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EDITORIAL

Measuring the impact of pharmacovigilance activities, challenging but important

1 | INTRODUCTION

Drug use is associated with a certain degree of risk. The benefit risk balance is guarded throughout the whole drug life cycle, during the pre-marketing development and testing, as well as after drugs have been approved for use in patients. Drug developers need to comply with rigorous guidelines set by regulatory agencies during the phases of drug development prior to their marketing to prove that these drugs are safe to use in patients.[1] But as not all risks related to their use are known at the moment of marketing authorisation, there is still need for drug safety monitoring during the post-marketing phase. The science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem in the post-marketing phase is commonly referred to as *Pharmacovigilance*.[2] The goal of pharmacovigilance is to reduce harm by more appropriate use of medicines. Pharmacovigilance activities aim to contribute to the protection and promotion of public health.

2 | INTENDED AND UNINTENDED EFFECTS OF PHARMACOVIGILANCE ACTIVITIES

In daily practice, there are a variety of pharmacovigilance activities which all influence different steps in the pharmacovigilance pathways (Figure 1). These complicated "pathways" of pharmacovigilance activities are often intertwined and complementary.[3]

Regulatory authorities have an important role in acting on and communicating about the quality, efficacy, and safety of the products they license.[4] Regulatory interventions such as withdrawals or restrictions of use of medicine can lead to therapeutic switching to alternative medicines, or even no alternative treatment, which may have patient or public health implications not foreseen and or intended at the time of intervention. In 2003, the FDA warned of an association between SSRI prescription and suicidality in paediatric patients (<18); subsequently, prescription of SSRIs in newly diagnosed adult patients decreased, without compensation by alternative medicines or treatment, leaving a potentially serious condition untreated.[5,6] The warning issued by the UK Committee on Safety Medicines in 1995, that oral contraceptive pills containing gestodene or desogestrel were associated with a higher risk of venous thromboembolism, has had a negative impact on public health. A significant number of women either switched brands or ceased contraception altogether following the announcement. National data suggested a strong association between the pill scare and a substantial increase in the number of unintended pregnancies.[7] Switching can also involve the use of alternative and complementary medicines (CAM) instead of conventional medicines because of the perception that these might be safer alternatives. However, these products are not without risks themselves.[8] In addition, health risks described for certain drugs may cause channelling of new drugs to patients with pre-existing morbidity. This may result in incorrect attribution of disease states to use of the newer drug.[9] For example, in the past, patients with strong risk factors for gastrointestinal adverse drug reactions were channelled to a new controlled release formulation of the non-steroidal anti-inflammatory drug (NSAID) ketoprofen, due to incorrect safety expectations for this product.[10]

3 | STUDIES ON IMPACT OF PHARMACOVIGILANCE ACTIVITIES

Assessment of the impact of pharmacovigilance actions at the population level is an area currently underinvestigated.

Methods, challenges, and interpretation of post-approval evaluation of effectiveness of risk minimisation measures have been described by Banerjee et al.[11] These evaluations typically investigate knowledge, attitudes, or behaviours of health care professionals or patients, the incidence of safety concerns, and their impact on the overall benefit-risk balance. A review of risk minimisation measures applied to EU centrally authorised medicines between 2006 and 2015 found that additional risk minimisation measures were imposed to approximately a quarter of them. Effectiveness measurements, though increasing in time, remained limited to a minority of instances.[12] Recently, Goedecke et al[13] provided a descriptive overview of the analytical methods for impact research as there is currently no common methodological approach to guide impact evaluation. They assessed 153 articles, of which 55% of studies measured changes in drug utilisation patterns, 27% evaluated health outcomes, and 18% targeted knowledge, behaviour, or changes in clinical practice. Unintended consequences like switching therapies or spillover effects were rarely evaluated.

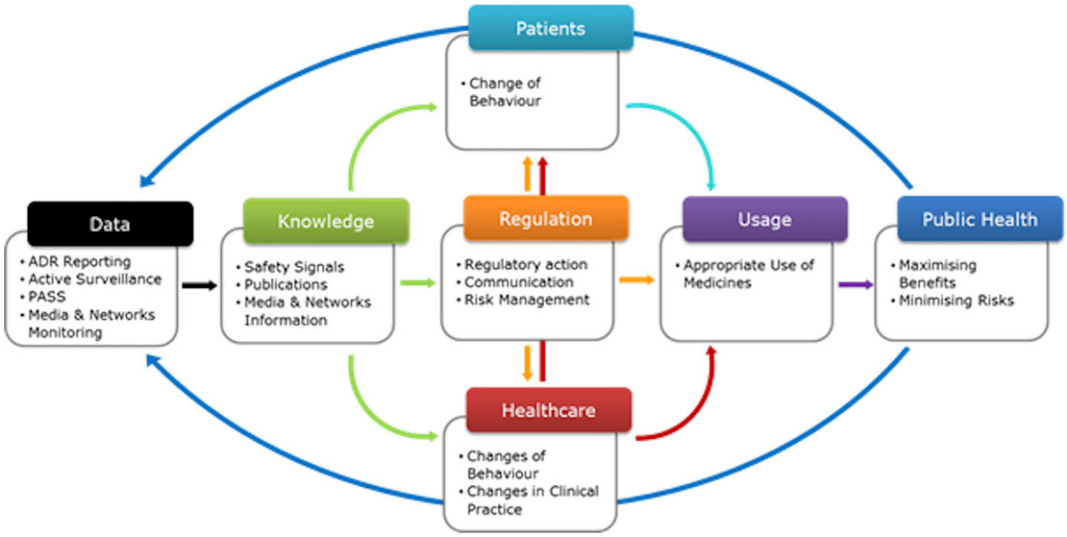

FIGURE 1 Pathways of pharmacovigilance activities[3]

4 | CHALLENGES OF MEASURING IMPACT

There are different challenges when measuring the impact of pharmacovigilance activities. These include the following:

1. The intertwining of the different steps of the pharmacovigilance pathway, which makes the assessment of impact for the individual steps complicated.
2. Taking into account the unintended effects and other simultaneous events such as changes in clinical practice or secular trends in health outcomes.
3. Determining and measuring the right outcomes, which can be challenging and might be further complicated by unavailability of data.

For instance, over-the-counter medication, without a medical prescription, or drugs which are not reimbursed, such as oral contraceptives in many countries, are rarely covered in secondary data sources.[3] Large electronic health care databases can be used to assess usage patterns of medication or the occurrence of disease and symptoms. However, heterogeneity in their structure, validity, and access across Europe complicates the conduct of multidatabase studies.[14] Also, different databases are unlikely to capture all impact-relevant outcomes, even when they are linked to one another. Data may be available on hard outcomes such as death, hospital admission, emergency room visit, or medical contacts; however, these might not be publically available to researchers. The assessment of changes in behaviours of health care professionals and patients needs a qualitative data collection approach in form of collecting questionnaires or performing interviews.[15]

Although measuring the impact of pharmacovigilance activities is challenging, more appropriate research is needed, as has also been described for drug safety science as a whole.[16] This requires various types of data, advanced study designs, and new methodologies that allow for a full evaluation of the impact on public health, taking into consideration the various factors that play a role throughout the pharmacovigilance pathway. The added value of new data sources and techniques, such as real-life monitoring, should be assessed.

In 2018, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) published guidance on methods for pharmacovigilance impact research. This guidance discusses challenges present with choosing the right study outcomes, as they are closely tied to the nature and objective of the pharmacovigilance activities and will be different for each drug and each type of risk. In addition, limitations of data sources, study design, and analytical methodology are discussed.[5]

5 | IMPORTANCE OF MEASURING PHARMACOVIGILANCE ACTIVITIES

The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (PRAC), the European Medicines Agency's (EMA) committee responsible for assessing and monitoring the safety of human medicine, launched a strategy in 2016 to improve safety monitoring practices and to determine which activities are most successful.[17]

No doubt, pharmacovigilance is important and has proved its value in practice by far. But to be able to measure the impact of pharmacovigilance, we need to generate more evidence about the effectiveness and public health consequences of pharmacovigilance activities at the population level. It also elucidates information which could aid in the optimisation of the functioning of the pharmacovigilance system. It can provide valuable information how to improve pharmacovigilance by identifying which pharmacovigilance activities are most successful and enablers and barriers for generating positive health impacts. It will provide opportunities to focus resources on those activities that make a difference in daily health care. Pharmacovigilance should become next to practice based more evidence based.

COMPETING INTERESTS

There are no competing interests to declare.

Keywords

pharmacovigilance, impact, risk minimisation

ORCID

Florence van Hunsel https://orcid.org/0000-0001-8965-3224
Helga Gardarsdottir https://orcid.org/0000-0001-5623-9684
Anthonius de Boer https://orcid.org/0000-0002-9485-8037

Florence van Hunsel[1]
Helga Gardarsdottir[2]
Anthonius de Boer[2,3]
Agnes Kant[1]

[1]*Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands*
[2]*Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*
[3]*Medicines Evaluation Board, Utrecht, The Netherlands*

Correspondence
Florence van Hunsel, Netherlands Pharmacovigilance Centre Lareb, 's Hertogenbosch, The Netherlands.
Email: f.vanhunsel@lareb.nl

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