Original Article

ROLE OF ARTIFICIAL INTELLIGENCE IN PHARMACOVIGILANCE: A CONCISE REVIEW

Pranali Wani[1]*, Arti Shelke[1], Mandira Marwadi[1], Vrushali Somase[1], Priyanka Borade[1], Kajal Pansare[2], Ganesh Sonawane[2]

[1] S.N.D. College of Pharmacy, Yeola, Nashik, Maharashtra (India).
[2] Assistant Professor, Divine College of Pharmacy, Satana, Nashik, Maharashtra (India).
Corresponding Author: Ms. Pranali Wani, S.N.D. College of Pharmacy, Yeola, Nashik, Maharashtra (India).
Email: pranaliwani243@gmail.com

DOI: 10.47750/pnr.2022.13.S07.747

Abstract

The healthcare industry, particularly pharmacovigilance recognizes the importance to support the growing amount of data collected from individual case safety reports (ICSRs). More healthcare and skilled experts are needed to capture and assess the data to deal with this growth. To keep up with the changing world, assistive technologies like artificial intelligence (AI) will need to be used on a large scale. In the field of pharmacovigilance, artificial intelligence may alter the everyday work life and career growth of drug safety professionals. By utilizing machine learning algorithms, artificial intelligence may enhance qualitative and quantitative data collection and assessment in the pharmacovigilance industry. Artificial intelligence is used to achieve advanced medical techniques such as personalized treatment that optimizes the risk-benefit ratio. In this review we have concisely focused on benefits of applying AI techniques in PV, role of drug safety professionals using AI, background of PV cognitive services, role of AI in 21st century PV, need of AI in real-world of PV, need of AI for drug toxicity and safety in PV, and challenges of using AI in pharmacovigilance.

Keywords: Pharmacovigilance, Artificial Intelligence, Drug Safety, Pharmacology, Cognitive Service.

Introduction

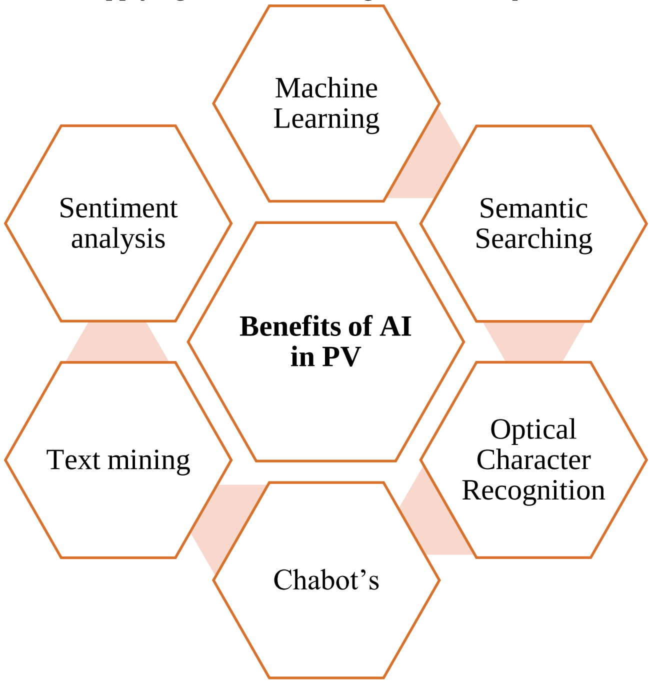
Pharmacovigilance is the study of adverse events assessment, prevention, detection and collection, evaluation of drug-related problems. Individual case safety report volume can be increase year to year, but 90% of adverse events (AEs) go unreported. Hence technologies must be necessary to maintain adverse events. Artificial Intelligence helps in decision-making in a complex situations. Cognitive services are developed to assess PV users for decision-making. Hence, use of AI is the strategy to overcome on AEs unreported data. Another strategy is the use of social media to aware of health information. Electronic Health Records (EHRs) represent patient narrative information. Using the above sources AEs can detect and improve. Due to transcription and data entry, manual efforts can be reduced by the AI as well as increased focus on scientific and medical evaluation of AEs, which is more beneficial for patient health(1). AI is defined as the task performing ability of digital computer which task requires human intelligence. AI is the use of the machine by the introduction of learning technologies to the machine with the help of data collected in the past to be used for solving problems that arise in the future. The AI helps in patient randomization and also increases the success rate of clinical trials. Diabetes retinopathy, diabetes, and cancer are the leading global health burdens in which AI has shown positive results in the detection, prevention, mitigation, and treatment of these diseases. PV data plays an important role in ensuring the safety of ongoing medical products. Once the AI implemented the PV data it is expected to be more accurate and quality reporting is provided. The first AI program was discovered by Netwell and Simon in 1995. The Father of AI is John McCarthy. In 1943, Warren McCulloch and Walter pits proposed the artificial neuron model and Donald

Hebb modify the strength of the connection between neurons. In 1966, researchers found an algorithm that solve a mathematical problem. In 1980, the expert system found programmed decision-making ability of human-expert. In 2011, IBM's Watson solve quiz, complex questions. Hence, Watson proved that computers can understand natural language. In 1972, in Japan scientists used AI for vision learning in robots by ML(2). AI can be classified into three groups, a) Rule-based static system: Automation obtain by a pre-defined set of rules, b) AI-based static system: Outcome obtained by set training data (supervised ML, NLP) and, c) Rule-based dynamic system: New data (New ICSRs) updated for future use. The rule-based static system was used for the validation framework of PV and the AI-based static system was used for the GMP framework. Due to the insufficient validation framework of existing technologies, it was needed to classify the intelligent automation system. AI is used in the stimulation of human intelligence basis on the Rule-based static system(3).

BENEFITS OF APPLYING AI TECHNIQUES IN PV

- Machine learning (ML): supervised learning used in PV for ICSR processing can teach ML algorithm where ground truth i.e., Human annotated answer file while unsupervised learning has no ground truth and is used for signal management.
- Semantic searching: enhance the accuracy of searchers understanding.
- Optical character recognition (OCR): identify text in scanned documents, also for verification of handwriting text.
- Chabot's: use NLP for conducting conservation of human via audio or text method.
- Text mining: examine collected data of resources into evidence form by transforming unstructured text to structure data.
- Sentiment analysis: meaning text extraction from context(4).

Figure 1: Benefits of Applying Artificial Intelligence Techniques in Pharmacovigilence



Natural language processing (NLP) of the computer system can understand human language and interpret it. ML is that area of AI that can give predictable outcomes without explicitly the programmed. Combinations of NLP and ML algorithm are cognitive service that helps to solve tasks when human intelligence requires. To develop cognitive service more efficient annotated corpus consisting of syntactic (sentences identify) and semantic (word/phrases identify) patterns are used(1).

ROLE OF DRUG SAFETY PROFESSIONALS USING AI

Drug safety professionals must have thinking skills about the system, communication skills, analytical assessment skills, leadership quality(5). Drug safety professionals must have done crash courses for soft skills. Retraining, updating algorithm is most challenging for drug safety professionals(6)(5).

BACKGROUND OF PV COGNITIVE SERVICES

a) Identification of Cognitive services: Cognitive services focused on the collection and collation of safety information. It's a very critical decision that the how to best result given ML algorithm to cognitive service which would be beneficial for assess, data entry of ICSR process. Hence contextual analysis is used by researchers. In cognitive service, the task can be broken and functions performed can be observed by the interviewer, and then PV makes decisions. Cognitive load is theory gives different categorizes of cognitive load, the effort for working memory. Cognitive load has 3 types:

1. Intrinsic (consist characteristics of information)

2. Extraneous (how the information is present to the user)

3. Germane (construction of schemes, pattern)

Based on the above cognitive load theory and contextual analysis PV cognitive service works(1).

b) Development of cognitive service:

1. Specific annotated corpus: Annotated corpus consists of data to teach cognitive service. When ICSRs selected, find out factors such as report type, country, no. of reported terms, the seriousness of ICSRs, seriousness of AEs, value for Investigators Brochures (IB), Summary of product characteristics (SPC), Prescribing Information (PI).

2. Building and allocating an annotated corpus: Specified corpus prepared to electronic format, all manual data transcript to machine-readable form and tagged via manual annotation process. After developing annotated corpus, sets are divided into training data to teach cognitive service, tuning data to increase parameter of service, testing data to give feedback of error. Developing annotated corpus predictive performance gives positive true performance understanding(1).

c) Measuring performance: Precision is called positive predictive value (PPV) which is the ability of cognitive service to correctly identify elements. But the risk is that very high precision may not capture all elements, but that captured are correctly captured. Precision is that which translates service shows many false negatives (FN). The recall is called sensitivity, having total results are correctly identified. But high recall is that which has the risk of translating service to false positive (FP). F1 score is the combined measurement of both precision and recall which is common for the evaluation of machine learning algorithms. True positive is positive and predict positive, true negative is labeled as negative and actual negative.

d) Validation of cognitive service: AQL used for sampling of manufacturing. Buyer when inspecting a batch of goods delivered by the supplier at that time AQL method used. For use of the AQL method, it is first to decide what is needed of measured. TPs are used to measure if cognitive service had high-quality outputs, TP gives incorrect results if prediction and ground truth did not correctly classify PV concept. The next step of AQL is tolerance which consists consider the worst quality of cognitive service, defect categories, tolerance percentage. The next step of AQL is inspecting the appropriate level which has I, II, III levels. Level I used for differentiation, III for strong binding. The last parameter of AQL considerations is lot size which is determined by the number of TPs in the annotated corpus.

e) AQL for PV cognitive service: When developers generate the results of cognitive service and give an F1 score below 75%, PV SME (Subject Matter Experts) reviews its errors. When the F1 score is above 75%, then PV SME reviews the TP result. If the number of TPs was less than 150, then PV SME should be done 100% review of TPs for high-quality service, but if TPs more than 150, then PV SME done randomize TPs and select appropriate AQL for a sample of TPs and review the results. But in both cases, TP error must ≤4% then and then service passed, and if it was not, then sent back to the developer for further training. If in case cognitive service fails to be trained successfully due to inconsistent ground truth then the process of either fixing of annotated corpus or reannotation of new training data is another option. Who- DD coding is used as a source of ground truth because it is an international standard for prediction? If annotations were used for ground truth, it produces a big difference between predictions. Hence reviewer used metadata to match predictions with ground truth. Combinations of metadata and annotation used for multiple seriousness criteria, which describe the seriousness of AEs.

f) Applications of validation framework to cognitive service:

1. Cognitive service review, quality check, and give feedback to developer for improving models which are done by Machine learning (ML) service on a sample of new data by analyses and identify the error.

2. Protect health information and personally identifiable information, secure file transfer.

3. AI automation becomes prevalent in PV due to focus on task or data collection, concentrate on healthcare cases.

4. PV industry needs a long-term solution to an unsustainable volume of ICSRs hence AI gives excellent process benefits for patients.

5. There are 51 decision points were identified related to data ingestion, data collection, data collation of ICSRs case management by AI in PV chain which decreases cognitive burden.

6. AI in PV used the AQL process for consistent and reproducible results(1).

ROLE OF AI IN PV IN 21st CENTURY

In Real-world evidence, not for only cancers but many more serious and life-threatening diseases PV must create sure plans, for that AI is at least part of the solution. In the big data outcomes world, patient-level information from individual consumers is not always the same as validated data for that AI is a source that produces electronically valuable healthcare information. In the 21st century, PV activities have a must need for updating the post-marketing surveillance of biosimilar. The first approach of AI in PV is that should develop a new epidemiological concept based on an understanding of the difference between the concept of “generic” and “biosimilar”. AI will help to ease what was lacking today in the PV ecosystem by developing actionable evidence on safety and effectiveness. In the artificial sciences, Herbert Simon defined “design thinking” as the “Transformation of existing conditions into preferred ones”. Critical thinking is the analysis of action-orientated ideas which is developed by AI. Dr. Donald Therese said at a recent conference, “The fear is not about we will find new information, but it is that we would overwhelm with our current capacity of poor-quality information”.

That is the question that arises to appropriately handle 21st-century demands for PV data. In many healthcare areas treatment plans design, electronic health records to manage medication AI is already working. AI has the biggest impact in genomics and genetics for identifying patterns, mutations, and linkage disease. But for actionable, our knowledge requires to prove the analytical method to produce a conclusion but it is restricted due to access to data that are confidential(7).

NEED OF AI IN THE REAL-WORLD OF PV

Increase in volume of data, many unstructured data, and speed for data refreshers is a serious challenge for PV professionals. 20 years ago, the US institute of medicine reported on drug safety that: "To err is to be human", argued on a renewed focus on unnecessary error reduction for patient safety". Using right data methods, processes, tools, patient safety definitely can increase. Unsupervised pattern recognition can detect clusters of AEs such as syndromes symptoms. Supervised pattern recognition helps to find a correlation between previous properties to extent in real-world data(8).

NEED OF AI FOR DRUG TOXICITY AND SAFETY IN PV

In the future, toxicity and safety dare includes polypharmacy, pre-clinical drug safety, post-marketing surveillance hence ML and DL are applied to it. In the 2008 to 2017 period FDA approved 321 novel drugs. In that period FAERS (FDA adverse event reporting system) recorded 10 million AE reports in which 5.8 million were serious reports, 1.1 million were death-related AEs. When a new drug is approved before it is under clinical trials, confirm that is it safe and then marketed, then assess AE reports up to date information on drug safety which is a PV task. But it's impossible to test all effects of drugs and assess AEs on populations. Hence, agencies now use databases of AE reports spontaneously and take follow-up analyses. Drug toxicity is the identification of AES of drug components on humans, animals, and the environment which is a major step in drug design hence pre-clinical evaluation of drug done before going to clinical trials. Toxicity can be evaluated by target-based prediction and QSAR. NLP neural nets such as attention mechanisms and multi-task learning are used in PV. Recently they apply in chemoinformatics, predict ADEs by annotated datasets. For drug safety within silico molecule with own wanted chemical properties emerges using GANs (Generative Adversarial Network) type of ML model(9).

i) Software: TargeTox and PrOCTOR are used as open-source toxicity prediction tools. TargeTox data detect protein target and boosting gradient identify toxicity score, based on diffusion state distance subset to calculate the closest protein bound to the drug. Hence TargeTox can generate protein network data and toxicity predicts PrOCTOR is the target-based toxicity prediction software that also predicts chemical properties score. Compared with TargeTox it has many features with 48 variables, also consists of 50 decision trees, and predicts the outcome. It can use multiple types of target and structure-based features to predict toxicity(10).

ii) Post-Marketing Surveillance: The classical methods to evaluate and assess AEs include the Naranjo algorithm, Venulet algorithm, and WHO-UMC system. For Post-marketing PV, AI methods are needed to extract information because FAERS cannot be mining methods to identify AE's.

iii) EHR mining: It includes the diagnostic procedure, medication codes, continuous lab tests, semi-structured and unstructured medical reports, and notes.

iv) Structured HER data: Zhao et.al assign nine strategies about how to use drugs, diagnoses, and measure features for ADR prediction. The bayesian method represents the effect of drug-using primary care data and prescription. Structure data has the big advantage that it easily pre-processed for ML and DL algorithms(11)(12).

v) Preclinical toxicity: For it ML algorithm use which interprets model at low order of complexity which predicts drug toxicity, inform mechanism of action. E.g. logistic regression

vi) Postmarket safety: DL algorithm used in Postmarket safety which has a high order of complexity, used for clinical decision making, safety analyses. E.g. CNN, RNN.

Traditional used ML includes logistic regression, random forest, support vector machines which are developed currently into a deep neural network to understand how predictors affect the risk of AE(13).

Innovative approaches in AIPV: Due to all AE not detect by clinical trial, hence AE detection, assessed by PV professional. AIPV helps for qualitative and quantitative data collection and assessment by ML algorithm. AI used in PV has a big impact on the industrial revolution, the biological world.AE occurs due to drug in particular patient recorded as ICSR and all data of drug collected and collated by PV professional. DL can sum up the information to give logic output(14). Celgene's Global Drug Safety and Risk Management (GDSRM) was started as an innovative function of ML algorithm use in PV. Automation critical thinking process based on action-oriented ideas, hence EMR as a source of information is convenient to use because it gives digital signature and encryption.AI used in PV for detection of AE from historical data to minimize risk(15)(16).

AI in PV Scope: According to psychologist Gardner, individual persons consist of ≥8 types of autonomous intelligence, such as verbal-linguistic, visual-spatial, mathematical-logical, kinaesthetic body, and interpersonal intelligence. AI is a broad term that represents computer science which includes ML and further includes DL. ML has three types such as supervised, unsupervised, reinforcement learning. Grey literature is a traditional form of ML(17)(18).

Table 1: Different characteristics of ML and Non-ML

ML	Non-ML (Statistical analyses, models)
Split data for testing, signify, classification, prediction.	Signify interference, p-value, interpret relations between variables, analyze the dataset.
Design for external hyperparameter before training use not from data estimated.	Direct model parameter estimated when parametric distribution occurs in model based on Bayesian model.
Arrange big data with millions of parameters	Arrange small to moderate sizes with a limited number of parameter datasets.
Represent automated feature	Represent manual feature
Performance improvement has many more chances such as running time, hyper parametric tuning.	By increasing sample size, performance improves.

APPLICATION OF AI

AI helps to reduce mortality chances by detection of diseases at an early stage from patients electronic footprints. Cyber-attack may cause serious health issues of an individual like heart hacking stimulators, death of a person may occur. Hence, implementation of regulation framing produces safe and effective use of AI in healthcare(9).

ADVANTAGES OF AIPV

- For spontaneous reporting signal detection GPS (Gamma Poison Shrinkage) is used.
- Information component can also be used for signal detection.

- Sources of data obtained to cognitive services are changes from healthcare professionals, dentists, physicians, patients, literature reviews, and social media.
- In 1961, the thalidomide disaster needs earlier detection of AE hence that it takes nearly two years for Australian obstetricians and germen pediatricians to identify phocomelia side effects. For that reason, the WHO sets regulations to prevent such tragedies.
- For rapid electronic identification of data points the spontaneous reporting system (SRS) is used because they are difficult to detect via manual research(6).

CHALLENGES OF USING AI IN PHARMACOVIGILANCE

Pharmacovigilance is a critical and essential function in healthcare. However, the use of artificial intelligence (AI) in this field is still a relatively new and developing field. One of the main challenges in adopting to AI is availability of structured and curated data for training the software to identify potential drug safety issues. Additionally, there are privacy concerns with using AI for pharmacovigilance, as data could potentially be used for other purposes without consent from individuals involved(19).

Conclusion

Artificial intelligence allows for the processing and analysis of large amounts of data and can be applied to various disease states. The automation and machine learning models can optimize pharmacovigilance processes and provide a more efficient way to analyze information relevant to safety, although more research is needed to identify if this optimization has an impact on the quality of safety analyses. It is expected that its use will increase in the near future, particularly with its role in the prediction of side effects and ADRs.

References

1. Mockute R, Desai S, Perera S, Assuncao B, Danysz K, Tetarenko N, et al. Artificial Intelligence Within Pharmacovigilance: A Means to Identify Cognitive Services and the Framework for Their Validation. Pharmaceut Med [Internet]. 2019;33(2):109–20. Available from: https://doi.org/10.1007/s40290-019-00269-0

2. NagaRavi Kiran T, Suresh Kumar N, Lakshmi GVN, Naseema S, Bhargav SB MS. Artificial Intelligence in Pharmacy. Der Pharm Lett. 2021;13(5):6–14.

3. Huysentruyt K, Kjoersvik O, Dobracki P, Savage E, Mishalov E, Cherry M, et al. Validating Intelligent Automation Systems in Pharmacovigilance: Insights from Good Manufacturing Practices. Drug Saf [Internet]. 2021;44(3):261–72. Available from: https://doi.org/10.1007/s40264-020-01030-2

4. Lewis DJ, McCallum JF. Utilizing Advanced Technologies to Augment Pharmacovigilance Systems: Challenges and Opportunities. Ther Innov Regul Sci [Internet]. 2020;54(4):888–99. Available from: https://doi.org/10.1007/s43441-019-00023-3

5. Danysz K, Cicirello S, Mingle E, Assuncao B, Tetarenko N, Mockute R, et al. Artificial Intelligence and the Future of the Drug Safety Professional. Drug Saf [Internet]. 2019;42(4):491–7. Available from: https://doi.org/10.1007/s40264-018-0746-z

6. Article R, Babu A. ARTIFICIAL INTELLIGENCE : AN INNOVATIVE APPROACH IN. World J Pharm Res. 2020;9(13):569–79.

7. Pitts PJ. 21st Century Pharmacovigilance: Intuition, Science, and the Role of Artificial Intelligence. J Commer Biotechnol. 2017;23(1):3–6.

8. Bate A, Hobbiger SF. Artificial Intelligence, Real-World Automation and the Safety of Medicines. Drug Saf [Internet]. 2021;44(2):125–32. Available from: https://doi.org/10.1007/s40264-020-01001-7

9. Kalaiselvan V, Sharma A, Kumar S. " Feasibility test and application of AI in healthcare "— with special emphasis in clinical , pharmacovigilance , and regulatory practices. Health Technol (Berl) [Internet]. 2020;(0123456789). Available from: https://doi.org/10.1007/s12553-020-00495-6

10. Aarushi, Naveen Nandal and Anuradha, Satyam Computers Scam- Pre and Post Analysis, International Journal of Psychosocial Rehabilitation, Volume 24, Issue 6, pp. 1817-1824.

11. Sreenivasa Rao VeerankI,"A Hybrid Cloud and Cluster Computing Paradigm for Life Science Applications",International Conference on Soft Computing and Intelligent Technologies [ICSCIT– 2021]",ISBN: 978-93-91535-15-5,24 December 2021,sreeni.bi@gmail.com, http://proceeding.conferenceworld.in/ICSCIT2021/44.pdf

12. Wang X, Hripcsak G, Markatou M, Friedman C. Active Computerized Pharmacovigilance Using Natural Language Processing, Statistics, and Electronic Health Records: A Feasibility Study. J Am Med Informatics Assoc [Internet]. 2009;16(3):328–37. Available from: http://dx.doi.org/10.1197/jamia.M3028

13. Bousquet C, Henegar C, Louët AL Le, Degoulet P, Jaulent MC. Implementation of automated signal generation in pharmacovigilance using a knowledge-based approach. Int J Med Inform. 2005;74(7–8):563–71.

14. Anna O. Basilea, Alexandre Yahia NPT. Artificial Intelligence for Drug Toxicity and Safety. Physiol Behav. 2019;40(9):624–35.

15 Basile AO, Yahi A, Tatonetti NP. Artificial Intelligence for Drug Toxicity and Safety. Trends Pharmacol Sci. 2019;40(9):624–35.

16 Schmider J, Kumar K, LaForest C, Swankoski B, Naim K, Caubel PM. Innovation in Pharmacovigilance: Use of Artificial Intelligence in Adverse Event Case Processing. Clin Pharmacol Ther. 2018;105(4).

15. Routray R, Tetarenko N, Abu-Assal C, Mockute R, Assuncao B, Chen H, et al. Application of Augmented Intelligence for Pharmacovigilance Case Seriousness Determination. Drug Saf [Internet]. 2020;43(1):57–66. Available from: https://doi.org/10.1007/s40264-019-00869-4

16. Ghosh R, Kempf D, Pufko A, Barrios Martinez LF, Davis CM, Sethi S. Automation Opportunities in Pharmacovigilance: An Industry Survey. Pharmaceut Med [Internet]. 2020;34(1):7–18. Available from: https://doi.org/10.1007/s40290-019-00320-0

17. Tricco AC, Zarin W, Lillie E, Jeblee S, Warren R, Khan PA, et al. Utility of social media and crowd- intelligence data for pharmacovigilance : a scoping review. BMC Med Inform Decis Mak. 2018;18:1–14.

18. Hauben M, Hartford CG. Artificial Intelligence in Pharmacovigilance: Scoping Points to Consider. Clin Ther [Internet]. 2021;43(2):372–9. Available from: https://doi.org/10.1016/j.clinthera.2020.12.014.

19. Salas, M., Petracek, J., Yalamanchili, P., Aimer, O., Kasthuril, D., Dhingra, S., Junaid, T., & Bostic, T. (2022). The Use of Artificial Intelligence in Pharmacovigilance: A Systematic Review of the Literature. Pharmaceutical medicine, 36(5), 295–306. https://doi.org/10.1007/s40290-022-00441-z.