

# Attitude of medical doctors to adverse drug reactions reporting in Bulgaria

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## Abstract

Adverse Drug Reactions (ADRs) pose a challenge for medical doctors (MDs) and other healthcare professionals (HCPs). Serious ADRs increase patient morbidity and mortality and generate a large financial footprint on healthcare costs.

Statistics show that about 6% of hospitalizations are due to ADRs and over 50% of them could be avoided. Two years after introducing the pharmacovigilance (PhV) requirements in the European Union, national regulatory PhV requirements were published in the Bulgarian pharmaceutical legislation. Nonetheless, MDs' awareness of the PhV topic still remains extremely important due to patient safety.

Spontaneous reporting of ADRs is essential to the success of a pharmacovigilance program. Underreporting of ADRs is common, especially among MDs and HCPs.

This study aims to analyse the attitude and the knowledge of graduated MDs towards the reporting of ADRs and drug safety in general. In addition, the study aims to examine their opinion, attitude, and recommendations so that reporting of ADRs becomes more regular.

## Keywords

Adverse Drug Reactions, reporting of ADR, pharmacovigilance risk minimisation measures, spontaneous reporting, benefit/risk ratio

## Introduction

Pharmacovigilance (PhV) is the process and science of drug monitoring once it is authorised and taking minimization measures to reduce any risks and increase the benefits of medicines.

Pharmacovigilance is a system for monitoring drug safety, evaluating it regularly and taking various measures in order to keep future patients safe. The term 'pharmacovigilance' relates to both the science and actions taken to ensure that medicines are safe, to reduce any risks and to increase the benefits thereof.

Good Pharmacovigilance Practice identifies the hazard and the potential risk factors within the shortest time limit to avoid or minimize harm for patients. Based on effective communication, this information allows evidence-based use of medicines and that has the potential for preventing many ADRs. It will ultimately help each patient to receive optimized therapy (Cox and Butt 2012). At the level of population, it will ensure the therapy effectiveness in the public health domain. Reducing public costs, as consequences of ADRs, is another key target of the PhV system.

Before a drug is authorised for use, evidence of its safety and efficacy is limited to the results from clinical

trials, where patients are under controlled conditions. At the time of a drug authorisation, it has been tested among a relatively small number of selected patients for a limited length of time. After authorisation, the medicinal products may be used in a large number of patients for a long period of time and even in combination with other medicines where side effects may emerge. Therefore, it is essential that the safety of all medicines is monitored throughout their use in healthcare practice (EMA Pharmacovigilance: Overview).

The World Health Organization (WHO) defined an 'adverse drug reaction (ADR)' is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function, this may cause death or disability and negatively affects the patient management and prognosis (WHO Briefing Note). ADRs are a global leading cause of death (Smith 2010). Side effects (also known as adverse reactions) can range from the inconvenient to the life-threatening effects. In some cases, it is possible to anticipate some potential side effects while others are less predictable. Some side effects can be caused as a result of prescribing or administration errors, while others are due to susceptibility of specific individuals or only occur after prolonged use (Howard and al. 2006). Spontaneous reporting of ADR is an important method of post-market surveillance (Abubakar et al. 2014).

Despite global concerns against medication safety, there is a lack of awareness and knowledge of pharmacovigilance and ADR reporting among MDs yet. Moreover, recent studies have indicated that ADRs are poorly reported by healthcare providers. It has been studied that only 2–4% of all adverse reactions and 10% of serious ADRs are reported worldwide. It is highly recommended that MDs report any suspected adverse reactions particularly those to newly authorized medicines and serious events. Therefore, the drug safety assessment must be considered an integral part of everyday clinical practice for MDs (Bahri and Harrison-Woolrych 2012).

In line with Article 57 (1)(d) of Regulation (EC) No 726/2004 (European Parliament 2004) which provides the legal basis for disseminating information on adverse reactions as well as, Directive 2001/83/EC, as amended, and Directive 2001/20/EC.

EMA has developed (Regulation (EC) No 726/2004, Directive 2001/83/EC, as amended, and Directive 2001/20/EC as amended) the process of Policy access of EudraVigilance which provides access to the stakeholders such as National Competent Authorities (NCAs), healthcare professionals (HCP), patients, consumers, and the pharmaceutical industry to the reported ADRs in EudraVigilance database. EudraVigilance is the system for managing, monitoring and analysing information on suspected adverse reactions (SAR) to drugs already authorised or being studied in clinical trials across the European Economic Area (EEA) Regulation (EU) 2022/20.

The European Medicines Agency (EMA) operates that system on behalf of the European Union (EU) medicines

regulatory network EudraVigilance supports safe and effective use of medicines by facilitating:

- electronic exchange of individual case safety reports (ICSRs) among NCAs), marketing authorisation holders (MAHs) and sponsors of clinical trials in the EEA;
- early detection and evaluation of possible safety signals;
- better product information for medicines authorised in the EEA. (EMA Pharmacovigilance: Overview).

Spontaneous adverse reaction reporting is the main backbone of PhV. It is required in order to create hypotheses about potential harms of medicines that need further evaluation. ADRs are a major cause of morbidity and mortality across the world, especially ADR-related hospitalizations contribute substantially to the economic burden in both developing and developed countries (Thakare et al. 2022).

The knowledge and perception of HCP toward the safety profile of medicines is essential. They should be aware of the potential occurrence of unexpected adverse reactions and report suspected adverse reactions to the National Competent Authorities (NCA) or the Marketing Authorisation Holder (MAH) in order to facilitate detection, monitoring and assessment of drug safety signals. MDs are aware no medicinal product is entirely safe for all patients and therefore they proceed with some measure of uncertainty (Smith 2010).

Quick reporting of ADRs to NCA is an important drug safety gauge but underreporting is a major challenge even in developed countries with adequate human and material resources. (Leenderste et al. 1890; Benisheva-Dimitrova et al. 2012). Factors that may contribute to underreporting among MDs include lack of knowledge and time, negligence to the patient in general.

Several interventions to solve the problem of underreporting of ADRs have been proposed (Hazell and Shakir 2006). Some studies have evaluated the effectiveness of educational interventions aimed at increasing reporting among MDs (Lee et al. 2008; Friese 2011). However, there are no studies published assessing opinions by medical doctors about regular educational activities related to PhV issues.

The aim of our study is to understand MD opinions for motivation of adverse drug reactions reporting (ADRs reporting).

Hence, this study was done to assess the pattern of ADRs in general and to create awareness in healthcare professionals about the Pharmacovigilance programmes.

## Materials and methods

The 20-question survey based on was conducted among 650 MDs in Bulgaria. with the kindly assistance of the Bulgarian Medical Association (BMA), based on a ready 20-item questionnaire.

The survey contains several sections:

- General information;

- ADR – Reporting – general information;
- Motivation for ADR reporting;
- ADR – reminder and ways of reporting;
- Risks information of medicinal products;
- Pharmacovigilance training of MDs;
- Continuing pharmacovigilance training;
- Consideration of side effects at prescribing medicines;
- Prevention of certain adverse drug reactions;
- Reference sources for medicinal products information;
- Proposal for pharmacovigilance improving.

Scientific methods of analysis are applied to achieve the scientific research objective:

- **Documentary method** – review and systematization of the results obtained from questionnaires, normative acts and other literary sources in Bulgaria and in the European Union, reports of international organizations, leading experts and NCA, etc. – in order to identify specific challenges related to pharmacovigilance. The selection and research of the scientific publications was carried out using certain keywords (drug product, pharmacovigilance, adverse drug reaction, physician, medical professional, spontaneous reporting, drug information, pharmaceutical legislation, risk minimization measure, benefit/risk ratio, rationale drug use), and searching the scientific databases: PubMed, Scopus, Google Scholar, ScienceDirect for a period of 20+ years (1993–2022).
- **Sociological method** – The survey card was distributed by e-mail, and the answers were received in the same way. Whenever additional clarifications were needed, they were again requested and received electronically.
- **Statistical methods** used in the processing and presentation of survey results:
  - » Statistical analysis: For descriptive analysis, continuous variables are described by mean, standard deviation (SD), median, and range.
  - » Categorical variables were described as percentages and statistical differences were assessed by the  $\chi^2$  test. Significance was determined at the 0.05 level (two-fold).
  - » Statistical analysis was performed using the statistical package SPSS version 14.0.

## Results and discussion

The survey was conducted only among MDs from all over Bulgaria. With the assistance of the BMA, a questionnaire was disseminated to 650 medical doctors from all over the country, consisting of 20 questions with several sections as described in the Methodology.

Exclusion criteria included inadequately completed questionnaires and MDs unwilling to participate in

the study. Validated completed questionnaires  $n = 480$  (73,8%) with answers to each question of all participants were evaluated.

The responding medical professionals have extensive professional experience (over 10 to 19 years) and 77% of them have a minimum of 10 years' professional experience.

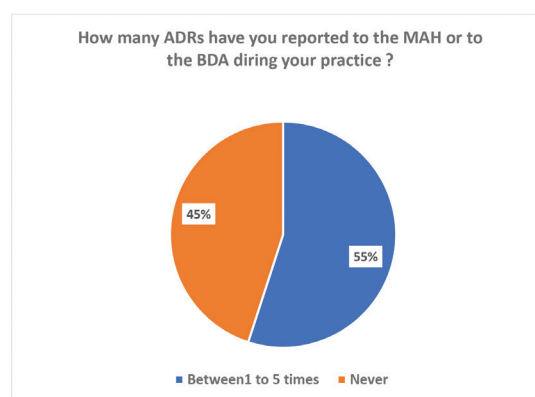
The main occupation of the majority of responding MDs is:

- 69% in outpatient practice – Diagnostic Consultative Centre (DCC),
- 10% working in a hospital and
- 21% work as general practitioners (GP) in outpatient care.

Under the item asking about their experience in the Bulgarian healthcare system, 75% of medical professionals have a minimum of 10–19 years of experience, 15% have less than 5 years of experience, 8% have 5 to 9 years of experience, and 2% have more than 19 years of experience.

The majority of medical doctors  $n = 360$ , (75%) are in the age group with accumulated professional experience and qualification between 10–19 years. Another responding group  $n = 24$ , (5%) includes MDs who have less than 5 years of experience, and the rest  $n = 72$  (15 %) comprises recently graduated doctors.

An important question of the survey asked them how many ADRs had been reported to a marketing authorization holder (MAH) or to Bulgarian Drug Agency (BDA) during their practice. MDs  $n = 264$  (45%) responded they

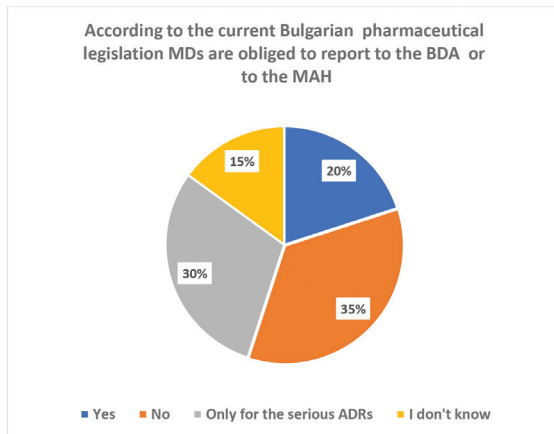


**Figure 1.** Reported ADRs to a Marketing Authorization Holder or to Bulgarian Drug Agency.

had never reported any ADRs during their career, and the rest  $n = 264$  (55%) had reported ADRs one to five times in their practice, which is also a dissatisfying result (Fig. 1).

According to a similar survey held ten years ago, in 2013, the proportion of participants reporting ADRs had been even lower – only 6.3% (Benisheva-Dimitrova et al. 2014).

It could be concluded that over the past years there has been some improvement in the awareness of MDs to report ADRs which could be seen like a positive tendency. Many studies stated that the reporting in this area is also unsatisfactory (Thakare et al. 2022).



**Figure 2.** Level of knowledge of ADRs reporting obligation.

Another important question is whether, under the current legislation in Bulgaria, physicians are obliged to report ADRs to the BDA and only 20% ( $n = 96$ ) of respondents are aware of their obligation to report all ADRs.

The rest of the participants 35% ( $n = 168$ ) replied that no ADRs must be reported, 30% ( $n = 144$ ) answered they are obliged to report serious adverse reactions only, and 15% ( $n = 72$ ) of doctors said they had no idea (Fig. 2).

Obviously, only 20% of all participating medical doctors are aware of this duty – reporting ADRs, and the rest of participants with negative responses are more than 50%. That could be explained that Pharmacovigilance is not part of the Medical University curriculum in the country and knowledge in that domain is based mostly on self-education. Maybe some knowledge is provided through medical representatives who are obliged to spread out the latest SmPC version of the medicinal products to HCPs.

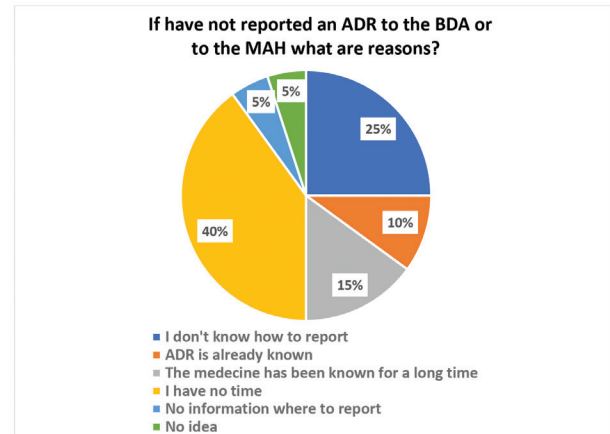
When asked about the confirmation of reported ADR, the survey doctors responded as follows: most of them were asked to confirm ADRs:  $n = 216$  (45%) were asked to confirm ADRs, but refused to answer;  $n = 96$  (20%) answered that they had not been approached, because the ADR is well known;  $n = 48$  (10%) were asked to confirm but they had no new data, and  $n = 120$  (25%) of MDs answered „Yes“.

Based on the question on the reason for not reporting an ADR, a disturbingly high proportion of the surveyed MDs answered they lack time  $n = 192$  (40%) and  $n = 120$  (25%) MDs said there was no point in reporting the ADR.

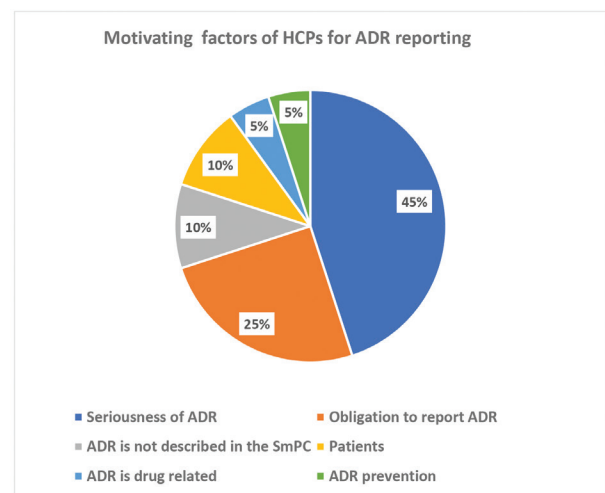
A relatively small number of HCPs answered they were not aware of (25%) or they could not find the reporting form or template (Fig. 3).

The next two answers show that MDs are not familiar with the drug safety processes in general:  $n = 48$  (10%) answered that an ADR is already known and  $n = 72$  (15%) answered that the drug had been long known and therefore reporting is unnecessary (Fig. 3).

When the medical doctors were asked which factors motivate them most to report ADRs and the reasons therefore, they expressed different stances. According to the survey  $n = 120$  (25%) of respondents perceive it as



**Figure 3.** Reasons for not reporting an ADR.



**Figure 4.** Motivating factors for reporting of ADRs.

their duty,  $n = 216$  (45%) explained the reason they reported an ADR was because it was a serious one. Only  $n = 24$  (5%) MDs stressed out the causality of ADR to the medicinal product as a step of patient prevention.  $n = 48$  (10%) stated that the ADR is not described in the SmPC and is unexpected (Fig. 4).

Asked which factors can motivate HCPs to report more often ADRs, expectedly more than half of the respondents  $n = 264$  (55%) answered that training on reporting ADRs would motivate them to report more often another  $n = 72$  (15%) indicated the need for a regular e-mail reminder.

Among the remaining participants, 48 (10%) received feedback on their reported ADRs and 24 (5%) wish the ADR reporting template to be simplified. Quite interesting is the response of  $n = 72$  (15%) of the MDs who said during the survey that ADRs should be automatically generated from the patient's file. Only a few ( $n = 3$ ) MDs, is a negligibly low rate, indicated a financial incentive.

Asked about the most appropriate way to increase the activity of adverse reaction reporting, a significant proportion of MDs  $n = 216$  (45%) pointed out that there was no need for a reminder to report ADRs,  $n = 96$  (20%) responded that could happen through the patient informa-

tion system used in their daily practice (e.g. pop-up) and it would be the most effective reminder option to report ADRs,  $n = 120$  (25%) responded that periodic reminders should be sent via an e-mail,  $n = 48$  (10%) responded ticked ‘other’, where medical representatives should remind them to report ADRs.

Asked about the quantity and quality of pharmacovigilance training, almost half part of the participants (45%) responded they had never been trained. About half of the study group are not familiar how to report ADRs. Those who shared some experiences are  $n = 76$  (16%) MDs who received training during their study, and  $n = 21$  (4.38%) MDs of the respondents who were trained in postgraduate courses. Another  $n = 125$  (26%) MDs answered they were self-educated /without specifying the way and  $n = 42$  (8.75%) did not indicate any way.

More than half of the respondents  $n = 264$  (55%) answered they needed no additional pharmacovigilance training on ADR reporting. That might be reason as a background of low reporting by respondents, because they are unfamiliar with the seriousness of ADR reporting and the PhV system.

According to their preferences on training, different ideas were shared,  $n = 24$  (5%) MDs indicated they wish to be trained once every two years, and  $n = 187$  (39%) MDs prefer once a year and only  $n = 25$  (1.04%) of respondents would like the training to be more frequent, e.g., 4–5 times a year.

Completely consistent with the answers to other questions, the respondents indicated that training in Pharmacovigilance  $n = 240$  (50%) was unnecessary. Other respondents  $n = 14$  (2.92%) stressed out that they prefer learning in the form of electronic games, and  $n = 15$  (3.13%) prefer learning in the form of electronic video. More serious training, such as a training session e.g., seminar, was pointed out by  $n = 96$  (20%) of respondents and the remainder  $n = 72$  (15%) MDs preferred training in the form of an educational lecture. Less than 10%  $n = 43$  (9%) of the respondents would like to be trained in reporting the ICRFs by using the Yellow Card, available electronically on BDA website (BDA 2023).

ADR reporting is a common practice worldwide and the tools provided for the monitoring, assessment, and submission of ICSRs form an essential document (Pal et al. 2011). Comparative analysis showcasing different tools for ADR reporting being used in different selected countries around the world (Hartigan-Go 2012). The comparative status of USA, United Kingdom, Netherlands, Ireland (Williams and Freely 1999) South Africa, Italy, Russia, Australia, Switzerland, New Zealand, Malaysia, Japan, Singapore, China, Germany, and India shows that the most common method of an ADR reporting tool is ADR reporting forms where different formats are used, such as online reporting, PDF/world forms, mobile application, helplines (Prakash et al. 2021).

The surveyed medical doctors use different sources for information about the medicinal products and possible new risks,  $n = 120$  (25%) by using the brochure received

from the MAH. A large percentage of respondents read information online –  $n = 168$  (35%),  $n = 24$  (5%) each use EMA or BDA websites,  $n = 96$  (20%) talk to another colleague, and only  $n = 48$  (10%) answer they do it very rarely.

The final question was about the respondents' suggestions how the pharmacovigilance process of ADRs reporting could be improved. Some of suggestions were the following:

- Training once a year in Pharmacovigilance in the form of seminars or in any other appropriate way.
- MAHs to provide professional short brochure up to 1–3 pages, with ADRs highlights and most important risks of certain patient groups. The information is preferred to be forwarded by e-mail mostly.
- Pharmacovigilance sessions at professional annual congresses.

## Analysis of BDA Reports 2018–2022 regarding ADRs reporting

According to BDA data for four consecutive years 2018–2022, there is a tendency to increase the ADRs reports (BDA 2022). The majority of ADRs reports received were submitted by physicians. In 2022,  $n = 1835$  local reports of ADRs were recorded by the Bulgarian Competent Authority. After validation 96% ( $n = 1772$ ) out of all submitted ADRs reports were evaluated as valid which prove the significance of the ADRs reporting during the pandemic and the awareness of the MDs, nevertheless that majority (90%) are not trained in ADRs reporting.

Additionally, to the survey, local ADRs reporting was evaluated based on the BDA annual reports (2019–2022) (BDA 2022). In 2022, valid local reports ( $n = 260$ ) of ADRs after administration of vaccines were collected by the BDA. Out of these,  $n = 238$  (91%) for vaccines against COVID-19 and  $n = 22$  (15%) reports of post-vaccinated adverse drug reactions. These messages constitute 14.6 % of the total number of valid primary ADRs. Most of the ADRs 87 % ( $n = 227$ ) were made by non-medical professionals (NMPs) and the rest  $n = 33$  (13%) just by medical professionals. It is obvious that during the pandemic, the NMPs were more active and responsible than the HCPs, because the NMPs were personally affected and sensible to any safety information.

Most validated ADRs by BDA were in 2021, when was the peak of COVID-19 and the several new vaccines against the COVID 19- disease were placed on the market.

## Conclusion

The survey revealed that the majority of medical doctors agreed that monitoring and reporting ADRs is beneficial for the patients. About 55% of the surveyed respondents have a very low annual reporting rate where 30% of doctors recognized that reporting ADRs is part of their duty, but most of them (40%) do not have time to report ADRs.

The majority of respondents (55%) in the survey believed that all unknown ADRs should be reported and access to detailed drug safety information is a must.

Regarding the continuous PhV training, 45% of MDs need to be trained in Pharmacovigilance, but the rest 55% of the MDS do not understand the need for training and they are not interested in such training.

In general, there is no system in PhV training in the country and therefore 90% of MDs have no experience how to ensure patient prevention against possible ADRs.

The information obtained from the survey corresponds to the results of the reported ADRs to BDA obtained from four consecutive annual BDA reports (2019–2022). The results obtained from the survey showing a very low annual rate of ADRs reporting for other HCPs as well corresponds to these BDA reports where the result is just 13%. (BDA 2022).

The results show medical doctors' unsatisfactory attitude towards the reporting of ADRs. The ADRs reporting is low among MDs, although some patients experienced ADRs.

In the course of their work and some of them have been trained to report ADRs – 45%.

Their attitudes towards ADRs reporting need to be developed, with targeted educational and post-educational strategies and training.

Currently, doctors are not familiar with the fact that ADRs reporting is mandatory.

Awareness-raising measures are needed to overcome this attitude towards pharmacovigilance processes, especially since they are addressed to HCPs involved in this process.

The study findings showed that the awareness of reporting ADRs and knowledge about reporting them is very poor among the responding medical practitioners.

The ultimate goal of pharmacovigilance is to prevent patients from being unnecessarily exposed to a negative consequence of drug therapy. The goal can only be achieved with proper reporting of ADRs by medical professionals.

MDs understanding of the safety drug profile is essential. HCPs should be aware of the potential for unexpected adverse drug reactions and report suspected adverse reactions to drug regulatory authorities to facilitate the detection and evaluation of drug safety signals. This is the only way to preserve the health of patients or reduce the risk for future patients while taking their prescribed medicinal products.

Many hospitalizations or prolonged hospitalizations could be avoided, in order to save significant public financial resource.

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