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Off-Label Drug Use in Pediatric Practice: Unsolved Problems

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Wide off-label use of drugs and prescription of unlicensed drugs remains a relevant problem of practical healthcare in pediatrics. The article presents analysis of the current world and Russian regulatory and legal issues in the sphere of off-label use of drugs in children. Results of foreign and Russian scientific studies demonstrating scale and structure of off-label drug prescription at pediatric establishments of various profiles, which were conducted within the past few years, are provided. It has been shown that such a therapeutic practice increases the risk of development of adverse reactions to the drugs. The authors present recommendations on the provision of safer use of drugs in children. The priority tasks are completion of adequate clinical trials of the use of drugs in children, improvement of the national pharmacovigilance system in the sphere of off-label prescription control, development of pediatric formularies, promotion of physicians' awareness of efficacy and safety of use of drugs in children.

Keywords: *off-label use of drugs, unlicensed drugs, clinical trials, children, adverse reactions.*

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RELEVANCE

Prescription of drugs in violation of the recommendations given in the formally approved package leaflet is a relevant issue of global healthcare. In foreign countries, this phenomenon is widely called “off-label drug use”, that is the use of drugs for the indications, in the age groups, dosage and by means of the routes of administration, that have not been approved (according to the corresponding package leaflet).

The most frequent case of off-label prescriptions in clinical practice is therapeutic use of a drug in the age group of patients, wherein the use of the drug has not been approved; or when a drug is not indicated for a specific disease, even though most drugs of the same group have been approved for use in therapy of such a disease; or when a drug is not used according to the approved indications for treating terminal conditions for life-saving purposes. Also, physicians frequently fail to consider pathophysiological peculiarities of similar diseases and prescribe the same drug for corrective purposes if the patient has any of these diseases despite the drug being recommended only for one of these conditions [1]. For instance, use of metformin for therapy of pancreatic diabetes and insulin resistance, developing, for example, secondary to chronic virus

hepatitis C or polycystic ovarian syndrome [2], which are not listed under the package leaflet's heading "Indications".

It should be mentioned that some off-label prescriptions have become strongly rooted in broad clinical practice. Thus, according to clinical guidelines "Premature rupture of membranes" authored by specialists of the Federal State Budgetary Institution (FSBI) "Kulakov Scientific Center of Obstetrics, Gynecology and Perinatology", the recommended drug of choice for tocolysis is nifedipine – a slow calcium channel blocker [3]. However, despite a large number of completed clinical trials [4, 5], wherein this drug was at least as clinically effective and safe as other known tocolytics, according to the package leaflet, the nifedipine's indications are stable angina, Prinzmetal's angina and arterial hypertension.

Use of unlicensed medicines (drugs or therapeutic means not registered in the country of prescription [6]) also remains an urgent medical issue. In Russia, medicines are considered unlicensed if they are produced and approved for use in foreign countries and are not registered in the Russian Federation. Apart from that, unlicensed medicines traditionally include chemical substances used as drugs and modifications of the approved drugs [7].

One of the most vulnerable groups in terms of such use of drugs is children. Thus, the rate of off-label prescriptions to children varies considerably and in some countries may reach 80% [8]. Off-label prescriptions to children include use of a drug in children younger or older than the formally approved age (according to the package leaflet); prescription of a drug for unregistered indications; use of a drug in the presence of contraindications; use in the dosage different from the given in the drug's package leaflet, violation of the number of administrations and duration of use; prescription of adverse drug combinations; use by means of a route of a drug's administration not listed in the package leaflet [7, 9].

Most data on the activity of drugs used in pediatrics are taken from clinical trials (CT) with adult subjects; however, complete extrapolation of such data on children is forbidden [10]. A growing body is different from a mature one in terms of the receptor apparatus of tissues and organs, absorption mechanisms and excretion processes, qualitative and quantitative composition of protein fractions of blood plasma etc. This not only changes the drug's pharmacodynamics and pharmacokinetics, but also defines peculiarities of the drug's use in children. Moreover, drugs may specifically affect a child's physical and cognitive development, bone tissue, immune and sexual maturation [7, 10]. All these facts require CT of drugs involving children as subjects; however, the number of such trials remains low (due to objective reasons). That is why the issue of high rate of off-label and unlicensed drug prescriptions in children remains very urgent in medical practice.

REGULATORY AND LEGAL ISSUES OF NON-REGULATED USE OF DRUGS IN CHILDREN

Off-label use of drugs in the EU and the USA is not forbidden legally [11, 12]; the practicing physician is accountable for such prescriptions. In particular, the physicians prescribing a drug off-label must be convinced that use of the drug in violation of the approved instructions is necessary for a patient's well-being, rely on solid scientific evidence of the drug's rational use, as well as keep record of such prescriptions and the adverse reactions (AR) induced thereby.

According to clause 4, article 37 of Federal Law No. 323-FZ "On the basic principles of health protection in the Russian Federation" of November 21, 2011, medical care in Russia is based on the developed standards, including the drugs registered in the Russian Federation (RF), **which are prescribed in accordance with the package leaflet**. Clause 5, article 37 of Law No. 323-FZ stipulates "prescription and use of the drugs not listed in the corresponding medical care standard in the presence of medical indications (individual intolerance, life-saving indications) following a decision of the medical panel. Moreover, according to Order No. 494 "On the policy of using drugs for life-saving indications" of the Ministry of Healthcare and Social Development of August 09, 2005, "...if needed, individual use of a drug **not registered** in the Russian

Federation for life-saving indications. The decision of prescription of the mentioned drug is made by a council of a specialized federal medical organization, executed in a protocol and signed by the head doctor or the director of the specialized federal medical organization.”

The issue of off-label prescriptions to children is largely connected with the fact that introduction of new indications to a drug’s package leaflets and extension of the approved age range are usually initiated by a pharmacological company and requires new pediatric clinical trials, which is a labor-intensive, expensive and in many cases economically unsound process. Developing the practice of conducting clinical trials with children as subjects, the US (Food and Drug Administration, FDA) and the EU (European Medicines Agency, EMA) regulatory bodies were gradually (from 1997 to 2007) formulating legislation in this sphere [13]. The applicable legal framework obliges drug manufactures to conduct clinical trials on children if the drug is designed for subsequent use in this category of patients and publish the obtained results. Stimulating instruments were preserved after introduction of imperative pediatric trials, such as prolongation of the drug’s patent protection of 6 months, in some cases – state financial support. According to clause 5, article 43 of Federal Law No. 61-FZ “On the drug distribution” of April 12, 2010, completion of pediatric clinical trials is advisory rather than mandatory in the Russian Federation and is possible “only if such a trial is required to promote children’s health or prevent development of infectious diseases in children or if it is designed to obtain data on the best dosage of the drug under investigation for treating children.”

Despite the measures aimed at increasing the number of clinical trials with children as subjects taken by regulatory bodies of the USA and the European Union, their number remains limited. One of the reasons is that the decision of a child taking part in a clinical trial is made by his/her parents or caretakers. V. Bang et al. demonstrated that 59.8% of the surveyed parents would allow their children to take part in clinical trials only if the disease is life-threatening; 51.3% of the respondents would agree to a CT only if a child developed a chronic disease. The percentage of parents who would allow their healthy children to take part in a CT is far lower. At the same time, only 30% of the surveyed parents know that children may be prescribed drugs for unregistered indications, while 73% of them consider off-label prescriptions illegal [14].

FREQUENCY AND STRUCTURE OF OFF-LABEL AND UNLICENSED PRESCRIPTIONS IN CHILDREN IN TERMS OF EVIDENCE-BASED MEDICINE

F. Saullo et al. surveyed 85 physicians of the Calabrian (a large region in Italy) Society of Pediatrics and demonstrated that 88% of the interviewed specialists do not have sufficient knowledge of the risk/benefit ratio of off-label drug prescriptions, while 40% of them often resort to this practice. Most prescriptions in violation of the formally approved package leaflets and instructions are associated with the therapy of respiratory diseases in children and the treatment of patients younger or older than the formally approved age [15].

Out of 355,409 under-18 patients hospitalized to US hospitals in 2004 taking part in a retrospective cohort study, 297,592 (78,7%) received at least one off-label prescription. Such use of drugs cost \$270,275,849 – 40.5% of the total expenses on drug provision to the hospitalized children [16].

Similar results were obtained in a study conducted in Germany in 2003-2006. In the analyzed period, 3,610 subjects (40.2%) out of 8 899 children taking part in the study received 3,802 (30%) drug prescriptions considered off-label. 22% of these prescriptions were classified as use of the drug in the dosage not listed in the package leaflet, 4.3% - as prescription of the drug for unregistered indications, 3.8% - as use of the drug in children younger or older than the formally approved age. The rate of such prescriptions was higher among boys (41.4%; compare with girls – 38.9%) and in the age group of 3-6 years (48.7%). It should be mentioned that 61.2% of off-label prescriptions were made by physicians; in all other cases such a use of drugs was associated with self-treatment. Most prescriptions in violation of the package leaflet were associated with cardiovascular drugs (code C in the WHO Anatomical Therapeutic Chemical

[ATC] Classification System) – 67.2%; the least – with drugs for treating diseases of the genitourinary system and sex hormones (code G); however, drugs for these groups of diseases were prescribed to this population relatively rarely. The off-label use of drugs (according to the ATC Classification System) varies in different age groups in terms of the total number of prescriptions – most off-label prescriptions to under-2 children were related to drugs for treating sensory organs (code S), diseases of the respiratory system (code R) and antiinfectives for systemic use (code J). Most prescriptions in violation of package leaflets to children aged 3-10 years were related to the drugs affecting alimentary tract and metabolism (code A), as well as code R and S drugs, whereas in the older age group (11-17 years of age) most prescriptions were related to the drugs for treating diseases of the alimentary tract, sensory organs and dermatologicals (code D) [17].

According to other authors, many inhalation bronchodilators, antimicrobial drugs, anticonvulsants and proton pump inhibitors are often prescribed to children in violation of the approved instructions in the USA [1].

It should be mentioned that despite the increase in awareness of effectiveness and safety of use of many drugs in children, the rate of off-label prescriptions of drugs does not decrease, but grows progressively, as indicated by results of the prospective study conducted by L. Lindell-Osuagwu et al. In order to identify use of unlicensed drugs and rate of drug use in violation of package leaflets the authors analyzed prescriptions made by pediatricians at the neonatal intensive care unit, the department of surgery and the general pediatrics ward of a large university hospital in Kuopio (Finland) in the range of 2 weeks in April-May 2011. The obtained results were compared to the data on the same parameters obtained in 2001: 119 patients observed in a 2011 study received 1,054 prescriptions in total; the rate of off-label prescriptions reached 79% - 21% more than in 2001. Moreover, the number of such prescriptions to neonates increased either – 51% in 2011 vs. 22% in 2001 [18].

High spread of drug use in violation of approved package leaflets in children are clearly demonstrated by results of other foreign studies as well [19-21].

The issue of unlicensed and off-label prescriptions to children has been actively studied in Russia lately.

Results of analysis of 2,375 spontaneous reports on the development of AR in children in 2009-2011 registered in a Russian database (subsystem “Pharmacovigilance” of the automated information system of the Federal Service on Surveillance in Healthcare) indicate a high rate of drug prescriptions in violation of approved package leaflets. Thus, 398 (16.8%) of these reports indicate off-label use of drugs; the drugs contraindicated to the treated age group were used in 41% of the cases; the dosage different from the options listed in the instructions was prescribed in 20.6% of the cases; an unreasonable route of a drug’s administration was used in 20.6% of the cases; 17.3% of the reports contained information on prescription of drugs for unregistered indications. Most reports on the use of drugs in violation of approved package leaflets were related to antiinfectives for systemic use [9].

In 2006-2010, a project was conducted at the Moscow Kostlyeva Russian children’s clinical hospital (RCCH); it resulted in 300 spontaneous reports of adverse reactions in 249 patients. 226 reports were analyzed for off-label prescriptions; 47 reports (20.8%) contained information on such a use of drugs. The most common non-regulated prescriptions (42.6%) were related to antiinfectives for systemic use. Most violations of package leaflets were associated with overdosing (36.2%), violation of age restrictions (32%) and use for unapproved indications (19.1%). Two-tier violation of instructions was observed in 6 cases (12.8%) [22].

A study by Kolbin et al. conducted at the neonatal resuscitation unit of the Saint Petersburg children’s city hospital No. 1 was dedicated to assessment of the rate of use of unlicensed drugs and off-label prescriptions in two groups of neonates with very low birth weight (VLBW). The first group consisted of 250 patients with VLBW taking antiinfectives within the timeframe from April 2004 to April 2007, the second group – of 249 patients undergoing a similar therapy in 1999-2002. Integrated data of the pharmacoepidemiological study indicate that use of unlicensed

drugs and off-label prescriptions are observed in 29% of cases. The authors also mention a general tendency towards a considerable increase in the use of unapproved drugs by 2007 in comparison with the period from 1999 to 2002 [23].

Analysis of the Russian national pediatric formulary showed that out of 380 international non-patented drugs only 138 (37.3%) have clear indications for the use in children [24]. Thus, 2/3 of the drugs used for treating children in Russia have not been studied in clinical trials of this population and, therefore, are not approved for use in pediatric practice.

ROLE OF OFF-LABEL PRESCRIPTIONS IN THE DEVELOPMENT OF ADVERSE DRUG-INDUCED REACTIONS

A particular problem of off-label prescriptions is connected to the fact that use of unlicensed drugs or use of drugs in violation of the approved instructions leads to the development of unexpected effects and adverse reactions more often than use of licensed drugs for approved indications. Results of an 8-month prospective pharmacoepidemiological cohort study of the patients hospitalized to the pediatric box unit of the Erlangen-Nurnberg university hospital (Germany) indicate a higher risk of AR development when drugs prescribed off-label are used. 156 children receive 740 drug prescriptions in total; 198 of the prescribed drugs (27.7%) were unlicensed or used in violation of instructions. 46 AR were registered in 31 patients within the observation period; only 5 of these patients were taking drugs in accordance with package leaflets [25].

A case-control study by J.R. Bellis et al. conducted in the framework of a prospective cohort study involved children aged from several days to 16 years hospitalized to inpatient hospitals of Liverpool (England) within the timeframe from October 01, 2009, to September 30, 2010. Cox regression model of proportional hazards was used to evaluate the impact of drug prescriptions in violations of recommendations of the formally approved instructions on the development of AR. 1,388 patients were prescribed 10,699 pharmacotherapy courses in total. The odds ratio of impact of unlicensed or off-label prescriptions on the development of AR in comparison with the drugs prescribed in accordance with approved instructions was 2.25 (95% confidence interval – 1.95-2.59).

Use of drugs in children younger or older than the approved age range led to adverse reactions more often than any other type of off-label prescriptions (odds ratio – 3.54; 95% CI – 2.82-4.44). Each additional use of drugs in violation of instructions led to an increase in the risk of AR development (odds ratio – 1.3; 95% CI – 1.2-1.3; $p < 0.001$) [26]. The listed data indicate danger of such a use of drugs in children.

T. Mukattash et al. conducted a first study of opinions of children on off-label drug prescription to children; it involved 123 students aged 10-16 years. It demonstrated that children are aware of the possible risks associated with such a use of drugs and consider an increase in the number of pediatric clinical trials necessary [27].

CONCLUSION

Thus, it is evident that off-label drug use in pediatric practice remains an urgent global issue. Progress in treatment of children cannot be achieved without large controlled clinical trials dedicated to effectiveness and safety of drugs in children. Extension of indications and age ranges, analysis of new dosage regimens and routes of drug administration in children should be considered one of the top-priority spheres of activity of pharmaceutical companies. An important condition of conducting clinical trials with children as subjects for Russian pharmaceutical associations is their ability to perform such trials in strict correspondence with the approved international requirements.

It is also necessary to improve the national pharmacovigilance system in the sphere of off-label prescription control. Practicing physicians may make a considerable contribution to the

resolution of this issue by means of timely reporting of the detected AR and other problems associated with off-label prescription of drugs to regulatory pharmacovigilance bodies. Making a decision to prescribe a drug to a child attempting to achieve the best clinical result, doctors should ultimately follow instructions listed in the formally approved drug package leaflets. If off-label prescription of drugs is unavoidable, doctors should follow recommendations of the national pediatric formulary and make their decisions on the basis of the reliable evidence-based data on effectiveness and safety of the prescribed drugs for the specific pathology (special literature, official web-sites). In any case, one should remember and follow the key principle of medicine – *primum non nocere*.

CONFLICT OF INTEREST

The authors of this article have declared absence of reportable financial support / conflict of interest.