REPORTING OF ADVERSE DRUG REACTIONS BY PATIENTS IN BULGARIA

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Abstract

Many adverse drug reactions (ADRs) are difficult to detect or predict, as they are rare or have a long latency period. They only become apparent after the medicine is released on the market. The primary goal of pharmacovigilance is the early recognition of unexpected ADRs after marketing authorization. Reporting suspected ADRs by patients has the potential to increase knowledge about the possible harmful effects of medicines. The publication aims to examine and analyze the participation of patients in the pharmacovigilance system in Bulgaria. Materials and methods: We conducted a web-based, anonymous survey to collect data on the participation of 440 Bulgarian patients in the reporting of ADRs. IBM SPSS (Statistical Package for the Social Sciences) version 26 was utilized for data processing. Results: There is an increase in the number of reported by patients ADRs for the period 2016-2020. However, a relatively low and unsatisfactory level of spontaneous patient reports is still observed. The conducted survey reveals that patients in Bulgaria have a high level of awareness regarding the essence of medication safety. The percentage of people who are aware of the possibility to directly report ADRs to the Bulgarian Drug Agency is also high. There is a lack of awareness regarding the reactions that need to be reported, as well as the methods of reporting. Conclusions: It is necessary to increase awareness about the importance of reporting ADRs. Significantly improving health literacy will greatly contribute to the effective functioning of the pharmacovigilance system.

Key words: *adverse drug reactions, medicines, pharmacovigilance, patients, treatment*

Introduction

The primary objective of contemporary society is to achieve a high quality of life and overall well-being for its citizens. A fundamental and largely defining characteristic of this well-being is good health. Medicinal products from various pharmacological classes play a crucial role in maintaining this health [1-4]. The development of a new medicine is a challenging and costly endeavour, as it must prioritize quality, efficacy, and safety [5-8]. Regarding the latter, a thorough assessment of potential adverse drug reactions (ADRs) associated with the new medication is essential [9, 10]. Some ADRs can be anticipated based on experiences with pharmacologically similar drugs, while others will be identified during clinical trials (CTs) conducted prior to approval for use. The identification of ADRs is subject to certain limitations. Due to the rarity of some ADRs or their prolonged latency periods, and the fact that others may only manifest after extended use of a medication or are confined to specific patient populations, they are often challenging to detect or predict at this stage. Consequently, many ADRs only become apparent after a medicinal product is launched in the market [11, 12]. The primary objective of pharmacovigilance is to facilitate the early recognition of unknown adverse effects following the approval of a medication [2, 13-17]. In addition to ADRs, the focus of pharmacovigilance includes medication errors, lack of efficacy, use for unapproved indications or those lacking sufficient scientific evidence, cases of chronic or acute poisoning, assessment of drug-related mortality, misuse or improper use of medications, and interactions with chemicals, other drugs, or food. Data on ADRs for a specific medication after its approval for use is collected from various sources: post-marketing safety studies (PASS), patient support programs, reports from non-medical sources, medical literature, online or digital media, and spontaneous reports of ADRs from healthcare professionals and patients. Reporting suspected ADRs by patients has the potential to increase knowledge about the possible harmful effects of medicines. Patients can provide firsthand accounts of their experiences with medications and potential ADRs. Consequently, they serve as a valuable source of information. Patient reports can shed light on over-the-counter (OTC) medicines or alternative and complementary therapies that the physician may not

be aware of, offering more detailed insights into how ADRs affect their quality of life. Patients are often more inclined to report associations that may seem unlikely from a medical perspective, yet could represent genuine signals [18, 19]. In 2012, changes in European legislation regarding drug safety monitoring granted patients and consumers across all member states the right to report ADRs directly to regulatory authorities [20-23]. In recent years, there has been an increasing focus on the involvement of patients and consumers in pharmacovigilance systems. The acceptance of adverse event reports from patients and their contributions to drug safety remain topics of ongoing discussion. There is a lack of comprehensive studies assessing the full value of spontaneous reports from patients, as well as the tangible benefits and impacts on drug safety activities.

Objective

The publication aims to examine and analyse the participation of patients in the pharmacovigilance system in Bulgaria.

Materials and methods

We conducted a web-based, anonymous survey to collect data on the participation of 440 Bulgarian patients in the reporting of ADRs. The selection and examination of scientific literature were conducted by searching for keywords in academic databases such as Google Scholar and ScienceDirect. The following English keywords were utilized: "medicinal product", "pharmacovigilance", "drug safety", "adverse drug reaction", "patient", "consumer", "spontaneous reporting", "self-reporting", "pharmacovigilance legislation" and "benefit/risk ratio". A total of 82 scientific publications that met the criteria were analysed (not all are included in the references). A review of the information available on the websites of the relevant organizations and regulatory bodies (World Health Organization, European Medicines Agency, Bulgarian Drug Agency etc.) has been conducted. A web-based individual survey featuring closed-ended questions has been developed and conducted. The survey is anonymous and targeted at patients and consumers. It comprises a total of 24 questions, including 4 related to demographic information and 20 substantive questions relevant to the study topic. Among the substantive questions, 8 are multiple-choice. A total of 440 patients and users participated, and their responses were analysed, achieving a response rate of 100%. IBM SPSS (Statistical Package for the Social Sciences) version 26 was utilized for data processing.

Results

The demographic characteristics of the patients and users included in the study are presented in Table 1.

Table 1. Demographic characteristics of the responders

In response to the first substantive question in the survey, "Do you suffer from a chronic illness?", nearly one in three respondents (27.3%) answered affirmatively (Table 2). This trend is more prevalent among older participants aged 41 to 64 years. Among individuals suffering from chronic illnesses, two-thirds (66.7%) have experienced or observed adverse reactions following medication use, whereas this figure is below half (48.4%) for those without chronic conditions. The difference of over 18 percentage points between the two groups indicates a correlation between chronic illnesses and the likelihood of experiencing or observing adverse reactions after taking medications, with a higher proportion of individuals with chronic conditions reporting such experiences. Nearly one-third (31.8%) of participants reported taking medications daily, including those not requiring a prescription. This behaviour is more prevalent among patients aged 41 to 64 years. The responses to this question may be linked to the well-documented trend of overconsumption of medications observed in the country in recent years, where many patients take medicines without a medical necessity. However, the high percentage of affirmative responses may also indicate a lack

of awareness. It is possible that the study participants are unable to distinguish between a medicinal product and a food supplement. Among individuals suffering from chronic illnesses, nearly three-quarters (74.2%) take medications daily, including over-the-counter drugs, while only a quarter (25.8%) do not use any medications. In contrast, among those without chronic conditions, just 15.9% take medications daily, leaving 84.1% who do not. The proportion of individuals who take medications daily is significantly higher among those with chronic illnesses (72.2%) compared to those without such conditions (15.9%). In response to the question, "Would you classify headache, fever, and fatigue as adverse drug reactions while taking medication?" 69.1% of the respondents answered affirmatively. The results are illustrated in Table 2. The high percentage of positive responses indicates that responders are well-informed about their medication and the potential adverse symptoms or effects, although they may not be certain that their experiences are directly caused by the medication itself. 46.1% of respondents (203 individuals) believe that the medications available on the market are safe, while 30% (132 individuals) are uncertain, and 23.9% (105 individuals) consider them unsafe. Notably, 50.4% of individuals with higher education perceive these medications as safe, in contrast to only 17.5% of those with secondary or primary education who share this view. The high percentage of respondents affirming the safety of market medications may be attributed to a lack of awareness regarding the inherent risks associated with medication use, as it can never be deemed 100% safe. Patients may hold the expectation that since these medications are approved by regulatory bodies, prescribed by doctors, and advertised on television, they must be "completely safe." However, it is crucial to understand that the approval of a medication is based on evidence indicating that its benefits outweigh the risks for most patients in specific contexts, which does not necessarily imply that the product is entirely safe. Over two-thirds (69.1%) of the respondents answered correctly regarding the essence of pharmacovigilance, defined as "the science and activities related to the detection, assessment, understanding, and prevention of adverse effects and other drug-related issues," which aligns with the definition provided by the WHO. Additionally, 27% believe that pharmacovigilance refers to the safe, rational, and effective use of medications, which is indeed one of the primary objectives of drug safety. Furthermore, 3% identified a systematic approach to detecting adverse drug reactions, while 0.9% mentioned the assessment of mortality related to drug misuse. This indicates that patients and consumers have a strong understanding of the term "pharmacovigilance". The next question pertains to the concept of "adverse drug reaction." A significant 88.6% of respondents correctly identified it as any unwanted and unforeseen response to a medication. Therefore, it can be anticipated that when patients report adverse drug reactions, they will provide valuable information. The following information derived from the survey pertains to individuals authorized to report ADRs. This question allows for multiple responses. A significant 90.2% identified medical professionals, while 84.1% of respondents acknowledged that patients and consumers can report ADRs. Additionally, 57.5% indicated that the manufacturer or holder of the marketing authorization is also a reporting entity. In relation to the previous question, the next item in the survey clarifies which authority is responsible for collecting and summarizing the ADRs in Bulgaria. Among the respondents, 92% correctly identified the Bulgarian Drug Agency (BDA). Patients and consumers are aware of the regulatory body in Bulgaria if they wish to exercise their right to report directly to the regulatory authorities. Nearly two-thirds of the respondents (62.5%) answered affirmatively to the question, "Are you aware of the option to report ADRs directly to the Bulgarian Drug Agency?". The responses indicate that the participants are informed about their right to report ADRs directly to the regulatory authorities. Among individuals with chronic illnesses, 65.8% are aware of the option to report directly to the Agency, while this figure stands at 61.3% for those without chronic conditions. When asked if they had experienced or observed ADRs because of medication use, just over half, specifically 53.4% (235 respondents), answered affirmatively. The significant percentage of individuals reporting experiences or observations of ADRs may again be linked to the high level of medication consumption. Among individuals who have experienced or

observed ADRs following medication use, 68.5% are aware of the option to report directly to the BDA. In contrast, the awareness rate among those who have not experienced or observed ADRs is 55.6%, indicating a difference of nearly 13 percentage points. In response to the question, "Have you reported the ADRs you have experienced/observed?" only 32.8% of individuals who experienced ADRs (235 respondents) answered affirmatively. Despite the participants being informed about the nature of ADRs and their right to report them directly to the relevant authorities, there remains a low level of reporting. The respondents who reported ADRs indicated that the primary source of communication was medical professionals (61%), followed by the Agency (36.4%) and the manufacturer/holder of the marketing authorization (32.5%). This question allowed for multiple responses. The trust and direct interaction with medical professionals may explain why patients and consumers favor this reporting method. The subsequent question regarding individuals who did not report any ADRs allows for multiple responses. Among the remaining 67.2% (158 respondents), the primary reason cited for not reporting the ADRs they experienced/observed was that the adverse reaction was already known (included in the patient information leaflet) at 66.5%. This was followed by the belief that the adverse reaction was not serious (26.6%) and uncertainty about whether the reaction was related to the medication (24.7%). Additionally, 19.6% indicated they did not know how to report it, while 12% mentioned they lacked the time to report. Other reasons included various factors (8.2%), attempts to report that were unsuccessful (1.9%), and a reluctance to share personal information (1.3%). When asked about the reasons contributing to the increase in ADRs, 60% of respondents identified drug interactions as a primary factor. Additionally, 59.1% indicated that patients often do not adhere to the instructions provided by their healthcare providers. Poor communication between doctors and patients was cited by 54.3% of participants, while 50% noted that patients frequently neglect to read the informational leaflets accompanying medications. Individuals who take medications on a daily basis are more likely to cite drug interactions as a reason for an increase in ADRs. In contrast, those who do not take medications daily often attribute the rise in ADRs to patients not reading the product leaflets. Furthermore, individuals who have experienced ADRs frequently mention self-medication with herbal remedies, over-the-counter medications, and prescription drugs obtained without a doctor's guidance. Almost all respondents (95.2%) answered affirmatively to the question, "Do you consider reporting ADRs necessary?". Paradoxically, among the 158 respondents who did not report the adverse drug reactions they experienced or observed, 150 believe that reporting such reactions is essential. This raises questions about the respondents' understanding of the importance of reporting ADRs.

Table 2. Frequency distribution of some responses

Discussion

A review of the scientific literature focusing on patient-reported ADRs has identified key factors influencing this reporting. These include a lack of awareness, confusion about who is responsible for reporting ADRs and to whom, uncertainty regarding the causal relationship between the observed reaction and the medication used, and a perceived lack of benefit from reporting ADRs. The conducted survey indicates that patients in Bulgaria possess a high level of awareness regarding the nature of drug safety and ADRs, medication treatment, and the potential side effects of drugs. A significant proportion of individuals are aware of the option to report ADRs directly to the Bulgarian Drug Agency, as well as those who have actually reported ADRs to the Agency. However, the study reveals a low rate of ADR reporting. Additionally, there is a lack of awareness concerning which reactions should be reported and the methods for reporting, which contributes to the underreporting of these incidents. There is a low level of awareness regarding the importance of reporting adverse events. This situation hampers the effective functioning of the pharmacovigilance system, particularly

in terms of user participation. However, there is a positive attitude towards the reporting of adverse events.

Conclusion

It is essential to raise awareness about the importance of reporting ADRs. Reporting ADRs has the potential to enhance understanding of the possible harms associated with medications, facilitates safer drug use, and ultimately leads to improved health outcomes. It is crucial for patients to recognize that every report matters and contributes to the overall safety of medications for all users. To achieve this, information regarding drug safety must be readily accessible to the public, enabling patients to understand their vital role as direct consumers in the rational and safe use of medications. Increasing health literacy will significantly support the effective functioning of the healthcare system.

Statement for Potential Conflicts of Interest

The authors declare that they have no potential conflicts of interest related to this research.

References:

1. Bigdeli M, Peters D, Wagner A. Medicines in health systems. Geneva: World Health Organisation. 2014;117.
2. The safety of medicines in public health programmes: pharmacovigilance, an essential tool. [Internet]. www.who.int. Available from: https://www.who.int/publications/i/item/9241593911
3. Cordell GA. Sustainable medicines and global health care. Planta medica. 2011 Jul;77(11):1129-38.
4. Vargas-Peláez CM, Soares L, Rover MR, Blatt CR, Mantel-Teeuwisse A, Buenaventura FA, Restrepo LG, Latorre MC, López JJ, Bürgin MT, Silva C. Towards a theoretical model on medicines as a health need. Social Science & Medicine. 2017 Apr 1;178:167-74.
5. Stowasser DA, Allinson YM, O'Leary M. Understanding the medicines management pathway. Journal of Pharmacy Practice and Research. 2004 Dec;34(4):293-6.
6. Ankier SI, Warrington SJ. Research and development of new medicines. Journal of international medical research. 1989 Sep;17(5):407-16.
7. Stinson JC. The development of new medicines: an overview. Biopharmaceuticals, an Industrial Perspective. 1999:269-87.
8. Tian Z, Gurnani H, Xu Y. Timing of Collaboration in Development of New Drugs with Learning of Efficacy. Available at SSRN 4884956. 2024 Jun 27.
9. Sartori D, Aronson JK, Norén GN, Onakpoya IJ. Signals of adverse drug reactions communicated by pharmacovigilance stakeholders: a scoping review of the global literature. Drug safety. 2023 Feb;46(2):109-20.
10. Fossouo Tagne J, Yakob RA, Dang TH, Mcdonald R, Wickramasinghe N. Reporting, monitoring, and handling of adverse drug reactions in Australia: scoping review. JMIR Public Health and Surveillance. 2023 Jan 16;9:e40080.
11. Al Meslamani AZ. Underreporting of adverse drug events: a look into the extent, causes, and potential solutions. Expert Opinion on Drug Safety. 2023 May 4;22(5):351-4.
12. Costa C, Abeijon P, Rodrigues DA, Figueiras A, Herdeiro MT, Torre C. Factors associated with underreporting of adverse drug reactions by patients: a systematic review. International Journal of Clinical Pharmacy. 2023 Dec;45(6):1349-58.
13. Cowley H. Pharmacovigilance: what is it and how to report adverse events. In Practice. 2024 Jan;46(1):44-9.
14. Jose J, Cox AR, Vibhu Paudyal. Principles and Practice of Pharmacovigilance and Drug Safety. Springer; 2024.

15. Kazi SM, Bais SK, Kore M. Review On: Pharmacovigilance. International journal of pharmacy & herbal technology. 2023;3(1):81-8.
16. Dr. Kanchana N. Dussa, Dr. A.Venkateshwar Reddy, Dr. Niranjan Panda, Dr. Sobia Noor. A Textbook Of Pharmacovigilance. AG PUBLISHING HOUSE (AGPH Books); 2023.
17. Bloem, Lourens T., Menno E. van der Elst, and Olaf H. Klungel. "Principles of Pharmacovigilance and Drug Regulation." Principles and Practice of Pharmacovigilance and Drug Safety. Cham: Springer International Publishing, 2024. 135-161.
18. Vikan M, Haugen AS, Bjørnnes AK, Valeberg BT, Deilkås EC, Danielsen SO. The association between patient safety culture and adverse events–a scoping review. BMC health services research. 2023 Mar 29;23(1):300.
19. Skelly CL, Cassagnol M, Munakomi S. Adverse events. InStatPearls [Internet] 2023 Feb 12. StatPearls Publishing.
20. Samara C, Garcia A, Henry C, Vallotton L, Cariolato L, Desmeules J, Pinçon A. Safety surveillance during drug development: comparative evaluation of existing regulations. Advances in therapy. 2023 May;40(5):2147-85.
21. Khan MA, Hamid S, Babar ZU. Pharmacovigilance in high-income countries: current developments and a review of literature. Pharmacy. 2023 Jan 6;11(1):10.
22. Londhe VP, Chanshetti R, Dhole SN. Past, Present and Future. Asian Journal of Pharmaceutical Research. 2024 Jun 1;14(2).
23. Grupstra RJ, Goedecke T, Scheffers J, Strassmann V, Gardarsdottir H. Review of studies evaluating effectiveness of risk minimization measures assessed by the European Medicines Agency between 2016 and 2021. Clinical Pharmacology & Therapeutics. 2023 Dec;114(6):1285-92.

Table 1. Demographic characteristics of the responders

Age	below 18 years 19-40 years 41-64 years over 65 years	0.2% 54.8% 42.7% 2.3%
Sex	Females Males	68.9% 31.1%
Level of education	Higher education Secondary education Primary education	87% 12% 0.9%
Residence	Capital Regional city Smaller town Village	75% 17.5% 6.6% 0.9%

Table 2. Frequency distribution of some responses

Question	**Distribution of responses**
Individuals with chronic illnesses/healthy individuals	27.3%/72.7%
Do you take any medications daily, including those that do not require a prescription?	Yes:31.8% No: 68.2%
Would you classify headache, fever, and fatigue as adverse drug reactions while taking medication?	Yes:69.1% No: 30.9%

The percentage ratio of individuals who consider market medications to be safe versus those who do not	Yes:46.1% No: 23.9% I don't know:30%
The level of awareness among respondents regarding the nature of drug safety	Full definition given by: 61.9% Safe, rational, and effective use of medications: 27 % Systematic approach to detecting adverse drug reactions:3% Assessment of mortality related to drug misuse:0.9% No answers: 7.2%
Definition of ADR	Full definition given by: 88.6% Other health issues related to the medications' use: 9.8 % Reactions due to medications' misuse: 1.6%
Who can report ADR (more than one answer is possible)?	Medical professionals: 90.2% Patients: 84.1% Manufacturers/MAHs:57.5%
What is the regulatory authority that summarizes the ADRs reported in Bulgaria?	Bulgarian Drug Agency: 92% Ministry of health:5% Regional Health Inspectorate:3%
Are you aware of the option to report ADRs directly to the Bulgarian Drug Agency?	Yes: 62.5% No: 37.5%
Have you experienced any ADR after using medication?	Yes:53.4% No:46.6%
Would you report any ADR if you encounter one?	Yes:96.1% No:3.9%
Have you reported the ADRs you have experienced/observed?	Yes:67.2% No:32.8%
What is your preferred channel to report ADRs (more than one answer is possible)?	Medical professionals:61% The Agency: 36.4% Manufacturers/MAHs: 32.5%
What were the primary reasons for not reporting the ADRs?	The ADR is already known: 67.2% The ADR was not serious: 26.6%) Uncertainty about whether the reaction was related to the medication: 24.7% No knowing how to report: 19.6 Lack of time: 12% Other reasons:(8.2%) Unsuccessful attempts: 1.9%.
Factors contributing to increase of ADRs	Drug-drug interactions: 60% Non-adherence to treatment: 59.1% Poor communication between doctors and patients:54.3% Patients frequently neglect to read the leaflets: 50% Self-medication with herbs and OTC products: 48.9% Medicines not suitable for the condition: 42.5% Poor communication between patients and pharmacists: 25.5%

Do you consider reporting ADRs necessary?	Yes: 96.2% No: 3.8%