GOOD PHARMACOVIGILANCE PRACTICE IN PEDIATRICS: PECULIARITIES OF UNLICENSED AND OFF-LABEL DRUG USE AMONG ADOLESCENTS OF CONSCRIPTION AGE

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Introduction. The safety of drug use in pediatrics remains one of the key global problems given the fact that the prescribing of medicines outside the instructions for their use (also known as the off-label medicines use), as well as the use of pharmacological agents that are not officially licensed for use in children (unlicensed), are both quite common and necessary phenomena due to the lack of special pediatric medicines for 75% of children's diseases.

The purpose. To outline main features of unlicensed and off-label drug use among adolescents of conscription age taking into account good pharmacovigilance practice in pediatrics.

Materials and methods of the research included bibliographic method, as well methods of system analysis and system approach, and also method of generalization and information synthesis.

Results. Good pharmacovigilance practices in pediatrics take into account several interdependent considerations regarding the detection of adverse reactions in children, in particular adolescents of conscription age, among which it is worth highlighting the consequences of the availability of limited data on the long-term use of drugs in the pediatric population and/or the insufficient possibility of involving this category of patients in premarketing clinical trials because of various reasons. Involving children in clinical trials can present challenges, such as scientific, clinical, ethical, and logistical concerns that have previously limited or prevented drug testing among children, particularly adolescents of conscription age. In addition, due attention should be paid to the appropriateness and timeliness of the implementation of educational and professional standards "pharmacovigilance professional" in institutions higher medical education of Ukraine, namely Bogomolets National medical university, and in the Register of Qualifications, respectively, whereas the training and retraining of specialists in the field of pharmacovigilance will contribute to greater awareness of future doctors and pharmacists on the detection and prevention of the occurrence of drugs ADRs, in particular in adolescents of conscription age, and this, in turn, will minimize the unlicensed use of medicines by new generation of pediatricians to children and expand their vision of adjusting the doses of drugs in the pediatric population during their off-label use, and will also facilitate timely reporting of adverse drug reactions to the State Expert Center of the Ministry of Health of Ukraine and, in general, will reduce the tendency of insufficient notification of drugs ADRs, in particular in children, among healthcare professionals.

Conclusion. Promoting continuity between pediatric drug development and risk management activities is key to improve these activities each other. Additional key aspects that can make pediatric medicines safer include training healthcare professionals/carers to enhance the identification and reporting of ADRs, in particular by implementation of educational and corresponding professional standards of "pharmacovigilance professional", and increase the level of pediatric engagement in pharmacoepidemiology. This will ensure the most appropriate use of medicinal agents among children so that drug use can be based on well-grounded information and thus off-label drug use can be adjusted and unlicensed medicines use can be decreased as well.

Key words: pharmacovigilance, pediatrics, adverse drug reactions, pediatric pharmacovigilance, good pharmacovigilance practices, off-label drug use, unlicensed drug use.

Introduction. The safety of drug use in pediatrics remains one of the key global problems given the fact that the prescribing of medicines outside the instructions for their use (also known as the off-label medicines use), as well as the use of pharmacological agents that are not officially licensed for use in children (unlicensed), are both quite common and necessary phenomena due to the lack of special pediatric medicines for 75% of children's diseases [1].

Pharmacology faces specific tasks to ensure the needs of pharmacovigilance among the pediatric population in order to minimize the risks of adverse drug reactions (hereafter – ADRs) in children, in particular adolescents of conscription age. Since the pharmacokinetic and pharmacodynamic safety profiles of drug use in children of various ages differ from the specified safety profiles in adults due to the anatomical and physiological features of the growing body, and the risk / benefit indicator of each individual drug also has its differences in the long term, pharmacovigilance in patients of children's age, including conscription one, requires separate regulation. In October 2018, after a public discussion, the European Medicines Agency (EMA) officially approved the "Guideline on good pharmacovigilance practices Product- or Population-Specific Considerations IV: Paediatric population" in order to overcome challenges related to the safety of the use of medicines in pediatrics, that will improve the practice of
existing pharmacovigilance procedures, highlighting the responsibilities and roles of each stakeholder in pediatric healthcare. These pediatric good pharmacovigilance practices expanded and supplemented the existing pediatric regulations (No. 1901/2006), which were put into effect in 2007 to ensure the compliance of drugs with the therapeutic needs of children [6].

The use of medicinal agents off-label and unlicensed among children and adolescents of conscription age in particular poses a significant public health concern as the pharmacological effects and potential health risks may remain unpredictable. First study in this area was performed in 1953 by the pediatrician F. Dost who claimed, that children’s pharmacokinetics differs from adults’ one, and drugs administration to child organism in reduced doses must not occur. As the corresponding processes vary in children’s organism (including drugs absorption, distribution, metabolism, and excretion), children have special needs concerning their diseases and drugs dosages, and also special medicinal forms are required to administer adequate doses to this vulnerable cohort of patients. Particularly children of young age are unable to swallow tablets properly and are extremely sensitive to the taste of medicines. Nevertheless, enormous number of drugs is not specifically developed for children. Among medicinal agents which were licensed by the European Medicine Agency (hereafter - EMA) between 1995 and 2005 only 1/3 was specifically officially suitable for children. There is a hope that this situation will improve with the introduction of Pediatric Good Pharmacovigilance Practices, which entered into force in 2018, but there is a high level of off-label drug use in children so far. Global studies on different levels report a widespread rate of off-label drug use in children and adolescents, taking into consideration adolescents of the conscription age, reaching from 3.2% to 80% [4].

**Aim of the research.** The paper aimed to outline main features of unlicensed and off-label drug use among adolescents of conscription age taking into account good pharmacovigilance practice in pediatrics.

**Materials and methods** of the research included bibliographic method, as well methods of system analysis and system approach, and also method of generalization and information synthesis.

**Results and their discussion.** Good pharmacovigilance practices in pediatrics take into account several interdependent considerations regarding the detection of adverse reactions in children, in particular adolescents of conscription age, among which it is worth highlighting the consequences of the availability of limited data on the long-term use of drugs in the pediatric population and/or the insufficient possibility of involving this category of patients in premarketing clinical trials because of various reasons. Involving children in clinical trials can present challenges, such as scientific, clinical, ethical, and logistical concerns that have previously limited or prevented drug testing among children, particularly adolescents of conscription age.

Most of the information about the effect of medicines used in pediatrics is borrowed from clinical trials with the participation of adults, however, due to the peculiarities of the growing child’s body, it is not always possible to transfer this information in its entirety to a child.

Despite the measures taken by the US and EU regulatory bodies to increase the number of clinical trials in the pediatric population, their number is still limited [2]. For example, as of May 2017, 30 332 clinical trials were registered in the EU clinical research register, of which 4681 clinical trials involved children, which is only 15.4% of the total number of conducted studies. Instead, these indicators as of August 2023 are 43 635 clinical trials in general, including 7225 clinical trials involving children, which is 16.6% of the total number [3]. Thus, analyzing the above indicators, we can observe an increase in the specific weight of clinical trials with the participation of children in the EU by 1.2% over the past 6 years, which, however, remains insufficient to avoid medication errors and improve the monitoring of ADRs. Also, these administrative measures did not have a significant impact on the frequency of use of unlicensed drugs and the number of off-label prescriptions.

A similar trend is connected, among other things, with the fact that the decision on the child’s participation in a clinical trial is made by his parents or legal representatives. As the research of Bang V. and co-authors showed, an extremely low percentage of parents agreed to participate in clinical trials of their healthy child. At the same time, only 30% of the parents who participated in the survey are aware of the possibility of prescribing drugs for children for unregistered indications, and 73% consider off-label prescribing to be illegal [5].

In addition, due attention should be paid to the appropriateness and timeliness of the implementation of educational and professional standards "pharmacovigilance professional" in
institutions of higher medical education of Ukraine, namely Bogomolets National medical university and also in Ukrainian military medical academy, and in the Register of Qualifications, respectively, whereas the training and retraining of specialists, in particular military and medical specialists, in the field of pharmacovigilance will contribute to greater awareness of future doctors and pharmacists on the detection and prevention of the occurrence of drugs ADRs, in particular in adolescents of conscription age, and this, in turn, will minimize the unlicensed use of medicines by new generation of pediatricians to children and expand their vision of adjusting the doses of drugs in the pediatric population during their off-label use, and will also facilitate timely reporting of adverse drug reactions to the State Expert Center of the Ministry of Health of Ukraine and, in general, will reduce the tendency of insufficient notification of drugs ADRs, in particular in children, among healthcare professionals.

Conclusions
1. Pediatric drug development in the EU has improved after the publication of the Pediatric Regulation (which may serve a good role model for our country), resulting in several pediatric indications were added for medicines already authorized in adults and a growing number of pediatric indications for innovative medicines may be observed.

2. By additionally enforcing the current legislation and encouraging different stakeholders to concentrate on specific priorities in the preparation of their pharmacovigilance activities we can reach the same outcome, and the Pediatric Good Pharmacovigilance Practices will promote a more reliable pharmacovigilance system in the EU and in this or that kind in Ukraine subsequently.

3. Promoting continuity between pediatric drug development and risk management activities is key to improve these activities each other. Additional key aspects that can make pediatric medicines safer include training healthcare professionals/carers to enhance the identification and reporting of ADRs, in particular by implementation of educational and corresponding professional standards of "pharmacovigilance professional", and increase the level of pediatric engagement in pharmacoepidemiology. This will ensure the most appropriate use of medicinal agents among children so that drug use can be based on well-grounded information and thus off-label drug use can be adjusted and unlicensed medicines use can be decreased as well.

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Мета дослідження. Стаття мала на меті орієнтувати основні особливості unlicensed та off-label застосування ліків серед підлітків призовного віку з урахуванням належні практики фармаконагляду в педіатрії.

Матеріали та методи дослідження включали бібліографічний метод, як і методи системного аналізу та системного підходу, а також метод узагальнення та інформаційного синтезу.

Результати та їх обговорення. Належні практики фармаконагляду в педіатрії враховують декілька взаємозалежних міркувань стосовно виявлення побічних реакцій у дітей, зокрема підлітків призовного віку, серед яких варто виділити наслідки наявності обмежених даних про довгострокове застосування ЛЗ в педіатрічній популяції та/або недостатню можливість залучення цієї категорії пацієнтів до племпермаркетингових клінічних досліджень з різних причин. Залучення дітей до клінічних випробувань може стикається з певними викликами, як-от наукові, клінічні, етичні та логістичні занепокоєння, які раніше обмежували або взагалі неперспективну стимуляцію тестування ЛЗ серед дітей, зокрема підлітків призовного віку.

Крім того, слід приділити належну увагу доцільністі та своєчасній впровадженні освітньої та професійної стандартизації фармаконагляду в закладах вищої медичної освіти України, а саме в Національному медичному університеті імені О.О. Богомольця, та в Реєстрі кваліфікацій відповідно, оскільки підготовка та перепідготовка фахівців у галузі фармаконагляду сприймається більшою обширою, ніж бажаними міркуваннями лікарів та фармацевтів з питань виявлення та попередження виникнення ПР ЛЗ, зокрема у підлітків призовного віку, й це, в свою чергу, зведе до мінімуму призначення педагогами нової генерації медикаментів unlicensed дітям та розширити їх бачення стосовно корекції доз ліків в педіатрічній популяції під час їх застосування off-label, а також сприятиме своєчасному підходу до професії реакції ЛЗ в Державному експертному центрі МОЗ України і в цілому знизить тенденцію до недостатнього сповіщення про ПР ЛЗ, зокрема у дітей, серед спеціалістів галузі охорони здоров’я.

Висновок. Сприяння безперервності між розвитком дитячих ліків та діяльністю з управління ризиками є ключовим для того, щоб ця захист могла покращити один одного. Додаткові ключові аспекти, які можуть зробити дитячі лікарські засоби безпечнішими, включають підготовку медичних працівників/опікунів для підвищення виявлення та звітності про ПР ЛЗ, зокрема шляхом імплементації освітньої та інформаційної стандартизації фармаконагляду в закладах вищої медичної освіти України. Це забезпечить найбільш доцільне застосування ЛЗ серед дітей, так що вживання ліків може бути засноване на добре обґрунтованій інформації, і, таким чином, використання ЛЗ off-label може бути скоригованим, а також використання нерегламентованих лікарських засобів може бути зменшеним.

Ключові слова: фармаконагляд, педіатрія, побічні реакції лікарських засобів, фармаконагляд в педіатрії, належні практики фармаконагляду, застосування ліків off-label, застосування ліків unlicensed.

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