Annals of Academy of Romanian Scientists
Online edition *Series: Medical Sciences*
ISSN 2285-4150 Volume 1, Number 1/2010

DRUG INFORMATION RESEARCH CENTER – PROMOTING THE RATIONAL USE OF MEDICINES FROM 2004

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Abstract. *Research and new medical knowledge in past decades had lead to uncommon increase of the quantitative and qualitative information on pharmacotherapy. There are new modern therapies and a vast number of drug products available on the market. It is not humanly possible to remember the vast information on drugs. There has also been a great explosion in the number of biomedical journals published each year. In this context, one of the most important prerequisites concerning the selection of drugs for rational pharmacotherapy is the availability and easy access to independent, objective, unbiased information about drugs.*

Keywords: drug information, rational drug use, drug safety.

Introduction

The concept of evaluating published research is not new, but the concept of evidence-based medicine expands to include the use of best-practice guidelines and databases in order to make healthcare decisions. Accordingly to US Pharmacopeia, it is an approach to 'practicing medicine in which the clinician is aware of the evidence in support of clinical practice and the strength of that clinical evidence'. "Evidence-based" is a term often used to describe medically-related reference resources. Unfortunately, sometimes it is used indiscriminately and without merit. For a clinical reference resource to truly be called evidence-based, conclusions must be based on the best available evidence. This can happen only if the evidence is consistently and systematically identified, evaluated and selected.

The provision of accurate and timely drug information to healthcare professionals is an important mechanism to promote safe and effective drug therapy. The term 'drug information' was coined in the early sixties and the first drug information center was opened at the University of Kentucky Medical Center in 1962 [1].

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Drug Information Centers are service units committed to 'providing drug information as it relates to therapies, pharmacoeconomics, education, and research programs' (US Pharmacopeia). In order to establish a Drug Information Center, a program must first meet specific criteria to provide dedicated space, trained staff, regular hours of operation, and sufficient reference and technological resources.

The first only self-existent Drug Information Research Center (DIRC) was established in Romania in March 2004 at the School of Pharmacy, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca with funding from the United States Pharmacopeia and United States Agency for International Development and from a CNCSIS grant. The center is a regional, pharmacist-operated, and free of charge service for healthcare professionals working in the area of Cluj-Napoca.

A major awareness program regarding the use of the service provided by the DIRC was conducted for physicians during their clinical meetings, in the first year of the center's existence. Over 20 clinics in Cluj-Napoca were covered during this program. During every meeting there was a short talk on drug information rendered by the center and the physicians were encouraged to send queries to the center by e-mail, fax or phone. The physicians and pharmacists could also visit the center in person to get information.

The organization of DIRC and its activities are similar to others analogous academic centers in other countries [2, 3]. The center is staffed by two researcher pharmacists trained in providing drug information and in pharmacovigilance. The center closely collaborates with specialists from the Pharmacology, Pharmaceutical Chemistry, Toxicology and Vaccines and Biological Medicines Department from the School of Pharmacy.

The DIRC primary role is "to give clear and definitive information on well-established essential drugs and promote their rational use". A secondary role would be "to keep up-to-date with pharmacological and therapeutic literature and to disseminate relevant information, as it becomes available" (US Pharmacopeia).

Over the last 5 years since the center was established, the services provided and the educational and research activities have become more complex.

The everyday service provided by DIRC include answering the physicians and pharmacists queries, information retrieval, review of the literature, tracking and evaluating adverse drug reactions and interactions.

The majority of inquiries are from hospital pharmacists and specialists, followed by general practitioners and the staff from the University. The most frequent questions involve basic information about drugs, adverse drug reactions, interactions, dosing in children or patients with renal and hepatic impairment, pharmacotherapy during pregnancy and lactation, comparative

efficacy and evaluation with other therapies. The queries are recorded using a customize software made for entering all the data and compare it with previous data. Some of the main reference books available at the center and used for information retrieval are listed in **Table I**. The center also has access to Micromedex Healthcare Series and to secondary indexing and abstracting databases like Medline, Cinahl, Science Direct, Springer link, Thomson ISI.

AHFS Drug Information
Meyler's Side Effects of Drugs
Stockley's Drug Interaction
Drugs in Pregnancy and Lactation
Applied Therapeutics
Pharmacotherapy
Martindale
USP DI Volumes I, II, and III
Drug Prescribing in Renal Failure
Nelson Textbook of Pediatrics
Handbook on Injectable Drugs
Drug Induced Diseases-Prevention, Detection and Management
Harrison's Principles of Internal Medicine
Goodman & Gillman's The pharmacological basis of therapeutics

Table I. Tertiary literature available at the DIRC

Despite the complexity of adverse drug reactions and drug interactions, most physicians are still keen to manage most cases on their own. The information on such management, though available, is not always easily acquired in a timely manner that would help expedite the management of these patients. Here the role of the DIRC would be to bridge this gap and offer timely and accurate information on how to best manage these situations as the drug information needed is readily available and easily accessed at the DIRC. Also the collaboration that the center have with specialists experienced in various aspects of pharmacology and toxicology will be further plus points that allow physicians to better manage their patients. We consider that all this expert advice service on pharmacological and toxicological problems is currently a

necessity for assisting the physicians in their decisions, taking into account the complexity of today's therapeutic agents and their potential adverse reactions and interactions.
Another responsibility of the DIRC staff includes assisting students and residents in learning to use information resources available at the center.

Past Educational Programs at DIRC

The Avian Flu Campaign
As one of its community services, DIRC initiated a campaign to raise awareness of avian influenza (AI) among pharmacists, physicians but also among schoolchildren in Cluj and neighboring counties.
In October 2005, in the south of Romania, a number of cases of avian influenza at the domestic birds were reported and the information provided by media was sometimes misleading, an awareness campaign on the subject was considered necessary. In the same time people from Cluj-Napoca were concerned about the risks, asking questions about the methods to prevent contamination with this new virus. The center also received a lot of questions from pharmacists and physicians on this topic.
The program was initiated at the end of October 2005, when DIRC elaborated informative leaflets for patients and a guide for general physicians and pharmacists. The guide included detailed information about the morphology of influenza viruses, genetic variability of virus, epidemiology, symptoms and complications. It also included information about the need for vaccination with influenza virus vaccine and about other alternative treatments in order to increase immunity. It was distributed to more than 200 physicians and pharmacies in Cluj-Napoca.
As in March 2006 there were new reports of avian flu in other districts from Romania, the DIRC started a new prevention campaign, "Stop Avian Flu", addressed to scholar children from villages around Cluj-Napoca. The DIRC staff educated over 2800 schoolchildren about Avian Flu and its prevention through leaflets, posters, and classrooms visits. The staff spoke to the children about prevention methods and the importance of proper hand washing. The leaflet and the poster are presented in **Figure 1 and 2**.

How to fight with avian influenza?

1. What is avian influenza?

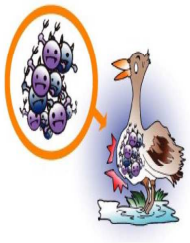
Avian influenza is a type of influenza. It was known previously to infect birds only, but human cases were reported, too.

2. What are the symptoms of avian influenza?

The initial symptoms of avian influenza are similar to those of other influenza viruses, including:

- ✓ fever,
- ✓ headache, muscle pain,
- ✓ runny nose, cough and sore throat.

However, it is more likely to develop complications and death.



3. How is avian influenza transmitted?

Avian influenza is transmitted from infected live birds to humans through direct or close contact. Human-to-human transmission has been reported very rarely.

4. Who is susceptible to contracting the disease?

People in close contact with sick poultry are more susceptible to contracting avian flu.

6. What can you do to prevent avian influenza?

- ✓ Avoid touching live or dead poultry or their droppings.

- ✓ Wash your hands thoroughly with soap and water immediately after contact with live or dead poultry, birds or their droppings

- ✓ Develop good body resistance by:
  - A healthy alimentation: vegetables, fruits
  - Physical exercises
  - Rest

- ✓ A good personal hygiene:
  - Clean clothes
  - Washing hands frequently
- ✓ Cover your nose and mouth while sneezing or coughing.
- ✓ **Tell your parents:**
  - To cook well the poultry meat and the eggs.
  - To not use the same dish for fresh meat and for cooked meat
  - To keep the birds in a cage
  - To air the room
  - To talk to your doctor if you are feeling sick.

Campanie iniţiată de UMF Iuliu-Haţieganu, Centrul de Informare asupra Medicamentului, U.S. Pharmacopeia şi Inspectoratul Şcolar Judeţean Cluj

Figure 1. General information and prevention methods leaflet

Figure 2. 'How to wash your hands' poster

Patient Education – a need for the rational use of antibiotics

Antibiotic resistance is a topic that has been approached ever since the first antimicrobial agent was introduced into therapy in 1940. Antibiotic resistance has been a prevailing issue world wide and mortality and morbidity associated to infectious diseases have increased along with therapy costs. There are several predisposing factors determining antibiotic resistance, the abusive use of antibiotics being one of the major factors.

Inappropriate prescription and use of antibiotics have been identified as major factors determining the increase of antibiotic resistance. Fighting antibiotic resistance requires the constant effort of health care authorities as well as the collaboration of physicians, pharmacists and patients. The constant contact with physicians and patients allows pharmacists to reduce antibiotic resistance through education [4].

The DIRC initiated a study followed by an educational program were patients were instructed regarding the use of antibiotics in case of flu and cold symptoms.

The study conducted by our team included a set of questionnaires and it was carried out in two stages:

Stage I – *pharmacists*, who work in community pharmacies in Cluj-Napoca, were asked to fill in a questionnaire with five questions and a section for suggestions. The questionnaire aimed to find out the way antibiotics are sold in pharmacies, if they are sold only with medical prescription and if pharmacists consider the appropriateness of initiating a campaign for patient information on the rational use of antibiotics. The questions required a simple answer.

Stage II – filling in of a questionnaire by the *patients* asking for antibiotics, especially by those who ask for the drug without medical prescription. After the completion of such a questionnaire each patient received a leaflet regarding the use of antibiotics for flu and cold symptoms.

The study results demonstrated that there was a need for a campaign for patient education in terms of the rational use of antibiotics, especially for those patients who asked for antibiotics without having a prescription for their flu and cold symptoms [4].

Encouraging adverse drug reactions reporting through the National Spontaneous Reporting System

In the past decades, spontaneous reporting systems were used for continuous, systematic surveillance for adverse drug reactions (ADRs), monitoring the safety of drugs after marketing and offering a fast and cost-efficient method of detecting ADRs. Inside this system, physicians report suspected associations between adverse reactions and drugs to a National or Regional Pharmacovigilance Center, on a voluntary basis.

Unfortunately, in Romania this system suffer from a high level of under-reporting since 363 adverse drug reactions were reported in 2008 at the National

Pharmacovigilance Centre within the National Drug Agency as compared with 22500 ADRs reported in France and 24616 in England.
The factors that cause this considerable degree of under-reporting of ADRs in Romania must be studied and understood, as this would enable the National Pharmacovigilance Center to take the appropriate measures to increase the reporting rates.
In this context we conducted a survey in order to assess the physicians' attitude towards voluntary reporting of ADRs, to study the factors involved in their decision for reporting or not an ADR and their knowledge regarding which ADR is essentially to report. A total of 200 questionnaires were distributed, 172 were returned complete, all analyses being therefore made on the completed questionnaires. 68% responders from the total number of physicians stated that they are not familiar with the Romanian National Spontaneous Reporting System (SRS). Further results of this study are presented in a previous published paper [5].
Taking into account the results of this study DIRC developed and distributed a *'Guide to Detecting and Reporting Adverse Drug Reactions'* in order to help health professionals to participate in the very important process of continuous surveillance of safety of the medicines which are used in their clinical practice. The main purpose of the guide was to raise awareness of the magnitude of the drug safety problem and to convince health professionals that reporting of adverse drug reactions is their moral and professional obligation.
Besides the educational programes developed for healthcare professionals and for patients, two **round tables** were organized by the DIRC:
„Challenges of antibiotics therapy"
The debated themes were:
- ✓ Antimicrobial agents use in renal and hepatic failure,
- ✓ Antimicrobial agents - drug interactions – clinical consequences,
- ✓ Bacterian resistance to antibiotics,
- ✓ Antibiotic associated colitis.

„Rheumatoid arthritis – modern therapeutic trends"
The themes discussed were:
- ✓ Principles of rheumatoid arthritis diagnostics,
- ✓ Principles of rheumatoid arthritis diagnostics,
- ✓ Drugs in arthritis rheumatoid,
- ✓ Monoclonal antibodies. New methods of obtaining monoclonal antibodies and uses of pharmaceutical forms,
- ✓ Anticytokine therapy in Rheumatoid Arthritis.

Present Perspectives – Drug Safety Research Studies at DIRC

Primum non nocere ('first of all be sure you do not harm') Hippocrates

The drug safety field has been receiving a lot of attention lately and it had also arisen the public interest, especially after some major recalls of popular medication worldwide, the most pertinent being the rofecoxib withdrawal in 2004 [6].

Regulatory authorities approve medicines based on the benefit-risk profiles under clinical trials conditions. But the safety profiles of drugs are dynamic and established over time by strict analysis of all data regarding connected issues. Pharmacovigilance, defined by the World Health Organization as being 'the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems' plays a key role in drug safety, ensuring that the patients receive safe medicines. The main concern of pharmacovigilance is to detect adverse drug reactions in terms of clinical nature, severity and frequency, as early as possible and with minimum patient exposure.

By the time of licensing, a drug was tested during clinical trials for short-time efficacy and safety on a limited number and carefully selected individuals; usually as few as 500 and rarely more than 5000 patients will have received the drug before its approval [10]. This provides limited statistical power. The most common type A adverse drug reactions (reactions that are an augmentation of the drug's pharmacological action) may already have been detected by the time of the drug authorization. On the contrary, type B adverse reactions (that are considered the patients' reactions and are not related to the known pharmacology of the drug), which are usually uncommon, are being detected only after licensing through postmarketing surveillance.

Therefore, for good reason, it is essential that new, but also well-known and trusted medicines are being continuously monitored for their safety under real-life utilization. More information is generally needed about their use in special population groups as children, pregnant women and the elderly and about their safety and efficacy in chronic use, especially in combination with other medicines. The risk factors and the drug-drug and drug-food interactions may usually come to light only after years from the approval of the drug [7, 8].

Although efforts for rational drug use are constantly made in order to decrease the frequency of adverse effects, numerous studies have demonstrated that the incidence of adverse drug reactions leading to patient hospitalization is ranging from 4 % up to 7,2%, the percentage of adverse drug reactions in hospitalized patients being even higher, up to 20% [9-11]. When it comes to the elderly population, this percentages may be even higher (up to 61,8%), inappropriate prescription being the leading cause for adverse drug reactions [12]. The most

common adverse reactions detected in these studies are type A, dose-dependent reactions, though predictable from known pharmacology of the drug. Adverse reactions can also occur as a consequence of drug interactions, though they can be considered preventable too. These percentages are high, proving that adverse drug reactions still represent a burden for the patients and for the public health systems.
Many published papers, including one published in the Romanian literature, intended to clarify the adverse drug reactions terminology that is still causing confusion among the healthcare professionals and to describe the appropriate approach for the recognition, attribution of causality and management of ADRs [13].
There are no recent adverse drug reactions monitoring studies taking place and being published in the Romania. Information on adverse drug reactions can only be collected if physicians report on a voluntarily basis using the National Spontaneous Reporting System.
As adverse drug reactions (ADRs) represent a major problem of the public health system, often leading to patient hospitalization, increased hospitalization periods and costs, the DIRC proposed, developed and implemented an intensive monitoring system in order to detect, evaluate and characterize adverse drug reactions and other drug-related problems in two departments of internal medicine in Cluj-Napoca. With the close collaboration of the physicians working in the two departments, we intend to evaluate the consequences of ADRs, their incidence and their preventability. In the first year since the system was implemented through a research grant, we already detected more than 130 ADRs that were serious enough to lead to hospitalization or to prolong the existing hospitalization. We also developed a database were the identified and evaluated ADRs are being stocked and which will be used for quantitative analysis using data-mining algorithms and generation of signals.
Other drug safety studies taking place at the DIRC include 'Monitoring the short and long-term safety of methylphenidate and atomoxetine in children with ADHD', 'Incidence and characterization of selective serotonine reuptake inhibitors adverse drug reactions directly reported by patients', 'Characterization and management of adverse drug reactions in patients with Hepatitis C', 'Risk factors in patients with anticoagulation therapy and INR ≥4' and 'Non-adherence as risk factor in diabetic patients with cardiovascular risk'.
Although there have been many attempts to improve the post-authorization surveillance of drugs, patients have participated directly in only a few of them. Patients are the ones who directly benefit from drugs but also experience their adverse effects. At an international level, in recognition of the fact that the patients are directly affected by ADRs and that they may notice features that otherwise might go unrecognized, patients are now able to directly report their side effects and participate to the spontaneous reporting system. [14]. In its drug

safety monitoring actions, DIRC proposed an on-line adverse drug reaction system were patients can directly report suspected adverse drug reactions.

Proactive safety surveillance of influenza A (H1N1) vaccines

In the recent A (H1N1) influenza pandemic context and the DIRC' participation to the EMEA - European Network of Centers for Pharmacoepidemiology and Pharmacovigilance, an influenza A (H1N1) vaccine pharmacovigilance strategy should be developed.

Limited data on the safety of influenza A (H1N1) vaccines will be available when Member States will start using them on a large scale in the course of the current influenza pandemic. Proactive post-authorization safety surveillance will have to be conducted to detect and assess adverse events following immunization (AEFIs) that may affect the benefit-risk profile of vaccines.

DIRC is planning to develop and implement two methods of proactive detection of AEFIs and one prospective observational study. The two methods aimed at detecting the adverse events are:

✓ A web-based ADRs reporting system which will be available for the vaccinated population;

✓ 200 general physicians from Cluj-Napoca will be passively reporting all adverse events and actively all pre-defined adverse effects of special interest (anaphylaxis, fever, seizures, convulsions, neuritis, Guillan-Barre syndrome, thrombocytopenia).

The observational prospective study will assess the vaccine safety in a cohort of 250 vaccinated healthcare professionals. The healthcare providers will be monitored at 3-5 days, one month, 3 and 6 months after the vaccination. The immune response after the vaccination will also be determined in a subgroup of this cohort.

Short conclusion

The use of medicines is an important aspect of clinical practice and of the public health system. Medicines are important not only because of their capacity to treat and to prevent diseases, but also because of the patients' confidence in the health system in their countries which is linked to the use of safe and effective drugs. Rational drug utilization has a direct impact on the patients and on drug related complications. The Drug Information Research Center can offer helpful, unbiased and objective information that can reduce the occurrence of drug-related problems. Information gathered during the drug safety studies taking place at DIRC may also assist in selecting the most appropriate drug for a patient, so that medicines can be used in an informed manner with the least chance to harm. This paper wants to emphasize the importance of drug information obtained through research studies and critical literature evaluation, towards drug safety and rational drug use.

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