Artificial neural network: A data mining tool in pharmacovigilance

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Abstract
Introduction: Pharmacovigilance ensures patient safety as well as drug safety. In India, there is still a lot to be done and learned to ensure that the work and activities done in the area of pharmacovigilance are safely implemented. The key issue in India is that adverse drug reaction (ADR) has been underreported. The number of patients who are hospitalized is growing due to adverse drug effects and figuring out the exact cause of ADRs is a problem, if a patient is treated concurrently with several medicines.

Methods: In the analysis, we will analyze the various types of evaluation scale to conduct the ADR evaluation and identify the trigger agents. For situations where various approaches may not be adequate prognostic models, neural networks emerged as advanced data processing devices.

Results: However, it is essentially statistical modeling tools that are used in neural network models, as the term implies.

Conclusions: These models are thus a replacement solution, offering resources that learn by themselves, while not requiring experts or advanced computer programs, to solve problems and discern patterns.

Keywords: Pharmacovigilance, adverse drug reactions, ADR assessment, neural networking.

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Introduction

The pharmacological sciences related to identification, evaluation, comprehension, and prevention, particularly in the long-term and short-term side effects of medicines are pharmacovigilance (PV) (Pipasha et al., 2007). PV is an important aspect of medical research. (Geneva et al., 2004). The under-reporting of ADRs is the greatest obstacle in the world due to the lack of time. The World Health Organisation (WHO) is known to have launched the program to report all adverse drug reactions (Skalli et al., 2012). Besides, herbal medicines, alternative medicines, and new drugs, blood products, biologicals, healthcare instruments, and vaccines have been broadened to include. PV also has several positions in recognizing, quantifying, and reporting the issues linked to drugs responsible for drug-related injuries. (Arnott et al., 2013). National PV initiatives, which plays a major role in raising public awareness on the safety of the medication, have also been launched (Faddegob et al., 2011). A “big data” approach to pharmaceutical monitoring includes defining the drug- ADE combinations by analyzing multiple electronic information networks, including adverse event reporting, medical literature, electronic health records, and social media. ADEs, including medical encounters, have a significant effect on patient safety, contributing to higher health care costs. This strategy was effective in the monitoring and decision-making of drug protection by the Food and Drug Administration and other regulatory agencies. Data mining may also aid drug makers in their...
attempts to track patient safety, to conform to risk management plans, and to gather worldwide information to supplement clinical trial data. There are many important benefits of using data mining for drug surveillance, but there are also many challenges. A variety of steps will in future be taken to expand the use of pharmacovigilance data mining (Kshirsagar et al., 2011).

**Need for Pharmacovigilance**

The research focuses on the dynamic comprehension mechanism and discusses the essence of the ADR in a patient who takes oral or parenteral or intravenous (I.V) medicines for disease. The drugs that are being sold globally have been checked and tested with animals and human subjects to ascertain the medicine's safety and to assess the exact adverse reactions to a particular disease. Some of it is still unknown, and some ADRs are observed in post-marketing testing. The ADRs that decrease quality of life, increase the hospitalization, and increase mortality are estimated to be important. An important Lazarou report in 1998 identified the estimate of 3-7 percent of all hospital admissions in ADRs as the fourth to sixth leading causes of death in the United States and ADRs (Kshirsagar et al., 2011).

**Pharmacovigilance data mining tools**

The goal of PV is to be accomplished through various types of studies intended to either "generate hypotheses" or "check hypotheses" or to discuss such objectives (Harpaz et al., 2016). The former is represented by random recording and tracking of drug incidents to detect unexplained ADRs, while the latter by case-control or cohort studies, to demonstrate (through risk assessment) whether any question previously posed is justifiable. Although the laws and regulations governing spontaneous reporting of ADRs between the countries are common:

- It is an individual voluntary notification by the writer except for medical firms legally "required" to report ADR to health authorities (e.g., professional healthcare, patient).
- A suspicion (no certitude is needed) is sufficient;
- A drug, patient, and event must be identifiable;
- The number of people exposed to the drug and the total number of unknown individuals.

In other words, the pre-condition for quantifying the risk is the accurate numerator and denominator (Coloma et al., 2013).

**Importance of Data mining**

Database data mining drug safety reports, medical literature, and other digital tools may contribute significantly to that knowledge on ADEs obtained during short-term clinical trials. Data mining can also provide an early warning mechanism to identify drug safety problems more quickly than traditional approaches. For these purposes, the FDA’s health and product safety experts are of particular interest to mining sources of ADEs (Department of Health and Human Services, 2017).

- Systemic, standardized, and realistic methods for larger data sets to be screened.
- Make use of the FDA, WHO, and other organizations' broad security databases.
- Positive public health improvements by speeding up and/or reliably detecting possible safety issues than conventional pharmacovigilance.

**History of Data Mining Mission**

Over the last 20 years, computerized data mining techniques have been developed by regulatory authorities and drug control centres to identify reporting relationships in random coverage databases suggesting possible adverse drug reactions. This method is now used for several commercial applications, including many pharmaceutical manufacturers. However, there are currently no guidelines or requirements of routine pharmacovigilance for the implementation of those approaches (Lindquist et al., 2000). The FDA Collaborative Health Assessment Methods Working Group is:

- To build a perspective on the consequences of pharmacovigilance and risk management for best price optimization of data mining.
- To better understand data mining database and best design and applications criteria, including issues of data quality; data mining;
- To better understand how different data mining techniques in the field of drug protection, for which there are no real and well-established targets, can determine performance characteristics, in particular, because they affect the interpretation of results;

**Neural network**

The Bavarian Faith Propagation Neural Network (BCPNN) algorithm is used by the Medication Center (MC) to identify drug case couples that statistically separate themselves from other records in the database. Members of the International Expert Panel of the MC then decide the associations between these drugs and the AE will further be tested. Because Bate, etc., as an example of false signal avoidance, is widely reported in the literature. Explained how Captopril’s connection to Cough was discovered by the unit. For the critical periods reported in Reactions Weekly from January to June 1998, Lindquist et al. analyzed case reports from the WHO database for the same duration. Researchers found that the conditions for WHO membership were met at the same time with or before 12 out of 43 pairs reported in reactions weekly as 'first posts.' In a retrospective evaluation, Lindquist et al. also described that the "gold standard" was either defined at any given moment or whether the correlation was reinforced or validated in the literature (Stahl et al., 2004).
The MC has been introduced recently as the triage logic for filtering the many associations created and submitted to reviewers for evaluation by the BCPNN. Such filters minimize the number of highlighted combinations in the combination database generated by the BCPNN search, to decide and concentrate on key fields. The filters currently in use show that accidents, adverse reactions to new drugs, and reactions of particular concerns such as drug reactions are increasingly increasing. Once these filtering techniques have been used for some time, UMC aims to determine how effective it has been in identifying 'potential signals' and to test if important signals have been enhanced at an early stage (Manson et al., 1996).

**Data mining Algorithm (DMAs)**

In frequentist and Bayesian approach, DMAs can be graded. The Netherlands Pharmacovigilance Center is one of the first to apply the Reporting Odds Ratio (ROR), while Evans et al. first used its Proportional Reporting Ratio (PRR). Gamma Poisson Shrinker (MGPS) is focused on legislation from Bayes that measures the risk of a possible accident triggered by the ingestion of a suspicious drug (post probable) and the Bavarian Confidence Neural Network (BCPN). Bayes legislation. (Witten et al., 1999). The probability calculation based on ADR and summary of major DMAs used for detection were presented in Table 1 and Table 2 respectively.

**Table 1**: Probability calculation based on the ADR

<table>
<thead>
<tr>
<th>Drug of interest</th>
<th>All other drugs in the database</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse drug reaction of interest</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>All other adverse drug reaction</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Total</td>
<td>A+C</td>
<td>B+D</td>
</tr>
</tbody>
</table>

A = Amount of both suspect drug and suspect adverse drug reactions records.
B = Number of records (except the medication of interest) that include suspect adverse drugs with other medicines
C = Number of accounts of certain adverse drug reactions involving a suspect drug (except in case of interest)
D = Amount of incidents of other medicines and other adverse drug reactions

**Table 2**: Summary of major DMAs used for signal detection

<table>
<thead>
<tr>
<th>DMA</th>
<th>Computation</th>
<th>Published threshold criteria</th>
<th>Advantage</th>
<th>Limitations</th>
<th>Regulatory Agencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayesian Multi-item Gamma Poisson Shrinker (MGPS)</td>
<td>( a(a + b + c + d) / (a + c) )</td>
<td>EBGM05 &gt; 2 N&gt;0</td>
<td>More accurate than the regular form often applicable*</td>
<td>Relatively non-transparent for individuals who are unfamiliar with Bayesian statistics</td>
<td>FDA (AERS)</td>
</tr>
<tr>
<td>Bayesian Confidence Propagation Neural network (BCPN)</td>
<td>( \log_2(a(a + b + c + d)/(a + b)) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Use thresholds commonly quoted. SD = Deviation Standard; EBGM = The Empirical Geometric Mean; 05 = Fifth Population of the post-distribution; i.e. the probability that the true relative reporting ratio exceeds the EBGM05. N= number of cases; IC = Information Component

**Systems of Administration and Reporting**

The vaccine system and the reporting of AEs differ from the system used in pharmaceuticals. Medicines are administered mainly by licensed practitioners on prescription within a healthcare system focused on the treatment of illness. Vaccines are mostly provided by doctors but are often distributed following the recommendations of public health by the comprehensive disease prevention system, through doctors’ offices, public health facilities, and the army. (Leone et al., 2010). AEs from each part of this system are often recorded at different
levels, which may affect the disproportionality determined by different algorithms. The recent vaccine program against smallpox, for example, was confined to military personnel and certain public health staff. There were also military and CDC safety surveillance programs outside the VAERS program, even though VAERS had provided all warnings of AEs in operation. When reviewing data mining work comparing the vaccine with other adult vaccines, this specific reporting mechanism and the possibility of higher reporting rates are to be taken on account (Maclure et al., 2012).

**Issues in interrupting data mining process**

**Adverse Event Coding**

There were also military and CDC safety surveillance programs outside the VAERS program, even though VAERS had provided all warnings of AEs in operation. In the review of data mining work that would equate PLV vaccinations with other adult vaccinations, this particular reporting mechanism and the possibility of higher reporting levels should be taken into account. MedDRA was introduced with ten times more preferred term codes (PT) than COSTART and was designed to use hierarchical systems and use more nuanced wording. As a result, it may be problematic to compare COSTART codes directly and MedDRA (Warner et al., 2012; Aronson et al., 2012).

**Product Age (Time on Market)**

Generally, spontaneous AE reports are dramatically increased and eventually decreased after several years, when the drug is first authorized for commercialization. Further specifics raise the probability that an accident will occur. There is evidence that more documented reactions mature with a drug and events associated with diseases are included in the registered AEs. A new dose scheme or an indication for a mature product may also lead to a new model of coverage or its launch in a new market.

**Targeted Surveillance**

Relevant monitoring activities include post-market epidemiological surveys, approvals of medications, and monitoring of risk management program’s needs. A targeted monitoring example is a facilitated coverage for many years following their approval of two prescription class X drugs during prescription. Unintended disclosure

**Selective Prescribing (Channelling)**

A variety of factors affect the prescribing decisions of physicians. Patient drug characteristics, including frequency and prognosis, may affect the likelihood of mistaken medicinal effect associations. The prescription can also be determined by restrictions on form payers and the insurance coverage level of a patient, which again creates the potential for confusing associations of drug events.

**Stimulated Reporting**

Advertising that is caused by publicity, litigation, and regulation (e.g. letters and withdrawals from products by the ‘Dear healthcare provider’) that lead to increased coverage and increase the anticipated outcome. To order to detect these impacts, a relative should be studied over time, but no clear guidelines are to place to accurately classify such consequences using data mining techniques.

**Conclusions**

However, since PV is highly regulated, its adoption would require quality guarantees as well as consistency and standardization. The use of AI methodology in PV is imperative. PV is still a vibrant feature of the general population and the clinicians. It is very critical that they are reported promptly and investigated after these adverse drug effects have been detected. Not only should the doctors be aware of the PV system, but the patients should be aware of it themselves, thus increasing their self-report and of the burden on the clinicians. India is still in that stage of PV, and further coverage is required to meet a worldwide standard for documenting such adverse events to provide successful use of drugs in the most vulnerable populations of children and pregnant women. Generally, DMAs should be carefully considered and directed by the correct clinical evaluation. To promote the effective use of the drugs to balance drug effectiveness, safety, and especially patient needs, this clinical perspective always should be considered.

**Conflict of Interest**

**References**


