Bulgarian Experience with Adverse Drug Reaction Reports from Patients and Consumers – Retrospective Data-base Study

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Background: Since 2012, in compliance with the changes in the European legislation, the Bulgarian Drug Agency (BDA) has been receiving adverse drug reaction (ADR) reports directly from patients as well as from healthcare professionals and marketing authorization holders (MAH). Adverse reaction reports from patients and consumers have different characteristics from those sent by healthcare professionals. Moreover, they may require specific algorithm and assessment methods in order to be informative and beneficial to the pharmacovigilance system.

Aim: The study aims to analyze the data-base of consumer reports in Bulgaria in order to distinguish and classify the main characteristics of the ADR reports from non-healthcare professionals.

Materials and methods: In-depth analysis of the Bulgarian data-base of consumer ADR reports for 2012-2016 was conducted. The criteria include patient demographic characteristics, preferred method of reporting, seriousness and expected-ness criteria and most frequently reported pharmacological groups.

Results: The data showed the current trends in patient reporting in the country. It also marked new courses for development of the spontaneous reporting system and collection of safety data. The analysis of the data-base showed a rather stable level of patient reporting with a tendency for constant growth every year. Bulgaria follows the world tendencies for high number of reports for insufficiently studied ADRs which meet the seriousness criteria. The review of the most frequently reported ATC codes could lead to the conclusion that the current pharmacovigilance methods are not sensitive enough for specific groups of medicines.

Conclusions: The results from the conducted study confirm the importance of patient reporting as a valuable source of information on adverse drug reactions. Moreover, it draws the attention to the lack of more sensitive methods for evaluation of drug safety in specific pharmacological groups. Maintenance of consumer-friendly ADR reporting system and innovative assessment algorithms should be the future directions for development in post-marketing surveillance.
investigation algorithm of any case study.\textsuperscript{1,2}

Bulgaria is one of the first countries to start monitoring the safety of medicines use with the creation of the national pharmacovigilance commission in 1974; it subsequently joined the WHO Programme for International Drug Monitoring in 1975. As part of the evolution of drug regulatory system in Europe, Bulgaria actively develops, improves and maintains the national drug surveillance system by receiving and analyzing safety data from healthcare professionals. In 2007, Bulgaria, while joining the EU, got directly involved in the drug regulation processes on European level and fully harmonized the national legislation in this respect. In 2012, the Bulgarian pharmacovigilance system accepted the changes in the pharmacovigilance legislation and the Bulgarian Drug Agency (BDA), the only national competent authority currently receives ADRs reports directly from patients as well as from healthcare professionals and marketing authorization holders (MAH).

**AIM**

The aim of the study was to analyze Bulgaria’s representative database of ADR reports from patients in BDA received in the first 5 years since the changes in the European and local pharmacovigilance legislation and to define the specific characteristics and trends of patient reporting.

**MATERIALS AND METHODS**

We analyzed all cases (n=342) in the BDA database of patient ADRs reports received between June 2012 and December 2016. The in-depth analysis of the cases was based on the following criteria:

- Method of reporting;
- Serious/non-serious ADRs ratio;
- Expected/unexpected ADRs ratio;
- Most frequently reported pharmacological groups according to ATC code;
- Demographic characteristics of patients (age and sex).

**RESULTS**

The total number of the reports included in the analysis was rather small in comparison with that in similar studies published in the literature. This could be explained with lack of adequate knowledge on pharmacovigilance system, the insufficient level of health education, and positive attitude in patient/consumers/reporters.\textsuperscript{3} Another possible explanation could be the physicians’ attitude towards direct patient reporting ADRs as 87% of them believe patient should report to physicians and only 24% - to the BDA.\textsuperscript{4} During the last two years of the analyzed period, 2015 and 2016, a rather stable number of reports has been achieved – 16 reports per 1 million inhabitants/year. Generally, the number of patient reports received in the BDA tends to grow, especially in 2014 when the number of consumer reports was 252% higher than that in the previous year (\textbf{Fig. 1}).\textsuperscript{5}

1. **METHOD OF REPORTING**

The analysis identified four ways of reporting ADR from patients:

- Via the marketing authorization holder;
- Via the web-based form on the website of the Bulgarian drug agency (www.bda.bg);
- Via e-mail directly to BDA;
- Through the national phone line for reporting ADR included in the patient leaflet.

During the first six months since the introduction of the new legislation (second half of 2012) the reports received in the BDA via the web-based form and those sent by the MAH were equal in number. This could be a sign of the low level of knowledge on pharmacovigilance system and recognition of BDA as the competent authority on medicinal products. Patients tend to contact the MAH rather than the executive state agency. The situation was the same in 2013 when the largest number of ADRs from patients was received via the MAHs. In 2014 the number of reports sent via the form on the BDA website showed a slight increase but it was still not comparable to the number of reports received via the MAHs.

Phone reporting was introduced at the beginning of 2015. The phone number is equally acces-
sible to all patients as it is included in the patient information leaflet of all medicinal products. This clearly highlights the importance of reading the patient leaflet before and during therapy. In 2015, the numbers of ADR reports received by phone and indirectly through MAHs were approximately similar. The phone call was the most preferred way of reporting ADRs in comparison with the number of ADRs reported via the BDA website and e-mail. In 2016, the number of sent web-based reports was twice as big compared to that in 2015. However, the most numerous groups were the phone reports and the indirect ones. The smallest amount of ADRs was reported via e-mail (Fig. 2). The results of a questionnaire study conducted amongst Bulgarian physicians showed that more than 57% of the participants declared their most preferred way of reporting ADRs to be an internet-based method followed by verbal reporting and a hard-copy form.4

2. SERIOUS/NON-SERIOUS ADRS RATIO
Only one patient report for serious ADR was received in 2012. In the following years, 2013, 2014, and 2015, consumers reported mostly serious ADRs. However, this does not correspond to physicians’ opinion – they consider the ADRs experienced by patients to be non-serious in most of the cases.4 In 2014 the amount of serious ADRs was four times bigger than that of the non-serious. This tendency changed for the first time in 2016 when the reports for non-serious adverse reactions were more numerous. Nevertheless, there was still not a very great difference in their number. This aspect of consumer reporting in Bulgaria follows the characteristics of patient reporting worldwide (Table 1). A recent study conducted in the Netherlands showed that the quality of clinical information patients give when reporting adverse reactions is comparable to that provided by 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.6

3. EXPECTED/UNEXPECTED ADRS RATIO
As to the probability of occurrence of ADRs, that is, whether these ADRs are included in the summary of product characteristics (SPC) and in the patient leaflet over the study period, there is no clearly defined tendency. Most of the reported ADRs in 2012 and 2013 were unexpected. Generally, physicians consider the drug-reaction relationship to be either possible or probable.4 In 2014, 2015 and 2016, reports concerned mostly known ADRs and during this three-year period the expected/unexpected ratio was quite stable. However, the analysis included cases which were difficult to assess in terms of whether the reported ADRs should be defined as expected or unexpected. Greater difficulties arose in analyzing the information when it was reported by the patient. Therein lies one of the widely recognized disadvantages of patient reporting – transferring the information from lay language to international coding standards. Moreover, some of the terms used in the SPC are rather general and therefore could include a variety of conditions (Table 1). In Denmark, for example, patients tend to report adverse reactions related to psychiatric disorders, to disorders involving the nervous and reproductive systems, with a special emphasis on the emotional aspects of the reaction. A study from 2017 in the 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 MAHs.2,7

4. MOST FREQUENTLY REPORTED PHARMACOLOGICAL GROUPS ACCORDING TO ATC CODE
In 2012, patient reports were equally spread across several pharmacological groups with ATC code J: anti-infectives for systemic use, ATC code C:
Table 1. Serious-to-non-serious and expected-to-unexpected ADRs ratios in patients’ reports, 2012-2016 (%)

| Serious | Non-serious | Year | Expected | Unexpected |
|---------|-------------|------|----------|------------|
| 10      | 90          | 2012 | 30       | 70         |
| 59      | 41          | 2013 | 46       | 54         |
| 18.5    | 81.5        | 2014 | 60.5     | 39.5       |
| 68.2    | 31.8        | 2015 | 65       | 35         |
| 47.8    | 52.2        | 2016 | 61       | 39         |

cardiovascular system, and ATC code M: musculoskeletal system. In 2013, the biggest part of the reports concerned anti-infectives medicinal products followed by ATC code N: nervous system and code R: respiratory system. In 2013, one report concerned an adverse reaction related to homeopathic product. In 2014, the majority of the reports from patients concerned medicines with ATC code J as well as code L: antineoplastic and immunomodulating agents which includes new active substances used in the management of autoimmune pathology. In 2015, the tendency is still kept as again the greatest amount of reports concerned anti-infectives. The introduction of new anticoagulant agents in clinical practice can account for the presence of ATC code B: blood and blood forming organs reports but also suspected adverse reactions related to use of medicines for respiratory, neurological and autoimmune diseases. In 2016, anti-infectives and immunomodulating agents were the most reported pharmacological classes as well as ATC code B. During the whole period the number of ADRs related to neurological and cardiological medicines was relevantly constant. In 2016, the number of reports for ATC code G: genito urinary system and sex hormones was quite high (Fig. 3).

5. DEMOGRAPHIC CHARACTERISTICS OF PATIENTS

Between 2013 and 2016, the patients who experienced ADRs were predominantly female. Male patients were more than female patients only in 2012. As to the age of patients taken from reports...
that include such information, the greatest number of patients were over 60 years old. The least active age group was between 15 and 30 years of age. A great part of the ADR reports concern patients in the age group of 1 to 15 years. This group included reports from parents or care-givers regarding their children and the reports of ADRs following vaccination (Fig. 4).

**DISCUSSION**

The present study shows that there are a solid, but not very high number of adverse reaction reports sent by patients or consumers. Many authors have commented that the insufficient level of reporting is probably the biggest disadvantage of the spontaneous reporting systems. Despite this known drawback, an analysis of the signals discussed at the 2012-2013 PRAC meetings shows that spontaneous reports have the biggest contribution in triggering safety signals (62%). Moreover, 60% of the discussed signals concern the safety of drugs that have been on the market more than 10 years. This data once more confirms the importance of spontaneous reporting system and the need of active post-marketing surveillance throughout the lifecycle of medicinal products.

We can conclude from the analysis of the database that as to the method of reporting patients preferred the phone call when reporting ADRs. As met the seriousness criteria. Moreover, the expectedness of the reported adverse events is difficult to evaluate and therefore many of the cases bring new knowledge on the benefits and risks of drug therapy. The high number of reports related to the use of medicines with ATC code J includes the post-vaccination reactions. Unfortunately, it could be explained also with the inappropriate use of antibiotics and over-the-counter sale in pharmacies. The conducted analysis shows that there is a complete lack of reports of ADRs related to homeopathic and herbal medicinal products. On the contrary, the Swedish Medical Products Agency has already used patient reports as a source of information for the evaluation of the safety concern of herbal medicinal product. In Bulgaria, the food supple-
ments market is growing stable every year and their questionable safety is an emerging issue - in 2016 several reports were received suspecting side effects caused by food supplements intake. In Bulgaria, the competent authority on food supplements is the Bulgarian Food Safety Agency.

According to our data of consumer reports the typical patient who experiences ADR in the country has the following profile: female, age 60-75 years and experiences adverse drug reactions related to the use of medicines ATC codes J, L or N.

**CONCLUSION**

The performed in-depth analysis of the centralized data-base of reported adverse drug reactions by patients shows that a rather stable level of patient reporting has been achieved in Bulgaria. There is a tendency of constant growth of the number of valid ADR reports every year. Phone call and web-based forms are the most preferred methods of reporting ADRs and communicating with the BDA which require developing a modern and accessible web-based platform for medicines related issues.

On the other hand, the serious/non-serious and expected/unexpected ADR ratios show that Bulgaria is following 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. 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, biological, herbal and homeopathic products need to be monitored more closely.

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Болгарский опыт работы по сигналам пациентов и потребителей о неблагоприятных последствиях применения лекарственных препаратов - исследование ретроспективной базы данных

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Введение: Начиная с 2012 года, в соответствии с изменениями в законодательстве ЕС, Болгарское исполнительное агентство по лекарственным средствам (БИАЛС) получает сигналы о неблагоприятных последствиях применения лекарственных препаратов (НППЛП) непосредственно от пациентов, а также от специалистов в области здравоохранения и владельцев лицензий на продажу (ВЛП). Сигналы о неблагоприятных реакциях у пациентов и пользователей различаются по своим характеристикам от тех, которые были направлены специалистами в области здравоохранения. Кроме того, они могут потребовать специфический алгоритм и методы оценки, которые могли бы быть более информативными и полезными для системы фармаконадзора.

Цель: Целью этого исследования является анализ базы данных о сигналах поставщиков в Болгарии, чтобы отличать и классифицировать основные характеристики сигналов о НППЛП, которые не являются специалистами в области здравоохранения.

Материалы и методы: Был проведен углубленный анализ болгарской базы данных сигналов о НППЛП от потребителей на период 2012-2016 гг. Критерии включают демографические данные пациентов, предпочтительный метод подачи сигнала, критерии оценки тяжести и ожиданий пациента и фармакологические группы, о которых сигналы чаще всего поступают.

Результаты: Данные выявили текущие тенденции при подаче сигналов от потребителей в стране. Они также уточнили новые направления развития сигнальной системы спонтанного репортинга и сбора данных, связанных с безопасностью. Анализ базы данных показал относительно стабильный уровень сигналов от пациентов с устойчивой тенденцией ежегодного роста. Болгария следует глобальным тенденциям в отношении большого числа недостаточно исследованных сигналов о НППЛП, которые соответствуют критериям оценки серьезности. Обзор наиболее часто сообщаемых кодов НППЛП может привести к заключению о том, что современные методы фармаконадзора недостаточно точны для специфических групп лекарств.

Выводы: Результаты исследования подтверждают значимость сигналов от пациентов как ценного источника информации о неблагоприятных последствиях применения лекарственных препаратов. Кроме того, в исследовании обращается внимание на отсутствие более точных методов оценки лекарственной безопасности в определённых фармакологических группах. Поддержание удобной для потребителя системы сигналов о НППЛП и инновационных алгоритмов оценки должно стать будущим направлением развития в постмаркетинговом исследовании.