ABSTRACT

Aim To identify the factors that influence physicians’ under-reporting in Bulgaria and their attitude towards adverse event reporting system and to estimate the role of self-education by providing educational materials.

Methods A randomized nested trial among physicians–general practitioners and specialists in Bulgaria was conducted by a validated questionnaire in order to evaluate their knowledge and attitude towards adverse event reporting system. One month after the intervention the participants were re-visited and were asked to answer the same questions again in order to estimate the change in their knowledge and attitude towards pharmacovigilance system and to obtain their evaluation for the materials provided.

Results The response rate was 91. Fifty seven (46.3%) physicians were not familiar with the pharmacovigilance system. The most common reason for non-reporting adverse drug reactions (ADRs) was uncertainty concerning the relationship between the suspected drug and ADRs, the ADRs were already known and the fact that the physician was not aware where they should report. Although 103 (83.7%) respondents in the entry survey and by 102 (82.9%) of those participating in the exit survey consider ADRs reporting as their obligation (p>0.05), only 50 (40.7%) and 31 (25.2%), respectively answered that they had ever reported ADRs; 109 (88.6%) of the surveyed physicians assessed the provided educational materials as useful for them.

Conclusion The physicians in Bulgaria have poor knowledge for the pharmacovigilance system; however self-education leads to a better knowledge and positive attitude towards ADRs reporting system. National drug regulatory authority should play a more active role in improving physicians’ adherence to the ADRs reporting systems and the developed educational pack can be used in nationwide campaign.

Keywords: pharmacovigilance, adverse event reporting, physicians, knowledge
INTRODUCTION

During the last decades it has been demonstrated that medicines' morbidity and mortality is one of the major health problems recognized by the healthcare professionals and the public (1). Serious adverse drug reactions (ADRs) are the 4th to 6th leading cause of death in the USA (1), and they cause the death of several thousand patients annually. The rate of hospitalizations due to ADRs in different countries is about 10% (2-4). In addition to the increased morbidity and mortality, treatment of ADRs is also a financial burden for the public. The treatment of ADRs impose high financial burden on health care systems. Some countries spend up to 15-20% of their healthcare budget for treatment of drug-related problems (5).

The information received during clinical trials before granting marketing authorization of the medicinal products is sometimes insufficient and incomplete in terms of ADRs. The post-marketing surveillance may detect less frequent but sometimes very serious ADRs (6-7). Spontaneous reporting systems of adverse drug reactions are the basic components of the comprehensive post-marketing surveillance of drug-induced risks. Spontaneous reporting systems are inexpensive and simple to operate. Despite the effectiveness of the system, underreporting is one of their major limitations: it has been estimated that reported ADRs do not exceed 10% of the occurred ones (8-11).

Physicians have a very important role in ADRs reporting (12-13), however very often the number of reports received is insufficient, and occurred less frequently for serious and unexpected reactions (14-16). Studies from different settings show poor and inadequate knowledge on the ADRs reporting systems as well as negative attitude which results in underreporting (17-31). Physicians’ education and training can improve their knowledge on the ADRs reporting system and result in an increased number of reported ADR cases (32-38).

The aim of this study is to assess physicians’ attitude towards adverse event reporting system and the role of self-education by distributing training materials for pharmacovigilance. As a result we evaluated the change in their attitude and willingness to participate in adverse event reporting system and physicians’ personal assessment of their (personal) knowledge on ADRs reporting system.

EXAMINEES AND METHODS

Study population and Settings

The study was conducted in Bulgaria, covering a population of 7.4 million. The study population includes all registered physicians in the country, 28 411 working in 344 hospitals, 1770 outpatient centers and 150 other healthcare centers (39). One hundred sixty seven hospitals are general medical hospitals and the rest are specialized hospitals (etc. oncology, pediatric, maternity, etc. which cover the population of a number of general medical hospitals); 1007 outpatient centers are single medical practices and the rest are medical centers with different types of organization.

Study design

A randomized nested trial was conducted among physicians, including general practitioners and specialists. Two-phase validated questionnaire was used as a voluntary direct anonymous standardized survey in order to evaluate the physicians’ knowledge and attitude towards adverse event reporting system.

The study was designed to have a test phase with 10 physicians and 9 of the received questionnaires were valid. The valid questionnaires were included in the final analysis in order to have greater representative sample.

In 2011 randomly selected physicians were visited, they were informed about the study and its objectives and requested to participate in it. The physicians were asked to complete a structured pre-validated questionnaire and were provided with interactive educational pack on the pharmacovigilance system and a reminder card how to report ADRs. One month later during the second visit the physicians were asked to answer the same questions again in order to estimate the change in their attitude and knowledge on the pharmacovigilance system and to obtain their evaluation for the provided materials.

Intervention

A special package of interactive educational materials on CD was developed. It consisted of presentations on the importance of the pharmacovigilance and additional documentation – guidelines and regulations, translated and adapted
brochure on the importance of spontaneous reporting by WHO (2002), as well as a reminder card and a standard ADR reporting form (yellow card). The materials provided were intended for self-education at time the participants in study find suitable for.

The presentation in the training package includes definitions of pharmacovigilance and ADR, and provides information on the importance and magnitude of the problem. It includes practical advice on how to recognize ADRs, what, where and to whom it must be reported. It contained demonstration of what happens with the information reported by the healthcare professionals. At the end of the presentation useful links were listed, where physicians could find additional information. In addition, all physicians were supplied with a hard copy of a reminder card as a modular desk pyramid which contains summarized information how to report ADRs and reasons why it is important to participate in the pharmacovigilance system.

**Statistical Analysis**

In 2011 the number of physicians in the country was 28411 (39). In order to determine the size of the sample, the Statcalc (40) module of the Epi Info software was employed. The sample size was estimated to 114 people at 95% confidence level, ±1% margin error accepted and proportion of 5%. The sample size was increased by 10%, up to 126 people, so that possible drop-outs and invalid primary registration papers could be compensated. Nine valid questionnaires were obtained from the test phase and they were added to the generated number of the sample size, up to 135 physicians.

In order to improve sample precision, region-based stratification was implemented: 50% of the sample size was selected from the largest regions which are also university centers, i.e. healthcare is most accessible and qualified (Sofia, Plovdiv and Varna) and where almost 50% of the population of the country is concentrated. The remaining 50% of the sample was collected in randomly selected “small” regions (Blagoevgrad, Vratsa, Kyustendil, Montana and Ruse) (40). In addition, in the biggest cities physicians have better continuing education incl. drug safety issues compared to their colleagues in smaller towns and rural areas.

In the designed nests equal number of general practitioners and specialists was surveyed because there was a difference in patients that they are working with, prescribing habits, level of knowledge and educational background as for example post-graduate specialization.

Physicians filled in the questionnaire on paper. The data are presented as percentage and the statistical analyses performed are descriptive analysis and chi-square test accepting p<0.05 as significant.

**RESULTS**

**Demographics**

A total of 135 physicians was surveyed from 6 population areas according to the methodology developed for the sample, and the sample size was exceeded by 13% as surveyed physicians from the test phase were included in the sample size. The response rate was 91%. Sixty three of them (51.2%) were general practitioners (GPs) and the rest were specialists in various healthcare centers (Table 1). One hundred and two (86.2%) of the physicians reported that their list of patients mainly consisted of adults, while 14 (11.4%) physicians provided care mainly to children. Fifty nine (48%) examined between 11 and 20 patients daily, 28 (22.8%) reported to examine 21-30 people daily, and 21 (17.1%) reported to examine one to 10 patients.

### Table 1. Demographic characteristics of the surveyed physicians

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%)</th>
<th>Mean (95% CI)</th>
<th>p (between GPs and specialists)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.5 (41.9-51.9)</td>
<td>0.131</td>
<td></td>
</tr>
<tr>
<td>GPs</td>
<td>49.9 (47.9-51.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialists</td>
<td>51.6 (49.8-53.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working experience</td>
<td>24.9 (23.5-26.3)</td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td>GPs</td>
<td>23.8 (21.9-25.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialists</td>
<td>26.4 (24.3-28.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.183</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44 (35.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>79 (64.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialty</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>111 (90.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12 (9.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of patients</td>
<td>0.486</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>106 (86.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric Patients</td>
<td>14 (11.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>3 (2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average patients per day</td>
<td>21.2 (19.3-23.0)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>GPs</td>
<td>26.1 (23.1-29.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialists</td>
<td>16.1 (14.3-17.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
“Are you familiar with the ADRs reporting system?”

Thirty seven of the participants in the entry survey (30.1%) answered that they were familiar with ADRs reporting system, while in the exit survey this proportion is significantly greater – more than half of all the participants responded positively 65 (52.8%) (p<0.05). Answer “Rather Yes” was given by 29 (23.4%) respondents in entry, and by 34 (27.6) in the exit survey. Thirty four (27.6%) of the participants in the entry survey reported that they were rather unfamiliar with the system, and in the exit survey their share diminishes to 12 (9.8%) (p<0.05). “Definitely No” answer was indicated by 23 (18.7%) of the participants in the entry survey and by 9 (7.3%) of the participants in the exit survey (p <0.05).

Reporting of ADRs

A hundred and three (83.7%) of the respondents in the entry survey and 102 (82.9%) of the participants in the exit survey considered ADRs reporting as their obligation, however only 50 (40.7%) physicians in the entry survey and 31 (25.2%) in the exit survey admitted that they had ever reported suspected ADRs. Forty (78.4%) of the participants in the entry survey and 24 (77.4%) of those in the exit survey (p>0.05) stated that they had reported to the market authorization holder (MAH). Only 5 (9.8%) of the participants in the entry and 6 (19.4%) of the participants in the exit survey (p<0.05) reported to the Bulgarian Drug Agency (BDA). Seventy-two in the entry and 71 in the exit survey (58.5% and 57.7%, respectively) answered that they would like to use an electronic method (e-mail, internet). Twelve participants (9.8%) in the entry and 16 (13%) of those participating in the exit survey would rather use a hard-copy form. Thirty-nine (31.7%) of those in the exit survey gave preference to verbal reporting (p>0.05).

According to the physicians surveyed, the observed ARDs among their patients were most often non-serious (92 physicians or 74.8% of the entry survey participants and 84 or 68.3% of those participating in the exit survey), and about 33 in the entry and 28 in the exit survey (26.8% and 22.8%, respectively) considered that the observed ADRs were relatively serious. The part of the serious ADRs is 4.1(5 physicians) and 7.3% (9 physicians), respectively, and that of the very serious – 4.9 (6 physicians) and 3.3% (4 physicians), respectively. Fifty nine of the participants in the entry and 62 in the exit survey (48% and 50.4%, respectively) believed that connection between the medicine and the ADR observed was possible; while a smaller number 54 in the entry and 50 in the exit survey (43.9% and 40.7%, respectively) consider it to be probable. Six participants (4.9% in the two surveys) believed that such connection was evident, and almost the same number of respondents (4.9% and 6.5%, respectively) was of the opinion that such connection was contingent. For 2 (1.6%) and 3 (2.4%) physicians the causality between a medication and an ADR was non-classifiable.

“Do you have/receive sufficient professional information on ADRs?” and “When was the last time you searched for additional information on ADRs?”

Fifty-eight (47.2%) of the physicians gave a positive answer in the entry survey, and in the exit survey 75 (61%) gave a positive answer. After educational intervention the negative answers decreased from 65 (52.8%) to 45 (36.6%) (p<0.05).

Fifty-eight in the entry and 61 in the exit survey (47.2% and 49.6%, respectively) admitted to have searched for information on ADRs within the last month. Within the last year this was the case for 39 in the entry and 37 in the exit survey (31.7% and 30.1%, respectively). Fourteen in the entry and 13 in the exit survey searched for information within the last 1-2 years (11.4% and 10.6%, respectively). Five physicians had to search for information on ADRs within the last 3-5 years (4.1% of those participating in the entry and exit surveys) or more than 5 years ago, respectively (4.1% compared to 3.3%) (p>0.05).

Reasons for non-reporting of observed ADRs

Forty six of the participants in the entry survey (37.4%) and (statistically) insignificantly more physicians in the exit survey (53 participants, 43.1%) admitted that they had not reported ADRs because they were not sure about the connection between the medication and the adverse reaction observed. Lack of time was an excuse stated by
15 (12.2%) of the entry survey participants and 18 (14.6%) of those participating in the exit survey (p>0.05) (Figure 1).

The pharmacovigilance system although medical professionals in Bulgaria were legally obliged to report ADRs to Marketing Authorization Holder (MAH) or Bulgarian Drug Agency (BDA). This was also supported by the data on low ADR reporting rate in the country which is 16.3 cases for population (41) of 10^4 which was way below the WHO recommended 200-300 cases/10^6 population (6). While most physicians in the present study believed it is their obligation to report ADRs, less than one fourth of them have ever reported adverse event. The main reasons indicated by them were the uncertainty in the connection between the medicine and the ADR, the fact that ADR is already known, lack of awareness as to whom they should report and lack of time. There were no significant differences in the attitude and awareness about pharmacovigilance system between the GPs and specialists, male and female respondents, in terms of the population, areas, age, length of service, number of patients daily and structure of patients list.

Pharmacovigilance activities are essential to ensure that doctors have enough information to prescribe drugs appropriately (42). Health care professionals usually do not have enough knowledge of ADRs or the voluntary reporting system (13). A lack of basic knowledge about ADRs and health professionals’ attitudes regarding the voluntary reporting system has been associated with under-reporting (43). Health care professional education and training are needed to improve the current ADR reporting system. Previous experiences reported strategies in which spontaneous ADR reporting is integrated with training and continuous education (44). Therefore, we decided to provide educational materials to the surveyed physicians. In fact, a distance-learning pharmacovigilance program was also associated with improved reporting of suspected ADRs by general practitioners and pharmacists (45).

The usefulness of the materials provided in the presented survey was directly assessed by the physicians. Almost all of the participants believed that the materials on ADRs provided to them are useful in their practice and they are going to implement the newly-acquired knowledge. Eighty of them (65%) expressed definite agreement as to the usefulness of these materials. Twenty-nine (23.6%) answered “Rather Yes”. A total of...
109 (88.6%) gave more or less positive answer with prevalence of certainty. A “Rather No” answer was given by 3 physicians (2.4%), and a definite disagreement with the necessity for training materials was expressed by only one respondent (0.8%). Upon comparison of the results from this study according to the two surveys – entry and exit, the analysis proves the existence of statistically significant difference in the physicians’ self-assessment about their awareness about pharmacovigilance system. There was a statistically significant increase in the number of the physicians that stated that there are familiar with the ADRs reporting system. This fact shows that the training did change the self-assessment of the respondents and in the exit survey there was a significantly larger proportion of participants who reported that they were already familiar with the ADRs reporting system.

In the presented study there is a decrease in the number of physicians after the educational intervention who stated that they had ever reported ADRs. The established differences between the responses in the entry and exit surveys can be explained by the fact that the trained physicians know whom they should report ADRs to. Prior to self-education they were not familiar with the system, i.e. part of the respondents who indicated that they had reported ADR cases in the entry survey came to realize that simply sharing information on such cases is not reporting them in compliance with the requirements.

The conducted study has a number of limitations, such as the relatively small sample size and the absence of control group. Furthermore, we consider that the time given to the physicians to work with the training materials was short and it was probably not sufficient enough for a detailed study of provided materials.

Due to the small number of ADR reports in Bulgaria, the organization for centralized ADR reporting as well as the fact that the training materials were distributed only among 0.35% of the practicing physicians, it is not possible to expect an increase in the number of reports. Such a fact would have been indirect evidence of their effectiveness and would have resulted in actual improvement in the pharmacovigilance system.

The cost-effectiveness of the programs such as ours, including all of the possible downstream benefits and harms, must be considered, but we did not evaluate that; it should be the subject of future investigation. However, recent cases of drug withdrawals have highlighted concerns about drug-safety monitoring (46, 47) and emphasized the importance of post marketing surveillance. Direct reporting by physicians has proved successful in identifying new ADRs (13).

The physicians have poor knowledge for the pharmacovigilance system, however, self-education leads to a better knowledge and positive attitude towards ADRs reporting system. The study identifies several factors that influence underreporting in Bulgaria and the results support the usefulness of the developed educational pack. The used questionnaire allow extrapolating and comparing results to different populations, including a similar but broader sample size of Bulgarian doctors in the future.

The most important determinant is the poor knowledge about ADRs reporting system and distribution of educational packs about pharmacovigilance may be very useful method for increasing their knowledge about adverse event reporting. However, further studies with larger populations and different types of education are necessary in order to evaluate the impact of strategies used to improve adherence to the ADRs reporting systems.

National drug regulatory authority should play a more active role in improving physicians’ adherence to the ADRs reporting systems. The provided educational pack can be used in a nationwide campaign for improving physicians’ adherence to the ADRs reporting systems thus increasing the number of received reports.

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TRANSPARENCY DECLARATION

Competing interests: none to declare.
REFERENCES


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