Research Article

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# Evaluation of Patients' Knowledge on the Black Triangle Symbol and Meaning – Bulgarian Perspective

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# Abstract

Introduction: One of the most significant new risk-minimization measure established in 2012 was the development of the concept of additional monitoring of medicinal products. More than 5 years after its implementation it remains unclear what benefits it brings to the pharmacovigilance system and knowledge. The conducted study aims to evaluate patients' level of knowledge on pharmacovigilance with a focus on the additional monitoring component.

Methods: For the purpose of the study a closed-ended questionnaire has been developed and validated. For the current study 316 question sheet were analyzed. Statistical methods used include quadratic analysis (Table 2\*2 was applied to a Fisher Exam), non-Particular Tests by Man-Whitney and Kruskal-Wallis and Kolmogorov-Smirnov test.

Results: 31,3% of the participants in the survey claimed they were informed about the possibility of direct ADR reporting to the national competent authority (NCA) with most of them not taking medicinal products on a daily basis. Only one out of five respondents (21,5%) declared themselves familiar with the meaning of the black triangle symbol. People without chronic diseases answered the question positively more frequently compared to everyday medicines users.

**Conclusion:** Based on the obtained results it cannot be concluded that the black triangle symbol for additional monitoring has served its purpose due to the fact that majority of the participants in the survey are not familiar with its meaning. In order to ameliorate the post-marketing surveillance of new drugs innovative approaches should be reconsidered. Multidisciplinary methods for additional monitoring must be implemented in order to reflect the complex nature of pharmaceutical system.

Keywords: Pharmacovigilance; Black triangle; Patients

# Introduction

Since 2012 the European pharmacovigilance system has been undergoing major legislative changes. Various new risk-minimization measures were developed and implemented in order to improve drug safety monitoring process and ameliorate the quality of the collected information. One of the most significant innovations was the development and enforcement of the concept of additional monitoring. A whole system was established to identify insufficiently studied medicinal products and those carrying high-risk of adverse drug reactions (ADR). Once recognized they are put under closer

and more active post-marketing monitoring – additional monitoring. They are distinguished from other medicines by a special warning symbol – reversed black triangle – which is put on product information documents and all relative materials. Its purpose is to stimulate both healthcare professionals and patients to be more cautious during therapy and report every undesired sign and/or symptom they consider related to the use of the medicinal product [1]. However, more than 5 years after the implementation of the additional monitoring system it remains unclear what benefits it brings to the pharmacovigilance system and knowledge. Many questions are brought up such as the criteria when including and removing products from the additional monitoring list, the placement of the symbol and the possible negative impact it could have on patients' attitude towards therapy with such medicines. In order to identify the weak points of the system and its overall efficiency, at the end of 2017 the European Medicines Agency / EMA/ launched EU-wide online questionnaire survey to evaluate the level of professionals' knowledge on the black triangle symbol and meaning.

Nonetheless, patients are also a valuable stakeholder in the drug safety system. The patients' compliance, adherence and satisfaction with the therapy have to be included in investigation algorithm of any case study [2,3]. For this reason we consider their knowledge and attitude should also be kept in mind when searching new approaches for development. With the conducted nested cohort based questionnaire study we aimed at evaluating patients' level of knowledge on pharmacovigilance system with a focus on the additional monitoring component.

# Methods

# Study Design

For the purpose of the study a closed-ended nested questionnaire has been developed and validated. The questions' sheet was individual, anonymous and targeted at people who don't have medical or health-related educational degree. The questionnaire consisted of two groups of queries. 4 questions on demographic profile of the respondents and 5 more specific questions on pharmacovigilance system. The sampling model was calculated to be among the respondents with a minimum volume of 267 people. The minimum sampling volume set was compliant with the requirements for a simple random sample, a ratio of 50% (maximum volume) and a maximum permissible error of  $\pm$  6%. The set minimum volume was exceeded and therefore the results can be assumed significant.

325 respondents took part in the study but 9 of the questionnaires have been discarded due to incompleteness and validation problems. For the current study 316 questions sheets were analyzed.

The query card starts with short communication explaining the purpose of the study and continues with the questions on demographic data – gender, age, educational degree and residence of the respondent.

# Statistical Methods

Quantitative variables were represented as median and range (minimum and maximum), and categorical ones - as absolute and relative frequencies. The following analytical statistical methods were applied:

• Quadratic analysis to assess the relationship between category variables (Table 2\*2 was applied to a Fisher test);

• Non-Particular Tests by Man-Whitney and Kruskal-Wallis for Comparing Quantitative Variables in Independent Samples;

• The form of the distribution of the quantitative variables was assessed by the Kolmogorov-Smirnov test.

# Conclusion

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Five years after the implementation of the additional monitoring concept it is questionable whether it has contributed to drug safety knowledge. The black triangle symbol remains insufficiently recognized by patients. In order to promote rational drug use and stimulate patient reporting new and inventive ways for education and information should be found. Enhancing involvement of patients, increasing use of real-world data, development and use of new scientific methods for assessment and simplification of administrative processes are few of the future goals of the EU pharmacovigilance system [4]. In order to ameliorate the post-marketing surveillance of new drugs innovative approaches should be reconsidered. Moreover, multidisciplinary methods for additional monitoring must be implemented so that it can reflect the complex nature of contemporary pharmaceutical system. The review of the most frequently reported pharmacological groups according to ATC codes could lead to the conclusion that the current pharmacovigilance methods are not sensitive enough for specific groups of medicines. The safety of vaccines, biologicals, herbal and homeopathic products need to be monitored more closely [5,6,7].

# Results and Discussion Demographic Profile of the Respondents

The majority of the participants in the study were female -63%. Median age of the respondents was 31.5 years, with youngest participant being 18 years old and the oldest 89. The median age of female respondents was 28.5 years compared to 36.5 years in the male participants group (Figure 1).

52.8% of the respondents have graduated from secondary school and those with university degree were 46.2%. People with higher education were older than those with school degree (median age 41 vs. 22 years). Over 4/5 of the participants declared that their current residency was the capital city (81%), 5.1% – another regional town, 10.4% – smaller town and 3.5% –village. As seen in figure 2, people living in the capital were more often with university degree compared to respondents from other parts of the country. However, there were no significant differences in the age group of respondents depending on their current residence.

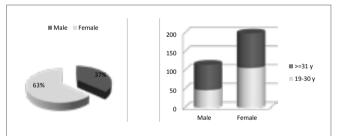


Figure 1. Age and gender distribution of the participants in the survey.

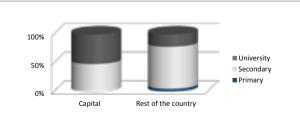


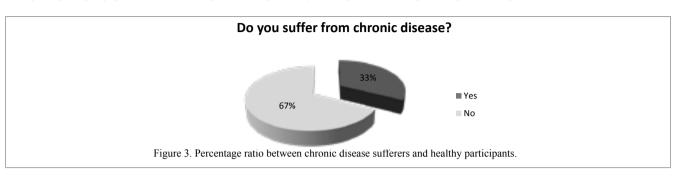
Figure 2. Distribution of the participants according to residence and educational degree.

# Survey Topic

The first survey-specific question shows the current health status of the respondents. Every one of three participants claimed to be suffering from chronic disease (33%) (Figure 3). This tendency was visible mostly in the older participants group (p<0.05) with median age 54 years against 24 years

median age of people who declare themselves healthy.

Table 1 shows statistical data on the correlation between chronic disease and general knowledge on the pharmacovigilance system.

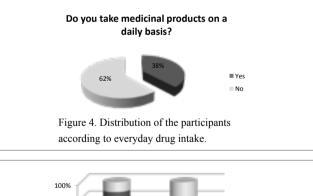


		E	Do you Suffer from Chronic Disease?			
		Yes		No		
		n	%	n	%	
Do you take medicinal products on a daily basis?	Yes	91	88,3%	30	14,1%	<0,001
	No	12	11,7%	183	85,9%	
Have you experienced ADR following use of medicinal product?	Yes	48	46,6%	67	31,5%	0,012
	No	55	53,4%	146	68,5%	
Are you familiar with the spontaneous ADR reporting system?	Yes	20	19,4%	79	37,1%	0,002
	No	83	80,6%	134	62,9%	
Are you familiar with the meaning of the symbol $\bigvee$ ?	Yes	15	14,6%	53	24,9%	0,041
	No	88	85,4%	160	75,1%	1

Table 1. Statistical data on the relation between chronic pathology and pharmacovigilance system.

More than 1/3 of the participants in the survey (38.3%) stated that they take medicinal products everyday including OTCs (figure 4). More often these were patients over 30 years (median age 49) and people with higher education. The respondents who claimed not to be taking medicinal products on a daily basis had median age 24 years. The answers to this question confirmed a well-known tendency for overconsumption of medicinal products and insufficient level of rationality in drug use. These trends are common in Europe in the past few years, especially having in mind that the median age of population is constantly growing. However, the big percentage of the obtained positive answers could be due to insufficient level of knowledge of the respondents. It remains unclear whether the survey participants were capable of distinguishing medicinal product from food supplement and medicinal products for example. The percentage of people who declared using medicinal products on a daily basis was expectedly higher in the population of chronic diseases sufferers (88.3%) (Figure 5).

One of three respondents claimed to have experienced ADR at least once following use of medicinal product (36.4%). This relatively high percentage could be related to the high consumption of medicinal products stated in the previous question (Figure 6).



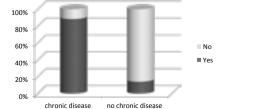
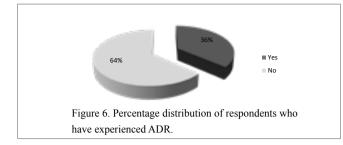


Figure 5. Distribution of the answers to the question "Do you take medicinal products on a daily basis?" according to chronic disease pathology.



The part of patients who have experienced ADR was relatively higher in the group of people taking drugs on a daily basis (44.6%) compared to those who don't (31.3%) (Figure 7). This could be due to the chronic use of medicines but also to undesired drug-drug interactions. The results from a recent study showed that patients' perspective should be incorporated in order to increase the effectiveness of risk-benefit assessment of drug-drug interactions [8].

31.3% of the participants in the survey claimed they were informed about the possibility of direct ADR reporting to the national competent authority (NCA). Interestingly enough, these were mostly people who don't suffer from chronic diseases and don't take medicinal products on a daily basis. The answers to this question can lead to the conclusion that respondents were not familiar with content of the patient leaflet as since 2012 (more than 5 years ago) information on the possible ways to report ADR to NCA is mandatory included in it. This represents one site of the bigger problem of underreporting of ADRs which is inevitably linked with lack of adequate knowledge on pharmacovigilance system, insufficient level of health education and positive attitude in patient/consumers/reporters [9].

According to the results of the study the additional monitoring symbol was not known enough among patients ( $\mathbf{\nabla}$ ) (Figure 8). Only one out of five respondents (22%) declared themselves familiar with the meaning of the black triangle symbol. Those were mostly younger participants with median age 25 compared to 34 years median age of participants with negative responses. Moreover, people without chronic diseases answered the question positively more frequently than others but this again could be due to their younger age.

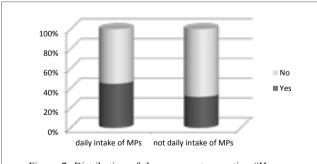
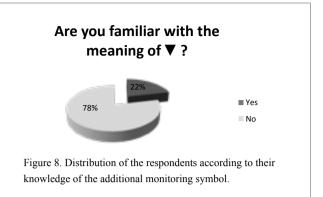


Figure 7. Distribution of the answers to question "Have you ever experienced ADR following drug use?" according to the everyday intake of medicinal products.



# Correlations between Demographic Data and Survey Answers

▶ There are no significant differences according to gender;

► According to age younger participants have answered more frequently that they are familiar with the meaning of the symbol black triangle.

#### Discussion

The results from the conducted questionnaire study showed a rather unsatisfying level of patients' knowledge on pharmacovigilance system. The percentage of the respondents who were familiar with the possibility of direct reporting of ADRs remains relatively small. This tendency is very worrying as the patients' point of view on ADRs represents a valuable source of drug safety information. A recent study conducted in the Netherlands showed that the quality of clinical information patients give when reporting adverse reactions is comparable to the healthcare professional reports. Both groups are willing to report a suspected ADR due to its severity which explains the bigger proportion of serious ADRs in the patient reports [10]. However, if patients are not aware of the possibility to report the benefit of their reports can never be obtained. A study from 2017 in Netherlands showed that the number of spontaneous reports from patients concerning ADRs listed as important medical events is comparable to the sum of these reports by both healthcare professionals and Marketing Authorization Holders [11].

In addition to this, participants in the survey did not recognize the patient leaflet as a source of drug information. Moreover, everyday medicine consumers were the less informed subgroup among the respondents. This indicates a rather significant gap in the overall health education and could pose important risk of irrational, ineffective and even dangerous medicines use. The insufficient level of patients' knowledge however, is undoubtedly related to the education of healthcare professionals as well. New and specific approaches should be constantly searched and developed in order to promote safety issues among the professionals in the healthcare system [12].

Based on the obtained results it cannot be concluded that the black triangle symbol for additional monitoring has served its purpose due to the fact that majority of the participants in the survey in Bulgaria are not familiar with its meaning and do not recognize it as an additional risk-minimization measure. Nevertheless, it is currently the only completely synchronized warning symbol in the EU. The majority of the warning and symbols are put on the packaging of the medicinal products. As well as any other elements of the dossier, the packaging is subject of strict regulations and should be approved by the national competent authority. The information it contains is practically the first one patients and consumers get in touch with. Therefore it seems reasonable for it to contain key warnings and recognizable visual elements to illustrate them.

The requirements on the structure and contents of medicinal products packaging are detailed in the EMA's Guideline on the packaging information of medicinal products for human use. The guideline contains information both on the obligatory and the recommendatory informational components which ought to be placed on the medical packaging. However, on national level there are big differences in the volume and visualization of the packaging information [13].

The black triangle truly does have the potential to be an effective riskminimization measure as its vision, meaning and scope are synchronized in the EU. However, the additional monitoring symbol is placed in the patient leaflet, SPC and additional materials but not on the medicines package. In addition to this, the list of medicines under additional monitoring includes molecules and biological products granted marketing authorization after 01.01.2011 and rapidly grow up. Nonetheless, this criterion is a little ambiguous as for example vaccines authorized before 2011 are not put under additional monitoring as opposed to those authorized since 2011. In this case the lack of black triangle symbol could not serve as a guarantee for better safety.

On the other hand, the presence of the black triangle on the packaging of medicinal products without a decent informational campaign on its meaning can lead to worsening of patient attitude towards therapy with such medicines. A recent study in Bulgaria showed that the serious/non-serious and expected/unexpected ADRs ratios in patient reports for the past 5 years follow the world tendencies for high level of reporting of unknown and insufficiently studied ADRs which meet the seriousness criteria. This is a solid proof of the benefit patient reporting brings. The risk/benefit assessment and the need of establishing a well-functioning high-quality system for receiving, validating and transmitting patient reports is clear [5,14].

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