Назначать Омакор беременным следует с осторожностью, только после тщательной оценки соотношения риска и пользы, когда польза для матери превышает потенциальный риск для плода. Препарат не должен применяться в период грудного вскармливания. **Способ применения и дозы*.** Внутрь, независимо от приема пищи. Во избежание развития возможных нежелательных явлений со стороны желудочно-кишечного тракта (ЖКТ) препарат Омакор может приниматься во время приема пищи. Гипертриглицеридемия. Начальная доза составляет 2 капсулы в сутки. В случае отсутствия терапевтического эффекта возможно увеличение дозы до максимальной суточной дозы – 4 капсулы. Вторичная профилактика инфаркта миокарда. Рекомендуется принимать по 1 капсуле в сутки. **Побочное действие*.** Желудочно-кишечные расстройства (в том числе вздутие живота, боль в животе, запор, диарея, диспепсия, метеоризм, отрыжка, гастроэзофагеальная рефлюксная болезнь, тошнота или рвота). *Перечень всех побочных действий представлен в инструкции по медицинскому применению.* **Передозировка.** Особые указания отсутствуют. Должна быть проведена симптоматическая терапия. **Взаимодействие с другими лекарственными средствами*.** При одновременном применении препарата Омакор с пероральными антикоагулянтами или другими препаратами, влияющими на систему гемостаза (например, ацетилсалициловая кислота или НПВП), наблюдалось увеличение времени свертывания крови. При этом геморрагических осложнений не наблюдалось. Ацетилсалициловая кислота: пациенты должны быть проинформированы о возможном увеличении времени свертывания крови. Совместное применение препарата Омакор с варфарином не приводило к каким-либо геморрагическим осложнениям. Однако необходим контроль соотношения протромбинового времени/международного нормализованного отношения (ПТВ/МНО) при совместном применении препарата Омакор с другими препаратами, влияющими на соотношение ПТВ/МНО, или после прекращения терапии препаратом Омакор. **Особые указания*.** Омакор должен применяться с осторожностью у пациентов с установленной гиперчувствительностью или аллергией на рыбу. В связи с умеренным увеличением времени свертывания крови (при приеме в высокой дозе, т.е. 4 капсулы в сутки) требуется наблюдение за пациентами, имеющими нарушения со стороны свертывающей системы крови или получающими антикоагулянтную терапию или другие препараты, влияющие на систему гемостаза (например, ацетилсалициловую кислоту или НПВП); при необходимости, доза антикоагулянта должна быть скорректирована. Необходимо учитывать увеличение времени свертывания крови у пациентов с высоким риском развития кровотечения. При терапии препаратом Омакор снижается уровень образования тромбоксана А2. Существенного влияния на уровень других факторов свертывания крови не наблюдалось. У некоторых пациентов наблюдалось небольшое, но достоверное повышение активности АСТ и АЛТ (в пределах нормы), при этом отсутствуют данные, указывающие на повышенный риск приема препарата Омакор пациентами с нарушением функции печени. Необходим контроль активности АСТ и АЛТ у пациентов с любыми признаками нарушения функции печени (в частности, при приеме в высокой дозе, т.е. 4 капсулы в сутки). Опыт применения препарата для лечения экзогенной гипертриглицеридемии (гиперхиломикронемии типа 1) отсутствует. Опыт применения препарата при вторичной эндогенной гипертриглицеридемии ограничен (особенно при неконтролируемом сахарном диабете). **Влияние на способность управлять транспортными средствами, механизмами*.** Ожидается, что препарат не оказывает или оказывает несущественное влияние на способность управлять транспортными средствами и работать с механизмами. **Условия хранения.** Хранить при температуре не выше 25 °С. Не замораживать. Хранить в недоступном для детей месте! Условия отпуска. Отпускают по рецепту.

***Полная информация представлена в инструкции по медицинскому применению.**

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a similar trial by Kuznetsova et al. [14] carried out in a smaller sample, 82% of internal medicine specialists and 100% of pediatricians prescribed drugs off-label. In this trial, the most frequent off-label administration of drugs was registered among physicians who work with specific populations that are excluded from clinical trials for ethical reasons (children, pregnant women). Nevertheless, drugs were administered off-label equally often in rheumatology and pulmonary medicine.

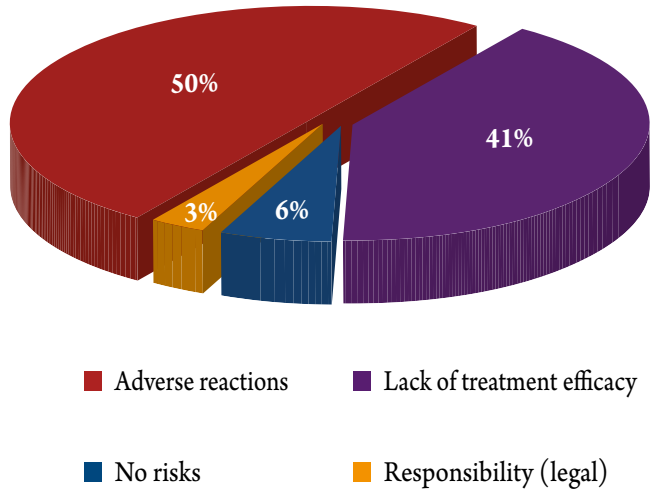
There was no difference in the frequency of administering drugs off-label depending on the place of work (outpatient facilities or hospitals). A total of 32.5% of respondents prescribed drugs off-label, including 4.8% of physicians who prescribed drugs off-label frequently or very frequently.

The analysis of the information on the off-label administration of drugs in nearly half the cases showed that the drugs were used to treat patients with COVID-19 following the interim guidelines [15]. Although the results of the trial were distorted by the pandemic situation due to the attention of the majority of physicians being focused on treating patients with COVID-19, the literature shows that the largest proportion (67.2%) of off-label drug prescriptions were made in cardiology (code C in the WHO ATC classification), while the smallest proportion of drugs are prescribed off-label involve the urogenital system and sex hormones (code G). However, such drugs are rarely administered in this population [16].

In the trial carried out in the Russian Children's Clinical Hospital (Moscow), the proportion of off-label drugs administration varied from 17 to 96% in different departments. The most common incidences of off-label drug administration were connected with age limits (32%) [17].

It is of concern that 6% of physicians prescribing drugs off-label are confident that there are no risks involved with this practice, while 20% of respondents believe that the off-label drug administration does not affect te treatment efficacy. Despite potentially serious legal liability in some European countries, the situation with off-label drug administration here is also problematic. According to the trial by Saullo et al. [13], in which 85 physicians from the Pediatric Society of Calabria were surveyed, although 88% of experts did not have enough knowledge about the benefit-risk ratio of off-label drug administration, 40% of them often apply such practices regardless. The drugs most frequently administered off-label are used to treat respiratory diseases in children and patients at ages for which the drug is not recommended [13]. In

Figure 8. Structure of responses by risks associated with off-label drug administration



2016, Titov et al. [18] published a Russian study on off-label drug use in pediatric patients in 2012 and 2015. This found that pharmaceutical drugs associated with clinically significant drug therapy complications were prescribed off-label in 58.7 and 47.5% cases in 2012 and 2015, respectively.

While here is no standard legal procedure for assessing the actions of off-label prescribers in Russia, various indirect sanctions and regulations on the off-label use of drugs could involve legal liability on the part of an HCP or a medical facility [5].

Significant improvements have been made in the national pharmacovigilance system in terms of off-label drug administration. Health practitioners can make a significant contribution to the solution of this problem through the timely reporting of adverse reactions to pharmacovigilance authorities [19, 20].

Conclusion

Despite the relatively rare occurrence off-label drug administration as shown by the trial and available publications, the present survey showed significant demand for medical information on the risks of administering drugs off-label as part of clinical practice. This issue became particularly relevant in 2020 when pharmaceutical drugs were widely prescribed off-label to treat COVID-19. It is planned to repeat the assessment of off-label drug administration frequency following the end of the COVID-19 pandemic to compare the results.

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