The value of direct patient reporting in pharmacovigilance

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> Nurses, pharmacists, doctors and patients each hold a piece of the puzzle and only by placing the pieces together will we be able to see the big picture at last. Everyone – patients included – needs to be invited to the big round table of medicine safety[1].

Introduction

The past decade has seen the impressive growth of patient involvement in healthcare, to the point that the term 'patient centricity' has been introduced steadily in all patient-related activities. This is particularly true in clinical research, where patients have gone from being passive recruited subjects to active participants thanks to the realization that if something is meant to benefit the patient, then the patient must be included in the process and his/her voice must be as relevant as that of the other stakeholders in order to obtain better-quality medicines that really improve lives. Much effort has been put into developing new methodologies for collecting the patient perspective along the clinical trial journey, as a result of which patient-relevant outcomes nowadays are an integral part of COAs (clinical outcome assessments) side-by-side with medically relevant outcomes. Even more interesting is the fact that regulatory agencies like the FDA and EMA are encouraging the involvement of patients in clinical research, and the FDA has gone as far as publishing a series of guidance documents (www.fda.gov/drugs/devoration-patients-voice-medical) on how to involve patients in research that are shaping the way the pharmaceutical industry is rethinking its approach to patient participation in clinical trials.

In this evolving scenario, pharmacovigilance has not been a large experimental ground for patient participation; on one hand this is because it has always been perceived as an area where only healthcare professionals have the right competence to deal with adverse events and the associated risks, and on the other hand, because patients have not been encouraged to play a more active role in this issue. The most important objective of pharmacovigilance has been, until recently, the detection and reporting of serious side effects, a task well accomplished by the very accurate current pharmacovigilance systems that guarantee patient safety and quick response to any alert.

However, with an increasing number of drugs being approved on shorter trials that involve fewer patients, getting accurate reports of adverse events and side effects after approval is becoming a necessity. Confirmation of this trend is not difficult to find, if we consider how much importance real world evidence has gained in regulatory evaluations, which means that reports coming from patients describing their experiences with new drugs, including minor adverse events, will likely play a bigger role in the future when regulators have to decide whether to grant approval.

Hard evidence can also be found in a recently published review of the FDA, 'Reported use of patient experience data in 2018 drug approvals', where patient experience data (PED) is defined as the systematic collection of meaningful data relating to the experiences, perspectives, needs, and priorities of patients.

Of the 59 approved new molecular entities in 2018, 48 include a table summarizing whether

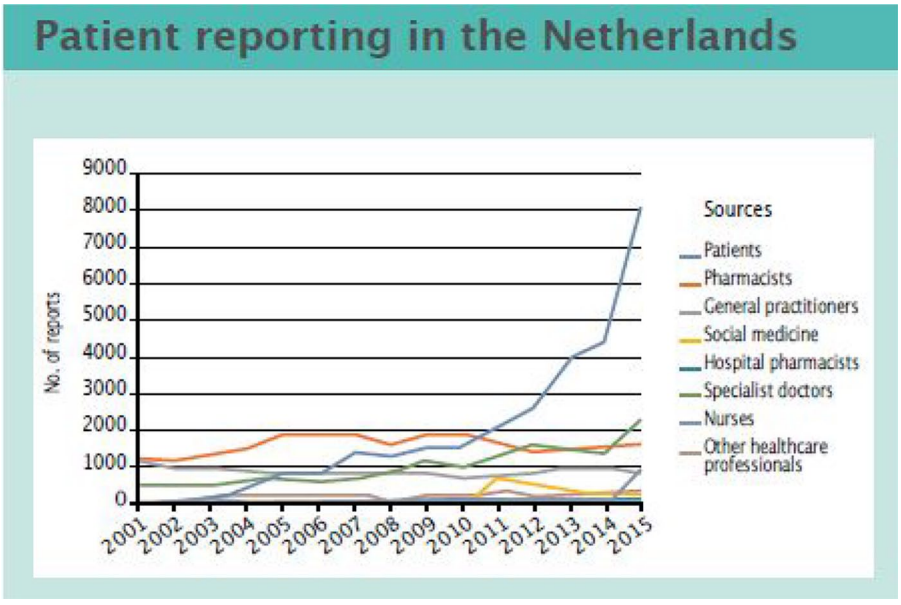

Figure 1. Patient reporting in the Netherlands. (Source: LAREB).[4]

PED was or was not used during the FDA drug review. Thirty-four of those 48 approvals (70.8%) reported using PED in the drug review. Patient-reported outcomes (PROs) represented the most significant source of PED, and were used in 60.4% of approved drug reviews.[2]

As a result, it is reasonable to assume that direct patient reporting in pharmacovigilance could in the future become a PED that will help regulators make a decision about approval. This is even more the case if we consider that minor adverse events are becoming more relevant to patients as they impact directly on their quality of life, while doctors often do not have the time to report them and often underestimate the burden of minor side effects for patients.

Expert patients, on the other hand, understand only too well that minor adverse events play an important role in a patient's decision to stick to the treatment plan or not. For example, a medium-intensity itch with no serious repercussions on health might seem perfectly endurable by most, doctors included, but when it occurs almost daily it might eventually lead to the patient giving up his/her treatment plan. Therefore, minor adverse events should be taken into careful consideration, and this is an issue in which patients can play a leading role. Moreover, chronic patients are increasingly eager to play an active part in the management of their care and to take more responsibility for their health issues, including pharmacovigilance. This is confirmed by looking at the growth in patient reporting in the Netherlands after 2003, when the Pharmacovigilance Centre LAREB implemented patient reporting to their spontaneous reporting system (Figure 1). The number of reports by patients grew rapidly, highlighting the need to evaluate the value of the patient reporting scheme and to compare experiences with other countries.[3]

The current situation

EU pharmacovigilance legislation passed in 2012 (Regulation No. 1027/2012 and Directive 2012/26/EU) required all countries across the EU to have a system that could receive reports directly from patients; however, some countries were quicker to adopt this new provision than others, and, above all, they did not all advertise the opportunity among patient communities. One of the best-known reporting systems is the Yellow Card Scheme, active in the UK, but some other national competent authorities (NCAs) were slow to set up a patient reporting system on their websites, and awareness among patients is, as a result, still sketchy.

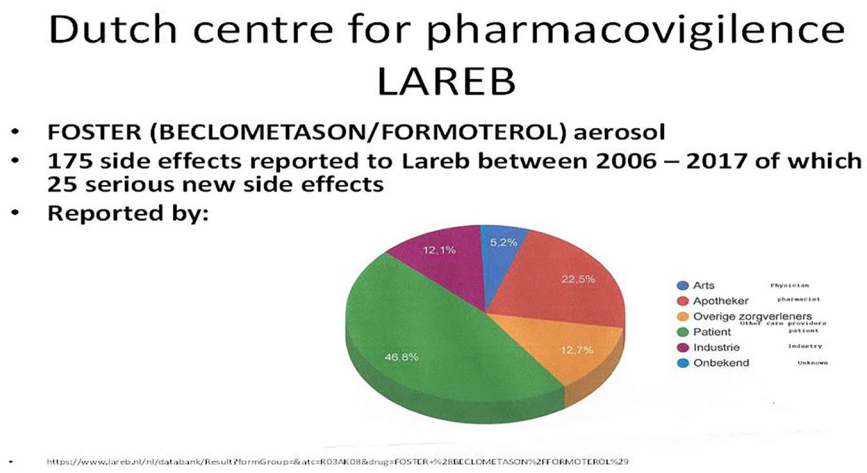

Figure 2. Percentage of side effects reported by different stakeholders.

Another important advancement that not many patients know about is the fact that they can receive direct alerts from the EMA about medicines in their disease area whenever the Pharmacovigilance Risk Assessment Committee (PRAC) issues a warning or a recall. This means that patients can find out about a medicine alert at the same time as their physicians, a huge step forward in recognizing that patients have a right to be informed about negative effects.

Direct patient reporting has represented a major breakthrough in empowering patients to manage the adverse events they experience – so much so that evidence from the EMA shows that the number of reports submitted directly by European patients and consumers through the NCAs and marketing authorization holders (MAHs) increased to 91% in 2018.[5]

This European data is supported by national trends. For example, LAREB has published data on the level of side effects reported by different stakeholders (Figure 2). These figures show that when patients are facilitated and encouraged to report adverse events, they actually do so. LAREB has a consolidated tradition in direct patient reporting research, with Van Hulsen and Rolfes writing their doctoral theses on the subject, confirming the potential value of patients' contributions and discussing how direct patient reporting could be better supported and the data improved.[6,7]

Further significant research on the value of direct patient reporting comes from Inàcio (University of Helsinki) and Matos (University of Seville).[8]

A study conducted in the UK, which evaluated the effect of patient reporting on signal generation, demonstrated that combining patients' reports with healthcare professionals' reports resulted in the generation of 47 new signals for serious adverse drug reactions (ADRs).[9]

Patient reporting without the influence of a healthcare professional is important, as doctors underestimate certain side effects and overestimate others in terms of importance or relevance to a patient. For example, doctors will often dismiss fatigue, whereas for the patient it is a symptom that impacts considerably on the quality of life. And even when side effects are reported, there are differences in how doctors and patients report them. Patients' reports are more focused on the subjective impact of the adverse event, whereas reports from health professionals include a lot of clinical information, but less on the experience of the patient.[10]

An interesting disease area to test the importance of combining patients' and healthcare professionals' reports to enhance pharmacovigilance is multiple sclerosis (MS), a chronic neurological condition that has witnessed a staggering increase in therapeutic choices over the past 10 years, making the issue of collecting reports of side effects from patients highly relevant. A French study investigating whether the use of a mobile application (an app) increased ADR reporting among patients with relapsing–remitting MS (RR-MS) receiving disease modifying drugs was launched in 2017, underlining the need to have more patient reporting of ADRs in a real-life

setting for the therapeutic management of RR-MS, and particularly for monitoring newly approved disease modifying drugs and to gain better knowledge of their safety profiles. Results of the study are not available yet, but it clearly marks a growing interest in the scientific community in direct patient reporting.[11]

Physician perspective

Pharmacovigilance is a continuing process throughout the lifetime of a medicinal product. At the time of a new drug's authorization, information on safety is relatively limited due to:

- small numbers of subjects included in clinical trials
- restricted population in terms of age, gender and ethnicity
- restricted comorbidity
- restricted co-medication
- restricted conditions of use
- relatively short duration of exposure and follow up
- statistical problems associated with looking at multiple outcomes.

Post-marketing studies are, therefore, essential to further evaluate long-term safety issues for specific drugs, comparing treated patients with a control group or with untreated patients.

Physician reporting is actually underpowered because of the cumbersome system of compiling pharmacovigilance reports, the lack of appropriate and flexible IT systems and a general lack of interoperability between NCA reporting systems and disease registries. For these reasons, physicians tend to report only major and unexpected adverse events and often underestimate the burden of minor side effects for patients.

Developing a culture of joint reporting ADRs by physicians and patients is a relevant goal to improve knowledge of a drug's safety profile and ameliorate patient care.

Furthermore, from the physician point of view, the use of disease registries to input pharmacovigilance information could be a chance to improve reports and to evaluate the relation between safety data and other patient information (demographic, clinical and paraclinical data).

Specifically in MS, the EMA recently recognized the potential value of using existing MS patient registries to conduct post-authorization studies (PASS) on safety and effectiveness of MS treatments (EMA, Report in Multiple Sclerosis Registry- Workshop 7 July 2017).

How to encourage direct patient reporting

Given the assumption that direct patient reporting in pharmacovigilance is beneficial as it provides added value, how can we encourage patients to be more involved in this activity? The key points are to inform and educate patients and to work on better ways to engage them in the whole process.

As far as information is concerned, a review of patient-centred pharmacovigilance published in 2018 highlighted a need for patient enlightenment on ADR reporting.[13] This shows that direct patient reporting in pharmacovigilance is still an unknown practice for the majority of patients, basically because they do not know about it or do not feel they are capable of doing it properly Indeed, the lack of patient information/education has been reported as one of the causes of poor patient reporting.[14] However, such obstacles could partly be overcome with simple interventions. Some examples include:

Doctors and nurses in hospitals could inform patients about the option to self-report side effects when they start treatment, of course explaining the difference between severe adverse events and minor side effects. This would also help patients to take co-responsibility for their own well-being and dissipate doubts about healthcare professionals not taking much notice of issues that are not life-threatening but are relevant to their lives, hence reinforcing the element of trust.

In addition, patient organizations can contribute considerably to dissemination of correct information about the importance of direct reporting in pharmacovigilance. They could include it as a topic in the many training initiatives they run.

Last, but not least, NCAs have a leading role to play in this area as they are responsible for setting up a direct reporting system. Some of them have been quite active, but others could be more clear in informing patients.

So, educating patients about direct reporting of side effects is not necessarily a costly, complicated task, but rather a goal that can be achieved through collaboration between different stakeholders.

The second key aspect alongside information is engagement. As in all activities aimed at patients, the more they are involved in the process, the more committed they are to the final result and to accepting direct reporting as part of their patient lives. An important enabling factor in this sense is digital technology. New tools are being made available to the public in some countries to help patients report side effects, and apps are being developed on a pilot basis in several European countries. One example is the Yellow Card Scheme in the UK, which was a paper-based form and is now available as an app developed by the Medicines and Healthcare Product Regulatory Agency. Its main advantage is that it eliminates the need to track down a paper form; however, apps also make patient direct reporting of side effects much easier, and hence more accessible to a larger segment of the patient population.

Another interesting source of pharmacovigilance information coming from patients could be further developed as part of patient support programmes (PSPs). Some PSPs already include side effect reporting functions, as well as risk-minimization tips; if this was made a standard feature of PSPs, the collection of pharmacovigilance information directly from patients could become a common practice.

Finally, part of the engagement process is to give feedback in return for active participation as this will act as a strong motivator, so one of the best ways to encourage people to report is to give something back, like access to the reporting database.

Direct patient reporting and social media: a useful source of information or a poisoned chalice?

Social media has become an integral part of patients' lives. It is very useful in providing a considerable amount of information about disease and therapies, and also helps patients connect with one another, typically through forums or blogs that have grown steadily over the last 10 years.

Sharing information among patients also includes information about adverse events. As such, pharmaceutical companies listen carefully to all the 'noise' generated around a medicine and its side effects on all social media where patients are active. Much effort has been put into this exercise, starting from the assumption that patients would feel more comfortable and open to sharing safety information with their peers, therefore paying particular attention to all side effects and adverse events reported by patients in their online conversations.

However, what has been really difficult to determine is the value of such spontaneous reports for the overall pharmacovigilance process. Can we trust what patients say? And above all, do they report their experiences in a useful way?

To this topic IMI (Innovative Medicine Initiative) dedicated part of the project WEB-RADR (Web-Recognising Adverse Drug Reactions), which looked at opportunities and challenges in using social media in pharmacovigilance as a rapidly evolving source of big, real-time data, which could provide new information on the actual use of medicines and potential safety issues.

Analytical results of WEB-RADR indicated limited value of social media in detecting or confirming signals for the majority of the drugs studied; therefore, WEB-RADR does not recommend the use of general social media, as exemplified by Facebook and Twitter, for broad statistical signal detection. However, there may be added value derived from social media channels for specific niche areas. Subject to further research, primarily to enhance adverse event recognition algorithms, the scope and utility of social media may broaden over time.[15]

Future challenges of direct patient reporting

In order to enhance the use of direct patient reporting in pharmacovigilance, some challenges need to be addressed. The first concerns the quality of reports by patients. If what patients report is not clear and does not include enough relevant detail to allow authorities or MAHs to act on it, there is no value in it. Making forms more user-friendly is certainly a sensible step, and electronic reporting can also be very useful as electronic forms are generally easier to use, more flexible

and can convey a patient's experience with side effects using different means (e.g. pictures). Ideally, reporting templates should be developed with patients' input for relevance and clarity.

A second challenge comes from the world of social media, which, despite not having so far proven a validated source of pharmacovigilance information, is set to grow in the future; therefore, their importance as a means to encourage patient reporting of adverse events cannot be overlooked. However, what could prove to be a challenge is possible malicious use of social media, where a large number of fake signals could be released.

Last, but not least, an additional challenge could be to develop a multi-stakeholder consensus in favour of a culture of joint reporting by physicians and patients as best practice to improve the knowledge of a drug's safety profile.

Conclusion

The value of direct patient reports in pharmacovigilance can be summarized as follows:

- They give more and better context than indirect reports from professionals
- They commonly describe the impact on people's lives, which clinicians rarely note
- Indirect and direct reports complement each other, generating multicultural knowledge
- Knowledge of ADRs and their importance accumulates faster
- Patients become active participants in their own care
- Patients learn how to manage their medicines and to communicate better with professionals

As in all areas of medicine development, including pharmacovigilance, the active role of patients brings innovation and more relevant information that contributes to making drugs safer and potential side effects more manageable in daily life. A multi-stakeholder approach to patient education on the importance to self-reporting could fill the gap between more experienced patients and the rest of the patient community, which would greatly enhance the statistical value of potential signals.

Further study is needed to refine the ways patients can offer their input to the pharmacovigilance system in order to optimize their experiential knowledge, with digital innovation likely to play a crucial role in the coming years, as well as social media, provided better and safer ways of collecting patients' spontaneous reports are found.

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