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One size does not fit all: a summary of signal detection methods

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ABSTRACT

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Introduction: The selection of an appropriate signal detection method is pivotal in the identification process of safety signals in pharmacovigilance. Nevertheless, the early detection of safety signals is even more important to prevent the occurrence of another thalidomide tragedy in humans. Spontaneous reports, follow-up studies, scientific literature, preclinical & clinical studies, are valuable sources of adverse events; but on the other hand, these reported adverse events are extremely diverse, hence comprehending this can result in formulating the right signal detection and evaluation strategies.
Methods: Broadly, signal detection methods fall into two categories: qualitative and quantitative, each having its significance; while the quantitative methods help to handle the voluminous data during signal detection, the qualitative one does its part to pick the rare signals.
Results: Hence, there is no single universal method that would be a perfect fit to identify safety signals from all data sources or for all types of adverse events. Further, the signal detection process involves a series of steps right from signal detection to its final assessment & submission, to regulatory authorities confirming a signal as a 'possible safety alert'. Finally, the completed task of finding a confirmed safety alert would be meaningless if it does not reach the end-users of the drug concerned.
Conclusions: Therefore, effective communication to health care professionals, patients including clinical trial subjects, pharmaceutical companies, and other stakeholders is equally important.

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Introduction

Ever since drug monitoring began after the thalidomide tragedy in the early 1960s, pharmacovigilance has been constantly advancing to improvise its primary function of identifying early warnings (signals) regarding the previously unknown adverse events of medicines. Any information suggesting a new potential association or new aspects of a known association between medicines and adverse event(s) that warrant a further investigation is a signal. Initially, the major issue was- Where to find such signals? However, with technological advancement, spontaneous reporting systems have now developed around the world to address it. Additionally, progress in automation technology has enabled the development in many countries, of comprehensive databases covering large populations (CIOMS, 2010). These huge data reservoirs

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contain a multitude of potential signals, and pharmacovigilance now concentrates on the question - How to identify early, relevant signals?

Clinical trials are primarily designed to test whether a drug is efficacious for a particular condition in controlled settings and has limitations (small sample size of the healthy subject or patients, lacks special population data, the single doses used in some initial stages, etc.), in their ability to produce enough data regarding adverse events, mostly when those are rare and unexpected. Therefore, at the time of marketing a drug, the knowledge of its tolerability is inevitably incomplete (Meyboom *et al.,* 1997). Over the years following the launch of a drug, there is an ongoing increase in knowledge regarding pharmacology, clinical use, and adverse events of the drug. Although pharmacovigilance is especially concerned with adverse events, a signal is more broadly defined as a set of data constituting a hypothesis that is relevant to strengthen the rational and safe use of a drug in humans or simply continue to justify the positive benefit-risk profile of the drug. Different signal detection methodologies have been implemented and the application of the appropriate method will help to identify safety concerns and further assess the impact and provide public health awareness.

Signal detection methodologies

The signal management process plays a critical role in the identification of signals and having a robust well-structured one, helps identify it much early. It has been well defined in EMA Guideline on Good Pharmacovigilance Practices (GVP) Module IX – Signal Management (EMA, 2017). Signal detection is the first step in signal management activity, which is followed by steps of validation, prioritization, assessment, and finally recommendations for action. There are various sources of signals ranging from clinical trials to large databases and different methodologies can be applied to different datasets. In general, two categories exist for signal detection that is qualitative and quantitative (statistical or automated signal detection methods) (CIOMS, 2010).

Qualitative methods solely involve manual review/case-by-case analysis of individual cases. However, with advances in spontaneous reporting systems, it becomes an increasingly time-consuming method given the growing volume of data; as well as less effective, especially for more data with complex associations, such as drug-drug interactions, syndromes, and when various covariates are involved (Egberts *et al.,* 2007). But it has its significance in picking up rare medically significant drug attributed events. And thus, this method is useful in the spare database and its application is difficult when the database is huge. Thus, with necessities, in the late 1990s, there was an intensified growth in the application of more complex methods to signal detection in pharmacovigilance, which was termed as a quantitative method. These enhanced quantitative methods include computer-aided statistical methodologies and Data Mining Algorithms (DMA). Generally, these methods focus on comparisons of relative reporting frequencies, also known as disproportionality analysis; these methods incorporate several assumptions relating to the number of reports one would "expect" to be recorded in the database. When a specific medicinal product induces a specific adverse reaction, this reaction is reported more often for this medicine than with the other medicinal products that do not induce the adverse reaction, so that the magnitude of a disproportionality metric is likely to be increased. For the same reaction, the extent of (under) reporting is assumed to be the same amongst different medicinal products. In quantitative methods, there is a possibility of over-representation of a specific drug-adverse event association in the comparator group. Thus, even though there is a strong association between the adverse event under investigation and a drug in a reference (comparison) group, disproportionality analysis may lead to a false-negative result for any other drug examined regarding this event (CIOMS, 2010).

These signal detection methods serve as a stepping stone for the identification of new information. However, without enough information in the source document, the assessment of signal evaluation will be incomplete. Likewise, cases reported from observational studies in patients with a spare number of cases are predominantly qualitative. However, even a single good case can be sufficient to establish a definitive causal association between the drug and the adverse event. For any case to qualify as a "good case" it should report satisfactory strength of evidence with regards to biological plausibility, close temporal relationship, no alternative etiology, and positive rechallenge, etc.

Further, adverse events are often unexpected, unusual, and unpredictable; and very diverse. Signals have qualitative and quantitative aspects and often differ from previous experiences. Adverse events are of different types particularly with regards to their mechanism of action, onset, and frequency of occurrence and may need different methods of detection. Adverse events can broadly be categorized as Type A, Type B, and Type C. Type A adverse event is quite common and is a consequence of exaggerated pharmacological effects of the drug. They are dose-related and tend to occur more frequently or severe with higher doses. Clinical trials (phase III and IV), spontaneous reporting, follow-up studies, prescription event monitoring (PEM), are major sources for providing information on these. However, most often these type A events are not detected during the clinical trials but are usually detected using spontaneous reporting only after marketing. With type A events of low specificity, quantitative and controlled signal assessment methods might be needed to confirm the relationship and measure the frequency along with the qualitative methods. Type B adverse events are usually unexpected and unpredictable "patient reactions" which are often allergic or idiosyncratic reactions and typically occur only in a minority of patients.

Type B events are often serious, may show little or no relationship with the dose of the drug. Type C events are serious and persistent and are produced after prolonged/chronic exposure to the drug. Type B or C adverse events are picked from population databases, large spontaneous-reporting systems, PEM, and follow-up studies. Hence quantitative signal detection methods are more apt to apply for these (Meyboom *et al.,* 2010).

The number of case reports needed to provide sufficient evidence for a signal may vary, depending on the nature of the events, the quality of the reports, and the evidence from different sources. Such qualitative signals mainly concern type B adverse events. The existing pharmacovigilance systems for reporting adverse events are especially effective in detecting type A and type B adverse events, but of limited value for type C events. Since type C adverse events may have a huge impact on public health, improvement of the monitoring of type C events should be a priority (Meyboom *et al*., 1997).

Discussion

Identifying safety signals is a constant challenge for regulators and pharmaceutical manufacturers. Ideally, signal detection should be rapid, real-time, and efficient to capture new safety concerns at the earliest to prevent adverse drug mishaps. Over the years, there has been a constant increase in the size of databases, posing challenges in signal detection methods. Thus, relying on a qualitative method for a large dataset becomes impractical. Hence, there has been a need for the increased application of more complex computer-aided statistical quantitative signal detection methods to address it. However, these complex methods rely on disproportionality analysis; these methods incorporate several assumptions that may lead to false-negative results, which is a major drawback. This disproportionality analysis fails to capture rare drug attributed events, which could likely be picked by the manual qualitative method. In addition, training on the quantitative method would require adequate resources and maybe a time-consuming process. Furthermore, regular updates of these complex methods may pose challenges to keep adapting to the latest updates. Currently, none of the signal detected methods have demonstrated any uniform superiority over others. Also, the reported adverse events are diverse and may not be caught easily by any signal detection method. Thus, it is important to take into account various parameters before deciding on an appropriate method of signal detection. Data mining methods are valuable in refining the voluminous and complex data and are credible to the signal detection methodologies. However, these statistical techniques are not a solution to the inaccurate and incomplete adverse event reports received and the unorganized spontaneous reporting system. Thus, there is a need on relying on the qualitative method as well. Further steps for detected signal involve series of evaluations to determine whether sufficient evidence exists to determine a causal association between the adverse event and the suspected drug. The role of signal detection does not end by establishing a confirmed drug-adverse event pair alone, and necessary prompt regulatory actions need to be taken appropriately to ensure adequate communication of safety concerns to health care professionals, patients, and consumers.

Conclusions

There is no ideal method of signal detection; '*One Method Does Not Fit All Datasets*'. Multiple parameters determine the choice of the appropriate methods and require a synergy of activities intending to identify safety concerns well early in time to prevent or warn of any drug mishaps.

Conflict of interest

No conflict of interest

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