CHAPTER PRESS PUBLISHERS

PATIENTS REPORTING ADVERSE DRUG REACTIONS

KODDUS ALI

-24-

Patients Reporting Adverse Drug Reactions

In recent years, the involvement of patients in drug safety monitoring during regular clinical practice has gained significant importance. The World Health Organisation defines pharmacovigilance as a process that includes identifying, evaluating, comprehending, and preventing adverse drug reactions (ADRs) and other drug-related problems.[1] While drugs undergo rigorous risk assessments, including clinical trials, prior to their release on the market, these pre-marketing clinical trials involve monitoring small, homogeneous, and highly selective populations for short periods of time, which can result in missed ADRs.[2] As drugs become more widely used under varying conditions, additional ADRs can be discovered, such as those caused by concurrent drug use or medication errors.[3]

Patient participation involves patients providing direct feedback regarding their ADR experiences without the involvement of a healthcare professional, which can provide valuable insights for pharmacovigilance.[4]

However, patient reporting also presents several challenges. The quality and reliability of patient reports are sometimes questionable, and obtaining accurate and complete information from patients can be difficult. Over-reporting of ADRs by patients and under-reporting of more severe ADRs are also concerns. Therefore, it is crucial to evaluate the actual impact of patient reporting on pharmacovigilance and identify strategies to enhance the quality and reliability of patient reports.

The thalidomide disaster prompted the initiation of coordinated international efforts to address drug safety concerns.[5] This drug, which was marketed as a sleep aid and anti-nausea medication, was widely promoted for use in pregnant women in over 20 countries from 1956 to 1961. However, it caused thousands of congenitally deformed infants due to in utero exposure to an unsafe drug.[1] This tragedy highlighted the need for systematic monitoring of drug safety after drugs are released to the market, leading to a shift in global drug safety efforts from reactive to proactive actions.[5]

In response, committees on drug safety were established in many countries, which oversaw pre-marketing drug safety surveillance as well as post-marketing

pharmacovigilance. One of the methods implemented to monitor drug safety during the post-marketing phase was the establishment of spontaneous reporting systems. These systems allowed for voluntary reporting of ADRs observed in daily practice and are mainly operated by national pharmacovigilance centres, which are typically associated with drug regulatory authorities and are funded (partially) through user fees paid by the pharmaceutical industry or relevant government health departments. Some centres, such as those in New Zealand, are independent organisations that work closely with drug regulatory authorities.[6]

The European Union (EU) began its pharmacovigilance efforts in 1965 with the introduction of medicines legislation, which involved establishing ADR systems in several European countries. The formation of the European Agency for the Evaluation of Medicinal Products (EMEA) in 1995, subsequently renamed the European Medicines Agency (EMA) in 2004, aimed to encourage cooperation among EU member states. To further enhance pharmacovigilance, the legal framework for drug safety within the EU was updated twice: first in 2004 to integrate the risk management strategy and then

in 2010 to reinforce pharmacovigilance through specific legislation.[7,8]

The legislation in 2010 addressed aspects such as the improvement of ADR reporting, pharmacovigilance obligations of marketing authorisation holders, the establishment of the EudraVigilance database for ADR reporting, and the creation of the Pharmacovigilance Risk Assessment Committee (PRAC) to provide technical expertise on safety issues. Overall, the European Union has taken proactive steps to improve the safety of medicines within the region and provide guidelines for pharmacovigilance efforts.

The latter legislation (Regulation No 1235/2010) implemented significant changes, such as the inclusion of patients as stakeholders in pharmacovigilance. The PRAC of the EMA is responsible for evaluating all aspects of risk management associated with medicinal products' therapeutic effects in the EU.[9] This includes the identification, evaluation, minimisation, and dissemination of ADRs[10]

Pharmacovigilance centres are informed of ADRs through various means such as phone calls, physical documents, and electronic forms for reporting.[6] Many of

these centres engage in data collection and analysis at the national level. The primary purpose of spontaneous reporting systems is to promptly identify new drug safety issues. A "signal" is defined as information from various sources, such as observations or experiments, indicating a possible causal relationship between an intervention and an adverse or beneficial event or a new aspect of a known association. This association must be considered likely enough to warrant further investigation.[11]

Signals can originate from a variety of sources, including spontaneous reports from healthcare professionals, patients, or pharmaceutical companies, observational studies, registries, clinical trials, and published literature. Signals are often evaluated through a systematic approach that involves data mining, quantitative analysis, and expert review. Signal detection is an iterative process that involves refining the signal through additional investigations and confirmation studies. Successful signal detection requires an efficient and robust pharmacovigilance system that facilitates data collection, analysis, and dissemination.

Real-life data collection allows for the assessment of the balance between the benefits and harms of a drug. As a

result, regulatory bodies must take appropriate measures to protect patient safety.[12] Case reports and case series have a high sensitivity for identifying novel information and play a critical role in medical education.[13] They facilitate the discovery of new diseases and unexpected effects (adverse or beneficial) and the investigation of mechanisms. Spontaneous reports, clinical trials, and observational studies are currently the three primary sources of post-marketing drug safety evidence. Studies conducted in Europe and the USA have shown that spontaneous reports are responsible for triggering the majority of new drug safety signals.[14,15]

In pharmacovigilance, signal detection methods can be classified into qualitative and quantitative approaches. Qualitative methods rely on the case-by-case analysis of individual or series of ADR reports. In this type of assessment, clinical-pharmacologic factors are primarily used to identify potential signals. However, for large spontaneous reporting schemes like the Yellow Card Scheme in the UK, it is not feasible to evaluate every report in detail due to the large volume of reports. Therefore, statistical techniques are applied as an initial step of signal detection.[16]

Signal detection aims to promptly detect new drug safety concerns. A signal refers to information from various sources such as observations or experiments, indicating a potential causal relationship between an intervention and an adverse or beneficial event, or a new aspect of a known association. This association must be considered likely enough to require further investigation. By using signal detection methods, pharmacovigilance centres can identify and investigate potential safety concerns related to the use of medicinal products, ultimately leading to improved patient safety.

Traditionally, patients were not actively involved in pharmacovigilance due to concerns about their limited medical knowledge, which could potentially lead to the submission of low-quality reports. As a result, healthcare professionals were primarily responsible for reporting potential ADRs.[4] However, attitudes towards the value of patient experiences have since changed, and in the 2000s, a dozen countries introduced patient reporting systems. Denmark and the Netherlands were the first European nations to implement such systems in 2003, followed by Italy in 2004 and the UK in 2005. Countries outside of Europe, such as Malaysia in 2007 and the Philippines in

2008, also began accepting ADR directly from patients.[6,17]

Patient reporting systems have been found to be valuable for several reasons. First, patients can provide unique perspectives on the effects of drugs on their daily lives that may not be captured by healthcare professionals. Second, patient reporting systems may be more effective in detecting rare and previously unknown ADRs that may not be reported by healthcare professionals. Finally, involving patients in pharmacovigilance can promote patient empowerment and help to build public trust in the healthcare system.[18]

The acknowledgement of patients as an important stakeholder in pharmacovigilance in Europe was formalised with the implementation of Regulation No 1235/2010 in July 2012. This regulation permitted patients across the EU to directly report their drug-related concerns to the national centre, signifying a significant shift towards increased patient involvement.[19,20] Moreover, since 2012, patients have had a representative as a full member of the PRAC, which has been deemed as a significant milestone in the advancement of pharmacovigilance. The patient representative's role is

critical in ensuring that regulators take into account the patient perspective and contribute to decisions regarding the timing and wording of risk communications, which are essential in ensuring drug safety. [21] The patient representative's participation has enhanced transparency in the drug regulatory process and has played a critical role in the development of policies and regulations that prioritise patient safety.

Detecting ADRs can occur through various channels, including direct observation by healthcare professionals or reports from patients themselves. Healthcare professionals, relying on their expertise and understanding, may choose to report an ADR after considering their patient's condition. These reports are vital in detecting new drug safety issues. However, healthcare professionals may only report a limited view of the patient's experience. Hence, direct patient reporting can offer first-hand information and provide valuable insights for pharmacovigilance.

Patient reporting of ADRs can help fill in the gaps left by healthcare professionals' reports, providing additional details that may be missed. Patients may report less severe ADRs, enabling the detection of new safety issues earlier,

which can ultimately improve drug safety. Moreover, patient reporting also enables the assessment of the impact of the drug on their daily lives, including their ability to carry out daily activities and work. Therefore, patient reporting is a critical component of pharmacovigilance, enabling healthcare professionals and regulatory agencies to obtain a more comprehensive understanding of drug safety issues.

A plethora of studies have investigated the significance and effect of patient reporting in pharmacovigilance. Although patient reporting comprises a range of aspects, only a few have been comprehensively studied. Most of these studies have concentrated on comparing the type of ADRs reported by patients and healthcare professionals. Additionally, some studies have examined the characteristics of ADRs, the reliability of the reported information, and the impact of patient reports in detecting signals.

Previous studies have predominantly focused on the general system organ class level of ADR reports made by patients.[22,25] However, some studies have delved more deeply into the specific ADRs reported by patients and healthcare professionals, uncovering similarities and

differences between the two groups.[22,24] In the UK patients and healthcare professionals frequently reported nausea and headache as ADRs, indicating similar observations. These studies shed light on the potential value of patient reporting in pharmacovigilance and the unique insights it can provide compared to healthcare professionals' reporting. However, further research is necessary to better understand the overall impact and contribution of patient reporting to the field.

Patient reports have become increasingly important in detecting ADRs in pharmacovigilance.[26-28] In the UK, research has demonstrated a shift towards patient-reported ADR signals, which rose from 15.6% in 2009 to 23.6% in 2010.[26] A retrospective analysis of the Yellow Card Scheme, which combines patient and healthcare professional reports, has shown that analysing them separately yielded different results.[16] The combination of these reports identified 508 new signals, with 10% involving serious ADRs not listed on the product's Summary of Product Characteristics (SPC). In contrast, 278 signals, or 11%, were no longer detected. The study also found that patients and healthcare professionals reported different ADRs, with patient reports revealing previously unrecognised, serious ADRs. The Yellow

Card Scheme data suggest that combining both types of reports may improve the detection of signals and contribute to drug safety. It is essential to consider patient reports in pharmacovigilance, as they provide unique information that may not be captured by healthcare professionals.[16]

Pharmacovigilance centres acknowledge the importance of patients as essential stakeholders in their field. While researchers have endeavoured to explore the potential of patient reporting to contribute to pharmacovigilance and improve patient experiences, there remains a dearth of comprehensive understanding regarding the exact influence of direct patient reporting on pharmacovigilance.

The identification of ADRs has shown promising advancements with the incorporation of patient reports; however, a few hurdles continue to prevail. These impediments include the intricacies involved in acquiring precise and comprehensive data from patients, and uncertainties surrounding the quality and trustworthiness of patient reports. Additionally, the potential for ADR over-reporting by patients, along with the probability of under-reporting more severe ADRs, demands careful

attention. Therefore, further research is imperative to assess the tangible influence of patient reporting on pharmacovigilance and to devise tactics for improving the calibre and dependability of patient reports to facilitate their successful integration into pharmacovigilance endeavours.

References

1. World Health Organization. The importance of pharmacovigilance: Safety monitoring of medicinal products. (Accessed: 18 July 2022) http://apps.who.int/medicinedocs/en/d/ Js4893e/.

2. Kaeding, M., Schmalter, J., & Klika, C. (2017). Pharmacovigilance in the European union: Practical implementation across member states (1st ed.). Springer.

3. Blenkinsopp, A., Wilkie, P., Wang, M., & Routledge, P. A. (2007). Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. Br J Clin Pharmacol, 63(2), 148–156.

4. Jones, J. K., Kingery, E., Andrews, E. B., & Moore, N. (2014). Mann‘s Pharmacovigilance (Vol. 2). Wiley.

5. Van Grootheest, K. (2004). Patients’ role in reporting adverse drug reactions. Expert Opin Drug Saf, 3, 363–368.

6. Van Hunsel, F., Härmark, L., & Pal, S. (2012). Experiences with Adverse Drug Reaction Reporting by Patients; An 11-Country Survey. Drug Saf, 35(1), 45–60.

7. Borg, J.-J., Aislaitner, G., Pirozynski, M., & Mifsud, S. (2011). Strengthening and rationalizing pharmacovigilance in the EU: where is Europe heading

to? A review of the new EU legislation on pharmacovigilance: A review of the new EU legislation on pharmacovigilance. Drug Safety: An International Journal of Medical Toxicology and Drug Experience, 34(3), 187–197.

8. Bahri, P., Arlett, P., Andrews, E. B., & Moore, N. (2014). Mann's Pharmacovigilance (Vol. 3). Pharmacovigilance Systems.

9. European Medicines Agency. Legal framework. (Accessed: 21 August 2022) ttp://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp

10. Santoro, A., Genov, G., Spooner, A., Raine, J., & Arlett, P. (2017). Promoting and protecting public health: How the European union pharmacovigilance system works. Drug Safety: An International Journal of Medical Toxicology and Drug Experience, 40(10), 855–869. https://doi.org/10.1007/s40264-017-0572-8

11. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module IX - Signal Management. (Accessed: 22 July 2022) www.ema.europa.eu/docs/.../ WC500129131.pdf

12. Health Action International. Direct Patient Reporting in the European Union: A Snapshot of Reporting Systems in Seven Member States. (Accessed: 7 July 2022)

http://apps. who.int/medicinedocs/documents/s22088en/s22088en.pdf

13. Vandenbroucke, J. P. (2001). In defense of case reports and case series. Annals of Internal Medicine, 134(4), 330–334. https://doi.org/10.7326/0003-4819-134-4-200102200-00017

14. Ishiguro, C., Hall, M., Neyarapally, G. A., & Dal Pan, G. (2012). Post-market drug safety evidence sources: an analysis of FDA drug safety communications: LETTER TO THE EDITOR. Pharmacoepidemiology and Drug Safety, 21(10), 1134–1136. https://doi.org/10.1002/pds.3317

15. Pacurariu, A. C., Coloma, P. M., van Haren, A., Genov, G., Sturkenboom, M. C. J. M., & Straus, S. M. J. M. (2014). A description of signals during the first 18 months of the EMA pharmacovigilance risk assessment committee. Drug Safety: An International Journal of Medical Toxicology and Drug Experience, 37(12), 1059–1066. https://doi.org/10.1007/s40264-014-0240-1

16. Hazell, L., Cornelius, V., Hannaford, P., Shakir, S., Avery, A. J., & Yellow Card Study Collaboration. (2013). How do patients contribute to signal detection? : A retrospective analysis of spontaneous reporting of adverse drug reactions in the UK's Yellow Card Scheme: A retrospective analysis of spontaneous reporting of

adverse drug reactions in the UK's yellow card scheme. Drug Safety: An International Journal of Medical Toxicology and Drug Experience, 36(3), 199–206. https://doi.org/10.1007/s40264-013-0021-2

17. Margraff, F., & Bertram, D. (2014). Adverse drug reaction reporting by patients: an overview of fifty countries. Drug Safety: An International Journal of Medical Toxicology and Drug Experience, 37(6), 409–419. https://doi.org/10.1007/s40264-014-0162-y

18. European Medicines Agency. The patient's voice in the evaluation of medicines. (Accessed: 14 August 2022) http://www.ema.europa.eu/docs/en_GB/document_library/ Report/2013/10/WC500153276.pdf

19. European Medicines Agency. EudraVigilance. (Accessed: 2 July 2022)

    http://www.ema.
    europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000491. jsp.

20. Härmark, L., Raine, J., Leufkens, H., Edwards, I. R., Moretti, U., Sarinic, V. M., & Kant, A. (2016). Patient-reported safety information: A renaissance of pharmacovigilance? Drug Safety: An International Journal of Medical Toxicology and Drug Experience, 39(10), 883–890. https://doi.org/10.1007/s40264-016-0441-x

21. European Medicines Agency. The patient's voice in the evaluation of medicines. (Accessed 3 July 2022) http://www.ema.europa.eu/docs/en_GB/document_library/ Report/2013/10/WC500153276.pdf

22. McLernon, D. J., Bond, C. M., Hannaford, P. C., Watson, M. C., Lee, A. J., Hazell, L., Avery, A., & Yellow Card Collaboration. (2010). Adverse drug reaction reporting in the UK: a retrospective observational comparison of yellow card reports submitted by patients and healthcare professionals: A retrospective observational comparison of yellow card reports submitted by patients and healthcare professionals. Drug Safety: An International Journal of Medical Toxicology and Drug Experience, 33(9), 775–788.

23. de Langen J, van Hunsel F, Passier A, de Jongvan den Berg LTW, van Grootheest AC. Adverse Drug Reaction Reporting by Patients in the Netherlands, Three Years of Experience. Drug Saf 2008;31(6):515-24

24. Banovac M, Candore G, Slattery J, Houyez F, Haerry D, Genov G, Arlett P. Patient Reporting in the EU: Analysis of EudraVigilance Data. Drug Saf 2017;

25. Leone, R., Moretti, U., D'Incau, P., Conforti, A., Magro, L., Lora, R., & Velo, G. (2013). Effect of pharmacist involvement on patient reporting of adverse drug reactions: first Italian study. Drug Safety: An

International Journal of Medical Toxicology and Drug Experience, 36(4), 267–276.

26. Foy, M., Gandhi, S., Cumber, S., & Jadeja, M. M. (2011). The Yellow Card Scheme: Patient reporting of Adverse Drug Reactions and Signals they have Generated (abstract OP40). Drug Saf, 34(10).

27. Hammond, I. W., Rich, D. S., & Gibbs, T. G. (2007). Effect of consumer reporting on signal detection: using disproportionality analysis. Expert Opinion on Drug Safety, 6(6), 705–712.

28. Van Hunsel, F., Talsma, A., van Puijenbroek, E., de Jong-van den Berg, L., & van Grootheest, K. (2011). The proportion of patient reports of suspected ADRs to signal detection in the Netherlands: case-control study. Pharmacoepidemiology and Drug Safety, 20(3), 286–291. https://doi.org/10.1002/pds.2092