ANALYSIS OF AWARENESS OF ADVERSE EVENT REPORTING AMONG PHYSICIANS AND NURSES AND CONTRIBUTION OF PHARMACOVIGILANCE TRAINING

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ABSTRACT

Özyıldırım A. Analysis Of Awareness of Adverse Event Reporting among Physicians and Nurses and Contribution Of Pharmacovigilance Training Yeditepe University Institute of Health Sciences Clinical Pharmacy Master Thesis. Istanbul, 2010.

Purpose: The aims of this research are to assess the awareness of Turkish physicians and nurses of pharmacovigilance and to study the impact of a seminar on their perception and attitude towards pharmacovigilance and adverse drug reactions (ADR) reporting. The existence of any differentiation among demographic groups is also investigated.

Setting: The study was conducted in the Vehbi Koç Foundation (VKF) American Hospital. 15 physicians from different specialties and 15 nurses participated in the research.

Methods: The participants were asked to answer two questionnaires before and after they attended an educational seminar on pharmacovigilance. The seminar aimed to provide the participants with the theoretical aspects and necessary knowledge about pharmacovigilance in order to help report ADRs. The first questionnaire, given before the seminar, aimed to acquire demographic information of the participants and to assess the knowledge and experience on ADR of the participants. The second questionnaire, completed after the seminar, measures the satisfaction of the participants attended in order to evaluate the impact of the seminar. The responses of the participants to the questionnaires were subjected to frequency analysis, and the existence of any difference between groups of participants based on profession and age, was investigated using non-parametric tests.

Results: Only 53.3% of the physicians and 60% of the nurses knew the correct definition of adverse drug reaction. All of the physicians and 60% of the nurses claimed that they had experienced an adverse drug reaction in their patients. 46.6% of the physicians and 40% of the nurses stated that they had never reported an adverse drug reaction. Only 45.5% of the respondents reported an adverse drug reaction to the correct authorities. Overall, only 36.3% (8 out of 22) of the respondents knew the correct definition of the ADR, had experienced an ADR and cared to report to a correct authority. Non-parametric tests demonstrate that the nurses and physicians differ significantly in their responses when they were asked whether they had experienced an ADR in their patients.

Conclusion: The results have shown that the practitioners are not aware of the importance of pharmacovigilance and do not know the correct definition of adverse drug reaction. The results of the second questionnaire demonstrate that an educational seminar would be very helpful to improve awareness and to increase ADR reporting. Nevertheless, elimination of ignorance on pharmacovigilance would not be sufficient if the attitude problem towards pharmacovigilance remains unsolved.
Key Words: Pharmacovigilance, Adverse Drug Reaction Reporting

ÖZET

Özyıldırım A. Doktorlar ve Hemşireler arasındaki Advers İlaç Etkileşimi Farkındalığı ve Farmakovijilans Eğitiminin Katkıları Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü Klinik Eczacılık Yüksek Lisans Tezi. İstanbul, 2010.

Amaç: Bu çalışmanın amacı Türk doktor ve hemşirelerin farmakovijilans ile ilgili farkındalıklarını ölçmek ve verilecek bir seminerin onların ADR raporlaması ile ilgili algılamaları ve tutumları üzerindeki etkisini incelemektir. Aynı zamanda, demografik ve profesyonel kriterlere göre oluşturulan gruplar arasındaki farklılıklar da test edilmiştir.

Kurulum: Bu çalışma VKF Amerikan Hastanesi'nde gerçekleştirilmiştir. Çalışmaya farklı alanlardan 15 doktor ve 15 hemşire katılmıştır.

Metot: Katılımcılardan verilen seminer öncesinde ve sonrasında iki anket doldurmaları istenmiştir. Seminerlerde katılımcılara pharmacovigilance ile ilgili teorik çerçeve ve gerekli bilgiler verilmesi hedeflenmiştir. Seminer öncesi verilen ilk anket katılımcıların demografik bilgilerini elde etmeyi, onların ADR ile ilgili bilgi ve tecrübelerini ölçmeyi amaçlamaktadır. Seminerden sonra verilen ikinci anket ise katılımcıların memnuniyetini ölçerek seminerin etkisini değerlendirmeyi amaçlamaktadır. Katılımcıların cevapları frekans analizleri ve nonparametrik istatistiki yöntemlerle incelenmiştir.

Bulgular: Doktorların sadece %53.3, hemşirelerin ise sadece %60'ı ADR tanımını doğru olarak bilmiştir. Tüm doktorlar ve hemşirelerin %60'ı daha önce bir ADR'a şahit olduklarını ifade etmiştir. Doktorların %46.6'sı ve hemşirelerin %40'ı daha önce hiç ADR raporlamadıklarını ifade etmişlerdir. Tüm katılımcıların sadece %45.%'i doğru kurumlara raporlama yapmıştır. Sonuç olarak eksiksiz cevap veren katılımcıların sadece %36.3'ü ADR'ın tanımını doğru bilip, bir ADR'a şahit olmuş ve bunu doğru bir kuruma raporlamıştır. Nonparametrik testler göstermiştir ki doktorların ve hemşirelerin daha önce bir ADR'a şahit oldunuz mu sorusuna verdikleri cevaplarda anlamlı bir farklılık vardır.

Sonuç: Bulgular göstermiştir ki katılımcılar farmakovijilansın önemi konusunda yeterince bilgiye ve farkındalığa sahip değildir. İkinci anketin bulgularına göre bu sorun verilecek seminerlerle çözülebilecektir. Ancak bilgisizliğin giderilmesi, farmakovijilansa karşı tutum sorununu çözmedikçe, ADR raporlamasını arttırmak için yeterli olmayacaktır.

Anahtar Kelimeler: Advers İlaç Etkileşimi Bildirimi, Farmakovijilans

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SYMBOLS & ABBREVIATIONS

ADR: Adverse Drug Reaction

VTE: venous thromboembolism

HRT: hormone replacement therapy

TADMER: Turkish Adverse Drug Reaction Monitoring and Evaluation Center

NHS: National Health System (United Kingdom)

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1. Introduction

Although the management of adverse events of drugs is not new and its history is as old as the word pharmaceuticals, yet the word "pharmacovigilance", which has become popular recently in Turkey, is still not known by many practitioners even in Istanbul, let alone the less developed small Turkish cities. Historically, the first known detection of an adverse drug reaction dates back, even centuries before the notorious thalidomide tragedy in 1961, to the Sumerians, who recorded the euphoric effect of the poppy in 4000 B.C. [1]. In fact, thalidomide is the 83rd event given in the chronological list prepared by Stephens (2004). Without doubt, adverse drug reactions (ADR) have attained more attention after thalidomide, which was launched as a safe and effective hypnotic and anti-emetic agent to be used for the treatment of nausea and vomiting in early pregnancy, and tragically turned out to be a potent human teratogen leading to major birth defects in an estimated 10,000 children [2].

Pharmacovigilance, derived from the Greek word; "pharmakon", a drug or medicine, and from the Latin "vigilans" watchful or careful, is defined as "all methods of assessment and prevention of ADR" (Mann and Andrews, 2002). World Health Organization (WHO) defines it as the science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions or any other drug-related problems. Mann and Andrews (2002) also state that pharmacovigilance is a broader concept than plain post-marketing surveillance and emphasizes the clinical and even pre-clinical development of drugs. Similarly, Shakir & Layton (2002) define pharmacovigilance as "the monitoring, detection, evaluation and responding to drug safety hazards in humans during premarketing development and post marketing"[3].

The definitions above raise a serious if not life-threatening issue; why cannot the adverse events of drugs be detected before they are marketed. Since the thalidomide tragedy, many regulatory mechanisms have been developed to control the drug

production in terms of both efficacy and safety. However, even these regulations have not been sufficient to produce safe products. Between 1975 and 2000, more than 30 drugs were withdrawn from the market due to ADR after marketing. The list of these drugs is given in Table 1 [2].

Table 1 : Drugs withdrawn in the U.K. by the regulators [2]

Brand name (drug substance)	**Year**	**Major safety concerns**
Secholex (polidexide)	1975	Safety concerns due to impurities
Eraldin (practolol)	1975	Oculomucocutaneous syndrome
Opren (benoxaprofen)	1982	Hepatotoxicity, serious skin reactions
Devryl (clomacran phosphate)	1982	Hepatotoxicity
Flosint (indoprofen)	1982	Gastrointestinal toxicity
Zomax (zomepirac)	1983	Anaphylaxis
Osmosin (indomethacin-modified release)	1983	Small instestine perforations
Zelmid (zimeldine)	1983	Neurotoxicity
Flenac (fenclofenac)	1984	Lyell's syndrome
Methrazone (feprazone)	1984	Serious skin reactions
Althesin (alphaxolone plus alphadolone)	1984	Anaphylaxis
Pexid (perhexilene)	1985	Hepatotoxicity, neruotoxicity
Suprol (suprofen)	1986	Nephrotoxicity
Merital (nomifensine)	1986	Haemolytic anaemia
Unicard (dilevalol)	1990	Hepatotoxicity
Glauline eye drops 0.6% (metipranolol)	1990	Uveitis
Halcion (triazolam)	1991	Psychiatric reactions
Micturin (terodiline)	1991	Arrhythmias
Teflox (temafloxacin)	1992	Multi
Centoxin (nebacumab)	1993	Mortality
Roxiam (remoxipride)	1994	Aplastic anaemia
Volital (pemolin)	1997	Hepatotoxicity
Romazin (troglitazone)	1997	Hepatotoxicity
Serdolect (sertindole)	1998	Arrhythmias
Tasmar (tolcapone)	1998	Hepatotoxicity
Ponderax (fenfluramine)	1998	Cardiac valvular disease
Adifax (dexfenfluramine	1998	Cardiac valvular disease
Posicor (mibefradil)	1998	Drug interactions
Trovan (trovafloxacin)	1999	Hepatotoxicity
Grepafloxacin (Raxar)	1999	QT prolongation

Mann and Andrews (2002) give three reasons as an answer to this question. To start with, the size of the data used in the clinical safety section of the pre-marketing

development period was too small to discover the undesired effects of drugs. Increasing the size of the data would delay the marketing of the drug, which may be urgent and crucial for patients. Moreover, the patients who use the licensed marketed medicines are different from the volunteers and patients who take part in the pre-marketing clinical trials. The latter consists of generally controlled patients who have only one disease and use only one drug. However, during the post-marketing phase larger populations are exposed to the product including elderly patients with polypharmacy and many serious diseases. This situation often increases the drug interaction risk and thus the ADR incidences. It has also been suggested that there might be too infrequent undesired effects, which are too rare to be observed in standard clinical trials [2].

Another problem is that the drugs listed in Table 1 were widely used but it took a very long time to detect their ADRs. This shows that the system is ineffective in discovering the ADR. As of 2002, the hospital admissions due to ADR constituted 2.4%-3.6% of all hospital admissions in Australia, and it is similar if not greater for other developed countries such as France and United States (Pouyanne et al., 2000). The significance of these percentages is an evidence of the inability of the system to monitor the post-marketing safety experience even after 30 years since the thalidomide tragedy [2].

To summarize, pharmacovigilance is a science that has to deal with complex dilemmas, such as whether to implement a longer licensing procedure involving a more complicated clinical trial period at a cost of delaying drug market launch and leading to inadequately managed patients; and pharmacovigilance has to solve fundamental methodological problems through the post-marketing drug safety monitoring.

As for the situation in Turkey, unfortunately, the healthcare sector lacks a developed and widely used ADR detection procedure. Many practitioners in Turkey do not even know what pharmacovigilance is, or how to report when they observe an ADR. Therefore, this study aims to discuss more basic questions, rather than advanced topics, such as the methodological problems of post-marketing monitoring, clinical trial analysis, or ADR of a selected drug class. The first question aims to analyze whether

practitioners, namely doctors and nurses, know what pharmacovigilance is. And, if not, would an informative seminar on this issue improve the awareness and increase the number of practitioners reporting ADR in a hospital setting?

The plan of the dissertation is as follows. The next chapter provides a brief review of the relevant literature. This section focuses on post marketing safety issues. The definition of ADR, risk evaluation and international evidence on underreporting and lack of sufficient awareness are also presented. Chapter 3 summarizes the methodology and sample used in the analysis. Chapter 4 presents the findings of the research. Chapter 5 discusses the relevance of the findings and the last chapter concludes the study.

2. Theoretical Background

Although there are exceptions, many patients are not aware of the fact that the drugs they use are at best acceptably safe with adverse effects and expected benefit. Even prescribers still seem to believe that licensed drugs are safe and get shocked when a drug turns out to have undesired effects and is withdrawn from the market. As the number of such stories in the media about drugs withdrawals due to ADR increases, pharmacovigilance attains more attention, and awareness about this issue increases.

The aims of pharmacovigilance are [1]:

- "*The identification and quantification of previously unrecognized adverse drug reactions (ADR)s.*
- *The identification of sub-groups of patients at particular risk of ADRs (the risk relating to dose, age, gender and underlying disease).*
- *The continued monitoring of the safety of a product, throughout the duration of its use, to ensure that its risks and benefits remain acceptable. This includes safety monitoring following significant newly approved indications.*
- *The comparison of ADR profile of products within the same therapeutic class.*
- *The detection of inappropriate prescription and administration.*
- *The further elucidation of a product's pharmacological/toxicological properties and the mechanism by which it produces ADRs.*
- *The detection of significant drug–drug interactions between new products and co-therapy with agents already established on the market, which may only be detected during widespread use.*
- *The communication of appropriate information to health-care professionals*
- *The refutation of 'false positive' ADR signals arising in the professional or lay media, or from spontaneous reports*"

2.1 ADR

Pharmacovigilance is particularly concerned with adverse drug reactions, or ADRs, which are officially described in European Union Directive 2001/83/EC as: *"A response to a drug which is noxious and unintended, and which occurs at doses normally used… for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."*

There are two types of ADRs. Type A reactions *are "common, predictable, usually dose-dependent and appear as excessive manifestations of the normal pharmacology/toxicology of the drug"*, whereas Type B reactions are *"uncommon, unpredictable, often independent of dose and usually represent abnormal manifestations of the drug's pharmacology/toxicology"* [2].

Almost 75% of all ADRs are Type A, which are rarely fatal. However, since they have gradual effects, they remain undetected for a long time and may result in morbidity for a patient many years after marketing [4]. On the other hand, Type B reactions have sudden and often dramatic effects and therefore are quickly detected. Compared to Type A, Type B reactions involve relatively high rates of serious morbidity and mortality [2].

Table 2: Characteristics of Type A and B ADRs [5]

Type A	Type B
Pharmacological	Hypersensitivity or idiosyncratic
Dose Related	Not dose related
Predictable	Unpredictable
Common	Rare
Usually not serious	Usually serious
Majority discovered before marketing	Majority discovered after marketing
Relatively low mortality	Relatively high mortality

Table 2 summarizes the specifications of this classification made by Rawlins & Thompson. Type-A ADRs are accepted as preventable. A Type-A ADR may result from many avoidable factors such as, *"error in dose or method of use, failure to*

recognize possible antagonistic or complementary drug-drug interactions, inadequate follow-up of therapy, inappropriate drug, avoidable delay in treatment, physician practicing outside area of expertise" [6]. A review of previous literature analyzed the characteristics and determinants of ADR-related hospitalizations on a population-based level in 2003, and concludes that a substantial portion of ADR, especially those which occur among elderly, is avoidable. [7]

Apart from this pharmacological classification, there are other factors, such as severity and reaction used for classification. A profile should be created for an ADR covering the following elements [1];

- *"Manifestation (clinical or laboratory), both subjective and/or objective.*
- *Graded, both for severity and seriousness.*
- *Frequency or incidence, both absolute and relative to similar drugs, with CIs.*
- *Mechanism of action.*
- *Causality.*
- *Predisposing factors, i.e. renal function, pharmacokinetic factors, etc.*
- *Treatment and its effect.*
- *Reversibility or sequelae."*

There are many studies on the frequency of ADRs. However, comparability of these studies is difficult, if not impossible, because many factors affecting the incidence figure vary among the countries in which these studies are conducted. Stephens (2004) analyzes these studies, and puts them into different groups as (1) ADR responsible for hospital admission, (2) ADR during hospitalization, (3) ADR reported at outpatient visits and (4) deaths due to ADR. Stephens report that ADR incidence during hospitalization varies between 1.7 and 29 percent. On the other hand, the incidence of death due to ADR as a percent of people taking drugs range from zero in Israel to 1.4 per 1000 in New Zealand. Another study states that there were 199000 deaths due to medication-related problems per year in USA [8]. Another statistic, obtained from a review of 36 articles, shows that 3.7 percent of patients admitted to a hospital due to ADR died [1].

2.1.1 Risk Analysis for ADR

The figures given above show the risk that a patient takes by having a medical treatment. The fact that these figures might be lower than reality due to underreporting increases the seriousness of the situation. Even these figures are very high, compared to other involuntary risks taken by a human. This comparison reveals how large the risk of death due to ADR is and raises two questions. The first one is whether the patients, let alone the market authorization holders and prescribers are aware of this risk, and the second question is what the acceptable ADR risk with a new medical treatment is.

The patient should be able to conduct a risk/benefit analysis before taking the medical treatment. However, the patients do not have the necessary understanding and the knowledge to make an assessment. The patient information leaflet, prepared to provide the patient with the necessary information, generally gives no clue about ADR frequency or severity. What is more, a study conducted in England shows that only 30 percent of the patients read the leaflet completely. Stephens (2004) claims that the prescribing physicians do not have the necessary information and comparative data on the drugs of the same class. It is also debated whether the pharmaceutical company tends to consider that the drug they produced is unique, more efficient and safer than it actually is. Therefore, even if the market authorization holder obtains all relevant information, this is rarely analyzed in the sense of providing prescribers the needed practical and useful guidance.

The second issue is the expression of risk. Physicians may use different terms for a given numerical risk. For example, the numerical equivalent of “often” varies between 27 and 91 percent with a mean of 59 percent among Canadian physicians. Another factor that may affect the risk perception is the difference between relative and absolute terms. Relative risk is the probability of an event in the actual group divided by the probability in the control group. For instance, consider a research study with a treatment and a placebo group consisting of 10000 patients. Let us assume that there are 1000

events in the treatment group and 2000 events in the placebo group. Then it can be said that the risk decreases by 10% in absolute terms and 50% in relative terms. When expressed in relative terms, the decrease in the risk can be perceived larger than it actually is [1].

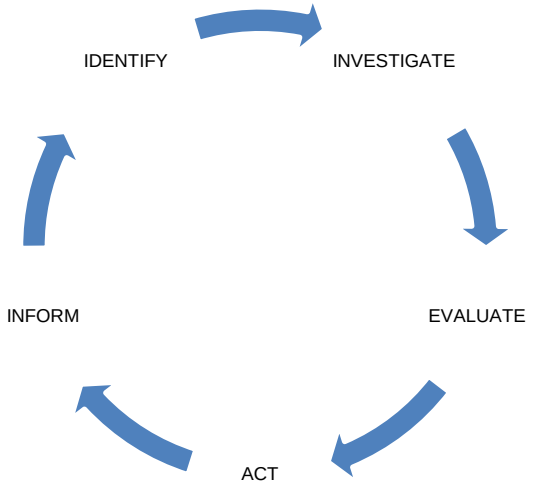
Of course, to be able to answer the second question, first the risk should be calculated properly. Since the calculation of risk is beyond the scope of this dissertation, only a few numerical analyses are given to show how large a sample to obtain risk estimation with an acceptable significance is required. For instance, if the true incidence of ADR is 1 in 100, then the probability of finding one case of ADR is 95% with a sample size of 300. The required sample size increases to 13.000, if the true incidence is 1 in 2000 and three cases of ADRs are required. It increases to 65.000 if the true incidence is 1 in 10000. These numbers are for the ADRs with no background, in other words ADR symptoms are not observed before the treatment. If the ADR results in an increase in an already existing hazard resulting from the disease, the change in the incidence of the hazard should be calculated. In this case, for example a sample of 10.000 patients is required to discover an increase of 1 in 100 where the background incidence is 1 in 10 with 95% probability. As the true incidence of ADR decreases, the number of patients required to observe at least one ADR case increases to unfeasible numbers. For rare ADRs, which require large numbers of patients to detect, the pre-marketing research will not be cost-effective.

2.2 Managing Drug Safety Issues with Marketed Products

This dissertation aims to deal with post-marketing safety issues, rather than pre-marketing clinical trials. Obviously, there are many reasons why there are ADRs that cannot be detected before the marketing period. The discussion above has made it clear that it is impossible to identify all drug safety issues before marketing. To start with, ADRs are rare and even a large number of patients may not be sufficient to detect the ADR in the clinical trial period. Other than that, the patients in the clinical trial period have different characteristics than the patients in the market. The latter are generally

older, have more than one disease etc. What is more, in practice, strict compliance to treatment regimens and to prescribing recommendations is less likely while, in the trial period, monitoring and control is high and the researchers make sure that prescribing recommendations are met by users. Therefore, safety management of marketed products will continue to be crucial even if better clinical trial procedures are developed. Safety management of marketed drugs consists of 6 cyclical stages as presented in Figure 1 [9].

Figure 1: Process of handling a drug safety issue [9]



2.2.1 Identification

The identification of an ADR involves assessment of information gathered from many sources. The collection of pharmaceutical product-related adverse events started after the thalidomide tragedy. The process starts with the basic pharmacological and pre-clinical studies and does not end until the product is withdrawn from the market. ADRs can be detected at any stage of this procedure. The post-marketing stage lasts for decades. At this stage, while most of ADRs are detected within the first few years of the product launch, new issues may emerge even after long years on the market.

There are two sources of information on which the identification procedure is based, namely the spontaneous reports and formal studies. These sources are screened for an alert, in other words, a signal, that "a drug may be associated with a previously unrecognized hazard or that a known hazard may be quantitatively (e.g. more frequent) or qualitatively (e.g. more serious) different from existing knowledge" [9].

Table3 gives the data sources. The formal studies can be subdivided into three groups [7];

Table 3: Data sources for AE surveillance programs [7]

Spontaneous reports
• To manufacturers
• To regulatory agencies
Literature case reports
• Single case reports
• Case report series
Studies (published or unpublished)
• Clinical studies
• Epidemiologic studies
Pre-clinical and toxicological data
• In vitro experiments
• Animal models
• Toxicological studies

2.2.1.1 Spontaneous adverse drug reaction reporting data

The largest contributor to the post-marketing surveillance of drug safety issues is spontaneous reporting. Spontaneous reports are unsolicited individual reports from

health professionals and, in some countries, consumers and other third parties of adverse events considered to be related to drugs being taken. In other words, they are not obtained from clinical research or medical literature. These reports are the result of the suspicion of prescribers and patients. The common problem of all spontaneous ADR reporting systems is underreporting, which will be discussed in the following chapters. Unfortunately, the Turkish health system is even farther away from having an underreporting problem, since even the meaning of pharmacovigilance is still not known among Turkish practitioners, let alone patients.

Spontaneous reporting systems provide huge information with very low costs, and are very useful when organized by experienced supervisors. Therefore, it has become the foundation block of the post-marketing surveillance systems [7].

To create a successful spontaneous system, a database from which data can be obtained in an utilizable format and a monitoring process that can handle the dynamic structure of the data are necessary. Such a system would provide a regular and systematic review of all new information, which may be associated with a potential ADR. There are two alternative methods of using this data. The first approach is to make a review based on a particular drug or a product. An alternative approach is to analyze a particular ADR by bringing all information together about that particular ADR and review all drugs that might be associated with it.

There are national and international spontaneous reporting systems throughout the world. The World Health Organization program coordinates these national centers. This program was launched in 1968, when the necessity of an ADR reporting system was acknowledged after the thalidomide catastrophe in 1961. The aim of the program is to provide the WHO member countries a facility to collaborate in the ADR monitoring and maintain a worldwide database, in which ADR reports collected from member countries, are stored. The database contains over 4.7 million reports as of February 2010. The partners of the program are National Pharmacovigilance Centers, WHO Headquarters, Geneva and the WHO Collaborating Centre for International Drug

Monitoring, the Uppsala Monitoring Centre, in Uppsala, Sweden. As of September 2009, 96 countries are members of the program, while 30 other countries are listed as "associate members", which are waiting for completion of compatibility studies of their reporting forms [10]. What is more, in member countries, local companies have to comply with the local regulatory reporting obligations, and international companies should collect worldwide data to be able to make benefit – risk evaluations and act responsibly to protect the public health [9].

Utilizing spontaneous reporting data

The spontaneous reporting system provides a very crucial feedback to assess the risks of healthcare products used in medical practice. On the other hand, it is also speculative by nature. Therefore, any spontaneous signal should be tested for consistency using various methods and be confirmed with formal studies. In other words, spontaneous assessment should be regarded as providing the constituents of signaling arguments, rather than a precise assessment method or estimator for calculation of incidence rates [11]. Such activities with a less formalized structure, are called pre-epidemiology in the public health literature [12].

In a spontaneous report, an event is associated with a medical treatment and all other possibilities are generally ignored. Previous literature has shown that placebos can be associated with adverse events [1]. Since spontaneous reports are subjective and speculative by nature, a large number of similar events associated with a particular product are required in order to be assessed as a signal. If the ADR is rare, since a small number of cases can be sufficient to evaluate as a signal, then , the number of unexpected events is the most important factor to decide whether it is a signal or not. Other information available, such as the level of drug usage and the strength of the evidence for a particular event, is also vital in assessing the likelihood of an ADR [9].

There are many different spontaneous report-signaling methods. A classification according to functional step and data strategy is given by Clark et al. (2002). A comparative analysis using spontaneous report signaling methods should be handled

very carefully due to underreporting. If the drugs that are compared have different durations, indications or there is a significant public awareness of adverse effects of one of these drugs, the comparison will not be dependable. Moreover, while evaluating worldwide data, the differences between countries, such as prescribing regulations, usage, and reporting culture should be taken into account [9].

2.2.1.2 Formal studies

Formal studies have important functions in hypothesis testing as well as in hypothesis generation. It has already been discussed that the signals generated from spontaneous reports should be tested by formal studies (hypothesis testing). Formal studies are also used to provide initial evidence regarding an ADR [9].

Such studies are often implemented with a focus on efficacy rather than safety. Obviously, a new drug with no or low efficacy would not be produced. At the early stages of trial, most of the products would fail safety tests on animals and early phases of human tests. At the design stage of the trial studies, where major statistical analysis with large samples is conducted, efficacy comes before safety. Since they use larger data compared to earlier stages of trial, it is vital to maximize the ability of studies to identify adverse effects [9, 13].

There are two groups in a randomized comparative study. Besides the group having the treatment, a comparator group uses placebo or an active drug. Since the randomization allows the groups to be similar, the causality between the product and ADR can be identified and the statistical analysis provides stronger estimations of the likelihood of a genuine adverse event associated with the medical treatment. If the control group is a placebo, an excessive number of adverse event observations in the treatment group, is accepted as strong evidence of causality between the drug and the adverse event. Likewise, if the comparator group is an active drug, an excessive number of adverse event observations in the treatment group, is accepted as strong evidence on causality between the drug and the adverse event. Moreover, if the comparator drug has a known ADR, a similar incidence of adverse event occurrence will be taken as evidence for

existence of ADR for this drug, even though there is a possibility that the events might be caused by neither drug [9].

2.2.1.3 Processes for identifying drug safety hazards

The crucial prerequisite of a successful drug safety system is the links between different groups working on drug safety to pool the necessary information for a complete analysis. There might be several groups in a pharmaceutical company or a regulatory body working on drug safety and a network between these groups to share information effectively should be constructed.

The aim of the drug safety process is to detect an arising signal as soon as possible, evaluate the case and publicize the issue in many ways, if it is an ADR. The first step of the procedure is the initial assessment to decide whether the issue requires a further analysis. The key principles of initial assessment are signified by the acronym "SNIP" [13];

- *"the strength of the signal;*
- *whether or not the issue or some aspect of it is new;*
- *the clinical importance, as judged by the seriousness of the reaction and severity of the cases;*
- *the potential for preventive measures."*

Table 4: Factors influencing the initial assessment of ADR signals [13]

Evidence to be considered	*Underlying issue*
1.The cases producing the signal	
Individual case assessment: temporal relationship Effect of dechallenge/ rechallenge, alternative causes	• Causality
Quality of the information regarding cases	• Documentation
Number of cases in relation to usage of the medicine	• Frequency/reporting rate
Severity of the reactions Seriousness of the hazard	• Implications for patients and public health
2.Other evidence	
Pharmacological or toxicological effects of the drug Known effects of other drugs in the class	• Mechanism
Pre-clinical studies Clinical trials Epidemiological studies	• Possible class effect • Existence of other evidence that may support or refute the signal

The assessment procedure depends on the type of the signal source. If it is a spontaneous report signal, which consists of a series of similar events related to a particular drug, the assessment will be based on the factors listed in Table 4. Without doubt, any analysis should factor in alternative causes, or in other words, other possible explanations for suspected ADR. The most common alternative causes are concomitant medication and coexisting disease. In the case of treatment with more than one drug, the ADR may arise due to other drug or due to the interaction between two drugs. In this case, the patient is suffering due to an ADR, which is not solely dependent on the suspected drug. The other possibility is that the adverse event arises from a complication of indication for suspected drug, or newly emerging/coexisting disease, and then the case is not an ADR. If the adverse event arises from the complication of the disease treated with the suspected drug, information obtained from spontaneous reporting is useless. In such circumstances, where spontaneous signaling is not sufficient, it is difficult to decide whether further investigation is required [13].

The other information source is formal studies. These studies can provide stronger results compared to spontaneous reporting, because they can be designed to be randomized, and therefore allow the researchers to make better estimations about causality and frequency of ADR. However, there is generally only one formal study on a particular issue, and there is no guarantee that formal studies always provide the correct answer. Previous literature documents many examples of formal studies providing seemingly wrong outputs, such as selegiline associated with increased mortality and neonatal vitamin K with childhood cancer [13-15].

There are three major reasons why a formal study may give false results, namely chance, bias and confounding. The strength of the statistical analysis is crucial for the initial assessment. Therefore, any other possible explanation should be examined to check whether the result is robust. Table 5 presents these other possible explanations that may lead to false positive and probable key evidence related with them [13].

Table 5: Assessment of causality based on formal studies [13]

Possible explanation	Key evidence to be considered
Chance	Levels of statistical significance and power of study Whether or not there was a prior hypothesis How many tests were performed?
Bias	Study design – how were patients allocated to treatments? How were the data on outcomes collected?
Confounding	What factors other than drug treatments could explain differences between groups? What steps have been taken to control for confounding in the design or analysis?
Causal	Extent to which chance, bias and confounding have been excluded as alternative explanations Availability of evidence from other sources that may support an association or explain it (e.g. a mechanism)

The aim of initial assessment is to decide how to move on. It can be decided to keep simple watch or to look for further evidence for the investigation stage. The strength of the evidence and the outcome of a general risk and benefit analysis are the major determinants of the final decision. The next step is investigation.

2.2.2 Investigation

At this stage, the aim is to clarify the concerns and analyze the outstanding issues, such as causality, mechanism, frequency and preventability. Further evidence is required for the assessment of these issues. Apart from the new laboratory and clinical studies implemented to test the hypothesis generated in the identification step, immediately available sources of retrospective information, such as epidemiological databases, can be used. Since clinical studies are beyond the scope of this dissertation, the focus is on epidemiological studies. These databases can be used for many important issues, such as ADR risk management, prescription audit, and disease registers. They have the potential to find quick answers to pharmacovigilance questions and allow the researcher to respond immediately [13, 16].

The information necessary for analysis, such as drug exposure, outcomes and medical information about individual cases may be recorded in separate databases. Recent advances in information technology have allowed the researchers to create links between information recorded in separate databases for a particular individual patient. Two examples of record-linkage are given by Evans and McDonald (1999). One is the MEMO system based in Tayside, UK, which links by utilizing community health index number, and the Information and Statistic division of the NHS which uses a probability matching method which tries to match records using surname, initial and birth date. Then a probability is calculated for the likelihood of the correctness of the match [16].

There are two major types of epidemiological studies. The cohort design involves defining a population and tracking this population to measure absolute and relative risks

by comparing the number of individuals exposed or not exposed to the drug of interest. The second alternative is case-control design, in which control groups are created from the population that is exposed to the drug of interest. Then different cases are defined to measure the change compared to prior exposure. Relative risk is obtained from these studies. Another alternative is a combination of cohort and control designs, which provides the advantages of both methods. It should be noted that epidemiological studies need not follow a signal and a hypothesis developed based on this signal. Proactive epidemiological studies might be performed even before a signal has actually been detected. The linked database discussed above allows researchers to accomplish such studies [13].

2.2.3 Evaluation

The third stage is evaluation, where new data obtained from purpose-designed studies are reviewed in the context of existing data. It should be analyzed to see whether there is any change compared to initial assessment by concentrating on the possibility of prevention.

At this stage, detection of possible risk factors is very crucial. If a rare ADR is identified along with many risk factors for particular groups, then, even though the benefits of the drug outweigh the hazard overall, it might be the case that for that particular group, the risk might be very high to take. An example is the interaction of venous thromboembolism (VTE) with hormone replacement therapy (HRT). The risk of VTE increases two to three times for users of HRT [17]. In other words, relative risk increases enormously. On the other hand, absolute risk is very low. The probability of VTE for a healthy middle-aged women is about 1 in 10 000 per year, whereas the benefits of HRT to an individual is significant, providing symptom relief and protection against osteoporosis. Thus the benefit risk ration of HRT for healthy patients would favor the treatment where as for patients with a high baseline risk of VTE, risk might be more important than benefits, if the benefits of the treatment are not substantial [13].

Table 6: The benefit- risk balance analysis [13]

Risks	**Benefits**
Who is at risk?	Who may benefit?
Magnitude of absolute risk	Magnitude of expected benefit
Risks associated with alternatives	Benefits associated with alternatives

Benefit-to-risk balance
Is it reasonable to accept the risk(s) to gain the potential benefits?
If so, in what circumstances?

It has been discussed how risk assessment and risk-benefit analysis is difficult for patients. The drug safety experts are expected to provide recommendations based on scientific evidence to help patients make their decisions. Unfortunately, there is no straightforward method to assess the risk- benefit balance to make recommendations. The points that should be taken into account are listed in Table 6. The following section discusses how to take action to improve drug safety after these steps.

2.2.4 Action

After a thorough assessment of identifying an ADR with sufficient information, a plan is required to provide appropriate information to health professionals and patients, so as to minimize the risk of the hazard. The nature of the action taken in response to a drug safety issue will depend on the "*seriousness of the hazard, frequency, preventability, nature of the disease, benefits of treatment, and availability of alternative treatments*" [13]. All alternative actions should be considered based on these factors to optimize the use of the drug by factoring in the benefit-risk trade-off the drug. The available options, after an ADR is detected, are listed below [18]:

- *"modifications to the product or its use or to the product information*
- *restriction of product availability*
- *suspension of product license or investigational-status approval*
- *withdrawal of the product from the market (voluntary by marketing authorization holder or mandatory by authorities)*

- *communication of new or reinforced information to the medical profession or the public"*

Rarely, the drug is withdrawn from the market. Generally, the hazard can be eliminated with modifications to its use. For instance, it might be targeted to a lower-risk group or measures can be taken to ensure it is contraindicated in patients with risk factors. The factors that affect the ability to prevent an ADR are listed in Table 7 [13].

Table 7: Factors that may impact on the potential for prevention of ADRs [13]

User characteristics
Demographics: age, sex, race
Genetic factors: polymorphisms (e.g. acetylator status)
Concomitant diseases (e.g. impaired hepatic or renal failure)
History of previous ADRs (e.g. allergy)
Compliance
Drug characteristics
Route of administration
Formulation (e.g. sustained versus immediate release, excipients)
Dosage regimen
Therapeutic index
Mechanisms of drug metabolism and route of excretion
Potential for drug interactions

2.2.4.1 Product Modification

The first alternative is drug modification. These modifications can be made by the regulatory authority or the pharmaceutical company. There are three types of modification, namely changes to the prescriber or consumer information (data sheets, etc.), restriction of product use or supply, and formulation/ manufacturing changes [13, 18].

Changes to prescriber or consumer information

Modifications to the product information should be made very carefully and be placed within a particular section. Misplacement, duplication or providing existing information may result in confusion. The product information sections are given in Table 8. The types of product information change include: "*the addition of new risk information to*

the sections covering ADRs, contraindications, warnings, precautions or interactions; changes in wording or emphasis to clarify or further specify adverse reactions; and restriction of indications, or in some cases, removal of information" [18]. Adding a therapeutic recommendation for adverse reactions treatment might be necessary in certain cases. The crucial point is that these changes in product information for professionals or patients should be made with the agreement of both regulators and manufacturers. In case of any changes, the new information should be announced quickly to the relevant interested bodies such as using the "Dear Health Care Professional Letters" or "Drug Safety Alerts" on Health Authorities' websites. Afterwards, a revision of the information on the package must be carried out.[13, 18].

Table 8: The product information sections [13]

Section	**Examples**
Indications/uses	Limiting the indications to particular conditions with the greatest benefits by removal of indications: (a) for which the benefits are insufficient to justify use; (b) for which use is associated with a greater risk of the ADR
Dosing instructions	Reductions in dose (may be applied to specific groups, e.g. the elderly); limitations on duration or frequency of treatment (especially for ADRs related to cumulative dose); provision of information on safer administration
Contraindications	Addition of concomitant diseases and/or medications for which the risks of use are expected to outweigh the benefits
Interactions	Addition of concomitant medications or foods that may interact; advice on co-prescription and monitoring
Pregnancy/lactation	Addition of new information relating to effects on foetus or neonate; revised advice about use in these circumstances based on accumulating experience
Warnings/precautions	Addition of concomitant diseases and/or medications for which the risks of use need to be weighed carefully against the benefits; additional or modified recommendations for monitoring patients
Undesirable effects	Addition of newly recognized ADRs; improving information about the nature, frequency and severity of effects already listed
Overdose	Adverse effects of overdose; management, including the need for monitoring

Restriction of product use and supply

Another alternative is to restrict the availability of the product. Selective restriction of the availability of a product does not only decrease the ADR risk by preventing more vulnerable patients using the drug but also allows the regulators and market authorization holders to control the safety of the product more affectively. There are well-known programs used in North America and Europe for investigational products. These products are licensed but have potential safety problems. In this way, availability of the product is restricted and provided upon informed consents to patients who when treated with these products are under continuous monitoring. Investigational products and even some marketed products, such as felbamate and clozapine, can be provided to patients who sign an informed-consent document [18].

Changes in formulation or in manufacturing

In some cases, changes in formulation and manufacturing may eliminate the risk and improve drug safety. This is not only related to the formulation of the product. A change in the appearance of the product or childproof packaging may eliminate the risks associated with the product. Other examples of this are "*a change in an excipient (or its elimination, in the case of a dye, for instance) shown to be responsible for an adverse reaction; a change in composition (e.g., lower strength of a tablet); a change in a delivery system (e.g., from capsule to tablet to avert oesophageal insult); a change in particle size or crystalline form to overcome bioavailability or drug-delivery problems that influence unfavorably the benefit-risk balance"* [18].

2.2.4.2 Suspension of product license or investigational-status approval

Many European countries allow for temporary suspension of the products with safety problems. Temporary suspension gives the manufacturer the time required to obtain more information and evaluate the safety profiles of the product before more patients are exposed to the drug. It allows market authorization holders to determine the magnitude of the

problem and take necessary precautions and to resume marketing the product without a new license application if the problem is solved [18].

2.2.4.3 Withdrawal of the product from the market

Withdrawal of the product is the last and least desirable option. However, if the risk associated with product outweighs its benefits, then the product should be withdrawn from the market. What is more, sometimes withdrawal might be necessary when the risks cannot be measured without a doubt and precautions needed to reduce the risk cannot be identified. Withdrawal of Dipyrone in USA and Sweden is an example of this. Dipyrone was withdrawn after reports of fatal agranulocytosis. However, epidemiological studies after the withdrawal showed that the excess risk of death from this reaction was 0.10 per million users a week. Considering the other risks, anaphylaxis, aplastic anaemia and gastrointestinal bleeding, the total risk of death increases to 0.11 per million users a week, which is very low compared with 1.66 for aspirin and 1.50 for diclofenac. The drug was re-approved in Sweden based on the evidence provided by the new data [18]. Occasionally, the product might be withdrawn from the market by the regulator, if the newly detected risk is believed to constitute an imminent hazard to patients. The withdrawal, whether voluntary or mandatory, should be accompanied by an alert for the public and an immediate product recall to health care professionals. In other words, any action taken to manage an ADR must be supplemented by an effective communication to professionals, which will be discussed in the following section.

2.2.4.4 Communicating drug safety issues

Informing concerned parties, including healthcare professionals, public and media, is very crucial, when a new drug safety issue occurs. Even if an appropriate action is taken in a timely manner to address a safety issue, lack of successful communication would render all these efforts valueless. This requires a good communication plan which defines the messages, the targeted audience, the channels to be used, the person in charge and responsible for signing them and the time of the announcement.

Table 9: Key requirements for a successful drug safety communication (ABOUT) [13]

Requirements	Comments
Accurate	Are the facts and numbers correct? Make sure you have included all the information that the reader needs to know
Balanced	Have you considered both risks and benefits; is the overall message right?
Open	Be honest about the hazard - don't hide or minimize it; make it clear what has led you to communicate
Understandable	Keep it as straightforward as possible – the reader is more likely to respond appropriately if the message is simple and clear
Targeted	Consider your audience and their specific information needs

Critical to the success of the communication is the quality of the message. Waller and Tilson (2004) states that the message should be "*accurate, balanced, open, understandable and targeted*". These requirements, recalled by the mnemonic 'ABOUT', are summarized in Table 9. Above all, the message must give the essential information clearly. To put the right message forward, it must be worded unambiguously and must not be diluted with irrelevant information [13].

The announcement can include changes "*in prescribing information or patient information leaflets, the addition of recommendations on the treatment of adverse reactions, and restriction of indications, reinforcement on the appropriate use of a product, on dosage reduction schedules, on use of alternative therapies, or on the appropriate patient population, or ''how to'' instructions on product administration*"[18].

In the communication plan, how to disseminate the information and the targeted audience must be determined. The alternative channels are "*dear doctor/health-professional letters, the use of patient leaflets and advertising campaigns to health professionals or consumers, journal publications (scientific or lay press), and educational programmes/ educational materials for health professionals or consumers via print, video, audio or computer (electronic) media*"[18].

2.3 International Evidence on ADR Underreporting and Pharmacovigilance Awareness

The underreporting of the ADRs is the main challenge facing pharmacovigilance. It is widely acknowledged that, although it is not possible to determine the correct rate of underreporting, previous experience has shown that only a small proportion of the ADRs are reported even in developed countries with sophisticated reporting systems [19]. Inman and Weber (1986) provide a number of examples of underreporting in many previous ADR cases. For instance, only 6 doctors reported a dozen of deaths among over 3500 from asthma due to excessive use of pressurized aeresols in 1960s. A more recent example is practolol. Practolol was marketed in 1970 under the brand "Eraldin" for the treatment of arrhythmias and high blood pressure. Its number of prescription had reached 900.000 by 1974 [20]. During these four years, only one ADR report was filed about conjunctivitis associated with the use of drug. After the announcement of the ADR, more than 200 reports were received [19]. The estimated number of practolol victims was 8000 as of 1980. More evidence of underreporting is provided by research, which studied the attitudes of the pharmacists towards reporting ADRs using surveys [21-23]. Based on the survey analysis using 1357 questionnaires and completed by healthcare workers in the Netherlands, Eland *et al.* (1999) reports that only 51% of general practitioners and 35% of specialists have ever reported an ADR. The result that hospital doctors report less frequently than general practitioners, demonstrates that the attitudes of different groups of doctors may change significantly. What's more, 86% of general practitioners, 72% of surgical specialists and 81% of medical specialists did not report an ADR that they had detected. These results show that underreporting results not only from inability of practitioners to detect the ADR, but also from their failure to report the ADRs that they detect. The research on this issue has shown that the magnitude of reporting varies between countries and depends on many factors. The most recognized factors in these studies are as follows [13];

- *The seriousness of the reaction*
- *Novelty of the drug*
- *Whether the effect is publicized*

As experienced in the case of practolol, a drug, which has been on the market for a while, can be overlooked. However, once an ADR associated with that drug is publicized, ADR reports start to come. Inman and Weber (1986) discuss the reasons why ADRs are not reported. They argue that the ADRs are not reported not because of failure to report a detected ADR, but because of failure to detect for most of the cases. They discuss that the doctors generally do not take into account the possibility that an ADR may be the cause of a symptom. What is worse, they may not even know that the drug is taken at all by the patient. It is argued that the patient's complete drug-history may not be available or that patients may purchase the drugs from the over-the-counter market without a prescription. They call the reasons behind the failure to report the "seven deadly sins", which are listed below [19];

- *Complacency: the doctors think that only safe drugs are marketed.*
- *Legal concerns: the doctors fear that they might be sued if they report a non-existing ADR by mistake.*
- *Guilt: The doctors are reluctant to accept that their patients are hurt by a drug they prescribed*
- *Research ambitions: The doctors might want to publish their findings, which would result in a delay of publicity of the ADR.*
- *Lack of communication between the reporting center and the professions.*
- Reluctance of reporting due to fear of appearing foolish if no such an ADR exists.
- *Lethargy: The doctors may not report an ADR they detect because there is no financial benefit or because they do not have time.*

Survey analysis in the previous literature tries to find out the reasons behind the failure of reporting even if an ADR is detected. The results of a survey conducted by Belton (1997) indicate that insufficient channels of reporting and knowledge on how to report are the main issues. Lack of availability of reports, the address or telephone number of the reporting agency and lack of information on how to report are argued to be the reasons for under-reporting. Another argument was the lack of time to report. On the other hand, contrary to the arguments of Inman and Weber (1986), concerns about legal

liabilities, patient confidentiality, or research ambitions, seem to be not significant [22]. These results are supported by the findings of other researchers. Using the outcomes of a survey with 322 respondents among hospital pharmacists in U.K., Green *et al.* (2001) discovered that almost half the respondents do not have a thorough knowledge about the issue to be reported. What is more, 86.1% of the respondents feel that ADR reporting is a professional obligation and the findings of the analysis shows that absence of a fee does not seem to be a factor [24].

These findings indicate that if the awareness of health-care professionals can be increased by promoting the reporting system and giving comprehensive education about ADR and necessity of ADR reporting. The next issue is facilitation of reporting. One of the major complaints is lack of time [13]. An easier and less time-consuming system of reporting, which would not be hard to launch considering the abilities of the information technology in the 21st century, might decrease the under-reporting enormously.

2.4 ADR Monitoring System and Institutions in Turkey

In 1985, the first Turkish institution on pharmacovigilance, known as the "Turkish Adverse Drug Reaction Monitoring and Evaluation Center "(TADMER), was established . TADMER became a member of the WHO program for International drug monitoring in 1987. Although Turkey was the 23rd member of the program, one of the first few among developing countries, it took 20 years to construct a legal basis for adverse drug reaction reporting. In 2004, the Drug Safety Monitoring and Evaluation Department was established within the General Directorate of Pharmaceuticals and Pharmacy of the Turkish Ministry of Health. Next, *"Regulation on the Monitoring and Assessment of the Safety of Medicinal Products for Human Use"* was published in the Official Gazette on March 22nd, 2005. With this regulation, TADMER evolved into the Turkish Pharmacovigilance Center (TUFAM) and a system under the guidance of regulatory agencies, whose principles are issued in "*Pharmacovigilance Guideline for Marketing Authorization Holders of Medicinal Products for Human Use*" was

formulated. The spontaneous ADR reporting system specified by these guidelines is summarized in Figure 2.

The Drug Safety regulation and the guidelines following this regulation define the responsibilities of the regulatory agency, namely TUFAM, the registration holder and the other partners of the ADR monitoring system. These responsibilities are summarized below.

Marketing Authorization Holders' Responsibilities

The market authorization holder is held responsible for the safety of their products. They are expected to have a pharmacovigilance unit to conduct pharmacovigilance activities, with at least one full-time pharmacologist, clinical pharmacologist or toxicologist or a physician or pharmacist. The company is allowed to transfer its responsibilities to a contracted pharmacovigilance service institution. Even if the company uses a contracted institution for pharmacological purposes, it should employ a full time product safety officer, who has sufficient background and necessary training provided by the Turkish Health Ministry. The product safety officer is responsible for providing all information relating to the risk and benefit analysis of the product to the Pharmaceutical General Directorate. The name of the product safety officer and the contracted company if employed should be notified within 7 days. The "c" and "d" clauses of 14th article of the regulation holds the registration holders responsible for informing TUFAM about any serious adverse effects occurring in Turkey and forwarding reports received through any means from abroad within 15 days (designated by Arrow 1 in Figure 2).

Responsibilities of Healthcare Professionals and Institutions

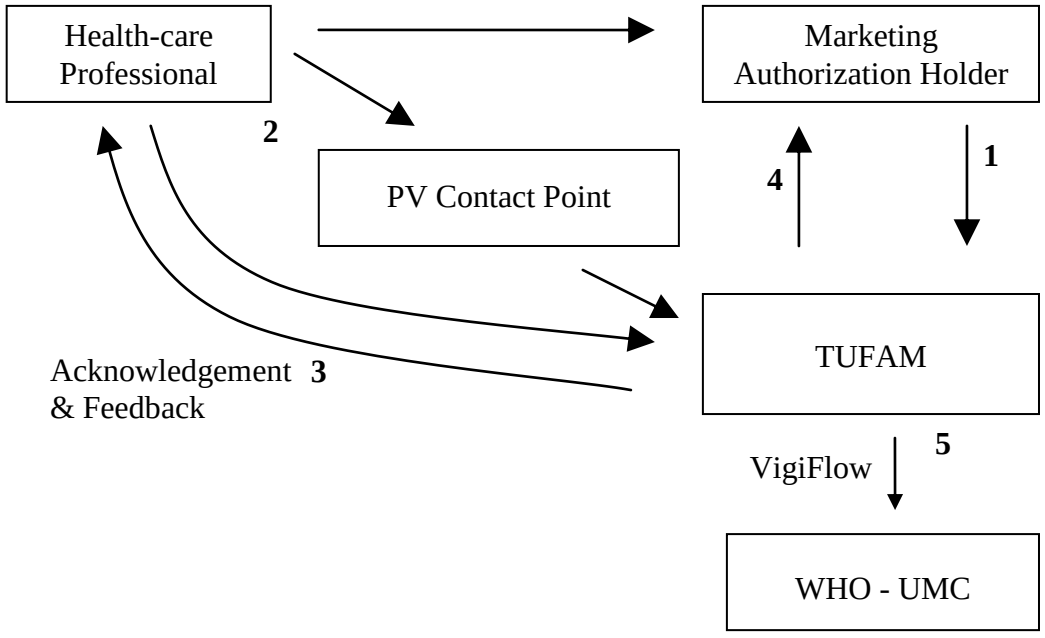
The 8th article of the regulation regards ADR reporting as one of the responsibilities of the healthcare professionals. They are expected to report any ADR to TUFAM or to the related market authorization holder. The 13th article sets a deadline and demands healthcare professionals to report serious ADR within 15 days. What's more, some of the healthcare institutions, namely, university hospitals, other training and research

hospitals and A-1 Group private hospitals defined by the Regulation on Private Hospitals, are required to establish an internal pharmacovigilance system and issue the relevant standard pharmacovigilance study procedures and implement them. To maintain a continuous information flow to TUFAM, a pharmacovigilance contact person must be appointed by the hospital administration. The background and the contact information of the appointed personnel are expected to be submitted to the Healthcare Ministry. The healthcare professionals can inform TUFAM via the pharmacovigilance contact point (Arrow in the Figure 2).

Responsibilities of TUFAM

The reporting responsibilities of TUFAM are set out in the 16th article. TUFAM is expected to inform the manufacturer (registration holder) about a suspected serious ADR occurring in Turkey within 15 days after it receives the report (Arrow 4 in Figure 2). TUFAM shall also forward these reports to the international database administered by WHO and UMC (Arrow 5 in Figure 2)

Figure 2: Spontaneous Reporting System defined by Turkish Regulation



The reports received are evaluated by the Monitoring, Assessment and Advisory Commission for Medicinal Products for Human Use. If the commission decides that a modification in the registration information, a withdrawal or a suspension is appropriate, it has to inform TUFAM within 15 days on this matter. In case of an emergency, the transaction pertaining to the suspension of the registration/permit shall be communicated on the working day following the day when the transaction was realized.

3. Methodology

Aim

The aims of this research are to assess the awareness of Turkish physicians and nurses of pharmacovigilance, and to study the impact of a seminar on their perception and attitude towards pharmacovigilance and adverse drug reactions (ADR) reporting. The existence of any differentiation among demographic groups is also investigated.

Study population

To achieve the main objective of the research, conducting a study with a large sample involving many health-care professionals from different institutions in different areas of Turkey would be ideal. However due to limited time and access, this wide reaching kind of study was deemed impossible. Therefore, VKF American Hospital was selected, not only because the researcher has certain access to the institution as the head of the hospital pharmacy, but also because VKF American Hospital is one of the most advanced hospitals in Turkey. The VKF American Hospital provides health-care service in 38 branches of medical specialty to over 131.000 patients per year with its 300 patient rooms (of which 60 are in intensive care units), 13 operating theatres as well as 541 doctors and 1028 paramedical and nursing staff. It has the JCI certificate indicating that the service offered meets international standards and the hospital is highly committed to patient safety. Moreover, as a private hospital, its patients are mostly well educated with upscale income level and have developed substantial consumer awareness.

Therefore, in terms of the first purpose of the research, it would be wrong to claim that the sampling is random. Both the professionals and the patients of VKF Amerikan Hospital might be expected to be more acquainted with ADR and pharmacovigilance compared with the rest of the Turkey. Regarding the second purpose of the research, sampling may not affect the outcome, since the aim is to measure the effectiveness of the educational conference.

To select the participants in the research study, convenience sampling in which participants were selected randomly depending on their ease of access was used. The research study population consisted of 15 nurses and 15 physicians. Nurses and physicians were included in the study as two different groups in order to analyze the difference in attitude towards Pharmacovigilance and reporting of ADR between them, if any exists. The critical limitation of the research was the lack of time of the participants. They were asked to attend an educational conference on pharmacovigilance and fill out two questionnaires before and after the conference. The researcher held two sessions of this conference, which lasted 30 minutes each.

Questionnaires

Considering the time limitation of the participants, the questionnaires of the research were designed to be concise and minimally time consuming. The first questionnaire, filled out before the conference, aimed to evaluate the acquaintance of participants with pharmacovigilance in general terms. It involved demographic and professional questions to measure any existing difference in knowledge on pharmacovigilance between different demographic and professional groups. The second questionnaire was filled out right after the education session. It aimed to measure the effectiveness of the conference and involved only three questions to assess the satisfaction of participants with the conference, and an open-ended question asking for recommendations and feedback from the participants.

Content of Educational conference slides and folders

The whole study population, 15 physicians and 15 nurses, attended the educational conference, which was given by the researchers. The conference aimed to provide the theoretical background and the necessary information about ADR reporting. It was also aimed to discuss the pharmacovigilance terminology to eliminate any confusion among health professionals due to misuse of terminology. The conference, which lasted around 30 minutes, due to the time limitation of the participants, summarized the information given in the second and third parts of this study. Nurses and physicians attended

separate sessions of the conference in order to be able to detect the difference between them, since the questions and participation in the discussions may have affected the content of the conference.

Statistical Analysis

The data was subjected to frequency analysis and nonparametric Kruskal-Wallis and Wilcoxon rank-sum tests to observe whether differences exist between groups defined by professional and demographic control variables.

4. Results

Results of the First Phase

The first phase of the research aimed to evaluate the acquaintance of the participants with ADR and ADR reporting. Table 10 gives the frequency analysis of the demographic and professional data of the participants distinguished according to their profession, more precisely whether the participant was a nurse or a physician.

Table 10: The socio-demographic characteristics of participants

	Physicians		**Nurses**	
Age	**Number(n)**	**Percentage(%)**	**Number(n)**	**Percentage(%)**
No answer	3	20	1	6.66
20-29	0	0	10	66.6
30-39	6	40	4	26.6
40-49	3	20	0	0
50-59	2	13.3	0	0
60+	1	6.66	0	0
Total	***15***	***100***	***15***	***100***
Sex	**Number(n)**	**Percentage(%)**	**Number(n)**	**Percentage(%)**
No answer	3	13.3	0	0
Male	6	40	1	6.66
Female	6	46.6	14	93.3
Total	***15***	***100***	***15***	***100***
Graduation year	**Number(n)**	**Percentage(%)**	**Number(n)**	**Percentage(%)**
No answer	3	20	1	6.66
1970-1979	1	6.66	0	0
1980-1989	4	26.66	0	0
1990-1999	6	40	4	26.6
2000-2009	1	6.66	10	66.6
Total	***15***	***100***	***15***	***100***
Specialty	**Number(n)**	**Percentage(%)**	**Number(n)**	**Percentage(%)**
No answer	3	20		
Pediatrics	7	46.66		
Family physician	3	20		
Emergency service	1	6.66		
General surgery	1	6.66		
Total	***15***	***100***		

Three of the physicians declined to provide socio-demographic data and one nurse did not provide information about herself. There was a substantial difference in age and

gender distribution between the groups. The average age for physicians was 43.4 and half of them were female. On the other hand, the average age for nurses was 28.6 and only one of them was male. There was no specialty information for nurses. Among physicians, almost half were pediatricians and the others included three family physicians (20%), a general surgeon and a physician who had a specialty in emergency service.

Table 11 provides the frequency analysis of the answers to the ADR related questions. The results are distinguished according to the profession of the participants. The rescaled data provides frequencies based on a different but simpler scale, which is used for analytical purposes. For instance, the first question asks for the correct definition of ADR and only the first answer is completely correct. Therefore, the frequencies of the correct and incorrect answers might provide a simpler profile for research purposes. The details of the incorrect answers increase the number of groups and therefore may make it harder to figure out the deviations among groups due to the insufficient number of data. Both scales are used in the analysis.

Having started with the first question, only 53.3% (n=15) of the physicians answered correctly by matching the definition exactly. Similarly, 60% (n=15) of the nurses gave the correct answer to the first question. The distribution of the incorrect answers between the second and third answer is different for nurses and physicians. 83.3%(n=6) of nurses chose the second answer, while 42.8% (n=7) of physicians chose it.

The second question asked whether the participants observed any adverse drug reactions in patients during their career. While 100% (n=15) of these physicians answered in the affirmative, only 9 (60%) of the nurses did so. It is also interesting to note that 7 of the physicians and 2 of the nurses who gave an incorrect answer to the first question claimed that he or she witnessed an ADR in patients. On the other hand, two nurses out of nine who gave a correct answer to the first question claimed that he or she had not observed an ADR in patients.

The third question asks the frequency of the participants ADR reporting. While only one physician claimed that he or she reported these ADRs once or twice a month, approximately 46.6% of physicians admitted that they reported ADRs rarely. On the other hand, 46.6% of physicians stated that they had never reported. The rescaled data frequency is similar for nurses. 53.3% of the nurses claimed that they reported rarely or more frequent than rarely. It is interesting to note that two physicians out of 7 who gave an incorrect answer to the first question claimed that they had reported ADR rarely or more than rarely. Furthermore, only 6 nurses out of 14 (one nurse did not respond to the third question) and 6 doctors out of 15 (12 out of 29 in total: 41.4%) who had given a correct answer to the first question, claimed that he or she had experienced an ADR in patients and reported at least rarely.

The fourth question asked about the authorities to whom the reports are submitted. There were four alternatives, namely TUFAM and pharmacist, drug company, other and nowhere. The response ratio is lower than on the other questions. Only 12 physicians and 10 nurses responded to this question. The rescaled data provided two groups; "correct reporting" includes the reporting to TUFAM and Pharmacists or the drug company and "no or incorrect reporting" includes reports to other or nowhere. Only 33.3% of the participants report to correct authorities. Physicians prefer drug companies, while nurses prefer TUFAM and physicians. This is probably because physicians have better connections with drug companies. It is interesting to note that only 3 out of 12 (three physicians don't respond to the fourth question) and 5 nurses out of 10 (5 nurses do not respond to either the third or the fourth question) gave a correct answer to the first question. They thus claimed that they had observed an ADR in patients, and had reported, at least rarely, to a correct authority. To put it another way, 36.3% of the participants (8 out of 22) know the correct definition of the ADR, have observed an ADR, and care to report at least rarely to a correct authority.

The last question asked the classes of the drugs reported. 60% of the participants (n=18) did not answer this question. The physicians listed the ADR reported classes as antibiotics (26.6%), analgesics (6.66%), and others including vaccines (6.66%) and

baby food (6.66%). The nurses mostly report ADRs for drug classes including, 26.6% oncology drugs, 6.66% central nervous system drugs and 6.66% cardiovascular system drugs.

Figure 3 demonstrates the average age of the participants grouped according to their answers to the questions designated in the rescaled form. The first line in the Figure 3 shows that the average age of the participants who give an incorrect answer to the first question (Rescaled parameter: 2) is lower. Similarly, the average age participants who claim that they have never observed an ADR (Rescaled parameter: 2) in a patient is lower. The difference between the groups defined by the third and the fourth questions is very low. Apparently, it shows that except for the second question, the averages of the ages of the participant are very close to each other. In other words, age is not a significant discriminating factor for responses to these questions.

Figure 3: Averages of the ages of the participants grouped according to their answers to the questions (Rescaled Parameters)

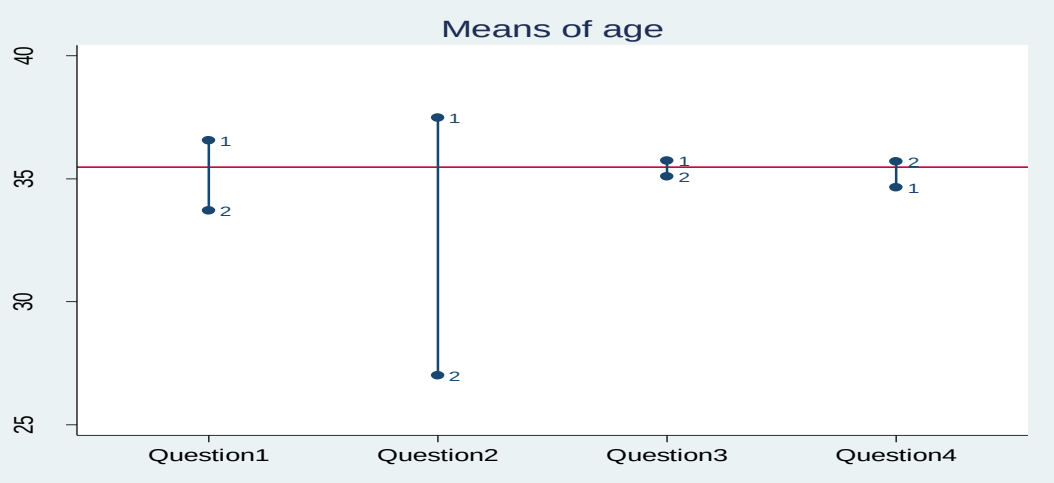


Table 11: The frequency analysis of attitude questions about ADR reporting										
			Physicians				**Nurses**			
	Questionnaire	**Rescaled Parameter**	**Data**		**Rescaled Data**		**Data**		**Rescaled Data**	
Question 1	**Answer**	**Answer**	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**
Which one of the followings best describes the 'Adverse Drug Reaction'?	It is an unwanted effect caused by a medicine when used at a normal dose in patients for pharmacological effects.	Correct (1)	8	53.3	8	53.3	9	60	9	60
	It is a noxious and unwanted effect caused by a medicine when used in recommended dosage.	Incorrect (2)	3	20	7	46.7	5	33.3	6	40
	It is an unwanted effect that occurs during treatment with a medicine and it does not necessarily have a causal relationship with the treatment.		4	26.7			1	6.7		
Total			**15**	**100**	**15**	**100**	**15**	**100**	**15**	**100**
Question 2	**Answer**	**Answer**	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**
Have you ever observed an adverse drug reaction in your patients during your career?	Yes	Yes (1)	15	100	15	100	9	60	9	60
	No	No (2)	0	0	0	0	6	40	6	40
Total			**15**	**100**	**15**	**100**	**15**	**100**	**15**	**100**

			Physicians				Nurses			
	Questionnaire	**Rescaled Parameter**	**Data**		**Rescaled Data**		**Data**		**Rescaled Data**	
Question 3	**Answer**	**Answer**	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**
How often do you report Adverse Drug Reactions?	At least once a month	Rare or more than rare (1)	1	6.66	8	53.3	2	13.33	8	53.3
	Very rare		7	46.67			6	40.00		
	Never	Never (2)	7	46.67	7	46.7	6	40.00	6	40
	No answer	No answer	0	0	0	0	1	6.67	1	6.7
Total			**15**	**100**	**15**	**100**	**15**	**100**	**15**	**100**
Question 4	**Answer**	**Answer**	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**
Where do you report adverse drug reactions?	Drug Company	Correct Reporting (1)	3	20	5	33.3	0	0	5	33.33
	TUFAM and Pharmacist		2	13.3			5	33.33		
	Nowhere	Incorrect or no reporting (2)	7	46.66	7	46.6	4	26.67	5	33.33
	Other		0	0			1	6.67		
	No answer	No answer	3	20	3	20	5	33.33	5	33.33
Total			**15**	**100**	**15**	**100**	**15**	**100**	**15**	**100**

The issue of the effect of age on the answers given was tested using nonparametric Kruskal-Wallis test. First, five groups of participants are defined according to their ages. These groups are 20+, 30+, 40+, 50+, and 60+, as shown in the Table 10. Then, the Kruskal-Wallis test is used to test whether the responses to the questions come from the same population. In other words, the aim is to test whether the participants in these age groups differentiate according to their responses to questions about ADR reporting. By looking at Figure 3, age seems to be a differentiating factor only for the second question. Table 12 gives the test results. The null hypothesis that all groups come from the same population is rejected only for the second question at 5% significance level. As expected, the age groups only differentiate according to their responses to the second question, which asks whether they have experienced an ADR in their patients. The test outputs obtained from "*Stata*" for both original data and rescaled data are provided in the Appendix.

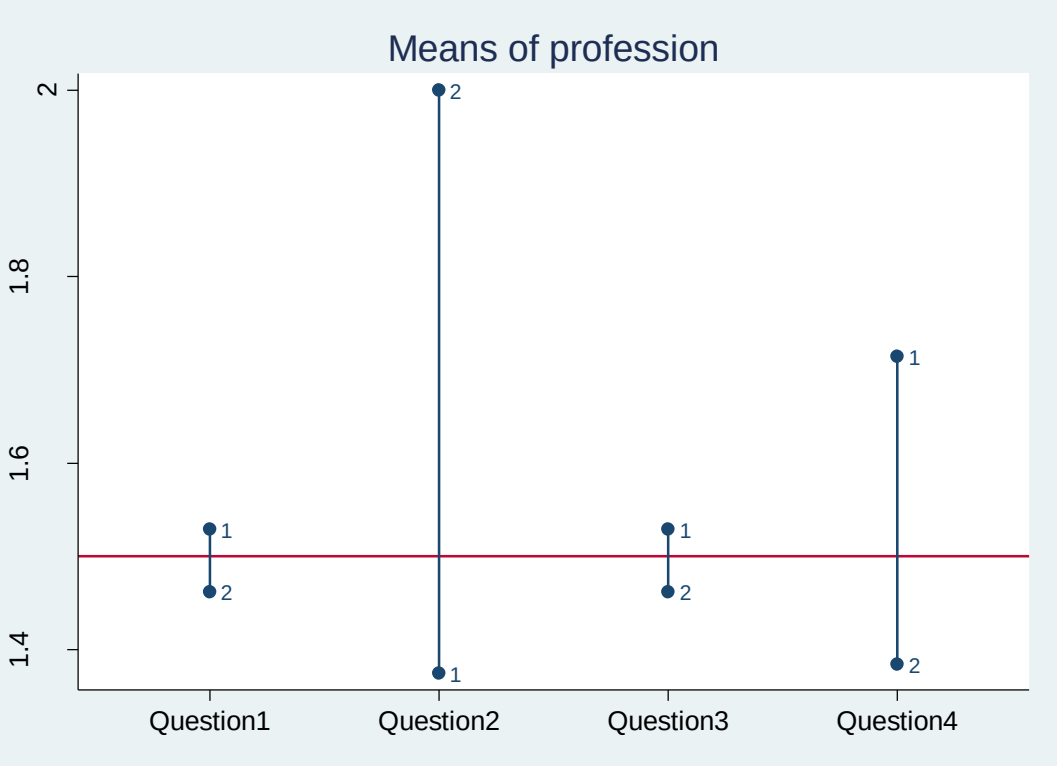
Table 12: Kruskal-Willkins Test Results for age groups with rescaled parameters

	Test Statistic	p-value (Chi-Square with 4 d.f.)
Question1	0.76	0.96
Question2	9.52	0.04
Question3	3.07	0.54
Question4	3.99	0.41

Figure 4 below demonstrates the averages of profession parameters (2 for Nurses and 1 for physicians) of the participants grouped according to their answers to the questions designated in the rescaled form. Since there are equal numbers of nurses and physicians, the average of the professional parameter is 1.5. For instance, since the average of the professional parameter of the participants who answer correctly to the first question is above 1.5, this means that more nurses than physicians answer correctly. However, the difference is not significant for the first question. Therefore, it would not be wrong to expect that profession is not a determining factor for the responses to the first question. In other words, no significant difference is expected between nurses and physicians

according to their answers to the first question. Similarly, the average of the professional parameters of the participants who claim that they have never observed an ADR (Rescaled parameter: 2) in a patient is two. This means that all participants claiming that they have never experienced an ADR in their patients are nurses. The professional parameter seems to be significant for the second and the fourth questions.

Figure 4: Averages of the profession parameters of the participants grouped according to their answers to the questions (Rescaled Parameters)



This issue is tested using nonparametric two-sample Wilcoxon rank-sum test. The Wilcoxon rank-sum test checks whether two independent samples of observations come from the same distribution. The groups are defined according to the profession of the participants. Next, the Wilcoxon test was performed for each of the question to test whether the responses to these questions of the participants in both groups have the

same distribution. Table 13 gives the test results. The null hypothesis that both professional groups have the same distribution is rejected only for the second question at 5% significance level. The test outputs obtained from Stata for both original data and rescaled data are given in the Appendix.

Table 13: Wilcoxon Test Results for professional groups with rescaled parameters

	Test Statistic	p-value (Stand. Normal Dist.)
Question1	0.36	0.72
Question2	-2.69	0.01
Question3	0.36	0.72
Question4	1.69	0.09

Results of the Second Phase

The second questionnaire, given after the conference, aimed to evaluate the satisfaction of the participants with the conference. The first question asked the participants to evaluate the contribution of pharmacovigilance education conference on a 3-point scale, namely no contribution (1), a little (2) and a big (3). The second question asked to evaluate the helpfulness of the conference on a 3-point scale, namely not helpful (1), somewhat (2), very helpful (3). The third question asked whether the participants expect an increase in ADR reporting rate by responding according to a 3-point scale, namely no increase (1), a little (2), and a lot (3). The final question was an open-ended one, asked for the comments and feedbacks of the participants. The responses of the physicians and nurses are given in Table 14 and Table 15 separately.

The physicians provide an overall positive response. None of them gave negative answers to the questions. 6 of the physicians (40%), who gave the highest grades for all questions, seemed to be very satisfied.

Table 14:**The evaluation of pharmacovigilance education conference by physicians**

Question 1	**Answer**	**Number(n)**	**Percentage(%)**
How do you evaluate the contribution of pharmacovigilance education conference to your pharmacovigilance knowledge?	A lot	12	80
	A little	3	20
	Non	0	0
Total		**15**	**100**
Question 2	**Answer**	**Number(n)**	**Percentage(%)**
How do you consider the helpfulness of presentation?	Very helpful	9	60
	Somewhat	6	40
	Not helpful	0	0
Total		**15**	**100**
Question 3	**Answer**	**Number(n)**	**Percentage(%)**
Do you consider that rate of adverse drug reporting to Pharmacovigilance Centre will increase by this conference?	A lot	9	60
	A little	6	40
	No increase	0	0
Total		**15**	**100**
Question 4	**Answer**		
Please write any additional recommendations (not mentioned in conference) about pharmacovigilance	Difference between effect of disease and drug adverse effect		
	How are the ADRs reports of physicians beneficial?		
	Are the complaints of patients sufficient for reporting or should we look for an observable symptom to report ?		
	Turkish word equivalents to adverse and vigilance should be found and used		

For the last question, some of the physicians provided some recommendations and feedback, which clarified the deficiencies of the training. These comments showed that the length of the conference was insufficient and should have been extended. One critical and insightful comment argued that the Turkish word equivalents of adverse and vigilance should be used. The nurses gave no response to this question. However, oral

questions and comments from nurses were received and deficiencies of the conference were addressed face to face at the end of conference.

Similar to the physicians, the nurses provided an overall positive response. Only the distribution of the answers to the first question was different. The equality of the distribution of both profession groups for the three questions in the second questionnaire was tested using the Wilcoxon test. The null hypothesis is that the distributions for both groups cannot be rejected at 5% significance level for all questions. This indicates that there is no significant difference between the responses of the nurses and the physicians to these questions.

Table 15: The evaluation of pharmacovigilance education conference by nurses

Question 1	**Answer**	**Number(n)**	**Percentage(%)**
How do you evaluate the contribution of pharmacovigilance education conference to your pharmacovigilance knowledge?	A big contribution	9	60.00
	A little contribution	6	40.00
	No contribution	0	0.00
Total		**15**	**100.00**
Question 2	**Answer**	**Number(n)**	**Percentage(%)**
How do you consider the helpfulness of presentation?	Very helpful	9	60.00
	Somewhat helpful	6	40.00
	Not helpful	0	0.00
Total		**15**	**100.00**
Question 3	**Answer**	**Number(n)**	**Percentage(%)**
Do you consider that rate of adverse drug reporting to Pharmacovigilance Centre will increase by this conference?	A lot increase	9	60.00
	A little increase	6	40.00
	No increase	0	0.00
Total		**15**	**100.00**

5. Discussion

This research is one of the few studies on the perception of pharmacovigilance among Turkish practitioners. Toklu and Uysal (2008) studied the awareness of pharmacovigilance of the community pharmacists in the Kadıköy district of Istanbul and demonstrated that they did not have sufficient knowledge about pharmacovigilance. This research differs from their study by assessing the knowledge and attitudes of hospital nurses and physicians towards adverse drug reactions. The role of hospital physicians and nurses is crucial since they have the chance to follow the impact of medication more closely than other practitioners.

The major limitation of this study is the number of participants. Only 30 participants attended the educational seminars and some of them did not respond to some of the questions. The second limitation is that this research was conducted in only one hospital. The VKF American Hospital is arguably one of the best-equipped hospitals in the most developed part of Turkey and has mostly well-educated patients who demand high quality of care. Therefore, the practitioners of VKF American Hospital are expected to be well informed about this issue. To put it another way, the sample used in the analysis is not random, and the outcome of the frequency analysis for the first questionnaire would be biased on the positive side, considering the whole hospital practitioners population in Turkey.

Pharmacovigilance has become more popular since the foundation of TUFAM and the launch of the Regulations on the Monitoring and Assessment of the Safety of Medicinal Products for Human Use in 2005. However, even though this regulation creates many responsibilities for practitioners, the findings of this research demonstrate that practitioners are not aware of the importance of pharmacovigilance.

The findings of this research also demonstrate that awareness of ADR and pharmacovigilance is below sufficient levels. Only 56.6% of all participants know the correct definition of ADR. Comparing the nurses and physicians, the success rate is 6.7% higher for the nurses. The Wilcoxon test shows that there is no significant difference between nurses and physicians. However, there is a difference between the

incorrect answers of the nurses and physicians. 42.8% of the physicians with wrong answers chose the second answer, while 83.3% of the nurses with the wrong answer selected it. Most of the nurses with incorrect answers were misled by the term noxiousness. This difference might indicate that nurses and physicians have different understandings of ADR, and education packages with different contents for nurses and physicians might be more helpful.

What is more, the percentage of nurses who observed an ADR in their patients was unexpectedly low. Only 60% of the nurses stated that they had observed an ADR in their patients, while all of the physicians claimed they did. It should be noted that 7 of the physicians and 2 of the nurses who didn't know the definition of ADR stated that they had experienced an ADR. Since they did not know what an ADR was, the event that they defined as an ADR might not have been an ADR. Therefore, any statistical inference based on this result might be misleading. Ignoring this issue, the results indicate that there is a significant difference between nurses and physicians. This might be a result of their profession or the difference in experience between these two groups. The comparative deficiency of nurses contradicts the findings of Ulfvarson et. al. (2008) who states that nurses who have close contact with the patients could acquire key information about ADR. Another explanation might be the age difference between groups. Nurses in the sample are younger and therefore have less experience. Furthermore, age was found to be a discriminating factor for this question using Kruskal-Wallis test.

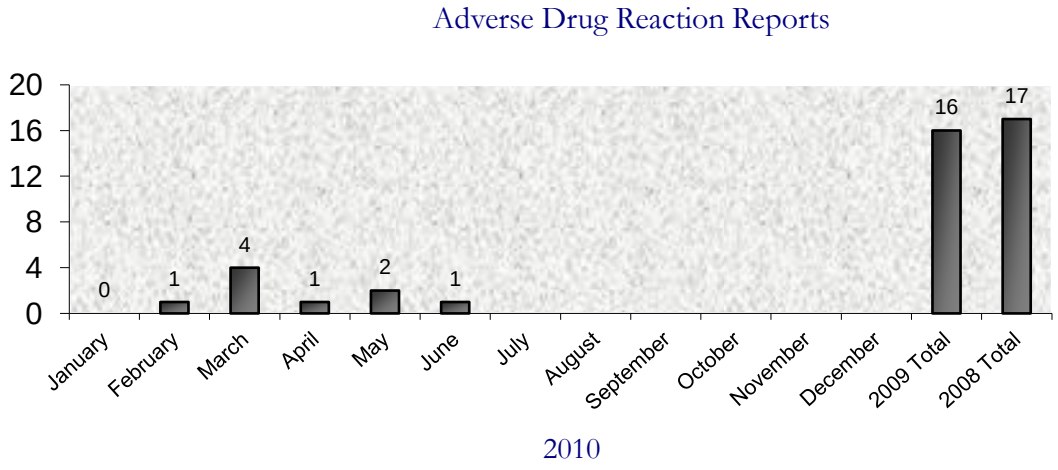
The responses to the third question show that the ADR reporting is very low. Only 10% of the participants stated that they reported at least once a month. The rate of the participants that reported rarely or more than rarely is 53.3%. The findings of Kruskal-Wallis and Wilcoxon tests indicate that age and profession don't influence ADR reporting.

The low rate of reporting might be the result of insufficient knowledge. The findings of the frequency analysis show that only 10 out of 22 participants reported an ADR to a correct authority, namely TUFAM, the pharmacist, or the drug company. 8 of the participants didn't respond to this question. The nurses and physicians seem to differ from each other by a 10 % significance level according to the authority they report. 20%

of the physicians preferred drug companies, while none of the nurses did. On the other hand, none of the physicians reported to TUFAM. The close connection of physicians to drug companies could be the explanation behind this difference. 31.2% of the participants who stated that they reported rarely or more than rarely, did not answer the fourth question.

Previous literature argues that knowledge and attitudes of the practitioners are the important factors affecting the ADR reporting [25]. The second questionnaire demonstrates that the knowledge of the participants can be improved significantly by providing a quick seminar. The participants in the seminar provided an overall positive response to the questions asking about the contribution and helpfulness of the seminar. 60% of the participants stated that the seminar they attended would result in a lot increase in ADR reporting. The rest stated that a little increase was expected.

Figure 5: ADR Reports Statistics in 2008, 2009 and 2010



However, the face-to-face interviews and discussions after the seminar revealed that the seminar had no impact on attitudes of some of the participants. Some of the physicians argued that if there was no legal obligation, they could see no reason or incentive to report an ADR. The overall hospital ADR reports statistics show that there is no

improvement in reporting after the seminar. Figure 5 represents the ADR reports monthly in 2010 and annually in 2009 and 2008. ADR reported in 2009 decreased to 16 from 17 in 2008. The total number of ADR reports in the first months of 2010 is 9. Since there is no reason to expect seasonality in the number of ADR reports, it would not be wrong to argue that there is no improvement. In addition, among the departments whose physicians attended to the seminar, only Emergency Service has reported ADRs since the seminar.

Therefore, based on the findings of the second questionnaire, the seminars seemed to improve the awareness of the participants, most of whom had inadequate knowledge on ADR reporting and pharmacovigilance. However, the fact that there has been no increase in ADR reports indicates that knowledge is not sufficient. As existing literature studying the underreporting in developed countries points out, there are many reasons other than lack of knowledge behind underreporting. Lethargy seems to be the major problem according to the face-to-face interviews and discussions after the seminars.

To sum up, even though educational seminars may increase the knowledge of the practitioners about ADR reporting, it would be wrong to expect a huge change in ADR reporting without an incentive or punishment. In other words, even if the knowledge of practitioners in Turkey is raised by educational seminars all over Turkey, the other reasons for not reporting defined by the existing literature as the seven deadly sins [19] would still remain to be dealt with.

6. Conclusion

In conclusion, this research demonstrates that the knowledge and awareness on ADR reporting is insufficient. Even though the sample used in the analysis is not random, considering that the American Hospital is one of the most developed hospitals in Turkey, it would not be wrong to argue that the situation for the whole practitioners population in Turkey is at least not expected to be better. The findings of the second questionnaire demonstrate that an educational seminar could improve the awareness of the participants. Nevertheless, although these seminars are necessary to provide the practitioners with the knowledge they require on ADR reporting, they did not result in an improvement in ADR reporting. Anyhow, during the discussions and face-to-face interviews after the seminars, some of the participants argued that since there was no incentive or penalty, there was no reason to report an ADR.

To sum up, the attitude problem, discussed widely by the existing literature, seemed to remain unsolved even after the seminars. Further studies could focus on how to eliminate the attitude problem to decrease ADR underreporting.

Appendix: Statistical Analysis Output from Stata

```
-------------------------------------------------------------------------
------------
       log:  G:\aslý\asli.smcl
  log type:  smcl
 opened on:   8 Apr 2010, 14:34:56

. kwallis soru1, by(yasg)

Kruskal-Wallis equality-of-populations rank test

  +------------------------+
  | yasg | Obs | Rank Sum |
  |------+-----+----------|
  |    1 |  10 |   134.00 |
  |    2 |  10 |   139.00 |
  |    3 |   3 |    36.50 |
  |    4 |   2 |    33.00 |
  |    5 |   1 |     8.50 |
  +------------------------+

chi-squared =     0.855 with 4 d.f.
probability =     0.9309

chi-squared with ties =     1.137 with 4 d.f.
probability =     0.8883


. kwallis Question2, by(yasg)

Kruskal-Wallis equality-of-populations rank test

  +------------------------+
  | yasg | Obs | Rank Sum |
  |------+-----+----------|
  |    1 |  10 |   175.00 |
  |    2 |  10 |   110.00 |
  |    3 |   3 |    33.00 |
  |    4 |   2 |    22.00 |
  |    5 |   1 |    11.00 |
  +------------------------+

chi-squared =     4.444 with 4 d.f.
probability =     0.3492

chi-squared with ties =     9.524 with 4 d.f.
probability =     0.0493

. kwallis soru3, by(yasg)

Kruskal-Wallis equality-of-populations rank test
```

```
  +-----------------------+
  | yasg | Obs | Rank Sum |
  |------+-----+----------|
  |    1 |   9 |   118.50 |
  |    2 |  10 |   124.50 |
  |    3 |   3 |    41.00 |
  |    4 |   2 |    35.00 |
  |    5 |   1 |     6.00 |
  +-----------------------+

chi-squared =     1.737 with 4 d.f.
probability =     0.7839

chi-squared with ties =     2.158 with 4 d.f.
probability =     0.7067

. kwallis soru4, by(yasg)

Kruskal-Wallis equality-of-populations rank test

  +-----------------------+
  | yasg | Obs | Rank Sum |
  |------+-----+----------|
  |    1 |   5 |    54.00 |
  |    2 |   9 |    75.00 |
  |    3 |   2 |    22.00 |
  |    4 |   2 |    34.00 |
  |    5 |   1 |     5.00 |
  +-----------------------+

chi-squared =     4.838 with 4 d.f.
probability =     0.3043

chi-squared with ties =     5.622 with 4 d.f.
probability =     0.2292

. kwallis Question1, by(yasg)

Kruskal-Wallis equality-of-populations rank test

  +-----------------------+
  | yasg | Obs | Rank Sum |
  |------+-----+----------|
  |    1 |  10 |   137.00 |
  |    2 |  10 |   137.00 |
  |    3 |   3 |    38.50 |
  |    4 |   2 |    30.00 |
  |    5 |   1 |     8.50 |
  +-----------------------+

chi-squared =     0.541 with 4 d.f.
probability =     0.9694

chi-squared with ties =     0.760 with 4 d.f.
```

```
probability =     0.9437

. kwallis Question3, by(yasg)

Kruskal-Wallis equality-of-populations rank test

  +------------------------+
  | yasg | Obs | Rank Sum |
  |------+-----+----------|
  |    1 |  10 |   132.00 |
  |    2 |  10 |   145.00 |
  |    3 |   3 |    37.00 |
  |    4 |   2 |    16.00 |
  |    5 |   1 |    21.00 |
  +------------------------+

chi-squared =     2.252 with 4 d.f.
probability =     0.6895

chi-squared with ties =     3.071 with 4 d.f.
probability =     0.5461

. kwallis Question4, by(yasg)

Kruskal-Wallis equality-of-populations rank test

  +------------------------+
  | yasg | Obs | Rank Sum |
  |------+-----+----------|
  |    1 |  10 |   111.00 |
  |    2 |   9 |   127.50 |
  |    3 |   2 |    27.00 |
  |    4 |   2 |    15.00 |
  |    5 |   1 |    19.50 |
  +------------------------+

chi-squared =     2.912 with 4 d.f.
probability =     0.5727

chi-squared with ties =     3.987 with 4 d.f.
probability =     0.4078


. ranksum soru4, by(pro)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

  profession |      obs    rank sum    expected
-------------+---------------------------------
           1 |       12         135         138
           2 |       10         118         115
-------------+---------------------------------
    combined |       22         253         253
```

```
unadjusted variance      230.00
adjustment for ties      -33.77
                        ----------
adjusted variance        196.23

Ho: soru4(profes~n==1) = soru4(profes~n==2)
             z =  -0.214
    Prob > |z| =   0.8304

. - preserve
ranksum Question1, by(pro)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

  profession |      obs    rank sum    expected
-------------+---------------------------------
           1 |       15         240       232.5
           2 |       15         225       232.5
-------------+---------------------------------
    combined |       30         465         465

unadjusted variance      581.25
adjustment for ties     -152.59
                        ----------
adjusted variance        428.66

Ho: Questi~1(profes~n==1) = Questi~1(profes~n==2)
             z =   0.362
    Prob > |z| =   0.7172

. ranksum Question2, by(pro)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

  profession |      obs    rank sum    expected
-------------+---------------------------------
           1 |       15       187.5       232.5
           2 |       15       277.5       232.5
-------------+---------------------------------
    combined |       30         465         465

unadjusted variance      581.25
adjustment for ties     -301.94
                        ----------
adjusted variance        279.31

Ho: Questi~2(profes~n==1) = Questi~2(profes~n==2)
             z =  -2.693
    Prob > |z| =   0.0071

. ranksum Question3, by(pro)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test
```

```
  profession |      obs    rank sum    expected
-------------+--------------------------------
           1 |       15         240       232.5
           2 |       15         225       232.5
-------------+--------------------------------
    combined |       30         465         465

unadjusted variance      581.25
adjustment for ties     -152.59
                        ----------
adjusted variance        428.66

Ho: Questi~3(profes~n==1) = Questi~3(profes~n==2)
              z =   0.362
    Prob > |z| =   0.7172

. ranksum Question4, by(pro)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

  profession |      obs    rank sum    expected
-------------+--------------------------------
           1 |       12         198         168
           2 |       15         180         210
-------------+--------------------------------
    combined |       27         378         378

unadjusted variance      420.00
adjustment for ties     -105.00
                        ----------
adjusted variance        315.00

Ho: Questi~4(profes~n==1) = Questi~4(profes~n==2)
              z =   1.690
    Prob > |z| =   0.0910


Two-sample Wilcoxon rank-sum (Mann-Whitney) test

  profession |      obs    rank sum    expected
-------------+--------------------------------
           1 |       15         255       232.5
           2 |       15         210       232.5
-------------+--------------------------------
    combined |       30         465         465

unadjusted variance      581.25
adjustment for ties     -214.66
                        ----------
adjusted variance        366.59

Ho: q21(profes~n==1) = q21(profes~n==2)
              z =   1.175
    Prob > |z| =   0.2399
```

```
. ranksum q22, by(pro)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

  profession |      obs    rank sum    expected
-------------+---------------------------------
           1 |       15       232.5       232.5
           2 |       15       232.5       232.5
-------------+---------------------------------
    combined |       30         465         465

unadjusted variance      581.25
adjustment for ties     -162.28
                     ----------
adjusted variance        418.97

Ho: q22(profes~n==1) = q22(profes~n==2)
             z =   0.000
    Prob > |z| =   1.0000

. ranksum q23, by(pro)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

  profession |      obs    rank sum    expected
-------------+---------------------------------
           1 |       15       232.5       232.5
           2 |       15       232.5       232.5
-------------+---------------------------------
    combined |       30         465         465

unadjusted variance      581.25
adjustment for ties     -162.28
                     ----------
adjusted variance        418.97

Ho: q23(profes~n==1) = q23(profes~n==2)
             z =   0.000
    Prob > |z| =   1.0000

. log close
       log:  G:\aslý\asli.smcl
  log type:  smcl
 closed on:   8 Apr 2010, 16:36:00
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Aslı Özyıldırım was born on 25/05/1977 in Eskişehir-Turkey. She received her Bachelor's degree in Pharmacy from Marmara University in 1999. Ever since then, she has been working as hospital pharmacist in various hospitals. She began her career at Florence Nightingale Hospital in 1999. In 2001, she was appointed the head of the pharmacy department and led the pharmacy department throughout many projects including the acquisition of the JCI certification. In 2003, she joined the team who configured and established the Anadolu Sağlık Merkezi. Between 2003 and 2007, as the head of the pharmacy, she constructed the department and served in many committees that managed various projects including total quality assurance, acquisition of JCI certification and implementation of computerized medication management system for the first time in Turkey. She led the team that won the Best New Hospital International Award in 2006 Barcelona Pyxis Meeting. Since 2007, she has served as the head of the pharmacy in VKF Amerikan Hospital. Her responsibilities include managing and improving the medication management system by implementing computerized technologies, participating the total quality assurance projects and JCI evaluation processes. She is not only the first pharmacist that experienced JCI evaluation process in Turkey, but also the only pharmacist in Turkey that has successfully passed JCI evaluation in three different institutions. She is married with one son.