

Pharmacovigilance and methods of Signal Detection

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ABSTRACT

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Pharmacovigilance serves to detect previously unrecognized adverse events associated with the use of medicines. The simplest method for detecting signals of such events is crude inspection of lists of spontaneously reported drug-event combinations. Quantitative and automated numerator-based methods like proportional reporting ratio. signal detection is important activity of pharmacovigilance for evaluating new risks of adverse drug reactions. Signal does not establish that drug and event are causally related but suggests that further investigation may be warranted to clarify the observed association. In India there is much needed awareness about pharmacovigilance and signal detection.

Keywords: Adverse Drug Reactions, Signal, Pharmacovigilance.

INTRODUCTION

Adverse drug events (ADEs) constitute a major public health problem. They are estimated to account for up to 5% of hospital admissions, 28% of all emergency department visits, and 5% of hospital deaths. Many ADEs, such as prescription errors, are preventable, and methods have been suggested to reduce these errors. However, other ADEs are unknown at the time of marketing as premarketing studies are generally small, of a short duration, do not detect late-onset or rare adverse effects and, by excluding patients with comorbid disease, have limited generalizability.¹

Between the years of 1956 and 1961, widespread use among pregnant women of the sedative thalidomide, was linked to the congenital malformation of phocomelia (deformed limbs) in almost 10,000 newborn babies world-wide. These unfortunate cases were observed in 46 different countries, including Germany, England, and the United States.²

In fact, the “thalidomide tragedy” is the catastrophe that reformed the regulatory drug testing and drug approval processes on a global scale, eventually leading to the emergence of the field of pharmacovigilance, or safety surveillance.³ Since then, regulatory agencies around the world have implemented surveillance methods, mainly based on spontaneous reporting in order to support timely signal detection, the identification of new adverse events (AEs).⁴

PHARMACOVIGILANCE:

Pharmacovigilance is defined by WHO as the science and activities relating to the detection, assessment, understanding

and prevention of adverse effects and any other drug related problem.⁵

It is the process of

- 1) monitoring medicines as used in everyday practice to identify previously unrecognized adverse effects or changes in the patterns of their adverse effects,
- 2) Assessing the risks and benefits of medicines in order to determine what action if any, is necessary to improve their safe use
- 3) Providing information to users to optimize safe and effective use of medicines
- 4) Monitoring the impact of any action taken.

Objectives and Aims of the Pharmacovigilance:⁶

- Contributing to the regulatory assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost effective) use.
- Improving patient care and safety in relation to use of medicines and all medical and paramedical interventions.
- Improving public health and safety in relation to use of medicines.
- Promoting understanding, education and clinical training in pharmacovigilance and its effective communication to the public.
- Detecting the frequency of (known) adverse reactions.

RECENT TRENDS IN PHARMACOVIGILANCE:

Over the past few years, relative emphasis of pharmacovigilance activities has shifted (Figure 1). Individual adverse event case handling remains highly regulated and timely reporting of individual case safety reports (ICSRs) to regulatory authorities and other

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stakeholders continues to be an important compliance matter. Because of the volume and complexity of adverse events data subjected to detection of safety signals, various statistical methods have been developed to aid routine monitoring of data, which are used in conjunction with more traditional pharmacovigilance approaches.⁷

Signal Detection

Most recently, working group VIII of the Council for International Organizations of Medical Sciences (CIOMS VIII) defined a drug safety signal as follows, adapting the definition proposed by Hauben and Aronson:

“Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action”.⁸

Data Sources and Statistical Data Mining Methods used in Safety Signal Detection:

Statistical data mining methods for application in pharmacovigilance emerged in the late 1990s, originally as a means of performing systematic signal detection in large databases from the spontaneous reporting systems (SRSs) of adverse event information maintained by health authorities and drug monitoring centers.¹⁰ Some of the databases that can be used for signal detection in the post-authorization drug safety surveillance are listed in Table 1.

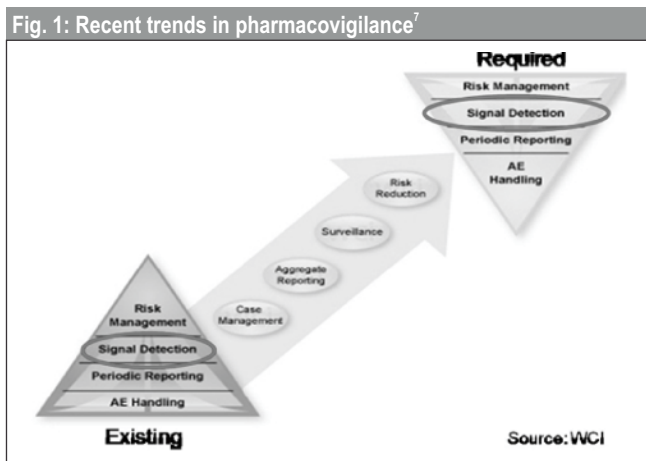
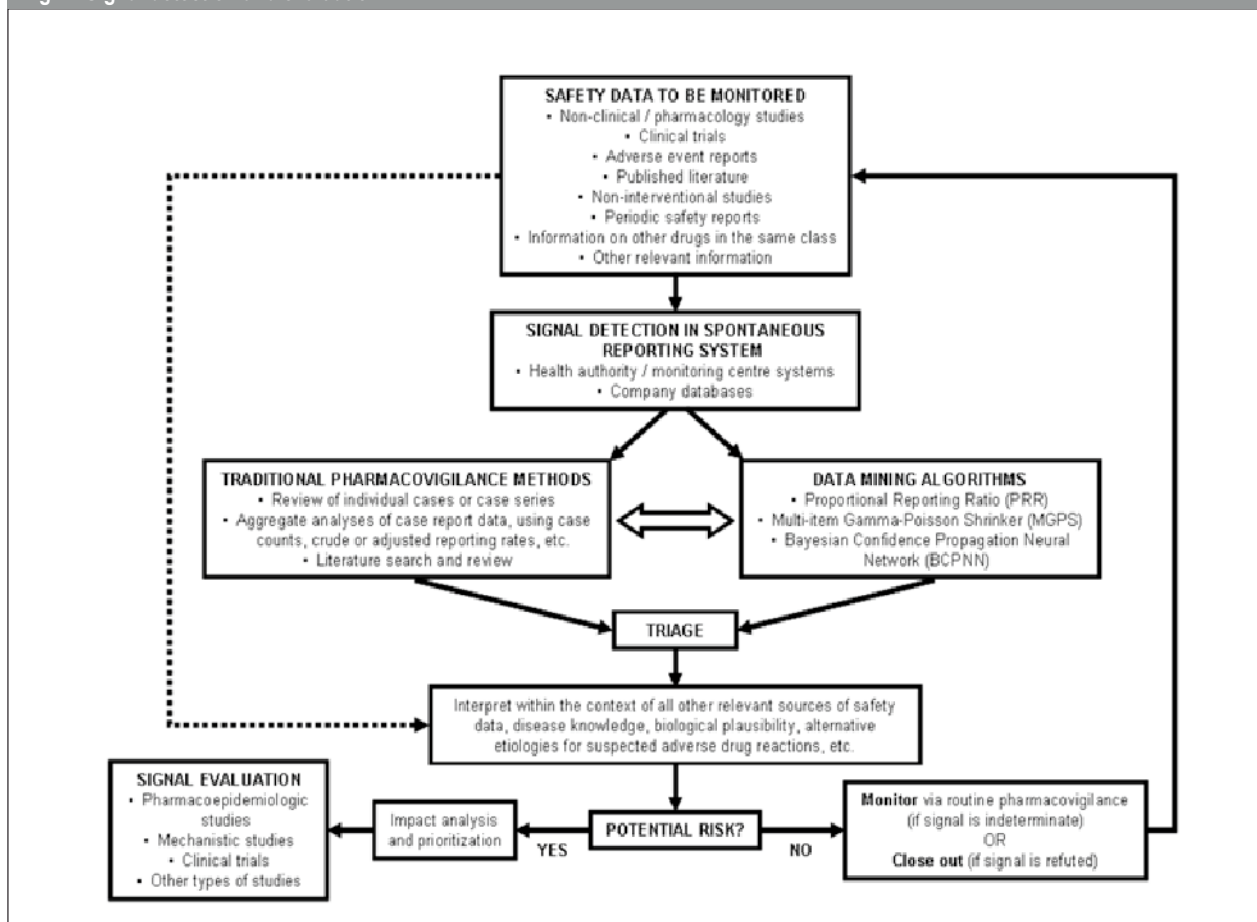


Fig. 2: Signal detection and evaluation⁹



Source database	Examples
Spontaneous reporting system (SRS) database	- Vigibase (WHO) - EudraVigilance (EEA) - AERS (USA) - Sentinel (UK)
Prescription event monitoring databases	- Drug Safety Research Unit (UK) - Intensive Medicines Monitoring Program (New Zealand)
Large linked administrative databases, or electronic health records (EHR) databases	- Healthcare insurance claims databases (managed by for profit Managed Care Organizations or government agencies)
Electronic medical records (EMR) databases	- General Practice Research Database (UK)

Stastical methods used for signal detection:¹²

a) Qualitative methods

b) Quantitative methods

1. Denominatore method

- Cumulative Sum
- Time Scan
- Poisson Method

2. Numeratore method

- Short Memory Schemes
- Proportional Reporting Ratios (PRRs)
- Bayesian Data Mining

From all these stastical methods, generally used methods are proportional reporting ratio and Bayesian method. Of these two, proportional reporting ratio is easy and convenient method which is used for particular one drug–event signal detection from spontaneous reports. Bayesian method is used when more combinations are used. It is limited when small number of data available.

In this paper, it is focused on proportional reporting ratio method which can be easily used for periodic signal detection.

Proportional reporting ratio (PRR):¹³

The PRR is a statistical method used to detect SDRs in pharmacovigilance databases such as EudraVigilance. This method relies on the principle that when a Signal of Disproportionate Reporting (involving a particular adverse event) is identified for a medicinal product (referred to medicinal product P), this adverse event is reported relatively more frequently in association with this medicinal product P than with other medicinal products. This relative increase in the adverse event reporting for the medicinal product P is reflected in a table based on the total number of individual cases contained in a pharmacovigilance database, as follows:

	Event (R)	All other Events	Total
Medical product (P)	A	B	A+B
All other medical Products	C	D	C+D
Total	A+C	B+D	N=A+A+C+D

The general criteria to run the PRR are as follows:

- The value **A** indicates the number of individual cases with the suspect medicinal product (P) involving an adverse event R.
- The value **B** indicates the number of individual cases related to the suspect medicinal product P, involving any other adverse events but R.
- The value **C** indicates the number of individual cases involving event R in relation to any other medicinal products but P.
- The value **D** indicates the number of individual cases involving any other adverse events but R and any other medicinal products but P.

The PRR is computed as follows:

$$PRR = [A/(A+B)]/[C/(C+D)]$$

Example:

- Proportion of individual cases of nausea involving a medicinal product 'Trade Name'= 5% (e.g. 5 reports of nausea amongst a total of 100 reports reported with medicinal product 'Trade Name').
- Proportion of reports of nausea involving all the other medicinal products in a database (but medicinal product 'Trade Name') = 5% (e.g. 5000 reports of nausea amongst 100,000 reports reported with all other medicinal products). Therefore, the PRR is equal to 1 (0.05/0.05).

The chi-square (χ^2) statistics

The Chi-square is a statistic, which is traditionally used in disproportionality analyses. In certain standard queries of the EudraVigilance Data Analysis System, the Chi-square is used as an alternative measure of association between the medicinal product P and the adverse event R based on the following calculation:

$$\text{chisquare} = \frac{(AD-BC)^2}{(A+B)(C+D)(A+C)(B+D)}$$

For instance, drug-event combinations with at least three reports, a PRR >3 and a chi-square >5 would represent a signal.

PRRs are relatively easy to understand and calculate and are now part of routine surveillance activities so this method has increasing evidentiary support. Computational ease of use is an important advantage considering the dynamic nature of the data and associated sequential scans of increasingly large data sets. Its greatest utility may be in highlighting drug-event combinations with intermediate PRRs, since those with very large scores were noted to involve recognized adverse events (e.g. rifabutin and uveitis), while pairs with PRRs near 1 may be triaged as likely background noise. Care must be taken when strong signals are detected for a given drug, since this will reduce the PRR for other adverse events with that drug. This could be addressed by excluding events with very strong signals.¹⁴

DISCUSSION

Today drug treatment is the most important intervention for curing diseases and maintaining mankind's well being. The number of drugs used per individual has successively increased over time. For many individuals the numerous drugs used are necessary, with undisputable benefits, though for some patients multiple drug therapies (polypharmacy) are a result of irrational and excessive drug use. No drug is absolutely free from harmful effects and polypharmacy increases the risk of reactions related to drug use, adverse drug reactions (ADRs), and ADRs as consequence of drug-drug interactions (adverse drug interactions).

For the developing pharmacovigilance it need three pillars:

- Collecting new information from reliable scientific resources such as marketing authorization holders, healthcare professionals, consumers, international/public bodies, journals, published and updated literature, etc.
- Classifying and analyzing the above information.
- Circulating its contents as well as any action taken on specific drug to all health sectors

There should be develop ADR reporting system database where all can report about adverse drug reactions.Awareness

should be made regarding reporting among patients, healthcare professionals, marketing stake holders etc.

ADR report should contain four elements then it can called case which then monitor for its seriousness, expectedness following four elements are considered:

1. Patient
2. Drug
3. Adverse drug reaction
4. Reporter

Signal detection is important part of pharmacovigilance activity.It gives the information about any new risk found in drugs or whether there is change in frequency of known ADR.This process of detecting signal proven not only by statistically but clinically also. There is more importance of clinical assessment of signal rather than stastical assessment.only one serious case can be signal if it is clinically proven.generally for this causality assessment scales like WHO-UMC scale,naranjo's scales are used.

In india pharmacovigilance is in its developing stage.though there is policies for pharmacovigilance in india but awareness amongst people is less.

Failure of implementing pharmacovigilance in India:

- Pharmacovigilance systems are not well funded and organized for a vast country like India to serve patients and the public.
- The information obtained to date in the zonal centers from various peripheral centers is often poor and not well-analyzed. There is insufficient research on ADRs in India, so the exact incidence of specific ADRs is unknown.
- Understanding by healthcare professionals (both in rural areas and urban cities and hospitals) and knowledge and motivation for pharmacovigilance is almost negligible. There is hardly any encouragement from the department of health to provide more training and create more awareness amongst them for better reporting.
- In India, there are several consumers' group who encourage patients to report any adverse reactions encountered by them, although there is no information for patients to report ADRs directly to the regulatory authority.

For developing pharmacovigilance and signal detection process these many obstacles should be solved. There should be more awareness programme done for this purpose by stake holders.

CONCLUSION

Pharmacovigilance is area of increasing interest and importance. More emphasis should put on pharmacovigilance

as new therapeutic principles are introduced. the availability of accurate and continuously updated information on possible risk with medicinal product is an essential for a timely and appropriate regulatory actions to be taken and for detecting the new signals. Risk need to be communicated taking into general perception and acceptance of risk in target general population.

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