Drug Development and Rational Use of Drugs

Rational Use of Drugs: Pharmaceutical Aspects of the Drug Selection

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Abstract

In this article, the problems encountered in the rational use of drugs are discussed, one of the areas of optimization of drug supply being the rational choice of drugs, particularly, a regulatory activity regarding the approach to the selection of standardized drug lists (drug formulary) for public drug supply, according to government guarantees and programs. The clinical aspects of the drug selection are expounded in detail. The characteristics of the drugs (original or generic drug (generics), the origin of drugs and the breadth of therapeutic index), have been taken into account. Certain stages have been analyzed, particularly drug use in individual diseases, drug selection, expert drug evaluation, and expert recommendations to include specific drugs in the drug list. Organizational steps have been proposed to implement the rational choice of drugs to be included in the drug formulary. IJBM 2012; 2(3):237-241. © 2012 International Medical Research and Development Corporation. All rights reserved.
Key words: rational use of drugs, drug selection, drug formulary, clinical aspects of drug selection.

Introduction

The problem of the rational use of drugs (DGs) is under the constant attention of the World Health Organization (WHO). To solve this problem WHO has implemented several steps [1]. The development and regulation of the use of the drug formulary that guaranteed by the government for health care based on the stage, type of aid and the therapeutic needs of the population are some of the most important activities that contribute to improving the drug supply to the population.

The study of legal documents regulating the organization of drug supply in the Russian Federation (at the level of federal subjects and medical organizations), revealed several flaws in tackling this problem (absence of territorial drug formularies for the hospital and emergency care, drug lists based on individual programs in the health care system etc.). The ineffectiveness of the implementation of the formulary system starting with the medical organization was marked, particularly with respect to the activities of the formulary committees and the availability of drug formularies not being observed in all health care organizations and the lack of drug selection criteria for inclusion of drugs in the formulary not concurring with the rational selection criteria, etc. In light of this situation, it is advisable to formulate and regulate specific approaches to drug selection at the territorial level, to provide the government guarantee in providing quality health care. Subsequently, the territorial drug formulary of the federal subjects of Russia should be regulated to set the standard for forming a drug list for the medical organization (MO) based on the specific structure of the MO and morbidity [2, 3].

The aim of this study is to offer optimal regulatory activity of applying the provisions of the formulary system.

Material and Methods

Normative legal acts and other regulatory documents in the field of medical and pharmaceutical activity include, drug supply, typical clinical and pharmacological articles and formularies, standards of health care and clinical guidelines for the treatment of diseases, reference books on drugs;

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survey data of the managers of the MOs and the results of scientific research in health care and pharmacy. The system, process and information analysis, management-audit, direct observation, comparative analysis, logical modeling, sociological methods (surveys, expert opinions, etc.) are applied.

Results

Organizational-pharmaceutical approaches were developed for the selection and use of DGs (drawing up of formulary lists at the territorial level), which include the organizational and clinical aspects of drug use (Fig. 1).
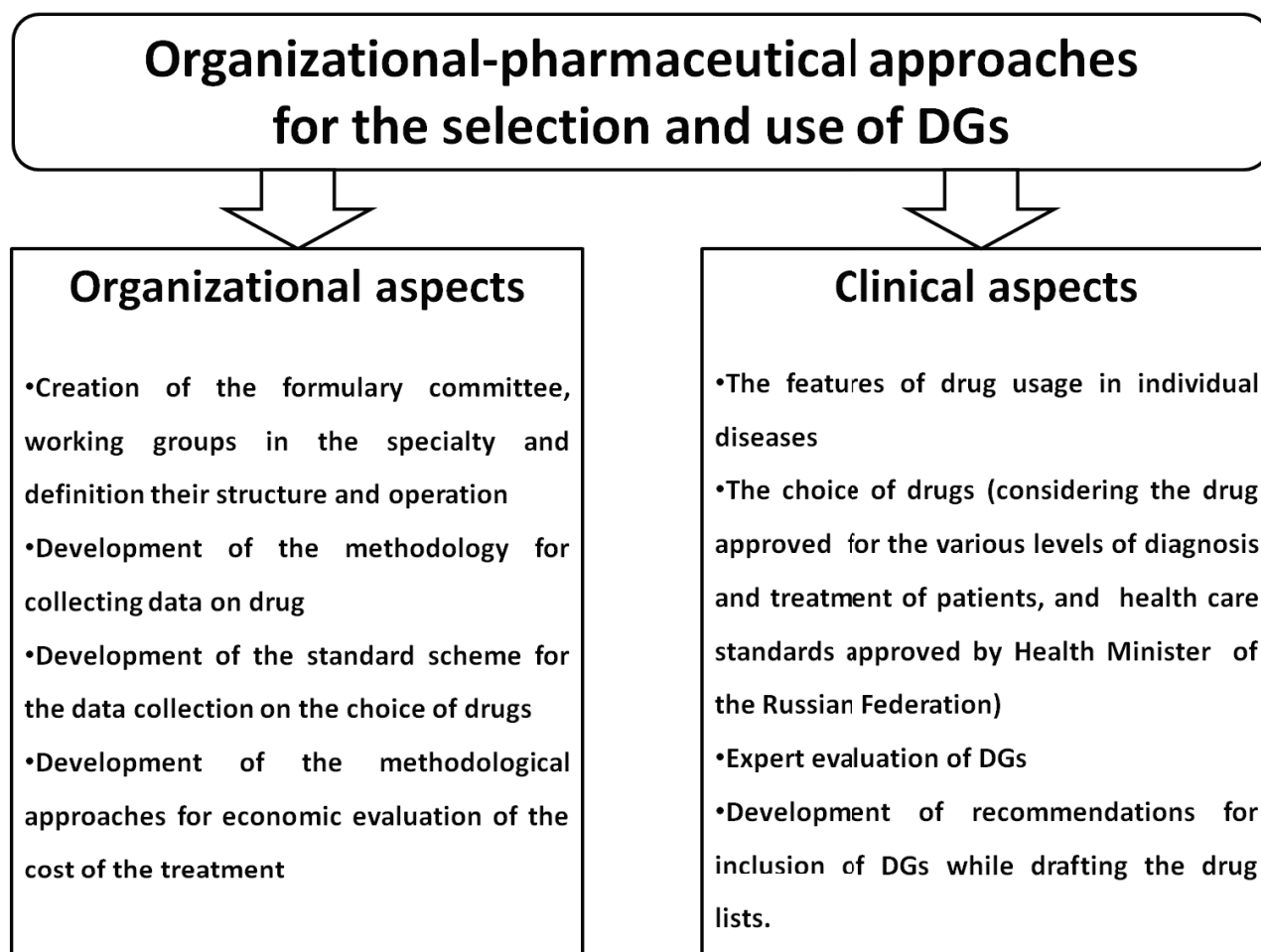
Currently, leading scientists have been paying minute attention to study and develop recommendations on the implementation of organizational approaches in the field of health care and pharmacy [4]. However, the clinical aspects of the choice and drug use have no less significance in the rational application of the drugs. Clinical aspects of the implementation of the formulary system involve a review of the characteristics of drug use in individual diseases, an expert drug evaluation, and the development of expert recommendations to include pertinent drugs in the drug list.

Discussion

The specialty of the drug as a product, which powerfully affects the functioning of the organs and organ systems of organisms, is predetermined by several factors, some of which are highlighted below: original drug or generics, the breadth of the therapeutic index, the origin of drugs, etc. The problem of the nonequivalent efficacy and safety of the generic version of the drug relative to the original drug is well recognized. Only by conducting direct comparative studies on the therapeutic equivalence between the original drugs and their generic forms, which are registered on the national market, will we get the required data necessary for the recognition of the equivalence of the generics in efficacy and safety. According to the Russian Federation's (RF) rules of legislation, a compact procedure of assessment including an expert evaluation of the generics is conducted for government registration of drugs. By implementing such a procedure, the information, which is obtained from clinical trials and published in the specialized press, as well as documents containing the results of the bioequivalence and (or) therapeutic equivalence of the drug for medical use, is presented [5]. The lack of mandatory requirements in the RF for the research of therapeutic equivalence of generics

Figure 1
The scheme of organizational and pharmaceutical approaches to the selection and use of drugs.

Organizational-pharmaceutical approaches for the selection and use of DGs

Organizational aspects

- Creation of the formulary committee, working groups in the specialty and definition their structure and operation
- Development of the methodology for collecting data on drug
- Development of the standard scheme for the data collection on the choice of drugs
- Development of the methodological approaches for economic evaluation of the cost of the treatment

Clinical aspects

- The features of drug usage in individual diseases
- The choice of drugs (considering the drug approved for the various levels of diagnosis and treatment of patients, and health care standards approved by Health Minister of the Russian Federation)
- Expert evaluation of DGs
- Development of recommendations for inclusion of DGs while drafting the drug lists.

against the original product determines the probability of occurrence of the substitutive drug that exerts a therapeutic effect, although not equal to the effect of original drug in the RF market. Among the large quantity of drugs, circulating in the Russian market is a group of drugs possessing a narrow therapeutic index. The use of drugs with such narrow therapeutic index calls for a careful selection of the effective dose for each patient, a balanced assessment in the choice of drug for the treatment and the possibility of generic substitution. Any change in the drug in such cases could lead to an unexpected deterioration of the patient's condition, either until deprivation of the effectiveness of the therapy or exacerbation of the disease or ultimately, hospitalization [6-9].

All drugs traded in the pharmaceutical market can be distinguished into two groups:

- DGs obtained by direct chemical synthesis (simple chemical, organic and inorganic compounds)
- DGs obtained by biotechnological production (DGs of biological origin).

DGs of biological origin differ from DGs produced by chemical synthesis in the size and complexity of the active substance; the inability to fully determine the molecular structure with modern analytical methods (referring to the complexity of the spatial structure); the heterogeneity of the product; the safety and effectiveness, depending upon the source material and manufacturing process; high sensitivity to the effects of the various factors (dosage form, transportation, storage conditions); and the ability to provoke an immune response in the organisms they are administered to treat [10].

The difficulty (impossibility) in replicating each of the production stages of the biotechnologically produced drug with very slight changes in the production process may contribute to the development of unpredictable changes in the clinical effects of the drug. Given these features, European and U.S. legislations have called for specific requirements for the generic registration of drugs of biotechnological origin [11].

The Russian legislation, however, neither specifies any particular definition of «biotechnological drug» nor provides mandatory requirements for registration or conducting post-marketing studies on such drugs. The Federal Act «On the inversion of drugs» specifies the impossibility of conducting a compact procedure of expert evaluation of immunological drugs, insulin and drugs registered for the first time in the Russian Federation [5].

Interestingly, even after the establishment of specific requirements, the regulatory authorities of Europe and America do not guarantee the interchangeability of the biotechnological drugs and analogs against traditional generics. In this respect, several countries use legislation to control the possibility of replacing biological drugs. Thus, some countries either prohibit the replacement of biological drugs with biosimilars (which is a replacement in pharmacy without clear indication from a physician) or do not recommend the replacement of biological drugs in the biosimilars. Among the regulatory sanctions can emphasize the prohibition to prescribe DGs of biological origin on INN (International Nonproprietary Names). Thus, these aspects point to the urgent need for precise regulation of the choice and use of generics.

The features of drug usage in individual diseases.

To implement the rational choice of drugs, certain aspects must be considered. Therefore, certain classes of diseases necessitate the use of drugs with extremely high sensitivity in patients, and some diseases necessitate the use of drugs with a narrow therapeutic index. According to the literature and clinical observations, epilepsy, schizophrenia, asthma, chronic renal failure, cancer, pain, and others constitute the classes of diseases in which the patients are particularly sensitive to a change in the equivalent therapeutic doses (on changing the brand of the drug) [13-15].

Given these features, some countries advocate a cautious approach to the replacement of the original drugs with generics to treat these diseases. For example, Spain does not permit replacing the drug in the treatment of asthma; in Denmark, the same applies to drugs used in the treatment of epilepsy; in Finland the drugs used to treat epilepsy, as well as insulins, immunoglobulins, vaccines, and anticancer drugs too cannot be replaced [12, 16, 17].

The choice of drugs.

In order to systematize the process of drug selection, a basis (including the territorial ambit of diagnosis and treatment of diseases, federal standards of health care, clinical guidelines and self-selected experts) must be established, for the formation of the drug list. Additionally, experts must be called in to develop the most important criteria determining the choice of drugs for inclusion in the formulary list. It is also important to regulate the possibility of the following types of substitution: replacement of one drug with another within the pharmacotherapeutic group; replacement of one dosage form with another; replacement of the original drug with generics, replacement of one generic with another generic form.

Expert evaluation.

To obtain the necessary information to select the inclusion drugs in the formulary list, it is necessary to conduct a series of consecutive tests such as: VEN-analysis [18], pharmaceutical expertise [19], frequency analysis, level of evidence of clinical efficacy, results of ongoing pharmacoeconomic studies, besides others [20].

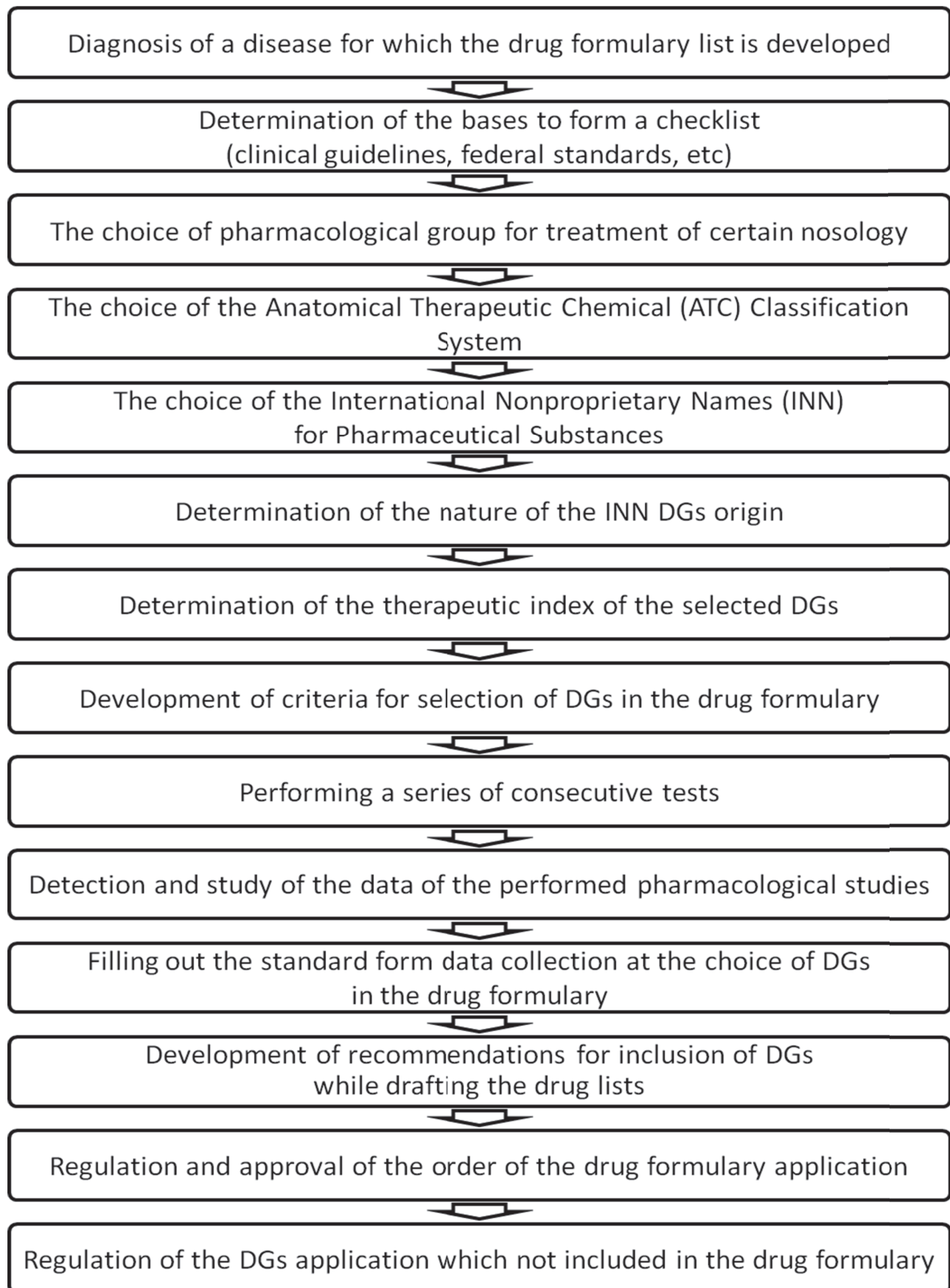### Development of recommendations for inclusion of DGs while drafting the drug lists.

After all the work is completed, suggestions on including drugs in the formulary list are included. It is possible to form several itemizations in the drug formulary: a basic list of DGs, an additional list of DGs (replacement options, drugs prohibited from the basic list), the list of drugs used in health care through voluntary health insurance, the list of drugs in the provision of paid medical services, etc.

Conclusion

The aspects discussed above made it possible to

Figure 2
The algorithm of rational drug choice for inclusion in the drug formulary.

Diagnosis of a disease for which the drug formulary list is developed

Determination of the bases to form a checklist
(clinical guidelines, federal standards, etc)

The choice of pharmacological group for treatment of certain nosology

The choice of the Anatomical Therapeutic Chemical (ATC) Classification
System

The choice of the International Nonproprietary Names (INN)
for Pharmaceutical Substances

Determination of the nature of the INN DGs origin

Determination of the therapeutic index of the selected DGs

Development of criteria for selection of DGs in the drug formulary

Performing a series of consecutive tests

Detection and study of the data of the performed pharmacological studies

Filling out the standard form data collection at the choice of DGs
in the drug formulary

Development of recommendations for inclusion of DGs
while drafting the drug lists

Regulation and approval of the order of the drug formulary application

Regulation of the DGs application which not included in the drug formulary

develop the algorithm of rational choice of drugs for inclusion in the drug formulary.

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