WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 13, 569-579. Review Article ISSN 2277– 7105

ARTIFICIAL INTELLIGENCE: AN INNOVATIVE APPROACH IN PHARMACOVIGILANCE

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Article Received on
03 Sept. 2020,

Revised on 23 Sept. 2020,
Accepted on 13 October 2020

DOI: 10.20959/wjpr202013-19023

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ABSTRACT

Background: As all the adverse events of a drug is not detected from clinical trials, occurrence of adverse events on a drug is more likely after being released into the market, due to inter-individual variability, increased number of diseases, the physiological condition or advancing age of patient. Detection, assessment and monitoring of adverse effects is the primary goal for all the drug safety professionals. However pharmacovigilance process might be a cumbersome process when the data volume increases in a hospital setting and more complex when done in a community settings. Introduction of artificial intelligence to pharmacovigilance sector can improve qualitative and quantitative data collection and its assessment by utilisation of machine learning algorithms. Advanced medical approaches like personalised medicine optimising risk-benefit ratio is acquired through artificial intelligence. **Method:** The review was done by referring research and review articles from sites like PubMed, Google Scholar, Science direct, IJOPP, Research gate and information regarding various databases are obtained from WHO-UMC site. **Observations:** Artificial intelligence methodologies could be the ultimate answer for the cumbersome workload of data collection and analysis in pharmacovigilance sector to provide a hassle-free, tailored, customised result and will bring up a huge impact in Fourth Industrial Revolution, fusing physical, digital and biological world.

KEYWORDS: Artificial intelligence, pharmacovigilance, automation, machine learning, database.

INTRODUCTION

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[1] It is of immense importance regarding assurance of safety and efficacy of a treatment plan. The most challenging aspect of pharmacovigilance is data collection and its assessment. However, complexity and inefficiency in healthcare disciplinary makes it a mental drudgery to the personnel. Hence, timely monitoring and development of innovative treatment plan is hindered due to lack of adequate information sources. Any adverse event caused by a drug to the patients should be recorded as ICSR (Individual case safety reports) and all the data regarding the drug should be collected and collated by pharmacovigilance experts. Above 10 million adverse events are reported by US FDA, from 2008 to 2017 out of which 5.8 million were serious and 1.1 million were death reports.[2] Therefore introduction of artificial intelligence to pharmacovigilance sector can improve qualitative and quantitative data collection. The machine learning algorithms follow human neuronal activities and sum up the information to synthesise a logic output by deep learning based on previous experiences. Celgene Global Drug Safety and Risk Management (GDSRM), started use of machine learning in pharmacovigilance operations.[3]

Automation tailors the critical thinking, which is a process of analysis to design thinking which is based on creation of action-oriented ideas.[4] Electronic medical records (EMR) is an excellent source of information, convenient option for patient data entry and storage as it provide encryption and digital signatures where information retrieval is possible unlike paper records which can only be stored at one place at a time and may be prone to wear and tear.

METHOD

The review was done by referring review and research journals from various websites like PubMed, Science direct, IJOPP, Google Scholar and from WHO, UMC websites. The search was mainly done using keywords like artificial intelligence, pharmacovigilance, automation, databases etc.

Emerging need of artificial intelligence

Artificial Intelligence is used for data analysis, in which large volume of complex data can be collected and collated to give a reproducible results that can be customised based on previous data entries. Even diverse data can be integrated together and prevent the repetitive entry of a data. Useful to detect a new adverse event or to recognise a change in pattern or severity of an adverse event from data history and thus aid in risk minimisation. The data obtained from various sources are entered, and classified on the basis of their standard reference, then annotations are assigned for coding the data, and data is processed using algorithms. Annotated corpus, the data used to teach the syntactic and semantic patterns of a language is created for developing cognitive services.[5] Natural language processing (NLP) is the ability of a computer system to understand and interpret human language. Automated data coding for clinical data management is done using MedDRA or WHODDE (WHO Drug Dictionary Enhanced), and thus the verbatim entered by an user is cross matched with terminologies or synonyms in the database to find the accurate key word in database.[6]

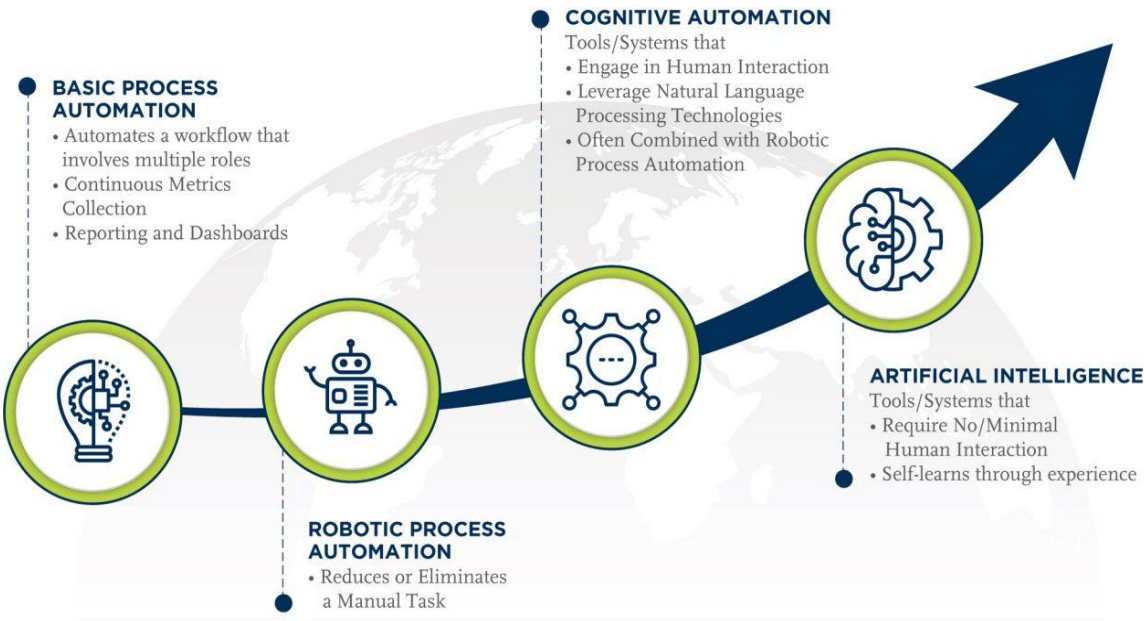

Fig. 1: Evolution of automation technologies.[7]

Some pharmacoepidemiology databases include New Zealand Intensive Medicines Monitoring Programme (IMMP) databases, the medicine monitoring unit (MEMO) databases and general practice research databases (GPRD) in the UK.[8]

All information about a patient can be compressed within a single file and any future entries can be easily added, screening any malicious reports.[9] Signal detection process can be augmented using automation for finding the causality assessment of a drug by using data mining.[10] E.g. : Gamma Poisson Shrinker (GPS) or Information Component (IC) are signal detection algorithms.[8,10] Gamma Poisson Shrinkage (GPS) is a disproportionality method commonly applied to spontaneous reporting systems for signal detection.[11] The WHO-UMC uses the Bayesian Confidence Propagation Neural Network to detect signal in ICSR database.[12]

Role of automation in various pharmacovigilance processes

A major drawback in pharmacovigilance is under-reporting of adverse events. The reason may be many from, lack of time, skill, infrastructure, to increased workload where the professionals are unable to handle huge case volumes, lack of recognition of a potential drug–adverse event association or fear of litigation.[8] This can significantly affect the signal generation. Sources of data may vary from healthcare professionals, dentists, physicians, patients or from a literature review or social media. Earlier, the individual case safety report forms where collected, packaged and distributed to regulatory agencies worldwide which require more time and manpower. The Thalidomide tragedy in 1961 arises the need for reporting adverse events of a drug. However it took about two years for its identification of causal relationship of drug with side effect that causes the phocomelia, by an Australian obstetrician and a German paediatrician.[13] Hence regulations and programs were initiated by WHO for prevention of such disasters. This leads to necessity of a centralised, unbiased, software system containing information about safety profile of a drug. Eudravigilance was introduced in Europe which is a fully automated, XML based messaging system that complies with ICH standards.[10,14] Spontaneous reporting system (SRS) focus on the rapid electronic identification of possibly related discrete data points that would be nearly impossible to detect through a conventional manual search.[8]

Various databases are available for reporting any adverse events occurring after a drug is being released into the market.

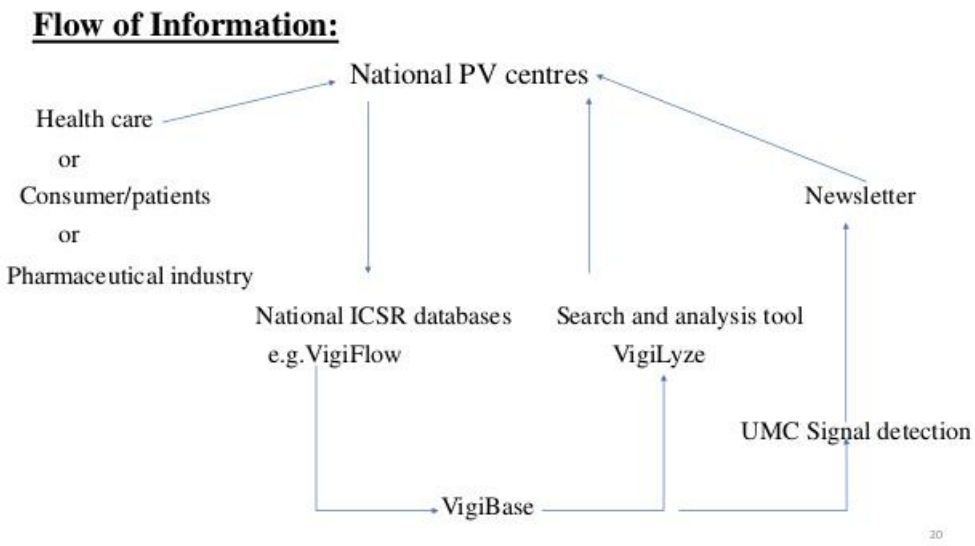

Fig. 2: Functionality of WHO-UMC Pharmacovigilance Databases.[15]

Vigibase is the largest WHO global database with over 20 million reports of ADR's, since 1968, where, ICSRs are reported and coded to MedDRA or WHO-ART and is checked with predefined criteria and reference standards, safeguarding the confidentiality of patient information.[16]

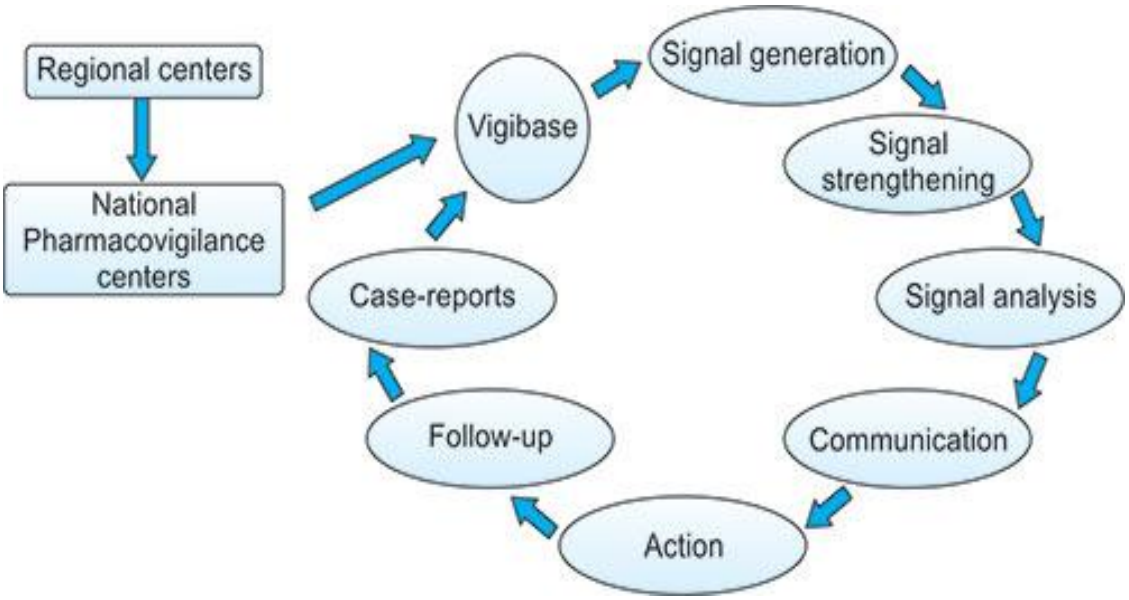

Fig. 3: Work flow of vigibase.[17]

VigiAccess is a user friendly interface by UMC that allows the public to browse information from Vigi Base.[18,19] VigiFlow is an ICH E2B compliant, ICSR management system available to national pharmacovigilance centres for collecting, processing and analysing data. It is a hassle-free way for sharing ICSR information and does not require a back up or

installation procedures.[16] VigiLyze is an online resource available to member countries of WHO program for searching adverse events in a specific region or with specific aspect.[16] VigiGrade measures the amount of information in structured format on reports as represented in Vigibase and provides a completeness score.[16,20] VigiMatch is used for identification of any duplicate records by matching record pairs with a match score.[16]

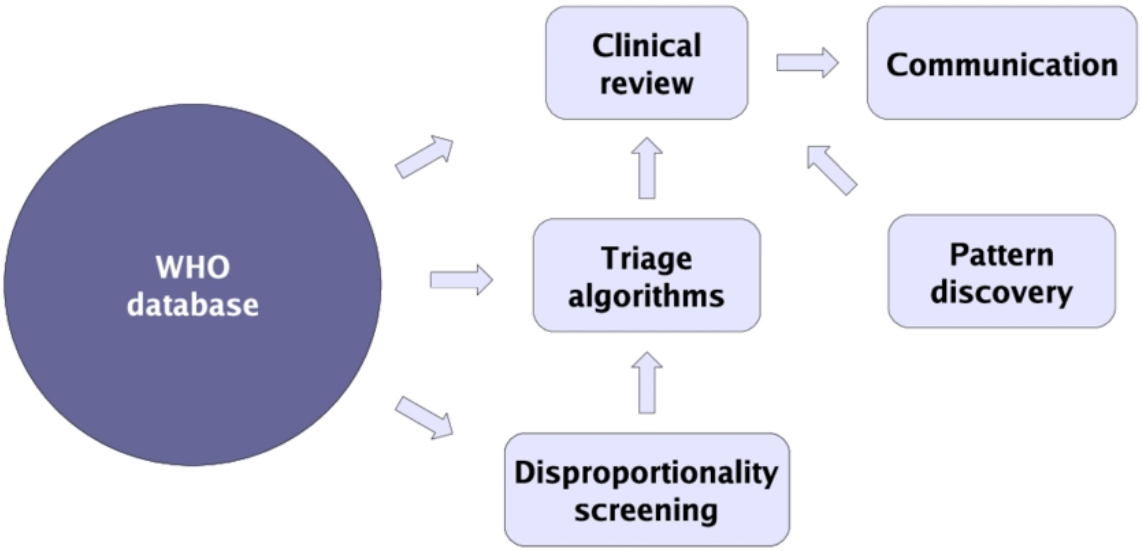

Fig. 4: Clinical data processing using databases.[21]

Different databases used in pharmacovigilance process

Databases used must meet standard regulatory requirements from ICH, ICSR etc. The compatibility and interoperability of database used must be regularly monitored and updated.

Oracle: Argus Safety Database.

It is suitable for handling large data volumes, its processing analysis and reporting in both E2B (R2) and E2B (R3) formats.[22]

AB Cube: Safety Easy

It is 21 CFR Part 11 / Eudralex Annex 11 and ICH E2B (R3) compliant-ready multivigilance database. Data updation and errors detection and inbuilt query makes it user friendly interface.[22]

Aris Global: ARISg/LifeSphere Safety

It is well established with its configuration options and module integration.[22]

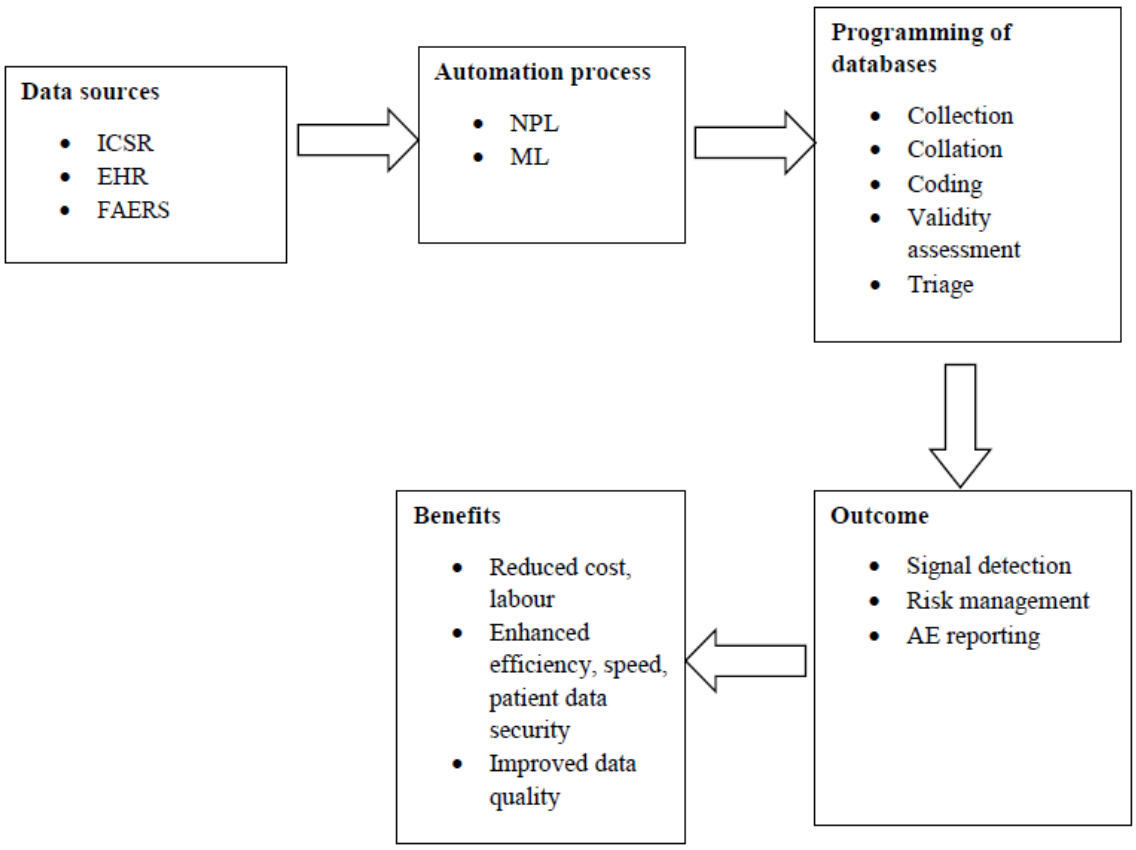

Fig. 5: Representation of automation in pharmacovigilance process.

Advantages of automation

- A single report on an adverse event of a drug does not provide adequate information regarding safety profile of that drug, many cases should be reported from different places to ensure the adverse effect produced and hence reporting from various places can be combined with the automation technology which produce customized and predictive report based on the occurrence, frequency, severity of adverse effects.
- Large volume of data can be processed at a time and act as a tactic for information processing.
- It is convenient for storage of files and there is no risk for deterioration as it ensure scheduled back up.
- Provides safety and confidentiality for patient details with strong password.
- It reduces man-power with its inbuilt voice and manuscript recognition ability (optical character recognition (OCR)) and formation of template for frequently used data.[5]
- Helps to gain a predictive results by determining causality relationship between drug and adverse effects.

- Facilitate screening of drug toxicity levels. Earlier, drug screening provides pharmacokinetic data based on the chemical structure of the compound which does not help much in ADR to be expected.[23]
- It reduces case processing cost and increases the workforce productivity.[12]
- Under reporting of adverse effects can occur due to lack of time which significantly affect signal detection process. Automated data reporting is a tedious process and hence saves time.

Strategies to overcome

A major drawback is that there is no any standardized guidelines for validation process in designing algorithm.[24] E.g.: OFFSIDES database in validation of side effects,[23] but not listed on official FDA label. It is a sophisticated technical method to be considered and hence chances for errors and instrumental bias should be ruled out for a better result. As only limited standard medical dictionaries are available (E.g.:MedDRA) it is awful to maintain the ambiguity of medical terminology required for designing the algorithm.

The operational efficiency with user interface is controversial and troubleshooting, updating and retraining of algorithm may be challenging to the DS professionals and data administrators. A crash course for the DS professionals to develop soft skills should be implemented. The software updation for including more features and for bug fixing should be scheduled regularly.

In 2013, a study conducted at Oxford University stated about 47% of all jobs in the USA are at risk due to automation or computerization.[25] Hence, job opportunities should be opened for professionals with soft skills. Expense for implementation and its maintenance are huge and time consuming, thus making the regulatory authority hesitant to accept automation technologies. And chance for missing, incorrect, or vague information, and duplicate reporting cannot be ruled out completely.[8]

CONCLUSION

Automation in pharmacovigilance sector can improve the efficiency in workflow process, reducing the workload and time. This customised technique will be deployed by conventional paper method, augmenting clinical decision making process. As risk minimisation is always the major concern, this tedious technique convert data and convey information to multiple targets simultaneously.

Cloud based integrated global ADR repositories reporting provides information on centralised adverse events reports from anywhere across the world. Use of mobile applications and social media has now been a trend and provide an open platform for anyone to report and for collection of AE data. In future, patient information leaflets, package inserts, medication guides can be replaced with mobile applications. Use of digitized medicines with ingestible sensors to track and collect patient's health data including AE detection will be dominating the future pharmacovigilance processes.

Funding

No funding.

Declaration of competing interest

None declared.

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