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# Pharmacoepidemiology

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***Abstract :*** *Pharmacoepidemiology is a branch of science that analyzes in a great number of people the usage, effects and costs of medication. Its most important aim is to define, describe medication treatments, estimate medication usage and effects by determining populations in a specific place and time. The importance of pharmacoepidemiology occurs when the pharmacological effects, adverse effects and interactions of the medications are ignored. The discipline, when not considered sufficiently, has a potential that could cause a high-level of increase in health expenses by creating conflict in the health systems of countries. In this study, it is aimed to define pharmacoepidemiology, to analyze its relation with other disciplines and to inform about pharmacoepidemiology usage areas.*

***Keywords*** *- pharmacoepidemiology, epidemiology, drug utilization*

## I. INTRODUCTION

In the recent years it can be seen that, concerns about drug safety have increased and studies regarding this issue have proliferated. While drug use ensures that patients receive better medical care, it can also cause more serious damages. Especially in foreign countries, there are enormous numbers of lawsuits being filed against pharmaceutical producers. Each year in America due to medicinal side effects 100,000 people lose their lives and 1.5 million people are hospitalized. It has been stated that 20 to 70 % of these hospitalizations are preventable cases [1]. These disservices caused by medicinal side effects have resulted in the development of the field of pharmacoepidemiology which investigates drug use by, and medicinal effects on, large numbers of people and drug costs.

The discipline of pharmacoepidemiology is considered to be very important on several accounts and to have a potential for growth in the future. Its features such as allowing better quantification of medicinal side effects, easily acquiring new information types which were not available in pre-marketing studies, as well as providing information on the characteristics of drug use, the effects of drug over-use and the effects of drug use on the economy increases the attention given to the discipline of pharmacoepidemiology everyday. In this study, the purpose is to define the discipline of pharmacoepidemiology, determine its points of divergence from clinical pharmacology, epidemiology and pharmacoeconomy, provide information about its areas of application and speculate on the future of the discipline.

Pharmacoepidemiology is a discipline which gained currency in the early 1980s when medicinal side effects were beginning to be studied by applying epidemiological methods. After the public, regulatory agencies and the industry started to have increased concerns over medicinal safety, drug surveillance and implementations of epidemiological techniques increased and pharmacoepidemiology began to be recognized as a new discipline [2]. In the recent years, especially the number of pharmacoepidemiological researches published in scientific medical journals has increased [3].

Pharmacoepidemiology investigates medicine use by, and the effects of medicine on, a larger number of people as well as the cost of drugs (pharmacoeconomy). Pharmacoepidemiological studies are focused at the level of society and are about health events regarding drug use [4]. Situations related to drug use can be beneficial or harmful and voluntary or involuntary. Therefore, the most important purpose of pharmacoepidemiology is to define populations in specific times and places and identify and explain drug treatments and make estimations about their uses and effects [5]. The concept clearly involves two components: "Pharmaco" and "epidemiology".

In order to study the effects and uses of drugs in communities, pharmacoepidemiology utilizes the methods of epidemiology. Understanding the basic principles of epidemiology is a prerequisite to understanding pharmacoepidemiology. Methods such as case reports, case series, ecological studies, case-control studies, cohort studies and randomized clinical trials which are used in epidemiological studies are also applied in pharmacoepidemiological studies. A case report in pharmacoepidemiology is a report on a single patient who has been using a drug and has experienced a specific – generally negative – result. In a case series, information regarding patients who have used a single drug or have experienced a common result is collected and their clinical results are evaluated. Ecological studies analyze long term trends; it investigates trends which appear in a specific time period or geographical area. In case-control studies, sick cases are compared and contrasted with

a healthy control group. In cohort studies, a group being treated with a drug and a comparison group are defined and they are followed over a time period by comparing the differences in their results. Comparison can be between drug users and non-users or between users of different drugs. The main aspect of randomized clinical trials is the random dispersion of patients in order to receive the relevant treatment; thereby the study groups are made as comparable as possible [1].

Pharmacoepidemiology is being used more commonly in order to evaluate healthcare systems and health-related behaviors. It is considered as the scientific backbone of therapeutic risk management. The reason is that pharmacoepidemiology investigates the benefits and risks, development, application and processes of strategy evaluations of a drug [6]. Subjects such as causality and repetition rates in reverse drug reactions, efficiency of new drugs in defined populations, drug prescription models and variations in certain healthcare facilities and areas and strategies to improve drug prescription constitute the field of interest of pharmacoepidemiology [1].

## II. THE HISTORICAL DEVELOPMENT OF PHARMACOEPIDEMIOLOGY

Drug regulations in many developed countries have the aim of ensuring safe and efficient drug provision with the participation of governments. The history of drug regulations in the USA starts with The Pure Food and Drug Act of 1906 which was designed to prevent food and prescription drug frauds and wrong labeling. The Pure Food and Drug Act movement is considered to be important because it constituted a proof of the efficiency and safety of the marketed drugs [7]. The act which was formed in this scope has given the authority to stop the sale of any drug only to the state. Widened into Food, Drug and Cosmetic Act movement in 1938, it imposed obligations on producers such as creating clinical data on drug safety and presenting the drug to the FDA before marketing [1].

It is seen that until the 1950s not enough attention has been paid to the side effects of drugs. During that period, attention was drawn to the issue when chloramphenicol, which is a type of antibiotics, began to cause aplastic anemia; the first book on the side effects of drugs was published by Meyler in 1952 with the title Side Effects of Drugs. After 1960, the FDA began to collect reports on the side effects of drugs and to support drug surveillance programs. In 1961, because a drug known as "the thalidomide disaster" increased birth defects which had previously been seen very rarely, the issue began to attract more attention [8]. The World Health Organization created a working group on the issue. For this purpose, The Committee on Safety of Medicines was formed in England in 1968 and the Medicines Act of 1968, which stressed license authorization, became a topic of discussion [9].

While in the past only the safety of drugs was being monitored, after the thalidomide disaster in 1962 changes were made in implementation [10]. With the 1962 reforms the FDA was given the authority to evaluate the efficiency of drugs and providing "solid proof of a drug's significant effects" became a new requirement in the US in addition to the drug clinical trials. This process which involved sufficient and well monitoring of drugs resulted in long drug approval periods in those days [1]. At this point, it can be said that one of the important issues discussed during the 1970s and 1980s in the US and Europe was delays in drugs [11][12]. It is seen that delays in drugs began to attract more attention with the increased fatalities in AIDS patients during the 1980s. In 1988, a group that wished to attract attention to the AIDS-related deaths protested against deaths caused by delays in drugs. When the same situation caused problems in the treatments of cancer and heart diseases the question 'whether the state, which is responsible for protecting patients from harmful or ineffective drugs, actually creates bigger problems for them' began to be asked [10]. Delays caused by drug approval processes increased the costs and exposed the patients to more difficult situations. However, it has been seen that delays in drugs which caused many problems during that period allowed safe and efficient drugs to be marketed in the future [1].

In the mid-1960s there were a series of publications on drug use [13][14]. These studies first of all provided descriptive information on how doctors utilize drugs and started a series of studies on the frequency and determinants of bad drug prescription. Based upon these developments it is considered that the 1960s is the beginning of the discipline of pharmacoepidemiology. New methods to investigate serious and infrequent drug effects observed in a large number of patients began to be searched; and the direction of the studies headed towards side effect case studies [1]. With the Boston Collaborative Drug Surveillance Program a hospital-based case study on hospitalized patients began and data on patients' life time drug exposure have been collected [15]. The Joint Commission on Prescription Drug Use is known as a committee of interdisciplinary experts formed to review the discipline of pharmacoepidemiology. The establishment of the Drug Epidemiology Unit in 1970 has contributed greatly to the historical development of pharmacoepidemiology [1].

## III. THE RELATIONSHIP BETWEEN PHARMACOEPIDEMIOLOGY AND OTHER DISCIPLINES

Pharmacoepidemiology has relationships with many disciplines [5][16][17][18]. Foremost among these are clinical pharmacology, epidemiology and pharmacoeconomy.

### 3.1. Clinical Pharmacology

Pharmacoepidemiology is the implementation of epidemiological methods, knowledge and logical justifications in the field of clinical pharmacology via focusing upon studies on the drug effects on, and drug use by, large numbers of people. Therefore it can be accepted as a sub-branch of clinical pharmacology. Pharmacology is the investigation of drug effects and clinical pharmacology is the investigation of drug effects on human beings [1]. Clinical pharmacology is a scientific discipline which investigates the efficiency and safety of drugs and seeks answers to clinical questions [19]. It is very difficult to provide a universal definition of clinical pharmacology which would be valid for the whole pharmaceutical sector [20].

Clinical pharmacology focuses on individuals or patient groups in a clinical environment [1]. It investigates the rational use of drugs on human beings; it plays a role in making new discoveries and works towards regulation and licensing by assuming responsibilities in regulating authorities [19].

Clinical pharmacology is traditionally divided into two fields: pharmacokinetics and pharmacodynamics. Pharmacokinetics investigates the relationship between the administrated doses of drugs and the obtained serum and blood levels [1]. By examining the profiles that drug substances form in biological liquids the discipline creates mathematical equations [21]. It is about drug absorption, distribution, metabolization and excretion. Pharmacodynamics investigates the relationship between drug level and drug effect. In other words, it examines the physiological, biochemical and pathological effects of drugs on the human body [22][23]. Pharmacoepidemiology includes all of these fields of study [1].

In attempts to optimize drug use the main principle of clinical pharmacology is the individualization of treatment or to make it harmonious with the needs of certain patients. The individualization of treatment requires determining the risk/benefit ratio appropriate for the patient. This in turn requires a prescription procedure in accordance with the question of how the patient's clinical condition can be managed so that a better treatment outcome is possible as well as towards creating a consciousness on the potential beneficial and harmful effects of the drug. Its relationship with pharmacoepidemiology is important at this point. Pharmacoepidemiology can be useful in providing information on the beneficial and harmful effects of drugs. It allows a better evaluation of the risk/benefit ratio in the use of a certain drug on a certain patient. Prominently, pharmacoepidemiology investigates the side effects of drugs [1].

Side effects are traditionally divided into Type A, which are caused by general pharmacological drugs, and Type B, which are abnormal effects [24][25]. Type A reactions (drug effects) tend to be common, related to dosage, predictable and less serious [26]. They can be treated by easily decreasing the drug dose [1]. Type B reactions (drug effects) tend to be rare, not related to dosage, unpredictable and potentially serious. They usually require stopping the use of drug [25].

Drug side effect studies consist of collecting morbidity and mortality reports related to the drug. However, determining the causality for the cases examined in the drug effects reports can be problematic in certain situations. Therefore, academicians, researchers, the FDA and policy makers gravitate towards the field of epidemiology. In order to limit the effects of subjectivity in determining causality comparisons are made between populations that have and have not been exposed to the effects of the drug with controlled studies. This marriage between the fields of clinical pharmacology and epidemiology has given birth to a new field: pharmacoepidemiology [1].

### 3.2. Epidemiology

Epidemiology is defined as the study of the distribution and causes of health-related events in certain societies and the use of gathered knowledge to control health problems [27]. Because it investigates drug interactions observed in many people, pharmacoepidemiology is clearly a sub-branch of epidemiology [1]. Epidemiology means conducting pharmacoepidemiological studies with a focus on society and establishing relationships between health cases and drug exposures [4].

First epidemiological studies have been conducted towards the etiologies of infectious diseases [27]. Later on it was directed towards chronic diseases [1]. The field of pharmacoepidemiology investigates the techniques of chronic disease epidemiology in drug use and effects [28]. Pharmacoepidemiologists make use of epidemiological causes, methods and knowledge to increase drug benefits and decrease risks [5].

It can be said that pharmacoepidemiology is a relatively new field which establishes a bridge between clinical pharmacology and epidemiology. Pharmacoepidemiology takes its focus of knowledge from clinical pharmacology and the research methods from epidemiology. In other words it applies the methods of epidemiology in the field of clinical pharmacology [1].

However there are clear differences between the two disciplines. Although pharmacoepidemiological studies usually focus on the evaluation of drug safety after marketing, epidemiology is increasingly becoming a basic research discipline for the development of drugs and vaccines. Epidemiological methods place a stress on the clinical trials of drugs before marketing [29]. Therefore, while those who practice pharmacoepidemiology focus on drug surveillance after marketing [1], epidemiology points out the importance of the pre-marketing phase for a drug for many pharmaceutical companies [29].

### 3.3. Pharmacoeconomy

Pharmacoepidemiology is a sub-discipline of epidemiology which is interested in the effectiveness, activity and safety of pharmaceutical products. Meanwhile pharmacoeconomy is a sub-discipline of health economy which is interested in the evaluation of monetary values of pharmaceutical products [5]. In a broader definition, pharmacoeconomy compares the results and costs of pharmaceutical products and services, investigates the cost analyses of pharmaceuticals and their effects on individuals, healthcare system and society and the alternative drug treatments and services in patient care outputs [30]. The discipline compares outcomes and costs by referring to cost-effectiveness, cost-minimization, cost-benefit and cost-utility analyses. The target of the comparison is to determine which alternative provides the best health outcome [31].

Pharmacoepidemiology and health economy have important roles in evaluating pharmaceutical products however the two disciplines differ on the stages of evaluation process. Pharmacoepidemiology becomes involved at the stage of developing a new product during the evaluations of product effectiveness (desired effects) and safety (the potential of undesired effects). In contrast to this, the health economy evaluations become involved at the phase which is closest to the final development stage once safety and effectiveness are established [5]. However, in ensuring drug safety and effectiveness pharmacoepidemiology and pharmacoeconomy are in cooperation. By applying more complicated analyses, epidemiologists utilize health economy to conduct better analyses, make estimations with minimum bias using delicate parameters and taking better decisions [5].

## IV. THE IMPORTANCE OF PHARMACOEPIDEMIOLOGICAL STUDIES

Pharmacoepidemiology is not just limited to drug interactions and drug use but is also applied in many fields such as beneficial drug effects, implementing health economy in drug effect studies, life quality studies and meta-analyses [1].

Pharmacoepidemiology is used in the field of health and health management more commonly every day. First of all, pharmacoepidemiology facilitates better quantifications of drug side effects. This way, it allows high predictability and it becomes easier to reach patients who have not been studied before marketing (the elderly, children and pregnant women) and interactions with other drugs used for similar indications can be more easily identified. Second, with the help of pharmacoepidemiology new types of information which would be impossible to acquire during pre-marketing studies can be obtained. Drug side effects which could not be previously detected can be discovered (rare effects and delayed effects); and it becomes easier to learn more about aspects of drug use, effects of drug over-use and reflections of drug use on the economy. Third, drug safety can be ensured and ethical and legal requirements can be realized [1].

**Tablo 1.** Reasons to perform pharmacoepidemiology studies

| |
|---|
| (A) Regulatory<br>(1) Required<br>(2) To obtain earlier approval for marketing<br>(3) As a response to question by regulatory agency<br>(4) To assist application for approval for marketing elsewhere |
| (B) Marketing<br>(1) To assist market penetration by documenting the safety of the drug<br>(2) To increase name recognition<br>(3) To assist in re-positioning the drug<br>(a) Different outcomes, e.g., quality of life and economic<br>(b) Different types of patient, e.g., the elderly<br>(c) New indications<br>(d) Less restrictive labeling<br>(4) To protect the drug from accusations about adverse effects |
| (C) Legal<br>(1) In anticipation of future product liability litigation |
| (D) Clinical<br>(1) Hypothesis testing |

(a) Problem hypothesized on the basis of drug structure
(b) Problem suspected on the basis of preclinical or premarketing human data
(c) Problem suspected on the basis of spontaneous reports
(d) Need to better quantitate the frequency of adverse reactions
(2) Hypothesis generating- need depends on whether
(a) it is a new chemical entity
(b) the safety profile of the class
(c) the relative safety of the drug within its class
(d) the formulation
(e) the disease to be treated, including
(i) its duration
(ii) its prevalence
(iii) its severity
(iv) whether alternative therapies are available

**Source:** Strom, 2000, p.64

The reasons for conducting pharmacoepidemiological studies are summarized in Table 1. The benefits of the studies are listed under four categories which are regulative, marketing, legal and clinical. The importance of each can change depending on the organizations and individuals making the decision to begin a study. The most understandable and compelling reason in pharmacoepidemiological studies is the regulative aspect. The concept of regulative refers to the fact that in the phase before approval for marketing, plans for pharmacoepidemiological study after marketing must be ready. Second, pharmacoepidemiological studies are also considered to be important in marketing studies. As product name becomes more commonly known, repositioning of drugs becomes possible and sales increase. Third, in the face of the fact that all drugs can have side effects, learning about legal practices related to the drug and clinical decisions as well as conducting pharmacoepidemiological studies on side effects are considered to be important. Finally, many pharmacoepidemiological studies are actually are considered as hypothesis tests. Through the formulation of hypotheses for unidentified clinical implementations and unknown drug interactions it allows better clinical decisions to be made [1].

## V. CONCLUSION

Pharmacoepidemiology is considered to have a very important role in increasing individual life quality by improving drug use across society. Therefore it is expected that the interest for the discipline of pharmacoepidemiology will increase in the future.

The relationship between pharmacoepidemiology and pharmacogenetics will become an important concern in the coming period. With the improvement of the techniques of molecular of biology and the application of these techniques in pharmacogenetic studies it is expected that exciting developments will take place towards determining the genetic foundations of drug side effects. These developments will be able to bring on new methods for collecting DNA information and facilitate the creation of new fields of study such as molecular pharmacoepidemiology [17].

There is an expectation that in the future, studies on drug use will improve but will become more complex. It is predicted that the healthcare industry will become more sensitive towards the over- , insufficient and inappropriate use of drugs. It is considered that this will in turn cause studies to focus on drug use evaluation programs and doctors' prescription practices. It is also presumed that interest towards pharmacoepidemiology, which applies the principles of health economy in drug effects studies and has emerged as a new discipline, will increase. It is expected that the pharmacoepidemiological approaches will in the near future bring to the fore the importance of herbal medicines in drug marketing. The standardization of herbal pharmaceutical products which are being marketed without safety or efficiency tests and thus preventing potential disasters are among the topics being discussed.

The fundamental problem of the discipline of pharmacoepidemiology which has a high growth potential and has made many contributions to health researches is considered to be the lack of human capital and proper education.

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