J. Adv. Res. Pharmaceutical Sciences & Pharmacology Interventions
Volume 2, Issue 2 - 2018, Pg. No. 1-6
Peer Reviewed & Open Access Journal

Research Article

Effect of Pharmacist Involvement on Patient Reporting of Adverse Drug Reactions in Bulgaria

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Abstract

Background: The World Health Organization (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse affects or any other possible drug-related problems". Adverse drug reactions (ADRs) are a significant cause of morbidity and mortality and contribute to the incidence of adverse events, resulting in increased healthcare costs. Healthcare providers need to understand their role and responsibility in the detection, management, documentation, and reporting of ADRs, all essential activities for optimizing patient safety. Pharmacists have an important responsibility in monitoring the ongoing safety of medicines. The aim of the study is to reveal what is the clinical responsibility of the pharmacist in the early detection of ADRs.

Methods: The study is an observational one. A questionnaire was prepared to investigate knowledge and attitude of pharmacists regarding ADR reporting. The questionnaire was given to 415 pharmacists. The study was conducted from May 2017 till September 2017 in Sofia, the capital of Bulgaria. We have used a documentary and statistic methods as well. The questionnaire includes questions on Factors Associated with ADR Reporting, which have been years of work experience as a pharmacist, the habit of detecting ADRs as part of pharmacists' duties, having the basic knowledge needed to report ADRs and the most frequently cited reasons for not reporting ADRs.

Results: 401 of the pharmacists surveyed work in an open-air pharmacy and 14 in a hospital pharmacy. 58.5% of the respondents are master pharmacists and 41.5% are managers of pharmacies. Lower reporting rates by pharmacists are observed in Bulgaria. Most of the respondents unanimously shared that they did not report on the ADRs either on the Bulgarian Drug Agency or the Yellow Card.

Conclusion: Underreporting of ADRs is a common phenomenon in spontaneous post-marketing surveillance programs. Underreporting may delay signal detection and cause underestimation of the size of a problem. It is important to address within the pharmacy profession that ADR surveillance is a priority and a professional responsibility.

Keywords: Adverse drug reactions, Pharmacists, Report

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How to cite this article: Hristov E, Ognyanov S, Deliyski T et al. Effect of Pharmacist Involvement on Patient Reporting of Adverse Drug Reactions in Bulgaria. *J Adv Res Pharm Sci Pharmacol Interv* 2018; 2(2): 1-6.

Introduction

Adverse drug reactions (ADRs) are a major cause of morbidity and mortality and contribute to the occurrence of adverse events, resulting in increased costs of healthcare. Healthcare providers need to understand their role and responsibility in identifying, managing, documenting and reporting ADRs, all major activities to optimize patient safety. During clinical trials, medications are usually tested in a controlled environment for a relatively small number of patients and usually for a limited period of time.[1] While the approval process involves extensive safety testing, these studies sometimes exclude adults, very young and comorbid patients. Patients with multiple drug therapy and patients with reduced renal and hepatic function are often excluded. For these patient populations, any vulnerability to ADRs may be omitted. It is also extremely difficult to predict how practitioners will practically use drugs in practice. In addition, side effects may occur at a low frequency that they are not detected in a small number of patients included in clinical trials; therefore, the widespread use of drugs in the general population may increase the chances of detecting a reaction which have not been reported previously for a particular drug during the market approval process.[2]

It has been suggested that postmarketing surveillance is necessary for the following reasons: 1). Preapproval drug trials can never be large enough to reveal every possible shortcoming or adverse effect of a drug.[3,6] Type B adverse drug reactions (ADRs), which cannot be predicted, are usually rare and may have an incidence of 1 in 10 000 or less. They therefore occur so occasionally during clinical trials that their occurrence may be considered coincidental[4,6]; 2). Preapproval trials can never be long enough.[3,6] Some ADRs become apparent only after months or years of continuous treatment. Benoxaprofen and practolol are examples of drugs that caused very severe ADRs which were missed in early postmarketing experience because of the time required for the reactions to develop[5,6]; 3). Once marketed, medicinal products are sometimes used in patient populations for which they were not tested.[3,6] Polypharmacy, altered pharmacokinetics in the elderly and varied renal function all influence the incidence of ADRs[5,6]; 4). Approved medicinal products are sometimes used for indications for which they have not been licensed.[3,6]

Pharmacovigilance is essential for optimising the benefit-risk balance of medicines on the market in the European Union (EU). The EU regulatory network for medicines includes the National Competent Authorities (NCAs) in the EU Member States (MSs), the European Medicines Agency (the Agency) and the European Commission (EC). This network constantly monitors, assesses and takes action regarding newly detected risks of medicines or when known risks have changed. A key tool for these pharmacovigilance activities is EudraVigilance, the European database for adverse drug reaction reports, which MSs and the Agency use for monitoring the safety of authorised medicines on the EU market. Every report of a suspected ADR submitted by a patient or healthcare professional contributes to safety monitoring and thus to the safe and effective use of medicines.

Bulgaria is a member of Uppsala Monitoring Centre (UMC) from 1974. According to Article 183 of Law on Medicinal Products for Human Medicine in Bulgaria, medical professionals including pharmacists working in hospital and community pharmacies are obliged to report immediately to the the Bulgarian Drug Agency and to the marketing authorization holder (MAH), any suspected, serious or unexpected ADR.

An ADR report can be made by filling in a form (electronic yellow card), description of the ADR in a letter or by communication of the information to a representative of the MAH.[7]

Healthcare providers need to understand their role and responsibility in the detection, management, documentation and reporting of ADRs, all essential activities for optimizing patient safety. Pharmacists have an important responsibility in monitoring the ongoing safety of medicines. In order to determine whether our pharmacovigilance system could be improved, and identify reasons for under-reporting, a study to investigate the role of pharmacists in ADR reporting was performed in Bulgaria.

The aim of the study is to estimate the knowledge and attitude of pharmacists regarding ADR reporting .

Materials and Methods

The study is an observational one. A questionnaire was prepared to investigate knowledge and attitude of pharmacists regarding ADR reporting. 415 masters of pharmacists were interviewed, 401 (96.6%) working in a comunity pharmacies and 14 (3.4%) in a hospital pharmacy. The distribution by sex is 305 women 110 men among pharmacists. 2% of the pharmacies are situated in a broad center, 40.7% are neighborhood and 8.5% are near a medical establishment. 58.5% of the respondents are master pharmacists and 41.5% are managers of pharmacies. The study does not require approval by an ethics committee.

Main outcomes measured: The knowledge of pharmacovigilance practice, reasons for not reporting ADR and perceptions of the Bulgarian pharmacists on pharmacovigilance practice were evaluated.

The study was conducted from May 2017 till September 2017 in Sofia, the capital of Bulgaria. We have used documentary method and data from Bulgarian Drug Agency (BDA).

We have also used a statistic method as: 1). Descriptive methods and assessment methods (descriptive statistics)-

Variance analysis of quantitative variables-mean value, standard deviation, median, minimum, maximum; frequency analysis of qualitative variables (nominal and ranging) that includes absolute frequencies, relative frequencies (in percent), cumulative relative frequencies (in percent), graphical images. 2). Methods for verifying hypotheses. We used the following parametric methods: T-Test Independent Samples-two-way equivalence check for normal distribution and One-Way Dispersion Analysis (Oneway ANOVA - Independent Sampling) - equality check of more than two averages using Post Hoc Tests for multiple comparisons. We analyzed the results obtained using nonparametric methods also: Methods of Kolmogorov-Smirnov and Shapiro-Wilk-checking for the normality of the distribution of a quantitative variable; Chi-square test or Fisher's exact test-search for a link between two qualitative variables; Kruskal-Wallis Test-comparing more than two independent groups with respect to the characteristics of a quantitative variable that does not have a distraction and Mann-Witney method-comparing averages (or medians) in two groups of one quantitative variable when the distribution is not normal. The critical level we use is α = 0.05. The corresponding zero hypothesis is rejected when the P value (P-value) is less than α. The SPSS for Windows 13.0 version was used to process survey data.

Results

The distribution of pharmacists by gender and by age groups are presented on figure1 and table 1 respectively. The distribution of pharmacists by working place and the distribution of pharmacies by location are shown on table 2 and figure 2.

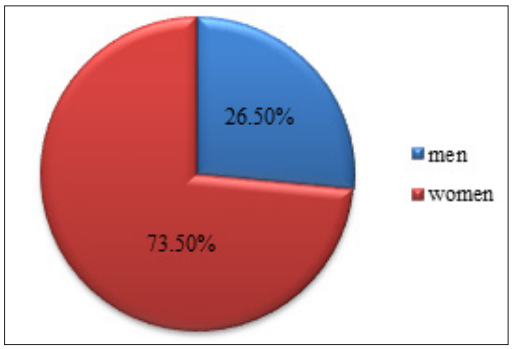

Figure 1.Distribution of pharmacists by gender

Table 1.Distribution of pharmacists by age group

Age	n-415
25-30 years	n-24 (5.8%)
30-65 years	n-391 (94.2%)

Table 2.Distribution of pharmacist by working place

Masters of pharmacists	n-415
Working in a comunity pharmacies	n-401 (96.6%)
Working in a hospital pharmacy	n-14 (3.4%)

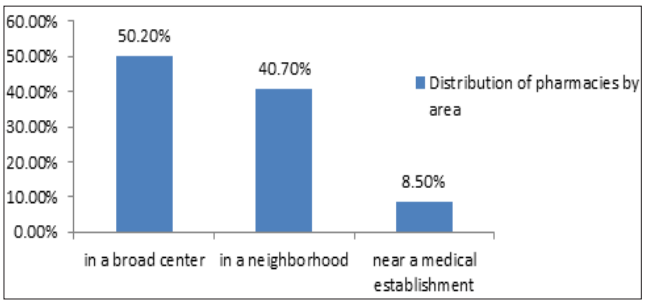

Figure 2.Distribution of pharmacies by location

The questionnaire includes questions on factors associated with ADRs reporting, which have been years of work experience as a pharmacist, the habit of detecting ADRs as part of pharmacists' duties, having the basic knowledge needed to report ADRs and the most frequently cited reasons for not reporting ADRs. According WHO to assess the causal relationship between the drug and ADRs are used algorithms by which the following categories can be defined: certain, probable, possible, unlikely, conditional/ unclassified, and unassessable. Our present study do not aim to analyze the type of ADRs. As is known, there are several channels for reporting adverse drug reactions in Bulgaria (Figure 3). 76.3% of the surveyed pharmacists indicated that doctors were able to do this, 69.5%-indicated masters pharmacists, 30.5%-dentists, BDA website and other medical specialists, 28.8%-patients' organizations, 3% said as a possible channel phone or mail, 16.9%-indicated all the channels mentioned above. More than half of the respondents are aware that pharmacists, along with other healthcare professionals, are a suitable channel for reporting ADRs in the use of medicinal products.

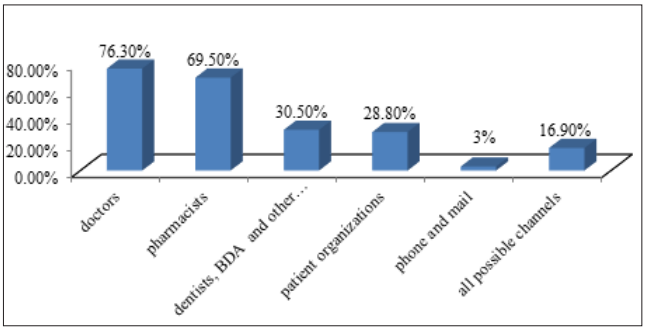

Figure 3.Channels for reporting adverse drug reactions in Bulgaria

Regarding the question: "Is there a standard reporting form for ADRs?"-55.9% are informed that there is one, 20.3% have no information and another 23.7% do not know about its existence (Figure 4).

Nearly half of the surveyed master pharmacists do not feel obliged to report the ADR reported by their patients. 69.9% or 2/3 of the respondents frankly admit that they are not familiar with the BDA's methodical guidelines on the order and manner of reporting suspected ADRs by medical professionals and the importance of the collected pharmacovigilance information (Figure 5).

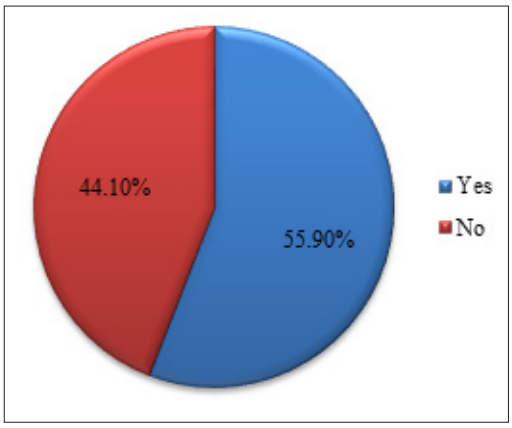

Figure 4."Is there a standard reporting form for ADRs?"-the answers of the surveyed pharmacists

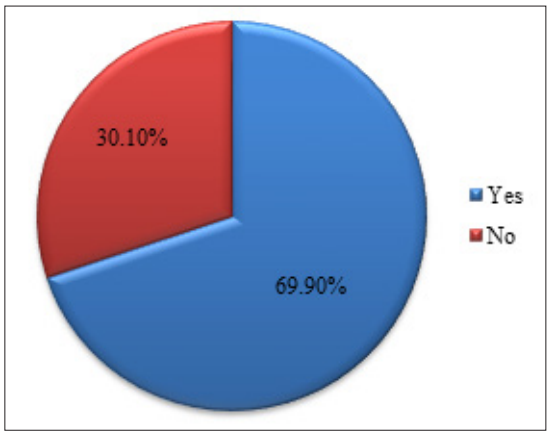

Figure 5.Answers of pharmacists regarding the question "Do pharmacists know the BDA`s methodological guidelines on ADR reporting?"

Around 1/3 (37.3%) of the surveyed master pharmacists know how to get and fill out the yellow card, the remaining 62.7% are unaware of it. In complete contradiction with the positive answer to the first question that they are one of the appropriate channels for reporting ADRs, more of the master pharmacists do not know how to get and fill out the yellow card.

Asked "How many times in 2016 have patients shared information on ADRs and have you reported them to the BDA or to the Marketing Authorization Holders (MAH)?"- 44.1% received information at least once but do not reported it to BDA, and the other respondents did not receive any information or reported once a year. The percentage of information received 2 and 3 times during the year is 3.4% and 4 and more times 1.7%. Respondents' responses show that patients trust and inform pharmacists about ADRs but pharmacists do not submit this information to the BDA and the MAH. 33.9% receive BDA newsletter "Adverse drug reactions", the remaining 66.1% have no information.

Asked "What do you think are the main factors that prevent you from actively participating in pharmacovigilance?"-58.6% have no basic knowledge and need additional training to meet the requirements of the Law on medicinal product for human medicine. 28.8% have no time to fulfill this obligation. For other reasons, 1.7% reported the lack of information from their patients or the lack of feedback from the patients being treated. Only 10.3% keep a patient's record and report on it the ADRs information shared by their patients. Regarding the tendency to send alerts to BDA for ADRs over the past 5 years, 47.5% believe that there is no change in the current practice master pharmacists not to be included from pharmacovigilance and only 15.3% report that the trend is growing, while 28.8% believe it is declining.

Discussion

According to the latest amendments to the Law on Medicinal Products for Human Medicine, patients may report adverse drug reactions at any time to medical specialists or at the same time as the recommended method of reporting by a medical practitioner (physician, pharmacist, midwife, nurse). In addition, there is an opportunity to make a direct alert for a suspected ADR in the Bulgarian Drug Agency.

The practice of pharmacist to have a leading role in the field of pharmacovigilance can be confirmed by a range of data in other countries. Although there is a national pharmacovigilance system in our country since 1974, the number of spontaneous messages tended to decrease initially, despite the significant increase in drug use since the early 1990s.[7] This percentage has increased in recent years. According to BDA's annual report, in 2012 this percentage decreased from 405 to 253, and in 2016 it reached 799 cases. The number of ADR reports received directly in the BDA for 2016 from medical professionals (187) and patients (78) remains comparatively small compared to reporting through the Marketing Authorization Holders (534). From the received messages no signal is generated by qualitative and quantitative methods of detection. Concerning educational activities to Improve reporting and articipation in scientific forums, a total of 6 reports were submitted to medical professionals, patients, and professional organizations in 2016. Two publications in scientific journals have been made. Two posters were presented at the International Congress of Pharmacy and a nomination for one of them was obtained.[7]

Data from a poll conducted survey shows that about 68% of the doctors surveyed in Bulgaria do not know how ADR cases are reported. Only 6% of respondents have ever reported ADR in their practice. These data differ significantly from doctors' habits in EU member states such as Sweden, France and the UK, for example, where rates range between 63% and 75%. Another factor is the belief that only harmless medicines are allowed for use in the country. Such naive treatment is not typical for doctors from most EU countries. Over half of respondents (58%) are unaware of possible sources of information on ADRs and scientific publications in this area.[7]

The system for drug monitoring and registration of ADRs in Bulgaria includes the whole process of identifying the possible unfavorable risk/benefit of authorized medicines, as well as taking regulatory measures. It is coordinated by the Drug Information and Safety Directorate (DLIB), a structural unit of the Bulgarian Drug Agency (BDA). According to the requirements of the legislation, the BDA-regulatory agency is obliged to: maintains a system of pharmacovigilance; encourages professionals to report suspected cases of ADRs; defines the requirements for spontaneous messages; develop guidelines for the collection, verification and presentation of ADR cases; carry out a scientific evaluation of ADR data and compare it with data on drug use; notify within 15 days the registration holder for receiving communications from the country and the EMA about the ADR cases of medicinal products authorized under the Mutual procedure.[7]

A major reason for monitoring newly registered medicines in the country is the very high percentage of medicines withdrawn from the market due to severe ADRs (~ 3%) worldwide. For comparison, Dunnidin's Center for Adverse Drug Reaction (CARM) is the New Zealand National Center for Monitoring of Adverse Reactions (New Zealand Center for Pharmacovigilance 2004). It collects and evaluates spontaneous reports of adverse reactions to medicines, vaccines, plant products, and nutritional supplements from healthcare professionals in New Zealand. Currently, the CARM database contains more than 48,000 reports providing New Zealand-specific ADR information for these products and serves to support clinical decision making for unusual treatment-related symptoms.[1]

National drug monitoring programs around the world differ in their sources of participation in the reporting of ADR by healthcare professionals. Unlike Canada or the United States, where most of the reports come from pharmacists, some countries such as France, Ireland, Malaysia, New Zealand, the Scandinavian countries and the UK make the most contribution from ADR reports coming from doctors (The Learning Center 1999). The reasons for the low levels of reporting by pharmacists in these countries have not been adequately analyzed.[1]

This is supposed to be due to the simple fact that pharmacists are excluded from ADR reporting in the national reporting program, such as the situation in Scandinavia (e.g. Finland and Sweden).[8] UK study concludes that hospital pharmacists require further stimulation and reporting training in order to enhance their role in reporting suspected ADRs in their national pharmacovigilance program.[9] Factors influencing insufficient reporting by pharmacists have also been investigated by some authors. Sweis D and Wong ICK conducted a study of hospital pharmacists in the UK, showing that they are more likely to report serious and rare side effects and those related to new drugs (predisposing factor: attitudes or beliefs).[10]

Van Grootest K et al. have investigated Community pharmacists in the Netherlands who show that the most frequently mentioned reporting barriers are ADRs that are already believed to exist or uncertainty about the causal relationship between ADRs and the drug (predisposing factor: the reporting procedure is too time-consuming (deactivation factor: time).[11]

Reporting on ADR needs continuous stimulation. It is important to develop a positive attitude towards pharmacovigilance among healthcare professionals, including pharmacists, so that ADR reporting can be accepted and understood routinely. Among these sins, the underlying causes of inadequate reporting of ADRs are ignorance and uncertainty, which are strongly related to the low knowledge of pharmacists and doctors about pharmacovigilance activities. As a result, researchers called for more educational interventions aimed at clarifying ADR reporting concepts and processes, including, who should be enrolled (all suspected adverse drug reactions) that can be registered. The authors also identify indifference as the main reason for the inadequate reporting of ADRs, mainly due to the lack of interest and contact between doctors and pharmacists. In doing so, they concluded that improving access to registration forms and simplifying the documentation process would help increase the reporting rate for ADRs while facilitating greater communication between pharmacists and pharmacovigilance centers. On the basis of their general findings, researchers have added another deadly sin to the inadequate reporting of ADRs: the lack of pharmacovigilance training for pharmacists and doctors.[2]

Conclusion

Underreporting of ADRs is a common phenomenon in spontaneous post-marketing surveillance programs. Underreporting may delay signal detection and cause underestimation of the size of a problem. The effectiveness of an ADR monitoring and reporting program depends on the awareness of all healthcare providers. It is important to address within the pharmacy profession that ADR surveillance is a priority and a professional responsibility. Pharmacists' knowledge, beliefs, behaviour and motivation play an important role in ADR reporting. Underreporting might be improved through activities focused on modifying such factors. It is essential to be organized more educations for pharmacists and more studies on ADR monitoring and reporting in Bulgaria are necessary.

Conflict of Interest: None

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Date of Submission: 2018-09-11
Date of Acceptance: 2018-11-22