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Adverse drug reactions that arise from the use of medicinal products outside the terms of the marketing authorisation

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A B S T R A C T

Background: New European (EU) pharmacovigilance (PV) legislation, introduced in 2012, widened the scope of an Adverse Drug Reactions (ADR) definition so that it also includes noxious and unintended response to a medicinal product arising from the use outside the terms of the marketing authorisation (MA), whereby the use outside the MA also includes off-label use, overdose, misuse, abuse and medication errors (MEs).

Objectives: To explore the ADRs arising from the use outside the terms of the MA reports in the Croatian pharmacovigilance database.

Methods: A retrospective, observational study of the HALMED PV database was undertaken before and after the implementation of the new legislation in Croatia. The outcome measure included ADRs arising from the use of the products outside the terms of the MA. An assessment was performed based on the information provided in a reference document, an SmPC, using predefined criteria.

Results: Among 679 ADRs included in the analysis, 162 (23,9%) ADR reports were related to the use outside of the MA, 370 (54,5%) were related to the use within the MA and 147 (21,6%) were adjudged as not-assessable. Our study demonstrated a significant increase in the number of ADRs arising from the use outside the terms of the MA after the implementation of the new legislation (P = 0,039), primarily due to a notable increase in the number of overdose reports received by the poisoning centre, while the number of ADRs caused by MEs did not change significantly (p = 0,672).

Conclusion: This study elucidated partial implementation of the new EU PV legislation and the need for instilling proper education for patients and HCPs, improving reporting systems and strengthening collaboration between relevant stakeholders.

Introduction

The burden of adverse drug reactions (ADRs) on healthcare systems is high, accounting for considerable morbidity, mortality, and extra costs.[1–6] Previous research has consistently shown that considerable proportion of all hospital admissions is due to ADRs and that an important part of these hospitalisations could have been avoided.[2,4,7] It has been found that around 5% of the hospitalisations in the European Union (EU) are caused by ADRs, leading to 197,000 annual deaths.[3] ADRs are the fifth most common cause of death in Europe and total up to an annual cost of approximately €79 billion.[3]

Ample evidence base suggests that 18.7–80% of ADRs are preventable, depending on the setting and the method used to assess their preventability.[7–9] New European (EU) pharmacovigilance (PV) legislation, introduced in 2012, widened the scope of an ADR definition so that it includes a response to a medicinal product which is noxious and unintended arising not only from the use of the medicinal product within, but also outside the terms of the marketing authorisation (MA) and occupational exposure.[10] The use outside the MA includes off-label use, overdose, misuse, abuse and medication errors (MEs). Furthermore, the importance of ADRs arising from the use outside the terms of the MA (ADRs outside MA) was recently demonstrated by a study exhibiting that MEs, accidental overdose or misuse of the substances were important reasons for EU withdrawals, revocations and suspensions.[11] It is a well-established fact that MEs are the most frequent among ADRs that arise from the use outside MA.[12]

In the light of the abovementioned and pursuant to the requirements introduced by the new EU PV legislation [10], the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action has been created to support following new requirements introduced by the European PV legislation of June 2012. SCOPE identified differences in coding practices and promotes the importance of coding according to unique guidance, thus enabling consistent assessment and comparison between the countries.[13] To further support the implementation of the new legal provisions amongst the stakeholders and prevent misunderstandings and potential risks to patient safety, the

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EU regulatory network published a series of guidance addressing the management and reporting of adverse reactions arising from the use of the medicinal products outside MA.[14–18] Furthermore, a recent study exploring the cases of reported MEs in EudraVigilance, prior to the release of Good Practice Guide (GPG) on recording, coding, reporting and assessment of medication errors,[15–17] brought to our attention that further research to assess the impact of EU regulatory guidance on error prevention strategies is required.[19]

The objective of our study was to explore whether the change in the definition of an ADR has influenced the reporting rate or/and quality of reports. To the best of our knowledge, this is the first comprehensive study of ADRs that arise from the use of medicinal products outside the terms of the MA in a national pharmacovigilance centre according to the new regulatory definitions in EU. Further objective of this research was to determine the frequency and characteristics of ADRs that arise from the use of medicinal products outside the terms of the MA.

Methods

Study design

A retrospective, observational study of ADR reports notified to the Croatian National Spontaneous Reporting Database (NSRD) was conducted for the years 2012 and 2016. Only reports with ADR causality assessment defined by the assessor as definite/certain, probable/likely or possible were included in the analysis.[20] Reports associated with vaccines were excluded as these are intended as a subject for future analysis.

Data source

In the Republic of Croatia, the majority of ADR reports are directly reported to the Regulatory Authority, namely the Agency for Medicinal Products and Medical Devices of Croatia (HALMED), by both healthcare professionals (HCPs) and non-HCPs, and subsequently entered into the NSRD.

For this research project, spontaneous case reports received and collected at HALMED and its regional centre, the Institute for Medical Research and Occupational Health (IMROH), were used. The information taken into account and extrapolated from the aforementioned databases encompassed and compared reports from the period before the implementation of the New EU PV legislation in Croatia (January 1, 2012–December 31, 2012) and following its implementation (January 1, 2016–December 31, 2016). Croatia became an EU member state on July 1, 2013 which was the date when the New EU PV Legislation was implemented. It should be noted that the earlier Croatian legislation on pharmacovigilance,[21] already in 2009 introduced the additional obligation of HCPs to report to HALMED any suspicions of MEs leading to ADRs, cases of overdose, addiction and medication abuse or misuse, as well as suspicions of counterfeited medicinal products resulting from the absence of therapeutical effects or the development of an ADR. Despite this advanced and forward-looking approach of the Croatian legislator, since these events were at that time still not covered by the legal definition of ADR, the ADR reporting mechanism could not be readily implemented for the reporting of such events. In respect of that, precise reporting mechanisms of these events were set up in Croatia in July 2013 by the new legislation[22] which transposed the changes in the ADR definition from the New EU PV legislation. However, the GPG on recording, coding, reporting and assessment of medication errors which was adopted in 2015, for the first time at EU level introduced the definitions of the relevant terms, reporting requirements and the recommendation that stakeholders should exchange information, which were the necessary preconditions for efficient reporting of these events. Therefore, the year 2016 was identified as the relevant year which follows the process of full implementation of the New EU PV legislation in Croatia.

In line with the information exchange recommendation from the GPG on recording, coding, reporting and assessment of medication errors, the cooperation between HALMED and IMROH started on January 1, 2016 as to achieve a more efficient monitoring of ADRs, particularly those associated with drug poisoning, i.e. drug overdose, hence to improve the safety of medicinal products use and protection of public health. Within this cooperation, IMROH regularly forwarded information on suspected poisoning with medicinal products to HALMED, which processed this information as ADR reports and submitted them to the national, European and worldwide adverse drug reaction databases. Hence, the Institute for Medical Research and Occupational Health database served as an ADR source in the data collection process of this study.

The criteria for a valid case report and definitions of the Individual Case Safety Report (ICSR) data elements are defined in the International Conference on Harmonization (ICH) guidelines.[23]

Individual Case Safety Reports are coded with the Medical Dictionary for Regulatory Activities (MedRA) terminology,[24] internationally used by regulatory authorities, pharmaceutical companies, and clinical research organisations to share regulatory information on medicinal products. To facilitate a precise description of the error, the Higher-Level Group Term (HLGT) 'Medication Errors' has been reorganised within MedRA version 18.0 and an additional HLGT 'Product use issues' created to encourage distinction between unintentional/accidental events and intentional acts (off-label use or misuse). MedRA version 20.0 was used in our study.

Data analysis

The process of obtaining the sample set of ADR reports and the time periods that would be addressed were initially agreed upon. Every fifth report for 2012 and every tenth report for 2016 were extrapolated from the database (number of ADR reports has doubled in 2016), forming thus two datasets, one starting with January 1, 2012 and the other, following with January 1, 2016. The number of extrapolated reports corresponded approximately to 10% of the total number of reports received in each of the years. If the fifth or tenth report, for 2012 or 2016, respectively, did not fulfil the inclusion criteria, the first one following, fulfilling the criteria was included in the analysis.

An assessment team, consisting of two pharmacists, one clinical pharmacist and two senior pharmacovigilance assessors, analysed whether an ADR was caused by the use outside the terms of the MA and an SmPC was used as a reference document. Each case was assessed by at least two assessors of different backgrounds. Any discrepancies in the assessment were discussed before reaching the consensus between the five assessors. In one case, more than one use outside the terms of the marketing authorization could be identified. Further analysis enabling description of the ADRs arising from the use outside the terms of the MA in terms of patient age group, reporter's qualification, seriousness of the report,[25,26] pertaining System Organ Class (SOC) according to MedDRA,[22] the Anatomical Therapeutic Chemical (ATC) classification, number of drugs used and co-morbidities was applied.

GVP Module VI- Collection, management and submission of reports of suspected ADRs to medicinal products,[14] GPG on recording, coding, reporting and assessment of medication errors[15] and Reflection paper on collecting and reporting information on off-label use in pharmacovigilance[18] provided the important definitions and clarification of terms used in this study.

The terms "before and after implementation of the new legislation" were used to specify the periods before the implementation of the new EU legislation in Croatia.

Statistical evaluation of data was performed using IBM SPSS statistical software (v 20). Comparisons were conducted with a significance level at $p < 0.05$.

Results

Altogether, 295 ADR reports spontaneously reported to the Agency for Medicinal Product and Medical Devices of Croatia before and 384 ADR reports following the implementation of the new legislation were included in the analysis. Following analysis, 162 (23,9%) ADR reports were related to the use outside of the MA, 370 (54,5%) were related to the use within MA and 147 (21,6%) did not contain enough information to allow for the assessment and were thus specified as not-assessable.

Characteristics of the adverse drug reactions

The median age of patients who experienced an ADR was 56 years (1–94 years), with 61,7% (N = 419) being female and 35,2% (N = 239) male. ADRs were reported to HALMED by a healthcare professional in 91% of cases, with physicians reporting in 57,3% (N = 353) of cases, followed by pharmacists (N = 242; 39,3%) and other healthcare professionals (N = 21; 3,4%). The remaining reporters regarded a consumer or other non-healthcare professionals (N = 62; 9,1%). We noted a significant increase in the number of reports as reported by IMROH (0 before the implementation as opposed to 60 following the implementation). Moreover, patients reported significantly more ADR reports (6,1% in 2012 vs 11,5% in 2016) than the remaining reporters following implementation of the new legislation ($\lambda^2 = 5{,}769$, $P = 0{,}016$).

Therapeutic drug classes the most frequently involved in ADRs included cardiovascular (ATC code C) and nervous system agents (ATC code N) followed by antineoplastic and immunomodulating agents (ATC code L), antiinfectives for systemic use (ATC code J) and other. On average, patients used 2 medicines (2,57 ± 0,086) and had 2 comorbidities (2,16 ± 0,086). Gastrointestinal (18,1%) and general disorders and administration site conditions (13,7%) were the most commonly reported ADRs followed by nervous system disorders (10,4%), skin and subcutaneous tissue disorders (9%) and psychiatric disorders (8,5%).

Adverse drug reactions outside the terms of the marketing authorisation

Out of the 162 ADR reports that aroused from the medicinal product use outside the terms of the MA, majority were due to medication errors (N = 155). Off-label use was identified in 87 reports, while misuse and overdose were identified in 11 and 39 reports, respectively. There were no reports of abuse among the analysed reports.

Comparison of adverse drug reaction (ADR) reports related with the use outside the terms of the marketing authorisation (MA) with the ADRs reports related with the use within the terms of the MA

ADR reports related with the use outside the terms of the MA were compared against the ADR reports related with the use within the use of the MA in terms of the year when an ADR was reported (before and after the implementation of the new legislation), patient characteristics (age, gender), number of drugs and comorbidities, seriousness of an ADR and ATC code of a suspected drug. A statistical difference was found in the following variables: seriousness, age, ATC class and a year when an ADR case was reported. A higher proportion of serious cases was found among ADRs caused by the use outside MA ($\lambda^2 = 10{,}01$; $P = 0{,}002$). Additionally, among ADRs outside the terms of the MA, the proportion of children was significantly higher than among the remaining reports ($\lambda^2 = 9{,}23$; $P = 0{,}002$). The most prevalent medication classes among ADRs outside the terms of the MA pertained to the nervous system agents (ATC code N) (31,5%), while the ones among the ADRs that arise from the medicinal product use within the terms of the MA were cardiovascular agents (ATC code C) (22,4%) (Fig. 1). A statistical difference was found between these two groups of ADRs in the number of suspected drugs belonging to the ATC code N with significantly more nervous system agents being among the ADRs outside the MA ($\lambda^2 = 18{,}737$, $P < 0{,}001$).

A significant increase in the number of ADR reports outside MA was observed following implementation of the new legislation ($\lambda^2 = 5{,}266$, $P = 0{,}039$). However, the number of MEs did not change significantly over time ($\lambda^2 = 0{,}794$, $P = 0{,}672$).

Detailed information on the differences between ADRs caused by the use outside the terms of the MA with ADRs within the use of the MA is provided in Table 1 and includes sociodemographic and clinical data. Comparison of System Organ Classes (SOCs) between the ADRs related with the use outside the terms of the MA and the ones within the terms of the MA are shown in Fig. 2.

Recognition of ADR reports caused by the use outside the terms of the MA by a reporter

A significant increase in the number of ADR reports outside MA as recognized by a reporter was found after the implementation of the new legislation; only 12 out of 61 ADR reports outside MA (19,67%) were recognized by a reporter before the implementation as opposed to 69 out of 101 ADR reports outside MA (68,32%) following the implementation of the new legislation. Overall, if excluding the cases reported by IMROH, in only 27 out of 128 reports (21,09%), reporters recognized an ADR as a consequence of use outside MA.

Not-assessable ADR reports

As previously mentioned, a rather high proportion of not-assessable cases was found (21,6%), with no difference regarding the implementation of the new legislation (59 out of 236 cases before the implementation *vs* 88 out of 384 cases after the implementation). However, significantly more not-assessable cases were reported by patients in comparison with other reporters ($\lambda^2 = 4{,}527$, $P = 0{,}033$). As the number of not-assessable ADR reports was fairly high, it was pivotal to further explore the reasons. In most cases, more than one reason was responsible for categorizing cases as not-assessable (34%), followed by the lack of information regarding the right dose (13,6%), medical history (13,6%), indication (11,6%), administration (6,8%) or other reasons altogether (20,4%).

Discussion

This study was the first comprehensive study of ADRs that arise from the medicinal product use outside the terms of the MA that informed the evidence base as to whether the implementation of the new EU PV legislation influenced the awareness of the need to report the ADRs that arise from the medicinal product use outside the terms of the MA. It has been recognized previously that the efforts to assess the importance of various types of errors are impeded by the lack of standardized taxonomy and nomenclature for reporting adverse events, errors, and risk factors.[25] Hence, this study was the first to use the clear terminology defined by the new EU PV legislation, and the first to have detected the reasons for proclaiming a certain ADR as not-assessable, thus potentially leading to actions that could improve reporting and minimize the number of incomplete reports precluding the assessment.

The main observation derived from this study was a rather high proportion of ADR reports that arise from the medicinal product use outside the use of MA, both before and after the implementation of the new EU pharmacovigilance legislation. In total, 24% of reports were assessed as being caused by MEs, off-label use, misuse or overdose, implying that around a quarter of all reports were deemed possibly or definitely avoidable, had the suspect medicinal product been used in accordance with the approved safety information. This finding is consistent with the broad range of figures (18.7–56%) suggested in the literature.[7–9,27-29]

Moreover, our study demonstrated a significant increase in the

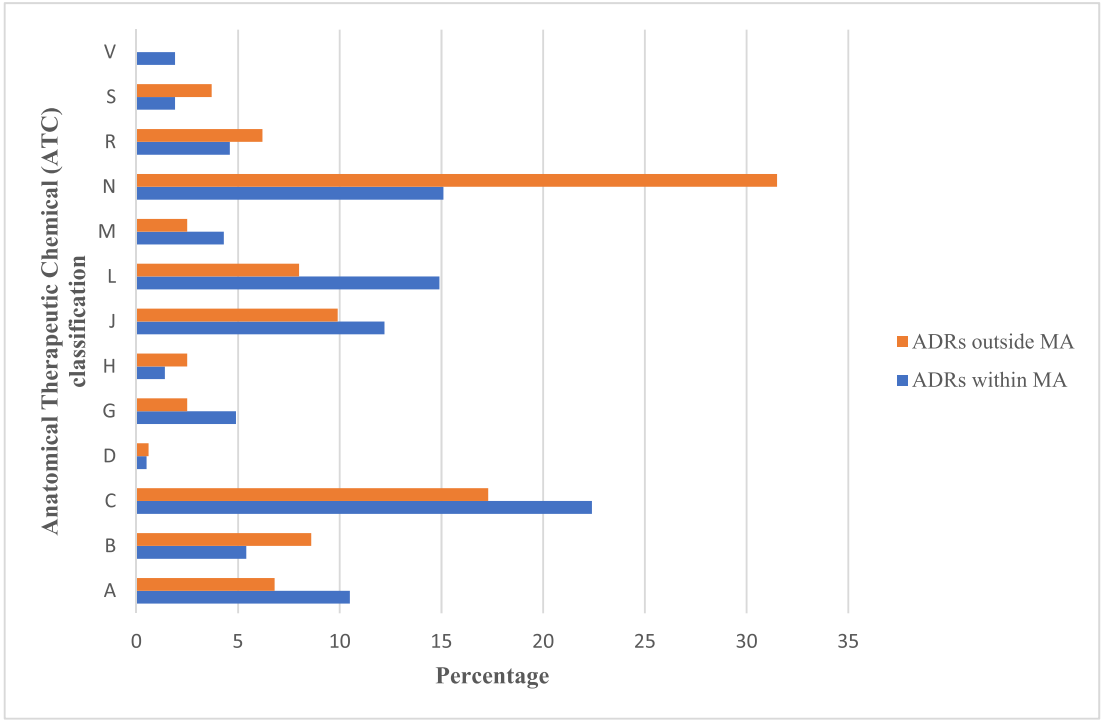

Fig. 1. Comparison of Adverse Drug Reactions (ADRs) outside the terms of the marketing authorisation (MA) with the ADRs within the terms of the MA according to the Anatomical Therapeutic Chemical (ATC) classification.

Table 1
Comparison of adverse drug reaction (ADR) reports related to the use outside the terms of the marketing authorization (MA) with the ADR reports related to the use within the MA.

Variables	ADRs outside the MA, N (%)	ADRs within the MA, N (%)	P value*
year			**0,039**
2012	61 (37,7)	175 (47,3)	
2016	101 (62,3)	195 (52,7)	
seriousness			**0,002**
yes	72 (44,4)	112 (30,3)	
no	90 (55,6)	258 (69,7)	
reports received by IMROH, yes/no (N)			
yes	34 (21,0)	20 (5,4)	**p < 0,000**
no	128 (79,0)	350 (94,6)	
age**			**0,002**
≤18	23 (14,2)	24 (6,5)	
> 18	119 (73,5)	312 (84.3)	
gender**			0,922
male	60 (37)	133 (35,9)	
female	100 (61,7)	226 (61,1)	
number of drugs**			0,451
≤3	122 (75,03)	267 (72,2)	
≥4	40 (24,7)	103 (38.1)	
number of comorbidities**			0,255
≤3	111 (68,5)	269 (72,7)	
≥4	13 (8,0)	46 (12,4)	
ATC			**p < 0,001**
Nervous system (N)	51 (31,5)	56 (15,1)	
other	111 (68,5)	314 (84,9)	

ADR, adverse drug reaction; IMROH, Institute for Medical Research and Occupational Health (poison centre); ATC, The Anatomical Therapeutic Chemical classification system; MA, Marketing Authorisation.
* P-value by the Chi-square test.
** Missing values in some reports.

number of ADRs that arise from the medicinal product use outside the terms of the MA between the two periods, before and after the implementation of the new legislation, primarily due to a notable increase in the number of overdose reports received by IMROH. However, the subgroup of ADRs caused by MEs did not change significantly between those two periods, thus denoting a partially successful implementation of the new EU PV legislation. A formal cooperation established between HALMED and IMROH was an initiative pursuant to the introduction of the new EU PV legislation, contributing to an increase in the frequency of reported ADRs that arise from the medicinal product use outside the terms of MA. Namely, the EU PV guidelines[17] stimulate cooperation between national PV centres and patient safety organisations (PSOs) or any other authorities, bodies, organisations or institutions responsible for patient safety incident reporting. However, like Croatia, not all EU Member States (MSs) have a long tradition of PSOs.[28] Hence, it was acknowledged that individual EU MSs may use other mechanisms to collect data on preventable ADRs that arise from the medicinal product use outside of hospital settings, for example through poison control centres, as is the case with IMROH in Croatia.

As previously recognized in the literature,[31–33] majority of all ADR reports that arise from the medicinal product use outside MA were due to medication errors, whereby we have confirmed recent data suggesting that PV centres may act as a significant source of medication error data.[35–39] Henceforth, measures that need to take place if we are to augment capturing relevant medication error data include revision of the ADR reporting form for reporting ADRs that arise from the medicinal product use outside the terms of the MA, education of both patients and HCPs, and strengthening collaboration between relevant stakeholders.

Another important finding was that, among ADRs that arise from the medicinal product use outside the terms of the MA, the proportion of serious adverse drug reactions was significantly higher than among ADRs that arise from the product use within the terms of the MA. ADRs that arise from the medicinal product use the terms of the MA differed from the ADRs that arise from the product use within the terms of the MA in terms of the age of the patients, with children experiencing significantly more ADRs that arise from the medicinal product use the terms of the MA. This can be explained by the fact that a substantial number of received reports came from IMROH, a national poison

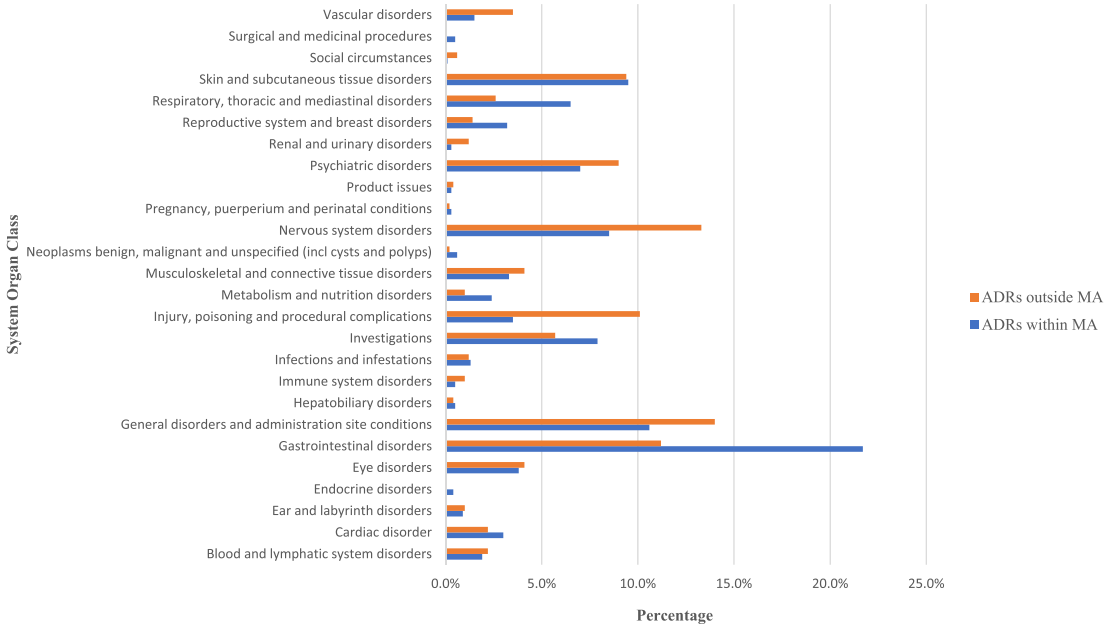

Fig. 2. Comparison of Adverse Drug Reactions (ADRs) outside the terms of the marketing authorisation (MA) with the ADRs within the terms of the MA according to System Organ Class.

control centre, acquiring cases of poisoning and accidental exposure to drugs by children mostly. Additionally, ATC code N drugs (Nervous system) were the most prevalent drugs in the group of ADRs that arise from the medicinal product use MA what could be explained by the influence of IMROH. Due to differences in data sources, employed methodology and dissimilar terminology, we cannot compare these findings with previous studies where avoidable ADRs did not differ from partly avoidable and unavoidable ADRs in terms of their seriousness,[39] nor where the incidence of avoidable ADRs was greater in subjects older than 65 years of age.[40,41]

Due to a lack of reported information needed for the conduct of proper assessment, a sizable number of not-assessable reports (21.6%) were found both before and after the implementation, indicating the need for the development of ADR reporting forms suitable for reporting cases related to the use outside the terms of the MA. Forms currently used were not designed for reporting ADRs outside MA and consequently are not adequate and do not allow capturing of the data needed for the quality assessment of ADRs outside MA; rendering one of the key underlying causes responsible for the high proportion of the not-assessable cases. Only a few EU Member States have separate forms for reporting MEs.[42] Reporting ADRs outside MA should be enabled and enhanced by the use of a prescribed format with pre-defined fields in which all the information related to such circumstances could be entered. Moreover, significantly more not-assessable cases were reported by patients in comparison with other reporters, stressing once again lack of both patient education and cognizance, and highlighting the importance of empowering patients by instilling proper education.

One of the most important changes introduced with the new PV legislation was the obligation on all national RAs and MAHs to accept ADRs received from patients. Recent data showed that the new EU PV legislation has made a positive impact on patient reporting by empowering and motivating patients to report ADRs.[43] A similar trend was observed in our study as the number of patient reports significantly increased following the implementation of the new EU PV legislation. In most cases both HCPs and patients have not recognized and reported use outside of the MA, suggesting the need for education of both HCPs and patients.

Strengths

The SCOPE Joint Action results showed a divergence between MSs' coding practices regarding coding of MEs during an ICSR management.[30] This represents a constraint in comparing frequencies and characteristics of MEs between MSs or in a use of data from EudraVigilance without further reassessment of cases. The main strength of our research lays with its design which includes systematic and unified approach in the assessment of received ADRs. We reassessed all subject cases to provide accurate figures on the frequency of MEs by both, a reporter and an assessor. Furthermore, the problem with recording the use outside of the MA in ADR databases has been recognized and addressed with the introduction of the new ICSR reporting format R3 in the new EV system that went live on November 22, 2017.

Limitations

Several limitations of our study should be pointed out. Firstly, the spontaneous reporting system of ADRs also including the use outside of the MA rendered the first major limitation, a well-known under-reporting.[34,44] We cannot provide a general estimate of the incidence of ADRs outside MA as it would require identification of all cases in a given setting.

Second, the study used a retrospective design, thus not allowing the follow up of cases to determine all the relevant circumstances for ADR occurrence.

Thirdly, the reporting form used for ADR collection was not customized for collecting data referring to medicinal product use outside the MA. It did not contain additional fields that would allow capturing more information about ADRs caused by the use outside of the MA, in particular root cause analysis and forming conclusions on the reasons for the event occurrence. Retrospective design and fact that the reporting form was not adapted to collect ADRs outside MA, resulted in a high number of cases being assessed as 'not assessable'.

Fourthly, the reporting rate could have been influenced by the availability of new reporting channels that were being actively promoted at that time. Namely, new web application introduced in 2012 and new mobile application introduced in 2016 could have affected reporting. However, as the results of our study showed that IMROH

cases were the most important source of ADRs outside MA, and IMROH cases are received exclusively via paper forms, it seems that new reporting channels did not have a big influence on the reporting of ADRs outside MA.

Finally, this is the first study employing new regulatory definitions and experience on its applicability is lacking. Nevertheless, no similar method designed and applied for the assessment of ADRs caused by the use outside of the MA has been available previously.

A clear limitation of this study is that the process is time consuming and was conducted manually; enabling the assessment of a limited portion of total number of received ADRs in one year.

Conclusion

The Croatian HALMED pharmacovigilance database contains a rather high proportion of ADR reports that arise from the use outside the terms of the MA and the proportion of serious ADRs in this group was significantly higher than among the remaining ADR reports. Moreover, a considerable portion of ADRs outside the terms of the MA was not-assessable nor recognized by a reporter, suggesting the need for targeted education and improving reporting systems, since forms currently used were not designed for reporting ADRs outside the MA. Our study demonstrated a significant increase in the number of ADRs arising from the use outside the terms of the MA after the implementation of the new legislation, primarily due to a notable increase in the number of overdose reports received by the poisoning centre, while the number of ADRs caused by MEs did not change significantly. In conclusion, this study elucidated partial implementation of the new EU pharmacovigilance legislation and the need for instilling proper education for both patients and HCPs, improving reporting systems and strengthening collaboration between relevant stakeholders.

Contributions of authors statement

The following authors have contributed substantially to the work in one or more of the following categories:

Nikica Mirosevic Skvrce: conceived of or designed study, performed research, analysed data, interpreted data, participated in writing the paper.

Iva Galic: analysed data, participated in writing the paper.

Carmen Pacadi: performed research and analysed data.

Neva Kandzija: performed research and analysed data.

Iva Mucalo: performed research, analysed data, interpreted data, participated in writing the paper.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sapharm.2019.10.003.

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