

# Adverse Drug Reaction Reporting by Patients: Experience of 12 European Countries

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## Research article

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# Abstract

Background Spontaneous reporting of suspected adverse drug reactions (ADRs) by a patient is an important method in minimizing safety risks related to medicine use. Patients as reporters of suspected ADRs are valuable participants of pharmacovigilance system. The aim of this study to examine the contribution of the patients to pharmacovigilance in European countries that started patient reporting schemes in 2012-2013 and to compare different tools used by their authorities to promote patients' reporting. Methods A web-based questionnaire was sent to the NCAs of the Europe countries. The received answers were systematized and compared with each other through meta-analysis. Pooled standardized mean difference (SMD) with 95% confidence interval (CI) was calculated in a random or fixed-effects model. Heterogeneity was determined using the Cochrane Q-Test. Results The performed meta-analysis demonstrates that the changes in the number of received ADR report over the analyzed period increased significantly in each country. The reported statistic from Ireland and Finland significantly differ from other reviewed countries. Personalized feedback is a part of the pharmacovigilance system in 5 (41,6%) countries. Only Finland and Ireland (16,6%) do not offer specific reporting forms to patients. The common source of information on direct patient reporting is the websites of NCAs. Other tools in use are information on social media pages, leaflets, posters, etc. Conclusions This is the first insight into patients reporting schemes implemented after the significant reform of the European regulatory system for pharmacovigilance. The statistical data received from the interviewed countries indicate that it is essential for countries with minimal experience in pharmacovigilance systems with direct patient reporting schemes to organize comprehensive campaigns on ADR reporting. However, some countries do not promote the patient's reporting schemes actively, which implies that the patient reporting is considered as mandatory and not as a supporting tool for safer medicines to consumers.

## Background

Because information about the benefits and dangers of drugs in real life is limited at launch, it is important to collect and analyze appropriate clinical patient data throughout a drug's life cycle (1). The primary source of information about medicines safety is health care and pharmacy professionals. However, the studies have shown that the doctors and pharmacists provide incomplete ADR reports or do not provide at all (2). The failure to provide adequate ADR reports by doctors and pharmacists is attributed to a lack of time on their side (3).

It was shown that the direct patient reporting of ADR could provide information about ADRs from other perspectives. The combined information about ADRs from healthcare professionals and the first-hand source has a significant impact on signal detection of new, rear, or serious ADRs (3). The amendments to the European Parliament Directive 2001/83/EC on the Community code relating to medicinal products for human use (Directive 2010/84/EU) obligate the Member States to take all necessary measures to encourage all parties within the health care system including patients to report suspected adverse drug reactions. The Member States should develop and provide the reporting formats for direct patient reporting (4).

In several countries, the direct consumers' ADRs reporting schemes are promoted since the beginning of pharmacovigilance systems or shortly after the start. For instance, the practice has been carried out in the US, New Zealand, the Netherlands, Denmark, Sweden. After the introduction of new European pharmacovigilance legislation in 2012-2013, 15 countries in Europe started the direct patient reporting to the competent authorities (5). Some studies have investigated the motives of patients to report ADRs, patient reporting schemes within and outside of Europe. In addition, the investigations have also focused on the methods used to promote ADRs reporting and sociodemographic and economic features as explanatory factors for population ADRs reporting (3, 6, 7, 8). However, little insight has been undertaken of relatively newly developed patient reporting schemes.

This study aimed to examine the contribution of the patients to pharmacovigilance in European countries that started patient reporting schemes in 2012-2013 and to investigate and compare different tools used by their authorities to promote patients' reporting.

## **Methods**

### **Questionnaires**

This study was a descriptive questionnaire-based study conducted among 15 countries that initiated the implementation of the direct patient reporting of adverse drug reactions in 2012-2013 together with new European pharmacovigilance legislation: Latvia, Estonia, Austria, Finland, Ireland, Belgium, Portugal, Slovakia, Spain, Lithuania, Germany, Greece, Luxembourg, Poland, and Bulgaria. A questionnaire was sent by email to the NCA of each surveyed country. The questionnaire was designed to collect statistical data (number of ADR reported by patients and total number of reports when direct patient reporting was started and the most recent years statistics available), methods for patients to report ADR, tools in use to promote patient reporting, and if personalized feedback about the reported ADR is given to the patient.

### **Meta-analysis**

A meta-analysis was performed to investigate the quantitative finding from different countries and to provide a numerical estimate of the significance of the change in ADR reporting by patients over the analyzed period in interviewed countries. The meta-analysis was performed on statistics of ADR reports by patients and a total number of reports when direct patient reporting was started, and the most recent years when statistics are available. The population changes over the years were also considered. The comparison was completed during a random-effects model and fixed-effects model to evaluate the changes in the number of received ADR reports over the analyzed period in interviewed countries. Confidence intervals (95%) for each data set were calculated. MedCalc software version 12 was used for data analysis. Heterogeneity was explored using Cochran's Q test of heterogeneity.

## **Results**

Out of 15 countries that were actively involved in the study survey, 12 countries remitted their responses through the questionnaires that were issued to them. The follow-up emails were sent out to the nonresponsive NCAs. However, the responses from Luxembourg, Poland, and Bulgaria were not received. The answers from 12 countries were representative of 80% of all study participants, which is a substantial portion for conducting a comprehensive study.

The main reporting methods used in the countries include post, e-mail, phone call, fax, and online internet-based methods (Table 1).

Table 1. The countries, NCA websites selected for the survey, presence of specific patient reporting form, methods of ADR report collection, and personalized feedback to the reporter.

Country	NCA Website	Specific patient reporting form	Methods of ADR report collection	Personalized feedback
<b>Austria</b>	<a href="http://www.basg.gv.at">http://www.basg.gv.at</a>	yes	Post, e-mail, phone call (only as an addition to written form), Fax, online	yes
<b>Belgium</b>	<a href="http://www.fagg-afmps.be">http://www.fagg-afmps.be</a>	yes	Post, e-mail, phone call, Fax, online	no, unless a question is asked
<b>Estonia</b>	<a href="http://www.sam.ee">http://www.sam.ee</a>	yes	Post, e-mail, phone call, Fax, online	yes
<b>Finland</b>	<a href="http://www.fimea.fi">http://www.fimea.fi</a>	no	Post, e-mail, phone call	no
<b>Germany</b>	<a href="http://www.pei.de">http://www.pei.de</a> , <a href="http://www.bfarm.de">http://www.bfarm.de</a>	yes	Post, e-mail, phone call, Fax, online	Only receive an acknowledgment, no assessment
<b>Greece</b>	<a href="http://www.eof.gr">http://www.eof.gr</a>	Yes, in the yellow card online. No, in the printed form.	Post, e-mail, phone call, Fax, online	as applicable
<b>Ireland</b>	<a href="http://www.imb.ie">http://www.imb.ie</a>	no	Post, e-mail, phone call, Fax, online	no
<b>Latvia</b>	<a href="http://www.zva.gov.lv">http://www.zva.gov.lv</a>	yes	Post, fax, online	Not personalized feedback/ standard text.
<b>Lithuania</b>	<a href="http://www.vvkt.lt">http://www.vvkt.lt</a>	yes	Post, e-mail, phone call, Fax, online	No, unless additional information is required
<b>Portugal</b>	<a href="http://www.infarmed.pt">http://www.infarmed.pt</a>	yes	Post, e-mail, phone call, online	yes (All reports receive a confirmation of submission and information on the ID of the report, additional information requests when necessary and causality assessment in case of Serious ADRs)
<b>Slovakia</b>	<a href="http://www.sukl.sk">http://www.sukl.sk</a>	yes	Post, e-mail, phone call, online	yes
<b>Spain</b>	<a href="http://www.aemps.gob.es">http://www.aemps.gob.es</a>	yes	We have a decentralized system, so in each region of Spain, the methods for patient reporting could be different. There is a web form developed by the agency at the national level.	yes, if the online form is used

The use of these methods is applicable in 7 (58%) countries: Estonia, Austria (phone call only as an addition to written form), Ireland, Belgium, Lithuania, Germany, and Greece. The online form of reporting is, however, not applicable in Finland, e-mail, and phone call in Latvia and fax in Finland, Portugal, and Slovakia. The ADR reporting system in Spain is decentralized. This implies that the reporting methods could differ based on each region. An online reporting method is, however, available at the national level. Of 12 countries, 10 (83%) provide specific patient forms that differ from the forms intended to be used by healthcare professionals. Only two countries (16,6%) (Finland and Ireland) in our study currently do not offer specific patient ADR reporting form.

The personalized feedback to patients reported ADR is given in 5 (41,6%) countries, Estonia, Austria, Portugal, Spain, and Slovakia. In other interviewed countries, the feedback is provided in some exceptions. For example, in Belgium, feedback is given only if the questions are asked by patients. In Portugal, all reporters receive a confirmation of submission and information on the ID of the report. Additional information is requested from patients when there is a necessity for it. Further, causality is assessed in case of serious ADRs in Spain. In the case where an online form is used for reporting, the other countries send an automatic letter of confirmation upon receiving the ADR report.

All interviewed NCAs have webpages where the information regarding ADR reporting and standardized information can be easily found. Other methods used by each country to promote patient reporting schemes are in Table 2. The most common methods besides the information on webpages are information on social media pages (e.g., Facebook), leaflets, posters. Ireland and Portugal actively collaborate with patient associations and provide information about ADR reporting to targeted populations. However, 3 (25%) countries, Latvia, Spain, Finland, do not promote the patient's reporting schemes actively and are limited to the information provided on the NCA webpages. Germany did not name the promotion tools, though the information could be found on the NCA webpage.

Table 2: The feedback, tools, and methods used to promote direct ADR reporting for the 12 countries.

Country	Promoting tools	Patient reports received by NCA in 2012*/2013 (number of reports; % of total reports received)	Patient reports received by NCA in 2017*/2018 (number of reports; % of total reports received)
<b>Austria</b>	Advertising , leaflets	14; 0,28%	264; 2,6%
<b>Belgium</b>	Yearly cross-European SCOPE campaign in November	23; 0,4%*	365; 6,6%*
<b>Estonia</b>	Social media (Facebook), articles in newspapers, information on NCA webpage	12; 5%*	184; 36%
<b>Finland</b>	Information on NCA webpage	315; 14%	650; 21%*
<b>Germany</b>	NA	310; 0,6%*	3468; 16%
<b>Greece</b>	PhV campaigns (NCA webpage, media, social media, interaction with patient organizations, etc.).	4,9%*	23,9%
<b>Ireland</b>	Public awareness campaigns, engagement with patient groups on specific safety issues and via the IPPOSI platform, provision of targeted publications in relation to medicines safety and ADR reporting	~55; 2%*	~3743; 36%
<b>Latvia</b>	Information on NCA webpage	4; 1%*	34; 5%
<b>Lithuania</b>	Information on NCA webpage, Social media (Facebook), publications	20; 5%	180; 12%
<b>Portugal</b>	Communication campaigns, leaflets, posters, infographics - which are disseminated in social media in order to achieve patients, training sessions for promoting reporting in collaboration with patient associations and articles in newspapers and magazines dedicated to the general public.	16; 1%	458; 5%
<b>Slovakia</b>	A collaboration with webpage Slovak patient ( <a href="https://www.slovenskypacient.sk/">https://www.slovenskypacient.sk/</a> ), planned publications.	17; 1,8%*	371; 38,8%
<b>Spain</b>	Information on NCA webpage	127; 1%	828; 6,8%

In Table 2, the received statistical data are listed for each country. The highest number of ADR reports completed by patients in the year of the start of patient reporting schemes is observed in Finland (14%), and the lowest patient reporting rate was in Austria (0,4%). For the final year of research 2017/2018, the highest number of patient ADR reports was observed in Slovakia, with an overall percentage composition of 38,8%. On the contrary, Austria recorded the least amount of patient ADR reports with a net percentage composition of 2,6%.

Meta-analysis was performed for comparison of received ADR reports over the period from the beginning of patient reporting schemes till the recent years. Since no total numbers of received ADR reports were not provided from Greece NCA, Greece was excluded from the meta-analysis. The results and forest plot of

the meta-analysis is demonstrated in Figure 1. The calculated results indicate that the number of direct patients reporting changed significantly in each country over the analyzed period. The significant differences between some countries were also observed. The meta-analysis also proposes that a higher number of different promoting tools are used the higher increase of ADR reporting is seen. The plots of Finland and Ireland are lined up on opposite sides of the meta-analysis plot. The rise of ADR from patients in both mentioned countries is significant. However, the observed increase in Ireland is higher. The promoting tools of ADR reporting that are in use in Ireland are related to close engagement with patient groups and targeted awareness campaigns. Finland promotes direct ADR reporting by informing patients on the NCA webpage only; therefore, the increase of reports could be related to other factors than promoting tools. This could also be applied to Latvia and Spain, which also publish information related to ADR reporting on the NCA webpage only.

## Discussion

All the countries interviewed in this study started patient adverse drug reaction reporting in 2012 or 2013 when the major reform of the European regulatory system for pharmacovigilance was implemented in July 2012 (4). The number of publications brought out some fundamental conclusions. First, the patient reporting of ADRs make a valuable contribution to pharmacovigilance by increasing the number of reporting of ADRs, thus favoring the possible detection of ADRs at the early stages. The first step after the implementation of the consumer reporting system is to raise awareness among the general public about the possibility and importance of reporting and encourage consumers actively to contribute to medicine safety (9-14). The present study has reviewed the first years of experience of consumer reporting schemes in 12 European countries. In addition, the tools that are in use to promote patient ADR reporting have also been explored.

Based on the numbers of received ADR reports for the 12 countries considered in the study, the problem of under-reporting ADRs is seemingly present in the countries reviewed. However, it is not easy to establish an accurate measure of the level of under-reporting in these countries. Based on the statistics of the study and existing research, it can, however, be deduced that the levels of under-reporting could reach 90% and more (1). Though the reasons for under-reporting by health-care professionals, pharmacists, and consumers were not analyzed in the present study, several surveys and research have documented potential causes. Some of the common reasons include lack of time, other priorities, and lack of awareness (15-18). Differently, from health-care professionals, the main barriers to consumers to report ADR are poor awareness, lack of knowledge about who should report and whom, difficulties with reporting procedures, high costs involved, and lack of feedback (19).

The success of direct patient reporting depends on the adequate knowledge of pharmacovigilance systems and the tools used to inform society (5). The methods used to educate patients about the possibility of reporting ADR vary among interviewed countries. For some countries, only a few tools are applied. They include the use of leaflets, posters, or information on the NCA webpage only. The countries that were interviewed in this study have five to six years of experience in direct patient reporting. As a

result, countries with minimal experience need to organize comprehensive campaigns on ADR reporting. Some of the key stakeholders that should form part of such discussions include general practitioners, pharmacies, patient organizations, and competent authorities. The lack of active forums and channels for promoting direct patient reporting scheme supports the results of previous studies that a negative attitude towards the new pharmacovigilance systems dominates among competent authorities. The patient reporting is considered as a regulatory mandate and not as a supporting tool for safer medicines (3, 19, 20). The results of the current study propose that the methods and their variety used to employ the patients actively to report ADR have an essential impact. Despite the meta-analysis results were the significant increase of ADR reports in each country was observed, the highest growth of direct patient reports over the analyzed time interval is found in Ireland, as well as the diversity of tools used to promote ADR reporting.

The main goal of the EU pharmacovigilance system is to enhance better and faster decisions in medicine and health care matters. A systematic review had shown that the median interval between the first reported adverse reaction and withdrawal of the medicine launched after 1960 is three years, which is two times shorter than for medicines launched before 1960 (22). The shortened period indicates that ADR signal detection and regulations of new medicines improved, however, insufficient. ADRs remain a significant health issue worldwide. Spontaneous ADR reporting by patients was shown to be a valuable tool for early safety signal detection (23, 24). NCAs need to focus on enhancing the patient to become an active figure in pharmacovigilance management. In the time when new technologies play significant roles in everyone's lives, NCAs should also become more flexible by engaging e-technologies and not just providing static information about ADRs.

## Conclusions

This is the first study that summaries the ADR reporting by patients in European countries that recently started patient reporting schemes. The number of ADR reports received from patients by regulatory agencies and the variety of methods used to promote direct patient reporting indicates the lack of adequate knowledge on the pharmacovigilance system and the insufficient level of health education. Going forward, it would be critical for health care practitioners in collaboration with health care agencies to establish concrete and reliable systems that can be used to tap information on the ADR of patients. One formidable means of achieving this noble objective is to maximize awareness to many people on the need to report ADR to health care providers. In carrying out the awareness campaigns, it would be essential to enlighten people on the significance of ADR reporting and its positive potential for improving the overall well-being of society.

## Abbreviations

ADR – adverse drug reaction

IPPOSI – The Irish Platform for Patient Organisations, Science and Industry

## Declarations

### Ethics approval and consent to participate

Ethics approval was not required for this study. The confirmation was received from the Kaunas Regional Biomedical Research Ethics Committee.

### Consent for publication

The respondents were informed about the research and usage of the data.

### Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality and study ethical approval conditions.

### Competing interests

The authors declare that they have no competing interests.

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### Authors' contributions

(AVJ) Involved in the conception of the research idea, study design, questionnaire development, and data collection. (AVJ, LK) Both authors analyzed data, interpreted the results, drafted the manuscript, revised, and approved the final manuscript.

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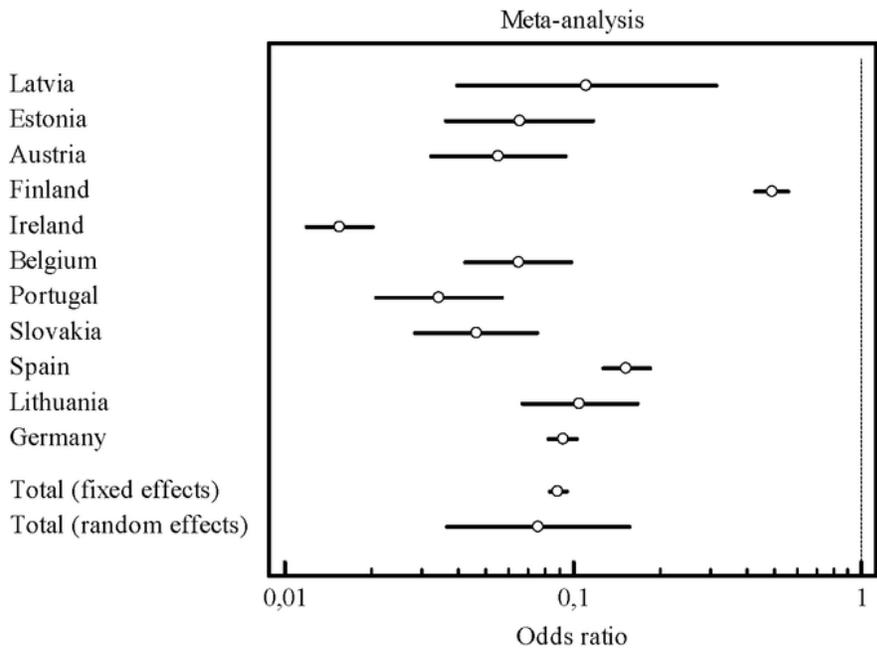
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## Figures



Q=845,3511; DF=10; p<0,0001

Study	Intervention	Controls	Odds ratio	95% CI
Latvia	4/2044000	34/1934000	0,111	0,0395 to 0,314
Estonia	12/1323000	184/1322000	0,0652	0,0363 to 0,117
Austria	14/8518000	264/8857000	0,0551	0,0322 to 0,0944
Finland	315/5450000	650/5509000	0,490	0,428 to 0,560
Ireland	55/4594000	3743/4857000	0,0155	0,0119 to 0,0203
Belgium	23/11035000	365/11322000	0,0647	0,0424 to 0,0985
Portugal	16/10487000	458/10277000	0,0342	0,0208 to 0,0564
Slovakia	17/5408000	371/5450000	0,0462	0,0284 to 0,0751
Spain	127/46728000	828/46658000	0,153	0,127 to 0,185
Lithuania	20/2944000	180/2794000	0,105	0,0664 to 0,167
Germany	310/80399000	3468/83019000	0,0923	0,0822 to 0,104
Total (fixed effects)	913/178930000	10545/181999000	0,0887	0,0829 to 0,0949
Total (random effects)	913/178930000	10545/181999000	0,0758	0,0366 to 0,157

**Figure 1**

The changes in the number of ADR reports received individually by each country and overall.