



## Signal Detection - An Imperative Activity of Pharmacovigilance

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### ABSTRACT

Signal detection is important and core activity of pharmacovigilance. The primary aims of pharmacovigilance are to collect, monitor, assess and evaluate information regarding adverse effects, especially those which are serious or unexpected; and also involve providing information about potential and investible hazards. The signal detection and its dissemination seem to be important utility of pharmacovigilance database. It has power to prevent the epidemics of serious adverse drug reaction before gross damage to community. The historical medical calamities could have been prevented if technique like signal detection and pharmacovigilance would have been practiced since that time.

**Keywords:** Adverse drug reaction, Pharmacovigilance, Signal, Bayesian Confidence Propagation Neural Network, Information component.

### INTRODUCTION

Drugs are among the miracles of this era. They have saved billions of life and will continue to do same in future. They have helped to bring improved health and longer life to the human. The practice of medicine should be assessable, available, affordable, and most importantly 'safe'. But we must understand that they are not without risk. Drugs do not always benefit the recipients instead they can harm some times. The damage done by the drugs can range from mild, moderate to severe or life threatening. This harm and damage done by drugs when it is given in dose normally used in men is called adverse drug reaction (ADR). Practically each and every drug can cause adverse drug reaction. World health organization (WHO) has defined adverse drug reaction as "A response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function". An adverse event is defined as harmful and inadvertent medical occurrence which may present during treatment, but does not have proven causal relation with drugs.<sup>1</sup>

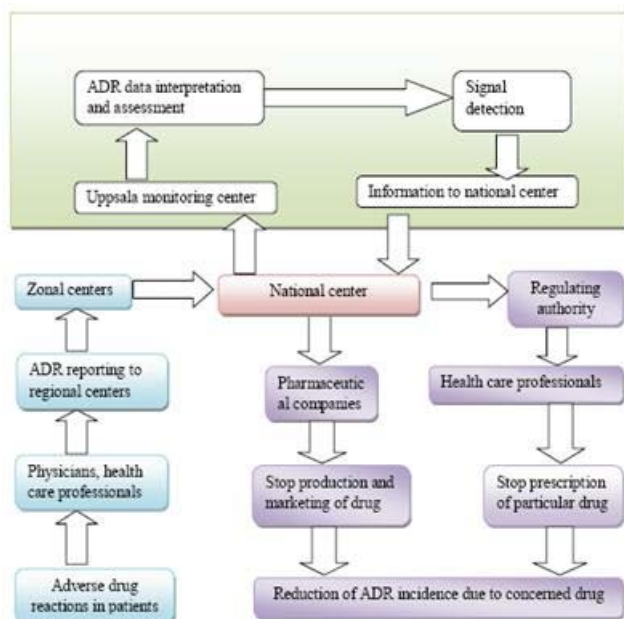
Adverse drug reactions are serious matter concern as it considerably affects morbidity and mortality. Adverse Drug Reactions are the 4<sup>th</sup> to 6<sup>th</sup> leading cause of mortality in the USA. More than 10% of hospital admissions are concerned with drug related events. More than 20% budget is spent on drug related events.<sup>2</sup> Hence it is very important to identify, monitor and assess and prevent ADRs. The discipline concerned with identification, monitoring and then prevention of ADR is called as pharmacovigilance. WHO defined pharmacovigilance as "The science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions or any other drug-

related problems".<sup>3</sup> The aims of pharmacovigilance are early detection of unknown safety problems, identification of risk factors, quantifying risks and ultimately preventing patients from being affected unnecessarily.<sup>4</sup>

One of the most important activities of pharmacovigilance is signal detection. The importance of signal detection was recognized after thalidomide disaster in early 1950s, then various efforts were started to prevent such tragedy. The primary function of pharmacovigilance is to recognize early warning with regard to previous adverse effects of drugs. The signal in pharmacovigilance is information of particular ADR with causal relation to a drug which is not reported previously. The WHO has defined a signal as: "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously".<sup>5</sup> The interpretation that a signal should be seen as a first hint that there is a need to look more closely at a drug and its associated reported ADR was given by Finney in 1974; according to him "A signal is a basis of communication between WHO and national centres; only rarely will it carry the force of a proven danger" and, "Signals are intended to arouse suspicions and to stimulate deeper investigation".<sup>6</sup> Amery in 1999 also stated that: "A signal may be defined as new information pointing to a previously unknown causal relationship between an adverse event, or its incidence, and a drug; the information must be such that if confirmed, it may lead to action regarding the medicine."<sup>7</sup> Signal is not a confirmatory finding, it require further evaluation and may get approved or neglected. Thus signal generation aims at timely identification of previously unsuspected adverse effects, but any signals require further evaluation



as they themselves do not prove that there is a safety problem”.



**Figure 1:** Pharmacovigilance refined data cycle

Signal detection is a challenging task. Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information. A signal is therefore a hypothesis based on evidence generated by ADR data and arguments. Signal is uncertain and preliminary in nature; the situation may change drastically over time and may get converted in ADR disaster. Signal is identified, accessed and generated by the Uppsala Monitoring Centre (UMC) based on information derived from the WHO database. Signal is primarily intended to inform national regulatory authorities. The distribution of signal by the UMC is currently restricted to National Centres, regulatory authority staff and to responsible international pharmaceutical companies. National authorities are responsible for deciding the further action including informing the signal to relevant health care professionals and to market authorisation holders. National authorities can order the inhibition of the production, sale and marketing the concerned products.

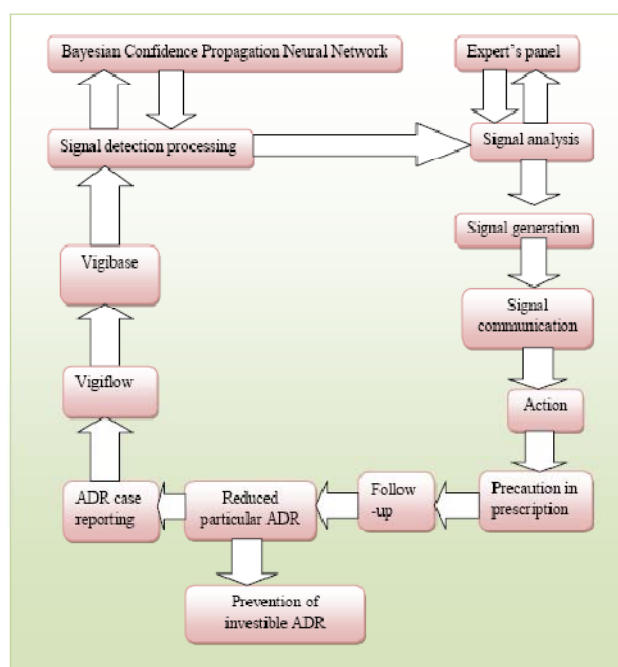
**Vigibase – The WHO Adverse Drug Reaction Database**

It is the WHO ADR database contains reports of ADRs received from national centres of member countries. It is maintaining the ADR data since 1978. In this computerised system the data regarding ADR is recorded, arranged and structured in hierarchical form in order to have an easy access to the data in future. The primary purpose of this database is to provide the evidence from which potential drug safety hazards can be detected. The database is available for the member countries through its search strategies and tools. Since 2002 access to the data has been widened and made more assessable.<sup>1</sup>

**The process of signal detection**

Detecting Signals is one of the primary objectives of the WHO Programme for International Drug Monitoring. The goal is to ‘Never miss a signal’. The process of signal detection is complex and full of uncertainty. Signals have both qualitative and quantitative aspects. The basic considerations that determine the evidence in a signal are quantitative strength of association, consistency of data, exposure response relationship, biological plausibility, experimental finding, possible analogies, nature and quality of data. Finding of ADR is sequential process consisting of (A) hypothesis generation; (B) strengthening of hypothesis; (C) Preliminary assessment of data; (D) evaluation and explanation. Unfortunately it is very difficult to establish a relation between a drug and ADR. The discovery of new ADR is hindered by various factors like the incidence of these ADR is low, relatively high frequency of background effects frequency, low exposure to the drug, lack of suggestive time and dose relationship. Majority of adverse effects are not new clinical entity but imitation of established diseases. Adverse effects closely resemble the symptoms of various disorders.<sup>8</sup>

Current system of pharmacovigilance is based on spontaneous reporting system. Member countries send their reports to the Uppsala Monitoring Centre where they are recorded processed and evaluated. When there are several reports of adverse reactions more than its usual trends to a particular drug these, it will lead to suspicion of signal. These out of trend ADR reports undergo preliminary evaluation by expert panel. Signal detection is a notice of a need for increased awareness of a possible hazard communicated to member countries. Now a day’s various methods of data mining is used for detection of signal.<sup>4</sup>



**Figure 2:** The flow chart illustrating the way of processing from ADR reports to the signals.

### The Old Method of Signal Detection

In the old method of signal detection, new drug-ADR combinations obtained from previous three months data during that time period was generated. This data generated was sent for analysis and review to pharmacovigilance expert's panel. The signal generated from expert's opinion was communicated to national centre of member countries. The data of drug-ADR was huge and it would continue to grow with time. It was very difficult to review the data effectively because of its large volume. The lack of automation, linking and follow up was very common in the signalling system. Thus it was need of that time to invent the new technique of signal detection.<sup>8</sup>

### The data mining and quantitative methods of signal detection

Data mining is a process of analyzing data from different perspectives and extracting the relevant information. It is often used to identify hidden patterns of associations or unexpected occurrences in large databases. Although various methods used for data mining in pharmacovigilance differ but all of them share feature that they express to what extent the number of observed cases deviates from the number of expected cases. Currently there are several methods used for data mining. Some of the important quantitative methods used for signal detection are Proportional reporting ratios (PPRs); Multi-Item Gamma Poisson Shrinker (MGPS) and Bayesian confidence propagation neural network (BCPNN). All the data mining methods are based on concept of disproportionality.

Proportional reporting ratios is a comparison of the proportion of reports for a specific ADR of concerned drug to that with the proportion of ADR due to all other drugs. It is analogous relative risk. With the use of same data it is also possible to calculate a 'reporting odds ratio'. It is a measure of disproportionality of reporting used to detect signals of disproportionate reporting (SDRs) in ADR databases. SDRs refer to statistical associations between particular medicinal products (P) and its adverse events i.e. drug-event pairs. This method predicts the assumption that when a SDR of concerned adverse event is identified for a 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 can be calculated from the data from a 2x2 contingency table (Table 1) which is formed by information available from pharmacovigilance database. In this contingency table, value A indicates the number of individual cases with the suspect medicinal product P involving an adverse event E, the value B indicates the number of individual cases related to the suspect medicinal product P, involving any other adverse events but E, the value C indicates the number of individual cases involving event E in relation to any other medicinal products apart from P and the value

D indicates the number of individual cases involving any other adverse events except E and any other medicinal products except P.<sup>10,11</sup>

**Table 1:** 2x2 contingency table for the computation of the PRR

	ADRs due to particular medicinal product (E)	All other ADRs	Total
Particular medicinal product (P)	A	B	A+B
All other medicinal products	C	D	C+D
Total	A+C	B+D	N=A+B+C+D

The PRR is expressed as:

$$PRR = \frac{A/(A+B)}{C/(C+D)}$$

The Bayesian confidence propagation neural network (BCPNN) method recognizes dependencies in a data set. This method uses Bayesian statistics integrated with neural network to analyse all reported ADR combinations. The data having unexpected strong relationships as compared to baseline data are highlighted. This method was used by WHO Collaborating Centre for International Drug. A related approach, the Multi-Item Gamma Poisson Shrinker (MGPS) is another approach used by the FDA for data mining of their spontaneous report's database. The MGPS identify signal scores for pairs, and for higher-order (e.g. triplet, quadruplet) of drugs- events combination that are significantly more frequent than their pair-wise associations would predict. All data-mining approaches used currently are not able to distinguish between new and previously known associations. Moreover, clinical scenario is not considered that is why there is still need for a reviewer to analyse these events.<sup>11</sup>

### The Neural Network

The neural network is a wide range of different architectural units capable of performing diverse range of task like prediction, classification, managing data sets and data mining. It is formed by combination of small processors, each of these having its own memory. There are communicating channels carrying numerical data in between small processors in order to allow its independent operation with being connected to others. Here the neural network is used to identify the dependencies in the database. It is efficiently capable of analysing the strength of association between drug and occurrences of particular ADR. The network is used to identify and count the occurrences of variable x (for specific drug), occurrences of variable y (for particular ADR) and occurrences of x and y together. The architectural property of neural network is completely used in recognition of unsupervised patterns for search of



previously unknown higher order dependencies in the datasets.<sup>9</sup>

### The Information Component

The Information Component (IC) is a measure of the strength of the quantitative dependency between specific drug and specific ADR. It is a logarithmic measure of disproportionality used to evaluate strength of association between drug and ADR. It is mathematically expressed as:

$$IC = \log_2 p(x, y) / p(x), p(y)$$

$$IC = \log_2 \frac{p(x, y)}{p(x), p(y)}$$

Where, p (x) is probability of specific drug 'x' being listed in a case report; p (y) is probability of specific ADR 'Y' being listed in a case report and p (x, y) is probability of specific drug- ADR combination being listed in a case report. The value of information component depends on number of case reports with drug 'x', on number of case reports with ADR 'y', on number of case reports with combination of specific drug and ADR and total number of case reports. It can also be stated that information component is the logarithm of ratio of observed rate of drug-ADR reporting to its expected rate with the assumption of null hypothesis.<sup>12</sup>

If a particular drug-ADR combination is reported more often than expected from the rest of the database then the value of IC will be positive. For no quantitative dependency the value of IC will be zero, while the combination is occurring less frequently than statistically expected it will be negative. The higher the IC value, more the combination stands out from the background. The system is able to handle the fact that there are more suspected ADRs than cases (that is, a total of more than one reported ADR per patient); and that more than one drug may be involved in any given case. The change in value of IC may occur with the addition of new data. The value of IC is less likely to fluctuate when it is calculated large numbers. The standard deviation for each IC provides a measure of the robustness of the value.<sup>9</sup>

### Bayesian statistics

The Bayesian statistics is named after an English mathematician Thomas Bayes (1702–1761). Bayesian logic is a discipline of logic applied to decision-making and inferential statistics. It is concerned with the prediction of future events using information of previous events. Bayes theorem was published in 1763 two year after his death with the title of 'An Essay Towards Solving a Problem in the Doctrine of Chances'. Bayes theorem was first mathematical method that could calculate the likelihood of a target occurrence in future trials when occurrences in prior trials are available. According to Bayesian logic, determining its probability is the only way to quantify a situation with an uncertain outcome. Bayesian logic has further developed in the 18th century by French theorist Pierre-Simon de Laplace, and in 20th and 21st century by

practitioners such as Edwin Jaynes, Larry Bretthorst, and Tom Lored. Currently, Bayesian logic has its applications in almost infinite range of research areas, including genetics, astrophysics, psychology, sociology, artificial intelligence, data mining and computer programming.<sup>13</sup>

### Bayesian Confidence Propagation Neural Network (BCPNN)

This new method of signal detection was developed to cope with problem of huge amount of ADR database for its effective assessment. Bayesian Confidence Propagation Neural Network (BCPNN) is sensitive and sophisticated method capable of detecting signals much earlier than other methods. BCPNN has been developed by UMC in collaboration with the Royal Institute of Technology, Sweden. UMC has been using the BCPNN since the fourth quarter of 1998 to produce quarterly line listings of associations. BCPNN is a great advance which is one of the best tools available for signal detection. It complements but do not replace other method of signal detection. This method can also be used for unsupervised pattern-recognition within data elements to determine complex relationships.<sup>1,4</sup>

BCPNN detect particular adverse reaction reports stand out of trend from the entire database. The associations are drug-ADR combinations that stand out statistically from the background of all reports in the database. The associations are referred to the panel of UMC international experts. BCPNN is an automated way of finding new drug-ADR combinations suspected to be signals through quantitative filtering of the vigibase data. This focuses clinical review on the potentially most important combinations of drugs and adverse reactions. The learning and inference are done using the principles of Bayes' law in BCPNN.<sup>14</sup>

The BCPNN can manage large data-sets, is robust in handling very incomplete data, and may be used within data-sets filled with complex dependencies to find patterns of information. BCPNN can measure the disproportionality called the Information Component (IC) which is used for filtering data. It can identify combinations which are statistically highly associated in comparison to rest of the stored data. Unexpected patterns in the data can be detected and how such patterns vary over time can be examined. BCPNN methodology can calculate the strength of relationship of drug-ADR combination. Relationships between particular drugs and specific ADRs which stand out of the background data can then be highlighted and investigated. The unique feature of this technique is that it considers all drug-ADR combinations in the database in an unbiased manner and it can early detect significant associations. It can calculate the inference despite of missing data with decreased certainty in the results. It is capable of performing the multi-variable analysis. The point estimate of IC is intuitively related to its confidence interval. The point estimate of IC can be derived from expected value, while confidence interval can be



calculated from variance. BCPNN approach is transparent, robust, producing reproducible result and most importantly it is time efficient despite of huge database. BCPNN accelerates but does not replace the traditional signal detection methods. There are considerable amount of drug-ADR combinations which are clinically important but not reported unexpectedly, hence other methods of signal detection are also necessary.<sup>15, 16</sup>

### Signal Detection of Group Effect

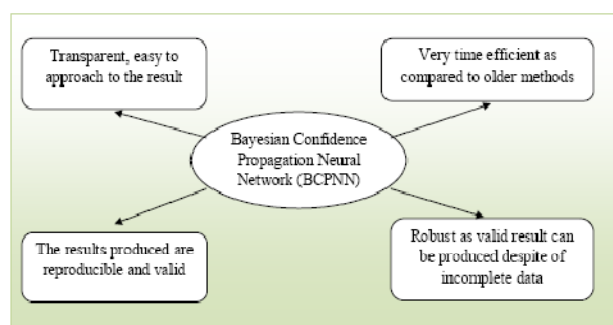
BCPNN can also be used for detecting relation between group of similar drugs and particular ADR. WHO Anatomical, Therapeutic Chemical Classification is generally used for grouping of drugs. The analysis is performed to calculate information component of drug-ADR combination and information component of ATC group-ADR combination. The clinical validity of comparison group must be considered before analysis. Many factors may affect the results like selection of drugs having interaction between them, differences in ADR terminology and regional variation.<sup>9</sup>

### International expert review panel

International expert review panel includes the specialist from various concerned disciplines which carry out monitoring and evaluation of signals and signalling processes. More than 30 international domain experts help the UMC and the WHO Programmers in detecting and evaluating new drug safety signals. International standards for signal reviewers' work have been developed. The assessment of drug-ADR combinations is carried out by automated procedure in the WHO database. The UMC team regularly searches Vigibase for new signals and uses a range of channels to make the results known to the regulatory authorities of member countries. The primary methods of signal dissemination signal document, combinations database, vigimed, WHO pharmaceuticals newsletter.<sup>4</sup>

### CONCLUSION

The piling of facts and data has no utility unless it is used for some useful purpose. Vigibase is used for detection of signal obtained from out of trend ADR reporting. Pharmacovigilance is not only restricted to collecting the ADR data but also to extract the signal to prevent the investible medical disaster and harm to patients. BCPNN has made a great development in signal detection and made it more simplified and efficient. BCPNN is capable of classifying task and quantifying pulp manufacturing process. Statistical data mining approaches have been developed and applied in the field of drug safety surveillance, adding to the toolkit of pharmacovigilance professionals. The development of statistical methods and technology to analyze large amounts of ADR data to detect signals for potential safety issues has minimized noise and enhanced the efficiency and effectiveness of pharmacovigilance activities. Figure 3 is showing the different properties of BCPNN.



**Figure 3:** different properties of Bayesian Confidence Propagation Neural Network (BCPNN)

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