DOI: 10.2478/cipms-2022-0021 Curr. Issues Pharm. Med. Sci., Vol. 35, No. 3, Pages 111-115

Current Issues in Pharmacy and Medical Sciences
Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: http://www.curipms.umlub.pl/

The drug safety information in domestic medical literature

Bartlomiej Ochyra[1], Maciej Szewczyk[2], Adam Przybylkowski[1*]

[1] Department of Gastroenterology and Internal Diseases, Medical University of Warsaw, Warsaw, Poland
[2] MS Pharm s.r.o., Praga, Czech Republic

ARTICLE INFO

Received: 04 January 2022
Accepted 02 September 2022

Keywords:
adverse drug event,
adverse drug reaction,
literature search,
literature monitoring.

ABSTRACT

Medical literature is an important source of drug safety information relevant for signal detection, safety profile analysis and risk-benefit assessment. The main goal of our study was to assess the utility of domestic medical literature as a source of drug safety information. All safety information identified for active substances published between 1.01.2018-31.12.2019 in domestic medical journals published in Poland were analyzed. Four thousand seven hundred eighty-nine drug safety information was reported for 500 active substances. Two thousand and forty-four submissions dealing with drug safety (48.28%) were identified in the 10 journals from the list of analyzed journals (3 of these were identified in the 2019 JCR and 5 of these were indexed in the main scientific databases and 9 of these had an affiliation to scientific society). There was a correlation between journal impact factor and scientific database indexation with the number of published individual literature reports and type of safety information. Journals publishing in Polish constituted source for about 40% of all safety information published in the examined period. Journals indexed in Medline were the source of about 37% of all safety information while 42% was published in Embase. Local medical literature is a source of valuable safety information but the list of journals for monitoring should be carefully selected with particular attention to journals with impact factor.

INTRODUCTION

Medical literature, including review of domestic journals, is an important source of drug safety information relevant for signal detection, safety profile analysis and risk-benefit assessment [1]. Local medical literature is recognized sources of valuable safety information, but due to the large number of local journals not being integrated in one single database, limited online access and publishing irregularities, the marketing authorisation holders (MAHs) have to face many challenges to comply with pharmacovigilance (PV) guidelines regarding drug safety monitoring.

According to the guidelines on good pharmacovigilance practices (GVP), MAHs have to establish the most relevant medical journals for the weekly literature review process of each product [1]. Official lists recommended by national competent authorities (NCAs) are uncommon and there are no common guidelines for the selection principles of the journals for the literature review process [2]. Moreover, it should be highlighted that the quality standards of the published literature reports, including the data completeness of individual case safety reports (ICSR) published in the literature, differ between journals [3-7]. Thus, the selection of journals may be crucial for signal detection and safety information identification.

EudraVigilance (EV) is the system for managing and analysing information on suspected adverse reactions to medicines that have been authorized or are being studied in clinical trials in the European Economic Area (EEA). Literature cases submitted to EV arise from a relatively heterogeneous set of articles, including systematic reviews, case reports and studies, and present diverse types of safety information of different impact on the risk-benefit balance, public health and the potential need for prompt regulatory action.

AIM

The main aim of this study was to determine whether there are key factors characterising journals that correlate with the number of individual literature reports published and the type of safety information provided. This could be a valuable indicator for the process of journal selection for the local literature review process.

* **Corresponding author**
e-mail: aprzybylkowski@wum.edu.pl

MATERIALS AND METHODS

The study was a retrospective analysis of local medical literature. Eighty-four Polish medical journals were selected for analysis based on methodology recommended by the Polish Society of Pharmacovigilance [2].

All safety information identified by review of full text articles from 84 local medical journals published in Poland were considered eligible for inclusion in this study. The study period covers two years from 1.01.2018 to 31.12.2019. Analysis was performed for all active substances categorized according to International Nonproprietary Names (INNs).

For the purpose of the study, 4 types of literature report were specified and analyzed:

- CASE: article describing an individual, identifiable patient;
- STUDY: article describing a group of trial subjects who experienced ADRs, but in which it is not possible to match a specified ADR to a specific trail subject;
- REVIEW: article with general non-case information;
- REPRINT: reprint of article with individual identifiable patient.

The following types of safety information was analyzed: Adverse Event (AE), Adverse Drug Reaction (ADR), Serious Adverse Event (SAE), Serious Adverse Drug Reaction (SADR), Designated Medical Event (DME), Drug exposure during pregnancy, Exposure during lactation / breast feeding, Overdose, Misuse, Abuse, Medication error, Lack of efficacy or Incomplete effect, Transmission of an infectious agent (e.g. via a contaminated injection), Occupational exposure, Off-label use, Drug interaction.

Four key factors characterizing the journal were analyzed: journal language (Polish and/or English), journal impact factor (presence on the 2019 Journal Citation Reports (JCR) released by Clarivate Analytics); scientific database indexation (Embase and MEDLINE); affiliation to scientific society. Statistical analysis was performed for each subgroup, these being type of literature report, type of safety information, journal title and key factors characterizing the journal, INN and Anatomical Therapeutic Chemical (ATC) Classification System code.

RESULTS

Basic characteristics of analyzed literature database

In total, 1,138 articles were identified as sources of safety information in 84 analyzed journals. Safety information was reported for 500 INNs. The aforementioned 1,138 articles describe 4,234 individual reports and 4,789 safety information

Type of literature report identified during local literature review

Most individual literature reports (3,710; 87.62%) were classified as cases – while reprints of articles with an individual identifiable patient were published only 19 times (Fig. 1).

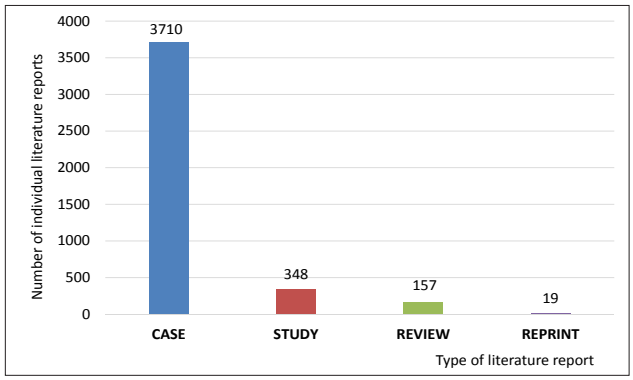

Figure 1. Number of individual literature reports per type of literature report

Type of safety information identified in local medical literature

During the studied period, 4,789 safety information was published in the Polish medical journals. However, author causality assessment adverse event and suspected product was not provided for 651 records from the analyzed literature database. The majority of the safety information was AEs (1,650; 34.45%). Special situations, such as transmission of an infectious agent and occupational exposure, were not identified (Table 1).

Table 1. Safety information per type

Type of safety information	Number of safety information (%)
AE	1650 (34.45)
ADR	886 (18.5)
SAE	258 (5.39)
SADR	163 (3.4)
Drug exposure during pregnancy/embryo or foetus has been exposed to the semen of a patient taking medicine	136 (2.84)
Exposure during lactation/breast feeding	3 (0.06)
Overdose	17 (0.35)
Misuse/Abuse	57 (1.19)
Medication error	34 (0.71)
Lack of efficacy or Incomplete effect	1268 (26.48)
Transmission of an infectious agent	0 (0)
Occupational exposure	0 (0)
Off-label use	48 (1)
Drug interaction	269 (5.62)
TOTAL	4789 (100%)

AE – Adverse Event, ADR – Adverse Drug Reaction, SAE – Serious Adverse Event, SADR – Serious Adverse Drug Reaction

Number of individual literature reports and type of safety information identified during local literature review per ATC code

Most individual literature reports (863; 20.38%) were for antineoplastic and immunomodulating agents and INNs from the group of alimentary tract and metabolism (813; 19.20%). The lowest number of individual literature reports (5, 0.12%) was reported for antiparasitic products, insecticides and repellents (Table 2).

Table 2. Number of individual literature reports and type of safety information per ATC code

ATC Level 1	Number of individual literature case reports	Number and type of safety information				
		DME	SADR	SAE	ADR	AE
A	813	36	19	57	121	401
B	269	5	16	29	49	115
C	755	22	10	40	122	388
D	210	5	10	17	43	64
G	47	0	0	1	10	18
H	37	0	0	5	2	18
J	384	23	20	31	44	166
L	863	41	56	46	274	207
M	77	5	2	4	20	31
N	643	23	32	23	182	192
P	5	0	0	0	1	1
R	70	2	0	3	10	30
S	47	0	0	1	2	15
V	14	1	1	1	3	3
TOTAL	4234	163	166	258	883	1649

ATC – Anatomical Therapeutic Chemical, DME – Designated Medical Event, SADR – Serious Adverse Drug Reaction, SAE – Serious Adverse Event, ADR – Adverse Drug Reaction, AE – Adverse Event

Number of individual literature reports and type of safety information identified during local medical literature review per INN

Safety information was reported for 500 different INNs, while twenty-six INNs were identified on the list of medicines under additional monitoring (these INNs were marked below with a star symbol*). The first 5 INNs with the highest number of individual literature reports and safety information are listed below:

- Most individual literature reports were for: acetylsalicylic acid (160; 3.78%), prednisone (101; 2.39%), cyclophosphamide (88; 2.08%), heparin (72; 1.70%), doxorubicin (68; 1.61%).
- DMEs i.e. medical conditions that are inherently serious and often medicine-related were reported most frequently for: acetylsalicylic acid (8; 4.91%), prednisone (5; 3.07%), etoposide (5; 3.07%), cyclophosphamide (4; 2.45%), metformin (4; 2.45%).
- SADRs were reported most frequently for: mycophenolic acid (8; 4.82%), carbamazepine (7; 4.22%), tacrolimus (7; 4.22%), rivaroxaban* (6; 3.61%), cyclophosphamide (5; 3.01%).
- SAEs were reported the most frequently for: acetylsalicylic acid (19; 7.36%), heparin (12; 4.65%), clopidogrel (8; 3.10%), vancomycin (7; 2.71%), cyclophosphamide (6; 2.33%).
- ADRs were reported most frequently for: prednisone (32; 3.62%), metoprolol (26; 2.94%), acetylsalicylic acid (22; 2.49%), cyclophosphamide (22; 2.49%), doxorubicin (18; 2.04%).
- AEs were reported most frequently for: acetylsalicylic acid (82; 4.97%), metformin (45; 2.73%), prednisone (37; 2.24%), heparin (33; 2.00%), atorvastatin (28; 1.70%).

Characteristics of the journal and number of published individual literature reports and type of safety information published

Eighty-four local medical journals were sources of safety information during the analyzed period. Fifty (59.52%) journals published in Polish only, twenty-three (27.38%) only in English, seven (8.34%) both in Polish and English and four (4.76%) in Polish or English. Five journals (5.95%) were identified in the 2019 JCR (all were indexed in the main scientific databases: 3 journals in both Embase and MEDLINE, 1 journal in MEDLINE only, and 1 journal in Embase). Twenty-four (28.57%) journals were indexed in one of the scientific databases analyzed (18 were indexed in Embase and 10 in MEDLINE). Thirty (35.71%) journals were published by scientific societies (scientific society affiliation). Journals publishing manuscripts written in Polish were source information for 77 (47.24%) DMEs, 61 (36.75%) SADRs, 102 (39.53%) SAEs, 331 (37.49%) ADRs and 766 (46.45%) AEs. Journals with journal impact factor were source information for 46 (28.22%) DMEs, 60 (36.14%) SADRs, 79 (30.62%) SAEs, 210 (23.78%) ADRs and 334 (20.25%) AEs. Journals not indexed in the scientific database were source information for 81 (49.69%) DMEs, 87 (52.41%) SADRs, 105 (40.70%) SAEs, 436 (49.38%) ADRs and 886 (53.73%) AEs. Journals with scientific society affiliation were source information for 58 (35.58%) DMEs, 85 (51.20%) SADRs, 126 (48.84%) SAEs, 371 (42.02%) ADRs and 640 (38.81%) AEs (Table 3). Two thousand and forty-four safety information (48.28%) was identified in 10 journals from the list (Psychiatria Polska, Oncology in Clinical Practice, Polish Heart Journal, Przegląd Lekarski, Polish Archives of Internal Medicine, Dermatology Review, Medycyna Praktyczna, Świat Medycyny i Farmacji, Forum Zakażeń, Polski Merkuriusz Lekarski).

Table 3. Journal characteristic and type of safety information published

Type of safety inform.	Total	Language of the publication		Journal Impact Factor		Scientific database Indexation			Scientific society affiliation	
		ENG	PL	With IF	Without IF	Not indexed	Medline Indexed	Embase Indexed	Yes	No
DME	163	86	77	46	117	81	55	71	58	105
SADR	166	105	61	60	106	87	65	74	85	81
SAE	258	156	102	79	179	105	106	133	126	132
ADR	883	552	331	210	673	436	307	356	371	512
AE	1649	883	766	334	1315	886	544	534	640	1009

DME – Designated Medical Event, SADR – Serious Adverse Drug Reaction, SAE – Serious Adverse Event, ADR – Adverse Drug Reaction, AE – Adverse Event, ENG – English, PL – Polish, IF – Journal Impact Factor

Journal impact factor correlated with the amount and type of safety information published in the journal. There is also a correlation between journal indexation in scientific databases (Embase/MEDLINE) and the number of SAEs, but there was no correlation between journal publication by scientific society and number of individual literature reports and type of safety information published in the journal (Table 4).

Table 4. Correlation between number of published individual literature reports and type of safety information and journal impact factor, scientific database indexation and affiliation to scientific society

Type of correlation	Metrics	Number of individual literature reports	Amount and type of safety information				
			DME	SADR	SAE	ADR	AE
Impact Factor	rho	0.226	0.387	0.310	0.288	0.164	0.220
	p-value	0.038	0.000	0.004	0.008	0.136	0.045
Database Indexation	rho	0.194	0.201	0.181	0.300	0.227	0.250
	p-value	0.078	0.067	0.099	0.006	0.038	0.022
Scientific society affiliation	rho	-0.069	0.014	0.033	0.050	0.057	-0.001
	p-value	0.535	0.898	0.763	0.649	0.605	0.996

DME – Designated Medical Event, SADR – Serious Adverse Drug Reaction, SAE – Serious Adverse Event, ADR – Adverse Drug Reaction, AE – Adverse Event, rho – Spearman's rank correlation coefficient, p-value – probability value

DISCUSSION

Medical literature, including local medical literature, is a valuable source of safety information and drug safety signals. According to the 2021 Annual Report on EudraVigilance, scientific literature screening resulted in 9% of all potential signals in 2021 and 18% in 2020 [8].

The efficiency of the local literature review depends on the process of journal selection and journal list creation. One of the current identified gaps is the lack of clear guidelines and selection principles of journals for the purpose of local literature review. An official list of local medical journals is rarely recommended by national competent authorities and PV scientific societies [2].

The main goal of this study was to assess if there are any key factors characterizing journals that correlate with the number of published individual literature reports and amount/type of published safety information. Based on our best knowledge, there has been no previous research trying to address this problem.

Eighty-four local medical journals were analyzed, whilst 2,044 safety information (48.28%) was identified from only 10 journals. This result indicates that selection of journals for the purpose of local literature review may be crucial. Among all the journals analyzed in our study there were 5 (5.95%) journals with impact factor (identified in the 2019 JCR), and 24 (28.57%) indexed in the main scientific databases, while 30 (35.71%) were published by a scientific society. All 5 journals were indexed in the main scientific databases. Our study demonstrates a correlation between journal impact and the amount of safety information published in the journal, including the number of reported DMEs, SADRs and SAEs. Our results are similar to findings from other studies that confirmed there is a difference in accuracy, quality and completeness of scientific publications from different journals [3-7].

Moreover, it is worth remembering about some of the limitations of the systematic literature review of scientific databases, such as: a) large number of local journals indexed in the main scientific databases translate only the abstract into English, b) journal supplements and conference papers may not be indexed, c) pharmacotherapy data is very often presented as treatment regimens or protocols only – which is challenging for the selection of product terms for search construction.

It can be hypothesised that healthcare professionals are more interested to publish their scientific findings, such as new, rare or unexpected ADRs, in certain journals due to their prestige and visibility within the scientific community. A similar hypothesis was also suggested by Chinoy *et al.,* who claimed that Pakistani medical journals do not receive enough good quality research manuscript submissions because the researchers aim to publish their work in journals with high impact factors, because this is often used as a criterion for promotions in academic career, grant allocations, and faculty output evaluations [9].

During our study, the majority of safety information was of L ATC code – antineoplastic and immunomodulating agents (56 of all SADRs and 274 of all ADRs) and N ATC code - nervous system agents (32 of all SADRs and 182 of ADRs). Similar findings were presented by Impicciatore *et al.*, who found that nervous system agents were the most frequent reported ATC group having caused adverse event(s) in analyzed literature reports [5].

It is worth adding that a causal relationship between a medicinal product and an adverse event was not stated by the author in the majority of analyzed scientific publications. Our findings are in line with these identified by Impicciatore *et al*., who stated that case reports from non-specialist journals still lack the information necessary for comprehensive evaluation. While in their work, they assessed literature reports retrieved from company safety databases, nevertheless, they found that causality assessment was expressed in 81% of all reports, but an objective probability assessment to support the causal link was present in only 20% [5]. Similar findings are given by William N. Kelly, who concluded that <1% (8/1094) of all literature reports from his study were objectively assessed for causality [6]. These results confirm that there is need to implement guidelines for submitting adverse event reports for publication, especially in non-specialist journals, where such instructions for authors are rarely encountered [10].

Due to the number of local medical journals and large amount of data identified during local literature review, there is a need for new or improved methods increasing the effectiveness and productivity of the process. Great expectations can be linked to automated data mining approaches. These methods can supplement existing ADR discovery techniques. However, extracting information from the medical literature requires elaborate Natural Language Processing (NLP) tools. Sill, recent studies have demonstrated its potential as a strategy for prioritising drug-event combination associations [11].

Our study suffers from some limitations. The study was based on 84 local medical journals, whilst there are almost 300 local medical journals on the Polish market, which would create a wider picture of the problem.

Most local journals publish at least the title and the abstract translated into English, however, the lack of sufficient information in these fields may hamper efficient monitoring of the medical literature and, consequently, prompt and effective signal detection. It would be interesting to assess in future studies if there is any difference in safety

information identification when the literature review process is based on full text review *vs.* title and abstract review.

CONCLUSION

Safety information is published for some INNs, whilst the safety profile of other INNs is probably well known enough to the medical community and do not generate literature publications. There are local medical journals that are a powerful source of safety information, while other journals do not publish any. Over all, literature case reports are the most frequent type of report published in local medical literature. Moreover, journal impact factor is correlated to the amount of safety information published in a journal, including the number of reported DMEs, SADRs and SAEs.

In line with our hypothesis, local medical literature is a source of valuable safety information, but the list of local monitored journals for the process of weekly literature review should be carefully selected, paying particular attention to journals with impact factor. Common guidelines on the selection principles for journals for the local literature review process, or official lists of local medical journals recommended by NCAs or PV scientific societies would be beneficial for the quality of the process.

FUNDING

This study received no funding.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ETHICAL STANDARDS

Not applicable.

ORCID iDs

Bartłomiej Ochyra https://orcid.org/0000-0003-1832-5164
Adam Przybyłkowski https://orcid.org/0000-0002-5851-2856

REFERNCES

1. European Medicines Agency (EMA). *Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products* (Rev 2). 2017.
2. Rymarczuk A, Bielski M, Lozak K, Ochyra B, Szewczyk M, Miernecka D, et al) Dobór czasopism medycznych wydawanych w Polsce dla celów przeglądów lokalnej literaratury medycznej w zakresie bezpieczeństwa stosowania produktów leczniczych. – Standard Polskiego Towarzystwa Bezpiecznej Farmakoterapii (PTBFarm). *Biuletyn Bezpieczenstwa Produktow Leczniczych*. 2020;15(1).
3. Ferguson J, Mockbee C, Erbele S, Muniz E. Evaluation of Published Case Reports' Standards and Notification. *Drug Inforn l.* 2002;36:303-7.
4. Hauben D, Aronson J. Gold Standards in Pharmacovigilance. *Drug Safety*. 2007;30:645-55.
5. Impicciatore P, Mucci M. Completeness of published case reports on suspected adverse drug reactions: evaluation of 100 reports from a company safety database. *Drug Saf*. 2010;33(9):765-73.
6. Kelly WN. The quality of published adverse drug event reports. *Ann Pharmacother*. 2003;37(12):1774-8.
7. Pontes H, Clément M, Rollason V. Safety signal detection: the relevance of literature review. *Drug Saf*. 2014;37(7):471-9.
8. EMA. *2021 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission*, EMA/719826/2021, 2022.
9. Chinoy MA, Ahmad T, Tayyab MA, Raza S. Evidence based medicine – where do articles published in local indexed journals stand? *JPMn*. 2009;59(1):5-9.
10. Kelly WN, Arellano FMmuBarnes J,-Bergman U, Edwards IR, Fernandez AM, et al. Guidelines for submitting adverse event reports for publication. *Pharmacoepidemiol Drug Saf*. 2007;16(5):581-7.
11. Shetty KD, Dalal SR. Using information mining of the medical literature to improve drug safety. *I Am Med Inform Assoc*. 2011;18(5): 668-74.