NORMATIVE DISSONANCE IN PEDIATRIC PHARMACOTHERAPY: BIOETHICAL ANALYSIS

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In this paper, we present a comprehensive bioethical and regulatory analysis of the use of drug therapy in children with oncological, rheumatological, cardiological and psychiatric diseases in the Russian Federation based on official Instructions for Medical Use and the latest clinical recommendations. This paper focuses on significant contradictions between clinical recommendations and drug registration documents registered in the State Register of Medicines of Russia. Insufficient scientific data on safety and effectiveness of medicines among children deserve particular attention as it results in serious therapy restrictions worsened by regulatory and legal barriers for pediatricians. The study is focused on medications for treatment of follicular lymphoma, systemic lupus erythematosus, schizophrenia and familial hypercholesterolemia, with an emphasis on age restrictions and contraindications.

Key words: follicular lymphoma, systemic lupus erythematosus, schizophrenia, familial hypercholesterolemia, pediatrics

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НОРМАТИВНЫЙ ДИССОНАНС В ПЕДИАТРИЧЕСКОЙ ФАРМАКОТЕРАПИИ: БИОЭТИЧЕСКИЙ АНАЛИЗ

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В статье представлен комплексный биоэтический и нормативный анализ применения медикаментозной терапии у детей с онкологическими, ревматологическими, кардиологическими и психиатрическими заболеваниями в Российской Федерации на основе официальных инструкций по медицинскому применению лекарственных препаратов и современных клинических рекомендаций. Основное внимание уделено выявлению существенных противоречий между клиническими рекомендациями и регистрационными документами лекарственных средств, зарегистрированных в государственном реестре лекарственных средств. Особое значение уделено проблеме отсутствия достаточной доказательной базы по безопасности и эффективности лекарственных препаратов у детской аудитории, что приводит к значительным ограничениям в назначении терапии, усугубляемым нормативными и правовыми барьерами для врачей-педиатров. Исследование охватывает лекарственные средства, применяемые при лечении фолликулярной лимфомы, системной красной волчанки, шизофрении и семейной гиперхолестеринемии, с акцентом на возрастные ограничения и противопоказания.

Ключевые слова: фолликулярная лимфома, системная красная волчанка, шизофрения, семейная гиперхолестеринемия, педиатрия

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A contradiction between the latest clinical recommendations and Instructions for Medical Use registered in the State Register of Medicines of Russia is an essential problem of pediatric pharmacotherapy. Some drugs recommended for treatment of adults lack prospective studies in pediatrics or are prohibited for use in children due to the absence of data on safety and effectiveness. Thus, significant difficulties for doctors in choosing therapy arise [1]. Because of the failure to perform prospective pediatric research or because of the lacking data on safe and effective treatment in children, it is difficult for doctors to supply children with access to certain medicinal preparations used in adults [1].

The goal of this study is to provide for a comprehensive bioethical and regulatory evaluation of drug therapy in children with oncological, rheumatological, cardiological and psychiatric diseases in the Russian Federation, to identify contradictions between clinical recommendations and official Instructions for Medical Use, and to highlight the ways to minimize regulatory and legal barriers to improving pediatric pharmacotherapy.

MATERIALS AND METHODS

Research analyzes Instructions for Medical Use of the medicinal products registered in the State Register of Medicines of Russia (as of August 2025) and the latest clinical recommendations for pediatric patients. Medicinal preparations were chosen based on four groups of diseases: oncological (follicular lymphoma) [2], rheumatic (systemic lupus erythematosus) [3], psychiatric (schizophrenia) [4] and cardiological (familial hypercholesterolemia) [5]. Contraindications, Pediatric population and Age groups were examined for each medicinal product. Methods of comparative analysis used in this paper allowed to identify discrepancies between clinical guidelines

Table. The most significant data on indications and contraindications for use of the investigational preparations in pediatric population with regard to age limitations and special conditions of use [1]

Group of diseases	Medicinal product, INN	Approved for use in children	Age limitation/notes[6]
Oncological diseases			
Follicular lymphoma	Mosunetuzumab	No	Do not use the drug in children below 18 years of age due to potential lack of effectiveness and safety (safety and effectiveness of Lunsumio® in children below 18 years of age have not been established yet)
	Bendamustine	No	Bendamustine-TL: Contraindications: pediatric population (lack of effectiveness and safety data)
	Obinutuzumab	No	Do not use the drug in children below 18 years of age due to potential lack of effectiveness and safety (safety and effectiveness of Gazyva® in children below 18 years of age have not yet been established)
	Lenalidomide	No	Do not use Mielanix in children below 18 years of age, as safety and effectiveness of the drug in children below 18 years of age have not yet been established
	Rituximab	No	Do not use Mabthera® 1400 mg in children and adolescents below 18 years of age
Rheumatic diseases			
Systemic lupus erythematosus	Methotrexate	Yes	Children and adolescents: do not use Methotrexate in children below 3 years of age due to limited effectiveness and safety data. When Methotrexate is used as an immunosuppressant to suppress immunity in children (in psoriasis, rheumatoid arthritis, juvenile chronic arthritis, dermatomyositis, and systemic lupus erythematosus), determine the appropriate risk/benefit ratio.
	Ciclosporin	Yes	Patients below 18 years of age: patients below 18 years of age may exhibit faster recovery of Ciclosporin as compared to adults. Therefore, pediatric patients require higher doses of Ciclosporin per kilogram of body weight to achieve the desired drug concentrations in the blood.
	Azathioprine	Yes	Overweight children: in a clinical trial, 18 children (3 to 14 years of age) were undergoing maintenance treatment with 6-MP, whereby the body surface was the basis for the dose calculation. The average area under the concentration-time curve from time zero to infinity (AUC0-∞) of 6-MP in the group greater than the 75th percentile was 2.4 times lower than that in the group less than the 75th percentile. Therefore, overweight children may need higher Azathioprine doses, and close monitoring of their response to treatment is advised.
	Cyclophosphamide	Yes	Rhadbomyosarcoma in children: Cyclophosphamide is used in complex polychemotherapy regimens depending on the stage of a disease and histological type of tumor. In standard cases, dose for III (residual macroscopic tumor after surgery) and IV (remote metastases) stage patients is 10 mg/kg of body-weight IV for 3 consecutive days. The treatment is repeated multiple times in combination with Vincristine and Actinomycin D (rhadbomyosarcoma international study II that established the VAC-protocol).
	Prednisolone	Yes	Do not use the preparation in children under 3 years of age
	Methylprednisolone	Yes	Methyliof must be cautiously used in children. The physician should carefully control growth and development of children who have been treated with Methyliof on a continuous basis. Children receiving prolonged daily therapy divided into several doses may have growth retardation. Long-term daily use of the product is possible only in children on absolute indications. Administration of the drug every alternate day may reduce the risk of the adverse effect or allow to avoid it. Children receiving long-term therapy with Methyliof are high-risk due to increased intracranial pressure (intracranial hypertension). High doses of Methylprednisolone can result in inflamed pancreas (pancreatitis) among children.
	Mycophenolic acid	No	Children and adolescents: children under 18 years of age should not be given the product due to non-effectiveness and probable lack of safety (safety and effectiveness of Mycophenolic acid in children under 18 years of age have not been established)
	Belimumab	Yes	Benlysta is used to – reduce disease activity in patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) receiving standard therapy; – treat active lupus nephritis in patients aged 5 years and older in combination with standard background immunosuppressive therapy.
	Tofacitinib	No	Children under 18: Children under 18 should not take Tofacitinib for rhematoid arthritis, psoriatic arthritis, ulcerative colitis, ankylosing spondylarthritis, novel coronavirus infection caused by COVID-19, as effectiveness and safety have not been established. Children aged 2 to 18 years: Tofacitinib might be used as monotherapy or in combination with Methotrexate for polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis (see Administration of Tofacitinib). Children under 2 years old: children under 2 years of age must bot be given the drug for polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis as its effectiveness and safety have not been established.
	Hydroxychloroquine	Yes	Contraindications: children under 6 years of age.

Table (continued)

Group of diseases	Medicinal product, INN	Approved for use in children	Age limitation/notes[6]
Psychiatric disorders			
Schizophrenia	Heloperidol	No	Children and adolescents: Heloperidol must not be used in children and adolescents under 18 years of age due to the lack of data on effectiveness and safety in this group of patients.
	Olanzapine	No	Children and adolescents: the drug must not be used in children under 18 years of age due to the lack of data on effectiveness and probable safety in this group of patients. Olanzapine must not be used in children and adolescents under 18 years of age.
	Clozapinum	No	Children and adolescents under 18 years of age (effectiveness and safety have not been established)
	Aripiprazole	Yes	Aripiprazole pharmacokinetics are comparable between children aged 10–17 years old and adults. Thus, no body weight correction is required.
	Quetiapine	No	Contraindications: children under 18 years old (effectiveness and safety have not been established)
	Chlorpromazine	Yes	Indications: it can be used in adults and children (1 year of age and older)
	Thioridazine	Yes	Indications: disturbed behavior and symptoms of a psychomotor activity
	Levomepromazine	No	Do not take Tisercin® if you are under 12 years of age
	Sulpirid	No	Children: safety and effectiveness of the drug in children under 18 years of age have not been established. Sulpirid is contraindicated in children under 18 years of age.
	Periciazine	Yes/No (depending on the dosage form)	1.Contraindications: children under 18 years of age (for capsules). 2. Neuleptil® can be used in children older than 3 years of age for severe behavioral disorders, agitation, and excitation.
	Biperiden	Yes	Biperiden is approved for use in children aged 3 years and older and adults
Cardiological diseases			
Familial hypercholesterolemia	Rosuvastatin	No	Safety and effectiveness in children below 18 years of age have not been established; limited drug data are available
	Bempedoic acid	No	Safety and effectiveness in children below 18 years of age have not been established; limited drug data are available
	Inclisiran	No	Safety and effectiveness in children below 18 years of age have not been established; limited drug data are available
	Fenofibrate	No	Safety and effectiveness in children below 18 years of age have not been established; limited drug data are available
	Omega 3 unsaturated fatty acids	No	Safety and effectiveness in children below 18 years of age have not been established; limited drug data are available
	Ezetemibe	Yes	Officially approved in children who are 10 years of age and older
	Evolocumab	Yes	Officially approved in children who are 10 years of age and older
	Simvastatin	Yes	Officially approved in children 10 years of age and older
	Atorvastatin	Yes	Officially approved in children 10 years of age and older
	Alirocumab	Yes	Contraindicated in children under 8 years of age due to the lack of data on safety and effectiveness for this group of patients.
	Pitavastatin	Yes	It is contraindicated in children under 6 years of age due to the lack of sufficient clinical data for this age group

and official instructions, reveal regulatory and bioethical aspects, and detect key challenges of choosing drug therapy in underage patients. This complex approach ensures systemic understanding of the problem and offers solutions.

RESEARCH RESULTS

Analysis of Instructions for Medical Use of the medicinal products during the research has shown as follows. The majority of registered medicinal products to treat oncology (follicular lymphoma) including Mosunetuzumab, Bendamustine, Obinutuzumab, Lenalidomide, and Rituximab are contraindicated for use in children under 18 years of age due to the lack of established safety and effectiveness data [6]. It significantly limits the choice of therapy in children and adolescents. The rate of rheumatic (systemic lupus erythematosus) drugs approved for pediatric pharmacotherapy was higher. Methotrexate, Ciclosporin, and Azathioprine can be used in the pediatric population but with regard to their age and need for proper monitoring of a patient's clinical condition [6]. Mycophenolic acid and Tofacitinib are contraindicated to children under 18 years of age due to the risk of non-effectiveness and potential side effects. Belimumab is used in patients aged 5 years and older in the presence of certain indications. Research has shown that the majority of antipsychotic agents (to treat schizophrenia) such as Haloperidol, Olanzapine, Clozapinum, Quetiapine, and Levomepromazine are contraindicated to children and adolescents under 18 [6]. However, Apiprazole and Chlorpromazine are approved for use

in pediatric pharmacology though additional consideration with regard to special conditions and age limitations is required. Certain drugs such as Periciazine and Biperiden have been approved in some children and adolescents depending on the dosage form and age. While studying cardiological drugs (to treat familial hypercholesterolemia), it has been established that some more frequently used statin-containing and lipid-lowering drugs such as Rosuvastatin, Bempedoic acid, Inclisiran, Fenofibrate and Omega-3 are contraindicated in children and adolescents under 18 due to the lack of safety and effectiveness for children. Meanwhile, Ezetimibe, Evolocumab, Simvastatin, Atorvastatin and Alirocumab are used in children with age restrictions, usually from 6–10 years of age. Pitavastatin should not be given to children under 6 years of age [7].

Thus, document analysis highlights significant gaps and limitations in the regulation of drug therapy in children with severe diseases. To ensure a wide and safe use of drugs in pediatric pharmacotherapy, further research and review of established standards are required.

The table presents the most significant data on indications and contraindications for use of the investigational preparations in pediatric population with regard to age limitations and special conditions of use.

If prescribing the drugs in pediatrics is associated with limitations, an obligatory collective decision is required. The therapeutic indications require prior medical consultation with a complex assessment of the possible risk and benefit ratio [8].

Documentary analysis shows significant gaps in the evidence and regulatory base regarding drug therapy of children with severe diseases. The obtained regulatory restrictions do not only narrow the therapeutic arsenal of a pediatrician but also underline the vital need in targeted clinical trials and subsequent review of regulatory documents. This is an essential condition for expanded possibilities of safe and effective use of novel medicinal products in pediatric practice.

COCLUSIONS

Thus, pediatric pharmacotherapy comes across an entire set of objective limitations that significantly narrow the therapeutic arsenal of a physician. The gap in evidence base seen among pediatric patients is the key factor that forms the basis of the issue. The gap is due to a number of challenges faced by pharmaceutical companies during organization of clinical trials. The challenges include an exceptional complexity of methodological planning, required ethical regulations and extremely high cost of such a research. As a result, the doctor is often forced to extrapolate the data obtained in the adult population, which inevitably involves an increased share of risk and professional responsibility.

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